

Efficacy Variables

Primary Efficacy The primary efficacy parameter is change in UPDRS Motor Score 20 minutes after dosing (active drug or placebo injections)

Secondary Efficacy

- The change in Dyskinesia Rating Scale 10, 20 and 90 minutes after dosing - 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
- Time to onset of perceived relief from 2.5 minutes through 40 minutes after injection
- AUC for UPDRS Motor Scores at predose, 10, 20 and 90 minutes
- The change in UPDRS Motor Scores at 10 and 90 minutes after dosing
- Webster's Step-Seconds Test from 2.5, 5, 7.5, 15, 20, 40 and 90 minutes after injection - 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

Safety Variables (pre- and post-study assessments)

- physical examination
- 12-Lead electrocardiogram (ECG)
- clinical laboratory testing
- special laboratory testing
- vital signs (VS) sitting and standing blood pressure and pulse
- time course of dose response also included assessment of Adverse Events (AEs), orthostatic VS and ECGs

Planned Statistical Analyses

The primary endpoint (change in UPDRS Motor Score from pre-dose to 20 minutes post-dosing) was to be analyzed based on an analysis of covariance (ANCOVA) model with the term treatment and pre-dose score as the covariate The primary contrast was to be pooled placebo (i.e. both placebo groups combined) vs pooled APM (both APM groups combined) (-1/2 -1/2 1/2 1/2) The primary efficacy analysis was to assess results of the Intent-To-Treat (ITT) population This population is comprised of all patients who were randomized to a treatment of APM or placebo, received treatment, and had any efficacy data collected (this had not been specified in the protocol but was assumed) A repeated measures ANCOVA might also be performed

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

- 1 APM vs pooled placebo (PL) (-1/2 -1/2 1 0)
- 2 APM + 2 mg vs pooled PL (-1/2 -1/2 0 1)

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

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

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

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

The change in Dyskinesia Rating Scale from pre-dose minutes 10, 20, and 90 minutes and the change in the Webster-Step Seconds from predose to 2.5 minutes through other prespecified timepoints up to and including 40 minutes were to be assessed using the Wilcoxon Signed Rank-Sum test. Changes were to be evaluated by a covariance-adjusted Wilcoxon Signed Rank-Sum test with pre-dose score at the covariate.

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

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

Analyses of the Per Protocol (PP) population had not been specified in the protocol but were also performed and presented.

Safety

Adverse events (AEs) were to be summarized with respect to severity, relationship to APM, body system, and treatment at occurrence. Incidence of adverse events was to be compared between treatment groups using a Chi-Squared test. For the time course of effects on orthostatic VS and ECGs, change from baseline at each timepoint and area under the curve (AUC) will be analyzed using ANCOVA with pre-dose value as covariate and treatment as a factor. A repeated measures ANCOVA may also be performed.

Number of patients planned 60

Number of patients enrolled 64

Number of patients analyzed

Intent-to-Treat 62 Total (19 APM, 13 placebo, 16 APM + 2 mg, 14 placebo + 0.2 ml)

Efficacy (per protocol) 61 Total (18 APM, 13 placebo, 16 APM + 2 mg, 14 placebo + 0.2 ml)

In theory, 20 patients were to be randomized to each APM group and 10 patients were to be randomized to each placebo group. The sponsor did not address why less (total 5) patients were randomized to the pooled APM group and more (total 7) were randomized to pooled placebo group.

Figure 13 Schematic Diagram of Study APO302

APO302 Study Flow Chart

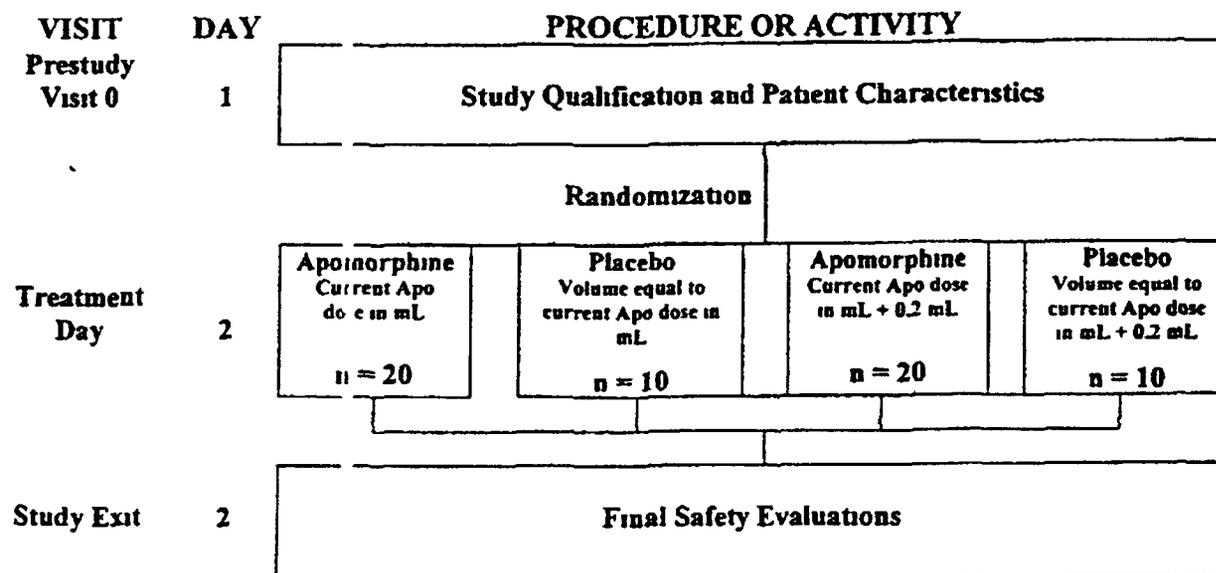


Table 41 Summary Schedule of Assessments / Events and Execution Sequence of Outcome Measures at each Timepoint

Table 7.5.1 Efficacy and Safety Evaluations- Time Course Of Apomorphine Effect							
	Immediate pre-dose*	2.5, 5 0, 7 5 minutes	10 minutes	15 minutes	20 minutes	40 minutes	90 minutes
Perception of Onset	X	X	X	X	X	X	
Webster Step-Seconds	X	X	X	X	X	X	
UPDRS Motor Score (items 18-31)	X		X		X		X
Dyskinesia Assessment	X		X		X		X
Orthostatic Monitoring w/ ECG	X				X		X
Adverse event assessment	X		X		X		X

* Perform Orthostatic Monitoring w/ ECG prior to motor assessments with a 5 min rest period after BP completion. This is to allow any hypotensive changes to stabilize prior to test medication injection and result in more complete absorption in the cutaneous vasculature

Protocol Amendments

There were no protocol amendments

Protocol Violations/Deviations

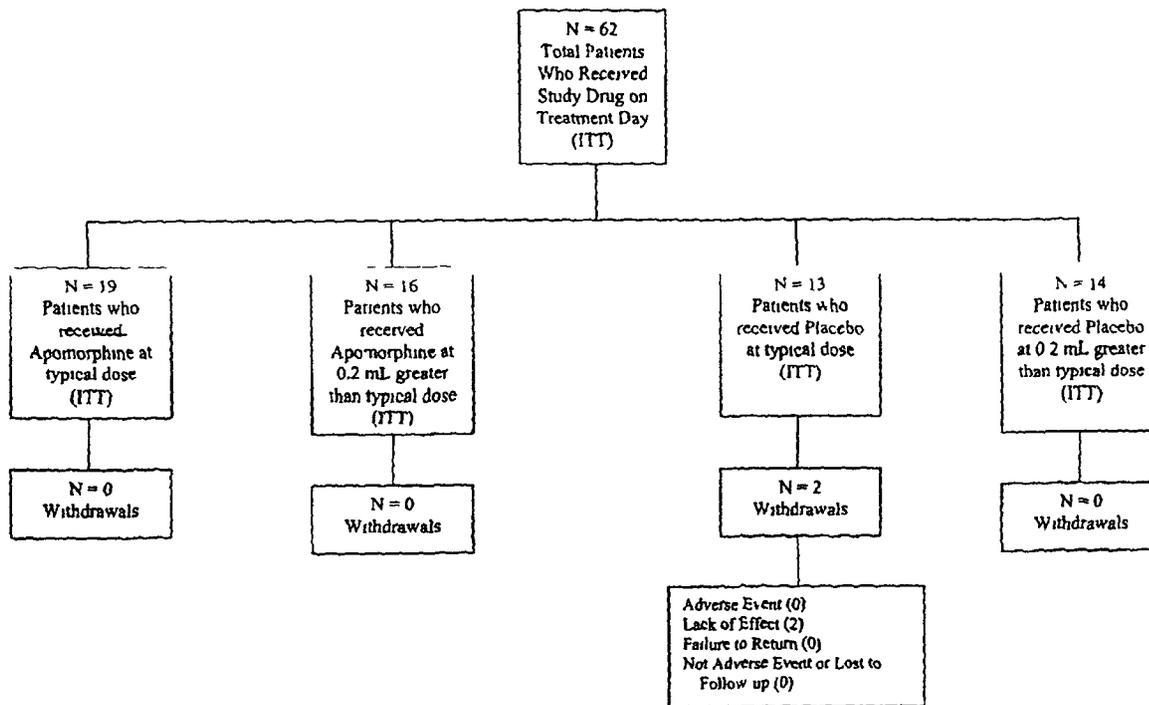
There were a few protocol violations/deviations. There was no definition provided for recognizing a distinction from a deviation or violation and thus these terms appeared to be used interchangeably. One patient in the APM group was not treated with APM for at least 3 months before enrolling in this study. Four other patients were granted protocol exceptions. Three patients in the placebo group were not taking a dopaminergic agonist as required by the protocol and one patient had a pre-existing dementia unrelated to antiparkinsonian medications. Three patients (1 placebo and 2 APM group) did not take their usual antiparkinsonian medications in the morning so that the first "Off" occurring after this therapy could be treated. These patients came to the clinic in an "Off" state, were treated and included in the ITT and Per Protocol analyses.

4 4 2 Results of Study APO302

Disposition of Patients

Figure 14 shows the disposition of patients. Patients (62) were randomized to one of four treatments (19 in APM, 16 in APM+2, 13 in PL, and 14 in PL+2) and were included in the ITT and safety populations. Two patients in the placebo group terminated the study early due to lack of efficacy. Both patients experienced considerable discomfort due to "Off" event and were given medication to reverse the event.

Figure 14 Summary of Patient Disposition



Demographic and Baseline Characteristics

A summary of baseline patient demographics is provided in Table 42. Although there were minor differences in the demographic characteristics of the different groups, they did not appear grossly significant. The sponsor reported that there were no statistical differences in baseline characteristics between the pooled placebo and pooled APM.

Table 42 Summary of Demographic Characteristics (ITT Population)

Variable	Total	pooled PL	Pooled APO	APO	APO+2	PL	PL+2	Pooled PL vs Pooled APO p-value [1]
Gender								
Male	45 (72.6%)	20 (74.1%)	25 (71.4%)	15 (78.9%)	10 (62.5%)	8 (61.5%)	12 (85.7%)	0.000
Female	17 (27.4%)	7 (25.9%)	10 (28.6%)	4 (21.1%)	6 (37.5%)	5 (38.5%)	2 (14.3%)	
Race								
Caucasian	60 (96.8%)	25 (92.6%)	35 (100.0%)	19 (100.0%)	16 (100.0%)	11 (84.6%)	14 (100.0%)	0.1856
Hispanic	1 (1.6%)	1 (3.7%)				1 (7.7%)		
Asian	1 (1.6%)	1 (3.7%)				1 (7.7%)		
Age								
N	62	27	35	19	16	13	14	
Mean	65.53	66.52	64.77	64.00	65.69	66.85	66.21	0.4709
Standard Error	1.19	1.90	1.52	2.07	2.30	2.95	2.54	
Minimum	42.00	42.00	48.00	52.00	48.00	46.00	42.00	
Median	67.00	67.00	67.00	63.00	68.50	72.00	66.50	
Maximum	87.00	8.00	87.00	87.00	77.00	80.00	81.00	
Age of Onset								
N	62	27	35	19	16	13	14	
Mean	50.83	50.44	51.13	51.61	50.56	49.08	51.71	0.8057
Standard Error	1.36	2.58	1.40	1.81	2.25	3.86	3.56	
Minimum	23.00	23.00	35.00	35.00	35.00	23.00	26.00	
Median	51.00	50.00	51.00	51.00	50.50	53.00	47.50	
Maximum	72.00	72.00	69.00	69.00	64.00	69.00	72.00	
Days since First APO Dose								
N	62	27	35	19	16	13	14	
Mean	433.66	444.11	425.60	368.89	492.94	468.69	421.29	0.6901
Standard Error	21.75	32.28	32.03	41.08	46.07	52.02	40.20	
Minimum	73.00	152.00	73.00	73.00	224.00	227.00	152.00	
Median	421.50	423.00	423.00	393.00	526.50	392.00	449.50	
Maximum	861.00	798.00	861.00	787.00	861.00	798.00	625.00	

[1] p value from Fisher's exact test for categorical variables ANOVA for continuous variables

Tobacco Use								
None/rare	36 (58.1%)	15 (55.6%)	21 (60.0%)	9 (47.4%)	12 (75.0%)	9 (69.2%)	6 (42.9%)	0.9103
Former 1 year	23 (37.1%)	11 (40.7%)	12 (34.3%)	9 (47.4%)	1 (6.3%)	3 (23.1%)	8 (57.1%)	
Current user	3 (4.8%)	1 (3.7%)	2 (5.7%)	1 (5.3%)	1 (6.3%)	1 (7.7%)		
Alcohol Use								
None/rare	45 (72.6%)	17 (63.0%)	28 (80.0%)	16 (84.2%)	12 (75.0%)	10 (76.9%)	7 (50.0%)	0.2605
Moderate	17 (27.4%)	10 (37.0%)	7 (20.0%)	3 (15.8%)	4 (25.0%)	3 (23.1%)	7 (50.0%)	

[1] p value from Fisher's exact test for categorical variables ANOVA for continuous variables

Baseline UPDRS scores, collected while patients were in an "On" state, are presented in Table 43. Mean scores for sections I, III, and total UPDRS appeared to be appreciably lower in the pooled placebo groups. Review of statistical differences in baseline UPDRS scores between pooled PL vs pooled APO treatment groups showed that baseline UPDRS Section III scores were borderline statistically higher in the pooled APO group than in the pooled PL group (p-values = 0.0531) for the ITT population. Total UPDRS scores were also borderline statistically higher in the pooled APO group than in the pooled PL group (p-values = 0.0698) for the ITT population.

Table 43 Summary of Baseline Disease Characteristics (ITT Population)

Variable	Total	Pooled PL	Pooled APO	APO	APO+2	PL	PL+2	Pooled PL vs Pooled APO p value[1]
Number of Patients with Baseline UPDRS while ON	61	27	34	18	16	13	14	
UPDRS Section I Subtotal								
N	61	27	34	18	16	3	14	
Mean	2.08	1.74	2.35	2.11	2.63	2.08	1.43	0.1919
Standard Error	0.232	0.160	0.298	0.378	0.473	0.625	0.388	
Minimum	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
Median								
Maximum								
UPDRS Section II Subtotal								
N	61	27	34	18	16	3	14	
Mean	14.64	13.85	15.26	15.67	14.81	15.23	12.57	0.3921
Standard Error	0.812	1.154	1.136	1.239	2.013	1.787	1.463	
Minimum	1.00	1.00	4.00	7.00	4.00	8.00	1.00	
Median								
Maximum								
UPDRS Section III Subtotal								
N	61	27	34	18	16	3	14	
Mean	22.89	19.41	25.65	26.44	24.75	22.62	16.43	0.0531
Standard Error	1.608	2.383	2.088	2.902	3.088	3.799	2.849	
Minimum	3.00	3.00	6.00	9.00	6.00	3.00	8.00	
Median								
Maximum								
UPDRS Section V Subtotal								
N	61	27	34	18	16	3	14	
Mean	7.46	7.37	7.53	7.06	8.06	7.85	6.93	0.8141
Standard Error	0.332	0.453	0.480	0.777	0.520	0.741	0.539	
Minimum	1.00	4.00	1.00	1.00	5.00	4.00	5.00	
Median								
Maximum								
UPDRS Total								
N	61	27	34	18	16	13	14	
Mean	47.07	42.37	50.79	51.28	50.25	47.77	37.36	0.0698
Standard Error	2.31	3.389	3.046	3.721	5.067	5.354	3.964	
Minimum	17.00	17.00	17.00	27.00	17.00	21.00	17.00	
Median								
Maximum								
Non Motor UPDRS Subtotal								
N	61	27	34	18	16	13	14	
Mean	24.18	22.95	25.15	24.83	25.50	25.15	20.93	0.2871
Standard Error	1.011	1.464	1.320	1.675	2.133	2.433	1.682	
Minimum	8.00	8.00	11.00	13.00	11.00	13.00	8.00	
Median								
Maximum								

Note: Assessments were performed while patient was ON. If assessment could not be performed while patient was ON it was not included.
 [1] p value from ANOVA

Apomorphine Dosage

Table 44 presents the range of APM doses and the mean value for both APM 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 > 2 mg up to 6 mg. The average APM dose in the patients randomized to the dose group 2 mg higher than their usual dose was 5.8 mg, but actually only 1.2 mg higher than the average dose of patients randomized to be treated with their usual dose (mean = 4.6 mg).

Table 44 Apomorphine Doses

Apomorphine Dose Range	Usual Apomorphine Dose Group mean dose = 4.6 mg range 2 - 10 mg (N = 19)	Usual Apomorphine Dose + 2 mg mean dose = 5.8 mg range 3.5 - 10 mg (N = 16)	Total Any Apomorphine Dose Group mean dose = 5.1 mg range 2 - 10 mg (N = 35)
≤ 2 mg	2	0	2
> 2 mg - ≤ 4 mg	10	3	13
> 4 mg - ≤ 6 mg	5	10	15
> 6 mg - ≤ 8 mg	0	2	2
> 8 mg - ≤ 10 mg	2	1	3

Efficacy Results

Primary Efficacy Endpoint

The primary efficacy endpoint of change in mean UPDRS Motor Score (items 18-31) from pre-dose to 20 minutes was analyzed based on an analysis of covariance (ANCOVA) model with term treatment and pre-dose score as the covariate. The assumption of normality was tested by Shapiro-Wilk test and the Kolmogorov Smirnov test, and the normal assumption was not violated. Therefore, the parametric ANCOVA model was considered as the primary analysis model, and the non-parametric test was the secondary model.

The primary comparison was pooled placebo (placebo and placebo + 0.2 ml) vs pooled APM (i.e. APM and APM + 2 mg). The sponsor reported that the patients in the pooled APM group experienced a reduction in the mean UPDRS Motor Score at 20 minutes of -24.2 points as compared to a mean reduction of -7.4 points for patients in the pooled PL group. The treatment difference between the two pooled groups was highly statistically significant with a p-value of < 0.0001. Results of change in mean UPDRS motor score from pre-dose and of change in percentage of UPDRS motor score from pre-dose at all post-treatment timepoints are presented in Table 45. The change for absolute values and for percentage was greatest at 20 minutes vs 10 and 90 minutes. The percentage decrease at 20 minutes approached 60% and 25% for the pooled APM and placebo groups respectively. The percentage change for the pooled APM group at 10 and 20 minutes was highly statistically greater than the change for the pooled placebo group at similar times.

Table 45 Primary Efficacy Analysis of Change in UPDRS Motor Score from Pre-Dose for Pooled Apomorphine vs Pooled Placebo (ITT Population)

Time from dosing	Pooled APM (n=35)			Pooled PL (n=27)			p-value	
	Mean (SE)	Change Mean (SE)	% Change Mean (SE)	Mean (SE)	Change Mean (SE)	% Change Mean (SE)	Change	%Change
0	42.0 (1.8)			40.6 (3.4)				
10	22.1 (2.3)	-19.9 (1.8)	-48.9 (4.4)	35.0 (4.2)	-5.6 (1.6)	-19.3 (5.4)	<0.0001	<0.0001
20	17.8 (1.9)	-24.2 (1.7)	-58.7 (3.8)	33.3 (4.4)	-7.4 (1.8)	-24.1 (5.6)	<0.0001	<0.0001
primary								
90	36.7 (2.6)	-5.2 (1.8)	-13.6 (4.3)	35.7 (4.3)	-4.9 (2.0)	-15.0 (2.9)	0.8558	0.9031

Source: sponsor's Table 14.2.1.1.1

Secondary Efficacy Endpoints

Change in UPDRS Motor Scores at Various Post-Treatment Times and in Area Under the Curve (AUC) for UPDRS Motor Score

The following results and analyses were for the ITT population. Table 46 summarizes results for the time course of the change (from pre-dosing) in UPDRS motor scores at 10, 20, and 90 minutes after dosing with each specific study treatment group. This table also shows mean UPDRS motor score at pre-dose for each group and the pooled groups. Although the differences among the groups seemed relatively small, the greatest difference for pre-dose motor function score was between the placebo groups. There was a highly statistically significant decrease ($p \leq 0.0003$) in UPDRS motor function score for each APM treatment group (e.g. pooled APM, APM, APM + 2 mg) relative to the pooled placebo group for both the absolute change in the UPDRS motor score both 10 and 20 minutes. No statistically significant decrements were observed at 90 minutes after injection for any of the APM treatment groups, indicating that the therapeutic effect had resolved by that time. The sponsor did present statistical analyses comparing results between both APM groups.

Percentage changes in UPDRS motor scores for specific treatment groups are not shown in Table 46. Percentage reductions were statistically significant (≤ 0.0044) for APM and APM + 2 mg groups vs pooled placebo at both 10 and 20 minutes but not at 90 minutes post injection. Although the mean percentage reduction was similar at both 10 (-60.4%) and 20 minutes (-63.0%) for the APM + 2 mg group, the mean reduction at 20 minutes (-55.0%) for APM group was considerably greater than that (-39.1%) observed at 10 minutes.

All APM treatment groups (e.g. pooled APM, APM, APM + 2 mg) resulted in a statistically significant decrement in the area under the curve (AUC) for the UPDRS motor score at all 3 timepoints (Table 47).

Table 46 Change in UPDRS Motor Score from Pre-Dose for Apomorphine Groups vs Placebo Groups (ITT Population)

Time from dosing	Mean Change in UPDRS			Mean Change in UPDRS			p-values			
	APM (n=19) Pre-dose	APM+2 (n=16) Pre-dose	Pooled APM (n=35) Pre-dose	PL (n=13) Pre-dose	PL+0.2 (n=14) Pre-dose	Pooled PL (n=27) Pre-dose	[1]	[2]	[3]	[4]
	43.3	40.4	42.0	44.4	37.2	40.6				
10	-16.5	-23.8	-19.9	-6.6	-4.6	-5.6	0.5412	0.0003	<0.0001	<0.0001
20	-23.7	-24.8	-24.2	-6.8	-7.9	-7.4	0.7742	<0.0001	<0.0001	<0.0001
90	-4.8	-5.8	-5.2	-4.1	-5.6	-4.9	0.8307	0.9608	0.8034	0.9494

[1] p-value from comparison of PL vs PL+0.2 using ANOVA
 [2] p-value from comparison of APM vs pooled PL using ANOVA
 [3] p-value from comparison of APM+2 vs pooled PL using ANOVA
 [4] p-value from pooled APM vs pooled PL using non-parametric analysis
 Source: Sponsor's Tables 14.2.1.1.2, 14.2.1.1.3, 14.2.1.1.4, 14.2.1.2.1

Table 47 Area Under the Curve for Change from Pre-dose UPDRS Motor Scores

Group	Mean (SE)		p-value
	Group A	Group B	
Pooled APM (A) vs Pooled PL (B)	-1348 (108.11)	-522 (141.59)	<0.0001
APM (A) vs Pooled PL (B)	-1280 (140.94)	-522 (141.59)	0.0005
APM+2 (A) vs Pooled PL (B)	-1429 (169.82)	-522 (141.59)	0.0001

Source: Sponsor's Table 14.2.1.3

Webster Step-Seconds Scores

The Webster Step-Seconds scores, which were obtained pre-dose and at 2.5, 5, 7.5, 10, 20, and 40 minutes post-dose, were analyzed by non-parametric analysis of covariance because data were not normally distributed. If a patient could not complete the test within the 60-second timeframe, a score of "9999" was used in the calculation. Table 48 presents the results of median changes in Webster Step second scores for the pooled APM and pooled placebo groups. Statistically significant differences in favor of a therapeutic benefit for the pooled APM group occurred at all timepoints between and including 7.5 and 40 minutes showing that this effect occurred rapidly. Nominal p-values are shown. The sponsor did not make any corrections/adjustments of p-values for multiple comparisons (i.e. multiplicity) of secondary efficacy endpoints. Neither did the sponsor present specific results for the APM and APM + 2 groups.

Table 48 Change from Pre-dose in Webster Step-Seconds Scores

Time from Dosing (min)	Pooled Apomorphine		Pooled Placebo		Nominal p-value
	N	Median change (min, max)	N	Median change (min, max)	
0	34		27		
2.5	35	-36.5 (-9774, 7799)	26	-36.5 (-1644, 9299)	0.3495
5.0	35	-50.0 (-9759, 9257)	27	-28.0 (-1042, 9299)	0.2777
7.5	35	-269.5 (-9899, 9257)	27	-58.0 (-1480, 9299)	0.0230
10	35	-400.5 (-9918, 0)	27	-78.0 (-8289, 9299)	0.0050
15	35	-426.5 (-9919, 0)	27	-66.0 (-9719, 9299)	0.0005
20	35	-462.5 (-9927, 8)	27	-39.0 (-9819, 9299)	< 0.0001
40	34	-445.0 (-9927, 0)	26	-62.5 (-9855, 9299)	0.0004

Source: Sponsor's Table 14.2.1.7

Patient Perceived Onset of Relief

There was no statistically significant difference ($p = 0.1502$ from Wilcoxon Rank Sum test) in the time to onset of relief between the pooled treatment groups as shown in Table 49 for the median times. The median time to onset of relief was 5.0 minutes for the pooled APO group and 7.5 minutes for the pooled PL group. An imputed value of 40 minutes was used for patients who did not declare a time for onset of relief from "Off". Neither was there a statistically significant difference ($p = 0.5364$ by ANOVA) in the mean time to patient declaration of onset of relief for the pooled APM group (6.9 minutes, $N = 34$) compared to the pooled placebo group (7.8 minutes, $N = 19$) based upon a statistical analysis of exact times declared by patients. A statistically significant difference between pooled APM and placebo groups was observed only when the Log-Rank test was used for statistical differences between both pooled groups and patients without declared times of relief had their times imputed to 40 minutes. In this analysis the mean time for pooled APM was 7.3 minutes (1 imputed time to 40 minutes) and the mean time for pooled placebo was 11.4 minutes (8 imputed times to 40 minutes).

Table 49 Time to Onset of Relief (Minutes) for ITT Population

n	Pooled Apomorphine		n	Pooled Placebo		p value
	Median	(Min Max)		Median	(Min Max)	
35	5.0	(2.5 40)	27	7.5	(2.5 40)	0.1502

Note: P values are based on Wilcoxon Rank Sum Test
 Note: Times are based on the time period (2.5, 5, 7.5, 10, 15, 20, 40 minutes) at which the patient first felt relief
 Note: An imputed time of 40 minutes was used for patients with no declared time of relief

Dyskinesia Rating Scale

Dyskinesia Rating Scale assessments were performed at pre-dose and at 10, 20, and 90 minutes post-dosing of study drug. The sponsor reported that the data were not normally distributed and therefore they were analyzed by non-parametric analysis of covariance. The median changes for both pooled APM and pooled placebo groups were 0 at all time points. However, though mean values were larger in the pooled APM group. The p-values for the treatment difference were 0.0021, 0.0001, and 0.2536 at 10, 20, and 90 minutes post-dosing, respectively. Thus, there appeared to be a statistically significant increase in dyskinesia ratings at 10 and 20 minutes, times when improved motor function also occurred. Increased dyskinesia ratings correlated with improved motor function.

Subgroup Analyses

The sponsor did not conduct any subgroup analyses for this study. The statistical reviewer (Dr Sharon Yan) did conduct subgroup analyses of the efficacy data for age and gender for this study and for other studies for comparison. The results of the mean change in UPDRS motor scores is shown in Table 50 for APM vs placebo for all studies including APO302. Descriptive statistics of efficacy results for subgroups are displayed on the basis of age (split at the age of ≥ 65 years for elderly and < 65 years for non-elderly) and gender. Because most patients were Caucasians, no subgroup analysis for race was performed. Due to the small sample size in each of the subgroups, no p-values are provided for the change from pre-dose UPDRS motor function scores for the subgroups.

The change in the UPDRS from pre-dose to post-dose seems to be consistent across gender and age group in four studies shown in Table 50. In Studies 301 and 303, the response in UPDRS is numerically larger in males than in females. However, such a difference in gender is not observed in Studies 202 and 302. An apparent age difference in the response of UPDRS is suggested in Study 303 with greater responsiveness in non-elderly patients, but such a difference is not suggested in the other three studies. An absolute conclusion cannot be made regarding statistically different responses (for UPDRS motor function scores) based upon in gender and age. Nevertheless, considering results across studies, this summary table does not suggest the likelihood for different responsiveness to APM with regard to age or gender.

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Table 50 Mean (SD) Change of UPDRS from Pre-dose to Post-dose by Gender and Age

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

For study APO2020, UPDRS motor score was supposed to be evaluated when patients were "On" or at 20 minutes, whichever occurred first

4.4.3 Discussion of Study Results

The pooled APM (i.e. combined APM and APM + 2 mg groups) showed a highly statistically significant decrease (i.e. therapeutic improvement) in the primary efficacy endpoint (i.e. change in the UPDRS motor function score) compared to that of the pooled placebo group. This was the primary statistical analysis comparison for the primary efficacy endpoint. The onset of a statistically significant difference and benefit relative to APM injection occurred as early as 10 minutes, was greatest at 20 minutes, and was no longer evident at 90 minutes. These results indicate a clear therapeutic benefit for APM rapidly reversing an "Off" in patients who have been repeatedly treated for at least 3 months. These results were essentially similar to those observed in Study APO301 of patients treated for at least 3 months previously. Demonstrating this effect was of interest to FDA and had been recommended by Dr. Temple, ODE 1, Office Director at an earlier meeting with the sponsor.

Overall, statistical comparisons of each APM group (that were supportive analyses) vs pooled placebo were similar in that each showed highly statistically significant motor function testing benefit at 10 and 20 minutes but no benefit at 90 minutes after treatment injection. The doses in the APM treatment group ranged between 2 to 10 mg, but most (≥ 5 patients) doses ranging from > 2 mg up to 6 mg. The doses in the APM + 2 mg group ranged between 3.5 to 10 mg with most (≥ 5 patients) doses were from > 4 mg up to 6 mg. Although these groups were expected to be different by a mean dose of 2 mg, the actual average dose difference was only 1.2 mg. The most

striking difference between both APM groups was that the + 2 mg APM group showed larger UPDRS motor score reduction at the early (10 minute) timepoint. Despite the fact that formal statistical comparisons were not presented for these groups, it does not seem likely that there would be statistical difference between these APM groups. Each patient's usual 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. Of clinical significance, the usual APM dose groups appeared to be effective based upon a secondary, supportive analysis. Considering that there were only 2 patients who were evaluated after receiving 2 mg APM in either group, it seems that it is difficult to draw a conclusion that 2 mg is an effective dose.

The sponsor noted that the addition of 2 mg of APM to the patient's usual outpatient dose did not result in any additional benefit to UPDRS motor function but did increase the frequency of adverse events. These results tend to support other results suggesting that maximal therapeutic benefit may occur at doses of 6 mg or less and that using a dose above 6 mg increases the risk of adverse reactions without clearly increasing the chances of additional efficacy.

Three patients (1 placebo patient, ~ 4 % of pooled placebo and 2 APM patients, ~ 6 % of pooled APM) were protocol violators and did not take their morning antiparkinsonian medication. Thus, their "Off" that was treated was clearly an induced "Off" from withholding medication. Considering that the percentage of these violators was similar in both pooled groups, it does not seem like this violation would have much impact on the overall results.

"Off" that was treated may have been spontaneously naturally occurring "Off", that could be an end of dose "Wearing Off" or an unpredictable "On/Off". The design was to treat the first "Off" that occurred after at least 1 hour after the patient took his/her normal, morning oral anti-parkinsonian medications. Although it might 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 because the sponsor did not conduct and present any analysis with respect to when the "Off" occurred relative to the last administration of usual medications. 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 often dosed at ≤ 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". If induced "Off" was frequently evaluated, it is debatable whether this could serve as a surrogate for an end of dose wearing "off".

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. Furthermore, increased dyskinesia was statistically greater for APM treatment at 10 and 20 minutes but not at 90 minutes post-injection and paralleled the statistically significant differences for motor function improvement. Thus, the occurrence of increased treatment-associated dyskinesia appeared to correlate with treatment improved motor benefit.

Of interest, it did not appear that patients can easily discern early after injection that they are "On" and have experienced an appreciable difference in motor function benefit by declaring the onset of relief soon after injection. Two different statistical analyses in which the perception of benefit of achieving "On" was based upon patient declaration of improvement did not suggest that patients can easily appreciate that they are "On" early after injection. In one analysis onset of relief time was the actual time the patient experienced and declared relief from "Off" (after treatment injection). In this analysis, there was no statistically significant difference ($P = 0.5538$) for mean time to onset of relief for 33 of 35 patients receiving APM (6.9 minutes) and for 19 of 27 patients receiving placebo (7.8 minutes). A statistically significant benefit of APM occurred only in a third analysis (Log-Rank test) when actual times of patient declared "On" were computed and there was imputation of relief times to 40 minutes for patients who did not declare relief and have experienced significant relief. Thus, it appears that you need to conduct multiple, various analyses to find one that shows a statistically significant difference. My conclusion from these data analyses is that it seems to be difficult for patients to perceive at an early time that they have experienced markedly improved motor function despite the fact that motor function scores performed a few minutes later showed marked improvement. This phenomenon can have potentially important implications for repeating dosing because it does not seem that there are reliable data that indicate that a patient can discern whether he/she did or did not have a good therapeutic response to an APM injection. If that is the case, how can a patient determine that a repeat injection is indicated because the original injection was not very effective? It is possible that patients might more reliably assess whether they have experienced significant improvement if patients were asked this question at a later timepoint rather than trying to declare the first time they perceive onset of relief. Nevertheless, this is speculative.

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.

Overall, these results were essentially similar to those from study APO301. This study, however, showed that the onset of therapeutic benefit as measured by UPDRS motor function score can be shown as rapidly as 10 minutes after APM injection and as measured by Webster's Step Seconds test as early as 7.5 minutes after injection.

4 4 4 Conclusions

Sponsor's Conclusions

- APM remains highly efficacious in relieving/reversing "Off" events experienced by patients who have undergone repeated treatment of "Off" episodes over a prolonged period of at least 3 months
- APM's beneficial effects on motor function began as early as 7.5 minutes after injection and persisted up to 40 minutes after injection
- The magnitude of the APM-induced improvement in motor function at 20 minutes after injection was substantial for the pooled APM group (vs the pooled placebo group) relative to the motor scores prior to injection
- APM improves the Webster Step-Seconds evaluation and the patient's subjective perception of onset of relief from "Off" as well as UPDRS motor score
- Increasing the dose of APM by 2 mg above the patient's usual dose does not provide increased motor benefit but does increase the incidence of adverse events
- APM produces a modest increase in dyskinesia

Reviewer's Conclusions

- I essentially agree with the sponsor's conclusions with the exception of one conclusion (regarding time of patient perception of relief) that I will describe. I do not agree that the data show that patients can reliably discern onset of relief at an early timepoint.
- The achievement of "statistically significant" improvement in various motor function outcome measures (time course of change in UPDRS motor function, Webster Step-Seconds evaluation, patient's subjective perception of onset of relief from "Off") after APM injection is related to nominal p values that have not been corrected or adjusted for multiplicity. For example, the sponsor has conducted secondary efficacy analyses by making multiple comparisons of multiple secondary efficacy endpoints across multiple treatment groups. Although I believe that the effect of APM is likely to be real on these various outcome measures, it is not possible to draw firm conclusions on these secondary endpoints based upon the sponsor's specific statistical approach and analyses of the secondary endpoints.
- The sponsor did not specifically 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

- 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 in the pooled APM group
- Results from this study confirmed those observed in Study 301 in which patients treated for \geq 3 months with repeated injections of APM continued to exhibit beneficial motor improvement soon after APM injection
- 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

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Clinical NDA Safety Review

Brand Name:	Not yet approved but rejected by FDA)
Generic Name:	Apomorphine
Sponsor	Bertek Pharmaceuticals, Inc
Indication	Parkinson's Disease
NDA Number:	21264
Receipt Date for Starting PDUFA Clock:	1/2/03
Clinical Reviewer:	Leonard P. Kapcala, M.D.
Review Author:	Leonard P. Kapcala, M.D.
Review Completed.	6/13/03

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Preface (Tables Not Consecutively Numbered)

One day prior to completing my review, a problem developed with my computer whereby the automatic consecutive numbering of tables became dysfunctional and my WORD program stopped numbering tables in consecutive order after editing. Despite attempts for help from the CDER HELP desk and other computer experts in DNDP, I have not been able to resolve this problem. Thus, tables are not always numbered consecutively. I provide this note to inform the reader.

In addition, page 106 is a blank page that could not be deleted and there is no page 136 that was numbered because of my computer bugs/dysfunction.

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1 EXECUTIVE SUMMARY, CONCLUSIONS, RECOMMENDATIONS

Introduction

The sponsor is seeking approval of

Although these patients supposedly were still having recurrent "off" episodes despite "optimal" oral antiparkinsonian medical therapy, it was not clearly shown that patients enrolled had been "optimally" treated. The disease characteristics of patients suggested that most patients appeared to have advanced Parkinson's disease. All patients were taking levodopa/dopa decarboxylase inhibitor. Essentially all patients (99 %) were taking a dopaminergic agonist and approximately 40 % had used a catechol-ortho-methyl transferase (COMT) inhibitor.

Exposure and Apomorphine Dosing

The clinical development program studied 536 patients who were treated with APM within 5 trials. There were 4 randomized, double-blinded, placebo-controlled pivotal trials. Whereas studies APO202 and APO302 were parallel group studies, studies APO301 and APO303 used a cross-over design. Studies APO202 and APO303 investigated patients who were naive to APM and studies APO301 and 302 studied patients who had been treated with APM for at least 3 months. Study APO401 was an open-label trial that was the main safety study and also included studies APO302 and APO303 as substudies. There were 6 Clinical Pharmacology studies that investigated pharmacokinetics (PK) and in some instances pharmacodynamic parameters (PD). These Clinical Pharmacology studies were conducted predominantly in healthy volunteers with the exception of 6 patients with Parkinson's disease who were evaluated in one PK/PD study.

Most of the APM exposure occurred at doses of ≤ 6 mg. For long-term exposure, 311 patients had received any APM dose for at least 6 months and 171 patients had received any APM dose for at least 12 months. Of these patients, 270 (87 %) patients had received an average dose ≤ 6 mg for at least 6 months, and 152 (89 %) patients had received an average dose ≤ 6 mg for at least 12 months. A total of 69 patients had received an average dose of > 6 mg for any duration and 22 patients had received an average dose of > 8 mg for any duration. There were 110 patients who received at least a single dose > 6 mg and only 34 patients received at least a single dose > 8 mg for any duration. The most common dose range was > 2 mg to 4 mg. The average daily dosing frequency was 3 and most patients (73 %) used an average of 1 to 4 injections daily.

Most of the exposure captured and analyzed in the safety database consisted of open-label experience. A major shortcoming of the clinical development program was that the exposure collected under randomized, double-blinded, placebo-controlled study conditions was minimal. Under these controlled study conditions, I estimated that there were only approximately 732 patient-days for APM treatment and only approximately 375 patient-days for placebo treatment.

Much of this treatment experience was derived from a single treatment on a single day. Thus, it was difficult to assess treatment-emergent adverse events (TEAEs) related to APM therapy because of this limitation. Causality of TEAE from APM treatment was suggested based upon an increase frequency in placebo-controlled trials and also occurrence of events within a relatively short period (e.g. generally ≤ 2 hours) after APM treatment under open-label conditions. The Safety Update was reviewed simultaneously with the ISS because the PDUFA clock started with the submission of the Safety Update.

Deaths

There were 14 deaths up to the time of Safety Update. The sponsor and investigators had thought that none of the 14 deaths were at least possibly related to APM treatment. However, there are seven cases (e.g. cardiac arrest, feet fractures leading to death, 4 pneumonias, meat aspiration) where there are insufficient details about the timing of APM dosing and the lack of other important details and pertinent negatives to exclude the possibility that APM played a role in an event that ultimately led to a patient's death. I do not have good reasons to suspect that APM contributed to death and I tend to agree with the sponsor that APM was not a likely contributor to any patient's death. However, I cannot exclude APM's potential role in several cases when I take a conservative approach because of limited or missing information about APM dosing related to the event of death or an event leading to death.

Treatment-Emergent Serious Adverse Events (SAEs)

There were a total of 227 SAEs in 536 patients. The most common SAEs (derived from open-label and controlled trial experience) occurring in $\geq 1\%$ of patients and in descending order of frequency were pneumonia, fall, hip fracture, myocardial infarction, urinary tract infection, dehydration, aspiration pneumonia, atrial fibrillation, cardiac congestive failure, unstable angina, hypotension, coronary artery disease, chest pain, hallucination, dyspnea, fecal impaction, and aggravation of Parkinson's disease. There were no SAEs occurring in APM treated patients in the controlled trial experience. Most SAEs were not considered to be at least possibly related to APM therapy. SAEs (a total of 15 in 13 patients) that were considered at least possibly related to APM therapy by the investigator included atrial fibrillation, bradycardia, sinus arrest, cardiac failure congestive, fall, lethargy, confusion, delirium, hallucination, mood disorder, drug-induced psychosis, hypotension, and postural hypotension. There were several SAEs that I could not exclude a potential causal/contributory role of APM because of limited or missing APM dosing information relative to the onset of the event.

The sponsor considered certain SAEs to be of special interest and causal assessments of APM relatedness were considered most likely when an event occurred soon after APM injection. These special SAEs of interest included trauma such as falls and bone/joint injuries and cardiovascular events including cardiac arrhythmia, heart failure, coronary artery disorder, hypotension and syncope. There were 5 patients who were considered to have an SAE of syncope. For SAEs involving trauma, the sponsor concluded that APM was an unlikely cause of the event or that its potential causality was uncertain. With few exceptions (e.g. syncope and sinus arrest, and hypotension and bradycardia occurring soon after APM injection), the sponsor

considered APM was an unlikely or uncertain cause of these SAEs My assessment was that it was not possible nor reasonable to exclude APM as a potential or contributory cause in the absence of important dosing information relative to the event

The rate of any SAE occurring within a certain time period since initiating APM treatment appeared to be relatively constant Overall, it was somewhat difficult considering what SAEs might be related to APM treatment considering the minimal number of patient-days of exposure under controlled conditions for comparison of SAEs during APM and placebo treatment

Treatment-Emergent Adverse Events (TEAEs) Causing Study Discontinuation

The most common reason for study discontinuation in any study was treatment-emergent adverse event (TEAE) The most common TEAEs in descending order of frequency were nausea, dyskinesia, dizziness, death, somnolence, hallucinations, back pain, and hypotension All of these except death and back pain were considered to be TEAEs typically associated with the safety/toxicity profile of APM The highest risk of developing a TEAE sufficient enough to prompt study discontinuation is highest within the first 7 days of treatment This risk progressively decreased over 6 months at which it appeared to plateau Although this risk is still relatively high between weeks 1 to 4 since starting treatment, the risk appears to decrease and plateau at 6 months after the onset of treatment When initial dosing of APM is considered, it is apparent that the occurrence of TEAEs and TEAEs associated with patient dropout are dose-related particularly with initial prescribed APM doses that are ≥ 6 mg

Treatment-Emergent Adverse Events (TEAEs)

Treatment-emergent adverse events (TEAEs) were assessed under randomized, double-blinded, placebo-controlled conditions Patients were studied under randomized, double-blinded, placebo-controlled parallel group (APM vs placebo) conditions for an in-patient phase ($\sim \leq 1$ week) and for an out-patient phase (up to 4 weeks) in study APO202, the best single study for assessing TEAEs in a controlled setting APM treatment was associated with a much higher incidence of each of the other adverse reaction categories (i.e yawning, dyskinesia, drowsiness or somnolence, nausea or vomiting, dizziness or postural dizziness, rhinorrhea, chest pain or pressure or angina, hallucinations or confusion, edema or extremity swelling) than the incidence in the placebo group The incidence of injection site complaints was similar and very high (≥ 85 %) in both groups Many of these SAEs were also confirmed to occur more frequently in APM vs placebo treated patients (naïve to APM) in study APO303 during a single treatment cross-over on different days Common TEAEs considered at least possibly caused by APM in clinical pharmacology trials were nausea/vomiting, lightheadedness/dizziness, and headache The most common specific TEAEs occurring in ≥ 10 % of all APM-treated patients (predominantly from open-label treatment) in descending order were nausea, fall, dyskinesia, dizziness (excluding vertigo), somnolence, yawning, injection site bruising, hallucinations, and vomiting Based upon observations from study APO303, the occurrence of TEAEs is dose-dependent and directly related to dose level

The rate of development (based upon patient-years of APM exposure) of number of TEAEs and

of patients with TEAEs is highest for the first week since initiation APM treatment. The pattern for the rate of the number of events/patient year and the number of patients who develop the event /patient year is similar to that observed for TEAEs prompting study discontinuation. These rates progressively decrease over time and seem to plateau after 30 days since starting APM. This plateauing appears to occur a few months earlier than the plateauing of rates (e.g. ≥ 6 months) for TEAEs prompting patients to drop out of a trial.

Injection site TEAEs with the ampoule formulation of APM were relatively common but did not stimulate any undue concern. However, there is no experience for anyone (patients or healthy subjects) receiving the pen injector formulation of APM containing benzyl alcohol at doses > 2 mg. Injection site reactions at high dose (up to 10 mg) and the safe use of this formulation using the injector pen should be studied.

The sponsor reviewed particular TEAEs of special interest (e.g. suggestive of fall, orthostatic hypotension, or postural dizziness). There were 128 patients who experienced 323 events (3 led to study discontinuation and 25 were SAEs) suggestive of falls. The sponsor did not make any comments here about causality of these events suggestive of falls. The lack of a having comparator placebo group treated under randomized, double-blinded conditions for a longer period (e.g. 3 months) as is usually the case in Parkinson's Disease trials, makes it difficult to determine the likelihood for APM in the causality of these events suggestive of falls.

There were 53 patients who experienced 70 events (11 led to study discontinuation and 6 were SAEs) possibly suggestive of orthostatic hypotension. The sponsor noted that APM was considered to have caused the event in at least 5 of these patients and that these events were observed at the initiation of dosing or at an in-office dosing visit. The sponsor commented that APM was not considered to be a likely cause of many of these events or that there was insufficient information available making the causal role of APM uncertain. Many of these events occurred at follow-up visits in which dosing had been administered at some time prior to the visit.

The sponsor acknowledged that there were 16 patients (3 %) who had experienced orthostatic hypotension, hypotension, and/or syncope and that it considered APM to be the cause of these events. However, this may be an underestimate if one considers that there was insufficient dosing information to include or exclude APM as a causal contributor to similar events in other patients.

There were 125 patients who experienced 203 events (13 led to study discontinuation and 1 was an SAE) possibly suggestive of postural dizziness. Approximately one-third of these patients had the initial event at the initiation of APM treatment. The sponsor did not note how much overlap there was between patients in this group and the group presented above for patients who had events suggestive of orthostatic hypotension.

Accidents (falls and bone and joint injuries) that were SAEs and hypotension as a TEAE were more frequently associated with concomitant vasodilator drug use. Not surprisingly, this probably reflects the increased risk for hypotension and events resulting from hypotension in patients who use APM in conjunction with a vasodilator drug.

Clinical Laboratory Results

The predominant experience for clinical laboratory data (chemistry, hematology, urinalysis) was based upon open-label, uncontrolled treatment in study APO401. Combined analyses from all clinical trials in the ISS Safety Update showed increments in the incidence of shift from normal (at baseline) to high value (at the end of treatment) for eosinophils (6 %), alkaline phosphatase (7 %), ALT (2 %), AST (2 %), BUN (10 %), creatinine (6 %), cholesterol (9 %), triglyceride (12 %), and glucose (12 %). There were also shift increments in the % of patients with a low value for hematocrit (14 %), hemoglobin (11 %), WBC (4 %), and glucose (3 %) at the end of treatment. Similar shift abnormalities were also observed for these analytes for results collected during the trial indicating that these abnormal results were persistent and not isolated findings from a single collection. Two patients developed a positive Coomb's tests (hemolytic anemia was not described) associated with APM treatment, but the overall significance of this finding is unknown, especially considering that this has been reported in the literature.

APO202 (randomized, double-blinded, placebo-controlled trial treating patients for up to approximately 5 weeks) showed infrequent shifts changes from normal at baseline to high or low value at the end of the trial. When considering all abnormal shifts that occurred in ≥ 2 APM-treated patients, there was a greater incidence (vs placebo) of shifts from normal to high for serum BUN, alkaline phosphatase, LDH, and cholesterol. There were no abnormal laboratory outlier results prompting concern in this study.

The overall significance of all these laboratory findings is questionable, particularly without a significant number of patients in a placebo control group for comparison during an extended period of treatment. The population under study is generally an older one in whom these types of abnormal changes are not unexpected. The only finding that does not necessarily seem expected is the % of patients with increments in the % of eosinophils in their differential blood counts. One can only speculate as to whether this finding suggests any phenomenon of an allergic or auto-immune nature.

Vital Signs (VS)

Based upon results from study APO303 (forced dose titration/escalation of patients naive to APM) APM can produce marked hypotensive effects on both sitting and standing systolic blood pressure and diastolic blood pressure. Overall, the mean maximal treatment difference (vs placebo) decrease in blood pressure (mm Hg) for sitting blood pressure was approximately 16 systolic/ 9 diastolic and for standing was 13 systolic/ 5 diastolic. Hypotensive effects of APM recurred with testing after prolonged treatment periods showing that there is no significant adaptation. There was a relatively minor dose-dependent slowing of pulse that overall was approximately 4 beats/minute with the highest dose (10 mg).

Because both sitting and standing diastolic blood pressure were similarly lowered, there was no significant orthostatic hypotension observed in different dose populations evaluated in study APO303 that permitted a selection bias because patients with APM intolerance to higher doses

did not escalate further. Nevertheless, there was still a dose-dependent increase in the frequency of individual patients who manifested orthostatic hypotension at various timepoints after APM injection. It seems likely that dose-dependent orthostatic hypotensive changes would be demonstrated if patients were evaluated by changing from supine to standing (more sensitive method for showing maximal changes) and most patients completed the forced APM dose titration up to 10 mg.

Significant increments in the incidence of various degrees of orthostatic hypotension occurred during orthostatic (supine to standing) blood pressure monitoring in the office both when APM was administered in the office and prior to the office visit. There were appreciable increments in the percentage of patients showing relative severe orthostatic hypotension (e.g. systolic decrease ≥ 40 mm Hg and/or diastolic decrease ≥ 20 mm Hg). There were also small increments in the percentage of patients showing a systolic decrease to a level ≤ 90 mm Hg and a diastolic decrease to a level ≤ 50 mm Hg.

Electrocardiographic Results

The only electrocardiographic results of note were those related to QTc. The sponsor used 3 lead Holter monitoring to assess effects of APM after dosing (20, 40, 90 minutes) in study APO303 in which patients (naive to APM) underwent forced dose titration/escalation. In addition to APM dose groups ranging from 2 to 10 mg, responses were also evaluated after placebo injection and administration of usual oral antiparkinsonian therapy. Treatment differences were calculated relative to placebo treatment and also to oral therapy. QTc changes over time were reference either to pre-dose QTc or to the "baseline" QTc (i.e. mean QTc from several collections prior to ever receiving any APM). Overall, QTc results based upon both Bazett (e.g. QTcB) and Fredericia (e.g. QTcF) QT corrections suggested QTc prolongation with the highest doses (8 mg and 10 mg) and greatest changes occurred at 40 minutes. All treatment differences (vs placebo or oral medication) for QTc change from pre-dose QTc or baseline QTc ranged between approximately 3 to 9 msec for QTcB and QTcF at 40 minutes after APM. The mean of all these QTcB calculated increments was 6.5 msec and the mean of all these QTcF calculated increments was 4.7 msec. Outlier analyses of various QTc categories did not suggest a dose-dependent increase in the frequency of a particular category. Although these QTc analyses based upon Holter monitor data suggested QTc prolongation, these results may be an underestimate of the actual extent of QTc prolongation induced by APM because this Holter methodology is not considered to be a valid one for accurately characterizing drug effects on QTc and is probably a less sensitive methodology than standard 12 lead ECGs.

Study APO302 (patients had been treated with APM for ≥ 3 months) used standard ECGs to evaluate QTc prolongation in patients randomized to placebo, their usual APM dose, or their usual dose + 2 mg. This study found QTc prolongation (QTcB or QTcF) effects at 90 minutes from APM that ranged between 4 to 8 msec for either APM treatment group and the pooled APM group. The treatment difference (vs placebo) treatment for both APM treatment groups ranged between 2 to 8 msec. There was no suggestion of dose-dependent differences between these groups but the average difference in dose was only approximately 1 mg. QTcB treatment difference for the pooled APM group was + 7 msec and QTcF treatment difference for the