CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208944Orig1s000

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 Number:	208944
Drug Name:	Amantadine Hydrochloride Extended Release Capsule
Indication:	Levodopa-Induced Dyskinesia
Applicant:	Adamas Pharma, LLC.
Dates:	Receipt Date: October 24, 2016
	PDUFA Goal Date: August 24, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiangmin Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	Hsien Ming Hung, Ph.D., Director
Medical Division:	Division of Neurology Products
Clinical Team:	Kenneth Bergmann, M.D., Clinical Reviewer
	Gerald Podskalny, D.O., Team Leader
	Eric Bastings, M.D., Deputy Director
	William Dunn, M.D., Director
Project Manager:	Anhtu Nguyen, R.Ph.

Keywords: clinical studies, mixed models, NDA review

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This review describes the statistical findings of Gocovri (amantadine hydrochloride extended release capsule) as a treatment of levodopa-induced dyskinesia. The review confirmed that Study ADS-AMT-PD301 and Study ADS-AMT-PD304 in the 505(b)(2) new drug application provided statistical evidences that Gocovri is efficacious as a treatment of levodopa-induced dyskinesia: Gocovri is statistically better than placebo in terms of change from Baseline to Week 12 in the Unified Dyskinesia Rating Scale total score.

2 INTRODUCTION

2.1 Overview

On October 24, 2016, Adamas Pharma, LLC. (the Sponsor) submitted a 505(b)(2) new drug application (NDA) for amantadine hydrochloride extended release capsule (ADS-5102 under the Sponsor's clinical development program) as a treatment of levodopa-induced dyskinesia (LID) for subjects with Parkinson's disease (PD). The NDA submission lists Food and Drug Administration approved drug Symmetrel® (NDAs 16020, 16023, 17118, and 18101) as the 505(b)(2) reference. The Sponsor submitted three clinical studies in the NDA application to support the efficacy claim of ADS-5102.

Table 1. List of studies in this review

Study Number	Phase and Design	Treatment Period (in week)	Study Arm (Number of randomized patients per arm)	Study Population
ADS-PAR-AM201	Phase 2, randomized, placebo-controlled, parallel-group, fixed dose	8	Placebo (22) 260 mg once daily (20) 340 mg once daily (21) 420 mg once daily (20)	Male and female subjects 30-85 years of age with Parkinson's disease
ADS-AMT-PD301	Phase 3, randomized, placebo-controlled, parallel-group, fixed dose	25	Placebo (63) 340 mg once daily (63)	
ADS-AMT-PD304	Phase 3, randomized, placebo-controlled, parallel-group, fixed dose	13	Placebo (39) 340 mg once daily (38)	

Source: reviewer's summary

The three clinical studies are summarized in **Table 1**. Study ADS-PAR-AM201, Study ADS-AMT-PD301, and Study ADS-AMT-PD304 are referred to as Study 201, Study 301, and Study 304, respectively, in the rest of this review. Study 301 and Study 304 are phase 3 studies to be reviewed in more detail in Section 3. In these studies, the dosing of 170 mg per capsule (or 340 mg daily) was reported by the Sponsor. The actual amantadine free base quantity was 137 mg per capsule (or 274 mg daily). Study 201 is a phase 2 study, with a design considered not sufficient for the evaluation of efficacy due to the short duration of the study (see the type C meeting minutes dated December 18, 2013). Nonetheless, Study 201 was submitted as a supporting study. It is summarized in the Appendix.

2.2 Data Sources

The electronic submission of this NDA is located at
\\cdsesub1\evsprod\NDA208944\0001\

The study reports are located at
\\cdsesub1\evsprod\NDA208944\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\lid\5351-stud-rep-contr\

The datasets are located at
\\cdsesub1\evsprod\NDA208944\0001\m5\datasets\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality and analysis quality are adequate. The reviewer was able to perform independent review using Sponsor's submitted datasets and confirm the Sponsor's analysis results.

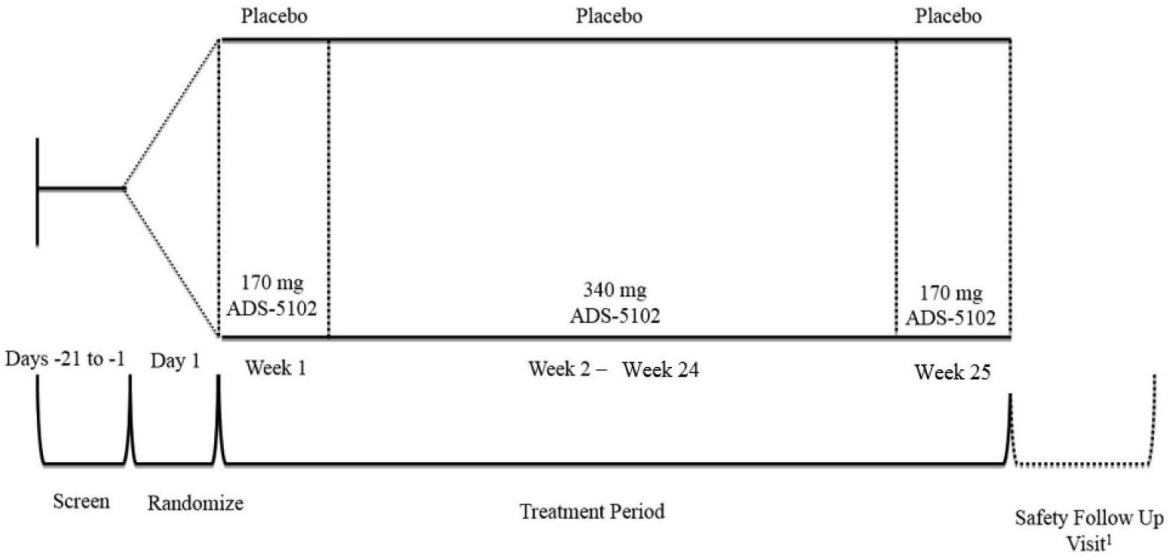
3.2 Evaluation of Efficacy

3.2.1 Study 301

3.2.1.1 Study Design and Endpoints

Study 301 was a double-blind, placebo-controlled, randomized, 2-arm, parallel-group, phase 3, multi-center study to evaluate the efficacy, safety, and tolerability of ADS-5102 as a treatment of LID in subjects with PD. A total of 120 patients were planned to be randomized in a 1:1 ratio to placebo and ADS-5102 340 mg once daily. Patients were screened in 42 study centers in the United States and 2 centers in Canada and randomized in 40 centers in the United States and 1 center in Canada.

Figure 1. Study 301 design schematic



[1] Applicable only for subjects who complete 25 weeks of treatment and decline participation in the open-label extension

Source: figure on page 38 of the Sponsor's statistical analysis plan

Figure 1 depicts the study design schematic. Following the completion of the Baseline visit, the subjects were scheduled to return to the clinic after 1, 2, 4, 8, 12, 18, 24, and 25 weeks of dosing. Subjects who complete 25 weeks of dosing have the option of entering the open-label extension

study ADS-AMT-PD302. For each patient assigned the ADS-5102 treatment, his/her study mediation was administrated as 170 mg ADS-5102 once daily (one capsule of 170 mg ADS-5102 and one capsule of placebo) for one week then 340 mg ADS-5102 once daily (two capsules of 170 mg ADS-5102) for 23 weeks, ending with 170 mg ADS-5102 once daily during Week 25.

The Sponsor made a decision to stop the trial early and allowed all randomized subjects to complete the study visit at Week 12. The Sponsor informed the agency of the decision on October 23, 2015 in the cover letter to the submission of Study 301 statistical analysis plan. In the cover letter, the Sponsor explained that the early stopping decision is made to accelerate their NDA submission (b) (4) and that the decision was not made due to any safety signal. According to the clinical study report of Study 301, the last patient completed the study on November 18, 2015. However, the other phase 3 study (i.e. Study 304) had the last patient complete the study on March 10, 2016. The Sponsor should have been able to allow all randomized subjects in Study 301 to complete the Week 24 study visit without actually delaying the NDA submission.

The primary efficacy endpoint was change from Baseline to Week 12 in the Unified Dyskinesia Rating Scale (UDysRS)[1] total score. The UDysRS has four parts with a range of 0-104 in total score (smaller scores indicate less severe symptoms):

I. Historical disability of on-dyskinesia impact
II. Historical disability of off-dystonia impact
III. Objective impairment
IV. Objective disability based on Part III activities

More details of the four parts and the imputation rules for the subscales (see **Figure 2**) are as follows:

IA. Historical disability of on-dyskinesia impact (Question 1, 0-4 points)
IB. Historical disability of on-dyskinesia impact (Question 2-11, 0-40 points in total)
IIA. Historical disability of off-dystonia impact (Question 12, 0-4 points)
IIB. Historical disability of off-dystonia impact (Question 13-15, 0-12 points in total)
III. Objective impairment (Question 16-22, 0-28 points in total)
IV. Objective disability based on Part III activities (Question 23-26, 0-16 points in total)

[1] Goetz, C. G., Nutt, J. G., & Stebbins, G. T. (2008). The unified dyskinesia rating scale: presentation and clinimetric profile. *Movement Disorders*, 23(16), 2398-2403.

Figure 2. Study 301 imputation rules for individual UDysRS subscale items and total score

	Subscale (Total) Items	Missing Items	Imputation (Y/N)	Imputation Method
Part IA	1	1	No	Assign a value of 0
Part I B	10	1	Yes	Average of non-missing items within the subscale
Part IIA	1	1	No	Assign a value of 0
Part II B	3	1	Yes	Average of non-missing items within the subscale
Part III	7	1	Yes	Average of non-missing items within the subscale
Part IV	4	1	Yes	Average of non-missing items within the subscale
Total Objective Score (Part III + Part IV)	11	Part III or Part IV	No	Missing
Total UDysRS Score	26	Part I B or Part II B or Part III or Part IV	No	Missing

Source: Table 2 on page 19 of the Sponsor's statistical analysis plan

The key secondary efficacy endpoints were

- The change from Baseline to Week 24 in UDysRS total score
- The change from Baseline to Week 12 in ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia)
- The change from Baseline to Week 24 in ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia)
- The change from Baseline to Week 12 in OFF time
- The change from Baseline to Week 24 in OFF time

The ON time without troublesome dyskinesia and OFF time were calculated from the PD home diary[2]. A set of two consecutive 24-hour PD home diaries (48 hours in total) were completed during screening and prior to each efficacy visit. If more than four 30-minute intervals were missing, the diary was considered not evaluable. If four or fewer 30-minute intervals were missing, each missing 30-minute interval was imputed by the average of the responses of the immediately preceding and subsequent completed non-missing intervals. If a 30-minute interval was missing at the beginning or end of a 48-hour diary reporting period, it was imputed by the closest completed non-missing interval.

[2] Hauser, R. A., Friedlander, J., Zesiewicz, T. A., Adler, C. H., Seeberger, L. C., O'brien, C. F., Molho, E. S. & Factor, S. A. (2000). A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. *Clinical neuropharmacology*, *23*(2), 75-81.

3.2.1.2 Statistical Methodologies

The efficacy analysis population was the modified intent-to-treat (mITT) population defined as all randomized subjects who were dosed and who provided at least one post-baseline assessment of the UDysRS.

The primary endpoint was analyzed using a mixed model with repeated measure (MMRM), with treatment, visit (three levels corresponding to Weeks 2, 8, and 12), and treatment by visit interaction as fixed effects and baseline value of the UDysRS total score as the covariate. The unstructured variance-covariance matrix and Kenward-Roger approximation were used for the analysis.

The Week 12 secondary endpoints were analyzed using similar MMRM analyses, with endpoint specific baseline as the covariate. The Week 24 secondary endpoints were also analyzed using the MMRM, except that the fixed effect visit had five levels: Weeks 2, 8, 12, 18, and 24.

In order to handle the multiplicity of endpoints, the primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of $\alpha = 0.05$, in the following order:

- 340 mg ADS-5102 versus placebo for UDysRS at Week 12
- 340 mg ADS-5102 versus placebo for UDysRS at Week 24
- 340 mg ADS-5102 versus placebo for ON time without troublesome dyskinesia at Week 12
- 340 mg ADS-5102 versus placebo for ON time without troublesome dyskinesia at Week 24
- 340 mg ADS-5102 versus placebo for OFF time at Week 12
- 340 mg ADS-5102 versus placebo for OFF time at Week 24

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2. Study 301 patient disposition, randomized population

Number (%) of Subjects	Placebo (N=63)	340 mg ADS-5102 (N=63)	All (N=126)
Randomized	63 (100.0)	63 (100.0)	126 (100.0)
Completed the study[a]	42 (66.7)	42 (66.7)	84 (66.7)
Withdrawn from study	21 (33.3)	21 (33.3)	42 (33.3)
Reasons for withdrawal			
Sponsor's decision: subject ongoing when study stopped	7 (11.1)	7 (11.1)	14 (11.1)
Subject discontinued study drug and wished to withdraw[b]	3 (4.8)	10 (15.9)	13 (10.3)
Subject unwilling to proceed	7 (11.1)	2 (3.2)	9 (7.1)
Subject lost to follow-up	1 (1.6)	1 (1.6)	2 (1.6)
Other	3 (4.8)	1 (1.6)	4 (3.2)

[a] Includes 5 subjects who completed the original protocol with study duration of 13 weeks.
[b] Subjects who discontinued study drug were encouraged to complete all study assessments.

Source: Table 8 on page 53 of the Sponsor's clinical study report body

The patient disposition is presented in **Table 2**. A total of 189 patients were screened, of which 126 (66.7%) randomized. Among the 126 randomized patients, 63 (50.0%) were randomized to the placebo group and 63 (50.0%) to the 340 mg ADS-5102 group. A total of five patients in the placebo group completed the study with duration of 13 weeks according to an early version of the protocol. A total of 84 patients completed the study: 42 in the placebo group and 42 in the ADS-5102 group. Compared to patients in the placebo group, more patients in the ADS-5102 group discontinued the treatment early due to adverse event (13 patients in the ADS-5102 group discontinued the treatment due to adverse event vs. 4 patients in the placebo discontinued for the same reason). The Sponsor's decision to stop the study early impacted the discontinuation rates noticeably.

Table 3. Study 301 patient demographics, mITT population

	Placebo (N=58)	340 mg ADS-5102 (N=63)	All (N=121)
Age (yrs)			
n	58	63	121
Mean (SD)	65.5 (8.70)	63.9 (9.43)	64.7 (9.09)
Median	66.0	64.0	66.0
Min, Max	43, 82	34, 81	34, 82
Age categories (yrs) n (%)			
<65	26 (44.8)	32 (50.8)	58 (47.9)
>=65	32 (55.2)	31 (49.2)	63 (52.1)
Sex n (%)			
Male	35 (60.3)	35 (55.6)	70 (57.9)
Female	23 (39.7)	28 (44.4)	51 (42.1)
Race n (%)			
White	51 (87.9)	60 (95.2)	111 (91.7)
Black or African American	1 (1.7)	0	1 (0.8)
Asian	3 (5.2)	2 (3.2)	5 (4.1)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (1.6)	1 (0.8)
Other	3 (5.2)	0	3 (2.5)
Ethnicity n (%)			
Hispanic or Latino	9 (15.5)	3 (4.8)	12 (9.9)
Not Hispanic or Latino	49 (84.5)	60 (95.2)	109 (90.1)
Height (cm)			
n	58	63	121
Mean (SD)	170.1 (8.81)	170.0 (9.04)	170.1 (8.89)
Median	170.0	170.2	170.0
Min, Max	152, 188	154, 188	152, 188
Weight (kg)			
n	58	63	121
Mean (SD)	78.38 (15.504)	76.10 (20.679)	77.19 (18.342)
Median	74.65	72.30	72.80
Min, Max	48.5, 115.0	41.5, 139.0	41.5, 139.0
Body Mass Index (kg/m^2)			
n	58	63	121
Mean (SD)	27.05 (4.701)	26.15 (6.226)	26.58 (5.543)
Median	26.61	25.38	26.17
Min, Max	17.8, 39.5	16.7, 48.0	16.7, 48.0
Estimated glomerular filtration rate (eGFR) by MDRD ($mL/min/1.73m^2$)			
n	58	63	121
Mean (SD)	91.2 (24.21)	97.5 (26.26)	94.5 (25.39)
Median	85.0	87.0	86.0
Min, Max	55, 166	60, 174	55, 174

Source: Table 14.1.4.1 on pages 119-120 of the Sponsor's clinical study report body

The patient demographic characteristics of the mITT population are summarized in **Table 3**. According to the Sponsor, five patients in the placebo group were randomized but excluded from the mITT population because three patients did not receive study drug and two patients did not have a post-baseline UDysRS assessment. The treatment groups appeared similar in terms of age, gender, and race. The mITT population was mainly White patients and had an average age of approximately 65 years. There were more male patients than female patients in the mITT population.

Table 4. Study 301 patient baseline characteristics, mITT population

Statistics	Placebo N = 58 Mean (SD)	ADS-5102 N = 63 Mean (SD)	All N = 121 Mean (SD)
UDysRS Total Score	38.5 (11.21)	40.9 (13.34)	39.7 (12.37)
PD Diary (hours)			
ON time without troublesome dyskinesia	8.5 (2.82)	8.3 (3.47)	8.4 (3.16)
ON time with troublesome dyskinesia	4.5 (1.96)	4.7 (2.54)	4.6 (2.27)
Total time with dyskinesia[a]	9.2 (3.16)	9.6 (3.23)	9.4 (3.19)
OFF time	3.0 (2.08)	3.2 (2.37)	3.1 (2.23)
Asleep time	8.1 (1.46)	7.8 (1.73)	7.9 (1.60)
MDS-UPDRS			
Part I	11.4 (4.04)	12.5 (6.18)	12.0 (5.29)
Part II	15.7 (5.85)	15.7 (6.77)	15.7 (6.32)
Part III	24.8 (12.19)	25.9 (14.49)	25.4 (13.39)
Part IV	11.3 (2.39)	11.8 (2.95)	11.6 (2.70)
MMSE	28.8 (1.23)	28.7 (1.52)	28.7 (1.39)
Hoehn and Yahr Stage	2.3 (0.56)	2.2 (0.54)	2.2 (0.55)

MDS-UPDRS: Movement Disorder Society - Unified Parkinson Disease Rating Scale; mITT: modified intent-to-treat; MMSE: Mini-Mental State Examination; N: number of patients; PD: Parkinson's disease; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Total time with dyskinesia includes non-troublesome and troublesome.

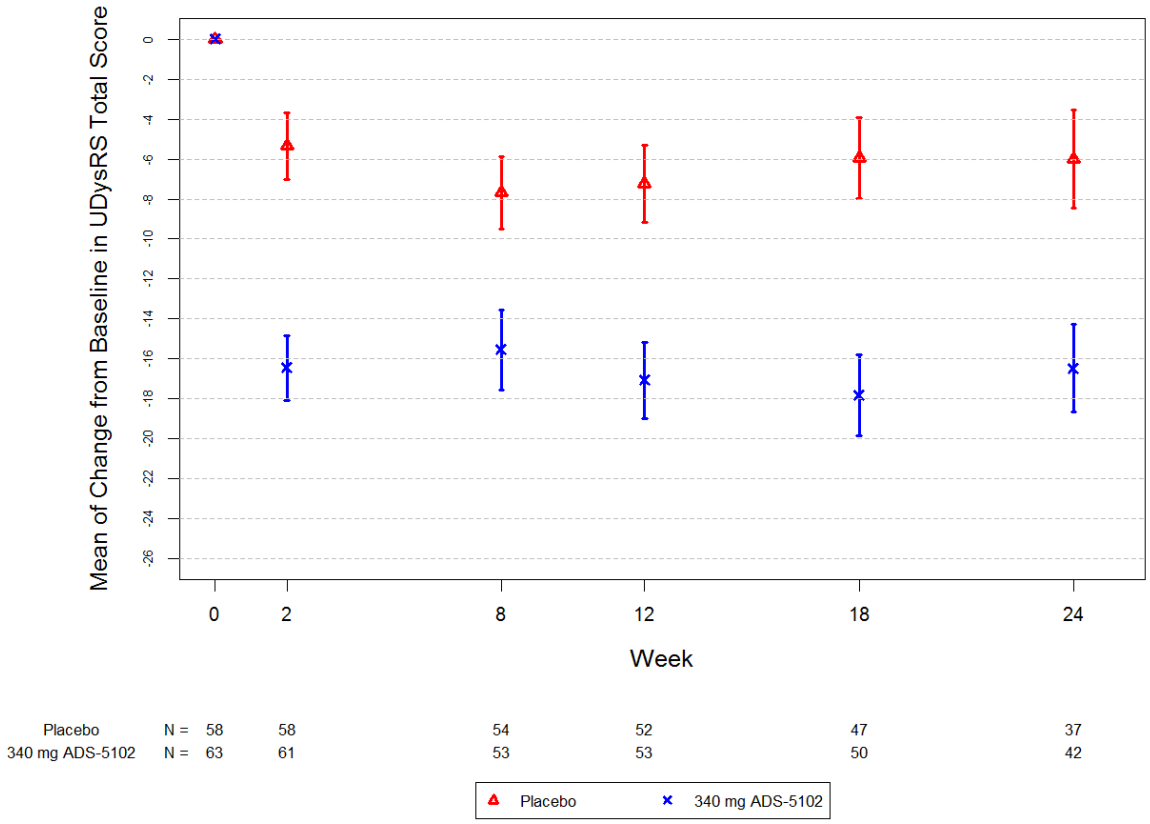
Source: selected from Table 14.1.7.1 on pages 128-131 of the Sponsor's clinical study report body

The patient baseline characteristics of the mITT population are summarized in **Table 4**. The ADS-5102 group appeared to have worse UDysRS total scores, PD Diary time, and MDS-UPDRS sub-scores, as well as larger standard deviations, than the placebo group. This might lead to an exaggerated treatment difference between the ADS-5102 group and placebo group.

In addition to these baseline characteristics, patients of the mITT population was diagnosed with PD with an average age of approximately 55.9 years (standard deviation (SD) = 9.16) for an average diagnose length of 9.2 years (SD = 4.14) at study baseline. On average, these patients started the levodopa treatment from the age of approximately 57.8 years (SD = 9.13) for a duration of 7.4 years (SD = 3.57) and experienced LID for approximately 3.7 years (SD = 2.84) at study baseline.

3.2.1.4 Results and Conclusions

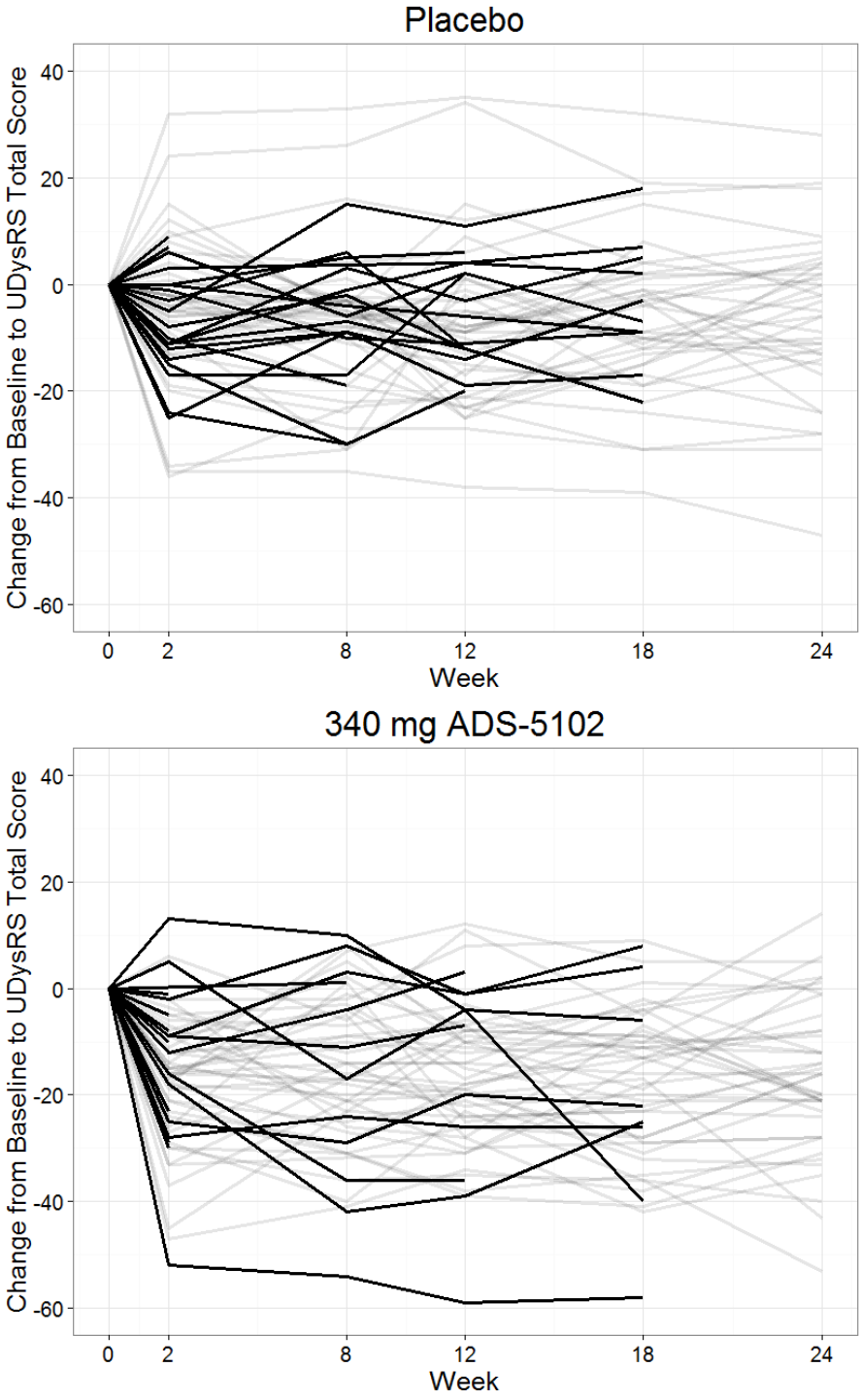
Figure 3. Study 301 mean (± standard error) of change from Baseline in UDysRS total score by week and treatment



Source: the reviewer

Figure 3 illustrates the mean of changes from Baseline in UDysRS total score by week and treatment for the Study 301 mITT population. The 340 mg ADS-5102 group appeared to have consistent average improvements of UDysRS total score based on the observed changes from Baseline values. Such improvements were on average greater than those from the placebo group. The mITT population sizes were 63 and 58 for the 340 mg ADS-5102 group and placebo group, respectively. The rates of missing observations at Week 12 were 15.9% and 10.3% for the 340 mg ADS-5102 group and placebo group, respectively; the rates of missing observations at Week 24 were 33.3% and 36.2% for the 340 mg ADS-5102 group and placebo group, respectively.

Figure 4. Study 301 time plots by treatment and patient



Source: the reviewer

In **Figure 4**, the top panel illustrates the time plots of all mITT patients in the placebo group; the bottom panel illustrates the time plots of all mITT patients in the 340 mg ADS-5102 group. For

both panels, the time plots for the completers were in gray while the ones for the non-completers were in black. No specific dropout pattern (by comparing the non-completers and completers in the same treatment group) was observed from each panel. In other words, there is little evidence from each panel that the missing at random assumption on which the MMRM relies was unreasonable.

Table 5. Study 301 analyses of change from Baseline to Week 12 and Week 24 in UDysRS total score, mITT population

		Week 12		Week 24	
		Placebo (N=58)	**340 mg ADS-5102 (N=63)**	**Placebo (N=58)**	**340 mg ADS-5102 (N=63)**
Baseline	Mean (SD)	38.2 (11.35)	40.9 (13.51)	37.7 (12.64)	41.0 (12.20)
	Median (Min, Max)	40.0 (8, 58)	41.0 (10, 76)	40.0 (8, 58)	42.5 (15, 70)
Week 12 or 24	Mean (SD)	31.0 (12.31)	23.8 (14.08)	31.6 (13.43)	24.6 (13.42)
	Median (Min, Max)	31.0 (1, 62)	23.0 (0, 67)	31.0 (9, 56)	29.0 (0, 49)
Change from Baseline	Mean (SD)	-7.2 (13.95)	-17.1 (13.90)	-6.0 (14.92)	-16.5 (14.26)
	Median (Min, Max)	-9.0 (-38, 35)	-18.0 (-59, 12)	-5.0 (-47, 28)	-16.0 (-53, 14)
MMRM Change from Baseline	LS Mean (SE)	-8.0 (1.64)	-15.9 (1.62)	-6.3 (1.94)	-15.6 (1.87)
	95% CI	(-11.3, -4.8)	(-19.1, -12.7)	(-10.1, -2.4)	(-19.3, -11.9)
MMRM Treatment Difference (Active - Placebo)	LS Mean (SE)	-7.9 (2.30)		-9.3 (2.70)	
	95% CI	(-12.5, -3.3)		(-14.7, -4.0)	
	P value	0.0009		0.0008	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit.

Source: Table 6 on page 35 of the Sponsor's integrated summary of efficacy

The analysis results of the endpoints of UDysRS total score are presented in **Table 5**. The summary statistics of the baseline values reported for Week 12 (or Week 24) in **Table 5** (as well as those reported in **Table 6** and **Table 7**) by the Sponsor were based on all subjects in the mITT population that had Week 12 (or Week 24) measurements, without any imputation. Based on the pre-specified analysis method, ADS-5102 was statistically significantly better than placebo (p-value = 0.0009) in terms of change from Baseline to Week 12 in UDysRS total score, with a least square ADS-5102-placebo difference of -7.9 points (95% CI = (-12.5, -3.3)); ADS-5102 was also statistically significantly better than placebo (p-value = 0.0008) in terms of change from Baseline to Week 24 in UDysRS total score, with a least square ADS-5102-placebo difference of -9.3 points (95% CI = (-14.7, -4.0)).

Table 6. Study 301 analyses of change from Baseline to Week 12 and Week 24 in ON time without troublesome dyskinesia (in hour), mITT population

		Time (hours)	
		Placebo (N=58)	**340 mg ADS-5102 (N=63)**
Week 12 Data			
Baseline	n	51	50
	Mean (SD)	8.45 (2.915)	8.10 (3.649)
	Median	8.25	8.31
	Min, Max	3.8, 15.3	0.0, 15.0
MMRM Change from Baseline at Week 12	LS Mean (SE)	0.82 (0.432)	3.56 (0.434)
	95% CI	(−0.04, 1.67)	(2.70, 4.42)
MMRM Treatment Difference at Week 12 (Active - Placebo)	LS Mean (SE)	2.74 (0.612)	
	95% CI	(1.53, 3.96)	
	P value	<0.0001	
Week 24 Data			
Baseline	n	36	42
	Mean (SD)	8.14 (2.844)	8.05 (3.526)
	Median	8.13	8.00
	Min, Max	3.8, 15.3	1.5, 14.8
MMRM Change from Baseline at Week 24	LS Mean (SE)	1.37 (0.456)	3.59 (0.440)
	95% CI	(0.46, 2.28)	(2.71, 4.46)
MMRM Treatment Difference at Week 24 (Active - Placebo)	LS Mean (SE)	2.22 (0.634)	
	95% CI	(0.96, 3.47)	
	P value	0.0007	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 8, and 12 [for Week 12 data] or Weeks 2, 8, 12, 18, and 24 [for Week 24 data]), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 16 on page 69 of the Sponsor's clinical study report body

The analysis results of the endpoints of ON time without troublesome dyskinesia are presented in **Table 6**. ADS-5102 was statistically significantly better than placebo (p-value < 0.0001) in terms of change from Baseline to Week 12 in ON time without troublesome dyskinesia, with a least square ADS-5102-placebo difference of 2.74 hours (95% CI = (1.53, 3.96)). ADS-5102 was also statistically significantly better than placebo (p-value = 0.0007) in terms of change from Baseline to Week 24 in ON time without troublesome dyskinesia, with a least square ADS-5102-placebo difference of 2.22 hours (95% CI = (0.96, 3.47)).

Table 7. Study 301 analyses of change from Baseline to Week 12 and Week 24 in OFF time (in hour), mITT population

		Time (hours)	
		Placebo (N=58)	**340 mg ADS-5102 (N=63)**
Week 12 Data			
Baseline	n	51	50
	Mean (SD)	3.01 (2.118)	3.29 (2.366)
	Median	2.75	3.25
	Min, Max	0.0, 9.0	0.0, 9.5
MMRM Change from Baseline at Week 12	LS Mean (SE)	0.32 (0.263)	−0.59 (0.265)
	95% CI	(−0.20, 0.84)	(−1.11, −0.06)
MMRM Treatment Difference at Week 12 (Active - Placebo)	LS Mean (SE)	−0.90 (0.373)	
	95% CI	(−1.64, −0.16)	
	P value	0.0171	
Week 24 Data			
Baseline	n	36	42
	Mean (SD)	3.14 (2.229)	3.11 (2.376)
	Median	2.88	2.94
	Min, Max	0.0, 9.0	0.0, 8.8
MMRM Change from Baseline at Week 24	LS Mean (SE)	0.22 (0.282)	−0.58 (0.268)
	95% CI	(−0.34, 0.78)	(−1.12, -0.05)
MMRM Treatment Difference at Week 24 (Active - Placebo)	LS Mean (SE)	−0.81 (0.389)	
	95% CI	(−1.58, −0.04)	
	P value	0.0406	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 8, and 12 [for Week 12 data] or Weeks 2, 8, 12, 18, and 24 [for Week 24 data]), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 17 on page 71 of the Sponsor's clinical study report body

The analysis results of the endpoints of OFF time are presented in **Table 7**. ADS-5102 was statistically significantly better than placebo (p-value = 0.0171) in terms of change from Baseline to Week 12 in OFF time, with a least square ADS-5102-placebo difference of -0.90 hour (95% CI = (-1.64, -0.16)). ADS-5102 was also statistically significantly better than placebo (p-value = 0.0406) in terms of change from Baseline to Week 24 in OFF time, with a least square ADS-5102-placebo difference of -0.81 hour (95% CI = (-1.58, -0.04)).

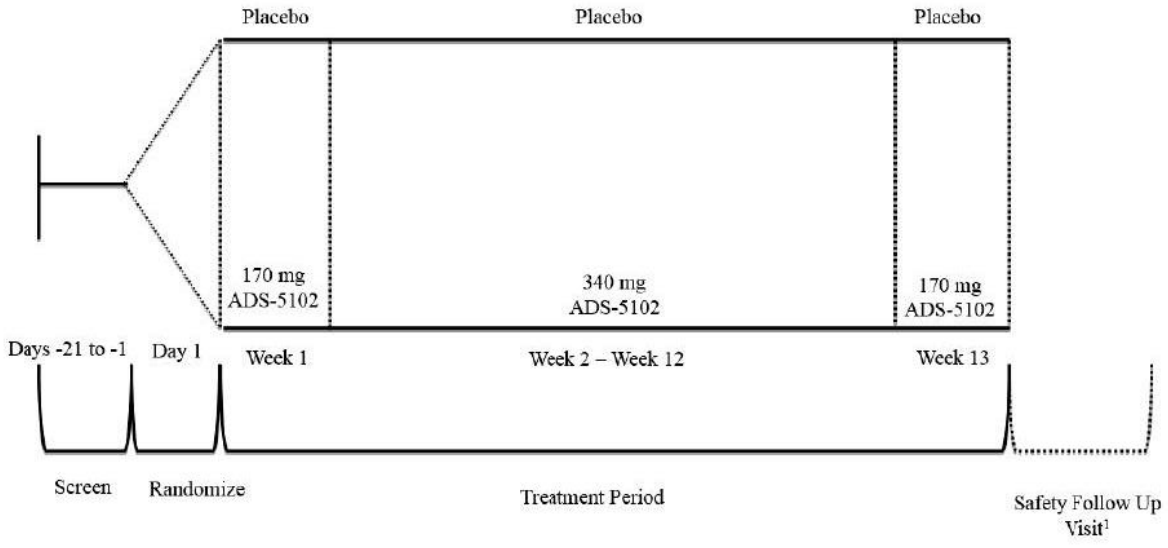
Because the Week 24 dropout percentages are high in each treatment group for the mITT population (33.3% and 36.2% for the 340 mg ADS-5102 group and placebo group, respectively), how to interpret the Week 24 results for the UDysRS, ON time without troublesome dyskinesia, and OFF time is an issue. In the original NDA submission, the Sponsor performed additional analysis on the Week 24 UDysRS endpoint using the per protocol (PP) population, defined as the subset of the mITT population who met inclusion criteria 6, 8, 9, completed 12 weeks of study treatment, and provided Week 12 UDysRS efficacy assessments. The Sponsor also performed additional analysis using the PP population who had Week 24 data. Although these analyses showed statistically significant results, they are not adequate to test the validity of the missing at random assumption of the MMRM method. The Sponsor was requested to provide several additional sensitivity analyses for the primary and key secondary endpoints. Two post-hoc sensitivity analyses were submitted as a result: (1) an analysis assuming the data are missing at random and using the multiple imputation method and (2) an analysis assuming the data are not missing at random (NMAR) and imputing missing observations in the placebo group with the multiple imputation method in (1) while imputing missing observations in the ADS-5102 group as if they had been obtained in the placebo group. The results of the additional sensitivity analyses provided nominal significant p-values and appeared consistent with results from the pre-specified analysis methods for the primary and key secondary endpoints, except that the sensitivity analysis assuming NMAR provided a non-significant nominal p-value for the Week 24 OFF time endpoint. It should be noted that biases could be introduced due to the post-hoc nature of the additional sensitivity analyses and that cautions are needed especially for the interpretations of Week 24 endpoint results due to the high dropout percentages. In addition, the impact of the Sponsor's decision to stop the trial early on the Week 24 efficacy results is difficult to assess and interpret.

3.2.2 Study 304

3.2.2.1 Study Design and Endpoints

Study 304 was a double-blind, placebo-controlled, randomized, 2-arm, parallel-group, phase 3, multi-center study to evaluate the efficacy, safety, and tolerability of ADS-5102 as a treatment of LID in subjects with PD. A total of 72 patients were planned to be randomized in a 1:1 ratio to placebo and ADS-5102 340 mg once daily. Patients were screened in 39 study centers and randomized in 32 centers in the Austria, France, Germany, Spain, and United States.

Figure 5. Study 304 design schematic



[1] Applicable only for subjects who complete 13 weeks of treatment and decline participation in the open-label extension.

Source: figure on page 74 of the Sponsor's statistical analysis plan

Figure 5 depicts the study design schematic. Following the completion of the Baseline visit, the subjects were scheduled to return to the clinic after 1, 2, 4, 8, 12, and 13 weeks of dosing. Subjects who complete 13 weeks of dosing have the option of entering the open-label extension study ADS-AMT-PD302, which was also the extension study for Study 301. For each patient assigned the ADS-5102 treatment, his/her study mediation was administrated as 170 mg ADS-5102 once daily (one capsule of 170 mg ADS-5102 and one capsule of placebo) for one week then 340 mg ADS-5102 once daily (two capsules of 170 mg ADS-5102) for 11 weeks, ending with 170 mg ADS-5102 once daily during Week 13.

The primary efficacy endpoint was change from Baseline to Week 12 in the UDysRS total score. The imputation rules for the UDysRS subscales were the same for Study 301 and Study 304 (see details in **Figure 2** in Section 3.1.1.1).

The key secondary efficacy endpoints were

- The change from Baseline to Week 12 in ON time without troublesome dyskinesia
- The change from Baseline to Week 12 in OFF time

The calculations and imputations of the ON time without troublesome dyskinesia and OFF time for Study 304 were the same as described in Section 3.2.1.1 for Study 301.

3.2.2.2 Statistical Methodologies

The efficacy analyses population was the modified intent-to-treat (mITT) population defined as all randomized subjects who were dosed and who provided at least one post-baseline assessment of the UDysRS.

The primary endpoint was analyzed using the MMRM, with treatment, visit (four levels corresponding to Weeks 2, 4, 8, and 12), and treatment by visit interaction as fixed effects and baseline value of the UDysRS total score as the covariate. The unstructured variance-covariance matrix and Kenward-Roger approximation were used for the analysis.

The key secondary endpoints were analyzed using similar MMRM analyses, with endpoint specific baseline as the covariate.

In order to handle the multiplicity of endpoints, the primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of $\alpha = 0.05$, in the following order:

- 340 mg ADS-5102 versus placebo for UDysRS at Week 12
- 340 mg ADS-5102 versus placebo for ON time without troublesome dyskinesia at Week 12
- 340 mg ADS-5102 versus placebo for OFF time at Week 12

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 8. Study 304 patient disposition, randomized population

Number (%) of Subjects	Placebo (N=39)	340 mg ADS-5102 (N=38)	All (N=77)
Randomized	39 (100.0)	38 (100.0)	77 (100.0)
Completed the study	35 (89.7)	29 (76.3)	64 (83.1)
Withdrawn from study	4 (10.3)	9 (23.7)	13 (16.9)
Reasons for withdrawal			
Subject discontinued study drug and wished to withdraw[a]	3 (7.7)	6 (15.8)	9 (11.7)
Subject unwilling to proceed	0	1 (2.6)	1 (1.3)
Other	1 (2.6)	2 (5.3)	3 (3.9)

[a] Subjects who discontinued study drug were encouraged to complete all study assessments.

Source: Table 8 on page 54 of the Sponsor's clinical study report body

The patient disposition is presented in **Table 8**. A total of 114 patients were screened, of which 77 (67.5%) randomized. Among the 77 randomized patients, 39 (50.6%) were randomized to the placebo group and 38 (49.4%) to the 340 mg ADS-5102 group. A total of 64 patients completed the study: 35 in the placebo group and 29 in the ADS-5102 group. Compared to patients in the placebo group, more patients in the ADS-5102 group discontinued the treatment early due to

adverse event (seven patients in the ADS-5102 group discontinued the treatment due to adverse event versus three patients in the placebo discontinued for the same reason).

Table 9. Study 304 patient demographics, mITT population

	Placebo (N=38)	340 mg ADS-5102 (N=37)	All (N=75)
Age (years)			
Mean (SD)	64.9 (9.08)	64.7 (9.66)	64.8 (9.31)
Median (Min, Max)	65.0 (42, 79)	66.0 (46, 80)	65.0 (42, 80)
Age categories (years), n (%)			
< 65	15 (39.5)	16 (43.2)	31 (41.3)
≥ 65	23 (60.5)	21 (56.8)	44 (58.7)
Sex, n (%)			
Male	20 (52.6)	19 (51.4)	39 (52.0)
Female	18 (47.4)	18 (48.6)	36 (48.0)
Race, n (%)			
White	38 (100.0)	36 (97.3)	74 (98.7)
Other	0	1 (2.7)	1 (1.3)
Ethnicity, n (%)			
Hispanic or Latino	0	5 (13.5)	5 (6.7)
Not Hispanic or Latino	38 (100.0)	32 (86.5)	70 (93.3)
Body mass index (kg/m^2)			
Mean (SD)	24.90 (4.825)	24.62 (4.480)	24.76 (4.629)
Median (Min, Max)	24.53 (17.7, 36.1)	23.46 (18.1, 35.3)	23.59 (17.7, 36.1)
eGFR by MDRD ($mL/min/1.73\ m^2$)			
Mean (SD)	97.6 (25.53)	94.4 (20.64)	96.0 (23.15)
Median (Min, Max)	97.5 (53, 155)	97.0 (54, 141)	97.0 (53, 155)

Source: Table 10 on page 57 of the Sponsor's clinical study report body

The patient demographic characteristics of the mITT population are summarized in **Table 9**. The treatment groups appeared similar in terms of age, gender, and race. The mITT population was mainly White patients and had an average age of approximately 65 years. There were slightly more male patients than female patients in the mITT population.

Table 10. Study 304 patient baseline characteristics, mITT population

	Mean (SD)		
	Placebo (N=38)	340 mg ADS-5102 (N=37)	All (N=75)
UDysRS			
Total score	41.2 (10.32)	40.2 (13.06)	40.7 (11.68)
Total objective score (Parts III & IV)	15.9 (7.00)	18.1 (7.99)	17.0 (7.53)
PD Diary			
ON time without troublesome dyskinesia (hours)	7.79 (3.249)	8.77 (2.457)	8.27 (2.909)
ON time with troublesome dyskinesia (hours)	6.02 (3.353)	4.71 (2.509)	5.37 (3.020)
Total time with dyskinesia[a] (hours)	10.52 (2.980)	9.04 (3.292)	9.79 (3.204)
OFF time (hours)	1.98 (1.687)	2.62 (2.015)	2.30 (1.871)
Asleep time (hours)	8.21 (1.643)	7.91 (1.502)	8.06 (1.572)
MDS-UPDRS			
Part I	9.9 (4.86)	11.3 (5.87)	10.6 (5.39)
Part II	14.8 (6.06)	14.1 (6.15)	14.4 (6.07)
Part III	21.4 (10.22)	21.2 (9.24)	21.3 (9.68)
Combined (Part I, II, and III)	46.1 (17.00)	46.6 (14.76)	46.3 (15.83)
Part IV	11.1 (2.40)	9.8 (2.78)	10.5 (2.66)
Part IV, Item 4.1	2.8 (0.94)	2.2 (0.81)	2.5 (0.92)
Part IV, Item 4.2	2.5 (0.51)	2.5 (0.61)	2.5 (0.55)
MMSE	28.7 (1.38)	29.1 (1.59)	28.9 (1.49)
Hoehn and Yahr Stage	2.4 (0.55)	2.1 (0.60)	2.2 (0.59)

[a] Total time with dyskinesia includes ON time with non-troublesome and troublesome dyskinesia.

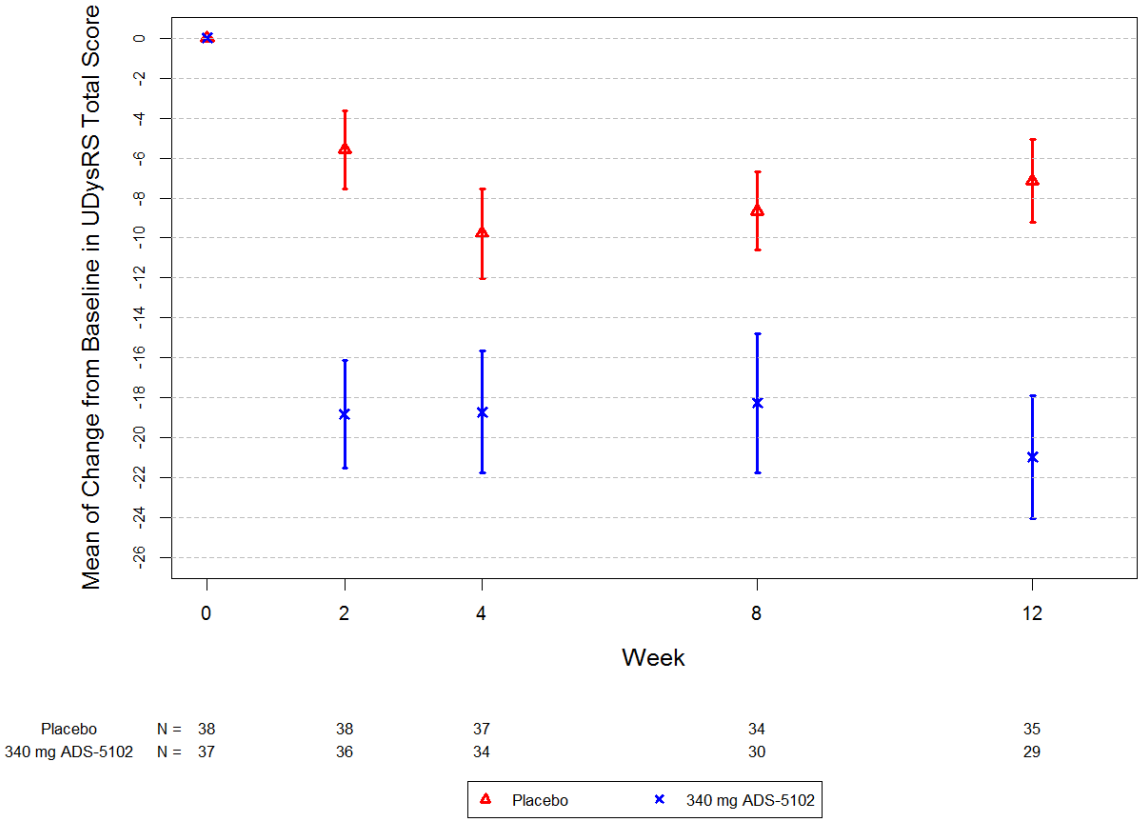
MDS-UPDRS: Movement Disorder Society - Unified Parkinson Disease Rating Scale; mITT: modified intent-to-treat; MMSE: Mini-Mental State Examination; N: number of patients; PD: Parkinson's disease; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

Source: Table 11 on page 58 of the Sponsor's clinical study report body

The patient baseline characteristics of the mITT population are summarized in **Table 10**. In addition to these baseline characteristics, patients of the mITT population was diagnosed with PD with an average age of approximately 54.7 years (SD = 9.43) for an average diagnose length of 10.6 years (SD = 4.67) at study baseline. On average, these patients have been on the levodopa treatment from the age of approximately 57.2 years (SD = 9.55) for a duration of 8.1 years (SD = 4.49) and experienced LID for approximately 3.9 years (SD = 2.86).

3.2.2.4 Results and Conclusions

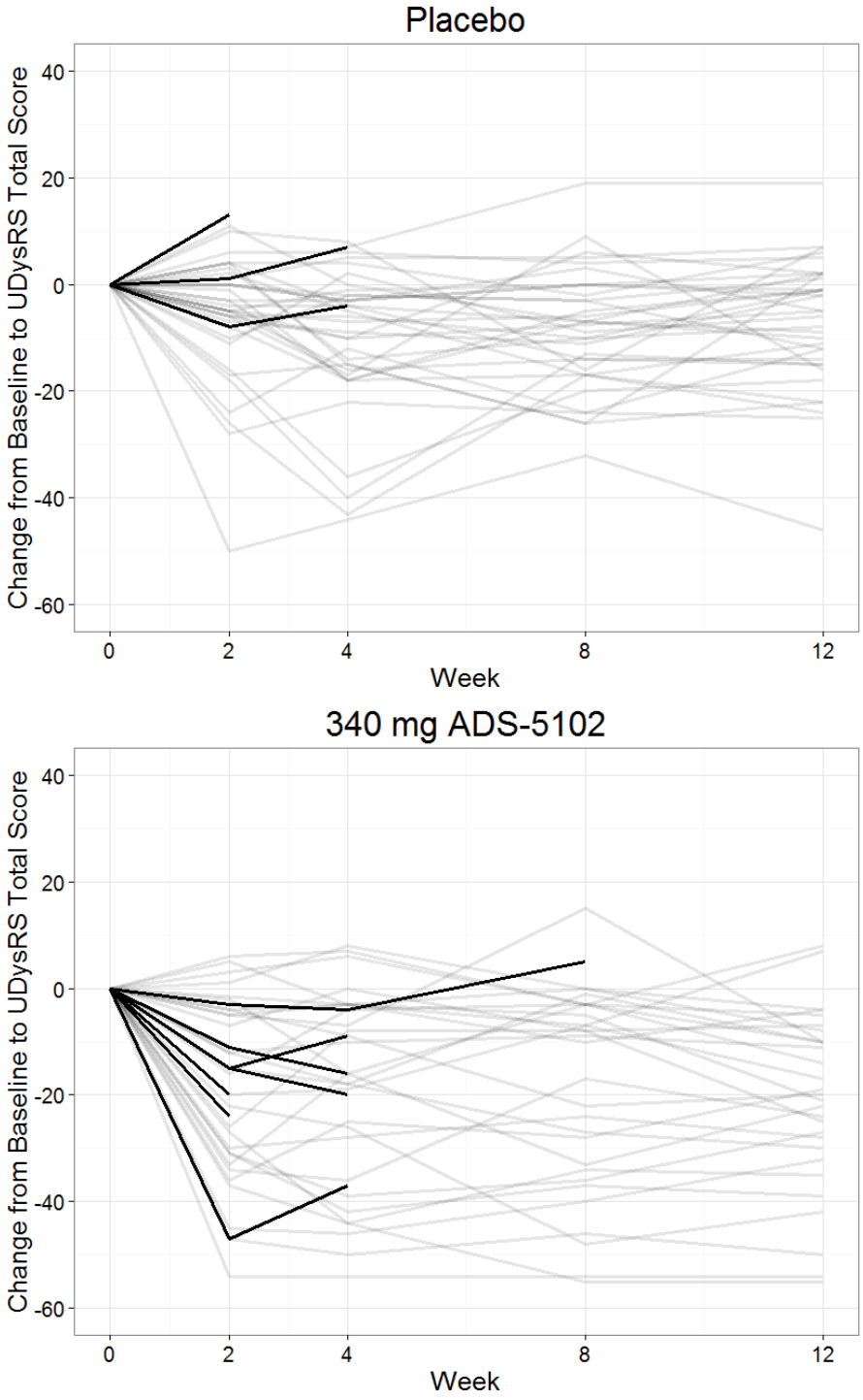
Figure 6. Study 304 mean (± standard error) of change from Baseline in UDysRS total score by week and treatment



Source: the reviewer

Figure 6 illustrates the mean of changes from Baseline in UDysRS total score by week and treatment for Study 304 mITT population. The 340 mg ADS-5102 group appeared to have consistent average improvements of UDysRS total score over the 12-week treatment duration. Such improvements were on average greater than those from the placebo group. The mITT population sizes were 37 and 38 for the 340 mg ADS-5102 group and placebo group, respectively. The rates of missing observations at Week 12 were 21.6% and 7.9% for the 340 mg ADS-5102 group and placebo group, respectively.

Figure 7. Study 304 time plots by treatment and patient



Source: the reviewer

In **Figure 7**, the top panel illustrates the time plots of all mITT patients in the placebo group; the bottom panel illustrates the time plots of all mITT patients in the 340 mg ADS-5102

group. For both panels, the time plots for the completers were in gray while the ones for the non-completers were in black. No specific dropout pattern (by comparing the non-completers and completers in the same treatment group) was observed from each panel. In other words, there is little evidence from each panel that the missing at random assumption on which the MMRM relies was unreasonable. The changes from Baseline in UDysRS total score of the dropped out patients in the placebo group were generally worse than those in the 340 mg ADS-5102 group.

Table 11. Study 304 analyses of change from Baseline to Week 12 in UDysRS total score, mITT population

		Placebo (N=38)	340 mg ADS-5102 (N=37)
Baseline	n	35	29
	Mean (SD)	40.4 (10.09)	41.7 (12.57)
	Median (Min, Max)	40.0 (21, 62)	42.0 (18, 63)
Week 12	n	35	29
	Mean (SD)	33.3 (14.35)	20.8 (11.83)
	Median (Min, Max)	32.0 (5, 63)	18.0 (0, 48)
Change from Baseline	n	35	29
	Mean (SD)	−7.1 (12.14)	−21.0 (16.60)
	Median (Min, Max)	−5.0 (−46, 19)	−20.0 (−55, 8)
MMRM Change from Baseline	LS Mean (SE)	−6.3 (2.08)	−20.7 (2.20)
	95% CI	(−10.5, −2.2)	(−25.1, −16.3)
MMRM Treatment Difference (Active - Placebo)	LS Mean (SE)	−14.4 (3.03)	
	95% CI	(−20.4, −8.3)	
	P value	< 0.0001	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 15 on page 63 of the Sponsor's clinical study report body

The analysis results of the endpoints of UDysRS total score are presented in **Table 11** (as well as those reported in **Table 12** and **Table 13**) by the Sponsor were based on all subjects in the mITT population that had Week 12 measurements, without imputation. ADS-5102 was statistically significantly better than placebo (p-value < 0.0001) in terms of change from Baseline to Week 12 in UDysRS total score, with a least square ADS-5102-placebo difference of -14.4 points (95% CI = (-20.4, -8.3)).

A total of seven patients in the ADS-5102 group discontinued the treatment due to adverse event versus three patients in the placebo discontinued for the same reason; one patient in the ADS-5102 group discontinued the treatment because the patient was unwilling to proceed. An additional post-hoc analysis was attempted by the reviewer to explore the potential impact of differentiable dropout between treatment groups: for patients who dropped out due to adverse event, their changes from Baseline to Week 12 in the UDysRS total score were assigned the worst score; for the patient dropped out because he/she was unwilling to proceed, the Week 2 and Week 4 scores showed improvements and his/her Week 12 change from baseline was imputed by the Week 4 score (last available value). The Wilcoxon rank sum test was performed after imputation and provided a nominally significant p-value close to 0.05. The statistical conclusion from the exploratory method does not differ from that from the pre-specified analysis method.

Table 12. Study 304 analyses of change from Baseline to Week 12 in ON time without troublesome dyskinesia (in hour), mITT population

		Time (hours)	
		Placebo (N=38)	**340 mg ADS-5102 (N=37)**
Baseline	n	35	29
	Mean (SD)	7.64 (3.234)	9.14 (2.388)
	Median	9.00	9.25
	Min, Max	0.8, 12.8	3.8, 13.8
MMRM Change from Baseline at Week 12	LS Mean (SE)	2.05 (0.526)	3.95 (0.562)
	95% CI	(1.00, 3.10)	(2.83, 5.07)
MMRM Treatment Difference at Week 12 (Active − Placebo)	LS Mean (SE)	1.90 (0.775)	
	95% CI	(0.35, 3.45)	
	P value	0.0168	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 16 on page 66 of the Sponsor's clinical study report body

The analysis results of the endpoints of ON time without troublesome dyskinesia are presented in **Table 12**. ADS-5102 was statistically significantly better than placebo (p-value = 0.0168) in terms of change from Baseline to Week 12 in ON time without troublesome dyskinesia, with a least square ADS-5102-placebo difference of 1.90 hours (95% CI = (0.35, 3.54)).

Table 13. Study 304 analyses of change from Baseline to Week 12 in OFF time (in hour), mITT population

		Time (hours)	
		Placebo (N=38)	**340 mg ADS-5102 (N=37)**
Baseline	n	35	29
	Mean (SD)	1.95 (1.687)	2.76 (2.104)
	Median	1.75	2.25
	Min, Max	0.0, 7.0	0.0, 7.5
MMRM Change from Baseline at Week 12	LS Mean (SE)	0.61 (0.313)	−0.49 (0.336)
	95% CI	(−0.02, 1.23)	(−1.16, 0.18)
MMRM Treatment Difference at Week 12 (Active − Placebo)	LS Mean (SE)	−1.10 (0.461)	
	95% CI	(−2.02, −0.18)	
	P value	0.0199	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 17 on page 68 of the Sponsor's clinical study report body

The analysis results of the endpoints of OFF time are presented in **Table 13**. ADS-5102 was statistically significantly better than placebo (p-value = 0.0199) in terms of change from Baseline to Week 12 in OFF time, with a least square ADS-5102-placebo difference of -1.10 hours (95% CI = (-2.02, -0.18)).

3.3 Evaluation of Safety

Please refer to Dr. Kenneth Bergmann's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Overall, there is no compelling evidence from the subgroup analyses in Section 4.1 that a specific gender, race, age, or geographic region subgroup benefits differently from ADS-5102.

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Study 301

Gender

Table 14. Study 301 subgroup analyses by gender of change from Baseline in UDysRS total score, mITT population

Gender	Change from Baseline in UDysRS total score	Placebo	340 mg ADS-5102
Week 12			
Female	N	20	26
	Means (SD)[a]	-8.01 (9.602)	-20.27 (15.630)
Male	N	32	27
	Means (SD)[a]	-6.75 (16.222)	-14.00 (11.459)
Week 24			
Female	N	11	20
	Means (SD)[a]	-5.29 (14.258)	-18.50 (14.562)
Male	N	26	22
	Means (SD)[a]	-6.31 (15.450)	-14.64 (14.060)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 15. Study 301 subgroup analyses by gender of change from Baseline in ON time without troublesome dyskinesia (in hour) , mITT population

Gender	Change from Baseline in ON time without troublesome dyskinesia	Placebo	340 mg ADS-5102
Week 12			
Female	N	19	25
	Means (SD)[a]	1.36 (3.419)	3.78 (4.021)
Male	N	32	25
	Means (SD)[a]	0.45 (3.299)	4.03 (4.331)
Week 24			
Female	N	11	20
	Means (SD)[a]	2.02 (3.022)	4.07 (3.620)
Male	N	25	22
	Means (SD)[a]	0.76 (3.224)	4.58 (4.151)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 16. Study 301 subgroup analyses by gender of change from Baseline in OFF time (in hour), mITT population

Gender	Change from Baseline in OFF time	Placebo	340 mg ADS-5102
Week 12			
Female	N	19	25
	Means (SD)[a]	0.09 (2.491)	-0.94 (1.400)
Male	N	32	25
	Means (SD)[a]	0.49 (1.929)	-0.39 (2.422)
Week 24			
Female	N	11	20
	Means (SD)[a]	-1.02 (1.371)	-0.97 (1.478)
Male	N	25	22
	Means (SD)[a]	0.91 (2.402)	-0.48 (1.877)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

For both gender groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without troublesome dyskinesia, and OFF time, except for the female group for OFF time at Week 24. In the placebo group, females were more likely to

drop out than males while in the ADS-5102 group, the males dropped out more often. It should also be noted that at Week 24, the dropout percentage of females in the placebo group and male in the ADS-5102 group exceeded 50% and 35%, respectively, so the statistics of changes from Baseline to Week 24 in UDysRS total score, ON time without troublesome dyskinesia, and OFF time in those subgroups might not be interpretable.

Race

As shown in **Table 3**, the majority of the mITT population was White. The numbers of patients in other races are so small that the analysis of patients in other races would not provide conclusive results on these populations.

Age

Table 17. Study 301 subgroup analyses by age group of change from Baseline in UDysRS total score, mITT population

Age Group	Change from Baseline in UDysRS total score	Placebo	340 mg ADS-5102
Week 12			
< 65 years	N	22	28
	Means (SD)[a]	-9.60 (12.017)	-16.14 (11.721)
≥ 65 years	N	30	25
	Means (SD)[a]	-5.50 (15.181)	-18.12 (16.177)
Week 24			
< 65 years	N	16	22
	Means (SD)[a]	-9.26 (15.016)	-17.23 (14.319)
≥ 65 years	N	21	20
	Means (SD)[a]	-3.52 (14.709)	-15.65 (14.518)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 18. Study 301 subgroup analyses by age group of change from Baseline in ON time without troublesome dyskinesia (in hour) , mITT population

Age Group	Change from Baseline in ON time without troublesome dyskinesia	Placebo	340 mg ADS-5102
Week 12			
< 65 years	N	21	28
	Means (SD)[a]	0.14 (2.688)	4.02 (4.818)
≥ 65 years	N	30	22
	Means (SD)[a]	1.25 (3.704)	3.76 (3.173)
Week 24			
< 65 years	N	16	22
	Means (SD)[a]	0.95 (2.268)	4.73 (4.597)
≥ 65 years	N	20	20
	Means (SD)[a]	1.30 (3.803)	3.90 (2.923)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 19. Study 301 subgroup analyses by age group of change from Baseline in OFF time (in hour), mITT population

Age Group	Change from Baseline in OFF time	Placebo	340 mg ADS-5102
Week 12			
< 65 years	N	21	28
	Means (SD)[a]	0.32 (2.210)	-0.44 (2.041)
≥ 65 years	N	30	22
	Means (SD)[a]	0.36 (2.127)	-0.96 (1.901)
Week 24			
< 65 years	N	16	22
	Means (SD)[a]	-0.13 (1.874)	-0.73 (1.765)
≥ 65 years	N	20	20
	Means (SD)[a]	0.68 (2.591)	-0.69 (1.664)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

For both age groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without troublesome dyskinesia, and OFF time. It should be noted that at Week 24, the dropout percentages of the age group by treatment subgroups are 29%

- 38%, so the statistics of changes from Baseline to Week 24 in UDysRS total score, ON time without troublesome dyskinesia, and OFF time in the those subgroups might not be interpretable.

Geographic Region

Study 301 was conducted mainly in the United States. A total of three out of the 121 patients in the mITT population were from the Canadian study center. No subgroup analyses by geographic region were performed.

4.1.2 Study 304

Gender

Table 20. Study 304 subgroup analyses by gender of change from Baseline in UDysRS total score, mITT population

Gender	Change from Baseline to Week 12 in UDysRS total score	Placebo	340 mg ADS-5102
Female	N	17	12
	Means (SD)[a]	-8.41 (13.134)	-25.92 (13.541)
Male	N	18	17
	Means (SD)[a]	-5.94 (11.378)	-17.47 (18.025)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 21. Study 304 subgroup analyses by gender of change from Baseline in ON time without troublesome dyskinesia (in hour), mITT population

Gender	Change from Baseline to Week 12 in ON time without troublesome dyskinesia	Placebo	340 mg ADS-5102
Female	N	17	12
	Means (SD)[a]	1.90 (3.972)	4.38 (4.068)
Male	N	18	17
	Means (SD)[a]	2.87 (2.849)	2.69 (2.277)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 22. Study 304 subgroup analyses by gender of change from Baseline in OFF time (in hour), mITT population

Gender	Change from Baseline to Week 12 in OFF time	Placebo	340 mg ADS-5102
Female	N	17	12
	Means (SD)[a]	0.85 (2.238)	-0.48 (1.554)
Male	N	18	17
	Means (SD)[a]	0.58 (1.805)	-0.98 (1.940)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

For both gender groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without troublesome dyskinesia, and OFF time, except for the male group for ON time without troublesome dyskinesia at Week 12. In the ADS-5102 group, the females' dropout percentages exceeded 30%. The statistics of changes from Baseline to Week 12 in UDysRS total score, ON time without troublesome dyskinesia, and OFF time for females under ADS-5102 might not be interpretable.

Race

As shown in **Table 9**, the majority of the mITT population was White. The numbers of patients in other races are so small that the analysis of patients in other races would not provide conclusive results on these populations.

Age

Table 23. Study 304 subgroup analyses by age group of change from Baseline in UDysRS total score, mITT population

Age Group	Change from Baseline to Week 12 in UDysRS total score	Placebo	340 mg ADS-5102
< 65 years	N	14	13
	Means (SD)[a]	-3.00 (11.563)	-19.62 (19.160)
≥ 65 years	N	21	16
	Means (SD)[a]	-9.91 (11.991)	-22.06 (14.762)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 24. Study 304 subgroup analyses by age group of change from Baseline in ON time without troublesome dyskinesia (in hour), mITT population

Age Group	Change from Baseline to Week 12 in ON time without troublesome dyskinesia	Placebo	340 mg ADS-5102
< 65 years	N	14	13
	Means (SD)[a]	1.96 (3.055)	2.60 (2.538)
≥ 65 years	N	21	16
	Means (SD)[a]	2.70 (3.692)	4.03 (3.586)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 25. Study 304 subgroup analyses by age group of change from Baseline in OFF time (in hour), mITT population

Age Group	Change from Baseline to Week 12 in OFF time	Placebo	340 mg ADS-5102
< 65 years	N	14	13
	Means (SD)[a]	0.43 (1.230)	-0.78 (1.996)
≥ 65 years	N	21	16
	Means (SD)[a]	0.90 (2.395)	-0.77 (1.647)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

For both age groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without troublesome dyskinesia, and OFF time.

Geographic Region

Table 26. Study 304 subgroup analyses by region of change from Baseline in UDysRS total score, mITT population

Region	Change from Baseline to Week 12 in UDysRS total score	Placebo	340 mg ADS-5102
Non-US	N	28	18
	Means (SD)[a]	-6.50 (12.776)	-27.50 (16.332)
US	N	7	11
	Means (SD)[a]	-9.71 (9.569)	-10.27 (10.753)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the region specific mITT population, without imputation.

Source: the reviewer

Table 27. Study 304 subgroup analyses by region of change from Baseline in ON time without troublesome dyskinesia (in hour), mITT population

Region	Change from Baseline to Week 12 in ON time without troublesome dyskinesia	Placebo	340 mg ADS-5102
Non-US	N	28	18
	Means (SD)[a]	2.31 (3.477)	4.03 (3.352)
US	N	7	11
	Means (SD)[a]	2.77 (3.440)	2.34 (2.730)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the region specific mITT population, without imputation.

Source: the reviewer

Table 28. Study 304 subgroup analyses by region of change from Baseline in OFF time (in hour), mITT population

Region	Change from Baseline to Week 12 in OFF time	Placebo	340 mg ADS-5102
Non-US	N	28	18
	Means (SD)[a]	0.52 (1.897)	-1.33 (1.658)
US	N	7	11
	Means (SD)[a]	1.48 (2.374)	0.14 (1.648)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the region specific mITT population, without imputation.

Source: the reviewer

For both region groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without troublesome dyskinesia, and OFF time, except for the US group for ON time without troublesome dyskinesia at Week 12. The dropout percentages of the ADS-5102 group are 10-15% higher than those of the placebo group under each region. The US region has small sample sizes under each treatment group, which made the comparison between treatment groups for the US region difficult to interpret.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Two statistical issues were identified. The first issue is the impact of high dropout percentages in Study 301 due to the Sponsor's decision to stop the trial early on the evaluation of efficacy. Discussions were provided in Section 3.2.1.4. It should be noted that biases could be introduced due to the post-hoc nature of the additional analyses and that cautions are needed especially for the interpretations of Week 24 endpoint results. The second issue is the differentiable dropout between treatment groups in Study 304. The statistical conclusion from the exploratory method by the reviewer does not differ from that from the pre-specified analysis method.

5.2 Collective Evidence

Study ADS-AMT-PD301 and Study ADS-AMT-PD304 provided efficacy evidences that Gocovri is efficacious as a treatment of levodopa-induced dyskinesia: Gocovri is statistically better than placebo in terms of change from Baseline to Week 12 in the Unified Dyskinesia Rating Scale total score.

5.3 Conclusions and Recommendations

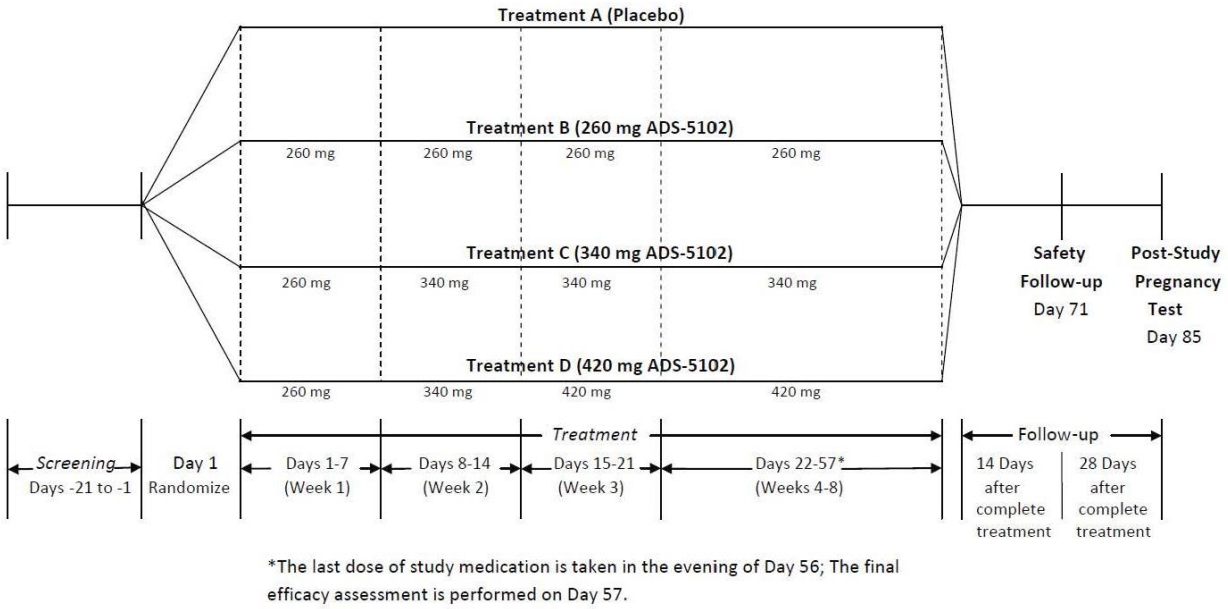
Based on the statistical evidences from Study ADS-AMT-PD301 and Study ADS-AMT-PD304, the reviewer concluded that Gocovri is superior to placebo in treating levodopa-induced dyskinesia.

A new efficacy study with a length no shorter than 24 weeks is recommended to confirm the efficacy of Gocovri beyond 12 weeks.

APPENDIX. Description of the Study Submitted by the Sponsor as Supporting Evidence for Drug Efficacy

Study 201 was a double-blind, placebo-controlled, randomized, 4-arm, parallel-group multi-center study to evaluate the efficacy, safety, and tolerability of ADS-5102 as a treatment of LID in subjects with PD. A total of 80 patients were planned to be randomized in a 1:1:1:1 ratio to placebo, 260 mg ADS-5102, 340 mg ADS-5102, and 420 mg ADS-5102. Patients were recruited in 31 study centers in the United States.

Figure 8. Study 201 design schematic



Source: figure on page 44 of the Sponsor's statistical analysis plan

Figure 8 depicts the study design schematic. Following the completion of the Baseline visit, the subjects were scheduled to return to the clinic on Days 8, 15, 29, 43, and 57 of dosing. A final safety follow-up was schedule for Day 71.

The primary efficacy endpoint was change from Baseline to Day 57/Week 8 in the UDysRS total score. The key secondary efficacy endpoints was claimed to be the change from Baseline to Day57/Week 8 in the Fatigue Severity Scale[3] (FSS) score. FSS is a 9-item self-reported scale. Each item of the scale has a range of 1 to 7, with 1 representing strongly disagree and 7 strongly agree. The range of the FSS is therefore 0-63. The FSS total score was represented by the means of all answered items.

[3] Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of neurology*, 46(10), 1121-1123.

In order to handle the multiplicity of endpoints, the primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of $\alpha = 0.05$, in the following order:

- 420 mg ADS-5102 versus placebo for UDysRS at Week 8
- 420 mg ADS-5102 versus placebo for FSS at Week 8
- 340 mg ADS-5102 versus placebo for UDysRS at Week 8
- 340 mg ADS-5102 versus placebo for FSS at Week 8
- 260 mg ADS-5102 versus placebo for UDysRS at Week 8
- 260 mg ADS-5102 versus placebo for FSS at Week 8

Table 29. Study 201 patient disposition, randomized population

Number (%) of Subjects	Placebo (N=22)	260 mg ADS-5102 (N=20)	340 mg ADS-5102 (N=21)	420 mg ADS-5102 (N=20)	All ADS-5102 (N=61)
Randomized	22 (100)	20 (100)	21 (100)	20 (100)	61 (100)
Completed the study[a]	20 (90.9)	17 (85.0)	18 (85.7)	12 (60.0)	47 (77.0)
Withdrawn from study	2 (9.1)	3 (15.0)	3 (14.3)	8 (40.0)	14 (23.0)
Reasons for withdrawal:					
eGFR < 50 mL/min/1.73 m^2	0	0	1 (4.8)	0	1 (1.6)
Intolerable/unacceptable AE	0	3 (15.0)	3 (14.3)	8 (40.0)	14 (23.0)
Other	2 (9.1)	0	0	0	0

[a] As recorded on the eCRF end of study page (Day 71 or Safety Follow-up Visit)
Subjects may each have more than one reason for withdrawal

Source: Table 6 on page 57 of the Sponsor's clinical study report body

The patient disposition is presented in **Table 29**. Among the 83 randomized patients, 22 (26.5%), 20 (24.1%), 21 (25.3%), 20 (24.1%) patients were randomized to the placebo, 260 mg ADS-5102, 340 mg ADS-5102, and 420 mg ADS-5102, respectively. The 420 mg ADS-5102 has noticeably more patients withdrawn from the study, compared to other treatment groups.

The treatment groups appeared similar in terms of age, gender, and race, as well as baseline FSS score, MMSE score, and Hoehn and Yahr score.

Table 30. Study 201 analyses of change from Baseline to Week 8 in UDysRS total score, mITT population

	Statistic	Placebo (N=22)	260 mg ADS-5102 (N=19)	340 mg ADS-5102 (N=20)	420 mg ADS-5102 (N=19)
Baseline	n	22	19	20	19
	Mean (SD)	39.2 (17.79)	40.2 (13.70)	44.1 (12.30)	41.2 (11.93)
	Median	38.0	38.0	42.0	42.0
	Min, Max	9, 79	19, 67	20, 72	19, 72
	Q1, Q3	29.0, 51.0	30.0, 53.0	36.5, 48.0	33.0, 48.0
Day 57/Week 8	n	22	19	20	19
	Mean (SD)	33.0 (16.35)	28.2 (18.24)	25.4 (17.22)	24.5 (12.32)
	Median	32.0	20.0	22.0	24.0
	Min, Max	10, 71	1, 72	1, 68	6, 53
	Q1, Q3	18.0, 41.0	16.0, 45.0	15.0, 30.5	13.0, 32.0
Change from Baseline	n	22	19	20	19
	Mean (SD)	−6.1 (14.08)	−12.0 (13.20)	−18.8 (10.84)	−16.7 (13.77)
	Median	0.0	−13.0	−17.0	−16.0
	Min, Max	−44, 19	−42, 12	−40, −4	−40, 5
	Q1, Q3	−14.0, 4.0	−20.0, −4.0	−25.0, −11.0	−30.0, −5.0
	LS Mean (SE)	−6.7 (2.68)	−12.3 (2.88)	−17.9 (2.82)	−16.7 (2.88)
	95% CI	(−12.0, −1.3)	(−18.0, −6.5)	(−23.6, −12.3)	(−22.4, −10.9)
Treatment Difference[a]	LS Mean	—	−5.6	−11.3	−10.0
	95% CI	—	(−13.4, 2.2)	(−19.1, −3.5)	(−17.8, −2.2)
	p-value	—	0.1595	0.0051	0.0131

P-values are based on the comparison between 260 mg ADS-5102 (and respectively 340 mg ADS–5102, 420 mg ADS–5102) vs. Placebo from the ANCOVA model with change from baseline as the dependent variable, treatment group as a factor, and the baseline value as a covariate.

[a] Active minus Placebo

Source: Table 14 on page 67 of the Sponsor's clinical study report body

Table 31. Study 201 analyses of change from Baseline to Week 8 in FSS score, mITT population

	Statistic	Placebo (N=22)	260 mg ADS-5102 (N=19)	340 mg ADS-5102 (N=20)	420 mg ADS-5102 (N=19)
Day 57/Week 8	n	22	19	20	19
Change from Baseline	LS Mean (SE)	−0.25 (0.267)	−0.06 (0.289)	−0.55 (0.280)	0.00 (0.287)
	95% CI	(−0.8, 0.3)	(−0.6, 0.5)	(−1.1, 0.0)	(−0.6, 0.6)
Treatment Difference[a]	LS Mean	—	0.2	−0.3	0.3
	95% CI	—	(−0.6, 1.0)	(−1.1, 0.5)	(−0.5, 1.0)
	p-value	—	0.6298	0.4314	0.5223

P-values are based on the comparison between 260 mg ADS-5102 (and respectively 340 mg ADS–5102, 420 mg ADS–5102) vs. Placebo from the ANCOVA model with change from baseline as the dependent variable, treatment group as a factor, and the baseline value as a covariate.

[a] Active minus Placebo

Source: Table 17 on page 72 of the Sponsor's clinical study report body

The analysis results of the UDysRS total score are presented in **Table 30**. The analysis results of the FSS score are presented in **Table 31**. 420 mg ADS-5102 was statistically significantly better than placebo (p-value = 0.0131) in terms of change from Baseline to Week 8 in UDysRS total score, with a least square ADS-5102-placebo difference of -10.0 points (95% CI = (-17.8, -2.2)). Based on the pre-specified hierarchy of testing, because the comparison of 420 mg ADS-5102 and placebo in the FSS score at Week 8 had a non-significant p-value of 0.5223, the testing should stop.

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

/s/

XIANGMIN ZHANG
08/11/2017

KUN JIN
08/11/2017
I concur with the revised review.

HSIEN MING J HUNG
08/11/2017

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 Number:	208944
Drug Name:	Amantadine Hydrochloride Extended Release Capsule
Indication:	Levodopa-Induced Dyskinesia
Applicant:	Adamas Pharmaceuticals, Inc.
Dates:	Receipt Date: October 24, 2016
	PDUFA Goal Date: August 24, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiangmin Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader
	Hsien Ming Hung, Ph.D., Director
Medical Division:	Division of Neurology Products
Clinical Team:	Kenneth Bergmann, M.D., Clinical Reviewer
	Gerald Podskalny, D.O., Team Leader
	Eric Bastings, M.D., Deputy Director
	William Dunn, M.D., Director
Project Manager:	Anhtu Nguyen, R.Ph.

Keywords: clinical studies, mixed models, NDA review

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

This review describes the statistical findings of Gocovri (amantadine hydrochloride extended release capsule) as a treatment of levodopa-induced dyskinesia. The review confirmed that Study ADS-AMT-PD301 and Study ADS-AMT-PD304 in the 505(b)(2) new drug application provided statistical evidences that Gocovri is efficacious as a treatment of levodopa-induced dyskinesia: Gocovri is statistically better than placebo in terms of change from Baseline to Week 12 in the Unified Dyskinesia Rating Scale total score.

2 INTRODUCTION

2.1 Overview

On October 24, 2016, Adamas Pharmaceuticals, Inc. (the Sponsor) submitted a 505(b)(2) new drug application (NDA) for amantadine hydrochloride extended release capsule (ADS-5102 under the Sponsor's clinical development program) as a treatment of levodopa-induced dyskinesia (LID) for subjects with Parkinson's disease (PD). The NDA submission lists Food and Drug Administration approved drug Symmetrel® (NDAs 16020, 16023, 17118, and 18101) as the 505(b)(2) reference. The Sponsor submitted three clinical studies in the NDA application to support the efficacy claim of ADS-5102.

Table 1. List of studies in this review

Study Number	Phase and Design	Treatment Period (in week)	Study Arm (Number of randomized patients per arm)	Study Population
ADS-PAR-AM201	Phase 2, randomized, placebo-controlled, parallel-group, fixed dose	8	Placebo (22) 260 mg once daily (20) 340 mg once daily (21) 420 mg once daily (20)	Male and female subjects 30-85 years of age with Parkinson's disease
ADS-AMT-PD301	Phase 3, randomized, placebo-controlled, parallel-group, fixed dose	25	Placebo (63) 340 mg once daily (63)	
ADS-AMT-PD304	Phase 3, randomized, placebo-controlled, parallel-group, fixed dose	13	Placebo (39) 340 mg once daily (38)	

Source: reviewer's summary

The three clinical studies are summarized in **Table 1**. Study ADS-PAR-AM201, Study ADS-AMT-PD301, and Study ADS-AMT-PD304 are referred to as Study 201, Study 301, and Study 304, respectively, in the rest of this review. Study 301 and Study 304 are phase 3 studies to be reviewed in more detail in Section 3. In these studies, the dosing of 170 mg per capsule (or 340 mg daily) was reported by the Sponsor. The actual amantadine free base quantity was 137 mg per capsule (or 274 mg daily). Study 201 is a phase 2 study, with a design considered not sufficient for the evaluation of efficacy due to the short duration of the study (see the type C meeting minutes dated December 18, 2013). Nonetheless, Study 201 was submitted as a supporting study. It is summarized in the Appendix.

2.2 Data Sources

The electronic submission of this NDA is located at
\\cdsesub1\evsprod\NDA208944\0001\

The study reports are located at
\\cdsesub1\evsprod\NDA208944\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\lid\5351-stud-rep-contr\

The datasets are located at
\\cdsesub1\evsprod\NDA208944\0001\m5\datasets\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data quality and analysis quality are adequate. The reviewer was able to perform independent review using Sponsor's submitted datasets and confirm the Sponsor's analysis results.

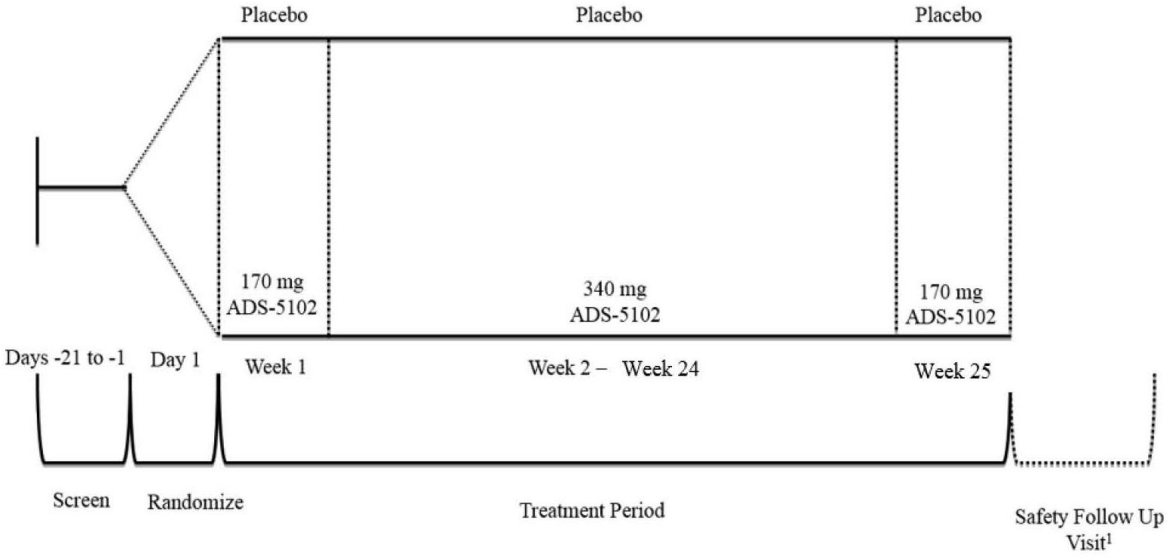
3.2 Evaluation of Efficacy

3.2.1 Study 301

3.2.1.1 Study Design and Endpoints

Study 301 was a double-blind, placebo-controlled, randomized, 2-arm, parallel-group, phase 3, multi-center study to evaluate the efficacy, safety, and tolerability of ADS-5102 as a treatment of LID in subjects with PD. A total of 120 patients were planned to be randomized in a 1:1 ratio to placebo and ADS-5102 340 mg once daily. Patients were screened in 42 study centers in the United States and 2 centers in Canada and randomized in 40 centers in the United States and 1 center in Canada.

Figure 1. Study 301 design schematic



[1] Applicable only for subjects who complete 25 weeks of treatment and decline participation in the open-label extension

Source: figure on page 38 of the Sponsor's statistical analysis plan

Figure 1 depicts the study design schematic. Following the completion of the Baseline visit, the subjects were scheduled to return to the clinic after 1, 2, 4, 8, 12, 18, 24, and 25 weeks of dosing.

Subjects who complete 25 weeks of dosing have the option of entering the open-label extension study ADS-AMT-PD302. For each patient assigned the ADS-5102 treatment, his/her study mediation was administrated as 170 mg ADS-5102 once daily (one capsule of 170 mg ADS-5102 and one capsule of placebo) for one week then 340 mg ADS-5102 once daily (two capsules of 170 mg ADS-5102) for 23 weeks, ending with 170 mg ADS-5102 once daily during Week 25.

The Sponsor made a decision to stop the trial early and allowed all randomized subjects to complete the study visit at Week 12. The Sponsor informed the agency of the decision on October 23, 2015 in the cover letter to the submission of Study 301 statistical analysis plan. In the cover letter, the Sponsor explained that the early stopping decision is made to accelerate their NDA submission (b) (4) and that the decision was not made due to any safety signal. According to the clinical study report of Study 301, the last patient completed the study on November 18, 2015. However, the other phase 3 study (i.e. Study 304) had the last patient complete the study on March 10, 2016. The Sponsor should have been able to allow all randomized subjects in Study 301 to complete the Week 24 study visit without actually delaying the NDA submission.

The primary efficacy endpoint was change from Baseline to Week 12 in the Unified Dyskinesia Rating Scale (UDysRS)[1] total score. The UDysRS has four parts with a range of 0-104 in total score (smaller scores indicate less severe symptoms):

I. Historical disability of on-dyskinesia impact
II. Historical disability of off-dystonia impact
III. Objective impairment
IV. Objective disability based on Part III activities

More details of the four parts and the imputation rules for the subscales (see **Figure 2**) are as follows:

IA. Historical disability of on-dyskinesia impact (Question 1, 0-4 points)
IB. Historical disability of on-dyskinesia impact (Question 2-11, 0-40 points in total)
IIA. Historical disability of off-dystonia impact (Question 12, 0-4 points)
IIB. Historical disability of off-dystonia impact (Question 13-15, 0-12 points in total)
III. Objective impairment (Question 16-22, 0-28 points in total)
IV. Objective disability based on Part III activities (Question 23-26, 0-16 points in total)

[1] Goetz, C. G., Nutt, J. G., & Stebbins, G. T. (2008). The unified dyskinesia rating scale: presentation and clinimetric profile. *Movement Disorders*, 23(16), 2398-2403.

Figure 2. Study 301 imputation rules for individual UDysRS subscale items and total score

	Subscale (Total) Items	Missing Items	Imputation (Y/N)	Imputation Method
Part IA	1	1	No	Assign a value of 0
Part I B	10	1	Yes	Average of non-missing items within the subscale
Part IIA	1	1	No	Assign a value of 0
Part II B	3	1	Yes	Average of non-missing items within the subscale
Part III	7	1	Yes	Average of non-missing items within the subscale
Part IV	4	1	Yes	Average of non-missing items within the subscale
Total Objective Score (Part III + Part IV)	11	Part III or Part IV	No	Missing
Total UDysRS Score	26	Part I B or Part II B or Part III or Part IV	No	Missing

Source: Table 2 on page 19 of the Sponsor's statistical analysis plan

The key secondary efficacy endpoints were

- The change from Baseline to Week 24 in UDysRS total score
- The change from Baseline to Week 12 in ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia)
- The change from Baseline to Week 24 in ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia)
- The change from Baseline to Week 12 in OFF time
- The change from Baseline to Week 24 in OFF time

The ON time and OFF time were calculated from the PD home diary[2]. A set of two consecutive 24-hour PD home diaries (48 hours in total) were completed during screening and prior to each efficacy visit. If more than four 30-minute intervals were missing, the diary was considered not evaluable. If four or fewer 30-minute intervals were missing, each missing 30-minute interval was imputed by the average of the responses of the immediately preceding and subsequent completed non-missing intervals. If a 30-minute interval was missing at the beginning or end of a 48-hour diary reporting period, it was imputed by the closest completed non-missing interval.

[2] Hauser, R. A., Friedlander, J., Zesiewicz, T. A., Adler, C. H., Seeberger, L. C., O'brien, C. F., Molho, E. S. & Factor, S. A. (2000). A home diary to assess functional status in patients with Parkinson's disease with motor fluctuations and dyskinesia. *Clinical neuropharmacology*, *23*(2), 75-81.

3.2.1.2 Statistical Methodologies

The efficacy analysis population was the modified intent-to-treat (mITT) population defined as all randomized subjects who were dosed and who provided at least one post-baseline assessment of the UDysRS.

The primary endpoint was analyzed using a mixed model with repeated measure (MMRM), with treatment, visit (three levels corresponding to Weeks 2, 8, and 12), and treatment by visit interaction as fixed effects and baseline value of the UDysRS total score as the covariate. The unstructured variance-covariance matrix and Kenward-Roger approximation were used for the analysis.

The Week 12 secondary endpoints were analyzed using similar MMRM analyses, with endpoint specific baseline as the covariate. The Week 24 secondary endpoints were also analyzed using the MMRM, except that the fixed effect visit had five levels: Weeks 2, 8, 12, 18, and 24.

In order to handle the multiplicity of endpoints, the primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of $\alpha = 0.05$, in the following order:

- 340 mg ADS-5102 versus placebo for UDysRS at Week 12
- 340 mg ADS-5102 versus placebo for UDysRS at Week 24
- 340 mg ADS-5102 versus placebo for ON time without troublesome dyskinesia at Week 12
- 340 mg ADS-5102 versus placebo for ON time without troublesome dyskinesia at Week 24
- 340 mg ADS-5102 versus placebo for OFF time at Week 12
- 340 mg ADS-5102 versus placebo for OFF time at Week 24

3.2.1.3 Patient Disposition, Demographic and Baseline Characteristics

Table 2. Study 301 patient disposition, randomized population

Number (%) of Subjects	Placebo (N=63)	340 mg ADS-5102 (N=63)	All (N=126)
Randomized	63 (100.0)	63 (100.0)	126 (100.0)
Completed the study[a]	42 (66.7)	42 (66.7)	84 (66.7)
Withdrawn from study	21 (33.3)	21 (33.3)	42 (33.3)
Reasons for withdrawal			
Sponsor's decision: subject ongoing when study stopped	7 (11.1)	7 (11.1)	14 (11.1)
Subject discontinued study drug and wished to withdraw[b]	3 (4.8)	10 (15.9)	13 (10.3)
Subject unwilling to proceed	7 (11.1)	2 (3.2)	9 (7.1)
Subject lost to follow-up	1 (1.6)	1 (1.6)	2 (1.6)
Other	3 (4.8)	1 (1.6)	4 (3.2)

[a] Includes 5 subjects who completed the original protocol with study duration of 13 weeks.
[b] Subjects who discontinued study drug were encouraged to complete all study assessments.

Source: Table 8 on page 53 of the Sponsor's clinical study report body

The patient disposition is presented in **Table 2**. A total of 189 patients were screened, of which 126 (66.7%) randomized. Among the 126 randomized patients, 63 (50.0%) were randomized to the placebo group and 63 (50.0%) to the 340 mg ADS-5102 group. A total of five patients in the placebo group completed the study with duration of 13 weeks according to an early version of the protocol. A total of 84 patients completed the study: 42 in the placebo group and 42 in the ADS-5102 group. Compared to patients in the placebo group, more patients in the ADS-5102 group discontinued the treatment early due to adverse event (13 patients in the ADS-5102 group discontinued the treatment due to adverse event vs. 4 patients in the placebo discontinued for the same reason). The Sponsor's decision to stop the study early impacted the discontinuation rates noticeably.

Table 3. Study 301 patient demographics, mITT population

	Placebo (N=58)	340 mg ADS-5102 (N=63)	All (N=121)
Age (yrs)			
n	58	63	121
Mean (SD)	65.5 (8.70)	63.9 (9.43)	64.7 (9.09)
Median	66.0	64.0	66.0
Min, Max	43, 82	34, 81	34, 82
Age categories (yrs) n (%)			
<65	26 (44.8)	32 (50.8)	58 (47.9)
>=65	32 (55.2)	31 (49.2)	63 (52.1)
Sex n (%)			
Male	35 (60.3)	35 (55.6)	70 (57.9)
Female	23 (39.7)	28 (44.4)	51 (42.1)
Race n (%)			
White	51 (87.9)	60 (95.2)	111 (91.7)
Black or African American	1 (1.7)	0	1 (0.8)
Asian	3 (5.2)	2 (3.2)	5 (4.1)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (1.6)	1 (0.8)
Other	3 (5.2)	0	3 (2.5)
Ethnicity n (%)			
Hispanic or Latino	9 (15.5)	3 (4.8)	12 (9.9)
Not Hispanic or Latino	49 (84.5)	60 (95.2)	109 (90.1)
Height (cm)			
n	58	63	121
Mean (SD)	170.1 (8.81)	170.0 (9.04)	170.1 (8.89)
Median	170.0	170.2	170.0
Min, Max	152, 188	154, 188	152, 188
Weight (kg)			
n	58	63	121
Mean (SD)	78.38 (15.504)	76.10 (20.679)	77.19 (18.342)
Median	74.65	72.30	72.80
Min, Max	48.5, 115.0	41.5, 139.0	41.5, 139.0
Body Mass Index (kg/m^2)			
n	58	63	121
Mean (SD)	27.05 (4.701)	26.15 (6.226)	26.58 (5.543)
Median	26.61	25.38	26.17
Min, Max	17.8, 39.5	16.7, 48.0	16.7, 48.0
Estimated glomerular filtration rate (eGFR) by MDRD ($mL/min/1.73m^2$)			
n	58	63	121
Mean (SD)	91.2 (24.21)	97.5 (26.26)	94.5 (25.39)
Median	85.0	87.0	86.0
Min, Max	55, 166	60, 174	55, 174

Source: Table 14.1.4.1 on pages 119-120 of the Sponsor's clinical study report body

The patient demographic characteristics of the mITT population are summarized in **Table 3**. According to the Sponsor, five patients in the placebo group were randomized but excluded from the mITT population because three patients did not receive study drug and two patients did not have a post-baseline UDysRS assessment. The treatment groups appeared similar in terms of age, gender, and race. The mITT population was mainly White patients and had an average age of approximately 65 years. There were more male patients than female patients in the mITT population.

Table 4. Study 301 patient baseline characteristics, mITT population

Statistics	Placebo N = 58 Mean (SD)	ADS-5102 N = 63 Mean (SD)	All N = 121 Mean (SD)
UDysRS Total Score	38.5 (11.21)	40.9 (13.34)	39.7 (12.37)
PD Diary (hours)			
ON time without troublesome dyskinesia	8.5 (2.82)	8.3 (3.47)	8.4 (3.16)
ON time with troublesome dyskinesia	4.5 (1.96)	4.7 (2.54)	4.6 (2.27)
Total time with dyskinesia[a]	9.2 (3.16)	9.6 (3.23)	9.4 (3.19)
OFF time	3.0 (2.08)	3.2 (2.37)	3.1 (2.23)
Asleep time	8.1 (1.46)	7.8 (1.73)	7.9 (1.60)
MDS-UPDRS			
Part I	11.4 (4.04)	12.5 (6.18)	12.0 (5.29)
Part II	15.7 (5.85)	15.7 (6.77)	15.7 (6.32)
Part III	24.8 (12.19)	25.9 (14.49)	25.4 (13.39)
Part IV	11.3 (2.39)	11.8 (2.95)	11.6 (2.70)
MMSE	28.8 (1.23)	28.7 (1.52)	28.7 (1.39)
Hoehn and Yahr Stage	2.3 (0.56)	2.2 (0.54)	2.2 (0.55)

MDS-UPDRS: Movement Disorder Society - Unified Parkinson Disease Rating Scale; mITT: modified intent-to-treat; MMSE: Mini-Mental State Examination; N: number of patients; PD: Parkinson's disease; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Total time with dyskinesia includes non-troublesome and troublesome.

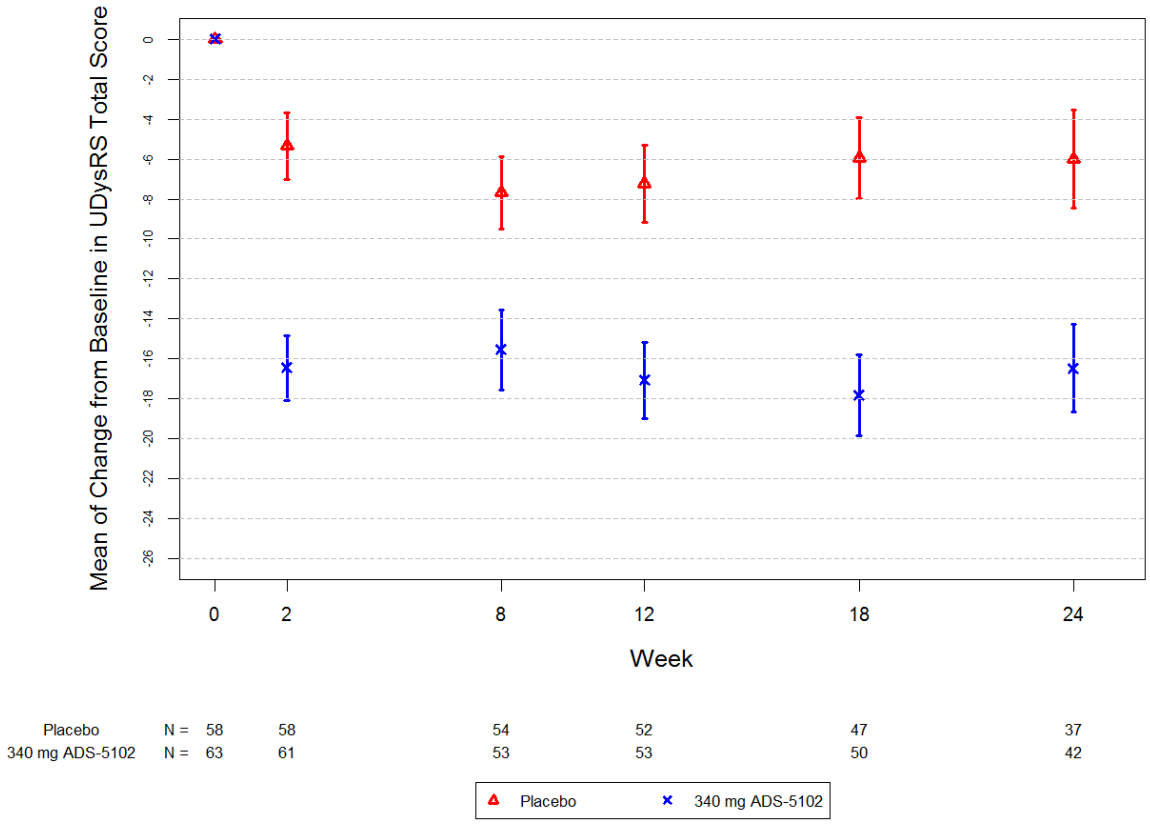
Source: selected from Table 14.1.7.1 on pages 128-131 of the Sponsor's clinical study report body

The patient baseline characteristics of the mITT population are summarized in **Table 4**. The ADS-5102 group appeared to have worse UDysRS total scores, PD Diary time, and MDS-UPDRS sub-scores, as well as larger standard deviations, than the placebo group. This might lead to an exaggerated treatment difference between the ADS-5102 group and placebo group.

In addition to these baseline characteristics, patients of the mITT population was diagnosed with PD with an average age of approximately 55.9 years (standard deviation (SD) = 9.16) for an average diagnose length of 9.2 years (SD = 4.14) at study baseline. On average, these patients started the levodopa treatment from the age of approximately 57.8 years (SD = 9.13) for a duration of 7.4 years (SD = 3.57) and experienced LID for approximately 3.7 years (SD = 2.84) at study baseline.

3.2.1.4 Results and Conclusions

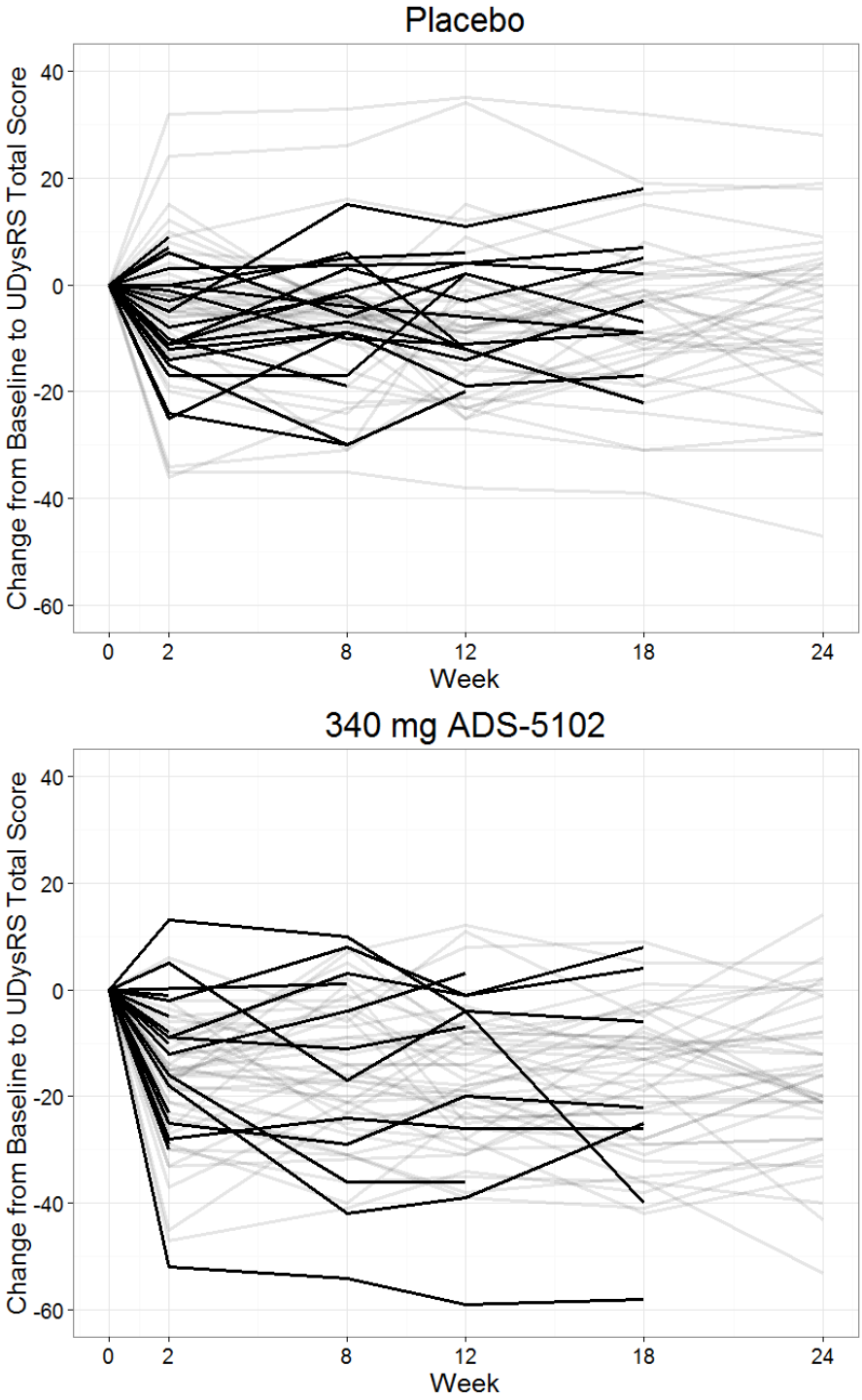
Figure 3. Study 301 mean (± standard error) of change from Baseline in UDysRS total score by week and treatment



Source: the reviewer

Figure 3 illustrates the mean of changes from Baseline in UDysRS total score by week and treatment for the Study 301 mITT population. The 340 mg ADS-5102 group appeared to have consistent average improvements of UDysRS total score based on the observed changes from Baseline values. Such improvements were on average greater than those from the placebo group. The mITT population sizes were 63 and 58 for the 340 mg ADS-5102 group and placebo group, respectively. The rates of missing observations at Week 12 were 15.9% and 10.3% for the 340 mg ADS-5102 group and placebo group, respectively; the rates of missing observations at Week 24 were 33.3% and 36.2% for the 340 mg ADS-5102 group and placebo group, respectively.

Figure 4. Study 301 time plots by treatment and patients



Source: the reviewer

In **Figure 4**, the top panel illustrates the time plots of all mITT patients in the placebo group; the bottom panel illustrates the time plots of all mITT patients in the 340 mg ADS-5102 group. For

both panels, the time plots for the completers were in gray while the ones for the non-completers were in black. No specific dropout pattern (by comparing the non-completers and completers in the same treatment group) was observed from each panel. In other words, there is little evidence from each panel that the missing at random assumption on which the MMRM relies was unreasonable.

Table 5. Study 301 analyses of change from Baseline to Week 12 and Week 24 in UDysRS total score, mITT population

		Week 12		Week 24	
		Placebo (N=58)	340 mg ADS-5102 (N=63)	Placebo (N=58)	340 mg ADS-5102 (N=63)
Baseline	Mean (SD)	38.2 (11.35)	40.9 (13.51)	37.7 (12.64)	41.0 (12.20)
	Median (Min, Max)	40.0 (8, 58)	41.0 (10, 76)	40.0 (8, 58)	42.5 (15, 70)
Week 12 or 24	Mean (SD)	31.0 (12.31)	23.8 (14.08)	31.6 (13.43)	24.6 (13.42)
	Median (Min, Max)	31.0 (1, 62)	23.0 (0, 67)	31.0 (9, 56)	29.0 (0, 49)
Change from Baseline	Mean (SD)	-7.2 (13.95)	-17.1 (13.90)	-6.0 (14.92)	-16.5 (14.26)
	Median (Min, Max)	-9.0 (-38, 35)	-18.0 (-59, 12)	-5.0 (-47, 28)	-16.0 (-53, 14)
MMRM Change from Baseline	LS Mean (SE)	-8.0 (1.64)	-15.9 (1.62)	-6.3 (1.94)	-15.6 (1.87)
	95% CI	(-11.3, -4.8)	(-19.1, -12.7)	(-10.1, -2.4)	(-19.3, -11.9)
MMRM Treatment Difference (Active - Placebo)	LS Mean (SE)	-7.9 (2.30)		-9.3 (2.70)	
	95% CI	(-12.5, -3.3)		(-14.7, -4.0)	
	P value	0.0009		0.0008	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit.

Source: Table 6 on page 35 of the Sponsor's integrated summary of efficacy

The analysis results of the endpoints of UDysRS total score are presented in **Table 5**. The summary statistics of the baseline values reported for Week 12 (or Week 24) in **Table 5** (as well as those reported in **Table 6** and **Table 7**) by the Sponsor were based on all subjects in the mITT population that had Week 12 (or Week 24) measurements, without any imputation. Based on the pre-specified analysis method, ADS-5102 was statistically significantly better than placebo (p-value = 0.0009) in terms of change from Baseline to Week 12 in UDysRS total score, with a least square ADS-5102-placebo difference of -7.9 points (95% CI = (-12.5, -3.3)); ADS-5102 was also statistically significantly better than placebo (p-value = 0.0008) in terms of change from Baseline to Week 24 in UDysRS total score, with a least square ADS-5102-placebo difference of -9.3 points (95% CI = (-14.7, -4.0)).

Table 6. Study 301 analyses of change from Baseline to Week 12 and Week 24 in ON time (in hour), mITT population

		Time (hours)	
		Placebo (N=58)	**340 mg ADS-5102 (N=63)**
Week 12 Data			
Baseline	n	51	50
	Mean (SD)	8.45 (2.915)	8.10 (3.649)
	Median	8.25	8.31
	Min, Max	3.8, 15.3	0.0, 15.0
MMRM Change from Baseline at Week 12	LS Mean (SE)	0.82 (0.432)	3.56 (0.434)
	95% CI	(−0.04, 1.67)	(2.70, 4.42)
MMRM Treatment Difference at Week 12 (Active - Placebo)	LS Mean (SE)	2.74 (0.612)	
	95% CI	(1.53, 3.96)	
	P value	<0.0001	
Week 24 Data			
Baseline	n	36	42
	Mean (SD)	8.14 (2.844)	8.05 (3.526)
	Median	8.13	8.00
	Min, Max	3.8, 15.3	1.5, 14.8
MMRM Change from Baseline at Week 24	LS Mean (SE)	1.37 (0.456)	3.59 (0.440)
	95% CI	(0.46, 2.28)	(2.71, 4.46)
MMRM Treatment Difference at Week 24 (Active - Placebo)	LS Mean (SE)	2.22 (0.634)	
	95% CI	(0.96, 3.47)	
	P value	0.0007	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 8, and 12 [for Week 12 data] or Weeks 2, 8, 12, 18, and 24 [for Week 24 data]), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 16 on page 69 of the Sponsor's clinical study report body

The analysis results of the endpoints of ON time without troublesome dyskinesia are presented in **Table 6**. ADS-5102 was statistically significantly better than placebo (p-value < 0.0001) in terms of change from Baseline to Week 12 in ON time without troublesome dyskinesia, with a least square ADS-5102-placebo difference of 2.74 hours (95% CI = (1.53, 3.96)). ADS-5102 was also statistically significantly better than placebo (p-value = 0.0007) in terms of change from Baseline to Week 24 in ON time without troublesome dyskinesia, with a least square ADS-5102-placebo difference of 2.22 hours (95% CI = (0.96, 3.47)).

Table 7. Study 301 analyses of change from Baseline to Week 12 and Week 24 in OFF time (in hour), mITT population

		Time (hours)	
		Placebo (N=58)	**340 mg ADS-5102 (N=63)**
Week 12 Data			
Baseline	n	51	50
	Mean (SD)	3.01 (2.118)	3.29 (2.366)
	Median	2.75	3.25
	Min, Max	0.0, 9.0	0.0, 9.5
MMRM Change from Baseline at Week 12	LS Mean (SE)	0.32 (0.263)	−0.59 (0.265)
	95% CI	(−0.20, 0.84)	(−1.11, −0.06)
MMRM Treatment Difference at Week 12 (Active - Placebo)	LS Mean (SE)	−0.90 (0.373)	
	95% CI	(−1.64, −0.16)	
	P value	0.0171	
Week 24 Data			
Baseline	n	36	42
	Mean (SD)	3.14 (2.229)	3.11 (2.376)
	Median	2.88	2.94
	Min, Max	0.0, 9.0	0.0, 8.8
MMRM Change from Baseline at Week 24	LS Mean (SE)	0.22 (0.282)	−0.58 (0.268)
	95% CI	(−0.34, 0.78)	(−1.12, -0.05)
MMRM Treatment Difference at Week 24 (Active - Placebo)	LS Mean (SE)	−0.81 (0.389)	
	95% CI	(−1.58, −0.04)	
	P value	0.0406	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 8, and 12 [for Week 12 data] or Weeks 2, 8, 12, 18, and 24 [for Week 24 data]), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 17 on page 71 of the Sponsor's clinical study report body

The analysis results of the endpoints of OFF time are presented in **Table 7**. ADS-5102 was statistically significantly better than placebo (p-value = 0.0171) in terms of change from Baseline to Week 12 in OFF time, with a least square ADS-5102-placebo difference of -0.90 hour (95% CI = (-1.64, -0.16)). ADS-5102 was also statistically significantly better than placebo (p-value = 0.0406) in terms of change from Baseline to Week 24 in OFF time, with a least square ADS-5102-placebo difference of -0.81 hour (95% CI = (-1.58, -0.04)).

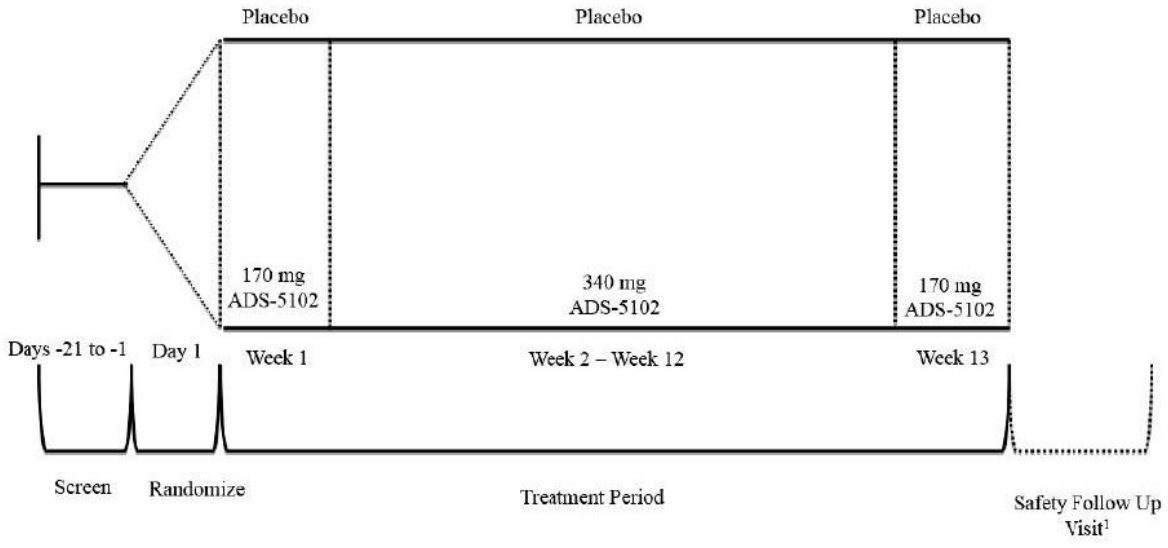
Because the Week 24 dropout percentages are high in each treatment group for the mITT population (33.3% and 36.2% for the 340 mg ADS-5102 group and placebo group, respectively), how to interpret the Week 24 results for the UDysRS, ON time, and OFF time is an issue. In the original NDA submission, the Sponsor performed additional analysis on the Week 24 UDysRS endpoint using the per protocol (PP) population, defined as the subset of the mITT population who met inclusion criteria 6, 8, 9, completed 12 weeks of study treatment, and provided Week 12 UDysRS efficacy assessments. The Sponsor also performed additional analysis using the PP population who had Week 24 data. Although these analyses showed statistically significant results, they are not adequate to test the validity of the missing at random assumption of the MMRM method. The Sponsor was requested to provide several additional sensitivity analyses for the primary and key secondary endpoints. Two post-hoc sensitivity analyses were submitted as a result: (1) an analysis assuming the data are missing at random and using the multiple imputation method and (2) an analysis assuming the data are not missing at random (NMAR) and imputing missing observations in the placebo group with the multiple imputation method in (1) while imputing missing observations in the ADS-5102 group as if they had been obtained in the placebo group. The results of the additional sensitivity analyses provided nominal significant p-values and appeared consistent with results from the pre-specified analysis methods for the primary and key secondary endpoints, except that the sensitivity analysis assuming NMAR provided a non-significant nominal p-value for the Week 24 OFF time endpoint. It should be noted that biases could be introduced due to the post-hoc nature of the additional sensitivity analyses and that cautions are needed especially for the interpretations of Week 24 endpoint results due to the high dropout percentages. In addition, the impact of the Sponsor's decision to stop the trial early on the Week 24 efficacy results is difficult to assess and interpret.

3.2.2 Study 304

3.2.2.1 Study Design and Endpoints

Study 304 was a double-blind, placebo-controlled, randomized, 2-arm, parallel-group, phase 3, multi-center study to evaluate the efficacy, safety, and tolerability of ADS-5102 as a treatment of LID in subjects with PD. A total of 72 patients were planned to be randomized in a 1:1 ratio to placebo and ADS-5102 340 mg once daily. Patients were screened in 39 study centers and randomized in 32 centers in the Austria, France, Germany, Spain, and United States.

Figure 5. Study 304 design schematic



[1] Applicable only for subjects who complete 13 weeks of treatment and decline participation in the open-label extension.

Source: figure on page 74 of the Sponsor's statistical analysis plan

Figure 5 depicts the study design schematic. Following the completion of the Baseline visit, the subjects were scheduled to return to the clinic after 1, 2, 4, 8, 12, and 13 weeks of dosing. Subjects who complete 13 weeks of dosing have the option of entering the open-label extension study ADS-AMT-PD302, which was also the extension study for Study 301. For each patient assigned the ADS-5102 treatment, his/her study mediation was administrated as 170 mg ADS-5102 once daily (one capsule of 170 mg ADS-5102 and one capsule of placebo) for one week then 340 mg ADS-5102 once daily (two capsules of 170 mg ADS-5102) for 11 weeks, ending with 170 mg ADS-5102 once daily during Week 13.

The primary efficacy endpoint was change from Baseline to Week 12 in the UDysRS total score. The imputation rules for the UDysRS subscales were the same for Study 301 and Study 304 (see details in **Figure 2** in Section 3.1.1.1).

The key secondary efficacy endpoints were

- The change from Baseline to Week 12 in ON time without troublesome dyskinesia
- The change from Baseline to Week 12 in OFF time

The calculations and imputations of the ON time and OFF time for Study 304 were the same as described in Section 3.2.1.1 for Study 301.

3.2.2.2 Statistical Methodologies

The efficacy analyses population was the modified intent-to-treat (mITT) population defined as all randomized subjects who were dosed and who provided at least one post-baseline assessment of the UDysRS.

The primary endpoint was analyzed using the MMRM, with treatment, visit (four levels corresponding to Weeks 2, 4, 8, and 12), and treatment by visit interaction as fixed effects and baseline value of the UDysRS total score as the covariate. The unstructured variance-covariance matrix and Kenward-Roger approximation were used for the analysis.

The key secondary endpoints were analyzed using similar MMRM analyses, with endpoint specific baseline as the covariate.

In order to handle the multiplicity of endpoints, the primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of $\alpha = 0.05$, in the following order:

- 340 mg ADS-5102 versus placebo for UDysRS at Week 12
- 340 mg ADS-5102 versus placebo for ON time without troublesome dyskinesia at Week 12
- 340 mg ADS-5102 versus placebo for OFF time at Week 12

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

Table 8. Study 304 patient disposition, randomized population

Number (%) of Subjects	Placebo (N=39)	340 mg ADS-5102 (N=38)	All (N=77)
Randomized	39 (100.0)	38 (100.0)	77 (100.0)
Completed the study	35 (89.7)	29 (76.3)	64 (83.1)
Withdrawn from study	4 (10.3)	9 (23.7)	13 (16.9)
Reasons for withdrawal			
Subject discontinued study drug and wished to withdraw[a]	3 (7.7)	6 (15.8)	9 (11.7)
Subject unwilling to proceed	0	1 (2.6)	1 (1.3)
Other	1 (2.6)	2 (5.3)	3 (3.9)

[a] Subjects who discontinued study drug were encouraged to complete all study assessments.

Source: Table 8 on page 54 of the Sponsor's clinical study report body

The patient disposition is presented in **Table 8**. A total of 114 patients were screened, of which 77 (67.5%) randomized. Among the 77 randomized patients, 39 (50.6%) were randomized to the placebo group and 38 (49.4%) to the 340 mg ADS-5102 group. A total of 64 patients completed the study: 35 in the placebo group and 29 in the ADS-5102 group. Compared to patients in the placebo group, more patients in the ADS-5102 group discontinued the treatment early due to

adverse event (seven patients in the ADS-5102 group discontinued the treatment due to adverse event versus three patients in the placebo discontinued for the same reason).

Table 9. Study 304 patient demographics, mITT population

	Placebo (N=38)	340 mg ADS-5102 (N=37)	All (N=75)
Age (years)			
Mean (SD)	64.9 (9.08)	64.7 (9.66)	64.8 (9.31)
Median (Min, Max)	65.0 (42, 79)	66.0 (46, 80)	65.0 (42, 80)
Age categories (years), n (%)			
< 65	15 (39.5)	16 (43.2)	31 (41.3)
≥ 65	23 (60.5)	21 (56.8)	44 (58.7)
Sex, n (%)			
Male	20 (52.6)	19 (51.4)	39 (52.0)
Female	18 (47.4)	18 (48.6)	36 (48.0)
Race, n (%)			
White	38 (100.0)	36 (97.3)	74 (98.7)
Other	0	1 (2.7)	1 (1.3)
Ethnicity, n (%)			
Hispanic or Latino	0	5 (13.5)	5 (6.7)
Not Hispanic or Latino	38 (100.0)	32 (86.5)	70 (93.3)
Body mass index (kg/m^2)			
Mean (SD)	24.90 (4.825)	24.62 (4.480)	24.76 (4.629)
Median (Min, Max)	24.53 (17.7, 36.1)	23.46 (18.1, 35.3)	23.59 (17.7, 36.1)
eGFR by MDRD ($mL/min/1.73\ m^2$)			
Mean (SD)	97.6 (25.53)	94.4 (20.64)	96.0 (23.15)
Median (Min, Max)	97.5 (53, 155)	97.0 (54, 141)	97.0 (53, 155)

Source: Table 10 on page 57 of the Sponsor's clinical study report body

The patient demographic characteristics of the mITT population are summarized in **Table 9**. The treatment groups appeared similar in terms of age, gender, and race. The mITT population was mainly White patients and had an average age of approximately 65 years. There were slightly more male patients than female patients in the mITT population.

Table 10. Study 304 patient baseline characteristics, mITT population

	Mean (SD)		
	Placebo (N=38)	340 mg ADS-5102 (N=37)	All (N=75)
UDysRS			
Total score	41.2 (10.32)	40.2 (13.06)	40.7 (11.68)
Total objective score (Parts III & IV)	15.9 (7.00)	18.1 (7.99)	17.0 (7.53)
PD Diary			
ON time without troublesome dyskinesia (hours)	7.79 (3.249)	8.77 (2.457)	8.27 (2.909)
ON time with troublesome dyskinesia (hours)	6.02 (3.353)	4.71 (2.509)	5.37 (3.020)
Total time with dyskinesia[a] (hours)	10.52 (2.980)	9.04 (3.292)	9.79 (3.204)
OFF time (hours)	1.98 (1.687)	2.62 (2.015)	2.30 (1.871)
Asleep time (hours)	8.21 (1.643)	7.91 (1.502)	8.06 (1.572)
MDS-UPDRS			
Part I	9.9 (4.86)	11.3 (5.87)	10.6 (5.39)
Part II	14.8 (6.06)	14.1 (6.15)	14.4 (6.07)
Part III	21.4 (10.22)	21.2 (9.24)	21.3 (9.68)
Combined (Part I, II, and III)	46.1 (17.00)	46.6 (14.76)	46.3 (15.83)
Part IV	11.1 (2.40)	9.8 (2.78)	10.5 (2.66)
Part IV, Item 4.1	2.8 (0.94)	2.2 (0.81)	2.5 (0.92)
Part IV, Item 4.2	2.5 (0.51)	2.5 (0.61)	2.5 (0.55)
MMSE	28.7 (1.38)	29.1 (1.59)	28.9 (1.49)
Hoehn and Yahr Stage	2.4 (0.55)	2.1 (0.60)	2.2 (0.59)

[a] Total time with dyskinesia includes ON time with non-troublesome and troublesome dyskinesia.

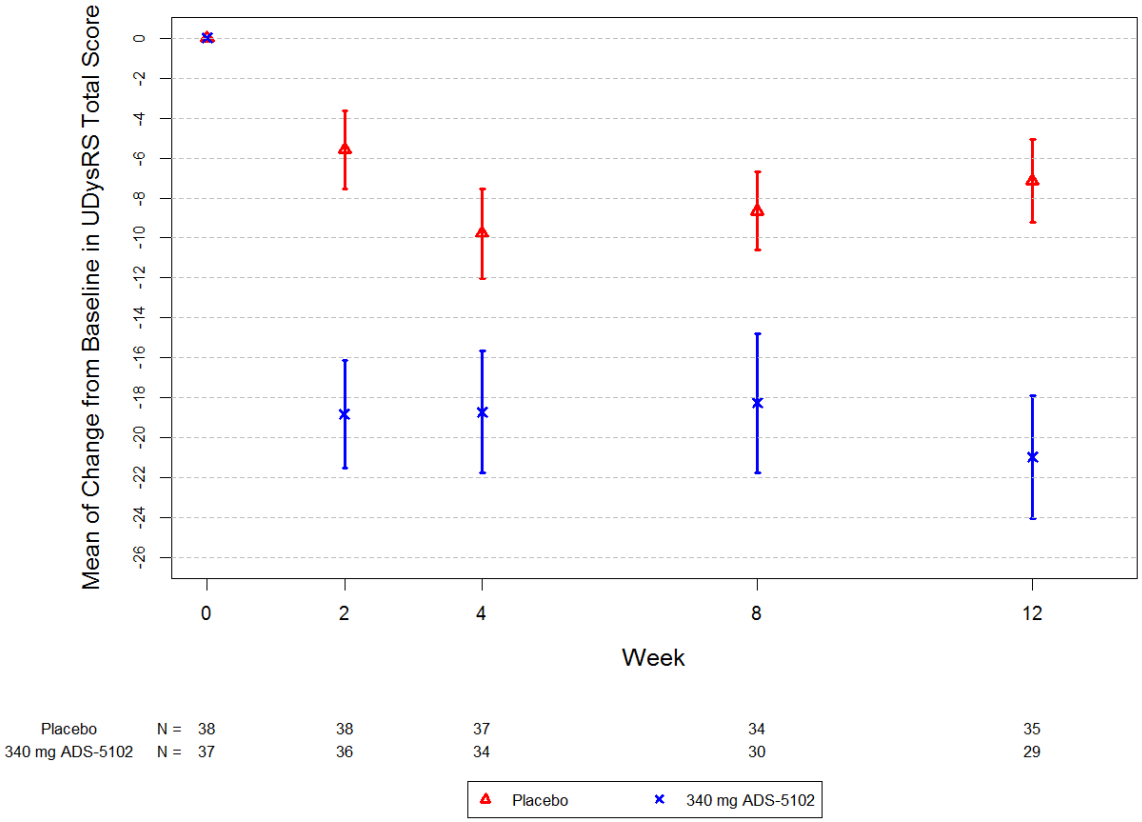
MDS-UPDRS: Movement Disorder Society - Unified Parkinson Disease Rating Scale; mITT: modified intent-to-treat; MMSE: Mini-Mental State Examination; N: number of patients; PD: Parkinson's disease; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

Source: Table 11 on page 58 of the Sponsor's clinical study report body

The patient baseline characteristics of the mITT population are summarized in **Table 10**. In addition to these baseline characteristics, patients of the mITT population was diagnosed with PD with an average age of approximately 54.7 years (SD = 9.43) for an average diagnose length of 10.6 years (SD = 4.67) at study baseline. On average, these patients have been on the levodopa treatment from the age of approximately 57.2 years (SD = 9.55) for a duration of 8.1 years (SD = 4.49) and experienced LID for approximately 3.9 years (SD = 2.86).

3.2.2.4 Results and Conclusions

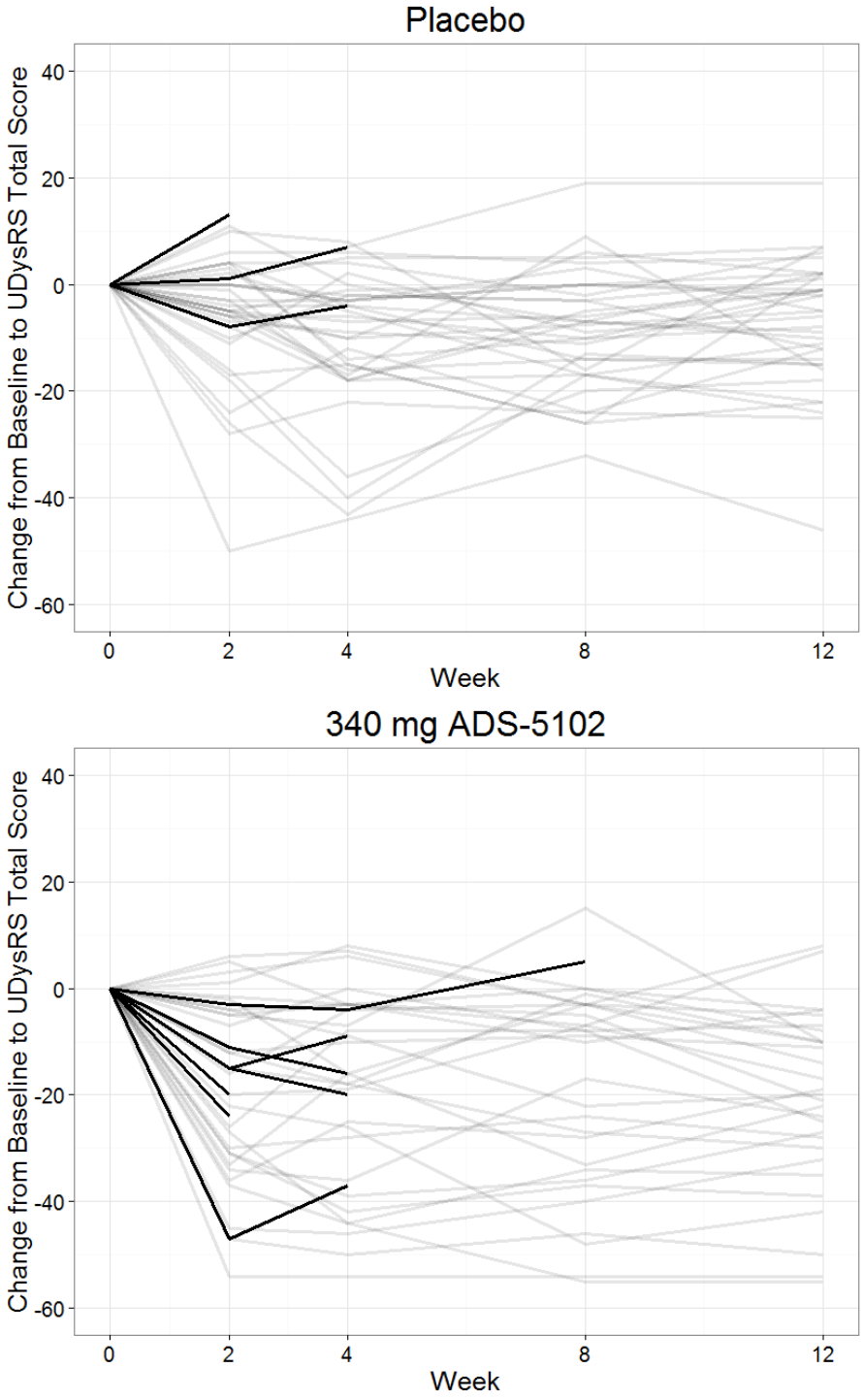
Figure 6. Study 304 mean (± standard error) of change from Baseline in UDysRS total score by week and treatment



Source: the reviewer

Figure 6 illustrates the mean of changes from Baseline in UDysRS total score by week and treatment for Study 304 mITT population. The 340 mg ADS-5102 group appeared to have consistent average improvements of UDysRS total score over the 12-week treatment duration. Such improvements were on average greater than those from the placebo group. The mITT population sizes were 37 and 38 for the 340 mg ADS-5102 group and placebo group, respectively. The rates of missing observations at Week 12 were 21.6% and 7.9% for the 340 mg ADS-5102 group and placebo group, respectively.

Figure 7. Study 304 time plots by treatment and patients



Source: the reviewer

In **Figure 7**, the top panel illustrates the time plots of all mITT patients in the placebo group; the bottom panel illustrates the time plots of all mITT patients in the 340 mg ADS-5102

group. For both panels, the time plots for the completers were in gray while the ones for the non-completers were in black. No specific dropout pattern (by comparing the non-completers and completers in the same treatment group) was observed from each panel. In other words, there is little evidence from each panel that the missing at random assumption on which the MMRM relies was unreasonable. The changes from Baseline in UDysRS total score of the dropped out patients in the placebo group were generally worse than those in the 340 mg ADS-5102 group.

Table 11. Study 304 analyses of change from Baseline to Week 12 in UDysRS total score, mITT population

		Placebo (N=38)	340 mg ADS-5102 (N=37)
Baseline	n	35	29
	Mean (SD)	40.4 (10.09)	41.7 (12.57)
	Median (Min, Max)	40.0 (21, 62)	42.0 (18, 63)
Week 12	n	35	29
	Mean (SD)	33.3 (14.35)	20.8 (11.83)
	Median (Min, Max)	32.0 (5, 63)	18.0 (0, 48)
Change from Baseline	n	35	29
	Mean (SD)	−7.1 (12.14)	−21.0 (16.60)
	Median (Min, Max)	−5.0 (−46, 19)	−20.0 (−55, 8)
MMRM Change from Baseline	LS Mean (SE)	−6.3 (2.08)	−20.7 (2.20)
	95% CI	(−10.5, −2.2)	(−25.1, −16.3)
MMRM Treatment Difference (Active - Placebo)	LS Mean (SE)	−14.4 (3.03)	
	95% CI	(−20.4, −8.3)	
	P value	< 0.0001	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 15 on page 63 of the Sponsor's clinical study report body

The analysis results of the endpoints of UDysRS total score are presented in **Table 11** (as well as those reported in **Table 12** and **Table 13**) by the Sponsor were based on all subjects in the mITT population that had Week 12 measurements, without imputation. ADS-5102 was statistically significantly better than placebo (p-value < 0.0001) in terms of change from Baseline to Week 12 in UDysRS total score, with a least square ADS-5102-placebo difference of -14.4 points (95% CI = (-20.4, -8.3)).

A total of seven patients in the ADS-5102 group discontinued the treatment due to adverse event versus three patients in the placebo discontinued for the same reason; one patient in the ADS-5102 group discontinued the treatment because the patient was unwilling to proceed. An additional post-hoc analysis was attempted by the reviewer to explore the potential impact of differentiable dropout between treatment groups: for patients who dropped out due to adverse event, their changes from Baseline to Week 12 in the UDysRS total score were assigned the worst score; for the patient dropped out because he/she was unwilling to proceed, the Week 2 and Week 4 scores showed improvements and his/her Week 12 change from baseline was imputed by the Week 4 score (last available value). The Wilcoxon rank sum test was performed after imputation and provided a nominally significant p-value close to 0.05. The statistical conclusion from the exploratory method does not differ from that from the pre-specified analysis method.

Table 12. Study 304 analyses of change from Baseline to Week 12 in ON time (in hour) without troublesome dyskinesia, mITT population

		Time (hours)	
		Placebo (N=38)	**340 mg ADS-5102 (N=37)**
Baseline	n	35	29
	Mean (SD)	7.64 (3.234)	9.14 (2.388)
	Median	9.00	9.25
	Min, Max	0.8, 12.8	3.8, 13.8
MMRM Change from Baseline at Week 12	LS Mean (SE)	2.05 (0.526)	3.95 (0.562)
	95% CI	(1.00, 3.10)	(2.83, 5.07)
MMRM Treatment Difference at Week 12 (Active − Placebo)	LS Mean (SE)	1.90 (0.775)	
	95% CI	(0.35, 3.45)	
	P value	0.0168	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 16 on page 66 of the Sponsor's clinical study report body

The analysis results of the endpoints of ON time without troublesome dyskinesia are presented in **Table 12**. ADS-5102 was statistically significantly better than placebo (p-value = 0.0168) in terms of change from Baseline to Week 12 in ON time without troublesome dyskinesia, with a least square ADS-5102-placebo difference of 1.90 hours (95% CI = (0.35, 3.54)).

Table 13. Study 304 analyses of change from Baseline to Week 12 in OFF time (in hour), mITT population

		Time (hours)	
		Placebo (N=38)	**340 mg ADS-5102 (N=37)**
Baseline	n	35	29
	Mean (SD)	1.95 (1.687)	2.76 (2.104)
	Median	1.75	2.25
	Min, Max	0.0, 7.0	0.0, 7.5
MMRM Change from Baseline at Week 12	LS Mean (SE)	0.61 (0.313)	−0.49 (0.336)
	95% CI	(−0.02, 1.23)	(−1.16, 0.18)
MMRM Treatment Difference at Week 12 (Active − Placebo)	LS Mean (SE)	−1.10 (0.461)	
	95% CI	(−2.02, −0.18)	
	P value	0.0199	

Summary statistics were computed using data from subjects who had values at both baseline and the specified post-baseline visit. The MMRM results were from a model that used all available data at each time point. In this model, the dependent variable was the change from baseline. The model included categorical effects for treatment group, visit (Weeks 2, 4, 8, and 12), and the interaction between treatment group and visit; the baseline value was included as a continuous covariate.

Source: Table 17 on page 68 of the Sponsor's clinical study report body

The analysis results of the endpoints of OFF time are presented in **Table 13**. ADS-5102 was statistically significantly better than placebo (p-value = 0.0199) in terms of change from Baseline to Week 12 in OFF time, with a least square ADS-5102-placebo difference of -1.10 hours (95% CI = (-2.02, -0.18)).

3.3 Evaluation of Safety

Please refer to Dr. Kenneth Bergmann's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Overall, there is no compelling evidence from the subgroup analyses in Section 4.1 that a specific gender, race, age, or geographic region subgroup benefits differently from ADS-5102.

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Study 301

Gender

Table 14. Study 301 subgroup analyses by gender of change from Baseline in UDysRS total score, mITT population

Gender	Change from Baseline in UDysRS total score	Placebo	340 mg ADS-5102
Week 12			
Female	N	20	26
	Means (SD)[a]	-8.01 (9.602)	-20.27 (15.630)
Male	N	32	27
	Means (SD)[a]	-6.75 (16.222)	-14.00 (11.459)
Week 24			
Female	N	11	20
	Means (SD)[a]	-5.29 (14.258)	-18.50 (14.562)
Male	N	26	22
	Means (SD)[a]	-6.31 (15.450)	-14.64 (14.060)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 15. Study 301 subgroup analyses by gender of change from Baseline in ON time (in hour) without dyskinesia, mITT population

Gender	Change from Baseline in ON time without dyskinesia	Placebo	340 mg ADS-5102
Week 12			
Female	N	19	25
	Means (SD)[a]	1.36 (3.419)	3.78 (4.021)
Male	N	32	25
	Means (SD)[a]	0.45 (3.299)	4.03 (4.331)
Week 24			
Female	N	11	20
	Means (SD)[a]	2.02 (3.022)	4.07 (3.620)
Male	N	25	22
	Means (SD)[a]	0.76 (3.224)	4.58 (4.151)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 16. Study 301 subgroup analyses by gender of change from Baseline in OFF time (in hour), mITT population

Gender	Change from Baseline in OFF time	Placebo	340 mg ADS-5102
Week 12			
Female	N	19	25
	Means (SD)[a]	0.09 (2.491)	-0.94 (1.400)
Male	N	32	25
	Means (SD)[a]	0.49 (1.929)	-0.39 (2.422)
Week 24			
Female	N	11	20
	Means (SD)[a]	-1.02 (1.371)	-0.97 (1.478)
Male	N	25	22
	Means (SD)[a]	0.91 (2.402)	-0.48 (1.877)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

For both gender groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without dyskinesia, and OFF time, except for the female group for OFF time at Week 24. In the placebo group, females were more likely to drop

out than males while in the ADS-5102 group, the males dropped out more often. It should also be noted that at Week 24, the dropout percentage of females in the placebo group and male in the ADS-5102 group exceeded 50% and 35%, respectively, so the statistics of changes from Baseline to Week 24 in UDysRS total score, ON time without dyskinesia, and OFF time in those subgroups might not be interpretable.

Race

As shown in **Table 3**, the majority of the mITT population was White. The numbers of patients in other races are so small that the analysis of patients in other races would not provide conclusive results on these populations.

Age

Table 17. Study 301 subgroup analyses by age group of change from Baseline in UDysRS total score, mITT population

Age Group	Change from Baseline in UDysRS total score	Placebo	340 mg ADS-5102
Week 12			
< 65 years	N	22	28
	Means (SD)[a]	-9.60 (12.017)	-16.14 (11.721)
≥ 65 years	N	30	25
	Means (SD)[a]	-5.50 (15.181)	-18.12 (16.177)
Week 24			
< 65 years	N	16	22
	Means (SD)[a]	-9.26 (15.016)	-17.23 (14.319)
≥ 65 years	N	21	20
	Means (SD)[a]	-3.52 (14.709)	-15.65 (14.518)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 18. Study 301 subgroup analyses by age group of change from Baseline in ON time (in hour) without dyskinesia, mITT population

Age Group	Change from Baseline in ON time without dyskinesia	Placebo	340 mg ADS-5102
Week 12			
< 65 years	N	21	28
	Means (SD)[a]	0.14 (2.688)	4.02 (4.818)
≥ 65 years	N	30	22
	Means (SD)[a]	1.25 (3.704)	3.76 (3.173)
Week 24			
< 65 years	N	16	22
	Means (SD)[a]	0.95 (2.268)	4.73 (4.597)
≥ 65 years	N	20	20
	Means (SD)[a]	1.30 (3.803)	3.90 (2.923)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 19. Study 301 subgroup analyses by age group of change from Baseline in OFF time (in hour), mITT population

Age Group	Change from Baseline in OFF time	Placebo	340 mg ADS-5102
Week 12			
< 65 years	N	21	28
	Means (SD)[a]	0.32 (2.210)	-0.44 (2.041)
≥ 65 years	N	30	22
	Means (SD)[a]	0.36 (2.127)	-0.96 (1.901)
Week 24			
< 65 years	N	16	22
	Means (SD)[a]	-0.13 (1.874)	-0.73 (1.765)
≥ 65 years	N	20	20
	Means (SD)[a]	0.68 (2.591)	-0.69 (1.664)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

For both age groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without dyskinesia, and OFF time. It should be noted that at Week 24, the dropout percentages of the age group by treatment subgroups are 29% - 38%, so

the statistics of changes from Baseline to Week 24 in UDysRS total score, ON time without dyskinesia, and OFF time in the those subgroups might not be interpretable.

Geographic Region

Study 301 was conducted mainly in the United States. A total of three out of the 121 patients in the mITT population were from the Canadian study center. No subgroup analyses by geographic region were performed.

4.1.2 Study 304

Gender

Table 20. Study 304 subgroup analyses by gender of change from Baseline in UDysRS total score, mITT population

Gender	Change from Baseline to Week 12 in UDysRS total score	Placebo	340 mg ADS-5102
Female	N	17	12
	Means (SD)[a]	-8.41 (13.134)	-25.92 (13.541)
Male	N	18	17
	Means (SD)[a]	-5.94 (11.378)	-17.47 (18.025)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 21. Study 304 subgroup analyses by gender of change from Baseline in ON time (in hour) without dyskinesia, mITT population

Gender	Change from Baseline to Week 12 in ON time without dyskinesia	Placebo	340 mg ADS-5102
Female	N	17	12
	Means (SD)[a]	1.90 (3.972)	4.38 (4.068)
Male	N	18	17
	Means (SD)[a]	2.87 (2.849)	2.69 (2.277)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

Table 22. Study 304 subgroup analyses by gender of change from Baseline in OFF time (in hour), mITT population

Gender	Change from Baseline to Week 12 in OFF time	Placebo	340 mg ADS-5102
Female	N	17	12
	Means (SD)[a]	0.85 (2.238)	-0.48 (1.554)
Male	N	18	17
	Means (SD)[a]	0.58 (1.805)	-0.98 (1.940)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the gender specific mITT population, without imputation.

Source: the reviewer

For both gender groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without dyskinesia, and OFF time, except for the male group for ON time at Week 12. In the ADS-5102 group, the females' dropout percentages exceeded 30%. The statistics of changes from Baseline to Week 12 in UDysRS total score, ON time without dyskinesia, and OFF time for females under ADS-5102 might not be interpretable.

Race

As shown in **Table 9**, the majority of the mITT population was White. The numbers of patients in other races are so small that the analysis of patients in other races would not provide conclusive results on these populations.

Age

Table 23. Study 304 subgroup analyses by age group of change from Baseline in UDysRS total score, mITT population

Age Group	Change from Baseline to Week 12 in UDysRS total score	Placebo	340 mg ADS-5102
< 65 years	N	14	13
	Means (SD)[a]	-3.00 (11.563)	-19.62 (19.160)
≥ 65 years	N	21	16
	Means (SD)[a]	-9.91 (11.991)	-22.06 (14.762)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 24. Study 304 subgroup analyses by age group of change from Baseline in ON time (in hour) without dyskinesia, mITT population

Age Group	Change from Baseline to Week 12 in ON time without dyskinesia	Placebo	340 mg ADS-5102
< 65 years	N	14	13
	Means (SD)[a]	1.96 (3.055)	2.60 (2.538)
≥ 65 years	N	21	16
	Means (SD)[a]	2.70 (3.692)	4.03 (3.586)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

Table 25. Study 304 subgroup analyses by age group of change from Baseline in OFF time (in hour), mITT population

Age Group	Change from Baseline to Week 12 in OFF time	Placebo	340 mg ADS-5102
< 65 years	N	14	13
	Means (SD)[a]	0.43 (1.230)	-0.78 (1.996)
≥ 65 years	N	21	16
	Means (SD)[a]	0.90 (2.395)	-0.77 (1.647)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the age group specific mITT population, without imputation.

Source: the reviewer

For both age groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without dyskinesia, and OFF time.

Geographic Region

Table 26. Study 304 subgroup analyses by region of change from Baseline in UDysRS total score, mITT population

Region	Change from Baseline to Week 12 in UDysRS total score	Placebo	340 mg ADS-5102
Non-US	N	28	18
	Means (SD)[a]	-6.50 (12.776)	-27.50 (16.332)
US	N	7	11
	Means (SD)[a]	-9.71 (9.569)	-10.27 (10.753)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation; UDysRS: Unified Dyskinesia Rating Scale.

[a] Obtained from all observations in the region specific mITT population, without imputation.

Source: the reviewer

Table 27. Study 304 subgroup analyses by region of change from Baseline in ON time (in hour) without dyskinesia, mITT population

Region	Change from Baseline to Week 12 in ON time without dyskinesia	Placebo	340 mg ADS-5102
Non-US	N	28	18
	Means (SD)[a]	2.31 (3.477)	4.03 (3.352)
US	N	7	11
	Means (SD)[a]	2.77 (3.440)	2.34 (2.730)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the region specific mITT population, without imputation.

Source: the reviewer

Table 28. Study 304 subgroup analyses by region of change from Baseline in OFF time (in hour), mITT population

Region	Change from Baseline to Week 12 in OFF time	Placebo	340 mg ADS-5102
Non-US	N	28	18
	Means (SD)[a]	0.52 (1.897)	-1.33 (1.658)
US	N	7	11
	Means (SD)[a]	1.48 (2.374)	0.14 (1.648)

mITT: modified intent-to-treat; N: number of mITT patients; SD: standard deviation.

[a] Obtained from all observations in the region specific mITT population, without imputation.

Source: the reviewer

For both region groups, ADS-5102 appeared superior to placebo in terms of change from Baseline in UDysRS total score, ON time without dyskinesia, and OFF time, except for the US group for ON time at Week 12. The dropout percentages of the ADS-5102 group are 10-15% higher than those of the placebo group under each region. The US region has small sample sizes under each treatment group, which made the comparison between treatment groups for the US region difficult to interpret.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Two statistical issues were identified. The first issue is the impact of high dropout percentages in Study 301 due to the Sponsor's decision to stop the trial early on the evaluation of efficacy. Discussions were provided in Section 3.2.1.4. It should be noted that biases could be introduced due to the post-hoc nature of the additional analyses and that cautions are needed especially for the interpretations of Week 24 endpoint results. The second issue is the differentiable dropout between treatment groups in Study 304. The statistical conclusion from the exploratory method by the reviewer does not differ from that from the pre-specified analysis method.

5.2 Collective Evidence

Study ADS-AMT-PD301 and Study ADS-AMT-PD304 provided efficacy evidences that Gocovri is efficacious as a treatment of levodopa-induced dyskinesia: Gocovri is statistically better than placebo in terms of change from Baseline to Week 12 in the Unified Dyskinesia Rating Scale total score.

5.3 Conclusions and Recommendations

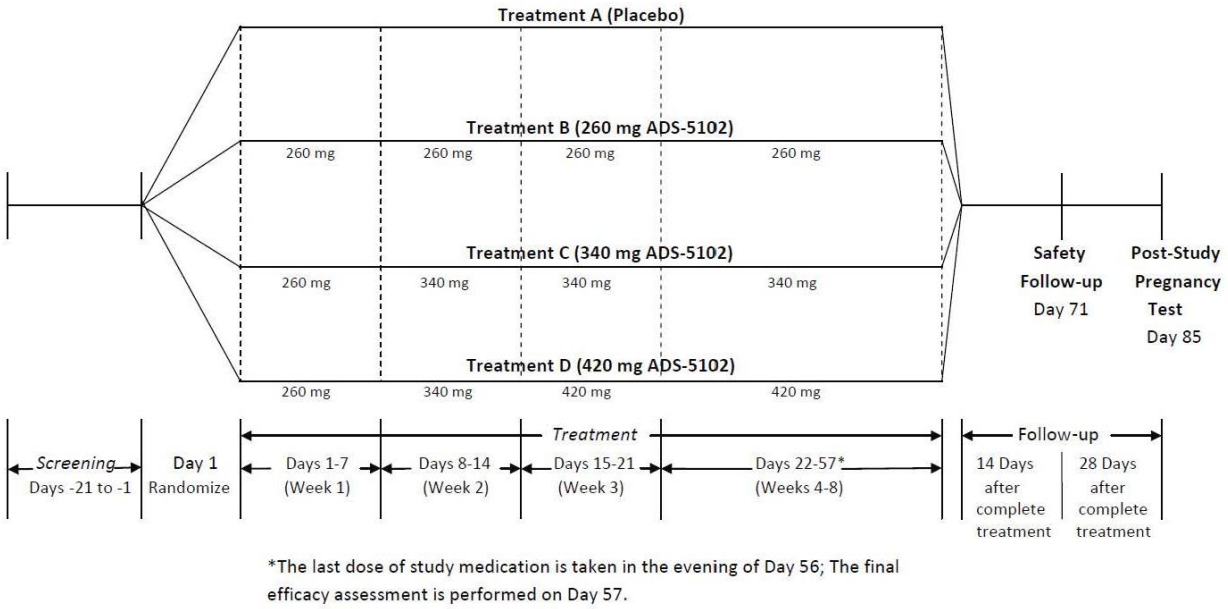
Based on the statistical evidences from Study ADS-AMT-PD301 and Study ADS-AMT-PD304, the reviewer concluded that Gocovri is superior to placebo in treating levodopa-induced dyskinesia.

A new efficacy study with a length no shorter than 24 weeks is recommended to confirm the efficacy of Gocovri beyond 12 weeks.

APPENDIX. Description of the Study Submitted by the Sponsor as Supporting Evidence for Drug Efficacy

Study 201 was a double-blind, placebo-controlled, randomized, 4-arm, parallel-group multi-center study to evaluate the efficacy, safety, and tolerability of ADS-5102 as a treatment of LID in subjects with PD. A total of 80 patients were planned to be randomized in a 1:1:1:1 ratio to placebo, 260 mg ADS-5102, 340 mg ADS-5102, and 420 mg ADS-5102. Patients were recruited in 31 study centers in the United States.

Figure 8. Study 201 design schematic



Source: figure on page 44 of the Sponsor's statistical analysis plan

Figure 8 depicts the study design schematic. Following the completion of the Baseline visit, the subjects were scheduled to return to the clinic on Days 8, 15, 29, 43, and 57 of dosing. A final safety follow-up was schedule for Day 71.

The primary efficacy endpoint was change from Baseline to Day 57/Week 8 in the UDysRS total score. The key secondary efficacy endpoints was claimed to be the change from Baseline to Day57/Week 8 in the Fatigue Severity Scale[3] (FSS) score. FSS is a 9-item self-reported scale. Each item of the scale has a range of 1 to 7, with 1 representing strongly disagree and 7 strongly agree. The range of the FSS is therefore 0-63. The FSS total score was represented by the means of all answered items.

[3] Krupp, L. B., LaRocca, N. G., Muir-Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of neurology*, 46(10), 1121-1123.

In order to handle the multiplicity of endpoints, the primary and key secondary endpoints were planned to be tested sequentially, each test at the two-sided significance level of $\alpha = 0.05$, in the following order:

- 420 mg ADS-5102 versus placebo for UDysRS at Week 8
- 420 mg ADS-5102 versus placebo for FSS at Week 8
- 340 mg ADS-5102 versus placebo for UDysRS at Week 8
- 340 mg ADS-5102 versus placebo for FSS at Week 8
- 260 mg ADS-5102 versus placebo for UDysRS at Week 8
- 260 mg ADS-5102 versus placebo for FSS at Week 8

Table 29. Study 201 patient disposition, randomized population

Number (%) of Subjects	Placebo (N=22)	260 mg ADS-5102 (N=20)	340 mg ADS-5102 (N=21)	420 mg ADS-5102 (N=20)	All ADS-5102 (N=61)
Randomized	22 (100)	20 (100)	21 (100)	20 (100)	61 (100)
Completed the study[a]	20 (90.9)	17 (85.0)	18 (85.7)	12 (60.0)	47 (77.0)
Withdrawn from study	2 (9.1)	3 (15.0)	3 (14.3)	8 (40.0)	14 (23.0)
Reasons for withdrawal:					
eGFR < 50 mL/min/1.73 m^2	0	0	1 (4.8)	0	1 (1.6)
Intolerable/unacceptable AE	0	3 (15.0)	3 (14.3)	8 (40.0)	14 (23.0)
Other	2 (9.1)	0	0	0	0

[a] As recorded on the eCRF end of study page (Day 71 or Safety Follow-up Visit)
Subjects may each have more than one reason for withdrawal

Source: Table 6 on page 57 of the Sponsor's clinical study report body

The patient disposition is presented in **Table 29**. Among the 83 randomized patients, 22 (26.5%), 20 (24.1%), 21 (25.3%), 20 (24.1%) patients were randomized to the placebo, 260 mg ADS-5102, 340 mg ADS-5102, and 420 mg ADS-5102, respectively. The 420 mg ADS-5102 has noticeably more patients withdrawn from the study, compared to other treatment groups.

The treatment groups appeared similar in terms of age, gender, and race, as well as baseline FSS score, MMSE score, and Hoehn and Yahr score.

Table 30. Study 201 analyses of change from Baseline to Week 8 in UDysRS total score, mITT population

	Statistic	Placebo (N=22)	260 mg ADS-5102 (N=19)	340 mg ADS-5102 (N=20)	420 mg ADS-5102 (N=19)
Baseline	n	22	19	20	19
	Mean (SD)	39.2 (17.79)	40.2 (13.70)	44.1 (12.30)	41.2 (11.93)
	Median	38.0	38.0	42.0	42.0
	Min, Max	9, 79	19, 67	20, 72	19, 72
	Q1, Q3	29.0, 51.0	30.0, 53.0	36.5, 48.0	33.0, 48.0
Day 57/Week 8	n	22	19	20	19
	Mean (SD)	33.0 (16.35)	28.2 (18.24)	25.4 (17.22)	24.5 (12.32)
	Median	32.0	20.0	22.0	24.0
	Min, Max	10, 71	1, 72	1, 68	6, 53
	Q1, Q3	18.0, 41.0	16.0, 45.0	15.0, 30.5	13.0, 32.0
Change from Baseline	n	22	19	20	19
	Mean (SD)	−6.1 (14.08)	−12.0 (13.20)	−18.8 (10.84)	−16.7 (13.77)
	Median	0.0	−13.0	−17.0	−16.0
	Min, Max	−44, 19	−42, 12	−40, −4	−40, 5
	Q1, Q3	−14.0, 4.0	−20.0, −4.0	−25.0, −11.0	−30.0, −5.0
	LS Mean (SE)	−6.7 (2.68)	−12.3 (2.88)	−17.9 (2.82)	−16.7 (2.88)
	95% CI	(−12.0, −1.3)	(−18.0, −6.5)	(−23.6, −12.3)	(−22.4, −10.9)
Treatment Difference[a]	LS Mean	—	−5.6	−11.3	−10.0
	95% CI	—	(−13.4, 2.2)	(−19.1, −3.5)	(−17.8, −2.2)
	p-value	—	0.1595	0.0051	0.0131

P-values are based on the comparison between 260 mg ADS-5102 (and respectively 340 mg ADS–5102, 420 mg ADS–5102) vs. Placebo from the ANCOVA model with change from baseline as the dependent variable, treatment group as a factor, and the baseline value as a covariate.

[a] Active minus Placebo

Source: Table 14 on page 67 of the Sponsor's clinical study report body

Table 31. Study 201 analyses of change from Baseline to Week 8 in FSS score, mITT population

	Statistic	Placebo (N=22)	260 mg ADS-5102 (N=19)	340 mg ADS-5102 (N=20)	420 mg ADS-5102 (N=19)
Day 57/Week 8	n	22	19	20	19
Change from Baseline	LS Mean (SE)	−0.25 (0.267)	−0.06 (0.289)	−0.55 (0.280)	0.00 (0.287)
	95% CI	(−0.8, 0.3)	(−0.6, 0.5)	(−1.1, 0.0)	(−0.6, 0.6)
Treatment Difference[a]	LS Mean	—	0.2	−0.3	0.3
	95% CI	—	(−0.6, 1.0)	(−1.1, 0.5)	(−0.5, 1.0)
	p-value	—	0.6298	0.4314	0.5223

P-values are based on the comparison between 260 mg ADS-5102 (and respectively 340 mg ADS–5102, 420 mg ADS–5102) vs. Placebo from the ANCOVA model with change from baseline as the dependent variable, treatment group as a factor, and the baseline value as a covariate.

[a] Active minus Placebo

Source: Table 17 on page 72 of the Sponsor's clinical study report body

The analysis results of the UDysRS total score are presented in **Table 30**. The analysis results of the FSS score are presented in **Table 31**. 420 mg ADS-5102 was statistically significantly better than placebo (p-value = 0.0131) in terms of change from Baseline to Week 8 in UDysRS total score, with a least square ADS-5102-placebo difference of -10.0 points (95% CI = (-17.8, -2.2)). Based on the pre-specified hierarchy of testing, because the comparison of 420 mg ADS-5102 and placebo in the FSS score at Week 8 had a non-significant p-value of 0.5223, the testing should stop.

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

/s/

XIANGMIN ZHANG
07/28/2017

KUN JIN
07/28/2017
I concur with the review.

HSIEN MING J HUNG
07/29/2017