

- Webster's Step-Seconds Test - From a sitting position, the patient stands, walks, turns around, walks back and sits. The number of steps taken with the right foot per round trip of 15 feet out plus 15 feet back and the time to accomplish the tasks are recorded
- Dyskinesia Rating - The patient walks, drinks from a cup, puts on a coat and buttons it. The dyskinesias present during these activities are determined. The dyskinesia causing the most disability for these tasks is scored on a scale of 0-4

Outpatient

Secondary efficacy variables were to be evaluated after receiving at least one dose of randomized study medication under outpatient conditions. The efficacy variables for the outpatient phase were all declared secondary and were to be collected in diaries by patients or patient care-givers. These efficacy variables included proportion of "Off" events aborted by injections and reduction of "Off" hours per day. Multiple other descriptive variables were analyzed.

Using outpatient diary records were to be collected to allow calculations of the following secondary efficacy response variables:

- 1) interval between injection and point of recovery as judged by the patient (in the case of injections resulting in no recovery, the recovery time was left blank and the interval could not be calculated)
- 2) percent of injections in which patient declared "Off" to be aborted (even in the case of injections resulting in no recovery, this categorical response could be calculated)
- 3) hours per day spent in "Off" time

Other Secondary Efficacy Parameters

Diary questions allowed additional assessments of many other details of disease and response to drug with complete itemization of diary questions described below:

- (1) Average time from "Off" state to "On" state
- (2) Average number of "Off" episodes per day
- (3) Average daily length of time in the "On" state without dyskinesia
- (4) Average daily length of time in the "On" state with dyskinesia
- (5) Average daily length of time in any "On" state
- (6) Average daily length of time asleep
- (7) Average "Off" state quality
- (8) Average response quality
- (9) Average dyskinesia rating
- (10) Average nausea/vomiting severity

- (11) Average duration of nausea/vomiting
- (12) Percentage of injections with nausea or vomiting

Safety Variables (pre- and post-study assessments)

- physical examination
- 12-Lead electrocardiogram (ECG)
- clinical laboratory testing
- vital signs (VS)
- Adverse Events (AEs)

Power and Sample Size

The primary parameter of interest, UPDRS motor examination items 18-31, had been used for determine the sample size. The mean and standard deviation for the UPDRS score were estimated as 27.0 (12.0) given placebo and 10.0 (12.0) given APM. A sample size of 8 patients assigned to placebo and 16 patients assigned to APM was to provide 87% power to detect a difference of 17 in the mean UPDRS score between placebo and APM, given a significance level of $\alpha = 0.05$.

Planned Statistical Analyses

Efficacy

The primary and secondary efficacy variables for the primary objective were to be analyzed for the primary efficacy population and the safety/intent-to-treat population. The secondary efficacy variables for the secondary objective were analyzed for the secondary efficacy (outpatient) population. All statistical tests were to be two-sided with 0.05 level of significance. All analyses were to be performed using SAS version 6.12.

For the UPDRS Motor Examination score (sum of items 18-31), the response ratio was calculated according to the formula: percent change in UPDRS motor score / percent change in UPDRS score. Dopaminergic Challenge. Descriptive statistics were to be presented by treatment group. An analysis of variance (ANOVA) with treatment group as a factor was performed on the response ratio and the assumptions of normality were to be tested. The difference between treatment groups also was to be assessed by the Wilcoxon Rank Sum test. If the assumptions of the ANOVA were not met, then the results of the Wilcoxon sum test were to be considered primary. Response ratios were also to be calculated for the hand-tapping test and the Webster's step-second score and were to be analyzed by the method described above/earlier.

The change in raw score from "On" state to "Off" state for the UPDRS Motor Examination score (sum of items 18-31) and the change from "On" state to "Off" state of the hand-tapping test score were to be analyzed using an analysis of covariance (ANCOVA) with the "Off" state score as a covariate and treatment group as a factor. Webster's step-seconds scores were to be treated such

that the maximum score was limited to 9999 steps*seconds This parameter was to be analyzed by the Wilcoxon Rank Sum test The Dyskinesia rating scale score from "On" state to "Off" state was to be calculated for each treatment group and to be compared by the Wilcoxon Rank Sum test

The percent change was also to be calculated for each score as $100 \times (\text{"On" score} - \text{"Off" score}) / \text{"Off" score}$ Summary statistics were to be presented by treatment group and an ANCOVA was to be performed with treatment as a factor and the "Off" state score as a covariate

Safety

The incidence of adverse events (AEs) were tabulated by body system, preferred (coded) term and severity The highest level of severity was to be counted if a patient experienced the same event more than once Frequency counts and percentages were to be displayed

Descriptive statistics for laboratory tests were to be presented as N (sample size), Mean, SEM (standard error of the mean), Min (minimum), Q1 (lower quartile), Median, Q3 (upper quartile), and Max (maximum) A one-way ANOVA was to be used to compare the difference between treatment groups

Actual values at final visit and percent change from baseline for vital signs and the ECG exam were to be presented as descriptive statistics, N (sample size), Mean, SEM (standard error of the mean), Min (minimum), Q1 (lower quartile), Median, Q3 (upper quartile), and Max (maximum) The comparison of the change from baseline across the two treatment groups was to be analyzed using ANCOVA with baseline as a covariate

Number of patients planned 30 (20 APM, 10 placebo)
 Number of patients enrolled 32 (3 not randomized, 20 APM, 10 placebo)

Number of patients analyzed

Intent-to-Treat	29 (20 APM, 9 placebo)
Primary Efficacy (inpatient)	29 (20 APM, 9 placebo)
Secondary Efficacy (outpatient)	26 (18 APM, 8 placebo)

or safety analysis. There was no definition provided for recognizing a distinction from a deviation or violation and thus these terms appeared to be used interchangeably.

4.1.2 Results of Study APO0202

Patient Disposition

The primary efficacy (inpatient) population is Intent-to-Treat (ITT) population. These patients were evaluated for a response after at least one dose of APM or placebo. The secondary efficacy (outpatient) population is a subset of the inpatient population. These patients received at least one dose and returned for at least one visit in the outpatient extension phase.

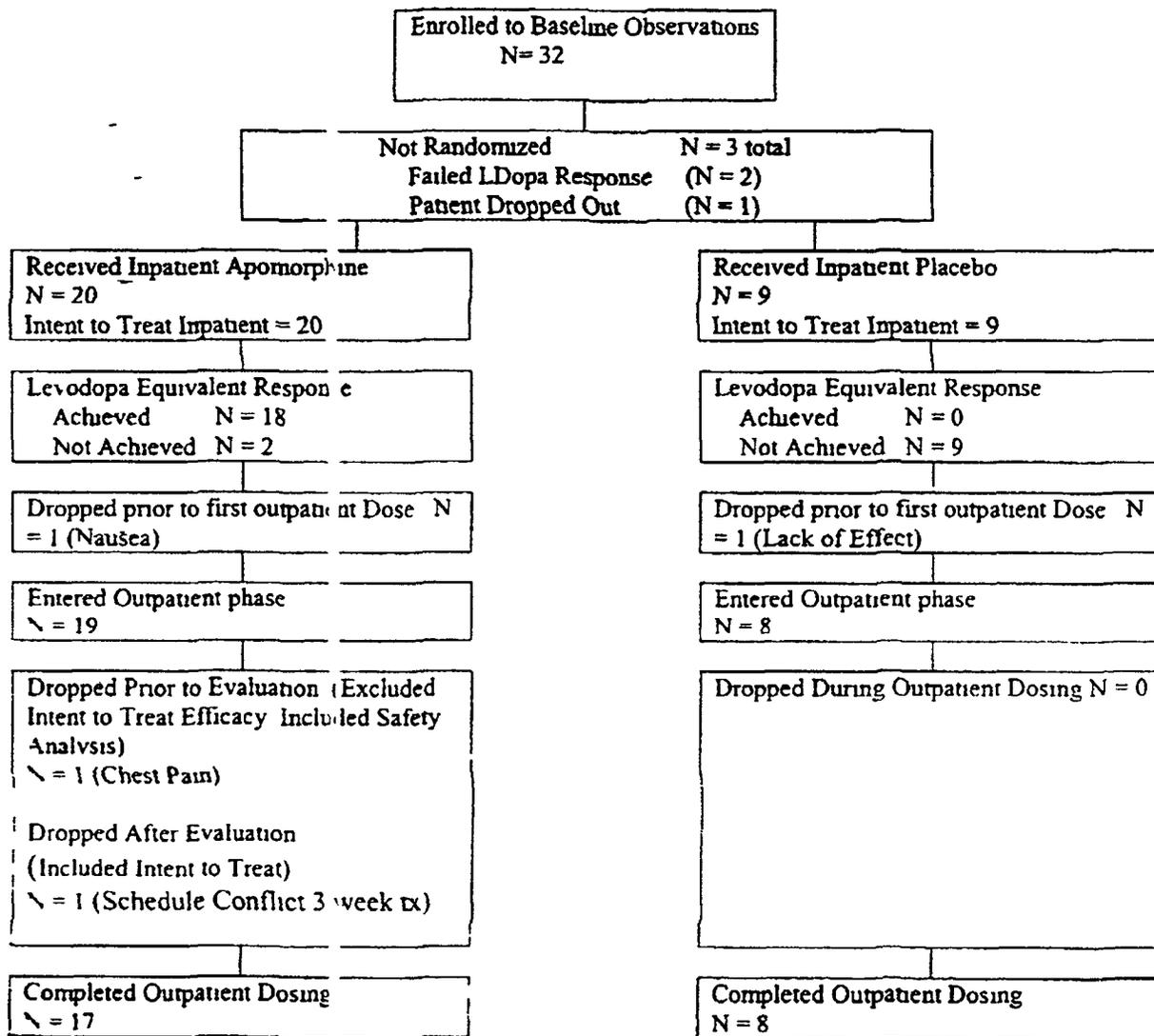
The disposition of patients in Study APO2020 is shown in Figure 4. A total of 32 patients were enrolled in the study. Three patients failed to progress to randomization and 29 patients were randomized (20 in the APM group and 9 in the placebo group) and received at least one dose of study medication.

Of the 20 patients receiving APM, 18 achieved a LD equivalent response (at least 90% of the UPDRS change previously demonstrated with LD). All 20 patients were included in the primary efficacy analysis. Of the 9 placebo patients, none achieved a therapeutically equivalent response to LD.

Three patients (all from APM group) discontinued prior to qualifying for the efficacy analysis for the outpatient phase due to adverse events or lack of effect. Twenty-six patients returned for at least one efficacy evaluation under outpatient conditions. All but one of these patients completed the trial.

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Figure 4 Study APO 202 Patient Disposition



Demographic and Baseline Characteristics

A summary of the patient demographic and baseline characteristics is provided in . 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 3 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

Dosage

Among APM 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 \pm std). Table 4 presents the inpatient dose titration results and shows that the majority of patients randomized to APM achieved a therapeutically equivalent response to LD (i.e. $\geq 90\%$ of the LD response) with 4 or 6 mg. However, some patients achieved this response at 2 mg and others at 8 and 10 mg. The single placebo patient with less than the maximum 1.0 mL dose discontinued titration after three injections because of lack of benefit.

Table 4 Inpatient Dose Titration Results for Levodopa Therapeutic 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

Efficacy Evaluations

Data Sets Analyzed

Three populations were defined for analyses

- 1 **Primary Efficacy Population/ Intent-to-Treat (ITT)** Patients who qualified for the study, were randomized to treatment and who received at least one dose of study medication during the titration phase (20 APM , 9 placebo) All patients from the safety/intent-to-treat population met these criteria
- 2 **Secondary Efficacy Population** A subset of the primary efficacy population that included all patients who returned for at least one visit in the long-term extension phase (18 APM , 8 placebo) Three patients (2 APM , 1 placebo) were excluded from this population analysis because they did not enter the outpatient therapy phase Patient 014 experienced chest pain during the first week of outpatient APM dosing and discontinued from the study Patient 003 received APM during inpatient dosing and did not begin outpatient therapy due to nausea/vomiting Patient 004 did not begin outpatient therapy due to lack of effect during placebo dosing
- 3 **Safety/Intent-to-Treat** This analysis was conducted in all patients who were randomized to treatment and received study medication (20 APM , 9 placebo)

Primary Efficacy Endpoint

The primary objective was addressed by efficacy measures obtained during the inpatient phase of the study The primary efficacy variable used to assess the primary efficacy endpoint was the UPDRS motor function (III) score The effect of treatment was assessment relative to the change from pre-dose to post-dose score

Primary efficacy was evaluated by evaluating a derived variable after receiving at least one dose of randomized medication The UPDRS motor examination score was to be assessed when the patient noted that he/she was "On" or up to 15 minutes after study medication (i.e. APM or placebo), whichever occurs first The primary efficacy analysis compared response ratios for APM vs placebo The response ratio was calculated by determining the maximal percentage response (i.e. % decrease in UPDRS motor score) to study medication relative and dividing this response by the response (i.e. % decrease in UPDRS motor score) to LD These data were mathematically transformed by various methods allowing for multiple representations of the data including raw score change, % change relative to pre-dose score and, response ratio (% change test drug over % change oral levodopa) Determination of the response ratio was the primary efficacy analysis of the primary efficacy endpoint, as it simultaneously compared APM to placebo and APM to LD

Table 5 summarizes the results of the primary efficacy endpoint, the ratio of the responsiveness to study medication compared to responsiveness to dopaminergic challenge with LD for the UPDRS Motor Examination score. The results of the Wilcoxon Rank Sum test were considered appropriate for the primary analysis because the ratios of results were not normally distributed.

Table 5 Effect of Treatment on Response Ratio - % Response After Study Drug / % Response After Dopaminergic (Levodopa) Challenge

Variable		Apomorphine (n=20)	Placebo (n=9)	p-value**
UPDRS Motor Score	Mean (std error)	0.96 (0.06)	0.0 (0.08)	<0.0001
	Median	0.97	0.00	<0.0001

* N=20 for UPDRS Motor 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

Efficacy Measurement Raw Score, Percent Change

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 response for the UPDRS motor exam score was found to be statistically significantly different between treatment groups in favor of APM (Table 6).

Table 6 Effect of Treatment on Motor Function Scores

Parameter	Study Phase	Mean (std err)	Apomorphine (N=20)	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	0.2902
		% Response	-64.67	-57.84	0.2695
	Study Drug Injection - Highest Dose	"Off" state score	39.65 (1.96)	36.33 (2.32)	
		Change	-23.85	-0.11	<0.0001
		% Response	-61.74	-1.04	<0.0001

* N=20 for all parameters during the dopaminergic challenge, for study drug injection N=20 for UPDRS motor score

** p-value for UPDRS motor score, hand-tapping score and Webster's step-second score were derived from 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

Table 7 shows the mean length of time from study medication injection until UPDRS motor exam relative to the mean length of time from dopaminergic challenge with LD until UPDRS

motor exam according to randomized treatment. There was no statistically significant difference for the mean time until testing for APM vs placebo treated patients.

Table 7 Effect of Treatment on Average Length of Time from Medication Administration to Time of UPDRS Motor Function Testing

Study Phase	Apomorphine (N=20) mean (std error)	Placebo (N=9) mean (std error)	p-value*
Dopaminergic Challenge - minutes from levodopa to time of UPDRS	54 (5.7)	46 (8.0)	0.4432
Study Drug Injection - Highest Dose minutes from injection to time of UPDRS	19 (1.5)	17 (1.7)	0.3944

Source data Table 10 and 11 - 9

*p-value calculated from an ANOVA model with treatment as independent variable

Subgroup Analyses

Table 8 shows results of UPDRS motor score changes/responses for each treatment group according to gender. Although the treatment effect of APM (vs placebo) was highly statistically significant for men and women, there was no statistically significant difference in responsiveness between men vs women. The sponsor did not present a subgroup analysis of gender for the primary efficacy analysis of the response ratio to study medication vs LD.

Table 8 UPDRS Motor Score and Change by Gender

Apomorphine Group	Pre Dose	Post Dose	Change	Percent Change	N of Cases
Female	39.1 ± 3.7	14.4 ± 1.8	-24.8 ± 2.7	-63.3 ± 3.1	8
Male	40 ± 2.3	16.8 ± 3.8	-23.3 ± 2.7	-60.7 ± 7.2	12
Placebo Group					
Female*	32	31	-1	-3.1	1
Male	36.9 ± 2.6	36.9 ± 3.4	0 ± 1.4	-0.8 ± 4.2	8
ANCOVA p value for Factor					
Treatment			0.0001	0.0001	
Sex			0.7074	0.9901	
Treatment * Sex			0.9880	0.8655	

*(mean ± sem except Placebo group Female N = 1 variance undefined)
Source Post Hoc Analysis 3/13/2000 uhwsdpe bysex2 1st Analysis = 1

The sponsor did not present any subgroup analyses for the primary efficacy variable (change in UPDRS motor score examination) for age or race. Because most patients were Caucasians there

is no reason to attempt a subgroup analysis by race. However, a subgroup analysis by age would be of interest.

Secondary Efficacy Endpoints

Secondary efficacy variables during inpatient assessments were hand-tapping scores, Webster step-seconds scores, and dyskinesia scores. These variables were measured as change from pre-dose to post-dose scores. Table 9 shows results for the hand-tapping test and the Webster's step-second score. The sponsor reported that the Wilcoxon Rank Sum test found a statistically significant difference between APM treatment and placebo treatment in favor of APM for the response ratio for the Webster's Step-Second Score. Results for the Hand-Tapping Score were not statistically different (i.e. $p \geq 0.05$) but approached statistical significance (i.e. $p < 0.05$).

Table 9 Effect of Treatment on Response Ratios of Hand-Tapping Score and Webster's Step-Second Score (Secondary Efficacy Endpoints)

Variable		Apomorphine (n=19)	Placebo (n=9)	p-value**
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

** 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 APM on Measurements for Secondary Efficacy Endpoints

Table 10 shows results of pre-dose/baseline measurements, absolute change, % response and p-values (for treatment differences) for hand-tapping scores, Webster step-seconds scores, and dyskinesia scores for various treatments (i.e. LD challenge and study medication treatment with APM or placebo). The sponsor reported that during the dopaminergic challenge phase of the study, no statistically significant differences were found between testing results for patients randomized subsequently to APM or placebo for any of the testing parameters. During the study drug injection phase, the mean percent response and mean absolute score change for the Webster's step-second score were statistically significantly different between treatment groups in favor of APM. Although the mean percent response of the hand-tapping score was not statistically significant, the mean absolute change was statistically significant in favor of APM. The dyskinesia rating scale also demonstrated a statistically significant difference between treatment groups by the Wilcoxon Rank Sum test during the study drug injection as reflected by an increase in dyskinesia with APM treatment.

Table 10 Effect of Treatment on Hand-Tapping Scores, Webster's Second Step Scores and Dyskinesia Rating Scale

Parameter	Study Phase	Mean (std err)	Apomorphine (N=*)	Placebo (N=9)	Nominal p-value**
Hand-Tapping Score	Dopaminergic Challenge	"Off" state score	236 05 (12 98)	216 22 (25 86)	
		Change	120 40	124 11	0 9764
		% Response	54 86	69 93	0 6827
	Study Drug Injection - Highest Dose	"Off" state score	265 21 (22 11)	255 00 (15 96)	
		Change	108 68	-11 89	0 0008
		% Response	87 85	-4 11	0 1028
Webster's Step-Second Score	Dopaminergic Challenge	"Off" state score	3293 38 (946 29)	3106 95 (1404 81)	
		Change	-3080 17	-2756 38	0 4470
		% Response	-70 80	-52 28	0 1645
	Study Drug Injection - Highest Dose	"Off" state score	3708 43 (1042 79)	3486 68 (1628 22)	
		Change	-3518 32	74	0 0009
		% Response	-66 37	- 01	< 0 0001
Dyskinesia Rating Scale	Dopaminergic Challenge	change	85	78	
		Median change	1 00	1 00	0 9179
	Study Drug Injection - Highest Dose	change	95	00	
		Median change	1 00	00	0 0012

* N=20 for all parameters during the dopaminergic challenge, for study drug injection N=20 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 and 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

Outpatient Diary Efficacy Assessments

After completion of inpatient efficacy assessment, patients continued the same randomized treatment in an outpatient setting and recorded responses that were subsequently analyzed as secondary efficacy endpoints Table 11 shows that APM resulted in a statistically significant shortening in the mean time to achieve an "On" state following injection of study treatment to abort a **spontaneously occurring "Off" state** The mean time to achieve an "On" state after APM was half that after placebo The mean % of aborted "Off" states was highly statistically significant with APM injection (Table 12) Whereas a relatively small percentage (e g 23 %) of "Off" states were aborted with placebo treatment, almost all (e g 95 %) "Off" states were aborted in response to APM treatment Although the mean change (- 1 7 hours) in average time (hours) in "Off" state was not statistically different for APM (- 1 7 hours) vs placebo (0 hours) injections, it approached statistical significance (p = 0 008) with APM treatment as shown in Table 13

**Table 11 Effect of Treatment on Average Time from Injection to "On" State
(Secondary Efficacy Population Based Upon Outpatient Diary Data)**

	Apomorphine	Placebo	p-value
N	18	5	0 0005
Mean	22 08	44 75	
Standard Error	2 44	5 65	
Minimum			
Median	18 89	42 90	
Maximum			

From an ANOVA model with treatment as independent variable
Source Sponsor's Efficacy Table 8a

**Table 12 Effect of Treatment on Percentage of Aborted "Off" States
(Secondary Efficacy Population Based Upon Outpatient Diary Data)**

Treatment	N	Mean # Injections per Patient	Mean # of Aborted "Off" States per Patient	Mean % age of Aborted "Off" States	p-value
Apomorphine	18	63 72	61 17	95 24 %	0 0001
Placebo	8	58 25	9 75	23 14	

From Wilcoxon rank Sum Test
Source Sponsor's Efficacy Table 8b

**Table 13 Effect of Treatment on Average Daily Length of Time in the "Off" State
(Secondary Efficacy Population Based Upon Outpatient Diary Data)**

Treatment (Rx)	N	Baseline (hrs)	Post Rx	Mean Change from Baseline	Median Change from Baseline	p-value*	p-value**
Apomorphine	18	5 8	4 1	-1 7	-2 0	0 0880	0 0157
Placebo	8	6 5	6 5	0	0		

* From an ANCOVA model with change from baseline as dependent variable, and treatment and baseline value as independent variables

** From Wilcoxon Rank Sum Test

Source Sponsor's Efficacy Table 9

Many outcome measures (derived from outpatient diaries and primarily oriented to efficacy) were calculated and analyzed for statistical differences. Table 14 shows results of several, diary based efficacy outcome variables. The average number of "Off" episodes experienced by patients randomized to APM or placebo was similar. The mean daily length of time increased (1 e 0 6 hours) for the APM group and decreased (1 e - 1 3 hours) for the placebo group showing an average treatment difference of 1 9 hours. Although this difference was not statistically

significant ($p = 0.116$), possibly because of the relatively small number of patients in each group, this difference did approach statistical significance. There were no statistical differences in other outcome parameters including average daily number of hours in the "On" state with dyskinesia, average daily number of hours in any "On" state, and average daily number of hours asleep. Table 15 shows that APM treatment resulted in a statistically significant difference in the average time (hours) from onset of "Off" until onset of "On" state. The mean time from "Off" until "On" with APM was 1.21 hours, less than half of that (2.91 hours) for the placebo group.

Table 16 presents results of several quality outcome parameters of treatment. Table 16 shows that there were no statistically significant differences for average "Off" state, average response quality, average dyskinesia rating, or average severity of nausea/vomiting. The quality of the "On" response was characterized as no response or mild, moderate, or marked response and was graded as 0, 1, 2, or 3 with 0 for no response and 3 for marked response.

Table 17 shows the percentage of injections associated with nausea during treatment with APM and placebo. Although APM treatment was associated with a slightly higher mean number of injections per patient and much higher mean number of injections with nausea per patient, the mean percentage of injections with nausea was not statistically significant for the difference between treatment groups.

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**Table 14 Effect of Treatment on Time Parameters
(Secondary Efficacy Population Based Upon Outpatient Diary Data)**

Time Parameter Treatment (Rx)	N	Baseline	Post Rx	Mean Change from Baseline	p-value*
Average # of "Off" Episodes/Day					
Apomorphine	18	3 65	3 57	-0 08	0 4424
Placebo	8	3 42	3 09	-0 33	
Average Daily Length of Time in the "On" State (hrs)					
Apomorphine	18	9 70	10 31	0 61	0 1156
Placebo	8	8 32	6 99	-1 32	
Average Daily Length of Time in the "On" State with Dyskinesia (hrs)					
Apomorphine	18	1 40	1 64	0 24	0 2256
Placebo	8	0 92	2 15	1 23	
Average Daily Length of Time in Any "On" State (hrs)					
Apomorphine	18	11 11	11 95	0 85	0 2689
Placebo	8	9 24	9 14	-0 10	
Average Daily Length of Time Asleep (hrs)					
Apomorphine	18	6 55	6 65	0 10	0 4001
Placebo	8	8 37	7 69	-0 68	

*From an ANCOVA model with change from baseline as dependent variable, and treatment and baseline value as independent variables

Source Sponsor's Efficacy Table 10a

**Table 15 Effect of Treatment on Average Time from "Off" to "On" State
(Secondary Efficacy Population Based Upon Outpatient Diary Data)**

Average Time from "Off" to "On" State	Apomorphine	Placebo	p-value
N	18	8	0 0374
Mean	1 21	2 91	
Standard Error	0 17	1 21	
Minimum			
Median	0 96	1 77	
Maximum			

From an ANOVA model with treatment as independent variable

Source Sponsor's Efficacy Table 10b

**Table 16 Effect of Treatment on Quality Parameters
(Secondary Efficacy Population Based Upon Outpatient Diary Data)**

Variable	Apomorphine N = 18	Placebo N = 8	p-value (1)
Average "Off" State Quality (2)			0.5710
Mean	2.02	1.90	
Standard Error	0.11	0.10	
Minimum			
Median	2.00	2.00	
Maximum			
Average Response Quality(3)			0.4066
Mean	1.97	1.74	
Standard Error	0.15	0.23	
Minimum			
Median	1.92	1.50	
Maximum			
Average Dyskinesia Rating (4)			0.8135
Mean	1.60	1.54	
Standard Error	0.13	0.11	
Minimum			
Median	1.62	1.50	
Maximum			
Average Nausea/Vomiting Severity (5)			0.9029
Mean	1.57	1.54	
Standard Error	0.13	0.24	
Minimum			
Median	1.50	1.17	
Maximum			

- (1) From an ANOVA model with treatment as independent variable
 - (2) "Off" State Quality 1-mild, 2-moderate, 3-sever, 4-immobile
 - (3) Response Quality 0-none, 1-mild, 2-moderate, 3-marked
 - (4) Dyskinesia Quality 0-none, 1-mild, 2-moderate, 3-severe
 - (5) Nausea/Vomiting Severity 0-none, 1-mild nausea, 2-moderate nausea, 3-vomiting
- Source: Sponsor's Efficacy Table 11

**Table 17 Percentage of Injections with Nausea
(Secondary Efficacy Population Based Upon Outpatient Diary Data)**

Treatment	N	Mean # Injections per Patient	Mean # of Injections with Nausea per Patient	Mean % age of Injections with Nausea	p-value*
Apomorphine	18	63 50	2 78	4 25 %	0 1968
Placebo	8	57 75	0 25	0 63 %	

*From Wilcoxon rank Sum Test

Source Sponsor's Efficacy Table 12

4 1 3 Discussion of Study Results

APM showed a highly statistically significant decrease (i.e. therapeutic improvement) in the derived primary efficacy endpoint, the ratio of the response to APM / the response to LD challenge. These results indicate a clear therapeutic benefit for APM rapidly reversing an "Off" induced by withholding the patient's standard anti-parkinsonian treatment. Although the doses in the APM treatment group ranged between 2 to 10 mg, most doses that were considered therapeutically equivalent to the LD challenge were either 4 or 6 mg.

Many patients were tested for the primary efficacy endpoint after 15 minutes which was later than the protocol specified time for assessment (i.e. the occurrence of "On" or 15 minutes, whichever comes first). The sponsor did not present an individual listing showing the time of testing for each patient. However, when I reviewed some data showing times of study medication injection and time of "On" it appeared that the majority of patients were tested after 15 minutes. Most testing occurred by 30 minutes after injection of study medication. My discovery is supported by the sponsor's own data showing that the mean time to UPDRS motor function testing was 19 minutes for APM and 17 minutes for placebo. Although I consider these deviations to be major protocol violations/deviations, I still consider the conclusions drawn from these results to be valid. I consider the original design of the protocol to be suboptimal, and somewhat flawed because I would not want to assess the effect of APM at a time interval of 15 minutes or less if I was assessing a response only at a single timepoint (which is what was planned by the protocol). Although the pharmacodynamic effect of APM is thought to be relatively rapid, closely associated with plasma levels of APM, and to be maximal near C_{max}, T_{max} for APM (based upon the literature and the sponsor's data) occurs usually between 15 and 45 minutes and frequently near 30 minutes in many patients. Thus, testing likely occurred in many patients at time when the response to APM would likely be somewhat less than if it had been assessed at a somewhat later timepoint. Furthermore, the study was not designed to show a maximal response because to APM because the dose of APM selected for an individual patient was designed to mimic that of the patient's usual LD dose. Conceivably, the maximal patient response to APM could have possibly have been higher if patients had been studied after being randomized to a fixed, possibly higher dose or were potentially randomized to an "optimal" dose based upon previous testing. Thus, considering that the design of this study was likely

suboptimal for showing the maximal therapeutic response to the dose of APM used by each patient, the significant therapeutic effect reflected by the rapid reversal of "Off" under the conditions employed shows a clear benefit of the experimental treatment

Patients frequently underwent repeat testing to achieve the therapeutically equivalent dose of injectable study medication at intervals of ≥ 2 hours. However, technically the protocol did not stipulate that patients had to be "Off" or to exhibit a certain severity of pre-dose UPDRS motor score before repeat injection of study medication. But a review of pre-dosing UPDRS motor scores at repeat testing suggested that the UPDRS score had not decreased significantly compared to the original pre-dose score. Thus, in practice it does not seem that there was a problem by not requiring a certain pre-dose UPDRS motor score or a declaration of "Off" prior to repeat testing.

"Off" was induced by withholding the patient's usual anti-parkinsonian medications usually from the previous evening. Thus, the "Off" that was treated during the inpatient testing that evaluated the primary efficacy endpoint is technically not the same "Off" that might occur spontaneously in a patient taking his/her medication at regular intervals. It is debatable whether "Off" induced by withholding usual antiparkinsonian medications is a surrogate for end of dose "Wearing Off". However, the "Off" that was treated under double-blinded conditions as an outpatient and derived from diary based results, was spontaneously, naturally occurring "Off", that could be an end of dose "Wearing Off" and/or unpredictable "On/Off". All outpatient efficacy endpoints were secondary but I consider some of these to be substantially important in their clinical significance. APM was highly effective in aborting almost all (e.g. 95%) of these "Off" episodes compared to placebo that aborted only a small percentage (e.g. 23%) of these natural "Off" episodes. The mean time to reversal of "Off" was relatively rapid and similar to the mean reversal of "Off" shown in the inpatient setting.

APM decreased the mean amount of daily "Off" time by almost 2 hours vs no change mean daily "Off" for placebo. Although this effect was not statistically significant, it did approach statistical significance ($p = 0.0880$). Considering the relatively small number of patients studied as an outpatient (18- APM, 8 placebo), it is possible that studying a larger number of patients may have shown a statistically significant decrease in daily "Off" in the outpatient setting. In addition, the mean length of "Off" episodes for APM treated patients was statistically significant and less than half that of patients treated with placebo. I view these outpatient results as significantly complimentary to the inpatient testing results and supportive of the therapeutic benefit of APM "rescue" treatment to abort "Off" episodes acutely and relatively rapidly. The amount of total daily waking "Off" time (~ 1.7 hours, also treatment effect = APM - placebo) that seemed to decrease with APM treatment is slightly greater (interstudy comparison) than the overall treatment effect (~ 1 hour) for entacapone (COMT inhibitor) in decreasing total daily "Off" hours. It would be speculative to wonder how effective APM would be in reducing total daily waking "Off" hours if all patients studied had also been treated with an maximally tolerable, therapeutic dose of a COMT inhibitor such as entacapone.

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.

There were numerous other secondary efficacy outcome measures that were evaluated. Statistical adjustments were not made for multiplicity in these many comparisons. Regardless, that there were no corrections for multiplicity of statistical comparisons, a statistically significant effect was not usually observed for APM treatment vs placebo.

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.

4.1.4 Conclusions

Sponsor's Conclusions

- APM shows highly significant "rescue" from an "Off" state at times most commonly near 15-20 minutes after injection.
- The benefit of APM was similar to the magnitude of the motor benefit of dopaminergic challenge with the patient's normal LD dose but occurred much faster.
- The benefit of APM was not simply a demonstration of effectiveness upon a background of no treatment but it was a demonstration of incremental benefit when added to a regimen of "optimized" anti-parkinsonian therapy including LD and oral dopaminergic agonists.
- The suggestion of APM-induced efficacy in the outpatient setting supports the capability of patients or care-givers to administer APM effectively.

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.
- Although APM reverses/treats "Off" induced by withholding the patient's usual antiparkinsonian over night (based upon the primary statistical analysis of the primary efficacy endpoint), it is not clear if this is a surrogate for the spontaneously occurring end of

dose wearing "Off"

- It is difficult to conclude from this study whether 2 mg APM is an effective dose because there were only 3 patients (out of 20) who received this dose during the in-patient phase in which the primary efficacy endpoint was evaluated and APM was found to provide motor benefit
- Diary data collected during the outpatient-phase suggested that APM was effective in aborting most (95 %) spontaneously occurring "Off" episodes (compared to 23 % of spontaneously occurring "Off" episodes aborted by placebo) Although it might seem likely that many, if not most of the spontaneously occurring "Off" episodes that were aborted were end of dose wearing "off" episodes, the sponsor did not present any results indicating the type of "Off" episodes that were aborted
- It is not possible to conclude that APM is effective in aborting unpredictable ""On/Off" episodes because we do not know how successful APM was for aborting these type of "Off" episodes

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4 2 Study APO301/APOS-001 (Pivotal Study Showing Efficacy)

4 2 1 Description of Protocol APO301/APOS-001

Title of Study A Prospective, Randomized, Placebo-Controlled, Crossover Study of the Safety and Effectiveness of Subcutaneous Injections of Apomorphine in the Treatment of "Off" Episodes in Patients With "On/Off" or "Wearing-Off" Effect Associated With Late Stage Parkinson's Disease

Investigators / Sites

{ . }

Study initiation (first patient enrolled) date 9/28/99

Study completion (last patient completed) date 11/9/99

Protocol Description (Synopsis/Summary)

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

Study Design

Patients who had been receiving repeated injections with subcutaneous APM for ≥ 3 months were randomized to a single injection of placebo or their usual dose of APM on 2 consecutive days in a double-blind, cross-over study (Figure 5) Patients were treated with both sequences (1 e placebo and then APM or APM and then placebo) Experimental drug is to be administered in response to a significant "Off" event (in 75% of patients it is expected that pre-dose UPDRS score will measure ≥ 32)

On observation days 1 and 2, each patient is to receive a subcutaneous injection of double-blinded supplies of APM or placebo, according to the randomized crossover assignment The volume of the injected dose in mL is to be set equal to that typically used by the patient prior to study entry No other medications are to be used within one hour of this dose of test medication

On each observation day, the patient's usual anti-parkinsonian medications are 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 APM will be used Patients are to be observed for the first significant "Off" event which occurs at least one hour after morning dosing

Efficacy response to dosing will 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 predose and at 10, 20, and 60 minutes post dosing

Upon completion of the 60-minute observations, resumption of normal medications is allowed for the remainder of the day The patient needed not be confined to an inpatient environment Observation of response to test medication was to be conducted on separate days, which were typically to be scheduled sequentially, but might be separated by up to one week Study exit was to occur after completion of the observation of drug effect on the second observation day

Patients continued to be treated with an anti-emetic, domperidone, if they had been taking this drug prior to enrollment in this study

Treatment Duration For 2 days of treatment on dosing days 1 and 2, each patient was to receive either subcutaneous APM HCl (subject's usual dose, up to a maximum of 10 mg), or matched placebo Patients receiving APM HCl on day 1 would receive placebo on day 2 Patients receiving placebo on day 1 would receive APM HCl on day 2

Key Inclusion Criteria

- 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 antiparkinson 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 apomorphine subcutaneous injections for rescue therapy for Off events for 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 with a dose of $\leq 10\text{mg}$

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 apomorphine 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

Efficacy Variables

Primary Efficacy The primary efficacy parameter is change in UPDRS Motor Score 20 minutes after dosing on observation day 1 and 2 (active drug or placebo injections)

Secondary Efficacy

- the change in Dyskinesia Rating Scale 10, 20 and 60 minutes after dosing
- time to onset of perceived relief
- AUC for UPDRS Motor Scores at predose, 10, 20 and 60 minutes
- the change in UPDRS Motor Scores at 10 and 60 minutes after dosing

Safety Variables (pre- and post-study assessments)

- physical examination
- 12-Lead electrocardiogram (ECG)
- clinical laboratory testing
- special laboratory testing
- vital signs (VS)
- time course of dose response also included assessment of Adverse Events (AEs) and VS

Planned Statistical Analyses**Efficacy**

The primary endpoint of change in UPDRS Motor Score from pre-dose to 20 minutes was to be analyzed using a repeated measures analysis of covariance (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 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 ANCOVA with the terms treatment and pre-dose score. The same method was to be used to analyze the change in UPDRS motor score from pre-dose to 10 minutes and 60 minutes, and the AUC for UPDRS motor scores at all time points.

The change in Dyskinesia Rating Scale from pre-dose minutes 10, 20, and 60 minutes was to be assessed using the Wilcoxon Signed Rank test. For each subject, the difference of change from pre-dose for the two treatment groups was to be calculated and tested for a difference from zero. A parallel group analysis of day 1 data was to be used to analyze treatment effect using the Wilcoxon Rank Sum test.

The time (in minutes) from injection to patient declaration of first perception of significant relief of immobility (i.e. "On") was to be analyzed using repeated measures ANOVA. A second set of analyses was to be performed with missing values set at 60 minutes for patients who declared no time of relief within the observation period. The difference in times for the two treatment groups was analyzed using the Wilcoxon Signed Rank test. Day 1 data only were analyzed for treatment effect using the Wilcoxon Rank Sum test.

Safety

Adverse events (AEs) were to be summarized with respect to severity, relationship to apomorphine, body system, and treatment at occurrence. Incidence of adverse events was to be compared between treatment groups using McNemar's test. Change from baseline for vital signs was to be compared across treatment groups using paired t-tests. ANCOVA models were to be used to test for sequence differences with change as the dependent variable, and sequence and baseline visit value as independent variables.

Number of patients planned 16
 Number of patients enrolled 17

Number of patients analyzed
 Intent-to-Treat 17 (8 APM/placebo, 9 placebo/APM)
 Efficacy (per protocol) 16 (8 APM/placebo, 8 placebo/APM)

Figure 5 Schematic Diagram of Study APO301

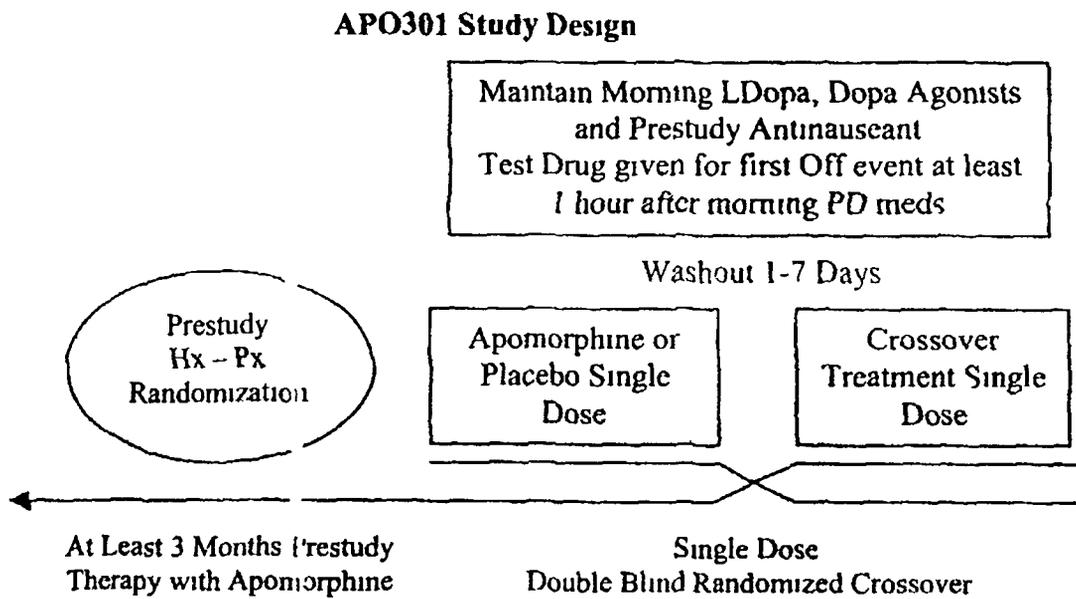


Figure 6 Summary Schedule of Assessments / Events

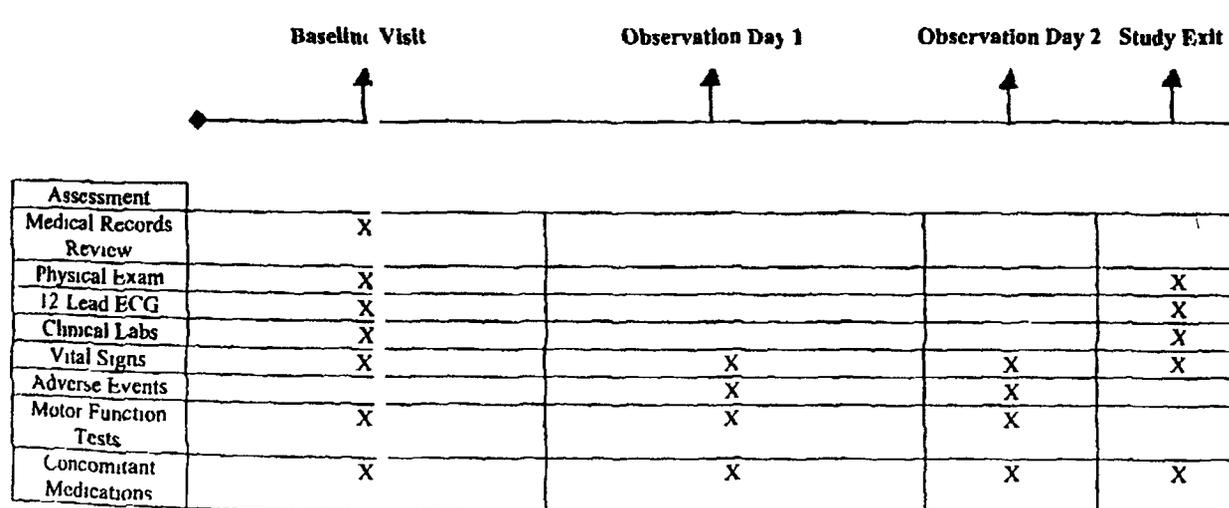


Figure 7 Execution Sequence of Outcome Measures at each Timepoint

	Immediate pre-dose	10 minutes	20 minutes	60 minutes
UPDRS motor score (items 18-31)	X	X	X	X
Dyskinesia rating scale	X	X	X	X
Adverse event assessment	X	X	X	X
Vital signs	X		X	X

Protocol Amendments

There were no protocol amendments

Protocol Violations/Deviations

Several patients exhibited various protocol violations/deviations. There was no definition provided for recognizing a distinction from a deviation or violation and thus these terms appeared to be used interchangeably.

Protocol violations/deviations of several patients were related to the efficacy analysis of a secondary efficacy endpoint. Eleven patients did not declare an onset of "On" on at least one of the observation days. Two patients failed to declare onset of "On" on both observation days. The method for analysis of this parameter was expanded to support two analyses. In the first, each

null field was treated as null. In the second, each null field was treated as 60 minutes, which represented the maximum time during which onset, could be documented to not have occurred.

One patient (01 007) 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.

4 2 2 Results of Study APO301/APOS-001

Disposition of Patients

Table 18 summarizes the disposition of patients. Seventeen (17) patients enrolled in the study and were randomized to the double-blind crossover treatment. All patients received at least one dose of study medication, but only 16 patients received both doses of study medication. One patient, a 52-year-old female, was unable to continue with required UPDRS and Dyskinesia evaluation on Day 1 and withdrew from the study because of severe "Off" pain. The ITT population evaluated for the primary efficacy endpoint included all 17 patients.

Table 18 Summary of Patient Disposition

Disposition	Apomorphine/ Placebo	Placebo/ Apomorphine	Total
Randomized – Received at least one dose of test med	8 (100%)	9 (100%)	17 (100%)
Safety	8 (100%)	9 (100%)	17 (100%)
Strict Intent to Treat Population	8 (100%)	9 (100%)	17 (100%)
Per Protocol Population	8 (100%)	8 (9*) (89%/100%)	16 (17*) (94%/100%)
Completed Study	8 (100%)	8 (89%)	16 (94%)
Withdrew due to Adverse Event	0 (0%)	0 (0%)	0 (0%)
Other	N/A	1 (01 005) (11%)	1 (6%)
Data source: Disposition Table 10 1 t_inv pdf, Listing 16 4 13 1_disp pdf, Listing 16 2 1 1_disc pdf, Reason for discontinuation Final analysis rules memo * Patient 01 005 does not qualify for per protocol analysis of UPDRS but does qualify for per protocol analysis of perception of onset of relief			

Demographic and Baseline Characteristics

Table 19 shows demographic and baseline characteristics of patients

Table 19 Summary of Demographic and Baseline Characteristics (ITT Population)

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%)

Apomorphine Dosage

The following table presents APM doses by treatment groups. Dosages were determined by the patient's usual subcutaneous APM regimen. Although the range of APM dosing varied between 2 to 10 mg per injection, most patients were treated with doses ranging between 3 to 5 mg.

Table 20 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

Efficacy Results

Sponsor's Primary Efficacy Endpoint

The primary efficacy endpoint of change in UPDRS motor score (items 18-31) from pre-dose to 20 minutes post-dose was analyzed using a repeated measures ANCOVA with the terms of sequence, subject within sequence, pre-dose score, treatment, and period. The sequence effect was tested using the subject within sequence mean square as the error term. All other effects were tested against mean square error from the ANCOVA.

Table 21 shows the results of APM and placebo treatment on the primary efficacy endpoint. Seventeen patients were treated on day 1 and 1 patient withdrew from study because of severe "Off" pain. The sponsor carried forward results from the first day to the second day. Pre-dosing UPDRS motor scores were similar on each study day. APM produced a marked decrease (i.e. improvement) of -21.3% in the mean motor score compared to placebo that resulted in a minimal change (i.e. -3.0%). The percentage change was -47.4% for APM and -5.9% for placebo. The mean UPDRS motor scores at pre-dosing were similar on both treatment days.

Table 21 Effect of Treatment on Change in UPDRS Motor Score (20 minutes) from Pre-Dosing for Primary Efficacy Endpoint for ITT Population

Time Relative to Dosing Mean (Std error) (% change from baseline)	Apomorphine N=17	Placebo N=17	p-value (1)	p-value (2)	p-value (3)
Pre-dose UPDRS Score	41.3 (2.49)	40.1 (2.23)			
20 min after injection	-20 (3.60) (-47.4%)	-3.0 (2.24) (-5.9%)	< 0.0001	0.2752	0.0736

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

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

(3) ANOVA with terms pre-dose score and treatment, using Day 1 data only

Source: Sponsor's Efficacy Table 14.2.1

Secondary Efficacy Endpoints

Table 22 summarizes results for the time course of the change (from pre-dosing) in UPDRS motor scores at 10, 20, and 60 minutes after dosing with each study treatment. APM treatment resulted in marked decrements in mean UPDRS motor scores at all 3 post-dosing timepoints studied. According to the main method of statistical analysis, the effect of APM was statistically significant at all timepoints. A beneficial effect was observed as early as +10 minutes after injection, was maximal at +20 minutes (i.e. the timepoint selected for the primary efficacy endpoint analysis), and persisted up through +60 minutes. The % change of UPDRS motor score was also greatest at 20 minutes.

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Table 22 Effect of Treatment on Time Course of Change in UPDRS Motor Score from Pre-Dosing for ITT Population

Time Relative to Dosing Mean (Std error) (% change from baseline)	Apomorphine N=17	Placebo N=17	p-value (1)	p-value (2)	p-value (3)
Pre-dose UPDRS Score	41.3 (2.49)	40.1 (2.23)			
10 min after injection	-15.4 (3.65) (-35.9%)	-2.7 (1.98) (-6.7%)	0.0086	0.2429	0.2678
20 min after injection	-20.0 (3.60) (-47.4%)	-3.0 (2.24) (-5.9%)	< 0.0001	0.2752	0.0736
60 min after injection	-12.6 (2.87) (-30.2%)	-0.4 (1.3) (-0.1%)	0.0009	0.8452	0.0018
Area Under the Curve	1572 (160)	2298 (132)	< 0.0001	--	0.0219

(1) Repeated measures ANCOVA with 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

The repeated measure ANCOVA analysis showed a statistically significant difference in 10, 20, and 60 minutes UPDRS motor scores between treatments of APM vs placebo. There is a statistically significant period effect at 10 and 20 minutes but not at 60 minutes. Analysis of Day 1 data in parallel groups supported a statistically significant greater reduction (p=0.0059) in UPDRS scores following APM compared to placebo injection only at the 60 minute timepoint.

To corroborate the results of the parametric tests and because normality assumptions necessary for the use of parametric statistical methods were not met, non-parametric test using the Wilcoxon Rank Sum Test were conducted as well. First sequence effect was tested by calculating the change from baseline UPDRS Motor Score for each subject in both periods, ranking the sum of the change from baseline UPDRS Motor Score for the two periods (a test of sequence effect), and comparing the two sequences using the exact Wilcoxon Rank Sum Test. The sequence effect was found not significant (p=0.6058). Secondly, to test the treatment effect, the difference of the change from baseline UPDRS Motor scores for the two periods. The treatment effect was found significant (p=0.0005). These results corroborate the parametric tests for treatment difference.

Dyskinesia Ratings

Results of post-treatment assessments (performed at 10, 20, and 60 minutes) of Dyskinesia Rating Scale compared to pre-dosing are shown in Table 23. The Wilcoxon Signed Rank test was used to analyze the differences in patients' responses because these data were not normally distributed. Wilcoxon Rank Sum test was also used for analysis of Day 1 data in parallel groups. There was a significant increase in dyskinesia after APM injection at 10 minute when data from both days were analyzed. When data were analyzed using the Day 1 data alone, the increase in dyskinesia was statistically significant at all times that were evaluated.