CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209184
Drug Name:	CVT-301 (Inbrija)
Indication(s):	(b) (4) intermittent treatment of OFF-period symptoms in patients with Parkinson's disease as an adjunct to a stable carbidopa and levodopa Parkinson's medication regimen
Applicant:	Acorda Therapeutics
Date(s):	Submitted on 12/5/2017 and PDUFA due date of 10/5/2018
Review Priority:	Standard
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Key Words:	MMRM, CMH test, MNAR, fixed sequential testing

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1. EXECUTIVE SUMMARY

This NDA submission contains one confirmatory clinical trial with a prospective, multi-center, double-blind, parallel group, placebo controlled, randomized study design to confirm the efficacy and safety of the study drug CVT-301 indicated for as-needed rapid relief treatment of OFF-state symptoms in adult patients with Parkinson's disease as an adjunct to a standard oral medication regimen.

The trial registered one primary efficacy endpoint and five key secondary efficacy endpoints. The trial tested statistical hypothesis on each of the five endpoints for placebo versus 84mg of CVT-301 and subsequently repeatedly tested the similar hypotheses for placebo versus 60mg of CVT-301. The 12 hypotheses were hierarchically ordered so that the fixed sequential testing method was applied to control an overall type 1 error.

This reviewer concludes that the NDA submission carries sufficient statistical evidence for study win on the primary hypothesis: difference between placebo and CVT-301 84mg in the change from pre-dose in the UPDRS part 3 motor score at 30 minutes post-dose at treatment visit 4.

A site in Poland was identified to drive large efficacy. Sensitivity analyses conducted show that the impact of the data from this site on the estimated treatment difference is limited in voiding the primary study result. An additional sensitivity analysis assessing the impact of violation of a missing data pattern assumption of the primary statistical method (MMRM) on the estimated treatment difference was conducted and shows that the primary study result holds.

2. INTRODUCTION

2.1. Overview

This NDA submission, resubmitted on 12/5/2017 after refused to file due to CMC-related issues, seeks the agency's approval of the study drug CVT-301 (proposed brand name Inbrija) indicated for as-needed rapid relief treatment of OFF-period symptoms in adult patients with Parkinson's disease as an adjunct to a standard oral medication regimen under the 505(b)(2) regulatory pathway with a reference drug of carbidopa/levodopa first approved in NDA 17555 under the brand name Sinemet. The agency directed the submission to be reviewed on standard with the PDUFA goal date of 10/5/2018.

Orally administered levodopa is the standard of care for management of motor symptoms for Parkinson's disease (PD) patients. However, with disease progression and extended duration of treatment, the beneficial effect of levodopa starts to wear off and patients frequently exhibit the development of motor fluctuations that include potentially disabling episodic OFF-period. To avoid a slow gastrointestinal tract delivery of levodopa, CVT-301 is a dry powder formulation of LD designed for pulmonary delivery using a proprietary breath-actuated inhaler device for acute intermittent treatment of Parkinson's disease OFF-period symptoms. The device part of the submission is reviewed by CDRH.

The sponsor conducted one confirmatory clinical trial CVT-301-004 with a prospective, multi-center, double-blind, parallel group, placebo controlled, randomized study design where the first patient was enrolled in the study on 12/4/2014 and the last patient completed the study on 12/6/2016 in total 339 Parkinson's disease patients experiencing OFF-period symptoms.

Table 2.1. List of all studies included in analysis

Study #	Phase and design	Study period	# of subjects (3 arms)	Study population
CVT-301-004	Phase 3, prospective, multi-center, randomized, double-blind, parallel group, placebo controlled	12/4/2014 - 12/6/2016	Placebo: 112 DVT-301 60mg: 113 DVT-301 84mg: 114	Patients with Parkinson's disease experiencing OFF-period symptoms

During the filing review process, a site (Site 5301) in Poland was identified to drive large efficacy on the primary endpoint and was informed to the Office of Scientific Investigations (OSI) for site inspection. OSI inspection identified no significant objectionable conditions or practices at this site and the final classification code is no action indicated. The details of the site issue and sensitivity analyses to assess the impact of the site on the treatment effect is presented in Section 3.2.3.

During the review process, the sponsor's analysis of a key secondary efficacy endpoint that is statistically significant to be qualified in a label was found to use a completer set and not to control for a potential confounding variable that is included in the primary analysis. The details of the issue and a sensitivity analysis to assess the impact of use of a completer set and omission of the variable on the treatment effect is presented in Section 3.2.5.

2.2. Data Sources

The data in this submission was provided by the sponsor electronically. Documents reviewed including clinical study report, statistical analysis plan and datasets/codes analyzed can be found at \\Cdsesub1\evsprod\NDA209184\0001\m5. Specifically, the dataset for the primary efficacy endpoint is adudrs3.xpt and the dataset for the statistically significant key secondary efficacy endpoint is adfa.xpt.

3. STATISTICAL EVALUATION

3.1. Data and Analysis Quality

All data files are accessible and in the appropriate ADAM format. The definition files describing what column names in data files stand for are provided to facilitate the review. This reviewer

could reproduce the numbers in the sponsor's reports and manipulate the submitted datasets to conduct additional analyses without much additional effort.

3.2. Evaluation of Efficacy

3.2.1. Study Design, Patient Disposition, Demographic and Baseline Characteristics

In the phase 3 study CVT-301-004, 351 patients with Parkinson's disease experiencing OFF-period symptoms recruited at 52 sites the US, Canada, Poland and Spain who met inclusion/exclusion criteria in a screening process were randomized in a 1:1:1 ratio to be treated with placebo, DVT-301 60mg or DVT-301 82mg for 12 weeks when patient's treatment visit 1 (TV1, baseline), treatment visit 2 (TV2), treatment visit 3 (TV3), treatment visit 4 (TV4) occur at day 0, day 28, day 56 and day 84, respectively.

Randomization was stratified by the Hoehn and Yahr scale rating category (H&T<2.5 versus H&Y≥2.5) as measured in the ON state to balance the severity of Parkinson's disease in each group and by screening spirometry results measured by the forced expiratory volume in 1 second (FEV1<60% versus FEV1≥60%) to balance the patient's inhalation capacity of the study drug in each group. An inhalable placebo pill is identical in appearance to a CVT-301 capsule and provides a sensation associated with dry powder inhalation to maintain double-blinding.

339 out of the randomized 351 patients showed up at TV1 and took CVT-301 or placebo. Those 339 patients who received at least one dose of CVT-301 or placebo were used as the primary analysis set of this study. Their demographic and baseline characteristics are shown in Table 3.1.

Table 3.1. Demographic and baseline characteristics of the primary analysis set

Characteristics		Placebo (n=112)	CVT-301 60mg (n=113)	CVT-301 84mg (n=114)	Total (n=339)
Age	<65	55 (49%)	54 (48%)	58 (51%)	167 (49%)
	≥65	57 (51%)	59 (52%)	56 (49%)	172 (51%)
Gender	Male	86 (77%)	80 (71%)	83 (73%)	249 (74%)
	Female	26 (23%)	33 (29%)	31 (27%)	90 (26%)
Race	White	107 (95%)	107 (95%)	107(94%)	321 (95%)
	Black	0 (0%)	3 (3%)	4 (4%)	7 (2%)
	Asian	4 (4%)	0 (0%)	2 (2%)	6 (2%)
	Other	1 (1%)	3 (2%)	1 (1%)	5 (1%)
Spirometry	FEV1<60%	6 (5%)	6 (5%)	7 (6%)	19 (6%)
	FEV1≥60%	106 (95%)	107 (95%)	107 (94%)	320 (94%)
Disease severity	H&Y<2.5	74 (66%)	74 (66%)	72 (63%)	220 (65%)
	H&Y≥2.5	38 (34%)	39 (34%)	42 (37%)	119 (35%)

All patients were trained on use of the inhaler device in both ON and OFF states during a screening period. For the 12-week treatment period, patients continued their usual prescribed

standard oral Parkinson's disease medication and self-administered CVT-301 or placebo as an outpatient at home as needed up to 5 times a day when they experienced OFF-period symptoms.

For treatment visits, patients were guided to arrive at the clinic as shortly as possible after taking their standard oral Parkinson's disease medication at home to increase the likelihood that patients were in the ON state and remain in the clinic until they transitioned into an OFF state prior to inhalation of CVT-301 or placebo.

The first self-administration of a treatment drug occurred at TV1. At TV2, TV3 and TV4, efficacy was assessed at the OFF state immediately pre-dose, 10 minutes post-dose, 20 minutes post-dose, 30 minutes post-dose and 60 minutes post-dose using the Unified Parkinson's Disease Rating Scale (UPDRS) part 3 motor score which is completed by a rater after performing an interview with a patient and examination of 14 motor functions specified in the items 18 to 31 of the UPDRS Part 3 questionnaire and is calculated as the sum of the 14 item scores (ranging from 0 to 108).

Drop-out rate is modest and evenly distributed at about 15% per treatment arm. Table 3.2 shows the disposition of patients of this study with drop-out reasons.

Table 3.2. Patient disposition

	Placebo	CVT-301 60mg	CVT-301 84mg	Total
Randomized	116	115	120	351
Came at TV1 and took a dose (primary analysis set)	112 (100%)	113 (100%)	114 (100%)	339 (100%)
Came at TV2	103 (92%)	103 (91%)	109 (96%)	315 (93%)
Came at TV3	97 (87%)	99 (88%)	102 (90%)	298 (88%)
Came at TV4	97 (87%)	96 (85%)	97 (85%)	293 (86%)
Completed study	97 (87%)	96 (85%)	97 (85%)	290 (86%)
Drop-outs	15 (13%)	17 (15%)	17 (15%)	49 (15%)
Reason for drop-out				
Consent withdrawal	10	9	9	28
Adverse event	3	3	6	12
Lack of efficacy	0	1	1	2
Lost to follow-up	0	2	0	2
Other	2	2	1	5

3.2.2. Endpoints, Statistical Methodologies and Results

The confirmatory trial registered 1 primary efficacy endpoint and 5 key secondary efficacy endpoints.

- Primary efficacy endpoint: change from pre-dose in the UPDRS part 3 motor function score at 30 minutes post-dose at TV4.
- Key secondary efficacy endpoint 1: proportion of patients achieving resolution of an OFF state

to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state at 60 minutes post-dose per an examiner's assessment.
- Key secondary efficacy endpoint 2: change from pre-dose in the UPDRS part 3 motor score at 20 minutes post-dose at TV4.
- Key secondary efficacy endpoint 3: proportion of patients who improved in the Patient Global Impression of Change (PGI-C) score at TV4.
- Key secondary efficacy endpoint 4: change from baseline to TV4 in patient-recorded total daily OFF time.
- Key secondary efficacy endpoint 5: change from pre-dose in the UPDRS part 3 motor score at 10 minutes post-dose at TV4.

The 12 hypotheses, the first 6 hypotheses on the above 5 endpoints for placebo and CVT-301 84mg and the last 6 hypotheses on the same 5 endpoints for placebo and CVT-301 60mg, were hierarchically ordered and the study-wide type 1 error rate is controlled at a two-sided 5% by the fixed sequential testing method: a next statistical hypothesis is to be tested only if a previous one in the testing order is statistically significant. It is stated that ITT population defined to be all patients as randomized who received at least 1 dose of inhalable CVT-301 or placebo will be used for all analyses of efficacy endpoints.

Primary hypothesis (hypothesis 1) tests the difference between placebo and CVT-301 84mg on the primary efficacy endpoint: the change from pre-dose in the UPDRS part 3 motor score at 30 minutes post-dose at TV4.

The treatment difference between the two arms was estimated using a mixed model for repeated measurements (MMRM) with a contrast. The model uses measurements on the primary efficacy endpoint at each postbaseline visit (TV2, TV3, TV4) as the dependent variable and includes treatment group (placebo, CVT-301 60mg and CVT-301 84mg placebo), visit (TV2, TV3 and TV4), interaction between treatment group and visit, stratification variables (Hoehn and Yahr scale rating and screening FEV1 spirometry score), baseline OFF-state UPDRS part 3 score as fix-effect covariates and patients as a random-effect covariate. An unstructured covariance structure was applied for MMRM using the Kenward-Roger method for a denominator degrees of freedom calculation.

Table 3.3 shows a statistically significant treatment effect difference on the primary efficacy endpoint between placebo and CVT-301 84mg.

Table 3.3. Evaluation on the primary efficacy endpoint for placebo vs CVT-301 84mg

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-3.92
95% confidence internal	(-6.84, -1.00)
P-value	0.009

Hypothesis 2 tests the difference between placebo and CVT-301 84mg on the key efficacy endpoint 1: the proportion of patients who achieve resolution of an OFF state to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state

at 60 minutes post-dose per an examiner's assessment.

Odds ratio of the odds of responding patients in CVT-301 84mg arm compared to the odds of responding patients in placebo arm was estimated using Cochran-Mantel-Haenszel (CMH) test stratified by the stratification variables (Hoehn and Yahr scale rating and screening FEV1 spirometry score).

Table 3.4 summarizes a statistically significant treatment effect difference on the key secondary efficacy endpoint 1 between placebo and CVT-301 84mg.

Table 3.4. Evaluation on the key secondary efficacy endpoint 1 for placebo vs CVT-301 84mg

Statistics	Placebo vs CVT-301 84mg
Common odds ratio (odds in CVT-301 84mg / odds in placebo)	2.4
95% confidence internal	(1.35, 4.26)
P-value	0.003

Reviewer's note 1

The analysis set used to evaluate this key secondary efficacy endpoint 1 is a completer set of patients who came in at TV4 (n=293). CMH test stratifying variables do not include the baseline OFF-state UPDRS part 3 score, which was included as a covariate in the primary statistical method of MMRM.

Hypothesis 3 tests the difference between placebo and CVT-301 84mg on the key efficacy endpoint 2: the change from pre-dose in the UPDRS part 3 motor score at 20 minutes post-dose at TV4.

The treatment difference between the two arms was estimated using a MMRM with a contrast in a similar fashion as in the evaluation of the primary hypothesis.

Table 3.5 summarizes a statistically insignificant treatment effect difference on the key secondary efficacy endpoint 2 between placebo and CVT-301 84mg, which implies that test results of subsequent hypotheses in the hierarchical testing order is not statistically valid.

Table 3.5. Evaluation on the key secondary efficacy endpoint 2 for placebo vs CVT-301 84mg

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-2.55
95% confidence internal	(-5.22, 0.13)
P-value	0.062

Hypothesis 4 tests the difference between placebo and CVT-301 84mg on the key efficacy endpoint 3: the proportion of patients who improved (much improved, improved or a little improved) in the Patient Global Impression of Change (PGI-C) score at TV4. PGI-C score is a 7-point scale that requires a patient to rate their overall condition regarding Parkinson's disease by answering the following question: how has the addition of study drug changed your Parkinson's

disease? A patient selects 1 of the following responses: 1=much improved, 2=improved, 3=a little improved, 4=no change, 5=a little worse, 6=worse or 7=much worse. The PGI-C score was completed on arrival at the clinic in the ON state at TV2, TV3 and at TV4.

Odds ratio of the odds of improved patients in CVT-301 84mg arm compared to the odds of improved patients in placebo arm was estimated using Cochran-Mantel-Haenszel (CMH) test stratified by the stratification variables (Hoehn and Yahr scale rating and screening FEV1 spirometry score).

Table 3.6 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 3 between placebo and CVT-301 84mg. Evaluation of this hypothesis 4 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.6. Evaluation on the key secondary efficacy endpoint 3 for placebo vs CVT-301 84mg

Statistics	Placebo vs CVT-301 84mg
Common odds ratio (odds in CVT-301 84mg / odds in placebo)	2.85
95% confidence internal	(1.56, 5.13)

Hypothesis 5 tests the difference between placebo and CVT-301 84mg on the key efficacy endpoint 4: the change from baseline (TV1) to TV4 in patient-recorded total daily OFF time assessed by a patient and recorded in his/her Parkinson's disease diary for 3 consecutive days prior to clinic visits.

The OFF time difference between the two arms was estimated using a MMRM with a contrast in a similar fashion as in the evaluation of the primary hypothesis but using the baseline daily OFF time as a fixed-effect covariate in the MMRM model instead of the baseline OFF-state UPDRS part 3 score.

Table 3.7 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 4 between placebo and CVT-301 84mg. Evaluation of this hypothesis 5 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.7. Evaluation on the key secondary efficacy endpoint 4 for placebo vs CVT-301 84mg

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	0.01
95% confidence internal	(-0.55, 0.56)

Hypothesis 6 tests the difference between placebo and CVT-301 84mg on the key efficacy endpoint 5: the change from pre-dose in the UPDRS part 3 motor score at 10 minutes post-dose at TV4.

The treatment difference between the two arms was estimated using a MMRM with a contrast in

a similar fashion as in the evaluation of the primary hypothesis.

Table 3.8 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 5 between placebo and CVT-301 84mg. Evaluation of this hypothesis 6 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.8. Evaluation on the key secondary efficacy endpoint 5 for placebo vs CVT-301 84mg

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-2.26
95% confidence internal	(-4.48, -0.04)

Hypothesis 7 tests the difference placebo and CVT-301 60mg on the primary efficacy endpoint: the change from pre-dose in the UPDRS part 3 motor score at 30 minutes post-dose at TV4.

The treatment difference between the two arms was estimated using a MMRM with a contrast in a similar fashion as in the evaluation of the primary hypothesis.

Table 3.9 summarizes an analysis result of treatment effect difference on the primary efficacy endpoint between placebo and CVT-301 60mg. Evaluation of this hypothesis 7 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.9. Evaluation on the primary efficacy endpoint for placebo vs CVT-301 60mg

Statistics	Placebo vs CVT-301 60mg
Least square mean difference (mean change in CVT-301 60mg – mean change in placebo)	-3.07
95% confidence internal	(-5.99, -0.16)

Hypothesis 8 tests the difference between placebo and CVT-301 60mg on the key efficacy endpoint 1: the proportion of patients who achieve resolution of an OFF state to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state at 60 minutes post-dose per an examiner's assessment.

The treatment difference between the two arms (odds ratio of the odds of responding patients in CVT-301 60mg arm compared to the odds of responding patients in placebo arm) was estimated using the CMH test in a similar fashion as in the evaluation of the hypothesis 2.

Table 3.10 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 1 between placebo and CVT-301 60mg. Evaluation of this hypothesis 8 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.10. Evaluation on the key secondary efficacy endpoint 1 for placebo vs CVT-301 60mg

Statistics	Placebo vs CVT-301 60mg
Common odds ratio	2.25

(odds in CVT-301 60mg / odds in placebo)	
95% confidence internal	(1.26, 4.02)

Hypothesis 9 tests the difference between placebo and CVT-301 60mg on the key efficacy endpoint 2: the change from pre-dose in the UPDRS part 3 motor score at 20 minutes post-dose at TV4.

The treatment difference between the two arms was estimated using a MMRM with a contrast in a similar fashion as in the evaluation of the primary hypothesis.

Table 3.11 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 2 between placebo and CVT-301 60mg. Evaluation of this hypothesis 9 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.11. Evaluation on the key secondary efficacy endpoint 2 for placebo vs CVT-301 60mg

Statistics	Placebo vs CVT-301 60mg
Least square mean difference (mean change in CVT-301 60mg – mean change in placebo)	-1.98
95% confidence internal	(-4.65, 0.70)

Hypothesis 10 tests the difference between placebo and CVT-301 84mg on the key efficacy endpoint 3: the proportion of patients who improved (much improved, improved or a little improved) in the Patient Global Impression of Change (PGI-C) score at TV4.

The treatment difference between the two arms (odds ratio of the odds of improved patients in CVT-301 60mg arm compared to the odds of improved patients in placebo arm) was estimated using the CMH test in a similar fashion as in the evaluation of the hypothesis 4.

Table 3.12 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 3 between placebo and CVT-301 60mg. Evaluation of this hypothesis 10 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.12. Evaluation on the key secondary efficacy endpoint 3 for placebo vs CVT-301 60mg

Statistics	Placebo vs CVT-301 60mg
Common odds ratio (odds in CVT-301 60mg / odds in placebo)	1.94
95% confidence internal	(1.08, 3.46)

Hypothesis 11 tests the difference between placebo and CVT-301 60mg on the key efficacy endpoint 4: the change from baseline (TV1) to TV4 in patient-recorded total daily OFF time assessed by a patient and recorded in his/her Parkinson's disease diary for 3 consecutive days prior to clinic visits.

The treatment difference between the two arms was estimated using a MMRM with a contrast in

a similar fashion as in the evaluation of the hypothesis 5.

Table 3.13 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 4 between placebo and CVT-301 60mg. Evaluation of this hypothesis 11 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.13. Evaluation on the key secondary efficacy endpoint 4 for placebo vs CVT-301 60mg

Statistics	Placebo vs CVT-301 60mg
Least square mean difference (mean change in CVT-301 60mg – mean change in placebo)	-0.10
95% confidence internal	(-0.66, 0.46)

Hypothesis 12 tests the difference between placebo and CVT-301 60mg on the key efficacy endpoint 5: the change from pre-dose in the UPDRS part 3 motor score at 10 minutes post-dose at TV4.

The treatment difference between the two arms was estimated using a MMRM with a contrast in a similar fashion as in the evaluation of the primary hypothesis.

Table 3.14 summarizes an analysis result of treatment effect difference on the key secondary efficacy endpoint 5 between placebo and CVT-301 60mg. Evaluation of this hypothesis 12 is not statistically meaningful since the evaluation of the previous hypothesis in the hierarchical testing order was not successful so p-value is omitted.

Table 3.14. Evaluation on the key secondary efficacy endpoint 5 for placebo vs CVT-301 60mg

Statistics	Placebo vs CVT-301 60mg
Least square mean difference (mean change in CVT-301 60mg – mean change in placebo)	-0.97
95% confidence internal	(-3.19, 1.24)

3.2.3. Site Issue and Sensitivity Analyses for the Primary Hypothesis

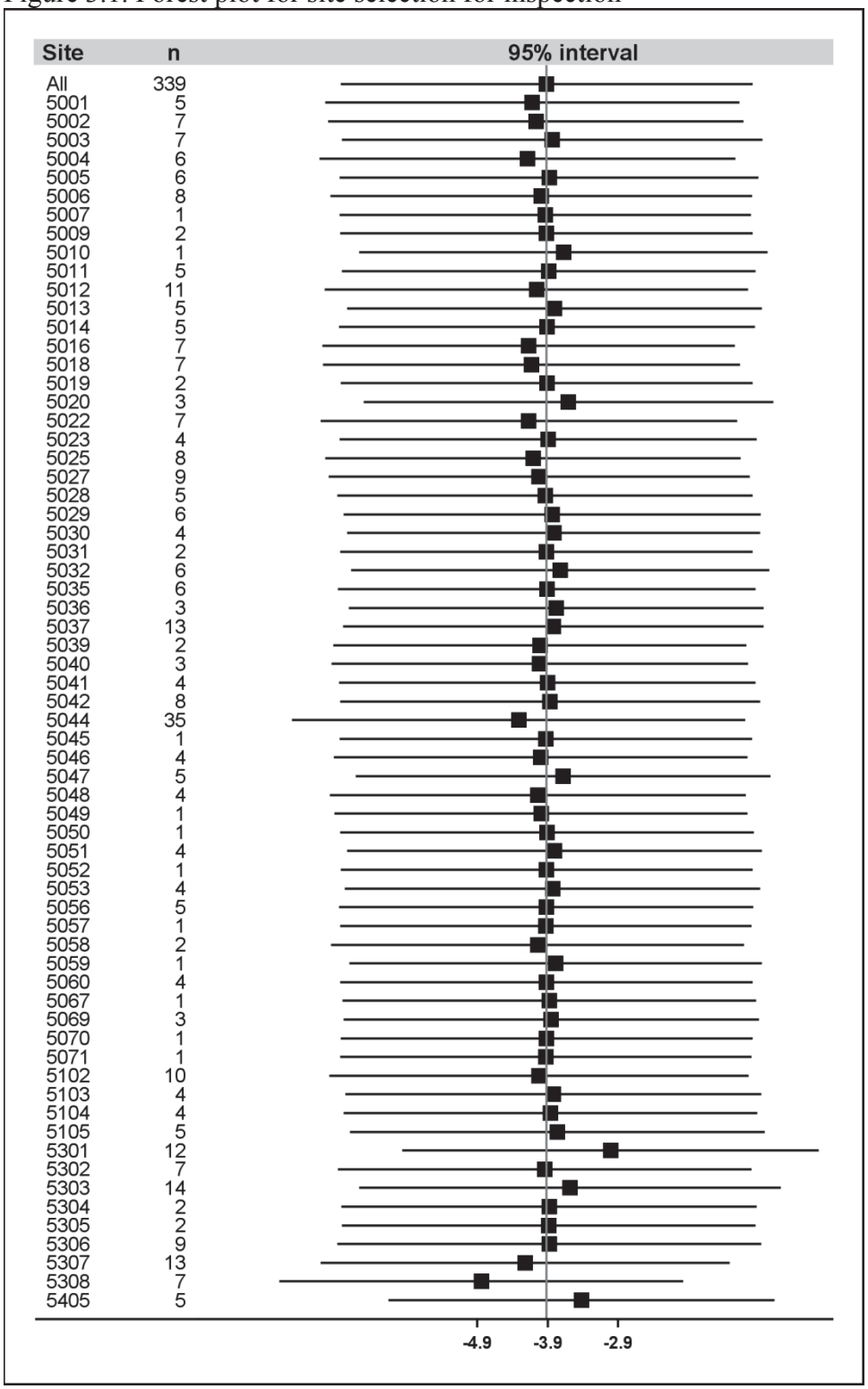
During the filing review process, Site 5301 located in Poland was identified that may have driven large efficacy in the study.

Figure 3.1 below is a forest plot made for site selection for Office of Scientific Investigation (OSI) inspection. The first row is a result from the primary analysis of data with all 52 sites included (n=339): the square indicates a point estimate (-3.92) of the difference in mean change from pre-dose in the UPDRS part 3 motor score at 30 minutes post-dose at TV4 between CVT-301 84mg and placebo and extended wings from the square indicate its 95% confidence interval with a p-value displayed on the left. From the second row are results from the primary analyses of data where observations from a site in the leftmost column were removed.

With 12 observations from site 5301 removed, the mean change difference between CVT-301 84mg and placebo decreases by -1 to -2.9 (CVT-301 84mg becoming less effective) and its p-

value 0.046 approaches the insignificant level of 5%.

Figure 3.1. Forest plot for site selection for inspection



A closer look at the data from Site 5301 indeed revealed large efficacy for patients in CVT-301 84mg arm and the best case (zero efficacy) for patients in placebo arm as shown in Table 3.15.

Table 3.15. Details of the Site 5301 data

Site	Visit	ID	Treatment arm	UPDRS score change
5301	TV4	CVT-301-004-(b) (6)	Placebo	0
		CVT-301-004-	Placebo	-12
		CVT-301-004-	Placebo	0
		CVT-301-004-	CVT-301 84mg	-20
		CVT-301-004-	CVT-301 84mg	-25
		CVT-301-004-	CVT-301 84mg	-16
		CVT-301-004-	CVT-301 84mg	-26
		CVT-301-004-	CVT-301 84mg	-25

To assess the effect of this site issue on the study result, this reviewer conducted sensitivity analyses using the pattern mixture model under two sensible missing data scenarios. Patients in Site 5301 are part of the ITT population and therefore should be considered in the primary analysis.

Sensitivity analysis under scenario 1 assumes that progression trajectories of patients in Site 5301 of Poland follows progression trajectories of patients in their respective arm in North America, which does not seem to have site issues, instead of their own region Europe, e.g., a treatment trajectory of a patient in Site 5301 assigned in a placebo arm is similar to that of a patient in a placebo arm in North America given their baseline characteristics and assessment values before dropping out.

UPDRS part 3 scores of patients in Site 5301 at TV2, TV3 and TV4 were made empty and their region information was coded to be North America. To create monotone missing data pattern, intermittent missing values were imputed using the MCMC methodology which assumes a multivariate normal distribution over all variables included in the primary analysis model (MMRM) by region. The MI procedure in SAS without a specified seed value was repeated 100 times creating 100 different datasets with a monotone missing data structure.

The remaining missing data with a monotone missing data pattern were imputed using a sequential procedure based on the MAR assumption by region. Patients with the first missing value at TV2 had their missing TV2 value replaced by an imputed value from a regression model with treatment group, stratification factors (Hoehn and Yahr scale rating and screening FEV1 spirometry score) and OFF-state baseline UPDRS part 3 score as covariates. Patients with their value missing at TV3 subsequently had their missing TV3 value replaced by an imputed value from a regression model with treatment group, stratification factors and OFF-state baseline UPDRS part 3 score and TV2 value as covariates. Similarly for replacing the missing values at TV4.

The region information of patients in Site 5301 was coded back to be European. Resulting data without missing data were used as input for the primary analysis model, producing 100 estimates

of treatment difference between placebo and CVT-301 84mg arm. the MIANALYZE procedure in SAS was applied to combine the estimates to derive an overall estimate of treatment difference for the primary efficacy endpoint.

Sensitivity analysis under the North America-based assumption provides statistically significant evidence for treatment difference between placebo and CVT-301 84mg. Table 3.16 summarizes the sensitivity analysis results.

Table 3.16. Sensitivity analysis 1 to assess the effect of the Site 5301 issue

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-3.37
95% confidence internal	(-6.32, -0.42)
P-value	0.025

Sensitivity analysis under scenario 2 assumes that progression trajectories of patients in Site 5301 follows progression trajectories of patients in their respective arm in the Europe, e.g., a treatment trajectory of a patient in Site 5301 assigned in a placebo arm is similar to that of a patient in a placebo arm in the Europe given their baseline characteristics and assessment values before dropping out from the study.

This is a harsh sensitivity analysis scenario since, as shown in Table 3.17, patients in placebo arm in Europe exhibited much greater UPDRS part 3 score reduction than patients in placebo arm in North America. Imputing the best case (zero reduction) of Site 5301 placebo patients with a big reduction pattern of European placebo patients acts against the sponsor's efficacy claim.

Table 3.17. Mean changes in UPDRS part 3 score at TV4 in North America and Europe

Region	Placebo	CVT-301 84mg
North America	-3.17	-6.30
Europe	-14.99	-19.78

Imputation and analysis procedures are similar to those in the sensitivity analysis under scenario 1 described above except that the region information of patients in Site 5301 was not coded to be US.

Sensitivity analysis under the Europe-based assumption still provides statistically significant evidence for treatment difference between placebo and CVT-301 84mg. Table 3.18 summarizes the sensitivity analysis results.

Table 3.18. Sensitivity analysis 2 to assess the effect of the Site 5301 issue

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-3.10
95% confidence internal	(-6.16, -0.03)
P-value	0.048

3.2.4. Additional Sensitivity Analysis for the Primary Hypothesis

Once it was shown that the impact of the Site 5301 issue on the primary efficacy analysis results is limited, an additional sensitivity analysis assessing the impact of violation of the missing data assumption of the primary statistical method (MAR assumption for MMRM) on the study results was conducted under an unfavorable missing data scenario where all drop-outs in either CVT-301 84mg or 60mg arm progress like patients in placebo arm after discontinuation.

Imputation and analysis procedures are similar to the pattern mixture model used in Section 3.2.2 for the sensitivity analysis assessing the impact of the Site 5301 issue except that the treatment arm information of drop-out patients was coded to be placebo before imputation and coded back to be their originally assigned treatment arm later.

Sensitivity analysis under this placebo-based assumption, as summarized in Table 3.19, provides statistically significant evidence for treatment difference between placebo and CVT-301 84mg.

Table 3.19. Sensitivity analysis to assess the effect of violation of the missing data assumption

Statistics	Placebo vs CVT-301 84mg
Least square mean difference (mean change in CVT-301 84mg – mean change in placebo)	-3.83
95% confidence internal	(-6.74, -0.94)
P-value	0.009

3.2.5. Sensitivity Analysis for the Hypothesis 2

As pointed out in Reviewer's note 1, the completer set of 293 patients who came in at TV4 was used to evaluate the hypothesis 2, the proportion of patients who achieve resolution of an OFF state to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state at 60 minutes post-dose per an examiner's assessment for placebo versus CVT-301 84mg. Moreover, the analysis method CMH test does not include as a stratifying variable the baseline OFF-state UPDRS part 3 score, which was included as a covariate in the primary statistical method of MMRM.

To overcome these deficiencies which may introduce bias into study results and incorporate the covariance structure among binary efficacy assessments in TV2, and TV3 and TV4, MMRM-based method (GLIMMIX procedure in SAS for binomial data with logic link) is applied to the ITT population. The model uses binary measurements on the key secondary efficacy endpoint 1 at each postbaseline visit (TV2, TV3, TV4) as the dependent variable and includes treatment group (placebo, CVT-301 60mg and CVT-301 84mg placebo), visit (TV2, TV3 and TV4), interaction between treatment group and visit, stratification variables (Hoehn and Yahr scale rating and screening FEV1 spirometry score), baseline OFF-state UPDRS part 3 score as fix-effect covariates and patients as a random-effect covariate. An unstructured covariance structure was applied for MMRM.

Odds ratio of the odds of responding patients in CVT-301 84mg arm compared to the odds of responding patients in placebo arm turned out statistically significant as shown in Table 3.20.

Table 3.20. Sensitivity analysis for the hypothesis 2

Statistics	Placebo vs CVT-301 84mg
Adjusted odds ratio (odds in CVT-301 84mg / odds in placebo)	2.65
95% confidence internal	(1.48, 4.75)
P-value	0.001

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1. Gender, Race, Age and Geographic Region

Since 95% of the ITT population for the primary analysis is white, a subgroup analysis for race was not conducted.

Table 4.1. Subgroup analysis for age, gender and region

Subgroup		Size	Placebo vs CVT-301 84mg, LS mean difference (95% CI)
Age	<65	167	-3.08 (-7.72, 1.56)
	≥65	172	-4.20 (-7.81, -0.59)
Gender	Female	90	-0.57 (-6.81, 5.67)
	Male	249	-4.61 (-7.95, -1.26)
Region	North America	268	-3.13 (-5.78, -0.49)
	Europe	71	-4.79 (-12.61, 3.03)

Notable is that the study drug CVT-301 84mg does not seems as effective in female Parkinson's disease patients even considering a sample size of the female subgroup is relatively small.

4.2. Other Special/Subgroup Populations

These subgroups were chosen as they were deemed as confounding factors and included in the primary statistical method (MMRM) as control variables.

Table 4.2. Subgroup analysis for other special populations

Subgroup		Size	Placebo vs CVT-301 84mg, LS mean difference (95% CI)
Hoehn & Yahr scale	<2.5	220	-2.49 (-6.13, 1.15)
	≥2.5	119	-6.66 (-11.67, -1.64)
FEV1 spirometry score	<60%	19	-7.68 (-16.25, 0.90)
	≥60%	320	-3.72 (-6.77, -0.67)
Baseline OFF-state UPDRS part 3 score	≤28	111	-3.88 (-7.88, 0.12)
	29 to 37	108	-6.69 (-10.97, -2.41)
	≥38	120	-1.55 (-8.34, 5.24)

The treatment effect of CVT-301 84mg seems larger in the subgroup with Hoehn & Yahr scale ≥ 2.5 and baseline OFF-state UPDRS part 3 score of 29 to 37.

5. CONCLUSIONS

This reviewer concludes that the NDA submission carries sufficient statistical evidence for study win on the primary hypothesis: difference between placebo and CVT-301 84mg in the change from pre-dose in the UPDRS part 3 motor score at 30 minutes post-dose at treatment visit 4.

A site in Poland was identified to drive large efficacy. Sensitivity analyses conducted show that the impact of the data from this site on the estimated treatment difference is limited in voiding the primary study result. An additional sensitivity analysis assessing the impact of violation of a missing data pattern assumption of the primary statistical method (MMRM) on the estimated treatment difference was conducted and shows that the primary study result holds.

This reviewer concludes that the NDA submission carries sufficient statistical evidence for win on the secondary hypothesis: difference between placebo and CVT-301 84mg in the proportion of patients who achieve resolution of an OFF state to an ON state within 60 minutes after study drug administration at the clinic at TV4 and maintain the ON state at 60 minutes post-dose per an examiner's assessment.

It was found that a completer set of patients who came in at treatment visit 4 has been used in evaluating the second hypothesis and that the statistical method (CMH test for odds ratio) did not include as a stratifying factor the baseline OFF-state UPDRS part 3 score, which was included in the primary analysis as a potential confounder. Both deficiencies may pose a risk of introducing bias into treatment effect estimates. A sensitivity analysis with a MMRM-type statistical method applied to the ITT population and including the baseline OFF-state UPDRS part 3 score as a covariate shows a treatment effect.

6. APPENDIX (SUMMARY OF THE SUPPORTIVE STUDY)

At the type-B EoP2 meeting held on 7/10/2014, it was agreed that results from the phase 2b study CVT-301-003 could be supportive for this NDA assuming solid results from the pivotal study CVT-301-004. This supportive study is a randomized, double-blind, placebo-controlled, parallel-group, multi-center study.

Table 6.1. Description of the supportive study CVT-301-003

Study #	Phase and design	Study period	# of subjects (2 arms)	Study population
CVT-301-003	Phase 2b, prospective, multi-center, randomized, double-blind, parallel group, placebo controlled	5/7/2013 - 1/21/2014	Placebo: 45 DVT-301: 44	Patients with Parkinson's disease experiencing OFF-period symptoms

89 Parkinson's disease patients experiencing OFF-period symptoms recruited at 21 sites in North America and Europe were randomized, stratified by Hoehn & Yahr stage (<2.5: low or ≥2.5: high)and country, in a 1:1 ratio to be treated with either CVT-301 or placebo over 4 weeks with in-clinic visits at week 1 (treatment visit 1: TV1), week 2 (treatment visit 2: TV2), week 3 (treatment visit 3: TV3) and week 4 (treatment visit 4: TV4) . 75 patients (84%) competed the study. Patients in the CVT-301 arm administered CVT-301 50mg during the first 2 weeks followed by CVT-301 64mg in the subsequent 2 weeks.

For the 4-week treatment period, patients continued to take their usual prescribed Parkinson's disease medication and self-administered CVT-301 or placebo as an outpatient at home as needed up to 3 times a day when they experienced OFF-period symptoms.

For in-clinic visits, patients were guided to arrive at the clinic as shortly as possible after taking their Parkinson's disease medication at home to increase the likelihood that patients were in the ON state and remain in the clinic until they transitioned into an OFF state prior to inhalation of CVT-301 or placebo.

The first dose of CVT-301 or placebo was given at TV1. At TV2, TV3 and TV4, efficacy was assessed at the OFF state immediately pre-dose, 10 minutes post-dose, 20 minutes post-dose, 30 minutes post-dose and 60 minutes post-dose using the Unified Parkinson's Disease Rating Scale (UPDRS) part 3 motor function score.

The primary efficacy endpoint was the mean change from pre-dose in the UPDRS Part 3 score over 10 to 60 minutes post-dose at TV4. The efficacy endpoint was analyzed by MMRM, where mean change from pre-dose in the UPDRS Part 3 score over 10 to 60 minutes post-dose at TV2, TV3 and TV4 was used as a dependent variable and Parkinson's disease severity, baseline OFF-state UPDRS Part 3 score, country, treatment, visit and treatment-by-visit interaction as covariates and patient as a random variable, on ITT population composed of all randomized patients who received at least 1 dose of inhaled CVT-301or placebo. The difference between placebo and CVT-301 on the primary efficacy endpoint is statistically significant as shown in Table 6.2.

Table 6.2. Evaluation on the primary efficacy endpoint for placebo vs CVT-301

Statistics	Placebo vs CVT-301
Least square mean difference (mean change in CVT-301 – mean change in placebo)	-6.63
95% confidence internal	(-9.84, -3.41)
P-value	<0.001

The supportive study tested many secondary hypotheses. One of them is the difference between placebo and CVT-301 on the change from pre-dose in the UPDRS part 3 motor function score at 30 minutes post-dose at TV4, which is comparable to the primary hypothesis of the confirmatory study CVT-301-004. The difference from the contrast analysis of MMRM is shown in Table 6.3.

Table 6.3. Evaluation on change from pre-dose at 30 minutes post-dose for placebo vs CVT-301

Statistics	Placebo vs CVT-301

Least square mean difference (mean change in CVT-301 – mean change in placebo)	-8.43
95% confidence internal	(-12.21, -4.65)

The statistical significance of the difference, however, cannot be assessed as the supportive study did not specify a hierarchical order for testing multiple hypotheses (or any other multiplicity adjustment scheme) to ensure that an overall type 1 error rate has been controlled.

REFERENCES

[1] Ratitch, B. and O'Kelly, M. (2011), "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures," in Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group), SP04, Nashville.

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/s/

SUNGWON N LEE
09/06/2018

KUN JIN
09/07/2018
I concur with the review.

HSIEN MING J HUNG
09/09/2018