CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209184Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209184

REFUSAL TO FILE

Acorda Therapeutics, Inc.
Attention: William Pfister, PhD
Senior Director Development, Regulatory Affairs
420 Saw Mill River Road
Ardsley, NY 10502

Dear Dr. Pfister:

Please refer to your New Drug Application (NDA) dated June 27, 2017, received June 27, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Inbrija (Levodopa Inhalation Powder).

After a preliminary review, we find your application insufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Chemistry, Manufacturing and Controls

1. As stated in your August 3, 2017, amendment, the Acorda Therapeutics, Inc., Chelsea, MA manufacturing site (FEI number 3011696115) is not ready for inspection, and will not be ready until September 1, 2017.

2. The NDA does not contain the proposed or actual master production record for the drug component (levodopa capsules). Submission of this information is required under 314.54(a)(1)(i).

While the issues below are not related to the refusal to file decision for this application, you should address them if the application is resubmitted.

Office of Medication Error Prevention and Risk Management

We refer to IND 115750 and your human factors (HF) validation protocol submitted to the Agency on July 13, 2016, and our Agency comments dated October 19, 2016. We also refer to your current June 27, 2017, submission of HF validation study results. Our preliminary review of your HF validation protocol and results identified the following deficiencies in your study methodology:

1. Your protocol submitted on July 13, 2016, stated that all patient participants will be trained. In our October 19, 2016, comments, we informed you that we find this

scenario is not reflective of real use without justification of how training all patient participants is reflective of real use. We acknowledge your response to justify the use of an all trained patient user group is supported by a training survey where respondents stated they believe they will receive training. However, you did not submit this justification for Agency concurrence prior to commencing your study. Your survey results did not confirm that every patient user will consistently receive training. As such, you should include data from 15 untrained patients and 15 untrained caregivers.

2. Your protocol submitted on July 13, 2016, states you will include a mixture of age, ethnicities, and education levels. In our October 19, 2016, comments to you, we communicated that it is unclear whether this approach is appropriate to ensure each user group is representative of the intended user population and we asked you to provide a justification for this strategy. However, 14 of the 15 participants presented in your June 27, 2017, submission were college educated. We do not believe that all intended users will have college degrees. You should provide data from users who have mixture of education levels, include those with less than college education level.

Office of Scientific Investigation

3. Please provide contact information for all clinical sites for Protocol CVT-301-004 including telephone number, fax number, and email address for the clinical investigator.

4. For Protocol CVT-301-004, two CROs are listed as responsible for clinical site monitoring: (b) (4). Please describe the specific monitoring functions performed by both of these CROs.

5. Please correct the bookmarks for the document BIMO-CVT-301-004-line-listing included in the submission. The bookmarks are correct up to Site #5045.

Controlled Substance Staff

6. Some of the data are not easily accessed:

   a. Not all links for studies (non-clinical and clinical) and references related to the assessment of abuse potential are functional.

   b. In many instances, links are not provided to the specific sections in the application addressing data of interest. For example, a link is provided to the whole ISS or study report, instead of directing the reviewer to a particular table or section. To facilitate the review of the application you should provide specific links to the topics discussed.

7. Under IND 115750 and throughout the development of this novel formulation, CSS provided detailed requests for the evaluation of dependence, withdrawal, and rebound to be implemented in the still on-going study # CVT-301-004E. However, you indicate, in the study report # CVT-301-004E, that only 7 out of 69 sites implemented these changes. Additionally, no data were submitted in the current NDA, as you apparently plan to submit these data at the 120 day update. If the application is resubmitted, this information should be provided at the time of resubmission. The acceptability of those data to address the evaluation of dependence, withdrawal, and rebound will be a review issue.

8. Provide information on overdoses, both intentional and unintentional. There is a link to the ISS in the abuse potential report, but no data on overdose were found in the ISS. Provide the summary of overdoses for all subjects who used 8 or more doses on any given day in all studies with links to CRFs included. The information on overdoses cannot be located in the ISS, nor can they be found in the study reports # CVT-301-004, CVT-301-004E, and CVT-301-005.

9. Provide drug accountability data for the entire clinical development program, along with discrepancies in the amount of the clinical supplies of the study drug dispensed and the amount of drug lost or otherwise not accounted for, and the reason for missing drug if known.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.'

If you have any questions, call Stacy Metz, PharmD, Senior Regulatory Project Manager, at (301) 796-2139.

Sincerely yours,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ERIC P BASTINGS
08/25/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115750

MEETING MINUTES

Acorda Therapeutics Inc.
Attention: William Pfister, PhD
Senior Director Development, Regulatory Affairs
420 Saw Mill River Road
Ardsley, NY 10502

Dear Dr. Pfister:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CVT-301 (Levodopa Inhalation Powder).

We also refer to the meeting between representatives of your firm and the FDA on September 28, 2016. The purpose of the meeting was to discuss and gain agreement on filing, content, and format of the 505(b)(2) NDA for CVT-301 (levodopa inhalation powder).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Stacy Metz, PharmD, Senior Regulatory Project Manager at (301) 796-2139.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 28, 2016; 2:00 – 3:00 PM EST
Meeting Location:	FDA White Oak: Bldg 22; Room 1315
Application Number:	IND 115750
Product Name:	CVT-301 (Levodopa Inhalation Powder)
Indication:	The intermittent treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a daily oral carbidopa and levodopa regimen
Sponsor/Applicant Name:	Acorda Therapeutics
Meeting Chair:	Billy Dunn, MD
Meeting Recorder:	Stacy Metz, PharmD

FDA ATTENDEES
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Gerald Podskalny, DO, MPHS, Clinical Team Leader
Susanne Goldstein, MD, Clinical Reviewer
Luann Mckinney, PhD, Nonclinical Pharmacologist
Xiangmin Zhang, PhD, Statistical Reviewer
Xinning Yang, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD, Pharmacometric Reviewer
Alicja Lerner, PhD, CSS Reviewer (phone)
Jovita Randall Thompson, PhD, CSS Reviewer
Miya Paternity, MD, Pulmonary Reviewer
Derya Coursey, PhD, CDRH Reviewer
Maryam Mokhtarzadeh, MD, Office of Combination Products, OSMP, OMPT
Patricia Love, MD, Deputy Director, Office of Combination Products, OSMP, OMPT Ebony Whaley, OSE/DMEPA Reviewer
Michelle Mathers, PharmD, Regulatory Project Manager
Stacy Metz, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

Sofia Ali, MSc, MBA, Senior Director, Program Management
Kathryn Ang, BA, DABT, Senior Toxicologist, Research & Development
Richard Batycky, PhD, Chief Technology Officer and Site Head
Todd Baumgartner, MD, Senior Vice President, Regulatory Affairs
Burkhard Blank, MD, PhD, Chief Medical Officer
Caroline Kim, PharmD, Rutgers University Post-Doctoral Fellow – Acorda Regulatory Affairs
Lawrence Marinucci, MS, Vice President, Clinical Biometrics
Harald Murck, MD, PhD, Executive Medical Director, Clinical Development
William Pfister, PhD, Senior Director Development Regulatory Affairs
Alexander Sedkov, MS, Biostatistician I, Clinical Biometrics
(b) (4)

1.0 BACKGROUND

At the pre-IND meeting in November 2012, and in subsequent correspondences and meetings, the Sponsor and the Division discussed aspects of the CMC, nonclinical, and clinical development programs that would support a 505(b)(2) NDA for CVT-301 using Sinemet® as the reference listed drug product (see FDA Type B Meeting Minutes dated August 7, 2014). The Sponsor informed the Division of the clinical plan for satisfying the long-term safety data needed for NDA filing (submitted September 3, 2014).

Seeking clarification of the Type B Meeting minutes dated August 7, 2014, Acorda requested a Type C Meeting (see FDA Type C Meeting Minutes dated March 23, 2016).

The purpose of this Type B pre-NDA meeting is to provide data and background information regarding the CVT-301 drug product, nonclinical, and clinical program in order to obtain the Division's agreement on the adequacy of the nonclinical and clinical program as well as the regulatory plans and content and format of the proposed 505(b)(2) NDA for CVT-301.

FDA sent Preliminary Comments to Acorda on September 26, 2016.

2.0 DISCUSSION

2.1. Regulatory Questions

Question 1:

Assuming that the Phase 3 study CVT-301-004 is positive, does the Division agree that the studies and information proposed would be adequate for NDA submission and review?

FDA Response to Question 1:

Whether the studies and information are adequate for NDA filing and substantive review will be determined after we receive your submission.

Meeting Discussion:
No further discussion at the meeting.

Question 2a:

Does the Division agree with the proposed pooling of data in the studies?

FDA Response to Question 2a:

No, we do not agree with the plan for pooling data in the ISS. You should present the data from your double-blind controlled studies in one pool and the data from open-label studies in a separate pool. In your briefing document, you have proposed (b) (4) We recommend submitting safety data for study CVT-301-005 separately, and you can pool the data from patients treated with CVT-301 with the data from other open-label studies.

Meeting Discussion:
No further discussion at the meeting.

Question 2b:
Does the Division agree with the proposed overall content to be provided in the ISS SAP table of contents?

FDA Response to Question 2b:

The proposed table of contents for the ISS is acceptable; however, the acceptability of the content of the NDA submission is subject to review.

Please see our response to Question 2a.

In addition, for exposure, you should to include:

- Exposure by days exposed at each dose and days exposed by number of doses used in the body of the ISS
- Exposure by duration should be for continuous exposure for each of the categories, i.e., ≥3 months, ≥6 months, ≥9 months and ≥ 12 months in the body of the ISS
- Patient's daily use of CVT-301, i.e., frequency of dosing, by day and by week in the body of the ISS.

For adverse events, you must include all treatment emergent adverse events, regardless of the perceived relation to study medication. Calculate patient exposure using the cut-offs listed above. These exposure tables should appear in the body of the ISS.

You need to ensure that the ISS is navigable and well organized to permit review. If your ISS contains multiple appendices, you should provide a master table of contents listing the location of the individual appendices. Each appendix should have its own TOC. Each TOC should have functioning hyperlinks or bookmarks to the related sections of the document. Post-text tables submitted in an appendix should be named in a logical fashion to identify the content and source of the data presented. Each appendix also needs to have clearly marked page numbers. The TOC for appendices containing only tables should also have functioning hyperlinks.

Meeting Discussion:
No further discussion at the meeting.

Question 2c:

Does the Division agree that the proposed literature search as outlined in Appendix 3 will adequately assess safety information from published sources?

FDA Response to Question 2c:

In order to rely upon published literature to support your submission, you need to bridge to the product referenced in the submitted publication. In addition, you must clearly define and justify the use of specific literature in support of your submission including articles where primary data is available for independent review by the division.

Meeting Discussion:
No further discussion at the meeting.

Question 3:

Does the Division agree with the approach for analysis of pulmonary safety data?

FDA Response to Question 3:

We acknowledge your proposal to use the pulmonary function test (PFT) laboratory spirometry data in your primary analysis of pulmonary safety. While you state that there was "duplication of spirometry assessments," there were differences between the collection of data at PFT laboratories vs. neurology sites. Importantly, the ON and OFF states, which can affect spirometry results, were patient-reported in the PFT lab, but assessed by site personnel at the neurology study sites. While it is acceptable to use the PFT lab spirometry data in your primary analysis, you should also conduct a sensitivity analysis of the spirometry data from the neurology study sites in order to ensure that these differences did not impact the pulmonary safety profile of your product.

Meeting Discussion:
No further discussion at the meeting.

Question 4a:

Does the Division agree with the plan for assessment and reporting of abuse potential?

FDA Response to Question 4a:
Yes. However, we have additional recommendations:

1. CVT-301 produces a dramatic rise of levodopa levels in plasma within the first 10 min after drug administration. This is approximately ~80 times higher than oral carbidopa/levodopa 25/100 in healthy volunteers and ~36 times higher in patients with Parkinson's disease (PD). This seems to indicate that very high levels of dopamine will be available in the CNS within a few minutes of drug administration, which produces circumstances similar to that found when potent stimulants such as amphetamine and cocaine are abused. Your abuse potential assessment should include an evaluation that considers and assesses these differences.

   Your abuse potential assessment should examine the abuse-related adverse event of CVT-301 collected with-in the first 10 minutes of drug exposure, making comparisons to the reference listed drug Sinemet when possible.

2. In addition, you should evaluate dependence/withdrawal and possible rebound in patients with PD. Dependence needs to be evaluated since dependence may relate to the safety profile of the drug.

3. You should also provide an assessment of abuse based on rates of nonmedical use of levodopa so that we can actually conclude that the rates of nonmedical use are negligible.

4. Additionally, adverse events from clinical studies in healthy subjects (Phase 1) should be pooled separately from studies (Phase 2/3) conducted in patients. The adverse events of interest for from studies of PD patients are identified below.

5. Because abuse of levodopa is mainly known in the population of patients with PD, your Abuse Potential Assessment Report, in which you plan to include the analysis of published literature, should include the following items:

   - Populations: analysis should to be performed separately for PD patients and healthy subjects
   - For the PD study population, the following adverse events are of particular interest: abuse, misuse, withdrawal, dependence, dopamine dysregulation syndrome, hedonistic homeostatic dysregulation, euphoria, high, overdose, misuse, diversion, hoarding of medication, neuroleptic malignant syndrome, hyperpyrexia and confusion, rebound

6. Search and analysis of adverse events from your clinical data and the post-marketing data for levodopa formulations in publically available data bases should include and use the same search terms listed above in point 5.

Sponsor's September 27, 2016 PreMeeting Comments
See Attached.

Meeting Discussion (focus on 1 & 2 above; no discussion for items 3-6):
An inspection of the individual plasma concentration time profiles of CVT-301 versus those of Sinemet does not directly address the concern pertaining to CVT-301's heightened plasma level and earlier onset (Tmax) within the first 10 minutes of use. The concern is whether these effects could cause more clinically significant abuse-related adverse events in comparison to Sinemet during the first 10 minutes of its use. Abusers often prefer and repeatedly abuse drugs that produce immediate euphoric effects, also referred to as a quick "rush" following a drug's administration. As previously recommended, you should examine CVT-301 for abuse-related adverse events collected within the first 10 minutes of drug exposure, making comparisons to the reference listed drug Sinemet.

Question 4b:

Does the Division agree that CVT-301 does not warrant drug scheduling?

FDA Response to Question 4b:
FDA decides on recommendations for scheduling after review of all relevant data submitted in the NDA.

Specific Recommendations

1. The dependence/withdrawal/rebound evaluation should be performed at the conclusion of Phase 2 or 3 studies lasting at least 4 weeks. The duration of the discontinuation period should be at least 3 weeks from drug discontinuation. The assessments should include reports of all adverse events that occurred during drug discontinuation. Also below is a list of disease-specific scales that should be administered at baseline, on the last 2 days of the treatment period and throughout the discontinuation period:
    - Stimulant withdrawal scale (Amphetamine Withdrawal Questionnaire, AWQ and/or Cocaine Selective Severity Assessment, CSSA)
    - Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory (DDSPC, Cabrini et al., 2009)
    - Unified Parkinson's Disease Rating Scale (UPDRS)
    - Depression Scale
    - Sleepiness Scale
    - Columbia Suicide Severity Rating Scale (C-SSRS)

2. You should summarize the animal studies related to abuse potential that have been performed.

General Recommendations

According to 21 CFR § 314.50 (5) (vii), the abuse potential section of an NDA includes a proposal for scheduling and all scientific data that form the basis of the proposal. The abuse potential assessment of a drug includes primary data, data analysis and a discussion of the following areas:

- Adverse events related to abuse potential from clinical studies
- Information and data related to abuse potential in integrated summaries of safety and efficacy (ISS and the Clinical Summary of Efficacy in Module 2, as you will not submit an ISE)
- Information related to overdose
- Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies
- Epidemiological data related to abuse

Your NDA should address all of the contents listed above.

You should provide the following information and data related to abuse potential from all clinical studies in the NDA, including raw data and adverse events coded with the most recent MedDRA terminology and the following:

- Descriptions and details of all reports in all clinical studies, including narratives of all incidents of abuse, misuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for, and related to drug withdrawal and withdrawal symptoms, and any other indication of dependence.
- Adverse events data related to abuse should be broken down by gender, age (18-55 and >55), and by population (healthy volunteers or patients with Parkinson's disease).
- Case narratives of patients in clinical trials who are discontinued from studies for lack of compliance to study medication or procedures, or who discontinue participation without returning the study medication.
- Tabulation of patients who were discontinued from the study, or dropped out for reasons related to potential abuse and diversion, including narratives describing reasons and follow-up information.
- All post-marketing safety reports of adverse events related to potential abuse.

The details of abuse potential evaluation are described in the FDA draft Guidance for Industry Assessment of Abuse Potential of Drugs, January 2010: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

You may submit protocols for our comment prior to initiating these studies.

Sponsor's September 27, 2016 PreMeeting Comments
See Attached.

Meeting Discussion:
In general, the Sponsor's plan is acceptable including the recent changes made to the protocol # CVT-301-004E to assess abuse potential of CVT-301. However, for clarity we summarize below all recommendations:

- You should administer the AWQ, UPDRS, Depression Scale, Sleepiness Scale and C–SSRS during the baseline visit, on the last day of treatment with study drug, and on days 1, 3, 6, 8, 11, 14, 17, 24 and 28 after discontinuation of treatment to provide a meaningful evaluation of withdrawal symptoms.

- Add the Amphetamine Withdrawal Questionnaire (AWQ) to your clinical assessments

- Add the Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory (DDSPC, Cabrini et al., 2009) to your assessments

- The sponsor should analyze the data for each time point separately to find out when the withdrawal symptoms peak and end, and whether withdrawal symptoms and/or rebound are present. Please present the scores for each scale in tables and summarize these results in figures.

- Analyze and report all adverse events that occurred during the withdrawal period by week (1, 2, 3 and 4)

- The dependence/withdrawal data can be submitted in 120-day safety update.

FDA Post Meeting Comment:
Please see the FDA response to the Question 2c of these meeting minutes.

Question 5:

Does the Division agree that a population PK analysis is not necessary for the NDA?

FDA Response to Question 5:
Yes.

Meeting Discussion:
No further discussion at the meeting.

2.2. Clinical Questions

Question 6a:

Does the Division find the methods for the primary analysis and sensitivity analyses to be acceptable?

FDA Response to Question 6a:

The proposed primary analysis focuses on TV4. Because we think that the changes from pre-dose in the UPDRS Part 3 score at 30 minutes are likely to be similar at TV2, TV3, and TV4, we recommend that you consider an alternative primary analysis method, for example, analyzing the average of the changes from pre-dose in the UPDRS Part 3 score at 30 minutes at TV2, TV3, and TV4 and handling the averages of non-completers properly.

You need to provide several sensitivity analyses for handling missing UPDRS Part 3 item(s) at a time point (e.g., 30 minutes post-dose) for each visit.

For dealing with missing data, including but not limited to missing visit(s) and missing UPDRS Part 3 item(s) at a time point, please follow the recommendations from "The Prevention and Treatment of Missing Data in Clinical Trials" (2010) by the National Research Council, which are available at the following link:

> *http://www.nap.edu/catalog/12955/the-prevention-and-treatment-of-missing-data-in-clinical-trials*

Meeting Discussion:

The sponsor believes that the treatment effect is maximal at TV 4 due to the decreasing placebo effect over time. The sponsor will conduct a sensitivity analysis comparing the changes from pre-dose in the UPDRS Part 3 to the average of the scores measured 30 minutes after dosing for visits TV2, TV3, and TV4.

Question 6b:

Does the Division agree with the overall statistical analysis plan (CVT-301-004 SAP)?

FDA Response to Question 6b:

- Although the proposed hierarchical testing procedure controls the family-wise type I error at the two-sided significance level of 0.05, we re-iterate our previous response and meeting discussion for Question 4c in the End of Phase 2 Meeting package held on July 10, 2014, where we recommend that you limit the number of key secondary endpoints and focus on a limited number of secondary endpoints that provide important efficacy information not derived from the change in UPDRS Part 3. By limiting the number of secondary endpoints, you may have more power to test CVT-301 DL1.
- You need to describe how you handle missing diary entries and provide several sensitivity analyses to handle missing diary entries.
- You need to provide several sensitivity analyses for each key secondary endpoint to study the impact of missing data.

- We are concerned about the expected 25% dropout rate. If the dropout rate is too high, the study results may be difficult to interpret.

Meeting Discussion:
The sponsor decided to keep the number and order of key secondary endpoints as submitted in the pre-meeting package.

Question 7a:

Does the Division agree with the plan of submitting an abbreviated interim clinical study report for CVT-301-004E in the initial NDA filing?

FDA Response to Question 7a:

Please clarify what you mean by an "abbreviated interim clinical study report."

Your initial NDA submission must include long term safety information for ≥300 patients treated continuously for 6 months, including ≥ 100 patients treated for one year, with at least 50 patients treated with the highest dose recommended in labeling. The NDA needs be complete at the time of submission, and the 120-day update should not contain the majority of the long-term safety information.

Sponsor's September 27, 2016 PreMeeting Comments
See Attached.

Meeting Discussion:

Given the variability in pulmonary function tests in this patient population, there is risk in submitting the application without the complete results. The sponsor acknowledged this risk. The sponsor clarified that at the time of NDA submission, they will submit an interim study reports for studies CVT-301-004E and CVT-301-005. The 120 day safety update will include final study report from CVT-301-005 and a further interim full study report for study CVT-301-004E.

Question 7b:

Does the Division agree with the overall statistical analysis plan as outlined in the current version of the study Protocol?

FDA Response to Question 7b:
The primary objective of Study CVT-301-004E is pulmonary safety. Although patients are blinded to dose level of treatment with CVT-301, study CVT-301-004E is an uncontrolled safety study. Your initial NDA submission needs to include the completed study report and final

datasets from this study. The data should pool the information from this study with open label studies, in the ISS.

Sponsor's September 27, 2016 PreMeeting Comments
See Attached.

Meeting Discussion:
Please refer to the meeting discussion for Question 11.

Question 8a:

Does the Division agree with the plan of submitting an abbreviated interim clinical study report for CVT-301-005 in the initial NDA filing?

FDA Response to Question 8a:

Please refer to our response to question 7a.

Sponsor's September 27, 2016 PreMeeting Comments
See Attached.

Meeting Discussion:
The sponsor clarified that the initial NDA submission will include long term safety information as noted in the discussion to Question 7a. In addition, at the time of the NDA submission, study CVT-301-005 will contribute more than 200 patients with 6 months of exposure including 100 patients treated for 1 year. The sponsor will submit a complete interim study report with the datasets up to the submission cutoff date for CVT-301-005 at the time of NDA submission. The final study report and complete datasets will be included in the 120 day update. A final clinical study report will be provided at the 120 day safety update.

Question 8b:

Does the Division agree with the overall statistical analysis plan (CVT-301-005 SAP)?

FDA Response to Question 8b:

Study CVT-301-005 is an open label pulmonary safety study. The study is not designed to provide supporting evidence of effectiveness for CVT-301. Because the study addresses a specific safety concern, the final study report needs to be included in the initial NDA submission.

Sponsor's September 27, 2016 PreMeeting Comments
See Attached.

Meeting Discussion:
Please refer to meeting discussion to Question 11.

Question 9:

Does the Division agree to the plan to submit the CVT-301-009 clinical study report at the time of the 120 day safety update?

FDA Response to Question 9:

The stated primary objective of Study CVT-301-009 is to investigate the safety and tolerability of CVT-301 co-administered with oral carbidopa/levodopa, in patients with PD. The final report for Study CVT-301-009 should be included in your initial NDA submission.

Meeting Discussion:
No further discussion at the meeting.

Question 10:

Does the Division agree that an ISE is not warranted for this NDA?

FDA Response to Question 10:

We agree that an ISE is not necessary. However, you must still submit the results of subgroup analyses for gender, age, and racial subgroups in your NDA, as required under 21 CFR 314.50(d)(5)(v). You should submit the subgroup analyses for pooled efficacy data in the Clinical Summary of Efficacy in Module 2. You should also include the results of these subgroup analyses in the individual reports for the efficacy studies in the NDA.

Meeting Discussion:
No further discussion at the meeting.

Question 11:

Does the Agency agree with the plan for the 120-day safety update?

FDA Response to Question 11:

Please refer to our response to question 7a. In addition, please estimate the amount of safety data you expect to submit at the 120 day safety update.

Sponsor's September 27, 2016 PreMeeting Comments
See Attached.

Meeting Discussion:
The size of the 120-day update with the accompanying pulmonary safety data may be substantial. The sponsor agreed to provide a table showing the number of patients and the remaining visits that would be included in the 120 day update.

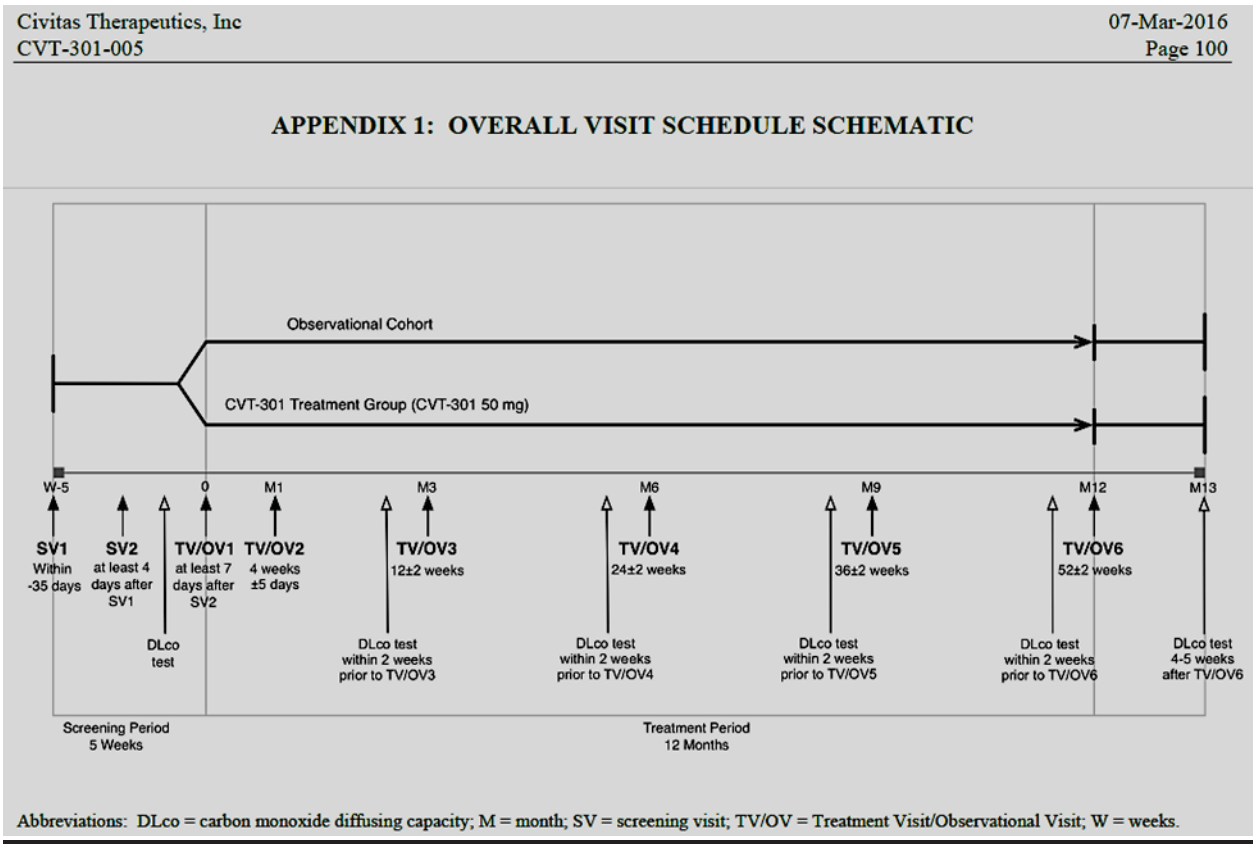
FDA Post-meeting Comment
The tables (tables 2 and 3) included in the sponsor's response (September 27, 2016) to the FDA's pre-meeting comments and Table 1 (in Acorda's PostMeeting response October 6, 2016) show it is likely that a substantial amount of safety information from additional patient visits (approximately 300) from studies CVT-301-004E and CVT-301-005 would be included in the 120-day update. This would include additional data for 1 or 2 study visits per added subject (from study CVT-301-004E) and one visit per added subject (from CVT-301-005); however, the table does not include the Month 13 visit (M13) for pulmonary function tests, scheduled 1 month after the TV6 visit (Study CVT-301-005 design schematic). The pulmonary function testing information from visit M13 should be included in the NDA submission and in the 120-day update for subjects who completed the M13 visit before the data cut-off date. The sponsor should present the new information accurately and clearly in the 120-day update, including updated versions of the ISS and the related datasets. The sponsor should present updated information for exposure, all adverse events, serious adverse events and adverse events leading to discontinuation, and subjects who discontinued/withdrew for any reason in adjacent table columns that list the safety information in the NDA submission, the 120-day update and the new cumulative totals. Please note that adverse events that become apparent from information included in the 120-day update could raise additional safety concerns late in the review cycle.

Table from the Acorda response to FDA request submitted October 6, 2016.

Table 1: Study CVT-301-005: Estimated Patient Exposure, by Study Visit, at NDA Submission and 120-day Safety Update

Treatment Visits	At NDA Submission		Additional Data at 120-Day Safety Update	
	CVT-301	Observational	CVT-301	Observational
Baseline (TV1)	272	127	N/A*	N/A*
1 Month (TV2)	258	124	N/A*	N/A*
3 Months (TV3)	243	119	N/A*	N/A*
6 Months (TV4)	236	110	N/A*	N/A*
9 Months (TV5)	225	107	N/A*	N/A*
12 Months (TV6)	114	55	108 additional patient visits	49 additional patient visits

*No additional data will be submitted for that visit; 100% of patients will be included in the initial NDA submission



The visit schedule for studies CVT-301-004E and CVT-301-005 are identical

Question 12:

Does the Division agree that Study CVT-301-010 will fulfill the requirements of the relative bioavailability study to Sinemet tablets the Reference Listed Drug Product for the 505(b)(2) NDA?

FDA Response to Question 12:

On face, we agree but the final determination of whether the results of Study CVT-301-010 provide an adequate bridge to the reference product is a matter of review.

Meeting Discussion:

No further discussion at the meeting.

Question 13:

Does the Division agree with the proposal on the data files and related documentation for individual clinical trials to support the NDA?

FDA Response to Question 13:
All analysis data files for pivotal studies should be in SDTM format. For studies CVT-301-001 and CVT-301- 002, you may submit the safety data in legacy format as long the datasets are navigable and can be analyzed independently. All of the analysis dataset should have a searchable pdf define file in addition to xml files. All of the variables should be decoded in the pdf define files, whether they are in legacy or SDTM formats. The define files should be searchable, with working hyperlinks from the table of contents to the information for each dataset in the define file. Please refer to the Data Standards For Studies section below for additional information.

Meeting Discussion:
No further discussion at the meeting.

Question 14a:

Does the Division agree with the proposed plan and literature search strategy to summarize levodopa clinical pharmacology data in the Clinical Summary Sections of Module 2 of the 505(b)(2) NDA?

FDA Response to Question 14a:

Yes, your proposal is acceptable.

Meeting Discussion:
No further discussion at the meeting.

Question 14b:

Does the Division agree with the proposed plan to summarize the Acorda-conducted clinical studies in Module 2 of the 505(b)(2) NDA?

FDA Response to Question 14b:

The table of studies you plan to include in the *Overview of Clinical Development Program* for CVT-301 appears be acceptable for the clinical overviews and summaries in Module 2 along with the ISS in Module 5. The summary table of studies presented in the Clinical Overview in Module 2, should also include the number of subjects in each arm, the primary endpoints and efficacy results for the primary endpoint for each study.

You should also include a summary of the information that you reference in your 505(b)(2) NDA. Please include a 3 column analysis of your proposed product label. In column one, show your proposed labeling text. In column two, show the source of the information reference in your label (e.g., section of the reference listed carbidopa levodopa product label). In column three, explain how you have bridged to the referenced product label or the product studied in a referenced publication.

Please refer to the FDA Guidance for Industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf. The guidance provides the location and space limitation of the clinical summary sections in Module 2.

Meeting Discussion:
No further discussion at the meeting.

2.3. Nonclinical Questions

Question 15a:

Does the Division agree that no additional nonclinical studies are required to support the 505(b)(2) NDA for CVT-301?

FDA Response to Question 15a:

On face, the submitted studies appear to be sufficient to support filing of a 505(b)(2) NDA for CVT-301, unless device-associated issues arise (e.g., leachables or extractables; see CDRH additional comments) that would require additional nonclinical studies. A final determination as to the adequacy of the nonclinical data will be a matter of review.

Meeting Discussion:
No further discussion at the meeting.

Question 15b:

Does the Division agree with the proposed plan and strategy for conducting a literature search to summarize levodopa nonclinical pharmacology, pharmacokinetic (including ADME), and safety data in the Nonclinical Summary Sections of Module 2 of the 505(b)(2) NDA?

FDA Response to Question 15b:

Your proposed literature search strategy appears reasonable.

Meeting Discussion:
No further discussion at the meeting.

ADDITIONAL COMMENTS:

1. Please identify all components and accessories of the device proposed to deliver the drug substance. Please include diagrams, dimensions, tolerances, and/or schematics for each device, accessory or component.

a. Identify all patient interface accessories and provide engineering drawings which show any breathing holes and/or valves. Please indicate whether each accessory is intended for single use, single-patient reuse, or multi-patient reuse.
b. Illustrate and explain the breathing gas path, including all valves and orifices, during inhalation and exhalation.

2. Provide a complete summary of all materials including any colorants that may come into contact with the patient's skin or the patient's airway. Also include the nature of body contact and contact duration. Please conduct the required biocompatibility tests identified by the appropriate category of your device based on the nature and duration of contact.

Please clarify whether the ultimate/cumulative exposure from repeated direct contact to the device is prolonged or permanent. For components of your device which are external communicating, tissue contacting (e.g. interior of the device or patient interface, tubing,), permanent duration, please conduct cytotoxicity, sensitization, genotoxicity, and implantation. For components with surface, mucosal contact, permanent duration, (e.g. the mouthpiece), please conduct cytotoxicity, sensitization, irritation, sub-chronic toxicity, and genotoxicity. For components of your device which are surface, skin contact, please conduct cytotoxicity, sensitization, and irritation testing.

In regards to the biocompatibility data for indirect contact with your subject device, it is not clear that you have evaluated risk associated with external communicating device portion of your final finished device. Please provide a listing of final finished components that come in contact with the gas path way. In addition, please clarify for each component of your device, whether it has contact with liquid or aerosolized medication or dry gas. For components of your device which are in contact with liquid or aerosolized medication, please provide an extractable and leachable study. In this study, please provide an exhaustive extraction at 50°C using a non-polar and a polar solvent, and then provide an inhalation risk assessment that characterizes each extract or each leachant which includes an exposure assessment and risk characterization. For components of your device in contact with dry gas, please perform an inhalation risk assessment for each volatile organic compound that may contaminate the dry gas path. In addition, please perform a particulate assessment for all particulate that contaminate the dry gas path using the EPA PM2.5 to determine the safety of the particulate from your subject device.

For additional information, please refer to the FDA Guidance titled "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" which can be located at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890.pdf

3. Provide performance testing of your device to show the aerosol performance. It is recommended that you conduct this testing with a cascade impactor consisting of at least six stages and report the following:
    a. The amount of drug in micrograms recovered on each impactor plate, throat, and outlet filter

b. The drug mass recovered in the cascade impactor in the respirable size range (i.e., 0.4 – 4.7 or 0.5-5 microns, depending on the type of impactor used) expressed as a percent of the total drug mass
c. The mass median aerodynamic diameter (MMAD- the diameter above and below which lies 50% of the mass of the particles) of the particles recovered in the impactor
d. The geometric standard deviation of the MMAD.

4. Provide the following testing to show that device performance is not effected by
    a. device flow resistance
    b. varying inhalation flow rates
    c. drug build up with continuous use
    d. orientation held during inhalation
    e. moisture level
    f. simulated lifetime use

5. An assessment of device robustness and reliability was not found in the present the submission. Please provide a complete assessment of the mechanical safety of the proposed device in accordance with applicable clauses of IEC 60601-1. While the proposed device does not contain electrical components, please note that test reports relating to drop, impact, stability, transportability, temperature, leakage, humidity preconditioning and cleaning are applicable to the proposed device.

6. Provide results of testing that shows the amount of force required to remove the mouthpiece and if it representative of the intended patient population.

7. Your labelling states that the user should be hearing the "whirl" sound to determine if the dose was delivered. Provide testing to show the required flowrate range for the "whirl" sound and how it is representative of the intended user population and its effect on the device performance.

Meeting Discussion:
No further discussion at the meeting.

FDA Post Meeting comment:
Combination products are subject to 21 CFR Part 4 Current Good Manufacturing Practice Requirements for Combination Products accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. For additional preliminary related information see the FDA Draft guidance for industry and staff *Current Good Manufacturing Practice Requirements for Combination Products* accessible at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf. Also, for information on locating device related information using the eCTD format we reference FDA "eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product*

Applications and Related Submissions Using the eCTD Specifications
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format--- Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for

clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

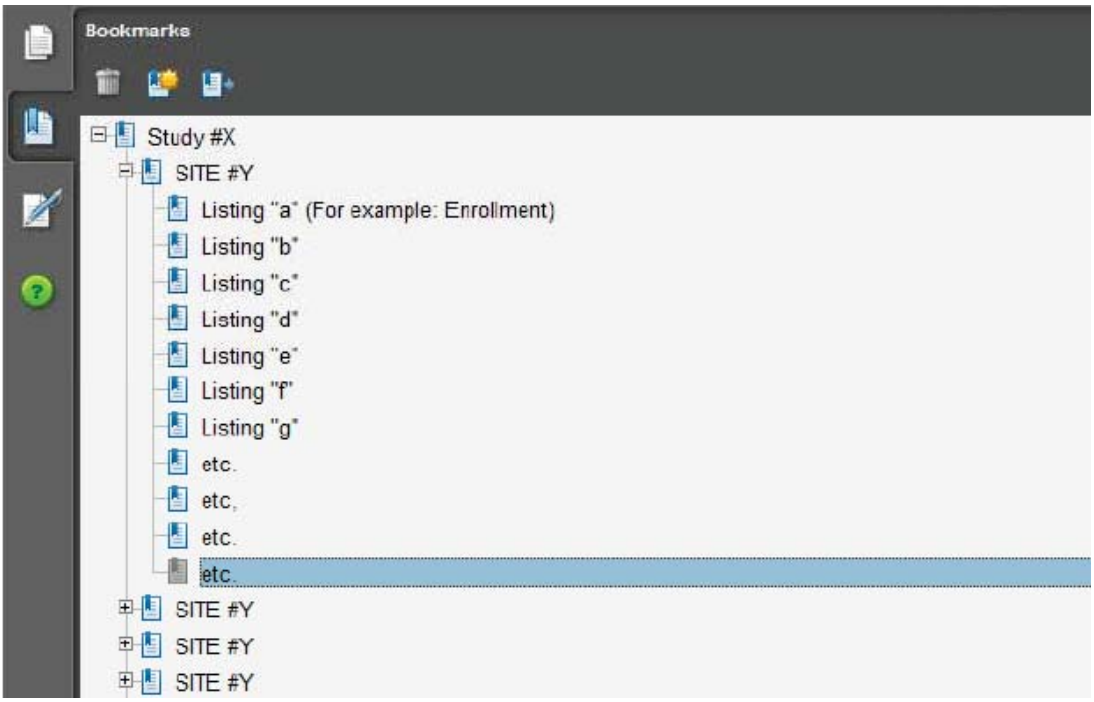
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

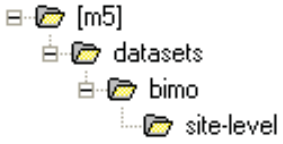
Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The Division agreed to provide final comment in the meeting minutes on the following items:

- Agreement from FDA that the initial NDA can be submitted with a full interim study report for study CVT-301-005, with the final report to follow at the 120-day safety update.

- Agreement from FDA on the plan to amend Study CVT-301-004E and that the data from these withdrawal assessments can be provided at the 120-day safety update.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

- **Sponsor's September 27, 2016 Pre Meeting Comments**

- **Sponsor PreNDA Meeting Slides**

Acorda's additional comments on FDA's "Meeting Preliminary Comments on CVT-301 pre-NDA meeting

Question 4a:
Does the Division agree with the plan for assessment and reporting of abuse potential?

FDA Response to Question 4a:
Yes. However, we have additional recommendations:

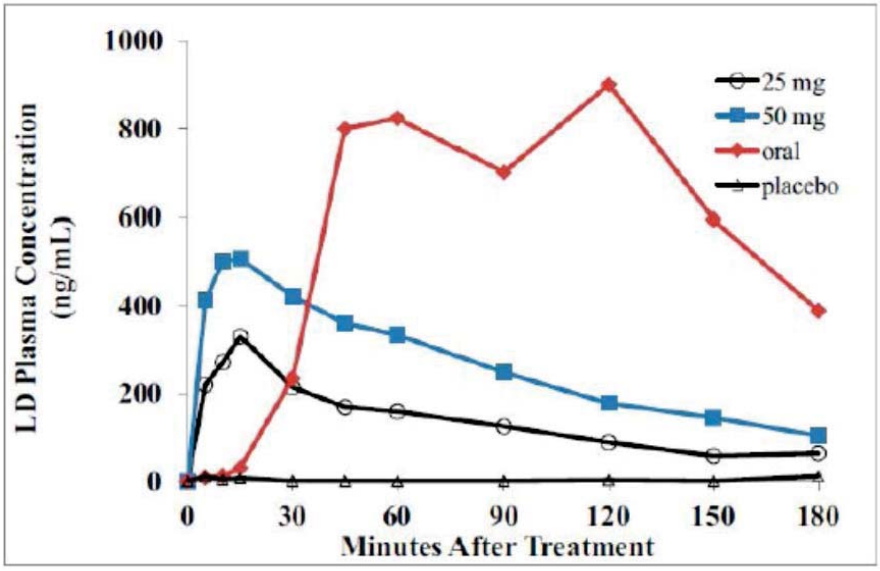
1. CVT-301 produces a dramatic rise of levodopa levels in plasma within the first 10 min after drug administration. This is approximately ~80 times higher than oral carbidopa/levodopa 25/100 in healthy volunteers and ~36 times higher in patients with Parkinson's disease (PD). This seems to indicate that very high levels of dopamine will be available in the CNS within a few minutes of drug administration, which produces circumstances similar to that found when potent stimulants such as amphetamine and cocaine are abused.

   Your abuse potential assessment should include an evaluation that considers and assesses these differences. Your abuse potential assessment should examine the abuse-related adverse event of CVT-301 collected with-in the first 10 minutes of drug exposure, making comparisons to the reference listed drug Sinemet when possible.

Acorda Comment (27 September 2016)

We agree in general with the analyses cited above, as consistent with the mean plasma concentration time profiles (Figure 10 in the Briefing Book).

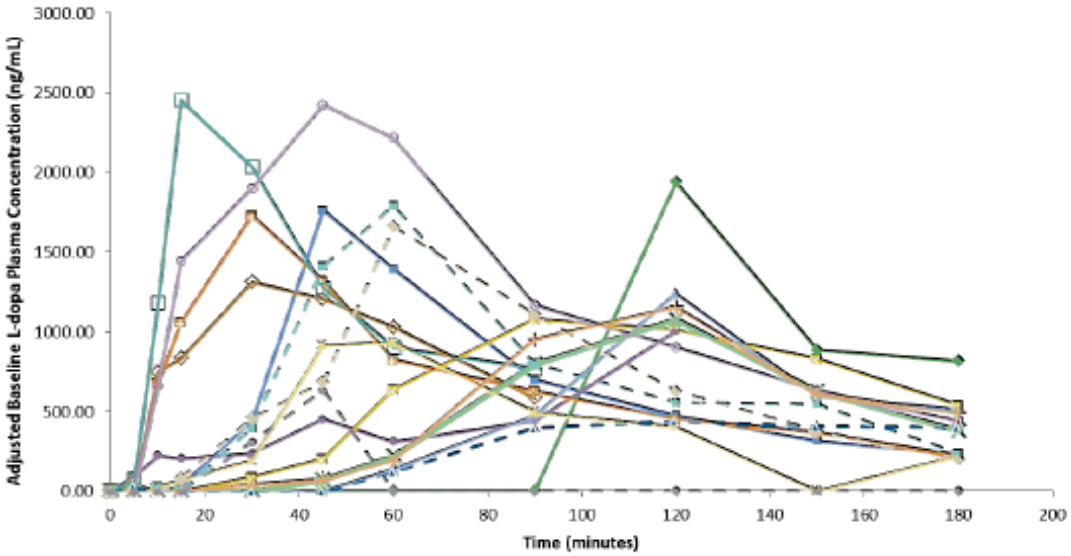
Figure 10: Median Incremental Plasma LD Concentration-Time Profile Following Administration of Oral CD/LD, CVT-301, or Placebo



*CVT-301 doses (25 mg, 50 mg) indicate target nominal LD FPD (mg)
Source: CVT-301-002 clinical study report, pharmacokinetic report Figure 2.

However, on closer inspection of the individual plasma concentration time profiles (Figure 9 in the Briefing Book), many patients display a sharp rise in plasma levels following oral administration of Sinemet, similar to that seen with CVT-301.

Figure 9: CVT-301-002 Variability in L-dopa Plasma Levels Following Oral Administration of 25/100mg CD/LD in Fasted Parkinson's Disease Patient



CD = Carbidopa; LD = Levodopa
Source: CVT-301-002 clinical study report.

Please see Table 13 below from the CVT-301-001 study report which demonstrates that the lag time differentiates the PK profile between oral and inhaled levodopa. PK modeling indicated that inhaled CVT-301 had much shorter lag time and faster absorption. The difference in lag time was about 10 min between inhaled and oral levodopa in the healthy volunteer study. Therefore, individual PK profiles (i.e., rate and extent of absorption of LD) overlap between CVT-301 and Sinemet IR tablets.

Table 13 Pharmacokinetic Parameters (Median Values) Estimated by Pharmacokinetic Modeling

Dose (mg)	T_{lag}(min)	$T_{1/2k01}$(min)	$T_{1/2l}$(min)	$T_{1/2ü}$(min)
CVT-301*	0.21	4.31	8.18	180.33
10				
20	<0.01	3.53	11.54	135.04
30	<0.01	5.47	33.38	167.66
50	0.29	7.37	26.12	142.46
Oral				
100(IDVWHG)	9.41	9.96	9.64	132.40
100 (IHG)	9.78	65.39	7.49	98.21

Acorda Comment (continued)

Further, we disagree with the characterization of CVT-301 to that of amphetamine or cocaine. The pharmacology of CVT-301 drug is much different with amphetamine and cocaine being dopamine reuptake inhibitors which produce high concentrations of synaptic dopamine. In contrast, as noted in Section 3.4 of Appendix 7 of the Briefing Book, CVT-301 produces increases in intracellular dopamine.

Regarding the abuse-related adverse events of interest occurring within the first 10 minutes of drug exposure, we will include this in the abuse liability assessment. However, we have looked at this in the completed and ongoing studies and reports of abuse related adverse events of interest are extremely rare.

2. In addition, you should evaluate dependence/withdrawal and possible rebound in patients with PD. Dependence needs to be evaluated since dependence may relate to the safety profile of the drug.

Acorda Comment (27 September 2016)

The PK profile for individual subjects overlaps between inhaled and oral administration. Secondly, over chronic administration there is no difference in exposure during chronic administration between the oral product and the inhaled product. Thirdly, CVT-301 is an adjunct to an oral levodopa/carbidopa regimen and the elimination kinetics of levodopa are comparable and would be no more abrupt than the oral product given alone. There is no reason to believe that inhaled administration would cause a substantially different withdrawal symptom compared to an oral product. For example, opioids will cause a withdrawal syndrome whether taken orally, injected, or inhaled. Similarly, tobacco use will cause a withdrawal syndrome whether by smokeless tobacco or smoking cigarettes. Data are being collected in Phase 3 clinical trials which should be sufficient to determine whether dependence/withdrawal/rebound occur.

We will be looking at the adverse event data from the ongoing Phase 3 studies for potential signals of dependence or withdrawal.

3. You should also provide an assessment of abuse based on rates of nonmedical use of levodopa so that we can actually conclude that the rates of nonmedical use are negligible.

Acorda Comment (27 September 2016)

These data are available in Appendix 7, Section 3.8 of the Briefing Book. If there are other specific data sources that FDA would like us review we will be pleased to include these.

4. Additionally, adverse events from clinical studies in healthy subjects (Phase 1) should be pooled separately from studies (Phase 2/3) conducted in patients. The adverse events of interest for from studies of PD patients are identified below.

Acorda Comment (27 September 2016)

We agree with the recommendation.

5. Because abuse of levodopa is mainly known in the population of patients with PD, your abuse Potential Assessment Report, in which you plan to include the analysis of published literature, should include the following items:

- Populations: analysis should to be performed separately for PD patients and healthy subjects
- For the PD study population, the following adverse events are of particular interest: abuse, misuse, withdrawal, dependence, dopamine dysregulation syndrome, hedonistic homeostatic dysregulation, euphoria, high, overdose, misuse, diversion, hoarding of medication, neuroleptic malignant syndrome, hyperpyrexia and confusion, rebound

Acorda Comment (27 September 2016)

We agree with the Agency's request and the published literature can be found in the report.

6. Search and analysis of adverse events from your clinical data and the post-marketing data for levodopa formulations in publically available data bases should include and use the same search terms listed above in point

Acorda Comment (27 September 2016)

We agree with the Agency's request.

Question 4b:

Does the Division agree that CVT-301 does not warrant drug scheduling?

FDA Response to Question 4b:
FDA decides on recommendations for scheduling after review of all relevant data submitted in the NDA.

Specific Recommendations

1. The dependence/withdrawal/rebound evaluation should be performed at the conclusion of Phase 2 or 3 studies lasting at least 4 weeks. The duration of the discontinuation period should be at least 3 weeks from drug discontinuation. The assessments should include reports of all adverse events that occurred during drug discontinuation. Also below is a

list of disease-specific scales that should be administered at baseline, on the last 2 days of the treatment period and throughout the discontinuation period:

- Stimulant withdrawal scale (Amphetamine Withdrawal Questionnaire, AWQ and/or Cocaine Selective Severity Assessment, CSSA)
- Dopamine Dysregulation Syndrome-Patient and Caregiver Inventory (DDSPC, Cabrini et al., 2009)
- Unified Parkinson's Disease Rating Scale (UPDRS)
- Depression Scale
- Sleepiness Scale
- Columbia Suicide Severity Rating Scale (C-SSRS)

Acorda Comment (27 September 2016)

Data are being collected in Phase 3 clinical trials which should be sufficient to determine whether dependence/withdrawal/rebound occur. In two of the clinical studies, data are being collected at the 2- or 4-week follow-up. The following data will be collected: adverse events, the Unified Parkinson's Disease Rating Scale (UPDRS), Depression Scale, Sleepiness Scale, and Columbia Suicide Severity Rating Scale (C-SSRS). We will assess adverse events associated with domains in the DDSPC including pathological gambling, compulsive shopping, hyper sexuality, binge eating, reckless driving, punding, compulsive medication use and violent behaviors. Does this meet your expectations?

2. You should summarize the animal studies related to abuse potential that have been performed.

Acorda Comment (27 September 2016)

Animal behavioral and dependence pharmacology are discussed in Section 3.3 of Appendix 7 of the Briefing Book.

FDA Response to Question 7

Question 7a:

Does the Division agree with the plan of submitting an abbreviated interim clinical study report for CVT-301-004E in the initial NDA filing?

FDA Response to Question 7a:

Please clarify what you mean by an "abbreviated interim clinical study report."
Your initial NDA submission must include long term safety information for >300 patients treated continuously for 6 months, including > 100 patients treated for one year, with at least 50 patients treated with the highest dose recommended in labeling. The NDA needs be complete at the time of submission, and the 120-day update should not contain the majority of the long-term safety information.

Acorda Comment (27 September 2016) to Question 7a:

The initial NDA submission will include the long term safety information for >300 patients treated continuously for 6 months, including > 100 patients treated for one year, with at least 50 patients treated with the highest dose recommended in labeling. It will include a full clinical study report with interim data for CVT-301-004E. The contribution of study CVT-301-004E for the overall safety data set is described below. The NDA submission will include the majority of the long term safety information.

Question 7b:

Does the Division agree with the overall statistical analysis plan as outlined in the current version of the study Protocol?

FDA Response to Question 7b:

The primary objective of Study CVT-301-004E is pulmonary safety. Although patients are blinded to dose level of treatment with CVT-301, study CVT-301-004E is an uncontrolled safety study. Your initial NDA submission needs to include the completed study report and final datasets from this study. The data should pool the information from this study with open label studies, in the ISS.

Acorda Comment (27 September 2016) to Question 7b:

The majority of the pulmonary safety will be provided by controlled study CVT-301-005. At the time of submission interim data from study CVT-301-004E contributes approximately 80 patients to the 300 patients treated for 6 months. The data from these patients will be presented in a full interim clinical study report for CVT-301-004E and data sets will be included in the NDA. The data from study CVT-301-004E and CVT-301-005 will be pooled for the ISS.

Question 8a:

Does the Division agree with the plan of submitting an abbreviated interim clinical study report for CVT-301-005 in the initial NDA filing?

FDA Response to Question 8a:

Please refer to our response to question 7a.

Acorda Comment (27 September 2016) to Question 8a:

The initial NDA submission will include the long term safety information for >300 patients treated continuously for 6 months, including > 100 patients treated for one year, with at least 50 patients treated with the highest dose recommended in labeling. At the time of NDA submission CVT-301-005 will contribute more than 200 patients with 6 months of exposure including 100 patients treated for 1 year. A full clinical study report

with interim data for CVT-301-005 and data sets will be submitted at time of submission. A final clinical study report will be provided as part of the 120 day safety update. The contribution of study CVT-301-005 for the overall safety data set is described below. The NDA submission will include the majority of the long term safety information.

Question 8b:

Does the Division agree with the overall statistical analysis plan (CVT-301-005 SAP)?

FDA Response to Question 8b:

Study CVT-301-005 is an open label pulmonary safety study. The study is not designed to provide supporting evidence of effectiveness for CVT-301. Because the study addresses a specific safety concern, the final study report needs to be included in the initial NDA submission.

Acorda Comment (27 September 2016) to Question 8b:

The majority of the long term safety data (i.e., >300 patients treated continuously for 6 months, including > 100 patients treated for one year) will come from the controlled study CVT-301-005. At the time of NDA submission CVT-301-005 will contribute more than 200 patients with 6 months of exposure including 100 patients treated for 1 year. A full clinical study report with interim data for CVT-301-005 and data sets will be submitted at time of submission. A final clinical study report will be provided as part of the 120 day safety update.

Question 11:

Does the Agency agree with the plan for the 120-day safety update?

FDA Response to Question 11:

Please refer to our response to question 7a. In addition, please estimate the amount of safety data you expect to submit at the 120 day safety update.

Acorda Comment (27 September 2016)

The NDA submission will include final study reports for all studies except for study CVT-301-004E and CVT-301-005 (Table 1). The 120 day safety updates will include the final study report from CVT-301-005 and a further interim full study report for study CVT-301-004E.

The estimated amount of safety data we will submit from studies CVT-301-005 and CVT-301-004E at NDA submission and the 120 day safety update are summarized in the tables below.

The safety database at the time of NDA submission will contain approximately 80% of the controlled long term patient exposure data. The 120 day safety update will contain 100% of the long term controlled patient exposure. This controlled data is supplemented by the data from the uncontrolled study CVT-301-004E. The majority of the long term safety data will be included in the initial NDA submission.

Table 1 Study Reports Included in the NDA Submission and at the 120 Day Safety Update

Study	At NDA Submission	At 120 Safety Update
CVT-301-001	Final Complete Study Report and Data Sets	N/A
CVT-301-002	Final Complete Study Report and Data Sets	N/A
CVT-301-003	Final Complete Study Report and Data Sets	N/A
CVT-301-004	Final Complete Study Report and Data Sets	N/A
CVT-301-004E	Interim Full Study Report and Data Sets	Interim Full Study Report
CVT-301-005	Interim Full Study Report and Data Sets	Final Study Report and Data Sets
CVT-301-006	Final Complete Study Report and Data Sets	N/A
CVT-301-007	Final Complete Study Report and Data Sets	N/A
CVT-301-008	Final Complete Study Report and Data Sets	N/A
CVT-301-009	Final Complete Study Report and Data Sets	N/A
CVT-301-010	Final Complete Study Report and Data Sets	N/A

Table 2 summarizes the estimated patient exposures at submission and 120 day safety update for study CVT-301-005 (12 month, controlled, open label safety study). The safety database at the time of NDA submission will contain approximately 80% of the controlled long term patient exposure data. The 120 day safety update will contain 100% of the long term controlled patient exposure.

These estimates are based on the following assumptions:

- *408 patients randomized*
- *278 active (CVT-301) vs 130 observational*
- *Estimated dropout rate (cumulative): 15% at 6 months, 20% at 12 months*

Table 2 Estimated Patient Exposure in Study CVT-301-005

Estimated Patient Exposures CVT-301-005	**NDA Submission**		**120-Day Safety Update**	
	CVT-301	**observational**	**CVT-301**	**observational**
≥ 6 Months	236	110	236	110
≥ 1 Year	114	55	222	104

Table 3 summarizes the estimated patient exposures at submission, 120 day safety update and at time of completion for study CVT-301-004E (12 month, randomized, dose-level blinded, uncontrolled extension safety study). These estimates are based on the following assumptions:

- *340 planned enrollment*
- *Estimated dropout rate (cumulative): 15% at 6 months, 20% at 12 months*

Table 3 Estimated Patient Exposure in Study CVT-301-004E

Estimated Patient Exposures CVT-301-004E	**NDA Submission**	**120-Day Safety Update (June 2017)**	**End of Study (May 2018)**
	Active (both doses)	**Active (both doses)**	**Active (both doses)**
≥ 6 Months	80	166	289
≥ 1 Year	25	157	272

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/s/

ERIC P BASTINGS
10/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115750

MEETING MINUTES

Civitas Therapeutics
Attention: Mary E. Taylor, MPH
SVP Quality and Regulatory Affairs
190 Everett Avenue
Chelsea, MA 02150

Dear Ms. Taylor:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CVT-301 (Levodopa Inhalation Powder).

We also refer to the meeting between representatives of your firm and the FDA on July 10, 2014. The purpose of the meeting was to discuss your nonclinical development plan and your clinical Phase 3 program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tracy Peters, Senior Regulatory Project Manager at (301) 796-2953.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Acting Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	July10, 2014, 2:00-3:00 PM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 115750
Product Name:	CVT-301 (Levodopa Inhalation Powder)
Indication:	Parkinson's disease
Sponsor/Applicant Name:	Civitas Therapeutics
Meeting Chair:	Billy Dunn, MD
Meeting Recorder:	Vandna Kishore, PharmD

FDA ATTENDEES

Robert Temple, MD, Deputy Center Director for Clinical Science, Acting Deputy Director, ODE1
Billy Dunn, MD, Acting Director, Division of Neurology Products (DNP)
Gerald David Podskalny, DO, MPHS, Clinical Team Leader, DNP
Susanne Goldstein, MD, Clinical Reviewer, DNP (via teleconference)
Lois Freed, PhD, Supervisory Pharmacologist
LuAnn McKinney, PhD, Pharmacologist
Kun Jin, PhD, OTS/OB/Biometrics I, Team Leader
Sharon Yan, PhD, Statistical Reviewer
Jagan Parepally, Ph.D., Clinical Pharmacology Reviewer
Banu Karimi-Shah, MD, Clinical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Miya Paterniti, MD, Clinical Reviewer, DPARP
Nicole Bradley, PharmD, Acting Deputy Director for Labeling
Vandna Kishore, PharmD, Senior Regulatory Project Manager
Tiffany Kong, PharmD Candidate, FDA Intern

SPONSOR ATTENDEES

Mark Iwicki, Chief Executive Officer
Richard Batycky, PhD, Chief Scientific Officer
Martin Freed, MD, Chief Medical Officer

Sean Plunkett, PhD, Director, Program Management
Mary E. Taylor, MPH, SVP Regulatory Affairs and Quality

(b) (4)

1.0 BACKGROUND

Civitas Therapeutics has requested a Type B End of Phase 2 (EOP2) meeting to discuss CVT-301 (Levodopa Inhalation Powder) and the clinical and nonclinical Phase 3 registration program. Civitas submitted this meeting request on April 16, 2014. The meeting package was submitted on June 12, 2014. The specific objectives/outcomes sought by the sponsor from the meeting are as follows:

1. Obtain agreement on the design of the pivotal Phase 3 efficacy study.
2. Obtain agreement on the design of the supporting safety studies.
3. Obtain agreement on the size of the safety database.
4. Obtain feedback on the nonclinical program for registration.

The Agency's preliminary responses to the questions presented in the meeting package were sent electronically to the sponsor on July 9, 2014. Section 2 is an account of the questions, the preliminary responses, and the meeting discussion.

2. DISCUSSION

2.1. Regulatory Question

Question 1:
Does the Agency agree that the use of Sinemet® (specified listed drug) and CVT-301 in the CVT-301-006 study is acceptable to establish the bridge requirement for the 505(b)(2) registration pathway?

FDA Response to Question 1:
The scientific rationale for bridging to Sinemet (reference product) from CVT-301 for pharmacokinetic comparison is acceptable.

Meeting Discussion:
There was no discussion during the meeting.

2.2. Nonclinical Questions

Question 2:
Does the FDA agree that following the completed 6-month inhalation toxicity study in rats, no additional nonclinical safety studies will be needed to support a marketing application, except for that needed to characterize the safety of drug-related impurities or leachables/extractables related to the device?

FDA Response to Question 2:
On face, the 6-month inhalation study in rat would appear sufficient to support an application; however, the adequacy of the study will be a matter of review. (Also, see preliminary response to Question 3.)

Meeting Discussion:
There was no discussion during the meeting.

Question 3:
Does the FDA agree that the safety margin provided by the completed 6-month inhalation toxicity study in rat is sufficient to support administration of up to a theoretical maximum of 300 mg/day LD FPD and that testing of the vehicle control in this study was adequate?

FDA Response to Question 3:
There is a ≈9-fold safety margin between the highest dose tested in the 6-month inhalation study in rat (174 mg/kg CVT-301, providing ~157 mg/kg levodopa) and a daily clinical dose of CVT-301 providing up to 300 mg levodopa, based on lung weight. Although minimal, this safety margin is sufficient for assessing the potential toxicity of CVT-301, including excipients.

Meeting Discussion:
There was no discussion during the meeting.

2.3. Clinical Questions

Question 4:
The following questions are related to the pivotal 12-week, placebo-controlled Phase 3 study, CVT-301-004: 4a – 4j.

4a. Does the FDA agree with the 12-week duration of the CVT-301 treatment period in the pivotal, placebo-controlled Phase 3 study CVT-301-004?

FDA Response to Question 4a:
Yes, we agree with the 12-week duration of study CVT-301-004.

Meeting Discussion:

There was no discussion during the meeting.

4b. Does the FDA agree with the primary endpoint and the planned statistical evaluation in the pivotal, placebo-controlled Phase 3 study CVT-301-004?

FDA Response to Question 4b:

Based on the information presented in your briefing package, there is a modest clinical effect (as measured by the UPDRS Part 3) as early as 10 minutes after administering a dose of CVT-301. However, the greatest difference in the treatment effect of CVT-301 versus placebo is at approximately 30 minutes after administration. Your plan to take the average of the change in UPDRS across several time points (10, 20, 30, 60 minutes post dose) may reduce the magnitude of the treatment effect observed with CVT-301 versus placebo. We recommend selecting a fixed time point, such as 30 minutes after administration of CVT-301, to assess the change in UPDRS Part 3 score.

The proposed primary endpoint is based on the average of the UPDRS Part 3 score post dosing. It is not clear how the average score will be derived, whether using a model or derived from data, and how contrast will be applied to the average score of Visit 3 and Visit 4. Please provide more details of the derivation of the data and provide SAS codes for the analysis model.

We are concerned about the expected 25% dropout rate. We recommend that you take measures to limit the number of patient dropouts from your clinical studies and, when possible, perform an end-of-treatment efficacy evaluation in patients who drop out of a study.

Meeting Discussion:

The sponsor wishes to describe the time course for the change in UPDRS Part 3 scores following a dose of CVT-301in the product label. The Agency would consider describing the time course of change in UPDRS Part 3 scores in the label, even if the primary endpoint was assessed at a single timepoint. Earlier (e.g., 10 minutes after dosing) UPDRS Part 3 assessments are associated with smaller treatment effects and including them in a primary outcome that uses the average change in Part 3 scores over 60 minutes may reduce the size of the treatment effect.

4c. (b) (4)

(b) (4)

4d. Does the FDA agree with the characterization and selection of doses per administration (approximately 35 and 50 mg LD FPD) in the pivotal, placebo controlled Phase 3 study CVT 301-004?

FDA Response to Question 4d:
Your Phase 2 efficacy data from patients with PD treated with 25 mg, 35 mg, and 50 mg of CVT-301 suggest 35 mg and 50 mg may be effective. However, higher doses of CVT-301 may show additional clinical improvement without causing a significant increase in dyskinesia. We suggest studying a higher dose of CVT-301 (e.g., 70 mg) in your larger pivotal efficacy studies.

Meeting Discussion:
The sponsor was concerned that higher doses of CVT-301 would increase the risk for troublesome dyskinesia. The goal is to treat off episodes without causing an increase in troublesome dyskinesia. The Agency noted that the 70 mg dose was not much higher than the 50 mg dose. In the initial clinical study, the 50 mg dose was not

associated with a substantial increase in dyskinesia and the 70 mg dose may provide a larger treatment effect without increasing troublesome dyskinesia.

4e. Does the FDA agree with the characterization and selection of the number of administrations of LD FPD per day in the pivotal, placebo-controlled Phase 3 study CVT-301-004?

FDA Response to Question 4e:
The maximum number of doses patients can receive per day is acceptable. Your protocol summaries allow patients to administer CVT-301 up to five times per day. Patients receiving the highest dose (50 mg) would receive an additional 250 mg of levodopa per day, in addition to a maximum oral levodopa dose of 1500 mg per day providing a total daily levodopa dose of 1750 mg. The total daily levodopa dose is below the maximum total daily levodopa dose of 2000 mg for approved Sinemet.

The recommended dose and frequency of administration described in labeling will depend on how patients actually used CVT-301 in the pivotal clinical studies, instead of the maximum allowed dose per day. If patients were allowed to use CVT-301 up to 5 times per day, but few patients administered more than 3 doses per day, there may be insufficient experience to support the inclusion of more than 3 doses per day in the label.

Meeting Discussion:
There was no discussion during the meeting.

4f. Does the FDA agree that the proposed placebo is adequate to provide appropriate blinding in the pivotal, placebo-controlled Phase 3 study CVT-301-004?

FDA Response to Question 4f:
The preliminary data presented for study CVT-301-003 and CVT-301-006 suggest the matching placebo can provide an adequate treatment blind for study CVT-301-004.

Meeting Discussion:
There was no discussion during the meeting.

4g. Does the FDA agree with the planned sample size for the pivotal, placebo-controlled Phase 3 study CVT-301-004?

FDA Response to Question 4g:
Based on the available pulmonary safety data from completed studies, your sample size appears acceptable. However if a new safety signal is noted during the development program, investigation for additional patients may be necessary.

Your current sample size estimation is based on average UPDRS Part 3 score over time points at 10, 20, 30, and 60 minutes post dosing. As a fixed time point is recommended (see FDA Response to Question 4b), the size of treatment difference to be detected and the sample size calculation needs to be updated.

Meeting Discussion:
There was no discussion during the meeting.

4h. Does the FDA agree that the characterization of safety (nonpulmonary) endpoints in the pivotal, placebo-controlled Phase 3 study CVT-301-004 are adequate?

FDA Response to Question 4h:
You should include orthostatic measurements (supine, standing) for blood pressure and pulse at each visit. You must perform a suicidality assessment at each visit, in all clinical trials. Please review the Draft FDA Guidance: Guidance for Industry Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials.

Meeting Discussion:
There was no discussion during the meeting.

4i. Does the FDA agree that the characterization of safety (pulmonary) in the Phase 3 clinical program is adequate?

FDA Response to Question 4i:
We generally agree with the characterization of pulmonary safety in the Phase 3 clinical program. We have the following additional comments:

- **Given the proposed lower FEV1 criteria of ≥ 50% in Study CVT-301-004, assess bronchodilator reversibility at screening. Exclude subjects with an FEV1 increase of ≥12% from baseline or ≥ 10% of predicted FEV1 after short-acting bronchodilator (NHLBI asthma guidelines 2007) as this would not fit with the expected physiology of Parkinson's Disease related pulmonary dysfunction.**

- **You propose to analyze the pulmonary function using descriptive statistics. If a difference in the mean change from baseline is seen for spirometry or DLco, statistical analysis of the difference may be necessary.**

Meeting Discussion:
The sponsor stated that pulmonary function in Parkinson's disease patients has baseline variability and the interpretation of reversibility with bronchodilator may be difficult to interpret. In the current protocol, pulmonologists review the spirometry

tracings/flow-volume loop morphology for patients with FEV1 <60% or FEV1/FVC <70% to identify subjects with possible abnormal spirometry outside of what would be expected with Parkinson's disease. Following similar criteria, Civitas proposed to assess bronchodilator reversibility only in patients with an FEV_1/FVC that is less than 70% of predicted. The Agency agreed that the plan as outlined by the sponsor appeared reasonable and requested that the sponsor provide adequate justification with their protocol.

Civitas was reminded to collect devices (both those that were noted to be working properly (at least 100 with active treatment) and those that were identified as having problems) for in vitro testing at the end of the Phase 3study. The sponsor stated it is planning on doing so.

4j. Does the FDA agree that the design of and patient population included in the 12-month, long-term Studies CVT-301-004E and CVT-301-005 are adequate?

FDA Response to Question 4j:
The following comments pertain to pulmonary safety.

- **We note that you plan to compare the active treatment arms of the long-term safety study to a "usual care" group in a separate study. Cross-study comparisons are problematic. Therefore, we recommend that a control group be included within Study 004E and Study 005 to provide for a comparison between inhaled and non-inhaled groups within the same study. Your NDA should include one year, controlled, pulmonary safety data on at least 100 patients exposed to CVT-301.**

- **We anticipate that if not properly planned for, missing data in this long-term study will be problematic in the interpretation of the results of the study. Provide a proposal for addressing missing data in the context of the FEV1 evaluation. You should consider methods that would minimize missing data and encourage patient adherence (e.g., patient retention incentives, study design characteristics, etc.). Advise patients of the importance of their continued study participation even if study treatment is discontinued to allow for an estimate of the treatment effect regardless of adherence to study medication. In addition, you should consider the likely reasons for discontinuation of study medication (e.g., discontinuation due to inadequate efficacy, discontinuation due to adverse effects on FEV1, etc.) and methods that would accurately represent these cases in the analysis. The actual reason(s) for discontinuation of study treatment should be carefully collected, avoiding non-informative terms such as "lost to follow-up". As recommended in the 2010 National Research Council report The Prevention and Treatment of Missing Data in Clinical Trials, you should explicitly define the causal estimand of interest that is being targeted, and should justify that the estimand is meaningful and can be estimated with minimal and reasonable assumptions.**

Meeting Discussion:
The sponsor expressed concern that the number of dropouts in the control arm of the long-term pulmonary safety study will limit the interpretability of the study results due to a large amount of missing data. The Agency acknowledged the limitations of missing data; however, cross-study comparison of information from the long-term open label safety study CVT-301-00\4E and 005 to the patients in the longitudinal observational studyCVT-301-005C is problematic. The Agency reiterated the importance of including a control arm within the long-term pulmonary safety studies (CVT-301-004E and CVT-301-005) and encouraged the sponsor to submit a study design for review.

Question 5a:
Does the FDA agree that the design of the Phase 1 special population study in adult asthmatic volunteers is adequate to characterize the potential to develop acute bronchospasm?

FDA Response to Question 5a:
Your proposed Phase 1 study in asthmatic adults is reasonable. To reduce risk to asthmatic subjects, add the following exclusion criteria:

1. **Subjects with more than 2 hospitalizations or emergency room visits, or more than 3 courses of systemic steroids in the past 12 months or 1 course within the past 8 weeks for respiratory illness**
2. **Asthma exacerbation within 8 weeks of before screening**
3. **Unscheduled or urgent visit to any medical facility for asthma-related problems within 8 weeks before screening**
4. **History of intubation or intensive care unit admission for asthma in the past 5 years**

Match the asthma study dose to the highest dose used in Phase 3 studies (see Response to Question 4d).

Meeting Discussion:
There was no discussion during the meeting.

Question 5b:
Does the FDA agree that the design of the Phase 1 special population study in adult smoker and non-smoker volunteers is adequate to characterize the potential effect of smoking on LD exposure following administration of CVT-301?

FDA Response to Question 5b:
From a pulmonary safety perspective, your proposed Phase 1 study in adult smoker and non-smoker volunteers is acceptable.

Match the smoker/non-smoker study dose to the highest dose used in Phase 3 studies (see Response to Question 4d).

Meeting Discussion:
There was no discussion during the meeting.

Question 6:
Does the FDA agree that a thorough QT study will not be required as a condition for approval of CVT-301?

FDA Response to Question 6:
The Cmax of the highest dose of CVT-301 should not exceed the exposure associated with marketed oral carbidopa/levodopa products. You will need to provide information that suitably bridges marketed oral Sinemet to CVT-301 at the anticipated marketed dosages.

Meeting Discussion:
There was no discussion during the meeting.

Question 7:
Does the FDA agree that Study CVT-301-006 is adequate to characterize and compare the metabolic profile of CVT-301 to that of oral Sinemet® (reference listed drug)?

FDA Response to Question 7:
The preliminary information provided in your submission suggests the results of study CVT-301-006 adequately compared metabolites from the selected oral formulation of carbidopa/levodopa to the high fill and low fill capsules (50 mg and 105 mg) of CVT-301.

Meeting Discussion:
There was no discussion during the meeting.

Question 8:
Does the FDA agree that the placebo-controlled Phase 2b study CVT-301-003 can serve as a supportive efficacy study for approval of CVT-301?

FDA Response to Question 8:
On face, CVT-301-003 has the ability to support an NDA along with robust efficacy results from CVT-301-004. However, the acceptability of these two studies as substantial evidence of efficacy remains a matter for review.

Meeting Discussion:
There was no discussion during the meeting.

Question 9:
Does the Agency agree that the company can submit the New Drug Application (NDA) with a safety database of ~400 patients exposed for 6 months and >100 patients exposed at 1 year, with a safety update containing over 500 patients exposed for 6 months and ~450 exposed for over one year, consistent with ICH guidance?

FDA Response to Question 9:
From a pulmonary safety perspective, your proposed size of safety database is acceptable.

Whether the NDA is suitable for filing remains a matter for review. The NDA should be complete at the time of submission. The 120-day update should not contain the majority of the long-term safety information. If there are technical problems reviewing the updated ISS or reviewing the datasets, it could delay the review of a large portion of the safety information in the NDA. If you need to revise the 120-day update to correct potential problems, it might constitute a major amendment.

Study CVT-301-005 incorporates a "dose level blind" into the study design but it remains uncontrolled. If maintaining the dose level blind will delay reporting the long-term safety information in your NDA submission until the 120-day update, you may wish to consider removing the dose level blind from the study design. The daily frequency of dosing will remain flexible regardless of the assignment by formulation strength that may result in patients taking overlapping or very similar total daily doses of CVT-301 in CVT-301-005.

Meeting Discussion:
There was no discussion during the meeting.

Question 10:
Does the Agency agree that the CVT-301-006 study demonstrates comparability of the 3 CVT-301 capsules of 17.4 mg LD FPD to 2 capsules of 25 mg LD FPD, such that the CVT-301-004 Phase 3 study will utilize the following? Reference is made to Table 1 for a summary of drug product.

- 2 capsules of 17.5 mg LD FPD = a 35 mg dose
- 2 capsules of 25 mg LD FPD = a 50 mg dose

FDA Response to Question 10:
Yes.

Meeting Discussion:
There was no discussion during the meeting.

Question 11:
Does the agency agree that the studies conducted to date, along with the planned studies, would be sufficient for registration?

FDA Response to Question 11:
Please see our comments in response to the questions above regarding your completed and planned clinical studies. The Office of Clinical Pharmacology does not have recommendations for additional studies at this time. You plan separate meetings for Chemistry, Manufacturing and Controls and device related issues; appropriate comments will be provided during these separate meetings with CMC and CDRH.

Meeting Discussion:
There was no discussion during the meeting.

ADDITIONAL COMMENTS:

In the synopses of clinical trials CVT-301-004, CVT-301-004E, and CVT-301-005, you state that "…randomization will be stratified by the patient's Hoehn and Yahr stage (<2.5 and ≥2.5) to balance the severity of disease in each group…"

Please clarify whether the Hoehn and Yahr stage will be measured in the ON or OFF state.

Meeting Discussion:
There was no discussion during the meeting.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor handout.

5 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

WILLIAM H Dunn
08/07/2014