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APPLICATION NUMBER

21-264

Statistical Review(s)



U S Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION ADDENDUM

NDA/Serial Number	21- 264
Drug Name	Apomorphine Hydrochloride Injection
Indication(s)	Parkinson's Disease
Applicant	Bertek Pharmaceuticals Inc
Date(s)	September 17, 2002
Review Priority	Standard
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1 Introduction

This review is an addendum to the original statistical review of the NDA 21-264 for the purpose of adding the analysis of the primary efficacy parameter by stratifying the type of "Off" episodes as spontaneous off or end-of-dose off for studies APO301 and APO302

The NDA of apomorphine was submitted to the Agency as a rolling NDA from May 6, 2002 to December 31, 2002. The Agency issued an approvable letter on July 02, 2003 in which the Agency commented on the type of "Off" in Studies APO301 and APO302 in the Clinical section of the approvable letter as follows

Indication You are seeking a claim for the treatment of two types of Off periods end-of-dose wearing Off and spontaneous Off. In the initial phase of APO202 you induced Off periods by withholding PD medication overnight. Such induced Off periods may be more complex given that they occur unrelated to time of dosing. In APO301 and APO302 patients received their morning doses of PD medication and were followed until the first Off of the day (at least 1 hour post dosing). Whether the results of APO301 and 302 address the efficacy of apomorphine for spontaneous Off periods depends on the distributions of time-to-Off in those studies. If many studied Off periods occurred well before the end of usual dosing interval the results would bear on spontaneous Off periods. If, however, the great majority of Off periods occurred close to the end of the usual dosing interval then the results bear more on end-of-dose Off. We therefore ask you to examine APO301 and APO302 to determine each patient's time-to-apomorphine-dosing and compare this to the patient's usual dosing interval. Please categorize patients based on whether the treated Off periods best represents end-of-dose wearing Off or spontaneous Off.

In response to the Agency's comments raised in the approvable letter, Bertek discussed with the division regarding the analysis plans to describe the type of "Off" during an August 7, 2003 telephone conference and a subsequent telephone conference with Dr Feeney. Subsequently, Bertek amended the application in their October 17, 2003 submission. The following analysis plans were agreed upon

It was agreed to classify the in-office "Off" episode for analysis by two definitions, separately

- The "1 hour rule" if the time of the in-office "Off" episode was within 60 minutes of the time for the next dose of conventional oral PD medication, then the "Off" episode was considered to be an "end-of-dose Off". Otherwise, the "Off" would be classified as "spontaneous "
- The "75% rule" if the "Off" episode occurred during the first 75% of the dosing interval, the "Off" would be considered spontaneous. Otherwise, the "Off" would be classified as "end-of-dose"

Both algorithms rely on a determination of the time to the next dose of conventional oral PD medication, specifically Sinemet. Although instructions for use of conventional oral

PD medication were documented in the Case Report Forms, some standardization was employed to ensure consistent interpretation of the dosing instructions for analysis. For example

- Patient did not take oral medication during sleep. Based on diary card assessment, the average sleep time in APO401 was 6.54 hours. For the purpose of determining a dosing interval, sleep time was assessed as 6, 6.5 and 7 hours to bracket the average sleep time in APO401.
- Patients took their first dose of conventional oral PD medication upon arising, and the remaining doses were to have been taken during the awake time (i.e., 18, 17.5 and 17 hours awake time for 6, 6.5 and 7 hours of sleep time, respectively).
- If specific Instructions for Use were described (e.g., every X hours, or at specific times during the day), the dose interval was defined by the instruction for use.
- If the instructions for use simply gave a frequency, (e.g., 5 times daily or QID), the dosing interval was determined by dividing the remaining doses (which would equate to the number of daily doses minus 1, since the first dose was taken upon waking) into the awake time.
- Based on August 7th teleconference with the Division, the instructions for use for Sinemet or (levodopa/benserazide for some of the UK patients) was used to determine the next dosing interval.

2 Analysis Results

The sponsor submitted analysis results based on the 1-hour rule and 75% rule as detailed above, using sleep times of 6, 6.5, and 7 hours. The results contained only period 1 for APO301. At the request from the medical team leader Dr. John Feeney and the medical reviewer Dr. Leonard Kapcala, I have performed analysis for the type of "Off" in order to confirm the sponsor's results and to obtain the results from both periods of APO301. The details of the analysis and the results are described below.

The submitted data contained information of dosing instruction, time from morning PD medication to "Off", and UPDRS scores of pre-dose, 20 minutes post dose, and change from pre-dose to 20 minutes post dose. The data contained information of 17 patients in protocol APO301 and 60 patients in protocol APO302. One patient in protocol 301 had only pre-dose UPDRS score. The patient's UPDRS score at 20 minutes post dose was carried forward from the pre-dose score. This patient was deleted from the analysis I performed, as was in the efficacy analysis in my original review. The original efficacy data for APO302 contained 62 patients. However, only 60 patients were included in the data submitted for analysis of type of "Off". The reason was not yet known at the time of the writing of this review. In addition, 4 patients in APO302 had missing values in time to "Off". Those 4 patients were included in the sponsor's analysis, and it is not clear how their type of "Off" was determined. Those 4 patients were excluded from the analysis I performed since their type of "Off" could not be determined.

The primary efficacy variable in both APO301 and APO302 was the change from pre-dose UPDRS Motor Scores at 20 minutes after injection of study medication. For each patient, the type of "Off" as spontaneous or end-of-dose was determined based on the 1-hour rule and 75% rule, using sleep times of 6, 6.5, and 7 hours. The analysis of change in UPDRS Motor Score was then carried out separately for each type of "Off", using analysis of covariance with treatment groups and baseline UPDRS score as a covariate. The differences between the results by using sleep times as 6, 6.5 and 7 hours were negligible, as were the difference by using 1-hour rule and 75% rule. Therefore, only the results using sleep time of 6.5 hours are presented. Note that 6.5 hours was the average sleep time found in Study APO401, as reported by the sponsor.

Table 1 presents the analysis results by using 1-hour rule with 6.5-hour sleep time. Table 2 presents the results by using 75% rule with 6.5-hour sleep time. The two tables only differ slightly.

Table 1 Mean Change in UPDRS Motor Score at 20 Minutes from Pre-dose by Type of "Off" (Spontaneous or End-of-Dose) Based on 1-Hour Rule and Assumption of 6.5 Hour Sleep

	"Off" Type	Time to Dosing	Apomorphine		Placebo		p-value	
			N	Mean (SD)	N	Mean (SD)		
APO301								
Period 1	Spontaneous	Pre-dose	5	42.00 (14.40)	4	37.75 (5.85)	3698	
		20 min	5	27.00 (15.83)	4	36.25 (5.25)		
		Change	5	-15.00 (23.10)	4	-1.50 (3.42)		
	End-of-Dose	Pre-dose	3	44.33 (8.50)	4	36.50 (8.19)		1751
		20 min	3	17.67 (7.37)	4	27.00 (9.90)		
		Change	3	-26.67 (5.51)	4	-9.50 (11.03)		
Period 2	Spontaneous	Pre-dose	4	40.75 (5.06)	5	43.40 (11.30)	0030	
		20 min	4	16.75 (8.62)	5	40.20 (4.82)		
		change	4	-24.00 (10.03)	5	-3.20 (12.91)		
	End-of-Dose	Pre-dose	4	34.75 (7.80)	3	37.00 (7.00)		0078
		20 min	4	12.50 (5.45)	3	40.00 (8.66)		
		Change	4	-22.25 (9.74)	3	3.00 (2.00)		
Combined (Period 1 and 2)	Spontaneous	Pre-dose	9	41.44 (10.67)	9	40.89 (9.25)	0058	
		20 min	9	22.44 (13.50)	9	38.44 (5.13)		
		Change	9	-19.00 (18.08)	9	-2.44 (9.41)		
	End-of-Dose	Pre-dose	7	38.86 (8.99)	7	36.71 (7.06)		0018
		20 min	7	14.71 (6.37)	7	32.57 (11.06)		
		Change	7	-24.14 (7.95)	7	-4.14 (10.33)		
APO302								
	Spontaneous	Pre-dose	12	36.92 (9.22)	5	38.20 (18.54)	0160	
		20 min	12	18.0 (10.30)	5	33.80 (25.83)		
		Change	12	-18.92 (8.10)	5	-4.40 (12.84)		
	End-of-Dose	Pre-dose	19	42.89 (10.15)	20	41.95 (18.67)		0001
		20 min	19	17.16 (12.20)	20	34.05 (23.37)		
		Change	19	-25.74 (9.14)	20	-7.90 (8.90)		

Table 2 Mean Change in UPDRS Motor Score at 20 Minutes from Pre-dose by Type of "Off" (Spontaneous or End-of-Dose) Based on 75% Rule and Assumption of 6.5 Hour Sleep

	"Off" Type	Time to Dosing	Apomorphine		Placebo		p-value	
			N	Mean (SD)	N	Mean (SD)		
APO301								
Period 1	Spontaneous	Pre-dose	5	42.00 (14.40)	4	37.75 (5.85)	3698	
		20 min	5	27.00 (15.83)	4	36.25 (5.25)		
		Change	5	-15.00 (23.10)	4	-1.50 (3.42)		
	End-of-Dose	Pre-dose	3	44.33 (8.50)	4	36.50 (8.19)		1751
		20 min	3	17.67 (7.37)	4	27.00 (9.90)		
		Change	3	-26.67 (5.51)	4	-9.50 (11.03)		
Period 2	Spontaneous	Pre-dose	4	40.75 (5.06)	5	43.40 (11.30)	0030	
		20 min	4	16.75 (8.62)	5	40.20 (4.82)		
		change	4	-24.00 (10.03)	5	-3.20 (12.91)		
	End-of-Dose	Pre dose	4	34.75 (7.80)	3	37.00 (7.00)		0078
		20 min	4	12.50 (5.45)	3	40.00 (8.66)		
		Change	4	-22.25 (9.74)	3	3.00 (2.00)		
Combined (Period 1 and 2)	Spontaneous	Pre dose	9	41.44 (10.67)	9	40.89 (9.25)	0058	
		20 min	9	22.44 (13.50)	9	38.44 (5.13)		
		Change	9	-19.00 (18.08)	9	-2.44 (9.41)		
	End-of-Dose	Pre-dose	7	38.86 (8.99)	7	36.71 (7.06)		0018
		20 min	7	14.71 (6.37)	7	32.57 (11.06)		
		Change	7	-24.14 (7.95)	7	-4.14 (10.33)		
APO302								
APO302	Spontaneous	Pre-dose	10	37.10 (10.00)	5	38.20 (18.54)	0337	
		20 min	10	19.60 (10.56)	5	33.80 (25.83)		
		Change	10	-17.50 (7.66)	5	-4.40 (12.84)		
	End-of-Dose	Pre-dose	21	42.24 (9.93)	20	41.95 (18.67)		0001
		20 min	21	16.48 (11.79)	20	34.05 (23.37)		
		Change	21	-25.76 (8.88)	20	-7.90 (8.90)		

It should be noted that all the p-values are considered as nominal p-values, as they are not intended to be used as to show the significance of the difference or to draw inference. The p-values are presented in the table simply as the test results by applying the primary efficacy analysis to the data.

3 Reviewer's Conclusion

As shown in Table 1 and Table 2, the average change from the pre-dose in the UPDRS Motor Score was higher in the apomorphine group than in the placebo group regardless of type of the "Off". The difference between the treatment groups in the change of UPDRS scores was consistent across the 2 studies and in both periods of study APO301.

Based on the results shown in Table 1 and Table 2 from the analysis of type of "Off", I conclude that apomorphine is efficacious in the acute treatment to reverse the "Off".

episodes with the magnitude of the effect independent of the type of "Off" episodes as whether an "Off" episode is "spontaneous off" or "end-of-dose off"

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

STATISTICAL REVIEW AND EVALUATION

NDA	21-264
DRUG NAME	Apomorphine Hydrochloride Injection
INDICATION	Parkinson's Disease
SPONSOR	Bertek Pharmaceuticals Inc
STATISTICAL REVIEWER	Sharon Yan
DATE OF DOCUMENT	September 17, 2002

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Statistical Review and Evaluation

1 Executive Summary

The submission of this NDA of Apomorphine for Parkinson's Disease consists of four clinical studies. Three of the studies, Studies APO202, APO301 and APO302, are double-blind and placebo controlled while Study APO303 is mainly an open label study for orthostatic effect but included a double-blind portion when subjects were titrated to 4 mg of the study drug. The statistical review of this NDA submission includes efficacy evaluation of the four studies.

1.1 Conclusions and Recommendations

The primary efficacy endpoints of the four studies are all based on the change in UPDRS from pre-dose to post-dose. Three of the studies (APO202, APO301 and APO302) showed a significant treatment difference in favor of apomorphine based on protocol specified statistical analysis. One study (APO303) has provided supporting evidence. Therefore, I conclude that the four studies, collectively, have provided sufficient evidence that apomorphine injection is effective in treating "Off" events in Parkinson's disease patients.

Significant period effect was noted in the crossover study of APO303, and analysis on the first period data did not show significant treatment effect. Although the study showed significant treatment difference on the primary efficacy analysis, the issue of period effect has hampered interpretation of the primary analysis results. Therefore, the conclusion of positive treatment effect could not be definitively drawn for Study APO303.

The same phenomenon of treatment-by-period interaction is observed in the other crossover study of APO301. The trends in the change of UPDRS in the two periods for the two crossover studies are similar (see Tables 12 and 19). However, due to the violation of normal assumption, the period effect of APO301 was evaluated by non-parametric analysis, which usually lacks the power in detecting the period effect. The period effect for APO303 was determined by parametric analysis, which is a more sensitive test. The results that APO303 showed a significant period effect and APO301 did not could be partly contributed by the small sample size of APO301.

There was a substantial deviation in the number of subjects randomized to each treatment group from what was planned. The deviation of the randomization scheme is an important issue about the trial conduct. The validity of the study is dependent on the cause of the deviation, which needs to be explained before any conclusion could be made.

There is also evidence that apomorphine injection increases dyskinesia. This finding is consistent among the four studies. The median change in the dyskinesia scale is 1 point for studies 202 and 301. In Study 202, 15 out of 20 patients receiving apomorphine had at least 1 point increase in

dyskinesia scale. The increase in dyskinesia scale after apomorphine injection is similar to the one seen after the dopamine challenge with slightly larger mean after the apomorphine injection. Although the median change in dyskinesia scale in Studies 302 and 303 is 0, a p-value of 0.001 for the treatment difference was obtained from the analysis at 20 minutes post-dosing.

1.2 Brief Overview of Clinical Studies

Four clinical studies (APO202, APO301, APO302 and APO303) are included in this statistical review. APO202 and APO301 are two prospective multi-center randomized placebo-controlled pivotal trials that documented the efficacy of apomorphine to reverse the hypomobility associated with "Off" episodes in apomorphine-naïve patients (APO202) and in patients receiving apomorphine for at least 3 months (APO301). Study APO 302 was not considered as a pivotal study. It had a similar design as Study APO301 except that the APO302 was parallel and APO301 was crossover. APO303 on apomorphine-naïve patients is a sub-study of APO401, which was designed to increase the US experience in long term use of apomorphine and to assess the safety of outpatient self-administration. A double-blind portion of 2 observation days was included in APO303.

1.3 Statistical Issues and Findings

Significant period effect was observed in Study APO303, and efficacy analysis on period 1 data only did not show significant treatment effect.

In Study APO301 normal assumption was not met ($p=0.0104$, Shapiro-Wilk test), and non-parametric analysis of Wilcoxon Rank Sum test, as specified in the protocol, was applied. Treatment effect was found to be statistically significant with a p-value of 0.0019 (see Table 11). Period effect was also tested by non-parametric analysis using the method given by Pocock (see Reference). No period effect was found by this non-parametric test. However, it is well known that the non-parametric test for period effect is not sensitive, and normally under powered to detect period effect even it exists. Given that the small size of the sample (8 subjects in each sequence), it is possible that the period effect exists but undetected.

By examining the primary endpoint for each treatment and period individually, it appears that in both Studies 301 and 303 the difference in the outcomes for the two periods was mainly caused by placebo effect in period 1, which disappeared in period 2. The treatment difference in APO301 was similar to APO202 and APO302, while the treatment difference in APO303 was substantially smaller than the other three studies.

In Study APO302 the number of subjects randomized to each treatment group was very different to what was planned. It was planned to have 40 patients receiving apomorphine and 20 patients receiving placebo. However, it resulted to have 35 patients receiving apomorphine and 27 patients receiving placebo. It was not clear how deviation from the planned ratio of assignment

occurred

As pointed out in Section 1.1, a significant increase in dyskinesia after apomorphine injection was seen in all four studies

2. Introduction

2.1 Overview

The four efficacy studies included in this NDA submission are all short studies to demonstrate that apomorphine injection is effective in aborting “Off” episodes. Study 202 had a parallel design not only to compare the response of apomorphine to placebo in aborting “Off” episodes, but also to compare the response of apomorphine to oral levodopa in patients in late-stage Parkinson’s disease. The patients included in this study were apomorphine naive and “dopamine responsive”, and apomorphine dose was based on patients’ response to their optimal oral dopamine dose. A total of 29 subjects were randomized (20 in the apomorphine group and 9 in the placebo group). Efficacy evaluation was based on two observation days: one day for dopamine challenge and another day for apomorphine injection at highest titrated dose. The primary endpoint was the change in UPDRS from pre-dose to post-dose measured as ratio of the change after apomorphine injection to the change after dopamine challenge.

Studies 301 and 303 were both crossover studies in which efficacy evaluations are based on two observation days in which a patient received apomorphine on one day and placebo on the other. Patients in Study 301 had previously received apomorphine for at least 3 months, while patients in Study 303 were apomorphine naive. Although Study 303 is a sub-study of APO401, which evaluated the safety of self-administered apomorphine in the outpatient setting, it included a double-blind portion of two visit days. Prior to receive titrated dose of 4 mg apomorphine, patients were randomized to receive 4 mg apomorphine injection on one day and placebo injection on the other in a double-blind crossover fashion. There were 17 patients evaluated in Study 301 and 51 patients evaluated in Study 303.

Study 302 had a parallel design with four treatment arms: apomorphine or placebo at patient's standard dose and apomorphine or placebo at 2 mL higher than patient's standard dose. A total of 62 patients were evaluated in the study.

2.2 Data Sources

SAS data files are provided in transport format for the four efficacy studies.

3. Statistical Evaluation

3 1 Evaluation of Efficacy

3 1 1 Clinical Study APO202

The title of the study is "A Prospective, Randomized, Double-Blind, Placebo-Controlled Parallel Groups Study of the Safety and Efficacy of Subcutaneous Injections of Apomorphine in the Treatment of "Off" Episodes in Patients with "On-Off" or "Wearing-Off" Effects Associated with Late-Stage Parkinson's Disease"

3 1 1 1 Study Objectives

The primary objective of the study is to examine the therapeutic response to apomorphine administration as a subcutaneous injection in the treatment of an induced "Off" state in Parkinson's disease patients

Secondary objectives of the study are to determine the effectiveness of apomorphine in aborting "Off" phenomena during chronic administration and to determine apomorphine's effect on total "Off" time during chronic administration

3 1 1 2 Study Design

The study was a double-blind, randomized, parallel-group, multi-center study to compare the safety and efficacy of the "Therapeutically Equivalent Dose" of apomorphine and placebo in the treatment of "Off" states in patients with motor fluctuations associated with late-stage Parkinson's disease. The study involved two general phases, an inpatient phase and an outpatient phase. Patients who were documented as Dopamine Responsive were to be randomized and titrated to a "Therapeutically Equivalent Dose" of apomorphine or placebo and followed during a long-term treatment extension using diaries to document the duration of "Off" periods while on study medication. Efficacy evaluation is based on data collected during the inpatient phase of the study.

A total of 30 patients were expected to complete the study with a ratio of 2:1 of active to placebo. The duration of the study was 4 weeks. An optimal drug regimen of oral antiparkinson drugs was to be established at least 30 days before the study and remained stable. The study was conducted in 4 centers in US.

3 1 1 3 Study Procedures

The study consisted of four visits. At Visit 1 patients were to report to the clinical site the night before dosing and remain there until completion of the clinical procedures. Patients were to fast from midnight until lunch the next day. The "Off" episodes were to be precipitated by withholding their

levodopa and dopamine agonist doses after midnight and in the morning. Following precipitation of an "Off" episode, Motor Function Tests was to be performed, and the patient's optimum dose of levodopa (immediate release levodopa) was to be administered. Motor Function Tests was to be repeated and recorded once an obvious clinical "On" state had occurred or within 60-120 minutes after the oral dose of levodopa. Patients were to be considered Dopamine Responsive if a 30% or greater improvement was observed from the "Off" state for the UPDRS motor examination (item 18-31). Following completion of this Dopaminergic Challenge procedure, patients were to resume their normal levodopa and dopamine agonist regimen and receive lunch. Patients who were documented to be Dopamine Responsive were to be scheduled for the second study visit within a week. Patients who were not Dopamine Responsive were to be discontinued from the study.

At Visit 2 Dopamine Responsive patients were to be randomized to receive either apomorphine or placebo subcutaneous injection. An "Off" phase was to be precipitated as previously described. Motor Function Tests was to be performed and repeated once an obvious clinical "On" state occurred or at 10 to 15 minutes after the injection, whichever came first.

A Therapeutically Equivalent Response to study medication was defined as the motor response following study medication administration that was at least 90% of the motor response for the UPDRS motor examination following the Dopaminergic Challenge. The dose of study medication eliciting a Therapeutic Equivalent Response was therefore termed as the Therapeutic Equivalent Dose. Patients who did not develop a Therapeutic Equivalent Response were to receive subsequent increasing single doses of study medication (0.4 ml -> 0.6 ml -> 0.8 ml -> 1.0 ml of 10 mg/ml apomorphine or placebo, respectively) at 2-hour intervals. Following each successive dose, Motor Function Tests were to be repeated once an obvious clinical "On" occurred or at 10 to 15 minutes after the injection, whichever came first. The dose titration procedure might be extended over multiple sequential days in a clinical setting if necessary. Administration of study medication was to terminate at Therapeutic Equivalent Dose of the study medication or at the maximum dose allowed by the protocol (1.0 ml).

Following completion of this dose finding procedure, patients were to be prescribed the Therapeutic Equivalent Dose of study medication and were to be discharged. Patients were scheduled for follow-up visits (Visits 3 and 4) at 2-week intervals for the next 4 weeks.

3.1.1.4 Selection of Patients

Main Inclusion Criteria

- Subjects in age of 30 to 80 years old,
- Men and non-pregnant, non-lactating women,
- Subjects with diagnosis of idiopathic Parkinson's disease who experience daily motor fluctuation in the form of "On-Off" or "Wearing Off" effect despite optimum doses of levodopa,
- Subjects classified as stage II - V of the Hoehn and Yahr scale for staging the severity of

Parkinson's disease,

Main Exclusion Criteria

- Subjects taking dopamine antagonist or depleting drugs excluding clozapine, anticholinergics and/or antihistamines with anticholinergic effects,
- Subjects with signs or symptoms suggestive of clinically significant orthostatic hypotension, schizophrenia, dementia, "parkinson-plus" syndromes or unstable systemic disease

3 1 1 5 Efficacy Evaluation

3 1 1 5 1 Efficacy Parameters

The primary efficacy parameter of the study was the change from pre-dose to post-dose in UPDRS Motor examination (items 18-31), measured as ratio of the percent change after dopamine challenge to the percent change after apomorphine injection

Secondary efficacy parameters include

- Hand-tapping test the sum of the number of taps recorded for each hand for 60 seconds,
- Webster's step-seconds score the number of steps taken with the right foot during the test is multiplied by the time to complete the test. A score of 9,999 was to be used for individuals unable to complete the test,
- Dyskinesia Rating Scale rated on a scale of 0-4 with 4 being the worst dyskinesia

3 1 1 5 2 Statistical Analysis Methods

For the primary efficacy variable of the UPDRS Motor Examination (items 18-31), the ratio of the percent change following study drug administration to the percent change following the Dopaminergic Challenge was to be calculated. An analysis of variance (ANOVA) was to be performed on the ratio and the normal assumption was to be tested. The differences between the treatment groups were also to be assessed by non-parametric methods such as the Wilcoxon Rank Sum test. If the assumption of the ANOVA were not met, then the non-parametric test was to be considered primary. Ratios were also to be calculated for the hand-tapping test and the Webster's step-seconds score and analyzed by the same method as the primary analysis.

The primary and secondary efficacy variables were to be analyzed for the primary efficacy population and the safety/intent-to-treat population. The change in the sum score of UPDRS Motor Examination, change in the sum score of the hand-tapping test and change in the Webster's step-seconds score were to be analyzed using an analysis of covariance (ANCOVA) with the "Off" state score as a covariate. The Dyskinesia Rating Scale score was to be analyzed by the Wilcoxon Rank Sum test.

3 1 1 6 Sponsor’s Analysis Results

3 1 1 6 1 Subject Disposition

A total of 32 patients were enrolled in the study. Three patients failed to progress to randomization and 29 patients were randomized (20 in the apomorphine group and 9 in the placebo group) and received at least one dose of study medication.

3 1 1 6 2 Demographic and Baseline Characteristics

A summary of the patient demographic and baseline characteristics is provided in Table 1. The sponsor reported that groups were not significantly different with regard to any demographic parameters. The patients in this study averaged 65 years of age, were primarily male and Caucasian, suffered from Parkinson’s disease for an average of 10 years, and suffered an average of 6 hours “OFF” time per day despite a background therapy involving at least two medications. There were no differences found between treatment groups for tobacco use or alcohol use.

Table 1 Summary of Demographic and Baseline Characteristics - Safety/ ITT Population

Parameter		Apomorphine (n=20)	Placebo (n=9)	Total (n=29)
Age (years)	Mean (std error)	66.1 (2.02)	61.6 (3.72)	64.7 (1.81)
Gender	Male	12 (60.0%)	8 (88.9%)	20 (69.0%)
	Female	8 (40.0%)	1 (11.1%)	9 (31.0%)
Race	Caucasian	19 (95.0%) ¹	8 (88.9%)	27 (93.1%)
	Other	(5.0%)	1 (11.1%)	2 (6.9%)
Parkinson's Disease (number of years)	Mean (std error)	9.2 (1.09)	12.3 (2.11)	10.2 (1.01)
Tobacco Use	None or Rare	12 (60.0%)	7 (77.8%)	19 (65.5%)
	Former User	7 (35.0%)	2 (22.2%)	9 (31.0%)
	Current User	1 (5.0%)	0 (0.0%)	1 (3.4%)
Alcohol Use	None or Rare	19 (95.0%)	9 (100.0%)	28 (96.6%)
	Moderate Use	1 (5.0%)	0 (0.0%)	1 (3.4%)
Time in "Off" State (hours per day)	Mean (std error)	5.86 (0.50)	5.86 (0.84)	5.86 (0.43)

Source: Sponsor's Table 11.2a

3 1 1 6 3 Dosage

Among apomorphine patients, inpatient doses which produced an acute change in UPDRS score at 90% of that achieved with oral levodopa doing was 5.4±2.4 mg (mean±std). Of the 20 patients receiving apomorphine, 18 achieved a levodopa equivalent response. None of the 9 placebo patients achieved a levodopa equivalent response. The single placebo patient with less than the maximum 1.0 mL dose discontinued titration after three injections declaring lack of benefit. The following table presents the inpatient dose titration results.

Table 2 Inpatient Dose Titration Results / N of patients with Levodopa Equivalent Response at Each Titration Dose Level

	0.2 ml 2 mg active	0.4 ml 4 mg active	0.6 ml 6 mg active	0.8 ml 8 mg active	1.0 ml 10mg active
Apomorphine	3	7	5	3	2
Placebo	0	0	1	0	8

Source: Sponsor's Table 11.3

3.1.1.6.4 Efficacy Evaluation

The primary efficacy parameter of the study was the change from pre-dose to post-dose in UPDRS Motor examination (items 18-31), measured as ratio of the percent change after dopamine challenge to the percent change after apomorphine injection.

Table 3 below summarizes the results of the ratio for the UPDRS Motor Examination score as well as the ratio for the hand-tapping test and the Webster's step-second score, which are considered secondary variables. It was determined that the ratios of none of the three variables were normally distributed and thus the results of the Wilcoxon Rank Sum test were considered primary.

The sponsor reported that the Wilcoxon Rank Sum test found a statistically significant difference between apomorphine treatment and placebo treatment in favor of apomorphine for the response ratios for the UPDRS motor examination score, the Hand-Tapping test and the Webster's Step-Second Score.

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Table 3 Ratio of % Change Following Study Drug Over % Change Following Dopaminergic Challenge

Variable		Apomorphine (n=*)	Placebo (n=9)	p-value**
UPDRS Motor Score (Primary)	Mean (std error)	0 96 (0 06)	0 0 (0 08)	<0 0001
	Median	0 97	0 00	<0 0001
Hand-Tapping Score	Mean (std error)	1 58 (0 59)	-0 15 (0 11)	0 0550
	Median	0 84	-0 04	0 0001
Webster's Step- Second Score	Mean (std error)	1 0 (0 09)	-0 04 (0 12)	<0 0001
	Median	1 00	0 00	<0 0001

* N=20 for UPDRS Motor Score, N=19 for Hand-Tapping Score and Webster's Step-Second Score

** p-values for the mean ratio were derived from the analysis of variance, p-values for the median ratio were derived from the Wilcoxon Rank Sum test

Source Sponsor's Table 11 4 1 1

Effect of treatment was also evaluated based on raw score change and percent score change. The sponsor reported that during the dopaminergic challenge phase of the study, no differences were found between the treatment groups for any of the parameters. During the study drug injection phase, the percent change for the UPDRS motor exam score and the Webster's step-second score were found to be statistically significantly different between treatment groups in favor of apomorphine. The dyskinesia rating scale also showed a statistically significant difference between treatment groups by the Wilcoxon Rank Sum test during the study drug injection.

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Table 4 Motor Function Scores - Summary of "Off" State versus "On" State

Parameter	Study Phase	Mean (std err)	Apomorphine (N=*)	Placebo (N=9)	Nominal p- value**
UPDRS Motor Examination	Dopaminergic Challenge	"Off" state score	41 80 (2 59)	39 89 (2 83)	
		Change	-26 60	-22 56	2902
		% Response	-64 67	-57 84	2695
	Study Drug Injection - Highest Dose	"Off" state score	39 65 (1 96)	36 33 (2 32)	
		Change	-23 85	- 11	< 0001
		% Response	-61 74	-1 04	< 0001
Hand-Tapping Score	Dopaminergic Challenge	"Off" state score	236 05 (12 98)	216 22 (25 86)	
		Change	120 40	124 11	9764
		% Response	54 86	69 93	6827
	Study Drug Injection - Highest Dose	"Off" state score	265 21 (22 11)	255 00 (15 96)	
		Change	108 68	-11 89	0008
		% Response	87 85	-4 11	1028
Webster's Step- Second Score	Dopaminergic Challenge	"Off" state score	3293 38 (946 29)	3106 95 (1404 81)	
		Change	-3080 17	-2756 38	4470
		% Response	-70 80	-52 28	1645
	Study Drug Injection - Highest Dose	"Off" state score	3708 43 (1042 79)	3486 68 (1628 22)	
		Change	-3518 32	74	0009
		% Response	-66 37	- 01	< 0001
Dyskinesia Rating Scale	Dopaminergic Challenge	change	85	78	
		Median change	1 00	1 00	9179
	Study Drug Injection - Highest Dose	change	95	00	
		Median change	1 00	00	0012

* N=20 for all parameters during the dopaminergic challenge, for study drug injection N=20 for UPDRS motor score and Dyskinesia Scale and N=19 for Hand-tapping and Webster's step-second score

** p-value for UPDRS motor score, hand-tapping score and Webster's step-second score were derived from an ANOVA for the change and % Response, p-value for the median change for the Dyskinesia rating scale were derived from the Wilcoxon Rank Sum test

Source Sponsor's Table 11 4 1 2

3 1 1 7 Reviewer's Analysis

3 1 1 7 1 Analysis of Primary Efficacy Parameter

The reviewer performed independent analysis specified in the study protocol and Statistical Analysis Plan. It is verified that the results reported by the sponsor are correct (see results in Table 3 and Table 4). As reported by the sponsor, there is a statistically significant difference between the treatment groups of apomorphine and placebo in the ratio of the % change in UPDRS following study drug injection to the % change of UPDRS following oral levodopa, in favor of apomorphine treatment. The ratio of the % change of UPDRS for the apomorphine group is close to 1 while the same ratio for the placebo group is about 0 (see sponsor's Table 3

and Table 4) It indicates that for those subjects who are responsive to the dopamine challenge, their average response to apomorphine treatment at the defined therapeutic equivalent dose is about the same as their response to oral levodopa treatment in terms of UPDRS scores. The average response to placebo treatment is about 0 in UPDRS scores.

3.1.1.7.2 Analysis of Secondary Efficacy Parameters

There are three secondary efficacy parameters in this study, hand-tapping score, Webster's step-second score and dyskinesia rating score. Since there were no multiplicity adjustment proposed, a general rule of 0.05/3 is used to determine the treatment effect of any of the secondary efficacy parameters. The treatment differences were found to be statistically significant in the hand-tapping score and Webster's step-second score based on the protocol specified analysis methods and the significance level of 0.05/3 (see Table 3).

Analysis of Wilcoxon's Rank Sum test and Cochran-Mantel-Haenszel (CMH) test were applied to the change score of dyskinesia from pre-dose to the post-dose of the study drug. Both analyses showed a statistically significant treatment difference, indicating that the treatment of apomorphine had an adverse effect on dyskinesia. In the apomorphine group, 9 subjects had an increase of 1 point and 5 had an increase of 2 points while all the subjects in the placebo group remained unchanged in the dyskinesia rating scale. The following table presents the number of subjects in each of the categories of the change scores in dyskinesia rating scale. Note that the scores from Visit 1 following dopamine challenge was not used in the analysis.

Table 5 Change in the Dyskinesia Score from Pre-dose to Post-dose of the Study Drug / Number of Subjects at Each Change Score

Treatment	change score after dopamine challenge				change score after study drug		
	-1	0	1	2	0	1	2
Apomorphine	0	5	13	2	6	9	5
Placebo	1	3	2	3	9	0	0
p-value*	0.813				0.002		

* p-value from CMH test for treatment difference between apomorphine and placebo

It appears that both oral dopamine and apomorphine injection had an adverse effect in the dyskinesia rating scale. After dopamine challenge at Visit 1, 15 subjects (50%) had an increase of 1 point and 5 subjects (17%) had an increase of 2 points in the combined group. There was no statistically significant difference found in the change of dyskinesia scale between Visit 1 and Visit 2 within the apomorphine group.

3.1.2 Clinical Study APO301

3 1 2 1 Study Objectives

The primary objective of this study was to measure the continued efficacy of apomorphine in patients who had previous exposure of at least three months duration

3 1 2 2 Study Design

The study was a double-blind, randomized, placebo controlled, multi-center, crossover design. The participation of each patient involved three visits, a baseline visit and two observation days. The shortest duration of patient involvement was 3 days.

Sixteen patients were to be studied, 17 were recruited and eligible for participation for the study. The study was conducted in 2 centers in UK.

3 1 2 3 Study Procedures

Patients who had been receiving apomorphine subcutaneous injections for rescue therapy for "Off" events for duration of at least three months were to be tested for response to medication administered to reverse individual "Off" events. Two individual "Off" events were to be studied on different days. Experimental drug was administered in response to a significant "Off" event.

Patients were to be randomized to receive either apomorphine on Day 1 and placebo on day 2, or vice versa, in a blinded manner, according to a predetermined schedule. On each observation day, the patients' usual anti-PD medications were to be taken in the manner typically used during outpatient pre-study use until arrival at the clinic. Following arrival at the clinic, no further non-study apomorphine was to be used. The volume of the injected dose in mL was to be set equal to that typically used by the patient prior to study entry. Patients were to be observed for the first significant "Off" event, which occurred at least one hour after morning dosing.

Efficacy response to dosing was to be assessed by capturing (1) the repeated measurement UPDRS motor scores and dyskinesia scores over a 60-minute interval and (2) the interval (in minutes) between injection and the time of patient declaration of the first perception of significant relief of immobility. Time course of dose response was to be determined by measuring the UPDRS motor score pre-dose and at 10, 20, and 60 minutes post dosing.

Upon completion of the 60-minute observations, resumption of normal medications was allowed for the remainder of the day. Patients needed not be confined to an inpatient environment. Study exit was to occur after completion of the observation of drug effect on the second observation day.

3 1 2 4 Selection of Patients

Main Inclusion Criteria

- Men and women of age ≥ 18 ,
- Patients with clinical diagnosis of idiopathic Parkinson's disease,
- Patients classified as stage (II-IV) of the Hoehn and Yahr scale (8) for staging the severity of Parkinson's disease,
- Patients must be on optimal oral therapy regimen. Optimized oral anti-Parkinson's medications must include levodopa/decarboxylase inhibitors, in either immediate or delayed release forms, plus at least one direct acting oral dopamine agonist for at least 30 days prior to randomization. Optimally maximized therapy is defined as the titrated drug regimen achieved through a thorough clinical process by which a tolerable balance is attained between "Off" time and adverse events including disabling dyskinesic movement.
- Patients must be currently receiving apomorphine subcutaneous injections for rescue therapy for "Off" events for duration of at least three months.
- The minimum apomorphine baseline dosing requirement is an average of at least 2 doses per day over the week prior to enrolment with doses of ≤ 10 mg.

Main Exclusion Criteria

- Patients under medical therapy for clinically significant psychoses or dementia not related to ingestion of anti-Parkinson's medication,
- Patients with a history of drug or alcohol dependency within one year prior to study enrollment,
- Patients with unstable and clinically significant disease of cardiovascular, hematologic, hepatic, renal, metabolic, respiratory, gastrointestinal or endocrinological systems or neoplasm within the three months before the start of the study.
- Patients with a history of allergy or intolerance to morphine or its derivatives, sulfur, sulfur containing medication, sulfites, domperidone, Tigan or other anticholinergics,
- Patients treated with experimental agents other than apomorphine intermittent subcutaneous injections within 30 days before study entry,
- Patients whose apomorphine regimen is characterized by continuous infusion or by administration methods other than intermittent subcutaneous injection.

3.1.2.5 Efficacy Evaluation**3.1.2.5.1 Efficacy Parameters**

The primary efficacy parameter was defined as the change in UPDRS Motor Score from pre-dose to 20 minutes after dosing.

Secondary efficacy parameters included

- Change in Dyskinesia Rating Scale score from pre-dose to 20 minutes after dosing.

- Time to onset of relief, as declared by the patient

Measurement of the time course of drug response was executed by the repetition of UPDRS motor score (items 18-31) and dyskinesia rating scale at time points of immediate pre-dose, 10 minutes, 20 minutes, and 60 minutes post-dosing

The Goetz Rating Scale for Dyskinesia was to be assessed as part of the time course of drug activity in each observation day. A rating of severity (from 0 through 4) was to be applied to dyskinesia after observing the patient walk, drink from a cup, and put on a coat and button clothing.

To provide a measure of the time of onset, the patient was asked to declare the time at which he/she perceived a significant improvement in immobility.

3.1.2.5.2 Statistical Analysis Methods

The primary endpoint of change in UPDRS Motor score from pre-dose to 20 minutes post-dosing was to be analyzed using a repeated measure ANCOVA with the terms sequence, subject within sequence, pre-dose score, treatment and period. The sequence effect was to be tested using the subject within sequence mean square as the error term. All other effects were to be tested against the mean square error from the ANCOVA. The data were to be examined for period effect and treatment-period interaction. If there was a significant treatment-period interaction (< 10) as measured by sequence effect in the above model, data from Day 1 only were to be analyzed as a parallel study design, using a one-way analysis of covariance (ANCOVA) with the terms of treatment and pre-dose score. This analysis was recognized as an assessment of robustness, not for straightforward interpretation if the analysis for both days was not significant.

The same method was to be used to analyze the change in UPDRS Motor Score from pre-dose to 10 minutes and 60 minutes.

The change in Dyskinesia Rating Scale from pre-dose to 20 minutes after injection was to be assessed using the Wilcoxon Signed Rank test. For each subject, the difference of the change from pre-dose values for the two treatment groups was to be calculated (A-B) and tested for a difference from zero. If a parallel design analysis was used due to a significant treatment-period interaction in the primary UPDRS analysis, the Day 1 data only was to be analyzed for treatment effect using the Wilcoxon Rank Sum test.

The time to onset of relief was to be analyzed using a repeated measure ANOVA with the terms of sequence, subject within sequence, treatment and period. Again, if a parallel design analysis was used due to significant treatment-period interaction in the primary UPDRS analysis, the Day 1 data only was to be analyzed for treatment effect using ANOVA with the term treatment.

It was anticipated that a significant number of subjects would have no declared time of relief. A second set of analyses was to be performed with missing values set to 60 minutes (the maximum observation time)

3.1.2.6 Sponsor's Analysis Results

3.1.2.6.1 Subject Disposition

Seventeen (17) patients entered the study and were randomized to the double-blind crossover treatment. All patients received at least one dose of test medication, while a total of 16 patients received both doses of test medication. One patient, a 52-year-old female, suffered severe "Off" pain and was unable to continue with required UPDRS and Dyskinesia evaluation on Day 1 and withdrew from the study.

3.1.2.6.2 Protocol Violation

Eleven patients did not declare an onset on at least one of the observation days. Two patients failed to declare onset on both observation days. One patient did not have scores for item 21 of the UPDRS Motor Assessment Test on observation Day 2 at the 10 minutes assessment point. This produced an error into the UPDRS total score, which was not corrected.

3.1.2.6.3 Demographic and Baseline Characteristics

The following table presents patients demographic and baseline characteristics.

Table 6 Summary of Demographic and Baseline Characteristics

Parameter		APO/Placebo N=8	Placebo/APO N=9	Total N=17
Age (years)	Mean (SD)	61.38 (2.672)	62.00 (2.068)	61.71 (1.615)
Gender	Male	6 (75%)	6 (66.7%)	12 (70.6%)
	Female	2 (25%)	3 (33.3%)	5 (29.4%)
Race	Caucasian	8 (100%)	9 (100%)	17 (100%)
Year of Disease	Mean (SD)	14.00 (1.24)	13.44 (2.10)	13.71 (1.26)
Tobacco Use	None or rare	4 (50%)	5 (55.6%)	9 (52.9%)
	Former user	3 (37.5%)	2 (22.2%)	5 (29.4%)
	Current user	1 (12.5%)	2 (22.2%)	3 (17.6%)
Alcohol Use	None or rare	4 (50%)	4 (44.4%)	8 (47.1%)
	Moderate	4 (50%)	5 (55.6%)	9 (52.9%)

Source: Sponsor's Table 11.2a

3.1.2.6.4 Dosage

The following table presents apomorphine doses by treatment groups. Dosages were determined by the patient's usual subcutaneous apomorphine regimens.

Table 7 Apomorphine Dose by Treatment Groups

Treatment	2 mg	3 mg	4 mg	4.5 mg	5 mg	8 mg	10 mg
Placebo/Apomorphine	1	5	2	0	1	0	0
Apomorphine/Placebo	1	4	0	1	0	1	1

Source: Sponsor's Table 11.3

3.1.2.6.5 Efficacy Evaluation

There were 17 subjects included in the sponsor defined ITT population and 16 subjects included in the per-protocol population. One subject who had pre-dose evaluation but withdrew prior to the 10-minute post-dose evaluation at Visit 1 was included in the sponsor's ITT analysis. All post-dose evaluation data of Visit 1 and all pre-dose and post-dose data of Visit 2 were carried forward from the pre-dose data of Visit 1. The sponsor presented efficacy results from both ITT population and per-protocol population. Only the results from per-protocol analysis, which included 16 patients, are presented in this review.

The primary endpoint of change in UPDRS motor score from pre-dose to 20 minutes was analyzed using a repeated measures analysis of covariance (ANCOVA) with the terms of sequence, subject within sequence, pre-dose score, treatment and period. Results are presented in the following table.

Table 8 Summary of Changes from Baseline in UPDRS Scores

Time Relative to Dosing Mean (Std error) (% change from baseline)	Apomorphine N=16	Placebo N=16	p-value (1)	p-value (2)	p-value (3)
Pre-dose UPDRS Score	40.3 (2.4)	39.1 (2.1)			
10 min after injection	-16.4 (3.8) (-38%)	-2.9 (2.1) (-7.1%)	0.096	0.505	0.519
20 min after injection (Primary endpoint)	-21.3 (3.6) (-50%)	-3.2 (2.4) (-6.2%)	< 0.001	0.438	0.178
60 min after injection	-13.4 (2.9) (-32%)	-0.4 (1.4) (0.1%)	0.013	0.533	0.059
Area Under the Curve	1456 (117)	2228 (119)	< 0.001	--	0.661

(1) Repeated measure ANCOVA with sequence, subject within sequence, pre-dose score, treatment and period

(2) P-value for period effect using subject within sequence MS as the error term

(3) ANCOVA with pre-dose score and treatment -- Day 1 data only

Source: Sponsor's Table 11.4.1.2

The sponsor reported that the repeated measure ANCOVA analysis found a statistically

significant difference in 10, 20, and 60 minutes UPDRS Motor scores between treatments of apomorphine and placebo. In this population there was a significant period effect at 20 minutes and at 10 minutes.

The sponsor reported that normality assumptions necessary for the use of parametric statistical methods were not met and non-parametric method of Wilcoxon Rank Sum Test was conducted to test the treatment effect. The difference of the change from baseline UPDRS Motor scores for the two periods (i.e., Period 1 - Period 2) was found significant between the two treatments with p-values of 0.0019, 0.0006, and 0.0030 at 10, 20, and 60 minutes post-dosing, respectively.

Dyskinesia Rating Scale assessment was performed at 10, 20, and 60 minutes after dosing of study drug. These data were not normally distributed, and thus Wilcoxon Signed Rank test was used to analyze the differences in patients' responses. Wilcoxon Rank Sum test was used for analysis of Day 1 data in parallel groups. The results are summarized in Table 9.

Table 9 Summary of Change from Baseline Dyskinesia Rating Scale Scores at 10, 20, and 60 minutes After Dosing

Time after Dosing Median (Min, Max)	Apomorphine (n=16)	Placebo (n=16)	p-value (1)	p-value (2)
10 min after injection	0 (0, 2)	0 (-3, 0)	0.156	0.451
20 min after injection	1 (-3, 3)	0, (0, 0)	0.507	0.098
60 min after injection	0 (-3, 3)	0 (-3, 0)	1.093	0.201

(1) From Wilcoxon Signed Rank Test

(2) From Wilcoxon Rank Sum Test - Day 1 data only

Source: Sponsor's Table 11.4.1.4

There was a significant increase in dyskinesia after apomorphine injection at 10 and 20 minutes post dosing. The incidence of dyskinesia was in 11 of the 16 patients after apomorphine and in 1 patient after placebo.

During the 60-minute study period, patients were asked to declare at what time they perceived a significant relief of "Off" state symptoms after injection of study drug. Due to some patients not declaring any relief during the study period, all missing values were set to 60 minutes, the end of the observation period. The data analyzed were not normally distributed, therefore the Wilcoxon Signed Rank test was used to detect differences between apomorphine treatment and placebo treatment. Results are summarized below.

Table 10 Summary of Time (Minutes) to Patient-Declared Relief

Method of Analysis	Apomorphine	Placebo	p-value	p-value
Missing set to 60 minutes				
Median (min, max) [N]	15 (2, 60) [17]	60 (9, 60) [17]	0.0102 ⁽¹⁾	0.2212 ⁽²⁾
Missing values deleted	13.3+-2.5 [13]	9.5+-0.3 [4]	0.0732 ⁽³⁾	0.3037 ⁽⁴⁾
Mean +-stderr [N]				

(1) From Wilcoxon Signed Rank test

(2) From Wilcoxon Rank Sum test - Day 1 data only

(3) Repeated measures ANOVA with terms sequence, subject within sequence, treatment and period

(4) ANOVA with the term treatment - Day 1 data only

Source: Sponsor's Table 11.4.1.5

3.1.2.7 Reviewer's Analysis

3.1.2.7.1 Analysis of Primary Efficacy Parameter

As reported by the sponsor, there was a statistically significant difference between the two treatments in the change of UPDRS at all post-dose time points based on the protocol specified analysis of ANCOVA. However, the normal assumption of the ANCOVA was not satisfied for data at 20 minutes post-dose ($p=0.0104$, Shapiro-Wilk test). Therefore, non-parametric analysis of Wilcoxon Rank Sum test was applied on (Period 1- Period 2) data as the primary efficacy analysis to examine the treatment difference. A significant treatment difference in favor of apomorphine was found at all time points. The following table presents the results.

Table 11 Change from Baseline in UPDRS - Non-Parametric Analysis

Time from Dosing	Sequence	Period 1 Median	Period 2 Median	Period1-Period 2 Median	p-value
10 minutes	APO/PL (n=8)	-14.5	2	-15.5	0.0044
	PL/APO (n=8)	-3	-13.5	10.5	
20 minutes	APO/PL (n=8)	-23.5	1.5	-20.5	0.0019
	PL/APO (n=8)	-3.5	-22.5	17.5	
60 minutes	APO/PL (n=8)	-17.5	2.5	-14	0.0053
	PL/APO (n=8)	-1	-5.5	5.5	

Period effect was examined by non-parametric analysis of Wilcoxon Rank Sum test comparing (Apomorphine - Placebo) for the two sequences, the method suggested by Pocock (see Reference). No period effect was found by the test ($p=0.6742$).

It is well known that this test of period effect is not sensitive and usually under powered to detect the period effect. Given the small sample size of 8 subjects in each sequence, it is possible that period effect existed but not detected. By breaking down the change of UPDRS by treatment and period, it is found that the magnitude of the change in UPDRS after apomorphine injection seems to be larger in period 2 than in period 1. There was an improvement in UPDRS after placebo injection in period 1, but not in period 2. The following table presents the results.

Table 12 Change in UPDRS by Treatment and Period

Treatment	Apomorphine	Placebo
Period 1		
Mean (SD)	-19.4 (18.7)	-5.5 (8.7)
Median	-23.5	-3.5
Period 2		
Mean (SD)	-23.1 (9.2)	-0.9 (10.3)
Median	-22.5	1.5

Carryover effect was also examined by analyzing the efficacy endpoint from (Period 1 + Period 2) data using the non-parametric Wilcoxon Rank Sum test. No significant carryover effect was found at any time point.

Based on the analyses presented above, I conclude that the study has showed positive treatment. However, caution should be applied in interpreting the data given the small sample size and the nature of the crossover design.

3.1.2.7.2 Analysis of Secondary Efficacy Parameters

At the pre-dose, 14 subjects had dyskinesia scale of 0, 1 had scale of 1, and 1 had scale of 3. At 20 minutes post-dosing, an increase of at least 1 point in dyskinesia scale occurred in 4 subjects in period 1 and in 5 subjects in period 2 after apomorphine injection while no subjects treated with placebo had an increase in dyskinesia scale in either period. See Table 9 for the p-values from the Signed Rank test for the difference in the change scale of dyskinesia between the two treatments.

The time to onset of relief is not analyzed because many patients did not claim the time. For sponsor's results, see Table 10.

3.1.3 Clinical Study APO303

Orthostatic hypotension is an adverse event that has been associated with Parkinson's disease, dopamine agonists in general and apomorphine specifically. The incidence of orthostatic hypotension during apomorphine dose escalation in late-stage Parkinson's disease patients is imprecisely known. At the request of the FDA, this study was conducted to determine the incidence and clinical significance of orthostatic hypotension during dose escalation in apomorphine-naïve patients. Forced titration to the maximum tolerated dose was elected over titration to an individual's effective dose to provide a measure of the margin of safety at therapeutic doses.

3 1 3 1 Study Objectives

The primary objective of APO303 was to determine the electrocardiographic and orthostatic effects of apomorphine during dose escalation in apomorphine-naive late stage Parkinson's disease patients. Although safety observations represent the primary objective of the study, the conduct of efficacy assessments at the 4-mg dose was an essential element of the study. For purposes of statistical analysis, efficacy assessment taken 20 minutes after double-blind dosing of 4 mg of apomorphine or placebo represented the primary statistical parameter.

3 1 3 2 Study Design

APO303 was designed as a 50-patient sub-study of the larger study, APO401, which evaluated the safety of self-administered apomorphine in the outpatient setting.

The study consisted of a pre-study visit, a baseline visit, and 6 titration visits. At Titration Visit 2 patients were randomized in a double-blinded crossover fashion to receive either 0.4 mL placebo or 0.4 mL apomorphine or vice versa at Titration Visits 2 and 3. Patients continued dose escalation with open-label apomorphine (6, 8, or 10 mg) at Titration Visits 4, 5, and 6 respectively until further dose escalation was prevented by intolerable side effects. After completion of dose escalation, the investigator selected an outpatient dose that was best balance of beneficial and adverse effects. Outpatient therapeutic use began at this selected dose with the recognition that dose adjustment could be performed at any time to improve the balance between beneficial and adverse effects.

The study was conducted in 22 centers in US.

3 1 3 3 Study Procedures

APO303 involved a dose escalation phase followed by a 6-month outpatient open-label treatment phase. During the dose escalation phase patients received pre-study assessments and were then tested on separate days for their response to single doses of test medication administered during an observed "Off" event. The observed "Off" event was the first such event that occurred in the clinic at least one hour after administration of the normal morning dose of oral anti-PD medication while withholding subsequent doses. The study design was predominantly open label such that at each titration visit the patient received one of the following medications in response to the first "Off" event:

- Patient's normal dose/time of oral anti-PD medication (Baseline Visit),
- Subcutaneous apomorphine injection at incremental doses beginning at 2 mg (0.2 mL) (Titration Visit 1), increasing by 2 mg (0.2 mL) at subsequent titration visits (Titration Visit 4, 5, or 6), or
- Double-blind crossover administration of 4 mg (0.4 mL) subcutaneous apomorphine or 0.4

mL placebo control injection (Titration Visit 2 and 3)

Upon arrival for each office visit, patients were administered a complete UPDRS assessment regardless of “On/Off” status, orthostatic monitoring, and concomitant medication

In-office dosing involved a 90-minute observation period of safety parameters including Holter monitoring, orthostatic changes, dyskinesia assessment and adverse events

Efficacy observations included time course assessments using repeated administration of the UPDRS Motor Exam – Section III, Items 13-31

3.1.3.4 Selection of Patients

Patients who enrolled in Bertek study APO401 were recruited to also participate in the APO303 sub-study during their APO401 Baseline Visit 1. All patients were recruited prior to receiving any apomorphine injections under APO401. All patients had to meet the inclusion and exclusion criteria outlined below.

Main Inclusion Criteria

- Men and non-pregnant, non-lactating women of any age > 18,
- Patients with a clinical diagnosis of idiopathic Parkinson’s disease,
- Patients classified as stage II – V of the Hoehn and Yahr scale for staging and severity of Parkinson’s disease,
- Patients with refractory motor fluctuations of any frequency or duration,
- Unless otherwise specified, enrolled patients must be on an optimally maximized oral therapy regimen. Optimized oral anti-PD medication included levodopa/carbidopa in either immediate or delayed release forms, plus at least one other anti-PD medication, which could include a direct acting oral dopamine agonist, a monoamine oxidase inhibitor (MAOI), or a catechol-O-methyltransferase inhibitor (COMT) for at least 30 days prior to enrollment into the study.
- Patients enrolled in APO401 who have completed initial baseline observation, but have not received apomorphine therapy as part of the APO401 protocol or at any other point in time.

Main Exclusion Criteria

- Patients with prior exposure to apomorphine,
- Patients under medical therapy for clinically significant psychoses/dementia,
- Patients with history of drug or alcohol dependency within one year prior to study enrollment,
- Patients with unstable and clinically significant disease of cardiovascular, hematologic, hepatic, renal, metabolic, respiratory, gastrointestinal or endocrinological systems or

neoplasm within three months before start of the study,

- Patients on methyl dopa therapy,
- Patients with a history of true allergy to morphine or its derivatives, sulfur containing medication, sulfites, trimethobensamide or other anticholinergics,
- Patients treated with other experimental agents within 30 days before study entry

3 1.3 5 Efficacy Evaluation

Patient Global Assessments were performed on each patient at the Pre-study Visit 1 (APO401 Baseline Visit 1) to establish the severity of their Parkinson's disease. This assessment included the complete UPDRS and Hoehn and Yahr scale.

At each clinic visit following Pre-study Visit 1, the time course of treatment effect was assessed before and after dosing with the patient's usual anti-PD medications (Baseline Visit only) or test medication (all other visits). Repeated use of UPDRS motor score and Dyskinesia Assessment were to be performed to assess the efficacy of apomorphine or placebo.

Dyskinesia Rating Scale

The presence and severity of the patient's dyskinesias were assessed according to the following scale:

0	None
1	Mild
2	Moderate
3	Severe

3 1.3 5.1 Efficacy Parameters

The primary efficacy analysis was based on data from the crossover portion of the study (TV2 and TV3) comparing 4 mg apomorphine to placebo, with primary efficacy parameter being the change in UPDRS Motor Score from pre-dose to 20 minutes after dosing.

Secondary efficacy parameters included:

- 1 Change in UPDRS Motor Score from pre-dose to 40 and 90 minutes after dosing,
- 2 Area under the curve (AUC) for UPDRS Motor Scores at 0, 20, 40, and 90 minutes,
- 3 Change in Dyskinesia Assessment at 0, 20, 40, and 90 minutes

3 1.3 5.2 Statistical Analysis Methods

The primary efficacy analysis involved the double-blind 4 mg/placebo crossover portion of the

study This took place at titration visits TV2 and TV3 The primary endpoint (change in UPDRS Motor Score from pre-dose to 20 minutes) was to be analyzed using repeated measures analysis of covariance (ANCOVA) with the terms of sequence, subject within sequence, pre-dose score, treatment and period The sequence effect was to be tested using the subject within sequence mean square as the error term All other effects were to be tested against the mean square error from the ANCOVA The data were to be examined for period effect and treat-period interaction If there was a significant treatment-period interaction ($p < 0.10$) as measured by sequence effect in the above model, data from TV2 only were to be analyzed as a parallel study design, using a one-way analysis of covariance (ANCOVA) with the terms treatment and pre-dose score This analysis was recognized as an assessment of robustness and might not be straightforward to interpret if the analysis for both days was not significant

The same method was to be used to analyze the change in UPDRS Motor Score from pre-dose to 40 minutes and 90 minutes It was also to be used to analyze the area under the curve for UPDRS Motor Score

The change in Dyskinesia Assessment from pre-dose to 20 minutes was to be compared across treatments using the Wilcoxon Rank Sum test For each subject, the difference of the change from pre-dose values for the two sequences was to be calculated (TV2-TV3) Treatment effect was to be tested for statistical significance by applying the Wilcoxon Rank Sum test to the ranks of these differences For each subject, the sum of the change from pre-dose values for the two sequences was also to be calculated (TV2+TV3) Carryover effect was to be tested for the statistical significance by applying the Wilcoxon Rank Sum test to the ranks of these sums If there was a significant carryover effect, the treatment effect was to be compared by applying the Wilcoxon Rank Sum test to the TV2 data only

The same method was to be used to assess the change in Dyskinesia Assessment from the pre-dose to 40 and 90 minutes

3.1.3.6 Results from Sponsor's Analysis

3.1.3.6.1 Subject Disposition

At the time of data cutoff for the final study report, all patients had completed the titration phase of the study There were still patients who were completing the outpatient portion of the study as of 31 January 2002

A total of 56 patients enrolled in APO303 dose titration study One subject proceeded to EV1, one subject withdrew consent, and 3 subjects discontinued due to AEs after TV1 and prior to the double-blind 4 mg titration visit Fifty-one subjects completed the first half of the double-blind portion of the study and 50 subjects completed both TV2 and TV3 (one subject proceeded to EV1 after the first portion of double-blind medication)

3 1.3 6 2 Demographic and Other Baseline Characteristics

Table 13 presents the baseline characteristics for crossover population. The sponsor reported that there were no differences between treatment groups in any baseline characteristics in the crossover population.

Table 13 Demographic Characteristics

Variable		Total	Placebo/APO	APO/Placebo	p-value ¹
Gender	Male	30 (58.8%)	14 (56.0%)	16 (61.5%)	.7793
	Female	21 (41.2%)	11 (44.0%)	10 (38.5%)	
Race	Caucasian	47 (92.2%)	23 (92.0%)	24 (92.3%)	1.0000
	Hispanic	3 (5.9%)	2 (8.0%)	1 (3.8%)	
	Other	1 (2.0%)		1 (3.8%)	
Age	N	51	25	26	.8291
	Mean (SD)	66.4 (1.2)	66.2 (1.8)	66.7 (1.7)	
	Median	67.0	67.0	66.0	
Age of Onset	N	51	25	26	.6207
	Mean (SD)	55.5 (1.4)	56.2 (2.1)	54.8 (2.0)	
	Median	54.0	55.0	54.0	
Tobacco Use	None/Rare	31 (60.8%)	15 (60.0%)	16 (61.5%)	1.0000
	Former	19 (37.3%)	9 (36.0%)	10 (38.5%)	
	Current	1 (2.0%)	1 (4.0%)		
Alcohol Use	None/rare	45 (88.2%)	21 (84.0%)	24 (92.3%)	.4189
	Moderate	6 (11.8%)	4 (16.0%)	2 (7.7%)	

¹ p-values from Fisher's exact test for categorical variables, ANOVA for continuous variables
Source: Sponsor's Table 14.1.2.2

Baseline disease characteristics are presented in Table 14 for the crossover population. The mean baseline total UPDRS scores were obtained while patients were in the "On" state, and were balanced across the populations. There were no differences between treatment groups in the total UPDRS scores or in any of the UPDRS section scores in the crossover population.

Table 14 Baseline Disease Characteristics

Variable	Total	Placebo/APO	APO/Placebo	p-value ¹
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APPEARS THIS WAY
ON ORIGINAL

Number of patients with baseline UPDRS while "On"				
	49	24	25	
UPDRS Section I sub-total				
N	49	24	25	
Mean (std-err)	3.08 (.29)	3.08 (.39)	3.08 (.43)	9954
Median	3.00	3.00	3.00	
UPDRS Section II sub-total				
N	49	24	25	
Mean (std-err)	18.27 (1.13)	17.21 (1.69)	19.28 (1.52)	3654
Median	18.00	15.50	20.00	
UPDRS Section III sub-total				
N	48	23	25	
Mean (std-err)	29.42 (2.48)	27.48 (3.75)	31.20 (3.32)	4596
Median	28.00	26.00	29.00	
UPDRS Section IV sub-total				
N	49	24	25	
Mean (std err)	6.76 (.46)	6.21 (.72)	7.28 (.57)	2480
Median	6.00	5.00	6.00	
UPDRS Total				
N	49	24	25	
Mean (std-err)	56.92 (3.51)	52.83 (5.27)	60.84 (4.64)	2589
Median	55.00	47.00	59.00	
Non-Motor UPDRS sub-total				
N	49	24	25	
Mean (std err)	28.10 (1.46)	26.50 (2.25)	29.64 (1.85)	2852
Median	27.00	25.50	30.00	

Note: Assessments were performed while patient was "On". If assessment could not be performed while patient was on, it was not included.

1 p-value from ANOVA

Source: Sponsor's Table 14.1.3.2

3.1.3.6.3 Efficacy Evaluation

The efficacy analysis of this study is based on the crossover population. This population was further divided into those patients who completed only the initial crossover visit (ITT subset) and those subjects who completed both crossover visits (Per Protocol subset). There were 51 subjects included in the ITT subset and 50 subjects included in the PP subset.

Primary efficacy Endpoint Analysis

The primary efficacy endpoint was the mean change in UPDRS Motor Scores from pre-dose to 20 minutes. Table 15 presents ANCOVA analysis of the change from predose mean UPDRS scores for the crossover population at 20, 40, and 90 minutes following placebo and apomorphine (4 mg) injection.

Table 15 Primary Efficacy Analysis: Change from Baseline in UPDRS

Time from	Placebo (N=51)	Apomorphine (N=51)	p-values
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Dosing (min)	Change from Baseline		Change from Baseline		[1]	[2]	[3]
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)			
0	42.5 (2.19)		42.7 (2.15)				
20	39.8 (2.42)	-2.8 (1.15)	31.5 (2.13)	-11.2 (1.61)	0.002	0.038	1.660
40	39.6 (2.55)	-3.0 (1.36)	29.1 (2.18)	-13.5 (1.65)	< 0.001	0.053	0.339
90	41.0 (2.56)	-1.6 (1.30)	37.6 (2.45)	-5.0 (1.26)	0.237	1.239	3.367

Note one subject had visit TV2 but not TV3. For the ITT analysis, this subject's TV2 primary efficacy data was also used for TV3. LOCF was used for missing values for 20, 40, and 90 minutes.

[1] Repeated measures ANCOVA with the terms sequence, subject within sequence, pre-dose score, treatment and period.

[2] p-value from sequence effect using subject within sequence MS as the error term.

[3] ANOVA with the terms pre-dose score and treatment, using Day 1 data only.

Source: Sponsor's Table 14.2.1.1

The sponsor reported that the mean change in UPDRS Motor Scores from pre-dose to 20 minutes post-dosing was significantly greater after 4 mg apomorphine vs placebo (-11.2 vs -2.8, p=0.0002). Also observed was a significant sequence effect (p=0.0038). The data was examined further to understand the cause of sequence effect. The placebo response for period 1 and period 2 was compared using ANCOVA with pre-dose score as a covariate. There was no significant difference between the placebo response in period 1 vs period 2, thus there appears to be no apomorphine carryover effect and the study design appears valid. The sequence effect appears to be due to a treatment-by-period interaction, with apomorphine showing a stronger treatment effect in period 2 than in period 1. When only Crossover Period 1 data was analyzed, the parametric analysis did not reveal a statistically significant difference (p=0.1660) between treatments.

The change in UPDRS Motor Scores from pre-dose to 20 minutes post-dosing indicated some noteworthy departures from normal distribution. Therefore, results were re-analyzed using the non-parametric statistical method, Wilcoxon Rank Sum Test. The median change in UPDRS Motor Scores from predose to 20 minutes following 4 mg apomorphine vs placebo injections was -8 vs -2 at TV2 and -12 vs -1.5 at TV3. The median difference (TV2-TV3) in UPDRS Motor Scores from pre-dose to 20 minutes for the two sequences was -8.5 vs 1.0 (p=0.0001), indicating a highly statistically significant difference between apomorphine and placebo treatments. The median sum (TV2+TV3) in UPDRS Motor Scores from pre-dose to 20 minutes for the two sequences was -7.5 vs -1.5 (p=0.0166), indicating a significant sequence effect. Using only the data for TV2 (the first crossover period), the median difference in the UPDRS Motor Scores between the treatment groups remained statistically significant (p=0.0206). Results from non-parametric analysis are presented in Table 16.

Table 16 Change from Baseline in UPDRS – Non-Parametric Analysis

Time from Dosing	Sequence	TV2	TV3	Difference	Sum	p-values		
		Median	Median	TV2-TV3	TV2+TV3	[1]	[2]	[3]

20	APO/PL (n=26)	-8	-1.5	-8.5	-7.5	0001	0166	0206
	PL/APO (n=25)	-2	-12	10	-15			
40	APO/PL (n=26)	-10.5	0.5	-8	-9.5	< 0001	0531	0028
	PL/APO (n=25)	-2	-14	10	-16			
90	APO/PL (n=26)	-5.5	1.5	-5	-3	0230	3554	1544
	PL/APO (n=25)	0	-5	5	-6			

Note One subject had visit TV2 but not TV3 This subject's TV2 data was also used for TV3 LOCF was used for missing values for 20, 40 and 90 minutes

[1] Test of treatment effect using Wilcoxon Rank Sum test on TV2-TV3

[2] Test of carry over effect using Wilcoxon Rank Sum test on TV2+TV3

[3] Test of treatment effect using Wilcoxon Rank Sum test on TV2 data only

Source Sponsor's Table 14.2.1.2

Secondary Efficacy Endpoint Analyses

Secondary endpoints included

- 1 The change in UPDRS Motor Score from pre-dose to 40 and 90 minutes after dosing (results shown in Table 13),
- 2 The area under the curve (AUC) for UPDRS Motor Score at 0, 20, 40, and 90 minutes,
- 3 The change in Dyskinesia Assessment at 0, 20, 40, and 90 minutes

Data from the mean change from baseline in AUC for UPDRS Motor Score are presented in Table 17 The sponsor reported a significant difference in the mean change from baseline in AUC for UPDRS motor score between treatments of apomorphine and placebo (-825 vs -199, $p < 0.0001$) However, a significant sequence effect was seen Results from the analysis of Day 1 data only did not reach statistical significance ($p = 0.834$)

Table 17 Area Under the Curve for Change from Baseline in UPDRS

Placebo			Apomorphine			p-values		
N	Mean	Stderr	N	Mean	Stderr	[1]	[2]	[3]
51	-199	98.353	51	-825	100.64	< 0001	0071	0834

[1] Repeated ANOVA with the terms of sequence, subject within sequence, pre-dose score, treatment and period

[2] p-value for sequence effect using subject within sequence MS as error term

[3] ANOVA with the terms of pre-dose score and treatment, using Day 1 data only

Source Sponsor's Table 14.2.1.4

Results from the analysis of change in dyskinesia rating scale are presented in Table 18 The sponsor found a significant increase in dyskinesia after apomorphine injection at all time points Sequence effect was not significant at any time point

Table 18 Median Change from the Baseline in Dyskinesia Assessment

Time from dosing (min)	Sequence	TV2	TV3	Difference (TV-TV3)	Sum (TV2+TV3)	p-value		
						[1]	[2]	[3]

20	A (n=26)	0	0	0	0	0223	3295	1760
	B (n=25)	0	0	0	0			
40	A (n=26)	0	0	0	0	0109	8511	0263
	B (n=25)	0	0	0	0			
90	A (n=26)	0	0	0	0	0333	7017	1446
	B (n=25)	0	0	0	0			

[1] Test of treatment effect using Wilcoxon Rank Sum test on TV2-TV3

[2] Test of carryover effect using Wilcoxon Rank Sum test on TV2+TV3

[3] Test of treatment effect using Wilcoxon Rank Sum test on TV2 data only

Source Sponsor's Table 14.2.1.3

3.1.3.7 Reviewer's Analysis

3.1.3.7.1 Analysis of Primary Efficacy Parameter

There was one subject who dropped out after Day 1 and did not have period 2 data. The sponsor used the subject's Day 1 data for both Day 1 and Day 2 in the analysis. In this reviewer's opinion, the subject's Day 1 data should not be carried forward to Day 2, and therefore, analysis based on sponsor defined per protocol (PP) analysis, which exclude the subject, is more appropriate. The analysis based on PP population gives the same p-value of 0.002 for the primary efficacy analysis.

The results from the normal test of the residuals from the primary ANCOVA model reveals no significant deviation from the normal assumption (p= 0.2217, 0.5183, and 0.2208 for 20 min, 40 min, and 90 min, respectively). Note that the sponsor reported a significant deviation of the data from the normal assumption. The difference between the results of the normal test between the one reported by the sponsor and the one obtained by this reviewer is due to the different data that the normal test was applied. The sponsor applied test to the original data, while I applied the test to the residuals from the primary model.

As reported by the sponsor, period effect was significant with a p-value of 0.0038 at 20 minutes post-dosing. ANOVA analysis applied to first period data of TV2 did not find statistically significant treatment effect at 20 minutes post-dosing (p=0.1660).

In determining the sample size for the study, the sponsor estimated the mean and standard deviation of change in UPDRS score of -5 (14) for placebo and -20 (14) for apomorphine. The estimated sample size was 25 for each treatment with a 96% power to detect a difference of 15 in the change of UPDRS scores. As shown in the following table, the difference in the mean UPDRS change between the treatments was about 5 points in the first period and about 12 points in the second period.

Table 19 Mean UPDRS Change by Treatment and Period

Treatment	Apomorphine	Placebo
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Period 1		
Mean (SD)	-9.5 (11.8)	-4.6 (10.4)
Median	-7	-1
Period 2		
Mean (SD)	-13.0 (11.0)	-0.6 (4.4)
Median	-12	-1

In summary, although the analysis showed a significant treatment difference by the protocol-specified method, a significant period effect has hampered interpretation of the result. When only first period data were analyzed, the study failed to show significant treatment effect. Therefore, I would conclude that the evidence provided by the study was not sufficient in order to conclude that apomorphine is effective.

3.1.3.7.2 Analysis of Secondary Efficacy Parameters

Area under the Curve (AUC) was analyzed. The result of the analysis agrees with the one obtained by the sponsor (see Table 17).

Most subjects had ratings of 0 at the baseline and every post-baseline time point. The following table presents the dyskinesia ratings in each category. Cochran-Mantel-Haenszel (CMH) test is also applied to confirm the findings about the difference in the change of dyskinesia ratings between the treatment groups.

Table 20 Change in Dyskinesia Rating Scales by Treatment and Time Points / Number of Subjects in Each of the Change Score

Time from Dosing	Apomorphine					Placebo				
	-2	-1	0	1	2	-2	-1	0	1	2
20 minutes	0	1	40	8	2	0	1	48	1	0
40 minutes	0	2	33	14	2	0	1	47	2	0
90 minutes	0	2	42	4	3	1	2	47	0	0

There are more subjects in the apomorphine group than in the placebo group who had an increase in dyskinesia rating score. The CMH test of the treatment difference at 20 minutes post-dose gives a p-value of 0.044, and the CMH test of treatment difference by controlling the time points gives a p-value of 0.001. The analysis confirms the result obtained by the sponsor, that apomorphine is likely to have an effect in increasing dyskinesia.

3 1 4 Study APO302

3 1 4 1 Study Objectives

The primary objective of this study was to measure the continued efficacy of apomorphine in patients who have had at least three months exposure to apomorphine

The secondary objective was to determine the time course of the onset of the drug activity of apomorphine

3 1 4 2 Study Design

This was a prospective, randomized, placebo-controlled, double-blind, parallel group, multi-center study Parkinson's Disease patients, optimally maximized on an oral therapy regimen, who were receiving apomorphine rescue for "Off" events for at least three months were randomized at a ratio of 2 1 2 1 to one of four dosing regimens apomorphine or placebo at their standard dose, or apomorphine or placebo at 0.2 mL greater than their standard dose One individual "Off" event was studied in a single day Sixty patients were expected for the study

A total of 60 patients, 40 receiving apomorphine and 20 receiving placebo, was expected to be enrolled in the study The study was conducted in 26 US sites

3 1 4 3 Study Procedures

Test medication was administered in response to a documented "Off" event that occurred at least one hour after administration of the typical morning dose of oral anti-parkinsons medications Efficacy response to dosing was assessed over a 90 minutes period by evaluating the overall time course of the dose response and the time to onset of the drug response The time course of the dose response relationship was determined by measuring the UPDRS Motor Score and dyskinesia score, immediately pre-dose and at 10, 20, and 90 minutes post-dosing The onset of drug response was measured by repeated administration of a modified Webster Step-Seconds Test, and the interval (in minutes) between injection and the time patient declaration of the first perception of significant relief of immobility

Study exit occurred upon completion of the 90-minutes observation period

3 1 4 4 Selection of Patients

Subjects were selected from a review of patients enrolled in the concurrent Bertek study APO401 All qualified patients were then invited to enter the study by the supervising physician or other suitably qualified study personnel at each site The following inclusion and exclusion criteria were applied

Main Inclusion Criteria

- Men and non-pregnant women of any age ≥ 18 ,
- Patients with clinical diagnosis of idiopathic Parkinson's disease,
- Patients classified as stage (II-IV) of the Hoehn and Yahr scale for staging the severity of Parkinson's disease,
- The patient was on an optimally maximized oral therapy regimen,
- Patients were currently receiving apomorphine injection for rescue therapy for "Off" events for a duration of at least three months,
- The minimum apomorphine baseline-dosing requirement was an average of at least 2 doses per day over the week prior to enrollment,
- Patients participating in Bertek APO401, an open-label study primarily designed to collect safety data, were eligible for participation in this trial without termination of participation in APO401

Main Exclusion Criteria

- Patients under medical therapy for clinically significant psychoses or dementia not related to ingestion of anti-parkinson medication,
- Patients with a history of drug or alcohol dependency within one year prior to study enrollment,
- Patients with unstable and clinically significant disease of cardiovascular (including orthostatic hypotension), hematologic (including Coombs' positive hemolytic anemia), hepatic, renal, metabolic, respiratory, gastrointestinal or endocrinological systems or neoplasm within the three months before the start of the study,
- Patients with a history of true allergy to morphine or its derivatives (including apomorphine), sulfur, sulfur containing medication, sulfites, sulfates, Tigan,
- Patients treated with experimental agents (other than apomorphine intermittent subcutaneous injections) within 30 days before study entry Patients with participation in MYLAN-sponsored study APO202 were excluded from participation in this study,
- Patients whose apomorphine regimen was characterized by administration methods other than intermittent injection,
- Patients who could not or would not sign an Informed Consent form

3 1 4 5 Efficacy Evaluation

3 1 4 5 1 Efficacy Parameters

The primary efficacy parameter was defined as the change in UPDRS Motor Score from pre-dose to 20 minutes after dosing

Secondary efficacy endpoints include

- Change in UPDRS Motor Score from pre-dose to 10 and 90 minutes after dosing,
- Percent change in UPDRS Motor Score from pre-dose to 10, 20, and 90 minutes after dosing,
- Area under the curve (AUC) for change in UPDRS Motor Score at 0, 10, 20, and 90 minutes,
- Time to patient-declared onset of relief (maximum observation time = 40 minutes),
- Change in Webster Step-Second Test score from pre-dose to 2.5, 5, 7.5, 10, 15, 20, 40, and 90 minutes after dosing,
- Change in Dyskinesia Assessment from pre-dose to 10, 20 and 90 minutes after dosing

3 1 4 5 2 Statistical Analysis Methods

The primary endpoint (change in UPDRS Motor Score from pre-dose to 20 minutes post-dosing) was to be analyzed based on an analysis of covariance (ANCOVA) model with the term treatment and pre-dose score as the covariate. The primary contrast was to be pooled placebo vs pooled apomorphine (-1/2 -1/2 1/2 1/2)

If this primary contrast is significant, the following pairwise comparisons were to be performed using the ESTIMATE statement in PROC GLM in SAS

- 1 APO vs pooled PL (-1/2 -1/2 1 0)
- 2 APO+2 vs pooled PL (-1/2 -1/2 0 1)

Results were to be confirmed with a stratified, non-parametric analysis using the two strata 1) typical dose and 2) 2 mg greater than typical dose. The stratified, covariance adjusted VanElteren statistic was to be used for the stratified analysis. The stratified analysis was to be used for the primary comparison of pooled APO vs pooled PL. If this primary comparison was significant, pair-wise comparisons were to be performed as described as above, using non-parametric analysis of covariance.

The same methods were to be used to analyze the change in UPDRS Motor Score from pre-dose to 10 minutes and 90 minutes. They were also to be used to analyze the area under the curve for change in UPDRS Motor Score.

The data was to be tested for normality using both the Shapiro-Wilk test and the Kolmogorov test. If significant departures from normality were observed, then the non-parametric analysis was to be considered primary.

For the following supportive analyses, only the pooled APO vs pooled PL comparison was to be performed

The change in Dyskinesia Assessment and the change in the Webster Step-Seconds Test score at each time point were to be assessed by a non-parametric analysis of covariance

The time (in minutes) to patient declared onset of relief was to be analyzed using the Wilcoxon Rank Sum test. It was anticipated that a significant number of subjects would have no declared time of onset of relief. An imputed score of 40 minutes was to be used if onset could not be documented. Instead of exact time value, the time period in which the onset occurred (2.5, 5, 7.5, ..., minutes) was to be used for this analysis.

In general, data were to be analyzed as reported. For analysis purpose, imputation of missing values might be performed using the last observation carry forward (LOCF). This was anticipated for missing UPDRS values, where either a single item or an entire time period might be missing. With imputation of missing UPDRS values, no imputation for UPDRS area under the curve should be required. For the non-parametric analysis of time to onset an imputed score of 40 minutes (maximum observation time) was to be used if onset could not be documented. For the Webster Step-Seconds, a score of 9999 was to be used if the patient was unable to complete the test within the 6-second timeframe or a patient's score exceeded 9999.

3.1.4.6 Sponsor's Analysis Results

3.1.4.6.1 Subject Disposition

Sixty-two patients received study medication in APO302 (19 in APO, 16 in APO+2, 13 in PL, and 14 in PL+2) and were included in the ITT and safety populations. Two patients in the placebo group terminated the study early due to lack of efficacy. Both patients experienced considerable discomfort due to "Off" event and were given medication to reverse the event.

3.1.4.6.2 Protocol Violation

One subject did not meet the inclusion and exclusion criteria. Three subjects in the PL group were not taking dopamine agonist as required per protocol. One subject in the PL+2 group was granted an exception for pre-existing dementia unrelated to anti-Parkinson medications.

Three subjects did not take oral Parkinson's disease medication on the Treatment Day as specified by the protocol and arrived at the clinic in an "Off" state. The data from these subjects were included in both ITT and PP analyses.

3.1.4.6.3 Demographic and Baseline Characteristics

A summary of baseline patient demographics is provided in Table 21. The sponsor reported that

there were no statistical differences in baseline characteristics between the pooled placebo and pooled apomorphine

Table 21 Baseline Characteristics - ITT Population

Variable		APO (n=19)	APO+2 (n=16)	PL (n=13)	PL+2 (n=14)	Total (n=62)	p-value [1]
Gender	Male	15 (78.9%)	10 (62.5%)	8 (61.5%)	12 (85.7%)	45 (72.6%)	1.0000
	Female	4 (21.1%)	6 (37.5%)	5 (38.5%)	2 (14.3%)	17 (27.4%)	
Race	Caucasian	19 (100%)	16 (100%)	11 (84.6%)	14 (10%)	60 (96.8%)	1856
	Hispanic			1 (7.7%)		1 (1.6%)	
	Asian			1 (7.7%)		1 (1.6%)	
Age	Mean	64.00	65.69	66.85	66.21	65.53	4709
	Stderr	2.07	2.30	2.95	2.54	1.19	
	Median	63.00	68.50	72.00	66.50	67.00	
Age of Onset	Mean	51.61	50.56	49.08	51.71	50.83	8057
	Stderr	1.81	2.25	3.86	3.56	1.36	
	Median	51.00	50.50	53.00	47.50	51.00	
Days since first APO	Mean	368.89	492.94	468.69	421.29	433.66	6901
	Stderr	41.09	46.07	52.02	40.20	22.75	
	Median	393.00	526.50	392.00	449.50	421.50	
Tobacco Use	None/Rare	9 (47.4%)	12 (75%)	9 (69.2%)	6 (42.9%)	36 (58.1%)	9103
	Former	9 (47.4%)	3 (18.8%)	3 (23.1%)	8 (57.1%)	23 (37.1%)	
	Current	1 (5.3%)	1 (6.3%)	1 (7.7%)	0 (0.0%)	3 (4.8%)	
Alcohol Use	None/Rare	16 (84.2%)	12 (75.0%)	10 (76.9%)	7 (50.0%)	45 (72.6%)	1605
	Moderate	3 (15.8%)	4 (25.0%)	3 (23.1%)	7 (50.0%)	17 (27.4%)	

[1] p-value from Fisher's Exact test for categorical variables, ANOVA for continuous variables

Source: Sponsor's Table 14.1.2.1

Baseline UPDRS scores, collected while patients were in an "On" state, are presented in Table 22. Review of differences in baseline UPDRS scores between pooled PL vs pooled APO treatment groups showed that baseline UPDRS Section III scores were statistically higher in the pooled APO group than in the pooled PL group with p-values of 0.0531 (Table 22) and 0.0489 for the ITT population and per-protocol (PP) population, respectively.

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Table 22 Baseline Assessment - ITT Population

Variable	APO	APO+2	PL	PL+2	Total	p-value [1]
Number of Subjects	18	16	13	14	61	

UPDRS	Mean	2 11	2 63	2 08	1 43	2 08	1919
Section I	Stderr	378	473	625	388	232	
Subtotal	Median	2 50	3 00	1 00	1 00	2 00	
UPDRS	Mean	15 67	14 81	15 23	12 57	14 64	3921
Section II	Stderr	1 239	2 013	1 787	1 463	812	
Subtotal	Median	15 50	14 00	14 00	13 00	14 00	
UPDRS	Mean	26 44	24 75	22 62	16 43	22 89	0531
Section III	Stderr	2 902	3 088	3 799	2 849	1 608	
Subtotal	Median	24 00	27 50	24 00	13 50	20 00	
UPDRS	Mean	7 06	8 06	7 85	6 93	7 46	8141
Section IV	Stderr	777	520	741	539	332	
Subtotal	Median	7 00	8 50	7 00	6 50	7 00	
UPDRS	Mean stderr	51 28	50 25	47 77	37 36	47 07	0698
Total	Median	3 721	5 067	5 354	3 964	2 311	
		47 00	51 50	41 00	35 50	43 00	
Non-motor	Mean	24 83	25 50	25 15	20 93	24 18	2871
UPDRS	Stderr	1 675	2 133	2 633	1 682	1 011	
Subtotal	Median	25 00	27 00	26 00	21 00	24 00	

[1] p-values from ANOVA

Source Sponsor's Table 14 1 3 1

3 1 4 6 4 Efficacy Evaluation

The primary endpoint of change in mean UPDRS Motor Score from pre-dose to 20 minutes was analyzed based on an analysis of covariance (ANCOVA) model with term treatment and pre-dose score as the covariate. The assumption of normality was tested by Shapiro-Wilk test and the Kolmogorov Smirnov test, and the normal assumption was found not violated. Therefore, the parametric ANCOVA model was considered as the primary analysis model, and the non-parametric test was the secondary model.

The primary contrast was pooled placebo vs pooled apomorphine. The sponsor reported that the patients in the pooled APO group experienced a reduction in the mean UPDRS Motor Score at 20 minutes of -24.2 points as compared to a mean reduction of -7.4 points for patients in the pooled PL group. The treatment difference between the two pooled groups carried a p-value of <0.0001. Results are presented in Table 23 and Table 24.

Table 23 Primary Efficacy Analysis - Pooled APO vs Pooled PL - ITT Population

Time	Pooled APO (n=35)	Pooled PL (n=27)	p-value
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from dosing	Mean (SE)	Change Mean (SE)	% Change Mean (SE)	Mean (SE)	Change Mean (SE)	% Change Mean (SE)	Change	%Change e
0	42.0 (1.8)			40.6 (3.4)				
10	22.1 (2.3)	-19.9 (1.8)	-48.9 (4.4)	35.0 (4.2)	-5.6 (1.6)	-19.3 (5.4)	< 0001	< 0001
20	17.8 (1.9)	-24.2 (1.7)	-58.7 (3.8)	33.3 (4.4)	-7.4 (1.8)	-24.1 (5.6)	< 0001	< 0001
primary								
90	36.7 (2.6)	-5.2 (1.8)	-13.6 (4.3)	35.7 (4.3)	-4.9 (2.0)	-15.0 (2.9)	8558	9031

Source sponsor's Table 14.2.1.1.1

Table 24 Primary Efficacy Analysis - Mean Change in UPDRS from Pre-dose - ITT Population

Time from dosing	Mean Change in UPDRS			Mean Change in UPDRS			p-values			
	APO (n=19)	APO+2 (n=16)	Pooled APO (n=35)	PL (n=13)	PL+2 (n=14)	Pooled PL (n=27)	[1]	[2]	[3]	[4]
10	-16.5	-23.8	-19.9	-6.6	-4.6	-5.6	5412	0003	< 0001	< 0001
20	-23.7	-24.8	-24.2	-6.8	-7.9	-7.4	7742	< 0001	< 0001	< 0001
90	-4.8	-5.8	-5.2	-4.1	-5.6	-4.9	8307	9608	8034	9494

[1] p-value from comparison of PL vs PL+2 using ANOVA

[2] p-value from comparison of APO vs pooled PL using ANOVA

[3] p-value from comparison of APO+2 vs pooled PL using ANOVA

[4] p-value from pooled APO vs pooled PL using non-parametric analysis

Source Sponsor's Tables 14.2.1.1.2, 14.2.1.1.3, 14.2.1.1.4, 14.2.1.2.1

Secondary Efficacy Endpoints

The secondary efficacy points are collected as supportive information and were analyzed by comparing only the pooled PL and pooled APO groups. The following secondary endpoints were evaluated:

- 1 Change in the UPDRS Motor Score from pre-dose to 10 and 90 minutes after dosing,
- 2 Percent change in UPDRS Motor Score from pre-dose to 10, 20, and 90 minutes after dosing,
- 1 Area under the curve (AUC) for change in UPDRS Motor Score at 0, 10, 20, and 90 minutes,
- 2 Time to patient declared onset of relief,
- 3 Change in Webster Step-Seconds Test score from pre-dose to 2.5, 5, 7.5, 10, 15, 20, 40, and 90 minutes after dosing,
- 4 Change in Dyskinesia Assessment from pre-dose to 10, 20, and 90 minutes after dosing

The following Tables present the results

Table 25 Area Under the Curve for Change from Pre-dose UPDRS Scores

Group	Mean (SE)		p-value
	Group A	Group B	
Pooled APO (A) vs Pooled PL (B)	-1348 (108 11)	-522 (141 59)	< 0001
APO (A) vs Pooled PL (B)	-1280 (140 94)	-522 (141 59)	0005
APO+2 (A) vs Pooled PL (B)	-1429 (169 82)	-522 (141 59)	0001

Source Sponsor's Table 14 2 1 3

There was no statistically significant difference in the time to onset of relief between the pooled treatment groups ($p= 1502$ from Wilcoxon Rank Sum test) The median time to onset of relief was 5 0 minutes for the pooled APO group and 7 5 minutes for the pooled PL group

The Webster Step-Seconds scores, which were obtained pre-dose and at 2 5, 5, 7 5, 10, 20, and 40 minutes post-dose, were analyzed by non-parametric analysis of covariance since data were not normally distributed If a patient could not complete the test within the 60-second timeframe, a score of "9999" was used in the calculation The following table presents the results

Table 26 Change from Pre-dose in Webster Step-Seconds Scores

Time from Dosing (min)	Pooled Apomorphine			Pooled Placebo			Nominal p-value
	N	Median change (min, max)		N	Median change (min, max)		
0	34			27			
2 5	35	-36 5	—	26	-36 5	—	3495
5 0	35	-50 0	—	27	-28 0	—	2777
7 5	35	-269 5	—	27	-58 0	—	0230
10	35	-400 5	—	27	-78 0	—	0050
15	35	-426 5	—	27	-66 0	—	0005
20	35	-462 5	—	27	-39 0	—	< 0001
40	34	-445 0	—	26	-62 5	—	0004

Source Sponsor's Table 14 2 1 7

Dyskinesia Rating Scale assessments were performed at pre-dose and at 10, 20, and 90 minutes post-dosing of study drug The sponsor reported that the data were not normally distributed and were analyzed by non-parametric analysis of covariance The median changes for both pooled apomorphine and pooled placebo groups were 0 at all time points, though the mean values were larger in the pooled apomorphine group The p-values for the treatment difference were 0 0021, 0 0001, and 0 2536 at 10, 20, and 90 minutes post-dosing, respectively

3 1 4 7 Reviewer's Analysis

A ratio of 2 2 1 1 was planned in the protocol in assigning patients to APO, APO+2, PL, and PL+2 groups It was planned that 40 subjects were to be enrolled in the two apomorphine groups and 20 subjects were to be enrolled in the two placebo groups with a randomization scheme of block of 6 subjects It was not clear why it ended up with 35 patients assigned to the two

apomorphine groups and 27 patients assigned to the two placebo groups. The information about the randomization assignment will be requested from the sponsor. All the reviewer's analysis results and conclusion are based on the data and are subject to changes upon additional information regarding to the randomization scheme are provided.

3.1.4.7.1 Analysis of Primary Efficacy Parameter

The protocol-specified analyses were performed to the primary efficacy parameter and all secondary efficacy parameters and the results reported by the sponsor were verified to be correct.

As shown in Tables 23 and 24, the treatment differences in contrasted comparisons of APO vs PL, APO vs combined PL and APO+2 vs combined PL were all statistically significant at 20 minutes post-dosing in favor of apomorphine. Therefore, I would conclude that apomorphine is effective in those Parkinson's disease patients after they had been exposed to apomorphine for rescue treatment for at least 3 months.

The efficacy was shown in both patient's standard dose and 2 mg higher than the standard dose. The apomorphine dose ranged from 0.2 mL to 1 mL with an average of 0.46 mL in the APO group and ranged from 0.35 mL to 1 mL with an average of 0.58 mL in the APO+2 group.

The time course of the UPDRS change from pre-dose suggests that apomorphine could be effective as early as 10 minutes post-dosing, and is not effective at 90 minutes post-dosing. Numerically, the change in UPDRS from pre-dose is larger in the higher dosing group than in the standard dosing group at 10 minutes post-dosing, but such difference seems diminish at 20 minutes post-dosing.

3.1.4.7.2 Analysis of Secondary Efficacy Parameters

Secondary efficacy parameters are subject to multiplicity adjustment, which was not proposed in the study protocol. There are six secondary efficacy parameters. Except for the time of onset of relief and area under the curve, others were measured at multiple time points. Altogether, 18 sub-secondary efficacy parameters are counted.

The treatment difference in time of onset of relief was not statistically significant by the protocol specified analysis method. The p-values from Webster Step-Seconds scores were subject to multiplicity adjustment. The data appear to suggest that there was treatment effect shown in the Webster Step-Seconds scores at 15, 20, and 40 minutes post-dosing.

The treatment difference in Dyskinesia Rating Scale also appears to be significant at 10 and 20 minutes post-dosing with more dyskinesia in the pooled APO group. More dyskinesia occurred in the higher dose group than in the standard APO group. The number of patients with at least one point increase in dyskinesia scale for APO and APO+2 were 5 and 10, respectively, at 10

minutes post-dosing, 7 and 10 at 20 minutes post-dosing, and 2 and 3 at 90 minutes post-dosing

4. Findings in Special/Subgroup Populations

4.1 Gender, Race, and Age

Descriptive statistics of efficacy results for subgroups were displayed on the basis of age (split at the age of 65 years for elderly and non-elderly) and gender. Since most patients were Caucasians, no subgroup analysis for race was performed. Due to the small sample size in each of the subgroups, no p-values are given. Tables 27 present the change from baseline UPDRS scores for the subgroups.

Table 27 Mean (SD) Change of UPDRS from Pre-dose to Post-dose by Gender and Age

Variable	APO202		APO301		APO303		APO302	
	APO	Placebo	20 minutes post-dose APO	20 minutes post-dose Placebo	20 minutes post-dose APO	20 minutes post-dose Placebo	20 minutes post-dose APO	20 minutes post-dose Placebo
Gender								
Male								
N	12	8	12	12	30	30	25	20
Mean	-23.3	0	-24.4	-4.8	-13.1	-3.1	-23.8	-9.0
SD	9.4	4.00	10.6	10.0	11.7	9.6	10.1	8.9
Female								
N	8	1	4	4	21	20	10	7
Mean	-24.8	-1.00	-14.5	1.5	-8.5	-1.8	-25.0	-2.7
SD	7.6		13.9	6.9	10.8	5.5	9.7	9.7
Age								
< 65								
N	11	6	9	9	22	21	16	11
Mean	-23.8	0.2	-21.9	-4.1	-15.2	-1.8	-24.3	-6.2
SD	10.3	4.7	18.0	12.5	13.5	5.0	10.7	10.5
≥ 65								
N	9	3	7	7	29	29	19	16
Mean	-23.9	-0.7	-20.4	-2.0	-8.2	-3.1	-24.1	-8.2
SD	6.4	0.6	9.1	3.7	8.7	9.9	9.4	8.8

The change in the UPDRS from pre-dose to post-dose seems to be consistent across gender and age group in four studies. In Studies 301 and 303, the response in UPDRS is numerically larger in males than in females. Such difference in gender is not observed in Studies 202 and 302. Age difference in the response of UPDRS is observed in Study 303, but not in the other three studies. No conclusion could be made for differences in gender and age in terms of response of UPDRS.

4.2 Other Special/Subgroup Populations

No analyses were performed for other subgroup populations

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

Statistical issues evolved in the crossover study of APO303, in which significant period effect was noted. When only period 1 data was analyzed, no treatment effect was found.

The first period data of APO303 is comparable to the data of APO202. Patients in APO202 and APO303 are apomorphine-naive, and APO303 had at least as many subjects in each treatment group in the first period as in APO202. However, the treatment difference in the mean change in UPDRS is only about 5 points in APO303, compared to 23 points in APO202.

Collectively, three of the clinical studies showed significant treatment effect by their protocol-specified analysis and had a mean change in UPDRS from pre-dose to post-dose of over 20 points after apomorphine injection. Study APO303 had a mean change of about 10 points.

5.2 Conclusions and Recommendations

Four clinical studies were included in this NDA submission. Efficacy measures of the four studies are all based on change from pre-dose in UPDRS Motor Scores and are collected in a period up to 90 minutes of observation after the injection of the study drug.

Patients in Studies 202 and 303 were apomorphine-naive patients while patients in Studies 301 and 302 had taken apomorphine for treating "Off" events for at least 3 months. The four studies, collectively, provided sufficient evidence that apomorphine injection is effective in treating "Off" events in Parkinson's disease patients.

Reference

Pocock, Stuart J. *Clinical Trials: A Practical Approach*. John Wiley & Sons, 1983.

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