CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product:	CVT-301
Indication:	"Off" periods in Parkinson's disease
Applicant:	Acorda Therapeutics, Inc
Review Division:	Neurology Products
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Reference ID: 4367298

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1 Executive Summary

1.1 Introduction

Acorda Therapeutics has submitted this NDA for Inbrija®, an inhaled formulation of levodopa (LD), for the intermittent treatment of "off" periods in Parkinson's disease patients as an adjunct to carbidopa/levodopa (CD/LD) therapy.

Pursuant to Section 505(b)(2) of the Federal food, Drug, and Cosmetic Act, Acorda Therapeutics is relying on the Agency's finding of safety for the listed drug (RLD) Sinemet oral tablets (NDA 017555, approved on MAY 2, 1975).

1.2 Brief Discussion of Nonclinical Findings

In a safety pharmacology study, a single 1-hour inhaled dose of 7.5 mg/kg of CVT-301 caused no abnormalities in respiratory or cardiovascular function in conscious Beagle dogs.

In a comparison study in rats, the C_{max} after drug inhalation was less than that seen after IV bolus, but greater than that seen after oral administration. Plasma levels remained greater than those resulting from oral administration through six hours post-dose.

CVT-301 was administered by inhalation in toxicity studies of 7 and 28 days to rat and dog and 6 months to rat. In all studies the NOAEL was the achieved HD, which ranged from 912 mg/m^2 and 1.05 mg/g lung weight (28-day dog) to 1008 mg/m^2 and 3.36 mg/g lung weight (6-month rat). In rat (nose-only inhalation) and dog (oro-nasal face mask) studies showed effects from the route of administration; histologic changes were nonspecific responses to the presence of drug powder particulates in the nasal cavity (rat) and bronchial bifurcation (dog). No systemic toxicity was observed.

Based on the achieved deposited dose in lung, the no adverse effect levels in rat and dog exceed the delivered dose of the recommended maximal human dose and offer a minimally acceptable safety margin.

No excipients, impurities, or leachables/extractables were found to be of concern and inhalation studies of the excipient DPPC (a component of pulmonary surfactant) at greater than clinically anticipated levels resulted in no differences from controls in either rat or dog.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical perspective, this marketing application is approvable.

1.3.3 Labeling

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Submitted draft labelling of sections 8.1 (PLLR), 12.1 (mechanism of action), and 13.1 (Carcinogenesis, mutagenesis, impairment of fertility) are unchanged from the PLR labelling of the RFD and are acceptable.

In Section 13.2, (Animal toxicology) the label should be changed to read:

> In rats, nose-only inhalation administration of INBRIJA® powder once daily for 6 months was not associated with adverse effects at approximately 4 times the maximum recommended daily dose of 420 mg, on a body surface basis.

2 Drug Information

2.1 Drug

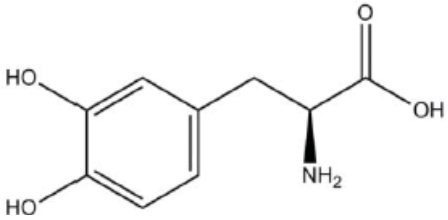
CAS Registry Number: 59-92-7

Generic Name: Levodopa (inhalation powder)

Chemical Name: (2S)-2-amino-3-(3,4-dihydroxyphenyl) propanoic acid

Molecular Formula/Molecular Weight: C9H11NO4/197.19 g/mol

Structure: Sponsor's figure



Pharmacologic Class: Aromatic Amino Acid Decarboxylation Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

DMF (b) (4)
IND: 115750
Label: Sinemet® (NDA 017555)

2.3 Drug Formulation

Powder-filled capsules that contain (b) (4) levodopa powder, (b) (4) dipalmitoyl phosphocholine (DPPC) and (b) (4) NaCl.

White, size 00 hydroxypropyl methylcellulose capsules in (b) (4)
42 mg levodopa per capsule.
Weight/weight:

- (b) (4)% levodopa, USP
- (b) (4)% 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)
- % NaCl, USP

Sponsor's table:

Ingredient	Function	Quality Standard	Quantity per Capsule	
			(b) (4)	42 mg-LD (% wt)
Levodopa	Active	USP		42.0 mg (b) (4)
DPPC	(b) (4)			
NaCl				
Formulation Total				(b) (4)
(b) (4)				
Size 00, HPMC capsule (white)	Capsule	Manufacturer specification	1 capsule	1 capsule
(b) (4)				

2.4 Impurities

Three process impurities were identified by the sponsor:

(b) (4)

In Study No. TSI-17-003 (eCTD 4.2.3.7.7), the impurities were evaluated *in silico* for potential mutagenicity and both were found to be negative by two different programs. (DEREK and Leadscope Model applier).

2.5 Comments on Novel Excipients

Dipalmitoyl phosphocholine (DPPC) is a non-compendial excipient specified at (b) (4)% of CVT-801. DPPC is found in normal lung surfactant and is a component (30.5 mg/mL) of artificial surfactant (Curosurf®, NDA 20-744) approved NOV,1999 for acute use in infants with respiratory distress syndrome at intratracheal doses of 2.5 mL/kg, resulting in a DPPC dose of 763 mg/kg. NaCl is a compendial excipient. Studies of the local/respiratory effects of inhaled DPPC in rat (AIRT-00-09) and dog (AIRT-00-10) were submitted to this NDA. No specific test article related-effects were reported.

2.6 Comments on Leachables and Extractables:

After being stored in the blister pack at the proposed commercial storage condition, the drug product contained leachables that exceed the Analytical Evaluation Threshold (AET) of 0.3 mcg/g. The leachables do not have structural alerts for mutagenicity.

In the submitted "Safety assessment of leachables from CVT-301 inhaler," dated MARCH 27, 2018, the sponsor determined a recommended daily safe dose (RfD) for each of the leachables that had been either identified in EPA IRIS or were derived from published NOAEL or LOAEL, per the methods in Appendix 1: Method for Establishing Exposure Limits found in ICH Q3D 2015, as recommended by the Product Quality Research Institute (PQRI) Leachables and Extractables Working Group. Calculations were based on a MRHD of 492 mg/day.

No leachables were found to be at levels that would be of toxicologic concern or would produce adverse effects with lifetime daily exposure.

Table: Safety margins of daily exposure to the RfD.

Leachate	CAS number	Highest observed level (µg/g)	Daily exposure‡ (µg/day)	RfD* (µg/day)	Margin (RfD/exposure)
(b) (4)					

* According to the sponsor: the daily dose at which lifetime exposure would not be associated with increased risk of adverse events; either identified in the EPA IRIS database or derived from published literature per the methods in Appendix 1: Method for Establishing Exposure Limits, found in ICH Q3D 2014.
‡ Based on MRHD of 492 mg/day of CVT-301.

2.6 Proposed Clinical Population and Dosing Regimen

Oral inhalation of the contents of two 42 mg capsules (84 mg) as needed for treatment of symptoms of OFF periods, up to 5 times a day resulting in a maximum daily dose of inhaled drug substance of 420 mg. The capsules are inserted into a proprietary device, which punctures the capsules, from which the patient orally inhales the contents.

2.7 Regulatory Background

A Pre-IND meeting (IND 115750) was held on SEP 25, 2012 and the IND was submitted on FEB 05, 2013 by Civitas Therapeutics.
In DEC 2014, Civitas Therapeutics was purchased by, and became a wholly owned subsidiary of, Acorda Therapeutics.
On JUN 27, 2017, NDA 209184 was submitted by Acorda Therapeutics.
On AUG 21, 2017, a Refuse to File letter was issued, based on inadequate time allowed to inspect a pivotal manufacturing site.
On DEC 5, 2017, the sponsor resubmitted the application
On FEB 15, 2018, the NDA was filed.

3 Studies Submitted

3.1 Studies Reviewed

Packaging leachables: Safety Assessment
Inhaled CVT-301:

- Safety Pharmacology (CV and respiratory) in dog
- PK and PD in rat
- Single dose in rat, dog, and monkey
- Toxicity: Repeat dose
    - 7-day studies in dog and rat
    - 28-day studies in dog and rat
    - 6-month study in rat

Inhaled excipient (DPPC):

- QSAR (DEREK) analysis
- Repeat dose
    - 28-day studies in dog and rat

3.2 Studies Not Reviewed

Study AIRT 13-03-2003: Two-week inhalation toxicity study of levodopa as a dry powder aerosol in the dog
Study AIRT 13-03-2011: Two-week inhalation toxicity study of levodopa as a dry powder aerosol in the dog
Study AIRK-13-01: L-Dopa formulation pharmacokinetic study in dogs

3.3 Previous Reviews Referenced

None

Reference ID: 4367298

4 Pharmacology

The primary and secondary pharmacology of levodopa are described in the labeling of the listed drug. Levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier and presumably is converted to dopamine in the brain.

4.3 Pharmacodynamics

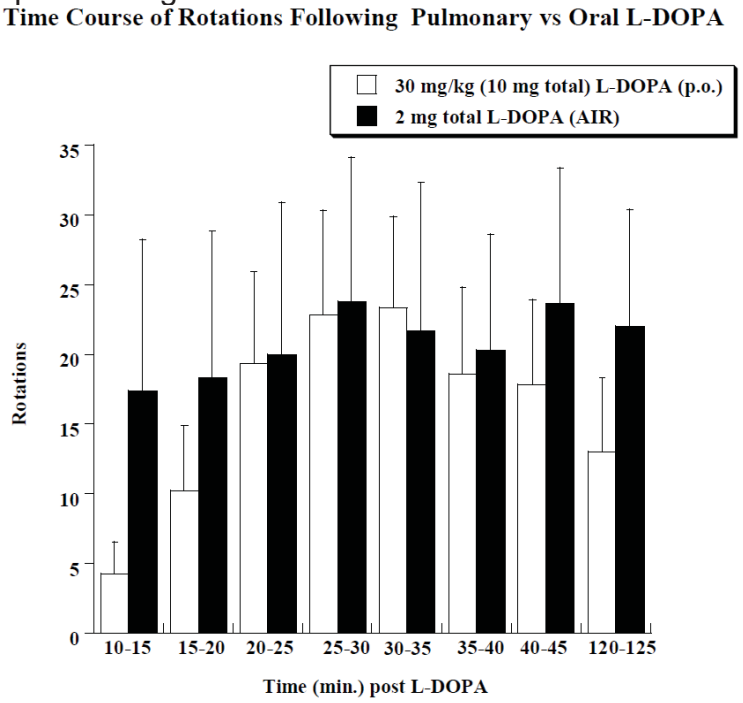
Study (b) (4) 10-16-00: Pulmonary L-Dopa Provides Pharmacokinetic and Pharmacodynamic Advantages over Oral L-Dopa in Rat Models: Implications for Improving the Treatment of Parkinson's Patients.
In a study in 6-OHDA-lesioned rats, apomorphine (0.1 mg/kg) and CD (200 mg/kg IP) were administered, followed by 0, 20, 30 mg/kg oral LD or 0.5, 1.0, 2.0 Intratracheal LD prior to testing for therapeutic effects on Parkinsonian-like symptoms.

Compared to oral delivery of 30 mg/kg LD, intratracheal delivery of 2 mg LD resulted in a 3-fold more rapid response in placing forefeet on the table when suspended over the table, when bracing against a 90 cm sideways displacement, and in correction of akinesia by weight bearing on a single fore-limb when suspended over a hard surface.

In the standard assessment of therapeutic effects in this Parkinson model:

- After oral administration of LD, rotations increased over time, peaked at 30 minutes post-dose and decreased minimally over 90 minutes.
- After intratracheal insufflation, the number of rotations peaked within 15 minutes and remained high through 125 minutes post-dose.

Sponsor's figure:



4.3 Safety Pharmacology

STUDY NO. 11-6770.
CVT-301: Cardiovascular and respiratory assessments following inhalation administration in conscious Beagle dogs. (b) (4)

After 25 mg (PO) CD, a single dose of 0 (air) or 7.5 mg (0.28 mg/L) CVT-301 for 1 hr (equal to 9.9 mg/kg) was administered by oronasal inhalation to 5 telemetered M Beagle dogs (2 C, 3 dosed), using a cross-over dosing regimen, with a 3-day washout between doses. Blood pressure, heart rate, body temperature, and PR, QRS, QT, and QTc R intervals were measured.

Sponsor's table:

Day	Dose	Target CVT-301 Dose (mg/kg)	Target Aerosol Conc (mg/L)	Achieved Aerosol Conc (mg/L)	Achieved CVT-301 Dose (mg/kg)
1	1	0	0	0	0
		7.5	0.28	0.41	10.5
4	2	0	0	0	0
		7.5	0.28	0.36	9.0

Inhalation resulted in an exposure of 9.9 mg/kg CVT-301 (LD exposure of 8.9 mg/kg) There was no mortality. Emesis 20 minutes after the end of exposure was reported in 2/5 dosed dogs. Compared to C, no test article-related effects on the cardiovascular and respiratory system were seen during exposure or up to 25 hours post-dose.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK

Study Number (b) (4) 10-16-00: Pulmonary L-Dopa Provides Pharmacokinetic and Pharmacodynamic Advantages over Oral L-Dopa in Rat Models: Implications for Improving the Treatment of Parkinson's Patients.

The study was conducted in M SD rat and intra-femoral cannulas were implanted under ketamine anesthesia. The animals were divided into three groups:

- 2 mg LD in methylcellulose and ascorbic acid was administered PO to 7 animals.
- 2 mg LD in 10 mg LD powder was administered by intratracheal blunt-tip insufflation to 6 animals.
- 2 mg LD was administered as an IV bolus via the femoral cannula to additional animals.

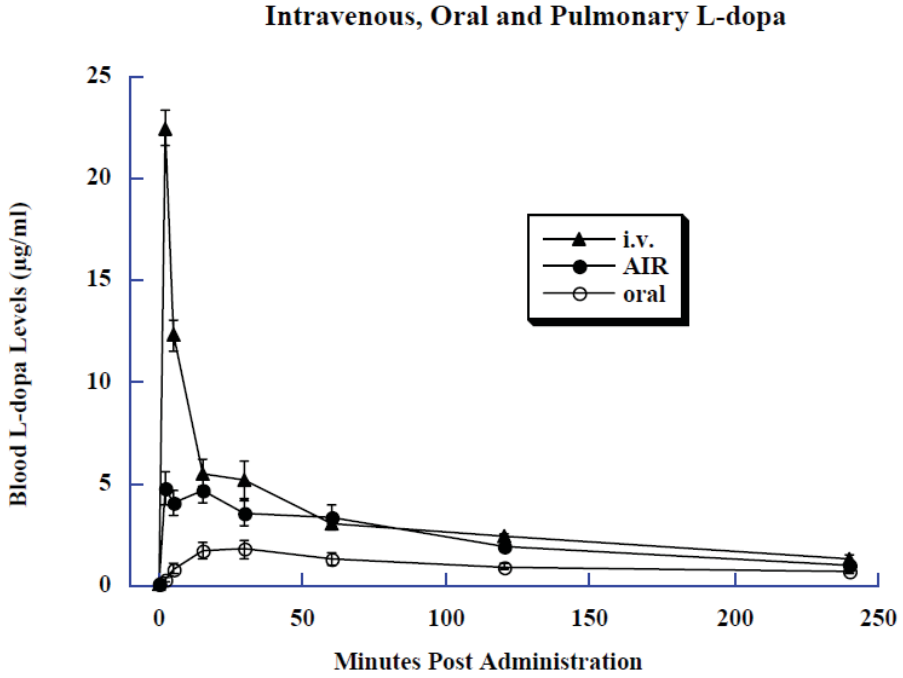
Carbidopa (200 mg/kg) was administered PO 1 hour prior to dosing with LD.

Blood samples were taken at 0, 2, 5, 15, 30, 60, 120 and 240 minutes post-dose.

The lungs of insufflated rats were removed at 1 and 30 minutes post-dose for levels of LD in lungs. (The number of animals in this sub-group was not provided).

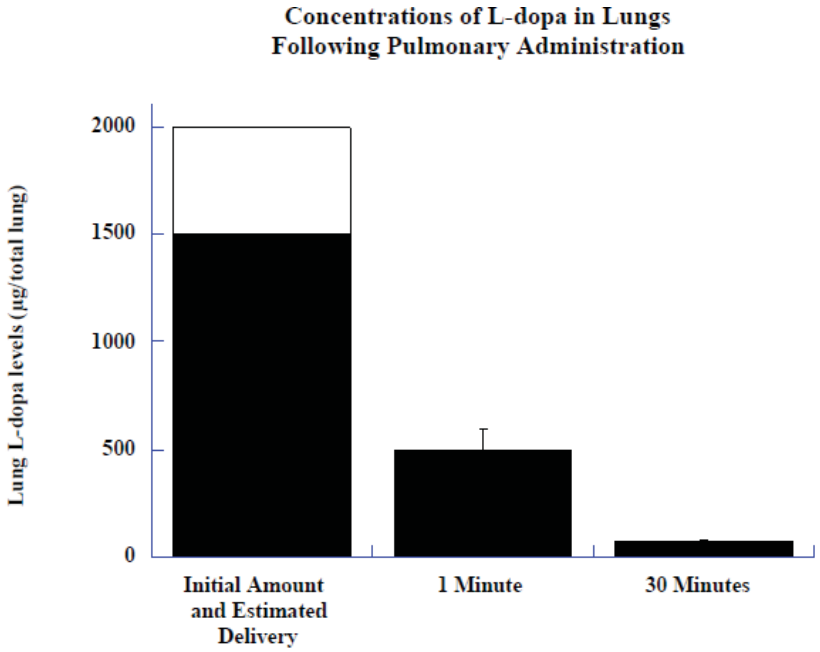
Intratracheal insufflation resulted in peak exposures immediately after administration with peak plasma levels lower than that from intravenous bolus but greater than that after oral administration. Within ~ 20 minutes, circulating levels were similar after intravenous or intratracheal administration.

Sponsor's figure: Levels of LD after 2 mg administered PO, IV bolus, or by insufflation.



Detectable levels of LD decreased rapidly in lungs. The sponsor reported that~ 67% of the L-Dopa initially delivered was cleared from the lungs within 1 minute, with ~ 5% remaining 30 minutes after administration.

Sponsor's figure: Lung levels of LD



6 General Toxicology

6.1 Single-Dose Toxicity

AIR-T-13-01: L-DOPA: Single dose intratracheal toxicity study in the rat. (Non-GLP)
Rats: 6/sex Crl:CD(SD)IGS.BR
Doses: C (3 mL room air), 5, 10, or 20 mg/kg AIR-L-DOPA (0, 2.5, 5, or 10 mg/kg LD);
Design: 3/sex were euthanized 24 hrs post-dose; 3/sex were euthanized 14 days post-dose.
Animals were dosed under fluothane anesthesia, using a "PennCentury Dry Powder Delivery Device." Pre-measured capsules were inserted into the device and drug was expelled from the device and into the trachea by puffs of room air. Four 3 mL single puffs of room air per dose was administered to all rats in C, LD, and MD; the HD was delivered in two half-doses, for a total of four 3mL puffs.
Mortality: 2 CM, 1 CF, 1 LDF, 1 HDM, and 1 HDF: gasping, cyanosis, and rales were observed antemortem in one decedent. Microscopic findings of congestion and hemorrhage were reported in the lungs and hemorrhage in the nasal cavity. Death was attributed to dosing procedures.
Clinical signs: Rales were observed in all groups, (including C) from 5-15 minutes post-dose and variably through Study Day 2.
Histopathology: C, HD, and decedents. Evidence of pulmonary inflammation was seen across all groups. Inflammatory reactions (bronchitis/bronchiolitis) were observed at 24 hours and 15 hours post-dose; at 15 days post-dose, tracheitis was also noted.

24 hours post-dose: Acute, random, pneumonitis, foamy histiocytes and inflammatory cell foci were seen in C, LD and HDM and C and LDF. Bronchitis/bronchiolitis was noted in LDM and CF and mucous plugs noted in 1 HDM and 1 HDF.

15 days post-dose: pneumonitis was seen in all dose groups and inflammatory cell foci in LD and MDM and LD, MD, and HDF. Foamy histiocytes were detected in C, MD and HDM and C, LD, and MDF and, mucous plug was seen in C and HDF and bronchiolitis in LD and HDM and C, MD and HDF. Tracheitis was found in 1 HDM, 3 CF, and 1 HDF.

AIR-T-13-04 Acute toxicology of an AIR-L-DOPA formulation in cynomolgus monkeys following single pulmonary administration
Cynomolgus: 8 M and 9 F C; 9 M and 8 F dosed.
Dose: Sham CM and F: air; 22mg/kg AIR-L-DOPA (11.0 mg/kg LD) administered to 9 M and 23.7 mg/kg AIR-L-DOPA (11.8 mg/kg LD) to 8 F. All animals were dosed with 25 mg CD PO 1 hour prior to dosing.
Design: The animals were restrained in a Spangler box under propofol anesthesia (IV bolus followed by continuous infusion) and test article or air was delivered by endotracheal tube. The respiratory patterns of the test animals were controlled: 6 breaths per minute with a 4 second hold prior to exhalation; target tidal volume of 75% of vital capacity. TK samples were taken at 0, 0.25, 0.5, 1, 2, 4, and 6 hours after the end of drug delivery. 4 CM, 5 CF, 5 dosed M and 4 dosed F were necropsied 24 hours post-dose; surviving animals were necropsied 14 days post-dose.
Mortality: None
Clinical signs: No difference was reported among groups; no test article-related changes were reported in body weight, food consumption, clinical chemistry, hematology, urinalysis, macroscopic findings, or organ weights.
Histopathology: Acute inflammation (alveoli and bronchi/bronchioles) was observed in both groups at the 24-hour necropsy. Four CM, 4 CF, 3 dosed M and 3 dosed F had erosion or ulceration of the tracheal epithelium, with and without acute inflammation, likely due to endotracheal intubation. 1 CF had similar changes after 14 days.

Sponsor's table:

Reference ID: 4367298

Incidence and Severity of Selected Respiratory Tract Lesions

	Sex:	Males				Females			
	Day of Necropsy:	2		15		2		15	
ORGAN / Diagnosis	Exposure Group (mg/kg):	0	20	0	20	0	20	0	20
LARYNX	Number Examined:	4	5	4	4	5	4	4	4
Inflammation, Acute	Number Affected (Average Severity)	3 (0.8)	3 (0.6)	2 (0.5)	2 (0.5)	3 (0.6)	3 (0.8)	1 (0.3)	0 (0.0)
TRACHEA	Number Examined:	4	5	4	4	5	4	4	4
Inflammation, Acute	Number Affected (Average Severity)	4 (1.3)	5 (1.8)	2 (0.5)	0 (0.0)	4 (1.4)	4 (1.0)	2 (0.5)	0 (0.0)
Ulceration/Erosion/ Attenuation	Number Affected (Average Severity)	4 (1.3)	3 (0.6)	0 (0.0)	0 (0.0)	4 (1.2)	3 (1.0)	1 (0.3)	0 (0.0)
LUNG	Number Examined:	4	5	4	4	5	4	4	4
Inflammation, Acute Alveoli	Number Affected (Average Severity)	3 (0.8)	2 (0.4)	0 (0.0)	1 (0.3)	4 (0.8)	3 (0.8)	0 (0.0)	0 (0.0)
Inflammation, Acute, Bronchi/Bronchioli	Number Affected (Average Severity)	2 (0.5)	5 (1.0)	1 (0.3)	2 (0.5)	5 (1.0)	3 (0.8)	2 (0.5)	2 (0.5)
Inflammation, Chronic-Active Interstitium	Number Affected (Average Severity)	4 (1.0)	5 (1.0)	4 (1.3)	4 (1.0)	4 (0.8)	2 (0.5)	4 (1.0)	2 (0.5)

Average lesion severity scores were calculated by adding the score for each animal in a group then dividing the result by the number of animals examined in the group.

Toxicokinetics:

The C_{max} was at the first sampling time immediately post-exposure (Time 0). Levels declined to below the LOQ (<50 ng/mL) by 6 hours post-exposure. A slightly higher exposure was seen in F, reflecting the slightly higher dose administered to F.

Sponsor's table: TK

Mean Levodopa Toxicokinetic Parameters for Males and Females

	T_{max} (hr)[a]	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)	AUC_{∞} (ng*hr.mL)
Males				
N	7	7	7	7
Mean	0.07	5011	3909	4162
SD	0.12	1886	1207	1173
Minimum	0.00	2069	2405	2698
Maximum	0.25	7843	5744	5848
CV(%)	171	38	31	28
Females				
N	6	6	6	6
Mean	0.00	6359	4816	4989
SD	0.00	1924	1679	1721
Minimum	0.00	3777	2931	2979
Maximum	0.00	9607	7539	7680
CV(%)	NC	30	35	35
Males and Females Combined				
N	13	13	13	13
Mean	0.04	5633	4328	4543
SD	0.09	1952	1458	1451

a: End of drug inhalation
AUC_{last} = Area under the plasma concentration-time curve from the end of dosing to the last quantifiable concentration.
AUC_{∞} = Area under the concentration-time curve from dosing extrapolated to infinity.
C_{max} = Observed maximum plasma concentration.
CV = Coefficient of variation.
NC = Not Calculated
SD = Standard deviation.
T_{max} = Time at which C_{max} occurred.

AIR-T- 13-02: Acute Toxicity of an AIR/L-DOPA formulation in beagle dogs following single pulmonary administration.
Beagle dogs: 6/sex
Dose: A single capsule dose of 0, 50 mg, or 100 mg was puffed by the proprietary clinical device via an endotracheal tube.
Design: Anesthetized, intubated, Beagle dogs in dorsal recumbency in a Spangler box were administered air or L-DOPA. TK samples were taken at 0, 0.25, 0.5, 1, 2, 4, and 6 hours after exposure. 3/sex of each group were instrumented for telemetry and were euthanized 24 hours post-dose. The surviving 3/sex were euthanized 14 days post-dose.
Clinical Signs: Emesis was noted in M and F in all groups and was attributed to anesthesia. GI effects, seen in dosed groups, were attributed to the test article. Softened, reddened, and/or mucoid feces were noted in M and F in all groups and at greater frequency in dosed groups. Diarrhea was seen in in one HDF throughout the 15-day recovery period.

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No test article related cardiovascular, hematologic, clinical chemistry, or urine analysis effects were reported. No test article-related effects on organ weights or gross findings were reported.

Histopathology: Microscopic findings were limited to lungs and the incidence and severity were dose related: at 24 hours post-dose, minimal hypertrophy of respiratory and terminal bronchiolar epithelium was observed in HD animals. After 14 days, the epithelium at the juncture of the terminal and respiratory bronchioles in HD was slightly hypertrophic accompanied by small aggregates of "small chronic inflammatory" cells. Similar, but minimal and less frequent changes were seen at the LD. The study pathologist considered the cause of the findings (manipulation during intubation vs test article) to be equivocal.

Toxicokinetics:

The sponsor reported up to 2-fold differences in the received dose in animals in the LD group and a 75% difference in received dose in the HD group. The C_{max} was at the end of exposure (Time 0), and plasma levels declined to 0 in the LD group, but levodopa was detectable in the HD at the last measurement of 6 hours post-exposure. Exposures increased in a slightly more than dose-proportional manner in M and in a dose-proportional manner in F.

Sponsor's table:

Summarized Levodopa Estimates[1]

Group	C_{max} (ng/mL)	AUC (hr*ng/mL)	$T_{1/2}$ (hr)
Male			
Low Dose	4279	2842	0.97
High Dose	10034	6335	0.84
Female			
Low Dose	3421	2235	1.04
High Dose	7041	4132	0.83

[1] Plasma concentrations were normalized to the group mean estimated inhaled levodopa (low dose = 3.3 mg/kg, high dose = 6.6 mg/kg).

Sponsor's figures: Mean L-Dopa concentration from the end of dose administration

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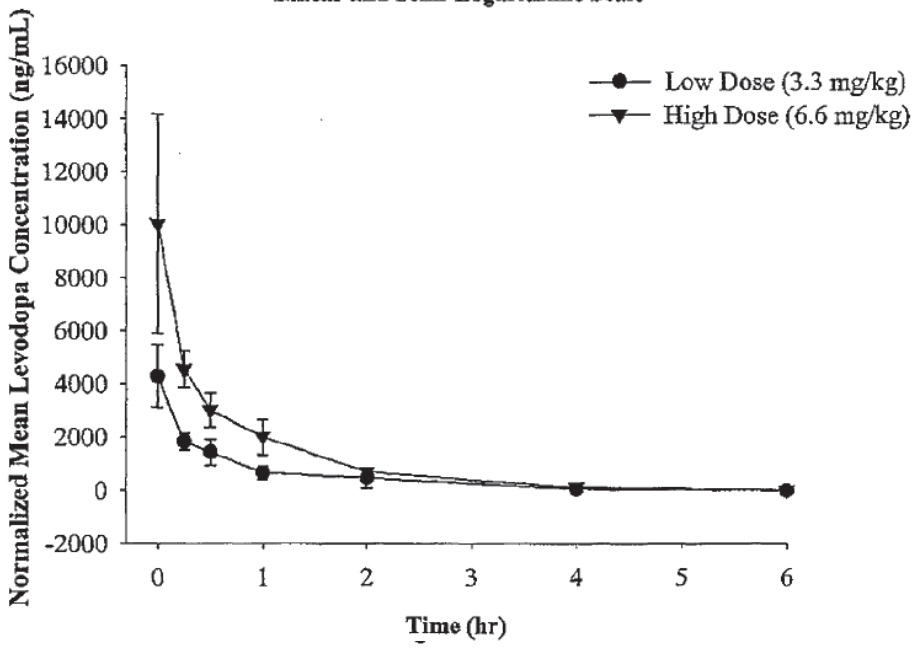
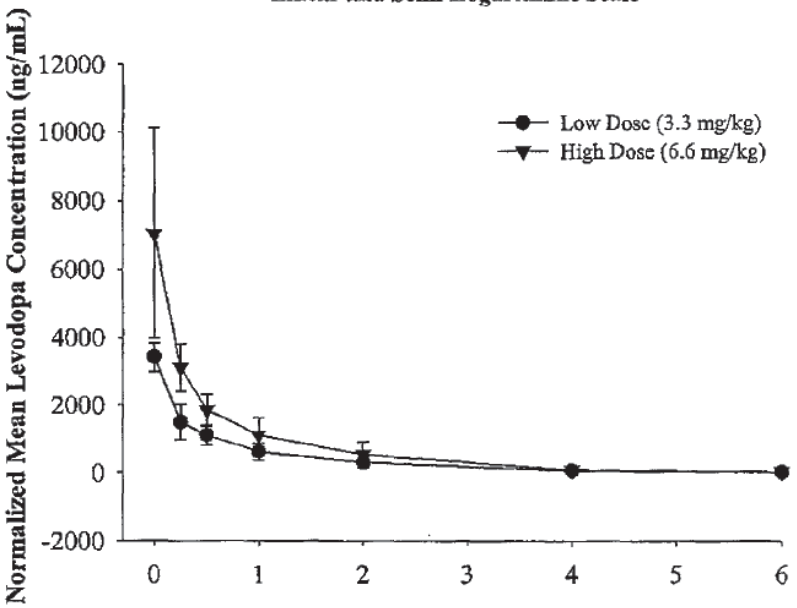
Normalized Mean (SD) Plasma Levodopa Concentration versus Time
Male Animals
Linear and Semi-Logarithmic Scale



Normalized Mean (SD) Plasma Levodopa Concentration versus Time
Female Animals
Linear and Semi-Logarithmic Scale



6.2 Repeat-Dose Toxicity

6.2.1 7-day Rat Dose Range Finding

Study no. 11-6380 CVT: 301: A 7-day dose range finding inhalation toxicity study in rats (Non-GLP)

Study no.:	11-6380
Study report location:	4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	JUN 14, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	CVT 301/B-0290003, 0004, 0005/86.1, 89.7, 88.4%.

Key Study Findings:

- Minimal focal to multifocal nasal epithelial degeneration.
- Minimal intra-alveolar hemorrhages
- NOAEL: HD (127.9 mg/kg/day)
  - o $AUC_{(last)}$: 36100 ng*hr/mL (M) and 37800 ng*hr/mL (F)
  - o C_{max}: 1100 ng/mL (M) and 9700 ng/mL (F)

Methods

Doses:	0, 11, 60.5, 60.5 BID, and 121 mg/kg/day
Frequency of dosing:	0, 11, 60.5, 121 mg/kg QD; 60.5 mg/kg BID
Route of administration:	Nose only inhalation
Dose volume:	60 minutes aerosol exposure/dose
Formulation/Vehicle:	Aerosol in room air: see table below
Species/Strain:	SD Rat: Crl:CD (SD) IGS BR
Number/Sex/Group:	5/sex
Age:	6.5 weeks
Weight:	M: 267-317 g; F: 194-247 g
Satellite groups:	6/sex TK (dosed only):3/sex at each of 0.08, 0.25, 0.5, 1, 2, and 6 hrs. post-dose on Study Days 1 and 7.
Unique study design:	60 min predose: oral gavage with 30 mg/kg carbidopa (CD) in 0.5% methylcellulose
Deviation from study protocol:	Minor: no impact on study outcome.

Sponsor's table:

Reference ID: 4367298

Mean aerosol concentrations and achieved doses were as follows:

Group	Target CVT-301 Dose (mg/kg/day)	Achieved CVT-301 Dose (mg/kg/day)	Target Aerosol Conc (mg/L)	Achieved Aerosol Conc (mg/L)
1	0.0	0	0	0
2	11	13.4	0.25	0.30
3	60.5	77.1	1.35	1.72
4	121 (60.5 mg/kg BID)	134.7 (67.4 mg/kg BID)	1.35 (BID)	1.51
5	121	127.9	2.70	2.86

Observations and Results

Mortality:

None

Clinical Signs and necropsy findings:

No test article-related findings were reported for clinical signs, body weights, food consumption, hematology, clinical chemistry, or gross pathology. Mean testicular weight in the group dosed BID was 7% less than C.

Histopathology:

Signed, dated pathology report: Yes

Adequate Battery: Yes

Peer Review: No

Histological Findings: Loss of cilia and thinning of the nasal epithelium were reported in groups administered greater than 11 mg/kg/day. Minimal acute intra-alveolar hemorrhages were reported in individual animals in the QD-MDM and BID-HDM and in two QD-HDF. Tracheal epithelial degeneration was reported in 1 QD-MDM and 1 HDM.

Sponsor's table:

Table 3.9.2-1: Microscopic Changes

	Males					Females				
CVT-301 dose (mg/kg/day)	0	13.4	77.2*	67.4**	127.9	0	13.4	77.2*	67.4**	127.9
# animals examined	5	5	5	5	5	5	5	5	5	5
Nasal Turbinates: Olfactory Epithelium, Degeneration (minimal)	0	0	1	2	1	0	0	2	3	2
Lung: Alveoli, Acute Hemorrhage (minimal)	0	0	1	1	0	0	0	0	0	2

* Administered QD (1x/day) ** Administered BID (2x/day)

Toxicokinetics:

There was modest accumulation of levodopa and no marked differences between M and F. Exposures (AUC_{last}) of levodopa were dose proportional on Study Days 1 and 7.

Reference ID: 4367298

The C_{max} was approximately dose proportional on Study Day 1 but less than dose proportional on Study Day 7.

Sponsor's table:

Table 3.2-1 Values of Plasma Toxicokinetic Parameters of Levodopa in Male and Female Rats following Nose-only Inhalation of CVT-301

			CVT-301[a]		Levodopa			
Day	Sex	Group	Nominal Dose (mg/kg/day)	Achieved Dose (mg/kg/day)	AUC_{last} (ng·h/mL)	C_{max} (ng/mL)	t_{max}[b] (h)	$T_{1/2}$ (h)
1	Male	2	11	12.8	3060	1580	1.08	0.768
		3	60.5	90.6	18900	7930	1.25	0.939
		4	121 (60.5 BID)	77.5[c]	27500	10700	1.5	1.27
		5	121	102.3	23700	8240	1.08	1.25
	Female	2	11	13.3	4650	2820	1.25	0.848
		3	60.5	94.6	32600	13100	1.25	1.02
		4	121 (60.5 BID)	80.5[c]	42000	15600	1.25	1.09
		5	121	107.4	41200	14300	1.5	0.995
7	Male	2	11	9.3	2930	2560	1.25	0.752
		3	60.5	74.7	15200	6260	1.25	0.930
		4	121 (60.5 BID)	65.2[c]	17400	7350	1.25	1.25
		5	121	119.8	36100	11000	1.5	1.60
	Female	2	11	9.7	3160	3040	1.25	0.577
		3	60.5	78.1	25000	11700	1.25	0.824
		4	121 (60.5 BID)	67.7[c]	22200	11700	1.08	0.962
		5	121	125.8	37800	9700	1.25	1.24

[a]Levodopa dose is 90% of the CVT-301 dose
[b]From the start of the inhalation dose period
[c]All samples collected after 1st daily dose and prior to 2nd daily dose

6.2.2 28-day rat

Study title: CVT 301: A 28-day Inhalation toxicity study in rats with a 21-day recovery period

Study no.: 11-6382
Study report location: 4.2.3.2
Conducting laboratory and location: (b) (4)
Date of study initiation: JUL 25, 2011
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: CVT-301/B2002-0001/100% (92.7% LD)

Key Study Findings:

- NOAEL: at the achieved HD of 114.5 mg/kg/day CVT-301 (103.1 mg/kg/day LD).
  - o $AUC_{(last)}$: 14200 ng.h/mL (M) and 25100 ng.h/mL (F)
  - o C_{max}: 7930 ng/mL (M) and 12900 ng/mL (F)

Methods

Doses:	0, 11, 60.5, 121 mg/kg/day (0.0, 0.26,1.42, 2.84 mg/L concentration in aerosol)
Frequency of dosing:	60 minutes duration, once daily
Route of administration:	Nose-only inhalation
Dose volume:	NA
Formulation/Vehicle:	Air
Species/Strain:	CD® IGS Rats (Crl: CD(SD)
Number/Sex/Group:	15 C and HD (10 dosed, 5 recovery); 10 LD and MD
Age:	9 weeks
Weight:	269.5-337.4(M); 176.2-232.58 (F)
Satellite groups:	3/sex C and 6/sex dosed TK group
Unique study design:	60 min prior to inhalation, CD (30 mg/kg) PO in distilled water at 5 mL/kg
Deviation from study protocol:	On Study Day 3, CD administered outside of 60 ± 10 minutes prior to TA administration. There was no apparent effect on the results.

Table: Achieved doses:

Group: Target Dose (mg/kg/day)	Achieved dose (mg/kg/day)	
	M	F
C: 0	0	0
LD: 11	13.6	14.5
mean	14.1	
MD: 60.5	57.2	60.7
mean	59.0	
HD: 121	111	118
mean	114.5	

Observations and Results

Mortality:

None

Clinical Signs:

Anogenital staining in HDM during Study Week 1 and throughout the study in HDF.
Facial staining in HDM and F.

Reference ID: 4367298

Body Weights:
No test article related changes were reported in absolute body weight or overall body weight gain, food consumption, ophthalmoscopic exam, hematology, coagulation, urinalysis, macroscopic pathology or organ weights.

Clinical Chemistry:
A 34% reduction in mean ALT (compared to C) was seen in in all M groups, and a 40% reduction in all F groups. A dose-related reduction in mean triglycerides was seen in all M groups (30%, 37%, and 47% in LD, MD, HD respectively)

Histopathology:
Signed, dated pathology report: Yes
Adequate Battery: Yes
Peer Review: No
Histological Findings:
There were no test article-related gross or microscopic findings reported.
Areas of epithelial alteration (squamous metaplasia) in the larynx were determined to be background lesions that are not uncommon in laboratory rats.

Sponsor's table:

	Males				Females			
CVT-301 (mg/kg/day)[a]	0	14.1	59	114.5	0	14.1	59	114.5
# animals examined	10	10	10	10	10	10	10	10
Larynx: Epithelial Alteration								
minimal	2	1	6	3	1	1	2	4
slight	0	0	1	1	0	0	0	0
Total Incidence	2	1	7	4	1	1	2	4

[a]Average achieved dose.

Toxicokinetics:
The $AUC_{(last)}$ increased with dose, proportionally in M and in a slightly greater than dose-proportional manner in F. No accumulation was evident by Study Day 28. The T_{max} was within 15 minutes after dosing ceased and the half-life ranged from ~0.5 - 1 hrs. on Study Day 1 and 0.6 - 1.5 hrs. on Study Day 28.

Sponsor's table:

Reference ID: 4367298

Day	Sex	Group	CVT-301[a]		Levodopa			
			Nominal Dose (mg/kg/day)	Mean Achieved Dose (mg/kg/day)	AUC_{last} (ng·h/mL)	C_{max} (ng/mL)	T_{max}[b] (h)	$T_{1/2}$ (h)
1	Male	2	11	17.4	4360	2640	1.08	0.622
		3	60.5	75	16400	7570	1.08	0.872
		4	121	132	38600	15200	1.08	1.02
	Female	2	11	18.5	2570	2090	1.08	0.574
		3	60.5	79.7	25400	14400	1.08	0.801
		4	121	140	35700	13300	1.25	0.736
28	Male	2	11	11.6	2160	1320	1.25	1.11
		3	60.5	44.9	4190	2200	1.08	1.00
		4	121	129	14200	7930	1.25	1.20
	Female	2	11	12.6	1010	798	1.08	0.585
		3	60.5	48.2	7330	5310	1.25	0.862
		4	121	139	25100	12900	1.25	1.45

[a]Levodopa dose is 90% of the CVT-301 dose
[b]From the start of the inhalation dose period (1 hour)

6.2.3 6-month rat

Study title: CVT-301: A 6-Month Inhalation Toxicity Study in Rats with a 1-Month Recovery Period

Study no.: 13-6422
Study report location: eCTD 0012 (16)
Conducting laboratory and location: (b) (4)
Date of study initiation: 04/03/2013
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: CVT 301: Lot numbers B-2002-0007, 0008, 0009, 0010, 0011, 0012, 0013, 0014, 0015, 0016; 99.93-99.98% purity.
CD: Lot number 76017; 99.6% purity
DPPC/NaCl: Lot number B-2008-0002; 100% purity

Key Study Findings

- Sporadic Piloerection within 60 minutes post-dose in dosed groups.
- One HDF on Study Day 90 and at necropsy: elevated liver enzymes
  - Correlated with acute hepatocellular necrosis.
- NOAEL for pulmonary exposure is the HD.

Reference ID: 4367298

- Study Day 180 C_{max}: 9000 ng/mL (M) and 8990 ng/mL (F)
- Study Cay 180 AUC_{last}: 19200 ng.h/mL(M) and 33600 ng.h/mL (F)

Methods

Doses:	0 (water), 18 (vehicle), 40, 120, 180 mg/kg/day CVT-301
Frequency of dosing:	Up to 90 minutes/once daily
Route of administration:	Inhalation, nose-only
Dose volume:	NA
Formulation/Vehicle:	8% Dipalmitoylphosphatidylcholine (DPPC) in 2%NaCl
Species/Strain:	Sprague Dawley CD rats
Number/Sex/Group:	10
Age:	12 weeks
Weight:	M: 285-432 g; F: 188-296 g
Satellite groups:	Recovery: 5/sex C, vehicle, HD. TK: 3/sex C and vehicle, 9/sex LD, MD, and HD
Unique study design:	All animals receiving test article were administered 30 mg/kg Carbidopa (CD) PO (5mL/kg) ~ 60 minutes prior to inhalation
Deviation from study protocol:	On Day 1, LDM and MDM were dosed with 5.0 mL CD (30 mg) per rat.

Dose selection:
Doses were based on DRF (No 11-6380) and the 28-day inhalation study in rat (No 11-6382). The HD (118 mg/kg/day) was the NOAEL in the 28-day study. The HD selected for the 6-month study was also 180 mg/kg/day "based upon the anticipated clinical doses."

Sponsor's formula for achieved dose:

The estimations of achieved dose were calculated using the formula:

$$\text{Dose (mg/kg/day)} = \frac{\text{C (mg/L)} \times \text{RMV (L/min)} \times \text{D (min)} \times \text{DF}}{\text{BW (kg)}}$$

Where

- C = CVT-301 concentration (mg/L) in air inhaled
- RMV = Respiratory minute volume (L/minute).
  The RMV was calculated from the formula
  $\text{RMV (L/minute)} = 0.608 \times \text{BW (kg)}^{0.852}$ (D.J. Alexander et al., 2008)
- D = Duration of exposure in minutes
- DF = Deposition Fraction (assumed as being 100%)
- BW = Bodyweight (kg)

Sponsor's table:

Reference ID: 4367298

Group	Target Aerosol Concentration (mg/L)	Achieved Aerosol Concentration (mg/L)	Delivered Dose (mg/kg/day)			
			Target	Achieved		
				Male	Female	Mean
1	0	0	0	0	0	0
2[a]	0.27	0.30	18	18	20	19
3	0.59	0.62	40	38	41	40
4	1.78	1.88	120	114	124	119
5	2.67	2.75	180	168	180	174

[a]Group 2 aerosol concentration refers to DPPC/NaCl only and contained no CVT-301.

Sponsor's table:

Particle size distribution measurements are summarized as follows:

Group	Gravimetric Mass Median Aerodynamic Diameter (μm)	Geometric Standard Deviation (σg)
2	1.9	1.67 – 2.17
3	2.1	1.62 – 2.03
4	1.9	2.11 – 2.78
5	2.5	2.00 – 2.77

Observations and Results

Mortality:
Four deaths were reported: 1 LDM on Study Day 82, due to a high grade oligodendroglioma; 1 LDF on Study Day 64, due to gavage trauma; and 2 MDM on Study Days 161 and 156 due to gavage error.

Clinical Signs:
A sporadic but dose-related increased incidence of piloerection was noted within 60 minutes of dosing in LD animals. The sponsor found the signs to be likely CD related.

Body Weights/Food consumption:
No test article-related effects were reported for body weights, food consumption, urinalysis or macroscopic pathology.

Hematology:
At the end of dosing, decreased red cell mass and MCHC, increased reticulocytes, platelets, MCV, and RDW was seen in one HDF. These changes correlated with extramedullary hematopoiesis in liver and the cause was not determined.

Clinical Chemistry: Samples taken on Study Day 90 and at necropsy on Study Days 108 and 216.

Compared to C, on Study Day 90, one HDF had an elevated AST (2X) and ALT (1.5X). At the Study Day 108 necropsy, the same HDF had an elevated AST (5X) and ALT (3X) compared to C. The enzyme levels correlated with a microscopic finding of minimal focal hepatocellular necrosis described as acute in the pathology narrative.

Organ Weights:
No test article-related effects were reported.

Reference ID: 4367298

Compared to CM, absolute and relative epididymal weights were lower in HDM after recovery. Because similar effects were not seen at the end of dosing and there were no histologic correlates, the sponsor found this to be unrelated to test article.

Histopathology:

Adequate Battery: Yes
Signed Pathology report: Yes
Peer Review: No
Histological Findings:

Nasal cavity:

Terminal necropsy: There was brown pigment (compatible with test article) noted in MDM and MDF and HDM on the epithelium of the anterior segment with associated intra-luminal neutrophils and epithelial erosion, hyperplasia, and squamous change. Minimal focal ulceration/erosion was noted in the respiratory epithelium in one MDM and one MDF.
Recovery necropsy: Changes were limited to epithelial pigment and intra-luminal neutrophils in one HDM.

Sponsor's table:

Text Table 3.11.2-1: Test article-related findings in the nose/turbinates in rats dosed with CVT-301 for up to 6 months

Group/sex		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Dose (mg/kg/day)		0	19[a]	40	119	174	0	19[a]	40	119	174
Pigment, Lumen											
	slight	0	0	0	4	2	0	0	0	2	0
	moderate	0	0	0	1	0	0	0	0	0	0
	Total	0	0	0	5	2	0	0	0	2	0
Inflammatory. Cells, Lumen											
	minimal	0	0	0	3	1	0	0	0	0	0
	slight	0	0	0	2	1	0	0	0	2	0
	Total	0	0	0	5	2	0	0	0	2	0
Inflammation, Respiratory Epithelium/Mucosa											
	minimal	0	0	0	2	1	0	0	0	0	0
	slight	0	0	0	0	1	0	0	0	2	0
	Total	0	0	0	2	2	0	0	0	2	0
Hyperplasia, Respiratory Epithelium											
	minimal	0	0	0	1	2	0	0	0	0	0
	slight	0	0	0	0	0	0	0	0	1	0
	Total	0	0	0	1	2	0	0	0	1	0
Squamous Metaplasia, Respiratory Epithelium											
	minimal	0	0	0	2	1	0	0	0	1	0
	slight	0	0	0	0	0	0	0	0	1	0
	Total	0	0	0	2	1	0	0	0	2	0
Erosion//Ulcer, Respiratory Epithelium											
	minimal	0	0	0	1	0	0	0	0	1	0
	Total	0	0	0	1	0	0	0	0	1	0
Number of tissues examined		10	10	10	10	10	10	10	10	10	10

[a]DPPC-Dipalmitoylphosphatidylcholine/Sodium Chloride

Tracheal Bifurcation:

Reference ID: 4367298

Minimal and slight loss of cilia and thinning of the apical respiratory epithelium was seen in all groups and both sexes. This change was present, at reduced severity, after recovery.

Sponsor's tables:

Text Table 3.11.2-2: Test article-related findings in the tracheal bifurcation in rats dosed with CVT-301 for up to 6 months

Group/sex		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Dose (mg/kg/day)		0	19[a]	40	119	174	0	19[a]	40	119	174
Loss of Cilia/ Epithelial Thinning											
	minimal	4	1	1	3	4	2	3	1	2	2
	slight	0	0	0	1	0	0	0	1	2	2
	Total	4	1	1	4	4	2	3	2	4	4
Number of tissues examined		10	10	9	10	10	10	10	9	10	10

[a]DPPC-Dipalmitoylphosphatidylcholine/Sodium Chloride

Text Table 3.11.2-3: Test article-related findings in the tracheal bifurcation in rats following a 1 month recovery period.

Group/sex		1M	2M	5M	1F	2F	5F
Dose (mg/kg/day)		0	19[a]	174	0	19[a]	174
Loss of Cilia/ Epithelial Thinning							
	minimal	1	1	1	0	1	1
	Total	1	1	1	0	1	1
Number of tissues examined		5	5	5	5	4	5

[a]DPPC-Dipalmitoylphosphatidylcholine/Sodium Chloride

Lungs: No test article effect was reported.
Minimal interstitial inflammation was seen in all groups at both terminal and recovery necropsy. Minimal bronchiolo-alveolar hyperplasia was seen in one MDM at terminal necropsy.
MSC:
After recovery, a mammary adenocarcinoma was diagnosed microscopically in one HDF.

Toxicokinetics: Study Days 1, 90, 180. Plasma LD levels by LC-MS/MS.
The C_{max} and $AUC_{(last)}$ increased with dose in a less than dose-proportional manner. Exposures were similar, or less than, single dose levels and no differences were noted between M and F.

Sponsor's tables:

Reference ID: 4367298

Nominal dose level (mg/kg/day)		C_{max} (ng/mL)					
		Day 1		Day 90		Day 180	
CVT-301	Levodopa	Males	Females	Males	Females	Males	Females
40	36	7330	6030	2830	3590	4020	4980
120	108	22200	17000	5340	9150	6020	11800
180	162	23800	23200	8990	6320	9000	8990

Nominal dose level		AUC_{last} (ng.h/mL)					
CVT-301 (mg/kg)	Levodopa (mg/kg)	Day 1		Day 90		Day 180	
		Males	Females	Males	Females	Males	Females
40	36	19000	11100	6970	7270	10800	10100
120	108	61900	48200	12900	20600	17300	26700
180	162	77800	72700	24900	20400	19200	33600

6.2.4 7-day study in dog

Study title: CVT-301: A 7-day dose range finding inhalation toxicity study in dogs

Study no.:	11-6381
Study report location:	eCTD 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	JUN 17, 2011
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	CVT-301/B-290006, 0007, 0008/ 99.9%

Key Study Findings

- A high incidence of emesis on Day 1 was dose-limiting at greater than the MTD of 20 mg/kg (achieved dose of 18.4 mg/kg/day). Target doses were reduced to QD 0, 5.5, 12.5, 20, or BID 12.5 from Study Day 2.
- Maximum Tolerated Dose/NOAEL was the 18.4 mg/kg/day achieved dose, when given as a single daily dose, corresponding to a Day 7 AUC_{last} and C_{max} of 5770 ng.h/mL and 4370 ng/mL, respectively, in males and 4760 ng.h/mL and 3690 ng/mL, respectively, in F.

Methods

Doses:	QD: 0 (Air), 5.5, 27.5, 55 mg/kg/day or BID: 27.5 mg/kg Study Day 2: QD 0, 5.5, 12.5, 20 mg/kg/day or BID 12.5 mg/kg/day
Frequency of dosing:	once or twice daily
Route of administration:	Oronasal (face mask)
Dose volume:	60 minutes of exposure to aerosol
Formulation/Vehicle:	Aerosols concentrations in room air (see below)
Species/Strain:	Beagle dog
Number/Sex/Group:	2
Age:	~ 9 months
Weight:	M: 8.5-11.8 kg; F: 5.5-7.8 kg
Unique study design:	25 mg carbidopa PO 60 minutes pre-dose.

Sponsor's table: Study design

Group	Daily Doses[a]		Number of Animals Total on Study[c]	
	Target CVT-301 Dose (mg/kg/day)	Target Aerosol Concentration[b] (mg/L)	M	F
1	0	0	2	2
2	5.5	0.21	2	2
3	27.5	1.04	2	2
	20[f]	0.75		
4	55 (27.5 BID)[d]	1.04 (BID)	2	2
	25 (12.5 BID)[f]	0.47 (BID)		
5	55[e]	2.07	2	2
	12.5[f]	0.47		

[a]CVT-301 doses equate to approximate target levodopa doses of 0, 5, 18 and 22.5 mg/kg/day.
b Calculated using the formula provided below, assuming a body weight of 8.5 kg.
c Toxicokinetic samples were collected on Days 1 and 7 (Days 2 and 7 for Group 5).
d Group 4 animals dosed on only 1 occasions on Day 1 due to clinical signs (emesis).
e Group 5 animals not dosed on Day 1 due to clinical signs in Group 4.

Reference ID: 4367298

f The dose levels were lowered due to clinical signs in Group 4 on Day 1 beginning Day 2 for Groups 3 and 5, and Day 3 for Group 4. Group 4 animals were habituated to the exposure system with air only on Day 2.

Dose selection:
The high dose was selected to provide adequate exposure margins in comparison to anticipated clinical doses and to exceed tolerated doses determined in previous studies of various CVT-301 formulations.

Sponsor's table: Doses achieved

Total Study

Group	Modified Target Total Dose[b] (mg/kg/day)	Achieved Total Dose[a] (mg/kg/day)	Target Aerosol Conc (mg/L)	Achieved Aerosol Conc (mg/L)
1	0	0	0	0
2	5.5	5.94	0.21	0.23
3	20	18.4	0.75	0.76
4	25 (12.5 BID)	33.1 (16.6 BID)	0.47 (BID)	0.69 (BID)
5	12.5	11.0	0.47	0.48

a Achieved dose based on actual dose duration for each animal.
b Modifications to target dose based on Day 1 emesis, initiated on Day 2 with the exception of Group 4 animals which were administered air on Day 2 and CVT-301 on Days 3 through 7.

Observations and Results

Mortality:
None
Clinical Signs:
Emesis was noted during the face-mask exposure and again within the first 10-15 minutes post-dose. The incidence of emesis declined from Study Day 2 in all dosed groups.
Body Weights:
No test article-related effects on body weights, food consumption, hematology or clinical chemistry values, urinalysis, organ weights, or macroscopic pathology were reported.
Histopathology:

Signed dated pathology report: Yes
Adequate Battery: A standard battery of tissues was taken. The respiratory tract was examined histologically. Note: three longitudinal sections of larynx were examined.
Peer Review: No
Histological Findings:
No test article related findings were reported.

Reference ID: 4367298

Toxicokinetics: Study Days 1 and 7 (BID group Study Days 2 and 7): 0.08, 0.25, 0.5, 1, 2, and 6 hours post-dose

Levodopa exposure increased at a slightly greater than dose-proportional manner in M and F. Accumulation was not reported and exposures in M and F were largely similar.

Sponsor's table:

Table 3.2-1 Mean Values of Plasma Toxicokinetic Parameters of Levodopa in Male and Female Dogs following Oronasal Inhalation of CVT-301

Sex	Day	Group	CVT-301[a]		Levodopa		
			Nominal Dose[b] (mg/kg/day)	Mean Achieved Dose (mg/kg/day)	AUC_{last} (ng·h/mL)	(C_{max} (ng/mL)	T_{max}[c] (h)
Male	1	2	5.5	3.36	969	534	1.25
		3	27.5	17.02	6410	3470	1.17
		4	27.5 BID[d]	25.22	4430	2520	1.08
	2	5	12.5	12.62	5150	4100	1.08
Female	1	2	5.5	3.60	1220	540	1.17
		3	27.5	12.51	4480	3150	1.38
		4	27.5 BID[d]	20.01	3440	2150	1.29
	2	5	12.5	9.60	4490	4110	1.08
Male	7	2	5.5	5.66	1140	653	1.08
		3	20	21.02	5770	4370	1.17
		4	12.5 BID	11.67	2470	1350	1.08
		5	12.5	9.70	2710	1820	1.29
Female	7	2	5.5	6.12	1760	1010	1.08
		3	20	19.20	4760	3690	1.17
		4	12.5 BID	12.08	2940	1750	1.17
		5	12.5	11.95	2530	1370	1.17

[a]Levodopa dose is 90% of the CVT-301 dose
[b]Nominal dose on Day 1 changed for Day 2 and subsequent doses due to emesis on Day 1
[c]From the start of the inhalation dose period (1 hour)
[d]Only one dose was administered on Day 1

6.2.5 28-day study in dog

Study title: A 28-day inhalation toxicity study in dogs with a 21-day recovery period.

Study no.:	11-6383
Study report location:	eCTD 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	AUG 12, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	CVT-301/B-2002-0001, B2002-0002, B2002- 0003, B2002-0004/100% CVT-301: LD 92.7%, 90.1%, 89.4%, and 88.2%

Key Study Findings:

- The NOAEL was at the HD (22 mg/kg BID) and at the achieved daily doses of up to 45.6 mg/kg/day (M) and 47.6 mg/kg/day (F).
  - C_{max}: 4040 ng/mL (M) and 303 ng/mL (F)
  - $AUC_{(last)}$: 9400 ng*h/mL(M) and 8210 ng*h/mL (F)
- Emesis was seen at all doses but was reduced or absent by the end of dosing.

Methods

Doses:	QD: 0, 11, 22 mg/kg/day or BID: 22 mg/kg/day.
Frequency of dosing:	60 minutes
Route of administration:	Oronasal (face mask)
Dose volume:	60 minutes of exposure to aerosols, or until emesis.
Formulation/Vehicle:	Aerosol concentrations in room air (see below)
Species/Strain:	Beagle dog
Number/Sex/Group:	C and HD: 6 (4+2 recovery); LD and MD:4
Age:	9.5-10 months
Weight:	M: 6.9-10.2; F: 5.0-8.9
Satellite groups:	NA
Unique study design:	Carbidopa administered 60 minutes pre-dose
Deviation from study protocol:	Minor, with no effect on study outcome

Sponsor's table: Experimental design

Reference ID: 4367298

Group	Daily CVT-301 Doses[a]		Number of Animals							
			Total on Study		Terminal Necropsy		Recovery Necropsy		Toxicokinetics[c] Days 1 and 28	
	Dose (mg/kg)	Target Aerosol Concentration[b] (mg/L)	M	F	M	F	M	F	M	F
1	0	0	6	6	4	4	2	2	6	6
2	11	0.42	4	4	4	4	-	-	4	4
3	22	0.83	4	4	4	4	-	-	4	4
4	44 (22 BID)	0.83 (BID)	6	6	4	4	2	2	6	6

[a]CVT-301 doses equate to target levodopa doses of 0, 10, 20 and 40 mg/kg/day.
[b]Calculated using the formula provided below, assuming a body weight of 8.5 kg.
[c]Toxicokinetic samples were collected on Days 1 and 28.

Dose Selection:
Doses were based upon the calculated clinical doses and a 7-day DRF study in dog (Study No 11-6381)

Sponsor's table: Achieved dose

Group	Target CVT-301 Total Dose[a] (mg/kg/day)	Achieved CVT-301 Total Dose[a] (mg/kg/day)		Target Aerosol Conc. (mg/L)	Achieved Aerosol Conc. (mg/L)	
		M	F		M	F
1	0	0	0	0	0	0
		0			0	
2	11	12.4	12.6	0.42	0.47	
		12.5				
3	22	20.8	23.0[b]	0.83	0.86[b]	
		21.9				
4	44 (22 BID) AM	22.1	23.8	0.83	0.85	0.87
		23.0			0.86	
	44 (22 BID) PM	23.5	23.8	0.83	0.90	0.87
		23.7[c]			0.89	

[a]Levodopa dose is 90% of the CVT-301 dose.
[b]Animals received only 34 minutes of exposure at 0.05 mg/L on Dosing Day 17.
[c]Total average achieved Group 4 dose M = 45.6, F = 47.6 mg/kg/day, mean 46.7 mg/kg/day

Observations and Results

Mortality:
None

Clinical Signs:
Emesis was noted in all dosed groups, (27 minutes and between 35 and 55 minutes after the start of dosing). Sporadic emesis was also noted within 10-15 minutes post-dose. The incidence declined after Study Week 2 and was absent or markedly reduced by the Study Day 28.

Reference ID: 4367298

Body Weights:
No test article-related effects on body weights, ophthalmoscopic exam, ECG, hematology, coagulation, urinalysis, organ weights, or macroscopic pathology were reported.

Food Consumption:
In Study Week 1, a dose-related 50% reduction in food consumption was noted in HDM.

Clinical Chemistry:
ALT was decreased in all dosed animals compared to individual baseline and compared to C. In males, ALT was decreased 26% to 31% from CM and in F, decreased 47% to 56% from CF.

Histopathology:

Signed, dated pathology report: yes
Adequate Battery: Yes (bone marrow smear not evaluated)
Peer Review: No
Histological Findings:
No test article related findings were reported.

Toxicokinetics: On Study Days 1 and 28, C samples were taken at 0.25 and 2 hours post-dose from C and all dosed TK animals at 3, 5, and 15 minutes and 1, 2,5, and 8 hours post-first-dose.
Exposures increased in a dose proportional manner, were similar in M and F, and no accumulation was noted.

Sponsor's table:

Reference ID: 4367298

Table 3.2-1 Mean (SD) Values of Plasma Toxicokinetic Parameters of Levodopa in Male and Female Dogs following Inhalation of CVT-301

Day	Sex	Group	CVT-301[a]		Levodopa			
			Nominal Dose[b] (mg/kg/day)	Mean Achieved Dose (mg/kg/day)	$AUC_{0\text{-}6h}$ (ng·h/mL)	AUC_{last} (ng·h/mL)	C_{max} (ng/mL)	T_{max}[b] (h)
1	Male	2	11	10.4	2730 (1060)	2840 (1080)	1850 (1080)	1.35 (0.44)
		3	22	15.6	6580 (3950)	6680 (3960)	2620 (1120)	1.58 (0.49)
		4	44 (22 BID)	36.2	4620 (1420)	6600[c] (2150)	3150[c] (1050)	1.17[c] (0.09)
	Female	2	11	10.7	4200 (910)	4330 (902)	3200 (1420)	1.31 (0.46)
		3	22	16.4	4770 (729)	4910 (735)	3020 (1200)	1.17 (0.10)
		4	44 (22 BID)	29.8	3920 (1220)	6630[c] (1550)	2300[c] (657)	5.07[c] (4.31)
28	Male	2	11	17.8	3370 (830)	3510 (851)	2490 (975)	1.21 (0.09)
		3	22	26.8	6700 (1350)	6870 (1360)	4540 (1580)	1.12 (0.09)
		4	44 (22 BID)	56.8	7760 (2900)	9400[c] (3130)	4040[c] (1560)	1.19[c] (0.09)
	Female	2	11	17.4	3940 (624)	4080 (622)	2870 (1040)	1.21 (0.09)
		3	22	27.7	8020 (1390)	8210 (1400)	4420 (2350)	1.35 (0.44)
		4	44 (22 BID)	55.9	6290 (1750)	8220[c] (2790)	3030[c] (834)	1.17[c] (0.09)

[a]Levodopa dose is 90% of the CVT-301 dose
[b]From the start of the inhalation dose period (1 hour)
[c]Kinetic sampling for Group 4 taken following first daily dosing period. Therefore, AUC_{last} for Group 4 animals includes exposure derived from the second dosing period.

Reference ID: 4367298

6.2.6 28-day study of DPPC in rat

Study title: 28-day inhalation dose study of DPPC in rats with a 14-day recovery period

Study no.:	AIRT-00-09 to
Study report location:	eCTD 4.2.3.7.7
Conducting laboratory and location:	(b) (4) 43201-2693
Date of study initiation:	FEB 1, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) /L1043/99.7%

Key Study Findings:

- The NOAEL was at the HD (20 mg/kg/day).
  - Toxicokinetics were not assessed.

Methods

Doses:	0, 2, 6, 20 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Nose only
Dose volume:	N/A
Formulation/Vehicle:	Air
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	12 + 6/sex recovery - C and HD
Age:	7 weeks of age
Weight:	M: 187.9-263.1 g; F: 133.2-203.6 g
Satellite groups:	N/A
Unique study design:	Estimated delivered dose (see below)
Deviation from study protocol:	Minor, with no impact on data.

Experimental design:

Sponsor's table: target dose

Reference ID: 4367298

Group Number	Target Exposure Time (minutes)	Target Total Aerosol Mass Concentration[a] (µg/L)	Target Inhaled Dose[b] (mg/kg/day)	Number of Rats	
				Core Tox	Recovery Subgroup
1-Air Control	360	0	0	12/sex	6/sex
2-Low Dose	40	112	2	12/sex	--
3-Mid Dose	120	112	6	12/sex	--
4-High Dose	360	112	20	12/sex	6/sex

a. Calculated on the basis of a 0.125 L/minute volume and a 250 g rat. Actual values for aerosol concentration and body weights were used in the calculation of the inhaled dose and may not reflect values listed in the table.

b. Target Inhaled Doses were provided by the Sponsor.

Sponsor's table: Estimated delivered dose and percent of target

Dose Exposure Group	Target Exposure Time (min/day)	Total Estimated Mass Inhaled (mg/kg/day)		% of Targeted Inhaled Dose	
		Male	Female	Male	Female
1-Air Control	360	0.0	0.0	100	100
2-Low Dose	40	2.4	3.6	120	180
3-Mid Dose	120	6.8	10.3	113	172
4-High Dose	360	24.6	36.6	123	183

Observations and Results

Mortality:
None
Clinical Signs:
No test article-related effects on clinical signs, body weights, ophthalmoscopic exam, hematology, clinical chemistry, urinalysis, macroscopic pathology, or organ weights were reported.
Food Consumption:
No test article related effects were reported. An increase in food consumption in LDF was attributed to shorter exposure times in that group.
Histopathology:
Signed and dated pathology report: Yes
Adequate Battery: Yes
Peer Review: Yes -Staff pathologist
Histological Findings: No test article-related findings were reported.
Toxicokinetics:
N/A Toxicokinetics of the test article were not evaluated.

Reference ID: 4367298

6.2.6 28-day study of DPPC in dog

Study title: 28-day inhalation dose study of DPPC in dogs with a 14-day recovery period.

Study no.:	AIRT-00-10
Study report location:	eCTD 4.2.3.7.7
Conducting laboratory and location:	(b) (4) 43201-2693
Date of study initiation:	FEB 28, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)/ L1043/99.7%

Key Study Findings:

- Nonspecific pulmonary histopathologic changes, attributable to the physical presence of particulate matter, were seen in all groups.
- The NOAEL was the HD.
- Toxicokinetics were not assessed.

Methods

Doses:	0, 2, 6, 29 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Head-dome inhalation
Dose volume:	N/A
Formulation/Vehicle:	Air
Species/Strain:	Beagle dog
Number/Sex/Group:	5/sex + 3/sex HD and C recovery
Age:	6-8 months
Weight:	6.9-13.9 kg
Satellite groups:	N/A
Unique study design:	Estimated delivered dose
Deviation from study protocol:	Minor, with no impact on study data

Experimental design:

Sponsor's table:

Group Number	Exposure Duration (min)	Target Aerosol Concentration (mg/L)	Target Daily Inhaled Dose (mg/kg)	Number of Dogs	
				Day 29 Necropsy	Day 43 Necropsy
1 – Air Control	60	0	0	5/sex	3/sex
2 – Low Dose	8	1.1	2	5/sex	0
3 – Mid Dose	20	1.1	6	5/sex	0
4 – High Dose	60	1.1	20	5/sex	3/sex

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Sponsor's table: Estimated delivered dose

Target Daily Inhaled Dose (mg/kg)	Exposure Duration (min)	Estimated Total Mass Inhaled Dose (mg/kg/day)	
		Males	Females
0	60	0	0
2	8	3	3
6	20	7	7
20	60	20	18

Observations and Results

Mortality:
None
Clinical Signs:
No test article-related effects on clinical signs, body weights, food consumption, ophthalmoscopic exam, respiratory dosimetry (respiratory rate, tidal volume and minute volume), ECG, hematology, clinical chemistry, urinalysis, or organ weights were reported.

Gross Pathology;
Two pulmonary foci in one HDM, and a pulmonary nodule in one LDM and one HDF. Relationship of these possible background lesions to test article was considered to be equivocal.
Histopathology:
Signed and dated pathology report: Yes
Adequate Battery: Yes
Peer Review: Yes (Staff pathologist)
Histological Findings:

- Pulmonary macrophage aggregates: 2/5CM, 3/5 LDM, 3/5 MDM, and 5/5 HDM: A common background lesion that is also considered to be a non-specific response to inhaled particulates. That the finding was limited to M was not explained.
- Focal squamous metaplasia and hyperplasia at the carina was considered to be a nonspecific response to the impact of inhaled particulates. Squamous metaplasia was present after recovery and in greater incidence in HDM.
- Idiopathic canine polyarteritis in one HDM was not considered to be test article related.

Reference ID: 4367298

Sponsor's table:

TEXT TABLE A. MICROSCOPIC LESIONS WITH DPPC DOSE-RESPONSIVE INCIDENCE TRENDS AT INTERIM SACRIFICE: INCIDENCES IN INTERIM SACRIFICE (POST-EXPOSURE) ANIMALS

ORGAN/Diagnosis	dose (mg/kg/day)	Males				Females			
LUNG									
Macrophage accumulation, alveolar	minimal	1	3	3	4	3	1	2	2
	mild	1	0	0	1	0	0	0	1
	total affected	2	3	3	5	3	1	2	3
	(average severity[a])	(0.6)	(0.6)	(0.6)	(1.2)	(0.6)	(0.2)	(0.4)	(0.8)
TRACHEA									
Squamous metaplasia	minimal	1	2	2	1	1	3	2	1
	mild	0	0	0	1	0	0	0	0
	total affected	1	2	2	2	1	3	2	1
	(average severity)	(0.2)	(0.4)	(0.4)	(0.6)	(0.2)	(0.6)	(0.4)	(0.2)
Hyperplasia, respiratory epithelium	minimal	1	0	1	1	0	2	1	0
	mild	0	0	0	0	0	0	0	1
	total affected	1	0	1	1	0	2	1	1
	(average severity)	(0.2)	(0.0)	(0.2)	(0.2)	(0.0)	(0.4)	(0.2)	(0.4)

[a]Average severities were calculated by summing the severity grades for all the animals within a treatment group and dividing by the number of animals in the group.

Sponsor's table:

TEXT TABLE B. MICROSCOPIC LESIONS WITH DPPC DOSE-RESPONSIVE INCIDENCE TRENDS AT INTERIM SACRIFICE: INCIDENCES IN FINAL SACRIFICE (RECOVERY) ANIMALS

ORGAN/Diagnosis	dose (mg/kg/day)	Males				Females			
LUNG									
Macrophage accumulation, alveolar	minimal	1			2	0			0
	mild	0			0	0			0
	total affected	1			2	0			0
	(average severity[a])	(0.3)			(0.7)	(0.0)			(0.0)
TRACHEA									
Squamous metaplasia	minimal	1			2	2			3
	mild	0			0	0			0
	total affected	1			2	2			3
	(average severity)	(0.3)			(0.7)	(0.7)			(1.0)
Hyperplasia, respiratory epithelium	minimal	0			1	2			0
	mild	0			0	0			0
	total affected	0			1	2			0
	(average severity)	(0.0)			(0.3)	(0.7)			(0.0)

[a]Average severities were calculated by summing the severity grades for all the animals within a treatment group and dividing by the number of animals in the group.

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7 Genetic Toxicology

7.1 DEREK report for DPPC

Sponsor's text: Results of *in silico* structural analysis

- **Mutagenicity in vitro in bacterium is INACTIVE**
  - No misclassified or unclassified features
- **Mutagenicity in vitro in Escherichia coli is INACTIVE**
  - No misclassified or unclassified features
- **Mutagenicity in vitro in Salmonella typhimurium is INACTIVE**
  - No misclassified or unclassified features

Reference ID: 4367298

8.0 Integrated Summary and Safety Evaluation

CVT-301/Inbrija® (levodopa inhalation powder) is a dry powder formulation of levodopa (LD) developed for oral inhalation for treatment of symptoms of OFF periods in Parkinson's disease (PD) as an adjunct to a carbidopa/levodopa regimen. Under Section 505(b)(2), this NDA relies on the findings of safety and effectiveness of the listed drug, Sinemet® IR LD/CD oral tablets (NDA 017555).

The clinical product is a dry powder administered by oral inhalation of the contents of two 42 mg powder-filled capsules (84 mg). The capsules are inserted into a proprietary breath-activated device, which punctures the capsules, and from which the patient orally inhales the contents. The doses may be repeated up to 5 times a day as needed, with a maximum daily dose of inhaled drug substance of 420 mg.

The drug product contains (b) (4) percent levodopa powder, (b) (4) percent dipalmitoyl phosphocholine (DPPC) and (b) (4) percent NaCl. Three process impurities that, according to the manufacturer's DMF for levodopa (LoA provided), do not exceed (b) (4) % were evaluated in silico and found to be negative for mutagenicity. There are no novel excipients and inhaled DPPC was evaluated in rat and dog toxicology studies (see below). Nine packaging leachates were assessed comparing the RfD (the daily Reference Dose at which lifetime exposure would not be associated with increased risk of adverse events) to daily exposures, calculated at slightly greater than the MRHD, and were found to be of no toxicologic concern.

The pharmacokinetics profile of levodopa was determined after administration to rat by individual intratracheal puffs and to dog by 60-90 minutes of inhalation. When compared to intravenous or oral administration of 2 mg of LD to rats, the C_{max} from 2 mg intratracheal LD was less than that resulting from intravenous bolus but was greater than that seen from oral administration. Within ~ 20 minutes of dosing, circulating levels were similar after intravenous and intratracheal administration and over the next 1-2 hours the levels of levodopa from either route remained greater than after oral administration.

In a Parkinsonian model of 6-OHDA-lesioned rats, 2 mg of intratracheal LD resulted in a more rapid and longer-lasting ameliorative response (increased rotations) when compared to oral administration of 30 mg of LD. The number of rotations peaked within 15 minutes and remained relatively stable through two hours post-dose. In contrast, rotations resulting from orally administered LD peaked at 25-35 minutes and then diminished through the observation period of two hours post-dose.

In a safety pharmacology study of CV-301, no test article-related functional effects on either the cardiovascular or respiratory system were seen in awake telemetered M Beagle dogs. Two single inhalation doses, 3 days apart, of 7.5 mg/kg of CVT-301 (achieved dose of 10.5 or 9.0 mg/kg) resulted in no observed differences from air controls.

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In single-dose inhalation studies, rats, dogs and monkeys were administered “AIR-L-Dopa,” which consisted of 50% (by weight) LD. In 3/sex SD rats, intrabronchial delivery of 0, 5, 10, or 20 mg/kg of “AIR-L-Dopa” in 3 mL pulses resulted in death (in C, LD and HD), pulmonary rales from 5 minutes post-dose through Study Day 2 (in C, LD and HD M and F), and histologic evidence of tracheitis and pulmonary inflammation in all groups. The manufacturer of the delivery device stated that the “air pulses should not exceed 2 mL per pulse” and the mortality and inflammatory changes were likely a result of faulty administration technique and excessive dose volumes.

In a single dose inhalation study in 6/sex anesthetized Beagle dogs (3/sex telemetered), “AIR-L-Dopa” (0, 50, 100 mg) was puffed by the sponsor’s proprietary clinical device through an endotracheal tube to the animals’ lungs. Telemetered animals were euthanized 24 hours post-dose; the remainder were euthanized 14 days post-dose. Emesis, seen in all groups, was attributed to the anesthesia. Soft/mucoid feces were limited to dosed groups and diarrhea was seen in one HDF through Study Day 15. At necropsy 24 hours post-dose, a dose-related hypertrophy of respiratory and bronchiolar epithelium was seen in HD. After 14 days, slight bronchiolar epithelial hypertrophy and inflammatory cells were seen in the HD and in LD at a lower frequency and severity.

In a single dose inhalation study in anesthetized cynomolgus monkeys, “AIR-L-Dopa” or air (C) was delivered via an endotracheal tube to 4 CM, 5 CF, 5 M (22 mg/kg) and 4 F (23.7 mg/kg). At 24 hours post-dose, changes compatible with endotracheal intubation were seen in both C and dosed animals. Histologic changes consisted of acute alveolar and bronchial/bronchiolar inflammation, laryngeal inflammation, and tracheal epithelial erosions. A similar pattern of histologic change, in reduced incidence, was seen 14 days post-dose.

In multiple dose studies of CVT-301 for 7, 28 and 56 days in rats and 7 and 28 days in dogs, after pre-dosing with carbidopa, CVT-301 was administered by inhalation. In a non-GLP 7-day study in 5/sex SD rats. the achieved high dose of 127.9 mg/kg/day was found to be the NOAEL. Test article-related effects were limited to minimal acute intra-alveolar hemorrhages and focal to multifocal nasal epithelial degeneration.

After 28 days of 60-minute daily nose-only inhalation administration of CVT-301 to 10/sex SD rats, the NOAEL was at the achieved HD of 114.5 mg/kg/day CVT-30 (103.1 mg/kg/day LD). Clinical chemistry changes, compared to C, were limited to a reduction in ALT in all M and F groups and a dose-related reduction in mean triglycerides in all dosed M groups. Minimal to slight squamous metaplasia in the larynx were seen in all groups. The highest incidence was noted in MDM and HDF, but there was little difference from C in other groups. These histologic changes are compatible with background and no test-article related effects were recorded.

After 6 months of 90-minute daily nose-only inhalation administration of CVT-301 to rats at 0, 120, or 180 mg/kg/day, the NOAEL for pulmonary effects was at the achieved HD of 168 (M) and 174 (F) mg/kg/day. Histologic changes were limited to minimal-to-slight amounts of brown pigment (compatible with test article), intraluminal neutrophils and

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minimal epithelial erosion, and hyperplasia and squamous change in the nose/turbinates of MDM and F and HDM. No test article-related effects were seen in trachea or lung.

In a non-GLP study in Beagle dogs (2/sex), CVT-301 was administered by face mask for 60 minutes once daily at 0, 5.5, 12.5, 20, or twice daily at 12.5 mg/kg. Emesis was seen at all doses and was dose-limiting at greater than the MTD of 20 mg/kg (achieved dose of 18.4 mg/kg/day). No in-life, macroscopic, or microscopic test article-related effects were seen.

Beagle dogs (4/sex plus 2/sex C and HD recovery) were administered QD 0, 11, or 22 mg/kg or BID 22 mg/kg of CVT-301 through oronasal (face mask) delivery for 28 days. Emesis was seen at all doses and ALT was reduced from baseline and as compared to C in all dosed groups. No other in-life, macroscopic, or microscopic test article-related effects were seen.

The excipient DPPC is approved for acute intratracheal administration to infants at levels of 763 mg/kg. As an excipient in CVT-301, DPPC levels would be up to 33.6 mg/day with chronic administration to adults. Although the DEREK report for DPPC indicated the compound was not predicted to be mutagenic, *in vitro* tests for mutagenicity were not provided. Because DPPC is a natural component of human pulmonary surfactant, further mutagenicity testing is not found to be necessary.

In toxicity studies of DPPC, 28 days of nose-only administration to SD rats (12/sex+6/sex recovery) at 0, 2, 6, or 20 mg/kg/day resulted in no in-life, macroscopic or microscopic test article related findings.

After 28 days of head-dome inhalation by Beagle dogs (5/sex plus 3/sex C and HD recovery) at 0, 2, 6, 29 mg/kg/day, there were no in-life or macroscopic test article-related findings. Microscopic evidence of particle inhalation was seen in all M dosed groups and changes at the carina (squamous metaplasia and hyperplasia) were attributed to the physical effects of particulate matter.

Interspecies conversion of inhaled drugs assumes that 1) in human, 100% of the achieved dose is deposited in the lungs, 2) in rat 10% of the achieved dose is deposited in lung, and 3) in dog 25% of the achieved dose is deposited. The assumed body weights are 0.3 kg in rat, 10 kg in dog and 60 kg in human and lung weights are 1.5g in rat, 110g in dog and 1000g in human.

Based on 90% content in CVT-301, the margin to the MRHD of levodopa was 7-fold in rat and 2-fold in dog. In the absence of histologic or macroscopic alveolar changes attributed to the drug substance, the margin in dog is minimal but acceptable. In the dedicated DPPC studies, the margin to DPPC at the MRHD was 14-fold (M) and 20-fold (F) in rat, and 12-fold (M) and 11-fold (F) in dog. Based on an 8% content in CVT-30, in the 6-month rat and 28-day dog CVT-301 studies, the margin to DPPC at the MRHD

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was 7-fold in rat and 2-fold in dog. There was no evidence of pulmonary changes, DPPC is a normal component of pulmonary surfactant, and these are sufficient.

Table: Safety Margins of the NOAEL to MRHD for Levodopa and excipient DPPC

Human: MRHD=420 mg/day levodopa. Mg/g of lung weight: 0.42 mg/g						
Study	**Species**	**Achieved dose at the NOAEL (mg/kg/day)**	**Deposited achieved dose (mg/kg/day)**	**Total delivered to lung (mg)**	**Mg/g deposited in lung**	**Margin to MRHD**
6-month	Rat	168 X 0.9=151	15.1	4.53	3.02	7
28-day	Dog	45.6 X 0.9= 41	10.3	102.6	0.93	2
Human MRHD = 37 mg/day DPPC, Mg/g of lung weight: 0.037						
28-day DPPC	Rat M	24.6	2.5	0.75	0.5	14
28-day DPPC	Rat F	36.6	3.7	1.11	0.74	20
28-day DPPC	Dog M	20	5	50	0.45	12
28-day DPPC	Dog F	18	4.5	45	0.41	11
6-month CVT-301	Rat	168 X 0.08 = 13.44	1.3	0.40	0.268	7
28-day CVT-301	Dog	45.6 X 0.08= 3.65	0.9	9	0.083	2

In summary, in rat and dog, aside from emesis in dog, one to six months of exposure to inhaled CVT-301 resulted in minimal clinical signs, little-to-no relevant clinical pathology, or macroscopic changes. Thorough in-life and post mortem examinations showed only minimal to slight histologic changes in upper and lower respiratory tracts and those were largely attributable to administrative procedures, with no adverse test article-related effects. The studies were of sufficient duration to support safety in chronic administration and, although the no adverse effect level in rat and dog were at the HD, those doses exceeded the recommended maximal human dose.

No impurities or leachables were found to be of toxicologic concern and inhalation studies of the excipient DPPC - at clinically anticipated levels - resulted in no differences from controls in either rat or dog.

From a nonclinical perspective, this application is approvable.

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/s/

LUANN MCKINNEY
12/21/2018

LOIS M FREED
12/21/2018

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: December 21, 2018
From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist
Subject: NDA 209-184 (Inbrija; levodopa oral inhalation powder; CVT-301)

NDA 209-184 was submitted by Acorda Therapeutics, Inc. for CVT-301 for the "treatment of symptoms of OFF periods in Parkinson's disease as an adjunct to a carbidopa/levodopa regimen." The NDA was submitted under 505(b)(2), with Sinemet (carbidopa/levodopa oral tablet) as the listed drug. Clinical development was conducted under IND 115750 by Civitas Therapeutics, Inc. ("now a wholly owned subsidiary of Acorda") and Acorda (change in contact, June 12, 2015).

CVT-301 contains (b)(4)% levodopa, (b)(4)% dipalmitoyl phosphatidylcholine (DPPC), and (b)(4)% sodium chloride and is to b delivered by a "capsule-based, breath-actuated inhaler." Nonclinical studies to support the new route and drug formulation and the NDA consist of the following:

- Cardiovascular/respiratory safety pharmacology study in dog
- 7- and 28-day inhalation toxicity studies in rat and dog and a 6-month inhalation study in rat.
- Evaluation of drug substance impurities and extractables/leachables from the device components

These studies were reviewed by Dr. McKinney (Pharmacology/Toxicology NDA Review and Evaluation, NDA 209184, LuAnn McKinney, DVM, December 21, 2018). Based on the review, Dr. McKinney has concluded that the nonclinical data support approval of the NDA.

The following provides a brief summary of selected nonclinical data for CVT-301.

Pharmacology and PK/ADME

The pharmacology of levodopa is well-understood. The sponsor conducted one primary pharmacology study to assess the effects of "a pulmonary form of L-Dopa" in an animal model of Parkinson's disease (6-OHDA lesioned rat). The sponsor reported evidence of efficacy in this study; however, it does not appear that CVT-301 was tested. The sponsor conducted a GLP cardiovascular/respiratory safety pharmacology study (doses of 0 and 7.5 mg/kg CVT-301 by oronasal inhalation) in Beagle dog (5 M); no effects on safety parameters were reported. No

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PK/ADME studies were conducted; plasma levodopa exposures were quantitated in the pivotal toxicity studies.

Toxicology
CVT-301 was not assessed in acute-dose toxicity studies.

Seven-day (non-GLP) dose-ranging and 28-day (GLP) inhalation toxicity studies of CVT-301 were conducted in Sprague Dawley rat and Beagle dog. Chronic (6-month GLP) inhalation toxicity was assessed only in Sprague Dawley rat.

Rat: In the 7-day study (5/sex/group; 6/sex/group for TK), CVT-301 was administered by nose-only inhalation at doses of 0, 11, 60.5, and 121 mg/kg QD and 60.5 mg/kg BID (121 mg/kg/day); corresponding levodopa doses were 0, 10, 55, and 110 mg/kg QD and 55 mg/kg BID (110 mg/kg/day). Carbidopa (30 mg/kg PO) was administered to all animals prior to inhalation dosing. The primary drug-related findings consisted of degeneration in the nasal turbinates (olfactory epithelium) and intra-alveolar hemorrhage at doses of 77.2 mg/kg/day and above. Based on the minimal severity of the findings, the sponsor considered all doses well-tolerated.

In the 28-day study (10/sex/group; 5/sex C and HD for a 21-day recovery; 3/sex C and 6/sex/dose group for TK), CVT-301 was administered by nose-only inhalation at doses of 0, 11, 60.5, and 121 mg/kg/day (levodopa doses of 0, 14.1, 59.0, and 114.5 mg/kg/day). Groups administered CVT-301 received carbidopa (30 mg/kg/day PO) within 60 min of initiation of inhalation dosing. There were no drug-related findings. According to the study pathologist, "All microscopic findings…are considered incidental and not related to test article…"

In the 6-month study (8-10/sex/group; 5/sex for C, LD, and HD for 1-month recovery; 3/sex C and LD and 9/sex MD and HD for TK), CVT-301 was administered by nose-only inhalation at doses of 0 (air), 40, 120, and 180 mg/kg/day; a separate group received excipient (18 mg/kg/day DPPC/NaCl) only. Groups administered CVT-301 received carbidopa (30 mg/kg/day PO) ~60 min prior to initiation of inhalation dosing. The primary drug-related findings were microscopic changes in nose/turbinates and the tracheal bifurcation (summarized below); none of the findings in nose/turbinates was detected with air only (Group 1), excipient only (Group 2), or at the low dose, in males or females.

TRACHAEL BIFURCATION FINDING	**MALES**					**FEMALES**				
	DOSES (mg/kg/day)*									
	0	**18#**	**40**	**120**	**180**	**0**	**18#**	**40**	**120**	**180**
loss of cilia/epithelial thinning										
minimal	4/10	1/10	1/9	3/10	1/10	1/10	3/10	1/9	2/10	2/10
slight	0/10	0/10	0/9	1/10	0/10	0/10	0/10	1/9	2/10	2/10
total	**4/10**	**1/10**	**1/9**	**4/10**	**4/10**	**2/10**	**3/10**	**2/9**	**4/10**	**4/10**

*levodopa doses of 0, 36, 108, and 162 mg/kg; achieved CVT-301 doses calculated to be 0, 19 (#DPPC only), 40, 119, and 174 mg/kg/day

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NOSE/TURBINATE FINDINGS	MALES		FEMALE	
	DOSES (mg/kg/day)*			
	120	180	120	180
pigment, lumen				
slight	4/10	2/10	2/10	0/10
moderate	1/10	0/10	0/10	0/10
total	**5/10**	**2/10**	**2/10**	**0/10**
inflammatory cells, lumen				
minimal	3/10	1/10	0/10	0/10
slight	2/10	1/10	2/10	0/10
total	**5/10**	**2/10**	**2/10**	**0/10**
inflammation, respiratory epithelium/mucosa				
minimal	2/10	1/10	0/10	0/10
slight	0/10	1/10	2/10	0/10
total	**2/10**	**2/10**	**2/10**	**0/10**
hyperplasia, respiratory epithelium				
minimal	1/10	2/10	0/10	0/10
slight	0/10	0/10	1/10	0/10
total	**1/10**	**2/10**	**1/10**	**0/10**
squamous metaplasia, respiratory epithelium				
minimal	2/10	1/10	1/10	0/10
slight	0/10	0/10	1/10	0/10
total	**2/10**	**1/10**	**2/10**	**0/10**
erosion/ulcer, respiratory epithelium, minimal	**1/10**	**0/10**	**1/10**	**0/10**

*levodopa doses of 108 and 162 mg/kg/day; achieved CVT-301 doses calculated to be 119 and 174 mg/kg/day

The toxicokinetic data for levodopa are summarized in the following table.

SAMPLING DAY	DOSE* (mg/kg/day)	MALES		FEMALES	
		C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{last} (ng*hr/mL)
1	40	7330	19000	6030	11100
	120	22200	61900	17000	48200
	180	23800	77800	23200	72700
90	40	2830	6970	3590	7270
	120	5340	12900	9150	20600
	180	8990	24900	6320	20400
180	40	4020	10800	4980	10100
	120	6020	17300	11800	26700
	180	9000	19200	8990	33600

*levodopa doses of 0, 36, 108, and 162 mg/kg; achieved CVT-301 doses calculated to be 40, 119, and 174 mg/kg/day

Dog: In the 7-day study (2/sex/group), CVT-301 was to be administered by oronasal inhalation at doses of 0 (air), 5.5, 27.5, 27.5 BID, and 55 mg/kg/day for up to 7 days; however, because of emesis, doses were lowered on Day 2 to 0, 5.5, 20, 12.5 BID, and 12.5 mg/kg/day. (At the lower doses, the corresponding levodopa doses were 0, 5, 18, 22.5, and 11 mg/kg/day.) Carbidopa (25 mg PO) was administered within 60 min of initiation of inhalation dosing. Emesis, a known effect of levodopa in dog, continued to be observed at all doses. No other drug-related effects were reported.

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In the 28-day study (4/sex/group; 2/sex C and HD for 21-day recovery; 4-6/sex/group for TK), CVT-301 was administered by oronasal inhalation at doses of 0, 11, 22, and 44 (22 BID) mg/kg/day. Corresponding levodopa doses were 0, 10, 20, and 40 mg/kg/day. Emesis occurred at all doses; however, tolerance developed and there were no effects on overall body weight. No other drug-related findings were observed. Plasma levodopa exposures (M-F) on Day 28 at the HD were 4040-3030 ng/mL for C_{max} and 7760-6290 and 9400-8220 ng*hr/mL for $AUC_{(0\text{-}6\ hr)}$ and AUC_{last}, respectively.

In humans, plasma AUC following a single 84-mg (2x 42 mg) orally inhaled dose was 1630 ng*hr/mL, or by calculation 8150 ng*hr/mL for the maximum recommended daily dose of 5x 84 mg (420 mg levodopa/day; 492 mg CVT-301/day).

In addition to the toxicity studies of CVT-301, the sponsor provided reports for 28-day (GLP) inhalation studies of DPPC alone (28-day study in rat [0 (air), 2, 6, and 20 mg/kg/day DPPC] and dog [0 (air), 2, 6, and 20 mg/kg/day]) and a summary of other information on DPPC (Toxicology Written Summary). According to the sponsor, "the total amount of [endogenous] DPPC in the alveolar regions of the lungs can be estimated to be as much as 4 g." At the maximum recommended daily dose of CVT-301 in humans, the daily exposure to DPPC is estimated to be ~39 mg. In addition, the sponsor notes that "…synthetic DPPC is processed and utilized similarly to endogenous DPPC, with similar turnover times and half-lives" (Jacobs H et al. Biochim Biophys Acta 257(4):1805-1810, 1982; 793:300-309, 1984; 837:77-84, 1985), although the referenced studies were conducted by the same laboratory and only in rabbit.

Reproductive and Developmental Toxicology

No studies were conducted by the sponsor, based on reliance on the listed drug labeling.

Genetic Toxicology/Impurities/Leachables/Extractables

No in vitro or in vivo studies were conducted by the sponsor. However, three process impurities, (b) (4) were identified. According to the sponsor, "The actual level of these impurities are each not more than (b) (4)% in the final drug substance at release or on stability," which is below the qualification threshold. The sponsor conducted a QSAR evaluation using rule-based (DEREK) and statistical-based (Leadscope Model Applier) models. All three impurities were negative for bacterial mutagenicity with both models.

The sponsor's analysis of drug-device compatibility identified no leachables or extractables of toxicologic concern.

Carcinogenicity

No studies were conducted by the sponsor, based on reliance on the listed drug labeling and the minimal CVT-301-related microscopic findings observed in the 6-month inhalation study in rat.

Conclusions and Recommendations

The battery of nonclinical studies conducted by the sponsor is generally consistent with recommendations made by the Division during clinical development (see Meeting Minutes,

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dated December 26, 2012, August 7, 2014, and October 27, 2016) and with relevant guidance. The highest doses tested in the toxicity studies do not provide a safety margin compared to the maximum recommended human dose (MRHD) of 420 mg/day, based on systemic levodopa exposure; however, the systemic effects of levodopa are well-known in animals and humans. Calculated lung levodopa and DPPC exposures (mg/g lung) achieved at the highest dose of CVT-301 (and the dose of DPPC in the vehicle control) tested in the 6-month inhalation toxicity study in rat are ~7-8 times those at the MRHD, which provides a minimally acceptable evaluation of local toxicity.

Overall, the nonclinical data submitted are adequate to support approval of the NDA.

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/s/

LOIS M FREED
12/21/2018