

**Table 23 Effect of Treatment on Change from Baseline Dyskinesia Rating Scale Scores at 10, 20, and 60 minutes After Dosing (ITT Population)**

Time after Dosing Median (Min, Max)	Apomorphine (n=17)	Placebo (n=17)	p-value (1)	p-value (2)
10 min after injection	0 (0, 2)	0 (-3, 0)	0 0156	0 0383
20 min after injection	1 (-3, 3)	0, (0, 0)	0 0507	0 0066
60 min after injection	0 (-3, 3)	0 (-3, 0)	0 1093	0 0159

(1) From Wilcoxon Signed Rank Test

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

Source Sponsor's Efficacy Table 14 2 2

**Patient Perceived Relief of "Off"**

During the 60 minute study period, patients were asked to declare at what time they perceived a significant relief of "Off" symptoms after study medication injection. Some patients did not declare any relief during the study period. When data were analyzed using the ITT population and actual data based upon patient declaration there was no statistical difference (Table 24) in the mean time to patient perceived relief of "Off". Data were also analyzed for the ITT population with respect to the median time to relief of "Off" and missing data were imputed to 60 minutes. There was a statistically significant difference (Table 25) in favor of APM when data from both days were used, but not when data were analyzed only with respect to Day 1.

**Table 24 Effect of Treatment on Mean Time (Minutes) to Patient Declared Relief (ITT Population)**

Variable		Apomorphine	Placebo	p-value (1)	p-value (2)
Time (minutes) to Patient Declared Relief	Mean (std error) N =	13 2 (2 5) 13	9 5 (0 3) 4	0 0732	0 3037

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

(3) ANOVA with term treatment - Day 1 data only

Data Source Sponsor's Table 14 2 3 1

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**Table 25 Effect of Treatment on Median Time (Minutes) to Patient Declared Relief with Missing Values Set to 60 Minutes (ITT Population)**

Variable		Apomorphine	Placebo	Treatment Difference (APM - Placebo)	p-value (1)	p-value (2)
Time (minutes) to Patient Declared Relief	Median (Min, Max) N =	15 (2, 60) 17	60 (9, 60) 17	- 40 (- 58, 50) 17	0.0102	0.2212

(1) From Wilcoxon Signed Rank Test

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

Data Source: Sponsor's Table 14.2.3.2

### Subgroup Analyses

The sponsor conducted and presented subgroup analyses on the basis of age (split at the median age of 64 years), gender, and investigator. Table 26 presents the results of mean changes in UPDRS motor scores from pre-dosing for these subgroups.

Subgroup analyses of the efficacy data at multiple timepoints showed that there did not appear to be any significant effect of age on responsiveness to APM. The age cutoff of 64 years old for assessing age effects was based upon the median age of patients. Patients above and below the cutoff appear to respond relatively similarly. Changes in UPDRS motor scores in females (n = 5) were less than those of males (n = 12). Changes in females were not statistically significant compared to results in males that were statistically significant at all timepoints.

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**Table 26 Change in UPDRS Motor Scores from Pre-dosing (Sub-group Analyses - ITT Population)**

Time Relative to Dosing (Mean)	Apomorphine	Placebo	p-value (1)	p-value (2)	p-value (3)
Age < 64 (n=8)					
10 min after injection	-13	-4	2912	8203	7524
20 min after injection	-17	-5	0265	7452	5084
60 min after injection	-9	-1	0077	7303	2085
Age ≥ 64 (n=9)					
10 min after injection	-18	-2	0061	2195	0379
20 min after injection	-23	-1	0008	0787	0273
60 min after injection	-16	0	0190	5782	0055
Female (n=5)					
10 min after injection	-9	0	2599	6526	8766
20 min after injection	-9	1	3608	9101	9437
60 min after injection	-12	1	1685	5866	3767
Male (n=12)					
10 min after injection	-18	-4	0468	1976	4465
20 min after injection	-24	-5	< 0001	1077	0639
60 min after injection	-13	-1	0141	7576	0162
Site 01 (n=14)					
10 min after injection	-15	-3	0217	4127	3158
20 min after injection	-21	-3	< 0001	4079	0852
60 min after injection	-14	0	0015	9776	0035
Site 03 (n=3)					
10 min after injection	-17	-4	NA	3486	NA
20 min after injection	-16	-1	NA	2806	NA
60 min after injection	-5	0	NA	8070	NA

(1) Repeated measures ANCOVA with terms 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) ANCOVA with terms pre-dose score and treatment - Day 1 data only

Data Source Sponsor's Table 11 4 2 8 1

**Reviewer's Analysis**

**Analysis of Primary Efficacy Parameter**

Results for the primary efficacy endpoint were reanalyzed because the statistical reviewer (Dr Sharon Yan), thought that a non-parametric analysis was appropriate because the data did not satisfy the assumption of normality

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 statistical reviewer (Dr Sharon Yan) thought that this analysis was not appropriate because 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. Dr Yan performed this non-parametric analysis and its results are shown in Table 27. A significant treatment difference in favor of APM was found at all time points.

**Table 27 Change from Pre-Dose for UPDRS Motor Score - 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	

Dr Yan also evaluated a Period effect by non-parametric analysis of Wilcoxon Rank Sum test comparing (APM - 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 recognized that this test of a period effect is not sensitive and is usually not powered to detect a period effect. Given the small sample size of 8 subjects in each sequence, it is possible that period effect exists but that this testing does not detect it. When results were reanalyzed to show the change of UPDRS motor score by treatment and period, the magnitude of the change in UPDRS motor score after APM injection seemed to be larger in period 2 than in period 1 as shown in Table 28. There was an improvement in UPDRS after placebo injection in period 1, but not in period 2.

**Table 28 Change in UPDRS Motor Score 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

A 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 these additional analyses of Dr. Yan, I agree with her and conclude that the study showed a positive treatment for the primary efficacy endpoint.

#### 4.2.3 Discussion of Study Results

APM showed a highly statistically significant decrease (i.e. therapeutic improvement) in the primary efficacy endpoint, the change in the UPDRS motor function score. The onset of a statistically significant difference and benefit relative to study medication injection occurred as early as 10 minutes, was greatest at 20 minutes, and persisted through 60 minutes. These results support a clear therapeutic benefit for APM rapidly reversing an "Off". There was a period effect resulting from cross-over design. However, additional analyses of this relatively small number of patients studied corroborated the therapeutic benefit of APM treatment of reversal of "Off".

A major conclusion derived from this study was that APM was capable of reversing "Off" after at least 3 months therapy with APM involving multiple subcutaneous injections of APM that was often administered on a daily basis. Demonstrating this effect was of interest to FDA.

The doses in the APM treatment group ranged between 2 to 10 mg, but most doses were  $> 2$  mg and  $\leq 5$  mg. Dose of APM had been determined according to the perception based upon outpatient experience of at least 3 months duration that the dose was "optimal" for that individual patient in terms of producing maximal efficacy with minimal toxicity. The sponsor did not conduct any analysis to assess a dose-dependent effect of APM. However, based upon results from this study, it is difficult to conclude that 2 mg is an effective dose because only 2 patients received this dose.

"Off" that was treated may have been spontaneously naturally occurring "Off", that could be an end of dose "Wearing Off" or "On/Off". The design was to treat the first "Off" that occurred after the patient took his/her normal, morning oral anti-parkinsonian medications. Although it may seem likely that spontaneously naturally occurring "Off" may have developed and been treated within the patient's interval for taking LD, it is not possible to know if this is true. The protocol did not allow other medication to be used until treatment of "Off" was assessed in the study. Thus, it is conceivable that some patients may have experienced an "induced" "Off" if the "Off" that occurred developed after the patient's normal dosing interval of his/her standard medications including LD that is usually dosed at  $\leq 4$  hour intervals during waking hours. The sponsor did not address this issue nor present data to allow one to determine if "Off" occurred beyond the patient's normal dosing interval for taking LD. In summary, we do not know if spontaneously occurring "Off" episodes were treated. However, even if many or most of these "Off" episodes were spontaneously occurring within the patient's normal dosing interval for administering levodopa/dopa decarboxylase inhibitor, we do not know if the "Off" was an end of dose wearing

"Off" or an unpredictable "On/Off" Even if induced "Off" was frequently evaluated, it is debatable whether this could serve as a surrogate for an end of dose wearing "Off"

Statistical adjustments were not made for multiplicity in the comparisons of secondary endpoints and nominal p-values were reported. Regardless, that there were no corrections for multiplicity of statistical comparisons, a statistically significant effect was not always observed for APM treatment vs placebo

Subgroup analyses of the efficacy data at multiple timepoints showed that there did not appear to be any significant effect of age on responsiveness to APM. The age cutoff of 64 years old for assessing age effects was based upon the median age of patients. Patients above and below the cutoff appear to respond relatively similarly. This cutoff is slightly higher than that ( $\geq 65$  years old) to define elderly patients in the CFR for Geriatric Labeling. Although changes in UPDRS appeared to be somewhat greater at all timepoints for patients  $\geq 64$  years old (vs younger patients), it is difficult to know if this is very meaningful considering the relatively small sample size in each group (9 vs 8). Changes in UPDRS motor scores in females ( $n = 5$ ) were less than those of males ( $n = 12$ ). Changes in females were not statistically significant compared to results in males that were statistically significant at all timepoints. It seems likely that females would show statistically significant results if the sample size was larger based upon the previous base of knowledge in treating females.

APM resulted in an increase in dyskinesia, another secondary efficacy variable. But the effect was relatively mild overall, and not necessarily unexpected in this population of advanced Parkinson's disease patients who are generally highly susceptible to the development of dyskinesia with dopaminergic stimulation.

The original ITT analysis of mean time until patient declared relief using actual declared times did not show a statistically significant benefit of APM (vs placebo). In fact, this analysis showed that the mean time to relief for APM (13.2 minutes) was longer than the mean time (9.5 minutes) for placebo. The perception of benefit of relief from "Off" with APM treatment was only suggested when an analysis was conducted in which missing data for declaring achievement of "On" were imputed to the last 60 minutes timepoint. This was done because there were many instances in which there was no declaration of "On". However, when these data were also analyzed only during the first period to avoid a period effect, there was no statistically significant benefit of APM. Thus, it does not seem that patients can easily discern at an early timepoint that they have experienced relief from treatment of "Off".

The sponsor noted that patients enrolled were supposedly still having "Off" episodes despite "optimized" anti-parkinsonian treatment. However, there was no attempt to show by specific criteria that patients had indeed been "optimized" with all other treatments for Parkinson's disease. My impression is that most patients enrolled were fairly advanced in their disease but it is arguable how well each had been "optimized" prior to enrollment.

## 4 2 4 Conclusions

### Sponsor's Conclusions

- APM is efficacious in relieving "Off" events experienced by patients who have undergone repeated treatment of "Off" episodes over a prolonged period of at least 3 months
- APM provides additional benefit for treating "Off" episodes in patients who have been receiving various "optimized" anti-parkinsonian regimens
- APM is highly effective in improving motor function over a significant period ranging from 10 to 60 minutes and showed a peak effect at 20 minutes
- The magnitude of the APM-induced improvement in motor function at "Off" is substantial approaching a 50 % decrease in UPDRS motor score compared to pre-dosing
- Dyskinesia from APM was significant but relatively mild and was most evident at the 20 minute timepoint

### Reviewer's Conclusions

- I agree essentially with the sponsor's conclusions with the caveat that it is not clear that one could determine whether or how well each patient had received "optimized" anti-parkinsonian treatment prior to enrollment
- These data do not show that patients can reliably discern onset of relief at an early timepoint
- It is not possible to conclude from this study that 2 mg APM is an effective dose because there were only 2 patients who received this dose
- Although APM clearly treats and reverses "Off" episodes, it is not possible to conclude that APM treats both end of dose wearing "off" and unpredictable ""On/Off" because we do not know if the "Off" that was treated was a spontaneously occurring "Off" episode nor the type of "Off" episode that was treated

### 4.3 Study APO303 (Pivotal Study Showing Efficacy)

#### 4.3.1 Description of Protocol APO303

**Title of Study** Study of Orthostatic Changes upon Apomorphine Dose Initiation in Late Stage Parkinson's Disease patients A Dose Escalation Study with a Double-Blind Placebo-Controlled Efficacy Determination at 4 mg

**Investigators / Sites** 21 U S

Study initiation (first patient enrollment) date 2/9/01

Study completion (last patient completed) date 8/21/02

#### Protocol Description (Synopsis/Summary)

##### Objectives

APO303, a sub-study using patients enrolled in APO401 (the long-term open label safety protocol), was designed to address DNDP concerns regarding adverse events particularly orthostatic hypotension, during dose introduction in APM-naïve patients

The primary objective of this study was to determine the electrocardiographic and orthostatic effects of APM during controlled in-patient dose introduction in APM-naïve late stage Parkinson's Disease (PD) patients Although safety observations represented the primary objective of the study, a control group was considered essential to properly interpret adverse events that occurred during dose titration Additional data comparing the efficacy and safety of subcutaneous APM, placebo and standard antiparkinson (anti-PD) therapy was derived from this experience

##### Study Design

This was to be a two-phase study that involved a controlled in-office dose titration phase followed by a 6-month outpatient open-label treatment phase Figure 8 shows the schematic flow chart for Study APO303 Figure 9 shows the schematic flow chart for Study APO303, that is a substudy of the parent study (APO401) During the in-patient dose titration phase, subjects **who were naïve to APM** were evaluated on separate days for the response to single doses of medication administered during an observed "Off" event (defined as first "Off" event that occurs at least one hour after administration of the normal morning dose of oral antiparkinson medication At the 0.4-mL titration level (e.g. APM is constituted as 10 mg/mL concentration), placebo was randomly introduced under double-blind crossover conditions over two Titration Visits (TV2 and TV3)

Figure 8 APO303 Flow Chart

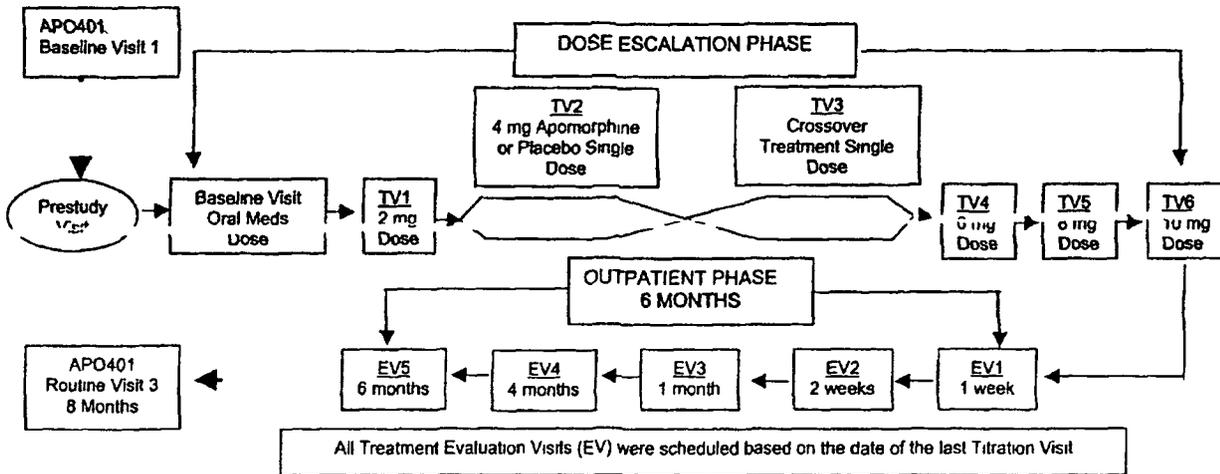
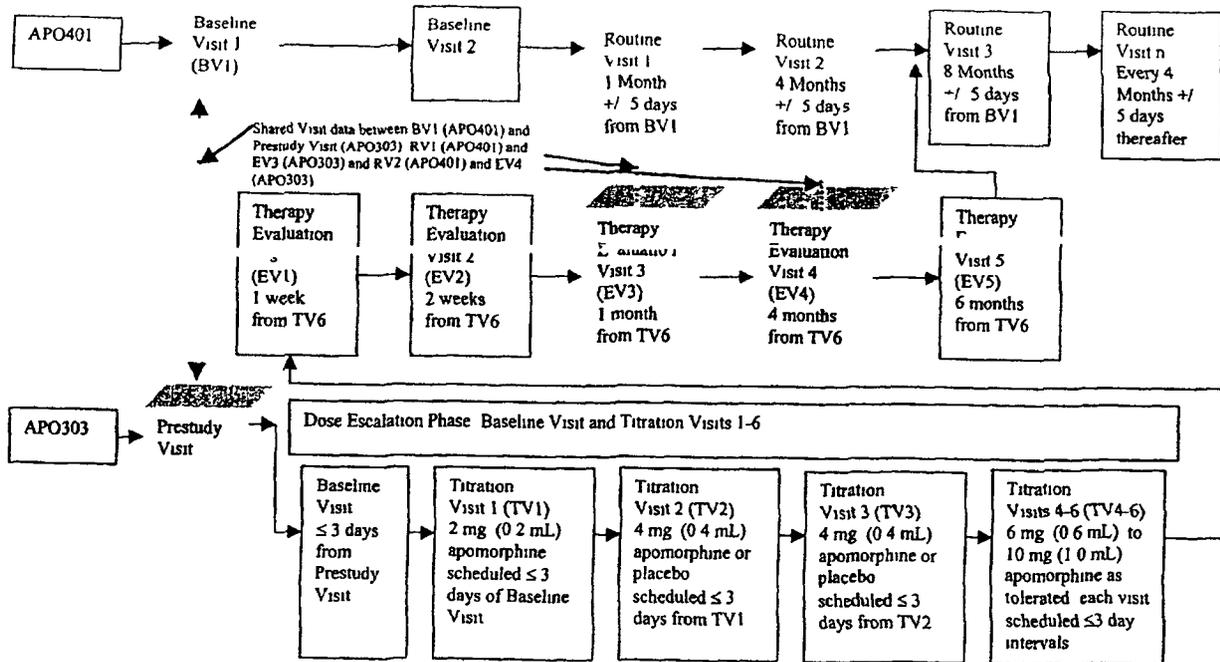


Figure 9 Flow Chart of Study APO303 and Study APO401



Evaluation of the acute response to oral anti-PD medication (Baseline) and to APM dose escalation between 2 and 10 mg (Titration Visits) was conducted under unblinded conditions except at the 4 mg titration level. The Schedule of Events for collecting efficacy and safety data is shown in Figure 10 and Figure 11. Patients naive to APM treatment were initially treated with 2 mg APM and orthostatic VS (sitting and standing blood pressure and pulse) and electrocardiographic responses (via Holter monitor) were studied immediately prior to dosing (i.e. pre-dose) and at 20, 40, and 90 minutes after APM. Patients would take their usual anti-parkinsonian medications at home and come to the clinic where their usual anti-parkinsonian treatment would be held until an "Off" occurred. At that time the patient would receive an injection of study medication and efficacy and safety data would be collected at the specified times. Titration visits (TVs) occurred at intervals of  $\leq 3$  days. Patients then underwent dose escalation to the 4 mg level and were studied to assess the acute effect of treatment with 4 mg APM and placebo under double-blinded conditions on separate days (during cross-over design) on orthostatic VS and Holter. Patients were then similarly studied to assess the acute effect of treatment (on orthostatic VS and Holter) of 6 mg, 8 mg, and 10 mg APM during successive visits of dose escalation. After the patient had reached the maximal, single dose (i.e. 10 mg or highest tolerable dose) of APM during dose escalation, an optimal, outpatient dose would be recommended to each patient based upon the patient's therapeutic and safety/tolerability responses.

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**Figure 10 Schedule of Events for Study APO303**

PROCEDURE	Study Qualification	APO303 DOSE ESCALATION PHASE			APO303 OUTPATIENT PHASE	
	APO401 Baseline Visit 1	Evaluation of Oral Parkinson's Disease Medications	Titration Visit 1 to 5	Titration Visit 6	Evaluation Visit 1 to 5 Wk 1& 2, Month 1, 4, 6	Study End / Return APO4
<b>Study Qualification and General Patient Characteristics</b>						
Concomitant Medications	•	•	•	•	•	•
Drug History/Diet Review	•					
Hochm and Yahr Stage	•					•
Informed Consent		■				
Medical Records Review	•					
<b>Efficacy and Safety Evaluations</b>						
Complete Physical Exam	•					•
Coombs Test <sup>1</sup>	•				•	•
Diary Review		•			•	
Dispense Trimethobenzamide	•					
Dispense Apomorphine				•	•	
Fasting Labs/Blood, Urine <sup>1</sup>	•				•	•
Review of Systems	•	•	•	•	•	
Serum Pregnancy Test <sup>1</sup>	•				•	•
UPDRS	•	•	•	•	•	
Vital Signs	•	•	•	•	•	•
<b>Time Course of Drug Effect (0, 20, 40, 90 minutes)</b>						
12 Lead ECG	•					•
Adverse Event Assessment		•	•	•	•	•
Apomorphine Testing			■	■	■	
Dyskinesia Assessment	•	•	•	•	•	
Existing Therapy Evaluation		■				
Holter Monitoring		■	■	■	■	■
Orthostatic Monitoring <sup>2</sup>		•	•	•	•	•

<sup>1</sup> All laboratories will be performed in APO401 study  
<sup>2</sup> Sitting and standing systolic and diastolic blood pressure and pulse measurements. Orthostatic monitoring performed before and after treatment to 0 at all testing visits.  
 ■ indicates events novel to APO303 protocol

**Figure 11 Efficacy and Safety Evaluations Time Course of Treatment Effect**

	As patient present, to the office <sup>1</sup>	Immediate pre-dose while patient is Off	20 minutes	40 minutes	90 minutes
Holter ECG		X	X	X	X
Orthostatic Monitoring	X	X	X	X	X
UPDRS Motor Score (items 18-31)		X	X	X	X
Dyskinesia Assessment		X	X	X	X
Adverse Event Assessment		X	X	X	X

<sup>1</sup>May be conducted while patient is On or Off

**Treatment Duration** 6 months

**Key Inclusion Criteria**

- Patients who met all qualifications for enrollment into APO401 and consented to participate in a controlled in-patient titration procedure were also a enrolled in APO303
- Patients had a clinical diagnosis of idiopathic Parkinson's Disease (classified as stage II-V of the Hoehn and Yahr scale for staging the severity of Parkinson's Disease)
- Patients experienced "On/Off" or "Wearing-Off" motor fluctuations despite optimized therapy with LD and one additional antiparkinson medication (i.e. oral dopamine agonist, monoamine oxidase inhibitor (MAO<sub>B</sub>), or a catechol-o-methyl transferase inhibitor (COMT) therapy) Patients must have been on an optimally maximized oral therapy regimen. Optimized oral anti-PD medications must have included levodopa/carbidopa inhibitor, in either immediate or delayed release forms, plus at least one anti-PD medication (direct acting oral dopaminergic agonist, MAO<sub>B</sub>, or COMT inhibitor per Protocol Amendment 1) for at least 30 days prior to randomization

**Key Exclusion Criteria**

- Patients with prior exposure to APM
- 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 methyldopa therapy
- Patients with a history of true allergy to morphine or its derivatives, sulfur containing medication, sulfites, trimethobenzamide or other anticholinergics
- Patients treated with other experimental agents within 30 days before study entry

**Efficacy Variables**

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

Secondary Efficacy

- Change in UPDRS Motor Score from pre-dose to 40 and 90 minutes after dosing
- AUC for UPDRS Motor Scores at 0, 20, 40, and 90 minutes
- Change in Dyskinesia Assessment at 0, 20, 40 and 90 minutes

The above parameters were also used to assess efficacy at other doses and were used by investigators to determine each patient's optimal APM dose

**Safety Variables** (pre- and post-study assessments)

- physical examination
- Holter monitor (electrocardiographic recordings at pre-dosing, 20, 40, and 90 minutes post-dose)
- clinical laboratory testing
- special laboratory testing
- orthostatic vital signs (VS) s(sitting and standing blood pressure and pulse at pre-dosing, 20, 40, and 90 minutes post-dose)
- Adverse Events (AEs)

**Planned Statistical Analyses**

**Efficacy**

The primary efficacy analysis involved the double-blind 4 mg/placebo crossover portion of the study This takes place at titration visits TV2 and TV3 The primary endpoint (change in UPDRS Motor Score from pre-dose to 20 minutes) will be analyzed using repeated measures analysis of covariance (ANCOVA) with the terms sequence, subject within sequence, pre-dose score, treatment and period The sequence effect will be tested using the subject within sequence mean square as the error term All other effects will be tested against the mean square error from the ANCOVA The data will be examined for period effect and treat-period interaction If there is a significant treatment-period interaction ( $p < 0.10$ ) as measured by sequence effect in the above model, data from TV2 only will 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 is

recognized as an assessment of robustness of a significant result from the repeated measures analysis for the two periods. The TV2 analysis may not be straightforward to interpret if the analysis for both days is not significant.

A supportive analysis will be performed using ANOVA with the model  $(TV2-TV3)=(\text{baseline } TV2 - \text{baseline } TV3) + \text{sequence}$ , where sequence addresses treatment effects and intercept corresponds to period effects. A similar analysis using the model  $(TV2+TV3)=(\text{baseline } TV2 + \text{baseline } TV3) + \text{sequence}$  would have sequence address carryover effects.

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

The change in Dyskinesia Assessment from pre-dose to 20 minutes will 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 will be calculated  $(TV2-TV3)$ . Treatment effect will 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 will also be calculated  $(TV2+TV3)$ . Carryover effect will be tested for the statistical significance by applying the Wilcoxon Rank Sum test to the ranks of these sums. If there is a significant carryover effect, the treatment effect will be compared by applying the Wilcoxon Rank Sum test to the TV2 data only.

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

The change in Dyskinesia Rating Scale was to be analyzed using the Wilcoxon Signed Rank test. The presence and severity of the patient's dyskinesias were assessed according to the following scale:

- |   |          |
|---|----------|
| 0 | None     |
| 1 | Mild     |
| 2 | Moderate |
| 3 | Severe   |

**Safety**

Safety assessments were to be considered exploratory in nature, and p-values associated with these statistical analyses were to be used for descriptive purposes.

Number of patients enrolled	56
Number of patients analyzed	
Efficacy-Crossover Intent-to-Treat (ITT) population	51
Efficacy-Crossover Per Protocol (PP) population	50
Safety	56

**Protocol Amendments**

There was 1 protocol amendment (11/16/01) that provided mainly for some relatively non-critical (with respect to efficacy) changes. These protocol changes addressed 1) clarification that Study APO303 was a secondary study to be conducted as part of the overall Safety study APO401 in patients who were naive to APM, 2) changing the collection of electrocardiographic data from 12 lead ECGs to 7-lead Holter monitor recordings (including the description of the Holter methods), 3) prioritization of orthostatic VS assessments over efficacy assessments, and 4) other relatively minor, administrative, grammatical/typographical changes.

**Protocol Violations/Deviations**

There were no protocol violations/deviations worthy of noting. There were no definitions provided for recognizing a distinction from a deviation or violation and thus these terms appeared to be used interchangeably.

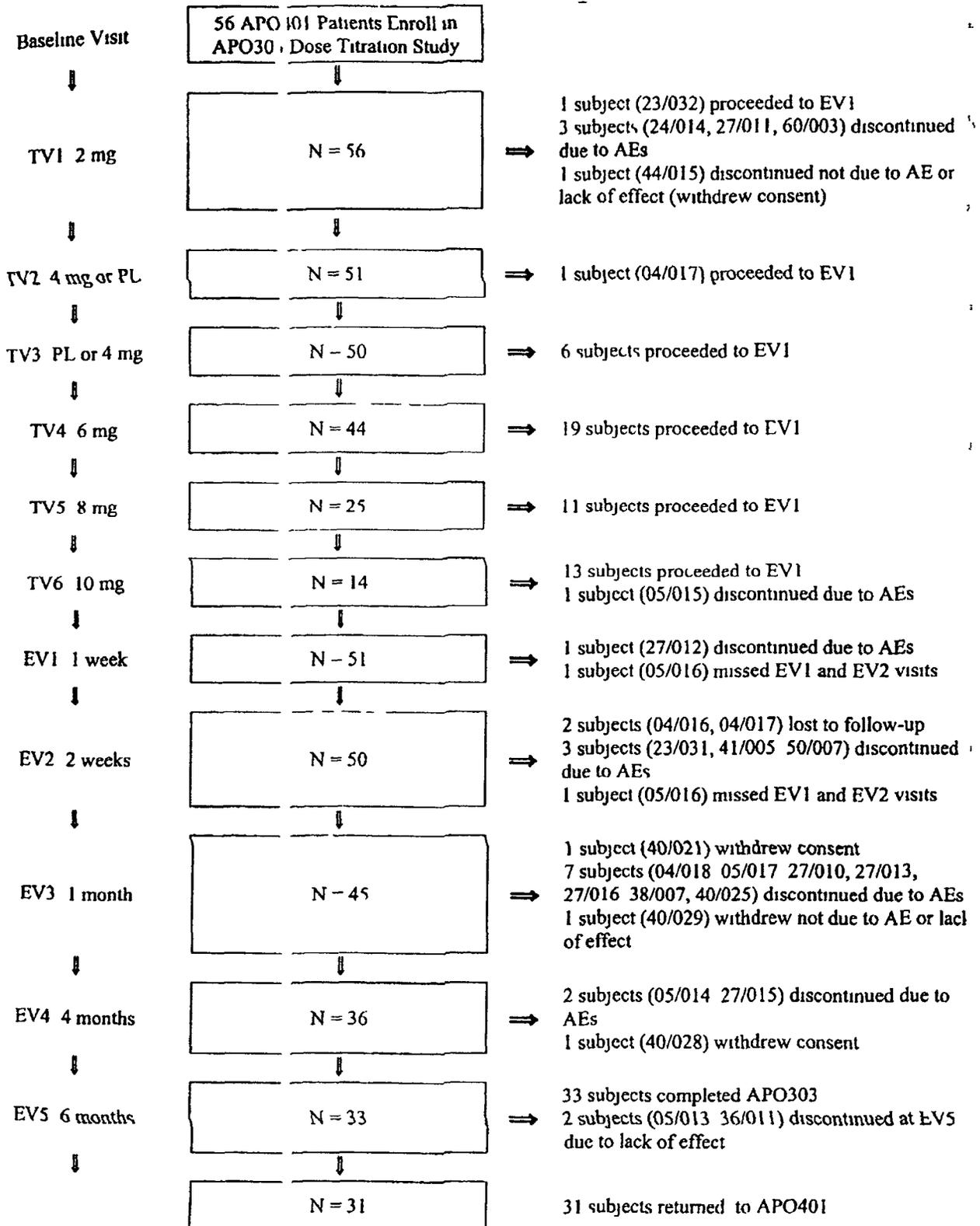
**4.3.2 Results of Study APO303**

**Disposition of Patients**

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

Figure 12 shows the disposition of patients in this study. 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).

**Figure 12 Disposition of Patients**



**Demographic and Other Baseline Characteristics**

Table 29 presents the baseline characteristics for crossover population

**Table 29 Demographic Characteristics**

Variable		Total	Placebo/APO	APO/Placebo	p-value <sup>1</sup>
Gender	Male	30 (58.8%)	14 (56.0%)	16 (61.5%)	0.7793
	Female	21 (41.2%)	11 (44.0%)	10 (38.5%)	
Race	Caucasian	47 (92.2%)	23 (92.0%)	24 (92.3%)	1.0000
	Hispanic	2 (5.9%)	2 (8.0%)	1 (3.8%)	
	Other	1 (2.0%)		1 (3.8%)	
Age	N	51	25	26	0.8291
	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	0.6207
	Mean (SD)	55.2 (1.4)	55.6 (1.9)	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%)	0.4189
	Moderate	6 (11.8%)	4 (16.0%)	2 (7.7%)	

<sup>1</sup> p-values from Fisher's exact test for categorical variables, ANOVA for continuous variables

Source: Sponsor's Table 14.1.2.2

Demographics were analyzed for the crossover population to assess whether there were differences between the patients who received apomorphine followed by placebo at TV2 TV3 or vice versa. There were no differences between treatment groups in any baseline characteristics in the crossover population.

Baseline disease characteristics of Parkinson's disease are presented in Table 30 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 significant differences between treatment groups in the Total UPDRS scores or in any of the UPDRS section scores in the crossover population.

**Table 30 Baseline Disease (Parkinson's disease) Characteristics**

Variable	Total	Placebo/APO	APO/Placebo	p-value <sup>1</sup>
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 (0.29)	3.08 (0.39)	3.08 (0.43)	0.9954
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)	0.3654
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)	0.4596
Median	28.00	26.00	29.00	
UPDRS Section IV sub-total				
N	49	24	25	
Mean (std-err)	6.76 (0.46)	6.21 (0.72)	7.28 (0.57)	0.2480
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)	0.2589
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)	0.2852
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.

<sup>1</sup> p-value from ANOVA

Source: Sponsor's Table 14.1.3.2

### Efficacy Evaluations

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. This review will focus analyses of the ITT population.

### Sponsor's Primary Efficacy Endpoint

The primary efficacy endpoint for the Crossover (ITT) Population was the mean change in UPDRS Motor Scores from pre-dose to 20 minutes. Results for this primary efficacy variable are shown in Table 31 that presents ANCOVA analysis of the change from predose mean UPDRS scores for the crossover population at 20 minutes following placebo and APM (4 mg) injection.

**Table 31 Primary Efficacy Endpoint Effect of Apomorphine (4 mg) on Change in UPDRS Motor Score from Pre-dosing at Titration Visit 2**

Time from Dosing (min)	Placebo (N=51)		Apomorphine 4 mg (N=51)		p-values		
	Mean (SE)	Change from Pre-Dosing Mean (SE)	Mean (SE)	Change from Pre-Dosing Mean (SE)	[1]	[2]	[3]
0	42.5 (22.19)	----	42.7 (2.15)	----			
20	39.8 (2.42)	-2.8 (1.15)	31.5 (2.13)	-11.2 (1.61)	0.0002	0.0038	0.1660

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

[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 predose to 20 minutes was significantly greater after 4 mg APM vs placebo (-11.2 vs -2.8,  $p=0.0002$ ). There was also a significant sequence effect ( $p=0.0038$ ). The data were examined further to understand the cause of the sequence effect. The placebo response for period 1 and period 2 was compared using ANCOVA with predose 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 APM carryover effect and the study design appears valid. The sequence effect appears to be due to a treatment-by-period interaction, with APM showing a stronger treatment effect in period 2 than in period 1. When only Crossover Period 1 data were 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. Results from this non-parametric analysis are presented in Table 32 not only for the 20 minute timepoint but also for the 40 and 90 minutes evaluations. The median change in UPDRS Motor Scores from predose to 20 minutes following 4 mg APM 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 10 ( $p = 0.0001$ ), indicating a highly statistically significant difference between APM 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 -15 ( $p = 0.0166$ ), 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 ( $p = 0.0206$ ).

**Table 32 Change from Baseline in UPDRS – Non-Parametric Analysis**

Time from Dosing	Sequence	TV2 Median	TV3 Median	Difference TV2-TV3	Sum TV2+TV3	p-values		
						[1]	[2]	[3]
20	APO/PL (n=26)	-8	-1.5	-8.5	-7.5	0.001	0.166	0.206
	PL/APO (n=25)	-2	-12	10	-15			
40	APO/PL (n=26)	-10.5	0.5	-8	-9.5	< 0.001	0.531	0.028
	PL/APO (n=25)	-2	-14	10	-16			
90	APO/PL (n=26)	-5.5	1.5	-5	-3	0.230	3.554	1.544
	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

Table 33 shows the effect of APM and placebo on change in UPDRS motor score at various timepoints over 90 minutes, including the 20 minute timepoint that was used for the primary efficacy endpoint. The UPDRS motor score changes at 40 and 90 minutes after injection of study medication were secondary efficacy endpoints. Table 33 also describes the test for normality results for each of the observations. The mean change from baseline in UPDRS Motor Scores after APM injection was significantly greater than that after placebo administration at 40 minutes post-dosing (-13.5 vs -3.0,  $p < 0.0001$ ) and at 90 minutes post-dosing (-5.0 vs -1.6,  $p = 0.0237$ ) for the crossover ITT population (Table 33). Data from 40 minutes, but not from 90 minutes, indicated a significant treatment-by-period interaction. Nevertheless, data from TV2, the first visit before cross-over, still indicated a statistically significant ( $p = 0.0339$ ) benefit of APM vs placebo.

Table 36 presents Wilcoxon Rank Sum analysis of the median change from predose UPDRS scores for the crossover (ITT) population at 20, 40, and 90 minutes following placebo and APM (4 mg) injection.

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**Table 33 Effect of Treatment on Time Course of Change in UPDRS Motor Score from Pre-dosing**

Time from Dosing (min)	Placebo (N=51)		Apomorphine (N=51)		p-values		
	Mean (SE)	Change from Pre-Dosing Mean (SE)	Mean (SE)	Change from Pre-Dosing Mean (SE)	[1]	[2]	[3]
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)	0.0002	0.0038	0.1660
40	39.6 (2.55)	-3.0 (1.36)	29.1 (2.18)	-13.5 (1.65)	<0.0001	0.0053	0.0339
90	41.0 (2.56)	-1.6 (1.30)	37.6 (2.45)	-5.0 (1.26)	0.0237	0.1239	0.3367

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

As it is evident from the data in Table 33, data for the Crossover (ITT) Population describing the change in UPDRS Motor Score from pre-dose to 20 minutes indicated some noteworthy departures from normal distribution. Therefore, results were re-analyzed using the non-parametric statistical method, Wilcoxon Rank Sum Test. The non-parametric results confirmed the robustness of the parametric analysis. The median change in UPDRS Motor Scores from predose to 20 minutes following 4 mg APM 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 predose to 20 minutes for the two sequences was -8.5 vs 10 (p = 0.0001), indicating a highly statistically significant difference between APM and placebo treatments. The median sum (TV2+TV3) in UPDRS Motor Score from predose to 20 minutes for the two sequences was -7.5 vs -15 (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 Score between the treatment groups remained statistically significant (p = 0.0206). The significant difference for period 1 is likely due to the smaller effect of period 1 outliers in the non-parametric analyses as compared to the parametric results.

As shown in Table 36, the Wilcoxon Rank Sum analysis does not account for the predose covariate. A non-parametric ANCOVA was also performed, with pre-dose as a covariate, and the results closely followed Wilcoxon Rank Sum Analysis. A treatment effect of APM was observed at all 3 post-treatment timepoints. However, there was definite statistically significant carry-over effects at 20 minutes and a borderline significant effect at 40 minutes. But when the data from the first visit were analyzed alone for these times (20, 40 minutes), the results remained statistically significant.

**Table 36 Effect of Treatment on Change in UPDRS Motor Score from Pre-dosing – Non-Parametric Analysis**

Time from Dosing	Sequence	TV2 Median	TV3 Median	Difference TV2-TV3	Sum TV2+TV3	p-values		
						[1]	[2]	[3]
20	APO/PL (n=26)	-8	-1.5	-8.5	-7.5	0.0001	0.0166	0.0206
	PL/APO (n=25)	-2	-12	10	-15			
40	APO/PL (n=26)	-10.5	0.5	-8	-9.5	<0.0001	0.0531	0.0028
	PL/APO (n=25)	-2	-14	10	-16			
90	APO/PL (n=26)	-5.5	1.5	-5	-3	0.0230	0.3554	0.1544
	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

Data from the mean change from baseline in AUC for UPDRS Motor Score at 20, 40, and 90 minutes are presented in Table 37. The sponsor reported a significant difference in the mean change from baseline in AUC for UPDRS motor score between treatments of APM 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 ( $p = 0.0834$ ).

**Table 37 Effect of Treatment on Area Under the Curve for Change from Baseline in UPDRS Motor Score**

Placebo			Apomorphine			p-values		
N	Mean	Std err	N	Mean	Std err	[1]	[2]	[3]
51	-199	98.353	51	-825	100.64	< 0.0001	0.071	0.0834

[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

Results from the analysis of the effect of treatment on the median change in dyskinesia rating scale are presented in Table 38. The sponsor found a statistically significant increase in dyskinesia after APM injection at all time points. The sequence effect was not statistically significant at any timepoint.

**Table 38 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

### Reviewer's Analyses

The following analyses are based upon discussions with the Statistical Reviewer (Dr Sharon Yan)

#### Analysis of Primary Efficacy Endpoint

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 its analysis. However, the statistical reviewer (Dr Yan) thought that this subject's Day 1 data should not be carried forward to Day 2, and therefore, that the analysis based upon the sponsor's defined per protocol (PP) analysis, which excluded the subject, was more appropriate. The analysis based on PP population provided the same p-value of 0.0002 for the primary efficacy analysis.

Results from the normal test of the residuals from the primary ANCOVA model revealed no significant deviation from the normal assumption ( $p = 0.2217, 0.5183, \text{ and } 0.2208$  for 20 min, 40 min, and 90 min, respectively). Although the sponsor reported a significant deviation of the data from the normal assumption, Dr Yan thought that the difference between the results of the normal test conducted by the sponsor and the one that she conducted was due to different data to which the normal test was applied. The sponsor had applied the test to the original data, whereas Dr Yan applied the test to the residuals from the primary model.

As reported by the sponsor, a period effect was significant with a p-value of 0.0038 at 20 minutes post-dosing. However, an ANOVA analysis applied to first period data of TV2 did not find statistically significant treatment effect at 20 minutes post-dosing ( $p = 0.1660$ ). Thus, APM did not produce a statistically significant effect on the primary efficacy endpoint when there was a reanalysis to avoid the period interaction.

When determining the sample size for the study, the sponsor had estimated the mean and standard deviation of change in UPDRS score to be -5 (14) for placebo and -20 (14) for APM.

The estimated sample size had been 25 for each treatment with a 96 % power to detect a difference of 15 in the change of UPDRS motor function scores Table 39 shows that the difference in the mean UPDRS motor score change between the treatments was approximately 5 points in the first period and approximately 12 points in the second period

**Table 39 Mean UPDRS Change by Treatment and Period**

Treatment	Apomorphine	Placebo
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, despite the fact that the primary statistical analysis showed a significant treatment difference suggesting therapeutic benefit of APM vs placebo according to the protocol-specified statistical method, a significant period effect hampered interpretation of the result. When only first period data were analyzed, the study failed to show a significant treatment effect. Thus, a reasonable conclusion is that this study did not show that APM is effective for the primary efficacy endpoint.

**Secondary Efficacy Endpoints**

My analysis and that of the statistical reviewer agrees with the one conducted by the sponsor for the change in AUC shown in Table 37.

Most subjects had ratings of 0 at the baseline and every post-baseline time point. Thus, the sponsor's presentation of data in Table 38 did not seem informative for showing the effect of treatment on changes in dyskinesia. In contrast, Table 40 (created by the statistical reviewer, Dr Yan) presents categorical changes in dyskinesia ratings according to treatment. The Cochran-Mantel-Hensel's test (CMH, determined as appropriate by the Statistical Reviewer) was applied to confirm the sponsor's findings about the difference in the change of dyskinesia ratings between the treatment groups. There are more subjects in the APM 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 results in 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. This analysis confirms the results obtained by the sponsor, that APM is likely to have an effect on increasing dyskinesia.

**Table 40 Time Course for Change in Dyskinesia Rating Scale from Pre-dosing by Treatment**

Time from Dosing	Apomorphine Treatment Change					Placebo Treatment Change				
	-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

### 4 3 3 Discussion of Study Results

APM at a single dose of 4 mg showed a highly statistically significant decrease (i.e. therapeutic improvement) in the primary efficacy endpoint, the change in the UPDRS motor function score. However, there was a statistically significant period interaction. When data from first treatment data were compared as if this were a parallel group design, there was no statistically significant effect of APM on the primary efficacy endpoint. Thus, this appears to be a "failed" study that does not ultimately show a statistically reliable effect of APM for the primary efficacy endpoint at 20 minutes after injection of study medication.

It may be important to be mindful of the APM dose (4 mg) that was evaluated when considering this as a "failed" study that did not show a statistically significant benefit of APM for the primary efficacy endpoint when data from only the first period were analyzed to avoid the period effect of the cross-over design. Patients were randomized only to a single fixed dose of APM. This is the only study in which APM's therapeutic benefit was assessed without consideration to an APM dose for each patient had been "optimized" during previous treatment or at least had been shown to be equivalent to the patient's typical dose of levodopa/dopa decarboxylase inhibitor.

Other supportive analyses of secondary efficacy endpoints show a benefit of APM on motor function. The onset of a treatment benefit relative to study medication injection occurred as early as 20 minutes, was greatest at 40 minutes, and persisted through 90 minutes. Overall, these results suggest a therapeutic benefit for APM reversing an "Off". Although the magnitude of the change at 40 minutes was slightly greater than that at 20 minutes, the changes were relatively similar and much greater than the improvement still observed at 90 minutes. The maximal change (i.e. decrease in UPDRS motor score) from pre-dosing was approximately 34 % at 40 minutes. Although there was a period effect resulting from cross-over design at 40 minutes, additional analysis corroborated the therapeutic benefit of APM treatment of reversal of "Off" in comparing APM (vs placebo) only on the first treatment day of the cross-over study.

"Off" that was treated may have been spontaneously naturally occurring "Off", that could be an end of dose "Wearing Off" or "On/Off". The design was to treat the first "Off" that occurred after the patient took his/her normal, morning oral anti-parkinsonian medications. Although it seems likely that spontaneously naturally occurring "Off" may have developed and been treated within the patient's interval for taking LD, it is not possible to know if this is true. The protocol did not

allow other medication to be used until onset of "Off" (at least 1 hour after normal morning dosing of anti-parkinsonian) and treatment of "Off" was assessed in the study. Thus, it is conceivable that some patients may have experienced an "induced" "Off" if the "Off" that occurred developed after the patient's normal dosing interval of his/her standard medications including LD that is usually dosed at  $\leq 4$  hour intervals during waking hours. The sponsor did not address this issue nor present data to allow one to determine if "Off" occurred beyond the patient's normal dosing interval for taking LD.

In addition, even if many or most of these "Off" episodes were spontaneously occurring within the patient's normal dosing interval for administering levodopa/dopa decarboxylase inhibitor, we do not know if the "Off" was an end of dose wearing "Off" or an unpredictable "On/Off". If induced "Off" was frequently evaluated because the "Off" episode occurred beyond the normal dosing interval for levodopa/dopa decarboxylase inhibitor, it is debatable whether this could serve as a surrogate for an end of dose wearing "off".

The improvement of motor function shown by acute treatment at all three timepoints ranging from 20 to 90 minutes after injection was similarly reflected by analyzing the change in AUC of UPDRS motor score that provides a more integrated assessment of benefit.

There were numerous secondary efficacy outcome measures that were evaluated and the nominal p-values were reported. Statistical adjustments were not made for multiplicity in these many comparisons. This approach should be kept in mind when considering statistical analyses of results of the secondary efficacy endpoints.

APM resulted in an increase in dyskinesia, another secondary efficacy variable. But the effect was relatively mild overall, and not necessarily unexpected in this population of advanced Parkinson's disease patients who are generally highly susceptible to the development of dyskinesia with dopaminergic stimulation.

The sponsor noted that patients enrolled were supposedly still having "Off" episodes despite "optimized" anti-parkinsonian treatment. However, there was no attempt to show by some criteria that patients had indeed been "optimized" with all other treatments for Parkinson's disease. My impression is that most patients enrolled were fairly advanced in their disease but it is arguable how well each had been "optimized" prior to enrollment.

#### **4.3.4 Conclusions**

##### **Sponsor's Conclusions**

- APM at 4 mg is effective in reversing "Off" episodes by improving UPDRS measured motor function in patients with late stage Parkinson's disease.

- The therapeutic benefit of APM in treating/reversing "Off" is demonstrable over an extended period ranging between 20 to 90 minutes
- APM produced an increase in dyskinesia

### Reviewer's Conclusions

- I cannot agree with the sponsor and conclude that 4 mg APM was shown to be an effective dose for reversing "Off" as per improvement in the UPDRS motor function score at the 20 minutes timepoint (i.e. the primary efficacy endpoint). My conclusion is based upon the fact that a period interaction appeared to be responsible for the treatment effect. When the first period data were analyzed separately, there was no statistically significant effect of the fixed dose of APM in this study.
- Overall, I interpret the APM data from supportive analyses of secondary efficacy endpoints as suggesting that 4 mg results in the greatest motor function benefit at 40 minutes and that this benefit (although decreased vs 40 minutes) persists up to 90 minutes after injection. Although the analysis of 20 minute data using only the first day of treatment comparing APM and placebo was not statistically significant, I believe that it is likely that there is a benefit at 20 minutes but that this study did not clearly demonstrate this effect.
- Although APM clearly treats and reverses "Off" episodes, it is not possible to conclude that APM treats both end of dose wearing "off" and unpredictable "On/Off" because we do not know if the "Off" that was treated was a spontaneously occurring "Off" episode nor the type of "Off" episode that was treated.
- I agree with the sponsor that APM produced an increase in dyskinesia.
- The sponsor did not note any conclusion for this study that APM provided an additional benefit to patients over that of "optimized" anti-parkinsonian treatment. The protocol required that patients who enrolled be on an "optimized" anti-parkinsonian treatment. However, it is not clear to me whether or how well each patient had received "optimized" anti-parkinsonian treatment prior to enrollment because there were no criteria for establishing the therapy had been "optimized." Optimization of Parkinson's disease therapy seemed to be subjective based upon the investigator's impression.

## 4.4 Study APO302 (Pivotal Study Showing Efficacy)

### 4.4.1 Description of Protocol APO302

**Title of Study** A Prospective, Randomized, Placebo-Controlled, Parallel Groups Study of the Continued Efficacy and Safety of Subcutaneous Apomorphine in the Treatment of Off Episodes in Patients With "On/Off" or "Wearing-Off" Effects Associated With Late Stage Parkinson's Disease After Apomorphine Use for at least a Three Month Duration

**Investigators / Sites** 26 U S Sites

Study initiation (first patient enrolled) date 7/10/01

Study completion (last patient completed) date 7/7/02

### Protocol Description (Synopsis/Summary)

#### Objectives

The primary objective of this study was to measure the continued efficacy of APM after previous exposure of at least 3 months duration

The secondary objective of this study was to determine the time course of onset of the therapeutic effect of APM

#### Study Design

Patients who had been receiving repeated injections with subcutaneous APM for  $\geq 3$  months were to be randomized in a 2:2:1:1 ratio respectively to one of four parallel treatment groups including 1) their usual dose of an APM injection, 2) their usual dose of an APM injection + 2 mg (maximal dose allowed = 10 mg), 3) the equivalent volume of placebo to their usual dose volume of an APM, or 4) the equivalent volume of placebo to their usual dose volume of an APM + 0.2 ml. Patients were supposed to take their typical morning oral anti-parkinsonian medical therapy and were to receive an injection of experimental medication to treat the first "Off" that occurred at least 1 hour after this typical morning regimen. No other anti-parkinsonian medical therapy was allowed until the onset of an "Off" and the completion of the 90 minute evaluation period after treatment injection. Patients were allowed to use COMT and/or MAO-B-B inhibitors. An anti-emetic was allowed (e.g. trimethobenzamide) if it had been used prior to enrollment.

Efficacy response to dosing was to be assessed by capturing 1) the repeated measurement of UPDRS motor scores and dyskinesia scores at various times over a 90-minute interval, 2) the interval (in minutes) between injection and the time of patient declaration of the first perception

of significant relief of immobility, and 3) onset of drug response by repeated administration of a modified Webster Step-Seconds test

Upon completion of the 90-minute observations, resumption of normal medications was allowed for the remainder of the day. The patient did not need to be confined to an inpatient environment.

**Treatment Duration** 1 day

**Key Inclusion Criteria**

- Patients (males and females)  $\geq 18$  years old
- Patients with a clinical diagnosis of idiopathic Parkinson's disease, i.e., not induced by drugs or caused by other diseases
- Patients classified as stage (II - IV) of the Hoehn and Yahr scale for staging the severity of Parkinson's disease
- The patient must have been on an optimally maximized oral therapy regimen. Optimized oral antiparkinsonian medications must have included 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
- Patients must have been receiving APM subcutaneous injections for rescue therapy for "Off" events for at least three months
- The minimum APM baseline-dosing requirement was an average of at least 2 doses per day over the week prior to enrollment with a dose of  $\leq 10$ mg

**Key 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 APM intermittent subcutaneous injections within 30 days before study entry
- Patients whose APM regimen is characterized by continuous infusion or by administration methods other than intermittent subcutaneous injection