Figure 3 Effect of Increasing Doses of Apomorphine on the UPDRS Motor Function Score Percentage Decrease from Pre-Dose for Patients Who Underwent Forced Dose Escalation of Apomorphine in Study 303

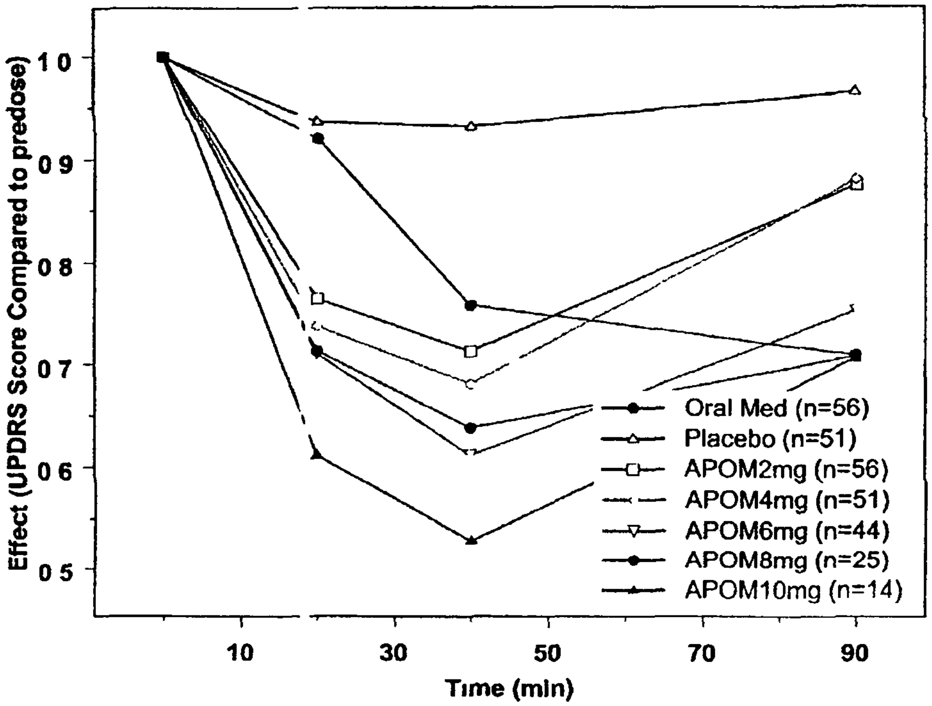
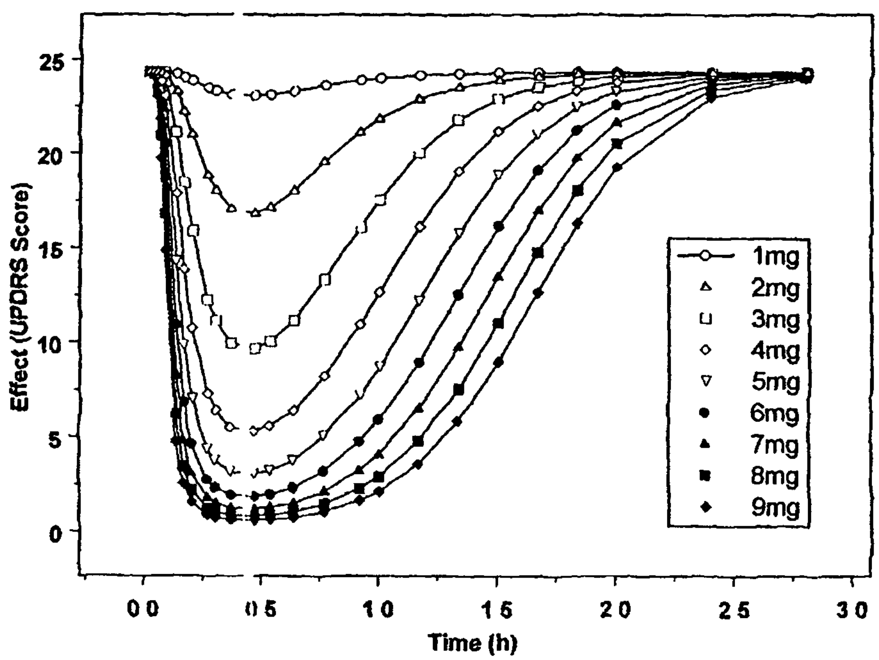


Figure 4



11.9 TEAES in Clinical Pharmacology Studies and Healthy Subjects

According to the ISS, 47 unique subjects participated in 4 Clinical Pharmacology studies including 6 patients with Parkinson's disease The remaining subjects were healthy volunteers or patients with renal or hepatic dysfunction Approximately 74 % were male, 68 % were Caucasian (30 % black, and the ages ranged from 20 to 79 years There were 3 PK studies including one each for assessing effects of renal and hepatic impairment on PK of APM The fourth study (APO073) assessed PK/PD relationships in a few patients with Parkinson's Disease

One healthy volunteer developed hypotension and bradycardia that was an SAE 30 minutes after 3 mg APM injection There were no deaths and no permanent drop-outs from a study Most common TEAEs in descending order were nausea, somnolence, dizziness, vomiting, yawning, and sweating increased Subjects exhibited various VS abnormalities including decreased and increased systolic and/or diastolic blood pressure, and bradycardia

There were no treatment-emergent clinical laboratory abnormalities of note except for a tendency of serum cholesterol and triglycerides and glucose to increase above baseline values after a single dose of APM

The sponsor submitted study results from 2 additional bioequivalence PK studies after the ISS was submitted These studies were conducted to assess the bioequivalence of a cartridge injectable formulation of with that of the formulation in the ampoule after 2 mg injections There were no new type of adverse reactions in these studies

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ON ORIGINAL

11.10 Clinical Laboratory Fındings

11 10 1 Approach to Clınıcal Laboratory Abnormalıtıes

Clınıcal laboratory evaluatıons (e g clınıcal chemıstry, hematology, Coomb's test, urınalysıs) were conducted ın all clınıcal trıals at baselıne/pre-treatment and after treatment ın all studıes and at varıous ıntervals durıng the study ın longer trıals (e g APO303, APO401) There were relatıvely mınor dıfferences ın the normal reference range for analyte results ın dıfferent studıes because a central laboratory was not used The sponsor conducted and presented varıous analyses of laboratory results The sponsor combıned results for APM treated patıents from placebo-controlled studıes (short-term) and open-label study (long-term) of APM Typıcally, there was a sıngle collectıon of laboratory evaluatıons after a sıngle treatment wıth APM and/or placebo ın short-term, controlled study and there were multıple collectıons of laboratory evaluatıons over a prolonged perıod of treatment wıth APM ın an open-label, long-term study Because the overwhelmıng bulk of results were obtaıned from open-label, uncontrolled study, the sponsor only presented results for APM-treated patıents The NDA contaıned shıft tables for abnormal laboratory results and for "clınıcally sıgnıficant" abnormal results from baselıne to any post-treatment tımepoınt and also to the end (or last post-treatment result) of the study Shıft tables showed the number of shıfts and percentages of patıents ın each shıft category Abnormal results were defined by the normal reference range for each analyte and ' clınıcally sıgnıficant ' abnormal results were defined by the sponsor (Table 31) Lıstıngs of abnormal laboratory results and for "clınıcally sıgnıficant" abnormal results of ındıvıdual patıents were also provıded The sponsor provıded a brıef descrıptıon of varıous clınıcally sıgnıficant abnormal results ın the ISS The sponsor further noted that ıt focused ıts analyses on patıents wıth clınıcally sıgnıficant abnormal results because there was no substantıve, placebo data for comparıson to APM therapy There were no analyses of laboratory analyte results for change from baselıne over a treatment perıod usıng summary statıstıcs (e g mean, SD, mın, med, max over tıme ın the ISS

I revıewed all the tables and lıstıngs However, the sponsor dıd not define clınıcally sıgnıficant abnormal laboratory results for all analytes ıncludıng some (e g sodıum, chlorıde, bıcarbonate, phosphorus, amylase) of whıch could be of clınıcal ımport Thus, when I revıewed the lıstıngs of abnormal results, I paıd partıcular attentıon to selected analytes that dıd not have a definıtıon of a clınıcally sıgnıficant abnormal result to see ıf there were any that I would consıder "clınıcally sıgnıficant "

The sponsor's revıew of clınıcally sıgnıficant laboratory results ın many ınstances ınvolved patıents who had a clınıcally sıgnıficant abnormal result of an analyte only at baselıne, at baselıne and post-treatment, and only at post-treatment but ın combınatıon wıth an abnormal baselıne result for the same analyte The sponsor dıd not analyze results and present case descrıptıons accordıng to the treatment-emergent concept Thus, my revıew focused on these brıef case descrıptıons of patıents that I consıdered to have treatment-emergent clınıcally sıgnıficant abnormal results My definıtıon of a treatment-emergent clınıcally sıgnıficant abnormal result entaıls 3 possıbılıtıes 1) normal analyte result at baselıne and clınıcally sıgnıficant crıterıon post-treatment, 2) abnormal result at baselıne that gets worse after treatment by ≥ 25 % from baseline and meets the clinically significant abnormal criterion, and 3) clinically significant abnormal result at baseline that gets worse by ≥ 25 % from baseline I used the 25 % cut-off because of the spontaneous biological variation that occurs for all analytes and also the methodological variation that is inherent in measuring any analyte based upon intra-assay and inter-assay factors

Table 31 Sponsor's Definition of Clinically Significant Values for Analyzing Outliers

Possibly Clinically Significant Values

Threshold criteria for identifying subjects with possibly clinically significant (PCS) abnormal values were defined as follows

Hematology
Hematocrit Male 37% Female ≤ 32%
Hemoglobin Male ≤ 11.5 g/dL, Female ≤ 9 5 g/dL
WBC ≤ 2,800/mm³ or ≥ 16 000/ m³
Eosinophils ≥ 10% or ≥ 700/mm³
Neutrophils ≤ 15% or ≤ 1 000/mm³
Basophils ≥ 5% or ≥ 400/ mm³
Monocytes ≥ 20% or ≥ 1,500/ mm³
Lymphocytes ≤ 10% or ≥ 80% ≤ 500/ mm³ or ≥ 4 500/mm³
Platelets ≤ 75 000/ mm³ or 700 000/mm³

Serum Biochemistry
AST ≥ 3 times upper limit of normal
ALT ≥ 3 times upper limit of normal
GGT ≥ 3 times upper limit of normal (if not ≥ 3 times upper limit of normal at baseline)
Alkaline phosphatase ≥ 3 times upper limit of normal
Urea ≥ 60 mg/dL
Creatinine ≥ 2 0 mg/dL
Uric acid Male ≥ 10.5 mg/dL, Female ≥ 8.5 mg/dL
Total bilirubin ≥ 2.0 mg/dl
Potassium ≤ 3 0 mEq/L or ≥ 5 8 mEq/L
Glucose ≤ 50 mg/dL or ≥ 80 mg/dL
Calcium ≤ 7 mg/dL or ≥ 1 5 mg/dL
Cholesterol ≥ 300 mg/dL
Triglycerides ≥ 300 mg/dl

Vital Signs

Pulse rate
≤ 50 bpm and a decrease of ≥ 30 bpm
≥ 120 bpm and an increase of ≥ 30 bpm
Systolic blood pressure
≤ 90 mmHg and a decrease of ≥ 30 mmHg
≥ 180 mmHg and an increase of ≥ 40 mmHg
Diastolic blood pressure
≤ 50 mmHg and a decrease of ≥ 20 mmHg

11 10 2Review of Clinical Laboratory Findings

The sponsor did not present an description, review, nor discussion of abnormal laboratory results but merely provided the data described earlier in the Approach to Clinical Laboratory Abnormalities The sponsor's ISS Table 101 0 showed shifts from baseline to the last post-treatment value Results (%) are presented based upon a maximal number of 536 patients Last post-treatment value could be low, normal, high, or missing The total % of missing post-treatment values was ≤ 11 % for each analyte Considering that there is no placebo group data for comparison, I will present shifts that appear to be numerically appreciable in %, that have the most potential for clinical import, and that I have deemed noteworthy Shifts (%) from a normal baseline value to a high value at the last-post-treatment evalution were noted for eosinophils (3 %), alkaline phosphatase (6 %), ALT (1 %), AST (1 %), BUN (7 %), creatinine (4 %), cholesterol (10 %), triglyceride (10 %), and glucose (9 %) Shifts (%) from a normal baseline value to a low value at the last-post-treatment evalution were noted for hematocrit (11 %), hemoglobin (8 %), WBC (3 %), and glucose (2 %) There were 2 patients (< 1 %) who developed a positive Coomb's test at the last post-treatment evaluation but there was no specific mention that either patient showed evidence of a Coomb's positive hemolytic anemia

The sponsor's ISS Table 100 0 showed shifts of number and percentage of patients from baseline to any post-treatment timepoint During review of this table, I particularly focused on analyte results suggesting shifts of interest presented above for shifts from baseline to the last post-treatment value I also looked for appreciable numerical increments (i e changes) in the % of high or low abnormal values at any post-treatment timepoint of analytes that had not been identified to be of interest during my review of Table 101 0 There were increments in the % of patients with a high value for eosinophils (6 %), alkaline phosphatase (7 %), ALT (2 %), AST (2 %), BUN (10 %), creatinine (6 %), cholesterol (9 %), triglyceride (12 %), and glucose (12 %) There were increments in the % of patients with a low value for hematocrit (14 %), hemoglobin (11 %), WBC (4 %), and glucose (3 %) All analytes that showed an abnormal shift of interest for the last post-treatment value (usually at the end of the study) were also observed in this analysis and appeared to be generally similar in magnitude There were 2 patients who showed a new positive Coomb's test during APM treatment so that the baseline result (4 patients with positive Coomb's test) increased from < 1 % to 1 % Thus, the number of patients who developed a new positive Coomb's test was not different than the result for the last post-treatment test and the total number of new positives at any time was 2 I interpret my comparisons as evidence that the shift observed for selected analytes for the last post-treatment value was not likely to be an isolated shift that was not present earlier in the trials I did not identify any shifts in the % of abnormal low or high values for any other analytes that I deemed noteworthy or of potential interest

The significance of these findings is questionable, particularly without a 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 There have been reports of development of positive Coomb's tests associated with APM and levodopa treatment but the overall significance of this finding is unknown

11 10 3 Analyses of Laboratory Outliers ("Clinically Significant" Abnormal Results)

I will summarize treatment-emergent clinical significant abnormal laboratory results that I have deemed worthy of noting

Patient APO401/27/012(APO303) was a 72 year old woman with a history of hypothyroidism, Raynaud's, stress incontinence, hypertension, heart murmur, hypercholesterolemia, pulmonary fibrosis, nodules, who developed clinically significant serum ALT of 135 (normal 6-37) and serum AST of 134 (normal 10-36) after 18 days after APM treatment (most recent average dose = 2 mg) was initiated She also had an elevated serum alkaline phosphatase 173 (normal 31-121) and serum LDH 248 (normal 80-240) At baseline her AST was normal (31) and ALT was minimally increased (44) The patient profile noted that the patient withdrew from the study for nausea after 12 days APM treatment These ALT and AST laboratory abnormalities had been listed as AEs in the patient profile Serum bilirubin was not listed as a clinically significant elevation Concomitant medications included amoxacillin, Eldepryl, Elavil, Lipitor, Norvasc, Sinemet, Tigan, and Tums Follow-up was not provided in the NDA In response to my inquiry for follow-up, the sponsor noted that the patient's liver enzymes normalized after discontinuation of atorvastatin (Lipitor) The sponsor's formal response about the temporal relationship between normalization of the liver enzymes and atorvastatin discontinuation remains outstanding

A 62 year old man (APO401/08/008) developed renal insufficiency with serum BUN of 77 mg/dL (normal 4-24) and serum creatinine of 2 9 mg/dL at the time of a myocardial infarction Serum BUN was 23 mg/dL at baseline and serum creatinine near the same time was normal at 1 1 The patient discontinued from the study because of the myocardial infarction after 487 days on treatment There was no outcome provided for this patient In response to my inquiry for follow-up, the sponsor noted that the patient's discharge summary indicated that "acute renal failure" resolved with hydration

There were 3 cases of clinically significant post-treatment hemoglobin abnormalities (10 9 –11 4 g/dL) that appeared to be treatment-emergent Two patients discontinued from study Follow results were not able to be found In response to my inquiry for follow-up, the sponsor noted that hemoglobin returned to normal in one patient, no repeat result was obtained in another patient, and follow-up was still pending for the third case

There were 2 cases of leukopenia (2300 and 2500) The patient with a WBC of 2500 showed a resolution of this clinically significant abnormality There was not outcome provided for the other patient In response to my inquiry for follow-up, the sponsor noted that the patient discontinued from study because of the cumulative effects of falls and hallucinations that had eben recurring for several months on APM treatment The leukopenia (2300) was revealed on 8/30/01 during an exit laboratroy test The investigator's site responded to the sponsor that the WBC "remained low through 10/5/01 " The patient died on [redacted] The cause of death is unknown and additional follow-up information on this case is pending to try to exclude leukopenia as contributing to this patient's death

There were 7 cases of patients with treatment emergent clinically significant increased percentage of eosinophils post-treatment There was evidence of stability for this abnormality in all patients except one

11.11 Vital Signs (VS)

11 11 1 Background

APM has potent cardiovascular effects including hypotension/orthostatic hypotension, presumably mediated via actions of D_1 and D_2 family subtype receptors Orthostatic hypotension is a cardiovascular adverse reaction of potentially great concern This adverse reaction is believed to occur via peripheral mechanisms based upon various animal studies

In view of APM's potent hypotensive effects, DNDP recommended to the sponsor that it collect orthostatic vital signs (VS) on patients in the development program, (especially in newly treated patient who are naive to APM), assess acute responses with respect to dosing, and follow responses over time In 9/00 the sponsor amended the protocol (i e Amendment 2) for study APO401 in order to address DNDP concerns about capturing information about orthostatic hypotension related to APM dosing, especially in new patients The relevant changes addressing this issue provided that 1) orthostatic vital signs (supine and standing blood pressure and pulse) should be measured at all visits, 2) orthostatic VS should be measured before and after the initial dosing of APM and at any other visit in which in-office dosing is executed, and 3) in-office dosing and before and after orthostatic VS assessments should be conducted in all patients who report TEAEs consistent with orthostatic hypotension Although orthostatic VS assessments were conducted before and after APM administration, the protocol did not specify collecting VS measurements at a specific time post-dosing The timing of measurements was left to the option of the investigator The sponsor had noted that it believed many assessments were made at or near the time the patient would have experienced “On” However, there is no way to confirm whether or not the sponsor’s belief is accurate

In addition, the sponsor conducted 2 studies (APO303, APO302) in which orthostatic VS (sitting and standing) were assessed before APM dosing and at particular times after injection Study APO303 was planned to address DNDP concerns about hypotensive effects and orthostatic hypotension in newly treated patients who were naive to APM Patents who were experiencing "Off" despite "optimal" treatment of Parkinson's disease were enrolled in study APO303 that was a substudy of APO401 for long-term, open label therapy Although DNDP had recommended studying orthostatic VS while changing from supine to standing as potentially the most sensitive way of studying effects on orthostatic hypotension, the sponsor studied changes from sitting to standing Patients were to receive APM 2 mg open-label and then undergo dose escalation of 2 mg increments every $\leq$ 3 days up to a maximal dose of 10 mg At the level 2 visit, patients would undergo a cross-over evaluation Patients were randomized to receive either placebo or 4 mg APM under double-blinded conditions and then receive the other treatment within 3 days In addition, the acute response to each patient's oral Parkinson's disease medications was also evaluated for comparison Patients were supposed to take their normal medication for Parkinson's disease in the morning, and were to come to the clinic to receive an injection for the first "Off" period occurring at least 1 hour after oral medications (that were then held until "Off" occurred) For all treatments, patient responses before and after treatment were studied for orthostatic VS (sitting and standing), Holter electrocardiographic data and UPDRS motor score assessments at, 20, 40, and 90 minutes After the completion of this dose escalation, patients would receive their optimal dose of open-label APM for up to 6 months with continued orthostatic VS assessments timed to dosing at various intervals

I consider Study APO303 to be the most important study designed to collected safety data on orthostatic VS and will therefore focus a large part of my review of VS on results from this study I have conducted some of my own analyses of the sponsor's data and have created several tables to help provide a comprehensive picture about cardiovascular effects of APM on VS I created my own tables because I did not find the format of the sponsor's data presentations "user friendly "

11 11 2 Orthostatic VS Timed to Apomorphine Dosing

Table 35 shows results of different doses of APM on systolic blood pressure (sitting, standing, and change from sitting to standing) at various times over 90 minutes relative to treatment with placebo and oral medication for comparison APM produced a potent dose-dependent (progressive from 2 to 10 mg) decrease in systolic blood pressure in both sitting and standing positions at all times The hypotensive effect was initially apparent at 20 minutes, was maximal at 40 minutes, and persisted at 90 minutes for the highest doses (e g ≥ 6 mg) Changes in patients treated with placebo were minimal over 90 minutes and as were changes at 20 and 40 minutes after oral medications However, mean decrements of a similar magnitude occurred at 90 minutes after oral medication for both sitting and standing systolic blood pressure illustrating the slow onset of the relatively mild hypotensive from patients' usual, oral antiparkinsonian medical therapy Of interest, there was no apparent effect of increasing doses of APM nor of any other treatment on orthostatic hypotension (i e difference in blood pressure between 2 different positions) considering mean changes from sitting to standing over time

Table 36 shows results of various treatment on the same parameters (presented in the preceding table) for diastolic blood pressure Similar , although not identical, changes as were described for systolic blood pressure occurred for diastolic blood pressure but these changes were of a lower magnitude There did not appear to be an orthostatic effect from increasing APM doses

Changes in pulse are presented in Table 38 APM appeared to have a relatively mild effect on decreasing both sitting and standing pulse This effect was most evident with higher doses of APM (e g ≥ 4 mg) primarily at 40 minutes The shape of the dose-response curve, if one exists, appears to be relatively mild in contrast to the more prominent one for blood pressure Changes after APM treatment at 20 and 90 minutes did not appear to be clearly distinguishable from changes observed with placebo or oral medication

I created Table 40 and Table 41 to demonstrate the treatment effect (vs placebo) of APM and oral medication on systolic blood pressure and diastolic blood pressure At the highest doses of APM, the treatment effect is greatest at 40 minutes, greater on systolic blood pressure vs diastolic blood pressure and the hypotensive effects on sitting and standing blood pressure are fairly similar in magnitude I did not present the treatment effect on the orthostatic changes because orthostatic changes were minimal and there did not appear to be clear orthostatic decrease based upon the patients who were studied (Table 35 and Table 36)

Oral medication and placebo groups showed mean decrements in pulse as did the APM groups and these decrements were even smaller than those observed with APM treatment Thus, the treatment effects of APM on pulse would be of lesser magnitude than the apparent mean changes observed without adjusting for placebo (Table 38)

I also analyzed and presented the treatment effect (vs oral medication) of APM on systolic blood pressure and diastolic blood pressure (Table 43 and Table 44) The main difference in considering the treatment effect with respect to oral medication compared to placebo is that the treatment effect at 90 minutes is much smaller This is because oral medication showed a mild to moderate hypotensive effect on both systolic blood pressure and diastolic blood pressure at 90 minutes (Table 35 and Table 36) What the effect would be if APM was administered at a similar time as oral medication for Parkinson's disease is unknown because this issue was not studied However, conceivably, the effects might be additive and blood pressure might be lowered to a greater extent than occurred when APM or oral medication was administered separately

Figure 5 illustrates the effects of all of these treatments (presented in the previous tables) on the time course of orthostatic VS changes This figure was created by the Biopharmaceutical reviewer, Dr John Duan Although it is clearly apparent that APM exerts dose-dependent hypotensive effects on both sitting and standing systolic blood pressure and diastolic blood pressure, the relative lack of effect on orthostatic VS changes is also readily apparent from this visualization I can suggest two reasons why orthostatic hypotensive effects were not observed in this study First, effects on supine and standing were not studied Changing from a supine to standing position is considered to be more sensitive method (than assessing changes from sitting to standing) for detecting orthostatic hypotensive effects of drugs Furthermore, there appeared to be a selection bias process whereby patients who experienced more significant adverse reactions including orthostatic hypotension dropped out of the forced titration Thus, patients who continued in the forced dose escalation were probably more tolerant of higher doses than patients who dropped out The dropout rate was progressively considerable between 6 mg (N = 44) to 10 mg (N = 14) If all patients who began this forced titration had been studied at all doses up to 10 mg, I believe that a dose-dependent progressive increase in the incidence and severity of orthostatic hypotension would have been observed I further believe that data contained in the following tables on the incidence of orthostatic hypotension in individual patients in study APO303 supports my view

Table 48 shows the incidence of orthostatic hypotension over 90 minutes after various doses of APM, placebo, and oral medication The incidence of orthostatic hypotension (defined as a ≥ 20 mm Hg decrease in systolic blood pressure or a ≥ 10 mm Hg decrease in diastolic blood pressure upon positional change) increased over time at doses of ≥ 4 mg APM This table also shows the % of patients with symptoms consistent with orthostatic hypotension prior to treatment and at various times post-treatment In general, these increments in % of patients with orthostatic symptoms and orthostatic hypotension followed a similar pattern However, discordance inpercentages showed that patients with orthostatic symptoms of hypotension do not necessarily manifest orthostatic hypotension using a standard definition

Table 49 shows a different analysis of the same data presented in Table 48 This analysis shows changes in the absolute incidence of orthostatic hypotension over time as well as the ratio of the incidence at a specific time relative to the incidence prior to treatment Ratios ≥ 1 5 were arbitrarily considered to represent a significant increment in the incidence of orthostatic hypotension All APM doses appeared to increase the frequency of orthostatic hypotension (relative to both placebo and oral medication treatment) There was some suggestion of dose-dependence with greatest increments occurring at APM doses ≥ 4 mg and at ≥ 40 minutes Of interest, actual ratios could not be calculated because the incidence at time 0 (i e denominator) was 0 Thus, this presentation showed that as patients progressively dropped out of the forced titration because of intolerance to increasing APM doses, the remaining patients able to tolerate the dose escalation did not manifest orthostatic hypotension prior to treatment Nevertheless, when these patients were challenged with high dose APM, orthostatic hypotension occurred in some It is also important to recall that orthostatic hypotension during this study was assessed by evaluating the response from sitting to standing instead of the more sensitive maneuver (e g supine to standing) for showing orthostatic hypotension

After patients complete the forced dose escalation, they were treated with their optimal dose as outpatients over a 6 month period and returned for similar orthostatic VS assessments after dosing at various intervals Results obtained at 1 week, 2 weeks, 1 month, 4 months, and 6 months still showed significant hypotensive effects and mild pulse slowing These changes with respect to dosing were similar to those observed during the forced titration The magnitude of the effects were somewhat lower than those occurring at the highest dose 10 mg but these patients were on lower doses The changes observed during this prolonged stage of repeated injection therapy seemed to be similar (for the average APM dose used) to results obtained when patients were initially studied during the forced titration These results clearly indicated that patient do not adapt to cardiovascular effects (blood pressure and pulse decrease) that occurred initially with the first treatment and treatment during the forced titration/escalation

In summary, this study showed that APM can produce marked hypotensive effects on both sitting and standing systolic blood pressure and diastolic blood pressure There was a dose-dependent increase in the frequency of individual patients who manifested orthostatic hypotension over time Orthostatic hypotensive changes in mean blood pressure were not shown in populations administered increasing doses of APM However, it seems likely that orthostatic hypotensive changes would be demonstrated if patients were evaluated by changing from supine to standing and most patients completed the forced APM dose titration Progressive dropout of patients who were not able to tolerate increasing doses of APM likely resulted in a selection bias process of patients who were relatively more tolerant to higher dose of APM and thereby somewhat less sensitive to adverse reactions including orthostatic hypotension Finally, it would be highly desirable to be able to assess effects of these higher doses on orthostatic VS by assessing changes in the most sensitive manner by evaluating changes from supine to standing to define the maximal risk more

Table 35 Dose-Dependent Effects of Apomorphine on Time Course of Orthostatic (Sit to Stand) Changes in Systolic Blood Pressure (mm Hg) in Study 303

Rx Group	Oral Medication N = 56			Placebo N = 50			APM 2 mg N = 56			APM 4 mg N = 51			APM 6 mg N = 44			APM 8 mg N = 25			APM 10 mg N = 14		
	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St
"Baseline", Pre-dose, Time 0	127 1	124 4	2 1	124 1	123 7	1 1	126 7	125 3	2 0	124 7	122 7	2 1	126 1	125 5	1 2	126 8	128 2	0 4	135 6	129 2	-6 0
Δ at 20' after Pre-dose	0 6	0 7	0 3	-0 6	1 2	1 3	5 3	2 4	1 4	8 0	8 7	0	-9 6	**-10 8**	-1 3	**-13 4**	**-13 9**	-0 6	**-14 5**	**-10.3**	3 8
Δ at 40" after Pre-dose	-1 6	1 5	0 5	0 1	1 4	0 8	3 2	2 4	0 8	6 8	7 7	-0 4	-9.1	-8 6	-1 2	**-13 5**	-9 3	3 4	**-16 1**	**-11 5**	1 2
Δ at 90' after Pre-dose	-6 3	-6 3	1 1	2 7	3 9	0 8	0 7	1 6	2 4	1 5	1 7	0 1	-4 7	-4 9	0 1	-9 0	9 7	1 0	-9 6	2 8	3 2

Data Source Sponsor's Corrected (5/23/03) Table 14 3 6 1 and Corrected Table 14 3 5 1 of Study 303 Report
All values are mean results
Δ sit to stand values are calculated from paired results Δ calculated by subtracting mean values from non-paired data may be different than paired data

Table 36 Dose-Dependent Effects of Apomorphine on Time Course of Orthostatic (Sit to Stand) Changes in Diastolic Blood Pressure (mm Hg) in Study 303

Rx Group	Oral Medication N = 56			Placebo N = 50			APM 2 mg N = 56			APM 4 mg N = 51			APM 6 mg N = 44			APM 8 mg N = 25			APM 10 mg N = 14		
	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St
"Baseline", Pre-dose, Time 0	77 6	77 9	0 4	75 4	75 3	- 0 4	77 6	76 4	1 3	75 7	76 6	1 2	75 5	75 4	- 0 3	79 1	79 2	0	82 9	80 2	- 1 5
Δ at 20' after Pre-dose	- 1 1	0 6	0 4	0 2	0 5	0 3	2 3	3 3	1 8	2 3	4 3	- 1 4	- 5 0	- 5 3	- 0 3	5 0	- 6 1	- 2 1	- 6 0	- 5 5	0 3
Δ at 40' after Pre-dose	- 0 8	1 7	1 0	0 6	0 7	- 0 5	3 2	2 9	0 4	0 9	4 6	3 3	- 3 6	- 5 5	- 2 3	5 4	- 5 5	- 0 4	- 8 4	- 4 3	1 8
Δ at 90' after Pre-dose	- 2 5	3 3	1 2	1 4	2 4	0	- 0 3	- 1 6	- 1 5	0 2	1 0	- 1 5	- 1 6	- 3 3	- 1 9	- 3 9	- 4 7	- 1 0	- 3 7	- 1 3	0 2

Data Source Sponsor's Corrected (5/23/03) Table 14 3 6 1 and Corrected Table 14 3 5 1 of Study 303 Report
All values are mean results
Δ sit to stand values are calculated from paired results Δ calculated by subtracting mean values from non-paired data may be different than paired data

Table 38 Dose-Dependent Effects of Apomorphine on Time Course of Orthostatic (Sit to Stand) Changes in Pulse (Beats/Minute) in Study 303

Treatment Group	Oral Medication N = 56			Placebo N = 50			APMPM 2 mg N = 56			APM 4 mg N = 51 APM			APM 6 mg N = 44			APM 8 mg N = 25			APM 10 mg N = 14		
	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St	Sit	St	Δ Sit to St
"Baseline", Pre-dose, Time 0	75 2	77 0	2 5	77 6	79 1	2 0	75 4	77 5	2 6	76 9	78 3	2 3	76 1	78 7	3 2	78 7	78 1	2 2	76 9	79 2	2 2
Δ at 20' after Pre-dose	-2 1	3 2	-0 9	-0 1	0 6	-0 8	0 5	1 8	1 5	1 6	2 0	-0 1	-0 8	-0 6	0 5	0 8	0 7	0 2	-3 9	-4 2	0 7
Δ at 40' after Pre-dose	-0 6	1 2	-0 6	-1 5	1 0	0 6	0 7	1 6	0 7	2 5	-3 2	-0 8	-2 0	-2 4	0 5	-2 9	3 3	-0 6	-2 4	-4 7	-0 5
Δ at 90' after Pre-dose	1 6	-2 1	-0 4	-0 1	1 4	1 6	1 5	0 4	1 0	1 5	0 4	2 0	-0 8	0 9	1 8	-1 6	-2 1	-0 5	-2 0	-1 0	1 8

Data Source Sponsor's Corrected (5/23/03) Table 14 3 6 1 and Corrected Table 14 3 5 1 of Study 303 Report
All values are mean results
Δ sit to stand values are calculated from paired results Δ calculated by subtracting mean values from non-paired data may be different than paired data

Table 40 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Placebo) on Time Course of Orthostatic Changes in Systolic Blood Pressure (mm Hg) in Study 303

Rx Group	Oral Medication - Placebo N = 56		APM 2 mg – Placebo N = 56		APM 4 mg – Placebo N = 51		APM 6 mg – Placebo N = 44		APM 8 mg – Placebo N = 25		APM 10 mg – Placebo N = 14	
	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand
Δ at 20' after Pre-dose	1 2	- 0 5	- 4 7	- 3 6	- 7 4	- 9 9	- 9 0	- 13 0	- 12 8	- 15 1	- 13 9	- 11 5
Δ at 40' after Pre-dose	- 1 7	- 2 9	- 3 3	- 3 8	- 6 9	- 9 1	- 9 2	- 10 0	- 13 6	- 10 7	- 16 2	- 12 9
Δ at 90' after Pre-dose	- 9 0	- 10 2	- 3 4	- 2 3	- 4 2	- 5 6	- 7 4	- 8 8	- 11 7	- 13 6	- 12 3	- 6 7

Treatment differences are calculated as Mean Treatment – Mean Placebo for the respective time and position

Table 41 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Placebo) on Time Course of Orthostatic Changes in Diastolic Blood Pressure (mm Hg) in Study 303

Rx Group	Oral Medication - Placebo N = 56		APM 2 mg – Placebo N = 56		APM 4 mg – Placebo N = 51		APM 6 mg – Placebo N = 44		APM 8 mg – Placebo N = 25		APM 10 mg – Placebo N = 14	
	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand
Δ at 20' after Pre-dose	- 0 9	- 1 1	- 2 1	- 3 8	- 2 1	- 4 8	- 4 8	- 5 8	- 4 8	- 6 6	- 5 8	- 6 0
Δ at 40' after Pre-dose	- 1 4	- 2 4	- 3 8	- 3 6	- 1 5	- 5 3	- 4 2	- 6 2	- 6 0	- 6 2	- 9 0	- 5 0
Δ at 90' after Pre-dose	- 3 9	- 5 7	- 1 7	- 4 0	- 1 2	- 3 4	- 3 0	- 5 7	- 5 3	- 7 1	- 5 1	- 3 7

Table 43 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Oral Medication) on Time Course of Orthostatic Changes in Systolic Blood Pressure in Study 303

Rx Group	Placebo - Oral Medication N = 56		APM 2 mg – Oral Medication N = 56		APM 4 mg – Oral Medication N = 51		APM 6 mg – Oral Medication N = 44		APM 8 mg – Oral Medication N = 25		APM 10 mg – Oral Medication N = 14	
	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand
Δ at 20' after Pre-dose	- 1 2	0 5	- 5 9	- 3 1	- 8 6	- 9 4	- 10 2	- 11 5	- 14 0	- 14 6	- 15 1	- 11 0
Δ at 40' after Pre-dose	1 7	2 9	- 1 6	0 9	- 5 2	- 6 2	- 7 5	- 7 1	- 11 9	- 7 8	- 14 5	- 10 0
Δ at 90' after Pre-dose	- 9 0	- 10 2	- 5 6	7 9	4 8	4 6	1 6	1 4	- 2 7	- 3 4	- 3 3	3 5

Treatment differences are calculated as Mean Treatment – Mean Oral Medication for the respective time and position

Table 44 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Oral Medication) on Time Course of Orthostatic Changes in Diastolic Blood Pressure in Study 303

Rx Group	Placebo - Oral Medication N = 56		APM 2 mg – Oral Medication N = 56		APM 4 mg – Oral Medication N = 51		APM 6 mg – Oral Medication N = 44		APM 8 mg – Oral Medication N = 25		APM 10 mg – Oral Medication N = 14	
	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand	Sit	Stand
Δ at 20' after Pre-dose	0 9	1 1	- 1 2	- 2 7	- 1 2	- 3 7	- 3 9	- 4 7	- 3 9	- 5 5	- 4 9	- 4 9
Δ at 40' after Pre-dose	1 4	2 4	- 2 4	- 1 2	- 0 1	- 2 9	- 2 8	- 3 8	- 4 6	- 3 8	- 7 6	- 2 6
Δ at 90' after Pre-dose	3 9	5 7	2 2	1 7	2 7	2 3	0 9	0	- 1 4	- 1 4	- 1 2	2 0

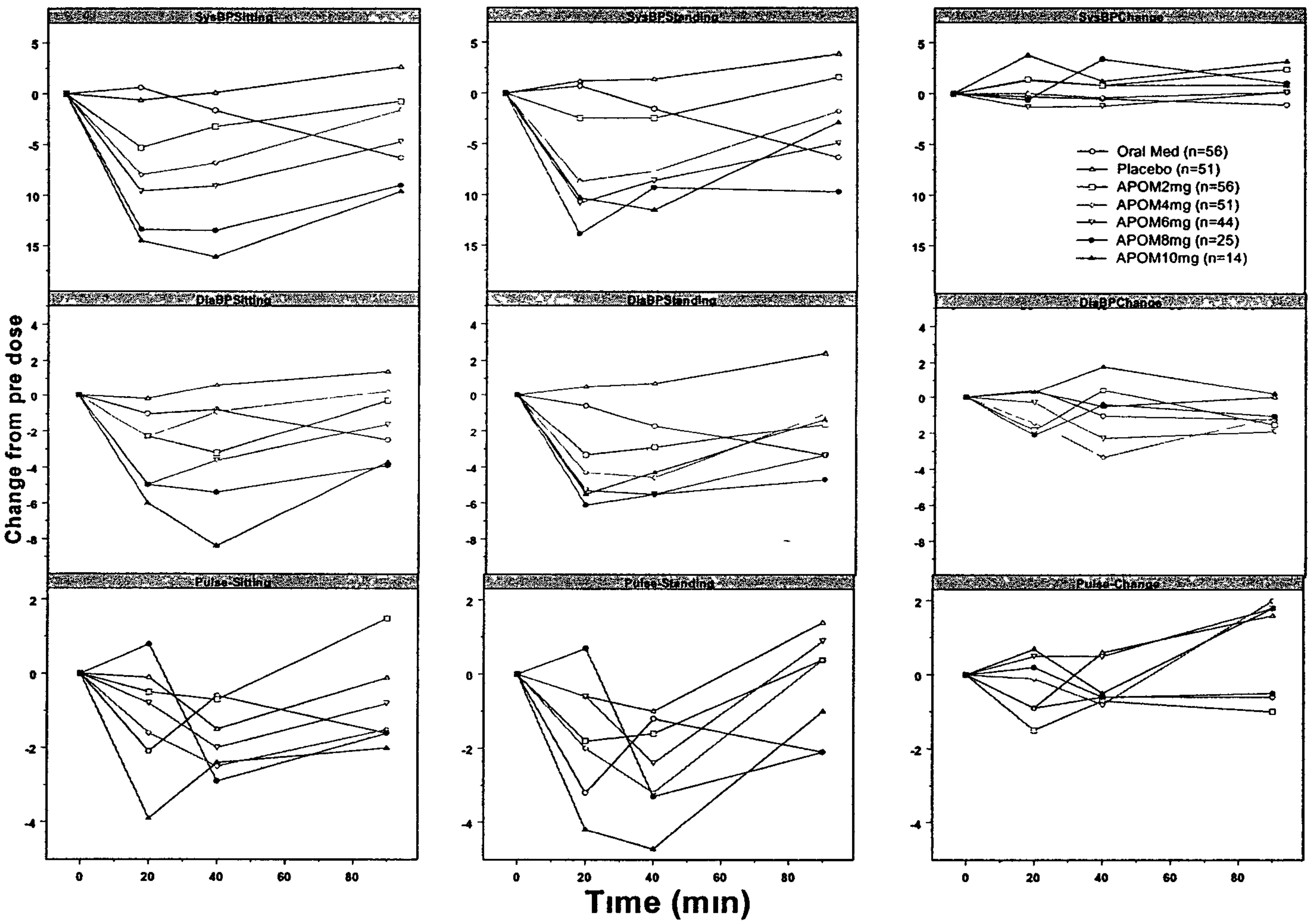

Figure 5 Time Course of Dose-Dependent Effects of Apomorphine on Orthostatic VS

Mean blood pressure and pulse changes from pre-dose at different time points for different treatment groups The left column shows the values at sitting, the middle column shows the values at standing, and the right column shows the value changes from sitting to standing The upper row shows the values of systolic blood pressures, the middle row shows the values of diastolic blood pressures, the lower row shows the values of pulse

Table 48 Dose-Dependent Effects of Apomorphine on Time Course of Incidence of Orthostatic Hypotension and Orthostatic Symptoms While Changing from Sitting to Standing in Study 303

	% of Patents with Orthostatic Hypotension				% of Patents with Orthostatic Symptoms			
Time	0	+ 20'	+ 40'	+ 90'	0	+ 20'	+ 40'	+ 90'
Oral Medication N = 56	8 9 %	8 9 %	12 5 %	14 3 %	7 1 %	10 7 %	7 1 %	5 4 %
Placebo N = 51	7 8 %	3 9 %	7 8 %	5 9 %	2 0 %	7 8 %	2 0 %	3 9 %
APM 2 mg N = 56	7 1 %	14 3 %	7 1 %	7 8 %	5 4 %	10 7 %	8 9 %	7 1 %
APM 4 mg N = 51	3 9 %	9 8 %	17 6 %	3 9 %	2 0 %	17 6 %	11 8 %	5 9 %
APM 6 mg N = 44	4 5 %	6 8 %	11 4 %	13 6 %	2 3 %	13 6 %	9 1 %	6 8 %
APM 8 mg N = 25	0 %	12 0 %	8 0 %	16 0 %	4 0 %	20 0 %	8 0 %	12 0 %
APM 10 mg N = 14	0 %	7 1 %	7 1 %	7 1 %	0 %	21 4 %	14 3 %	7 1 %

Data Source Sponsor's Table 14 3 7 1 of Study 303 Report
Orthostatic change = SBP decrease of ≥ 20 mm Hg or DBP decrease of ≥ 10 mm Hg
Orthostatic symptoms = Yes or No answer

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Table 49 Dose-Dependent Effects of Apomorphine on Time Course of Change in Incidence of Orthostatic Hypotension While Changing from Sitting to Standing in Study 303

	Incidence at Time 0	+ 20'		+ 40'		+ 90'	
Treatment		% change from time 0	Post-Rx Incidence / Time 0 Incidence	% change from time 0	Post-Rx Incidence / Time 0 Incidence	% change from time 0	Post-Rx Incidence / Time 0 Incidence
Oral Medication N = 56	8 9 %	0 %	1 00	3 6 %	1 40	4 4 %	**1 61**
Placebo N = 51	7 8 %	- 3 9	0 50	0 %	1 00	- 1 9 %	0 76
APM 2 mg N = 56	7 1 %	7 2 %	**2 01**	0 %	1 00	0 7 %	1 10
APM 4 mg N = 51	3 9 %	5 9 %	**2 51**	13 7 %	**4 51**	0 %	1 00
APM 6 mg N = 44	4 5 %	2 3 %	**1 51**	6 9 %	**2 53**	9 1 %	**3 02**
APM 8 mg N = 25	0 %	12 0 %	**12 0 / 0**	8 0 %	**8 0 / 0**	12 0 %	**12 0 / 0**
APM 10mg N = 14	0 %	7 1 %	**7 1 / 0**	7 1 %	**7 1 / 0**	7 1 %	**7 1 / 0**

Bold indicates increased ratio of Post-Treatment Incidence/Time 0 incidence ≥ 1 50

APO302 Orthostatic VS with Respect to APM Dosing

Patients, who had been treated for at least 3 months with APM were also studied under randomized, double-blinded, placebo-controlled, parallel treatment conditions Patients were randomized to receive one of four parallel treatment groups including 1) their usual dose of an APM injection, 2) their usual dose of an APM injection + 2 mg (maximal dose allowed = 10 mg), 3) the equivalent volume of placebo to their usual dose volume of an APM, or 4) the equivalent volume of placebo to their usual dose volume of an APM + 0 2 ml I will briefly describe results in these patients, who were studied for orthostatic (i e sitting and standing) VS before injection and at 20 and 90 minutes post injection, because they do not provide much additional, substantive information beyond that which was observed in study APO303 The average dose of APM was 4 6 mg (usual dose) and 5 8 mg (usual dose + 2 mg) in the two APM groups Results of each of these groups and the pooled APM group were compared to pooled placebo

The greatest decrements in sitting (- 14 0 mm Hg) and standing (-18 0 mm Hg) systolic blood pressure and in sitting (-34 mm Hg) and standing (- 3 8 mm Hg) diastolic blood pressure occurred at 20 minutes in the APM + 2 mg group Decrements were still observed at 90 minutes (~ 25 % as large as those observed at 20 minutes) showing that a hypotensive effect persisted for at least 90 minutes Significant but lesser magnitude decrements were observed in the pooled APM and APM groups, with the least decrements occurring in the APM group There were no significant decrements in the sitting or standing blood pressure in the pooled placebo group The greatest treatment difference (e g drug -placebo) occurred in the APM + 2 mg group was approximately - 15 mm Hg for sitting and standing systolic blood pressure and approximately - 6 mm Hg for sitting and standing diastolic blood pressure Both sitting and standing pulse were decreased similarly to a relatively mild extent, with the greatest effect (~ 6 beats/minute) occurring in the highest APM group

The sponsor conducted statistical analyses and the study report noted several statistically significant hypotensive effects on blood pressure in the different APM groups at 20 minutes The most highly statistically significant changes occurred in the APM + 2 mg group in both sitting and standing positions Although other various changes, that seemed substantial, were not statistically significant, I believe that these persisting hypotensive changes still suggested at 90 minutes are real One should also consider that this study was not powered to show statistically significant effects on blood pressure outcomes

Overall, these results were fairly similar to those observed in study APO303 when the highest dose groups (8 mg and 10 mg) were compared Also, because sitting and standing blood pressure were lowered to a similar extent, there was no significant decrease in the orthostatic response (i e difference between sitting and standing blood pressure) compared to the placebo group over time Most importantly, these results showed that patients treated with intermittent subcutaneous APM for a prolonged period (i e ≥ 3 months) still exhibit marked hypotensive responsiveness to APM and that there does not appear to be any significant adaptation to this response

11 11 3 Orthostatic VS Not Timed to Apomorphine Dosing

The sponsor presented analyses of the frequency of orthostatic hypotension using the standard definition discussed earlier and also presented a more severe definition The sponsor subsequently presented additional analyses of additional definitions of other severities of orthostatic hypotension in response to my request These analyses are shown in the following tables that present the frequency of various severities of orthostatic hypotension when assessed by changing from supine to standing in study APO401 These analyses included 1) results of patients dosed with APM in the office when post-treatment VS were collected at the discretion of the investigator, and 2) results of patients who came to the office but had received APM at various times prior to the visit Results were also categorized as new onset of orthostatic hypotension, persistent orthostatic hypotension, and orthostatic hypotension not occurring or not persistent according to definitions shown at the bottom of Table 50 and Table 51

The sponsor dıd not present an ınterpretatıon or dıscussıon of the requested tables Table 50 shows results of ın-office dosıng Small but consıderable percentages of patıents demonstrated varıous severıtıes of orthostatıc hypotensıon that was new ın onset (ı e not present at baselıne but observed after APM treatment) Of potentıal ımportance, some patıents showed severe systolıc orthostatıc hypotensıon wıth pressure drops that were ≥ 30 or ≥ 40 mm Hg and 3 of 47 exhıbıted systolıc blood pressure less than 90 Relatıvely mıld dıastolıc orthostatıc hypotensıon that was new ın onset after APM treatment occurred ın 17 % of patıents The percentage of patıents showıng more severe dıastolıc orthostatıc hypotensıon was less but clearly notable and of potentıal sıgnıficance For example, 2 of 47 patıents decreased theır dıastolıc by at least 20 mm Hg to a final level below 50 mm Hg The majorıty of patıents dıd not manıfest any level of orthostatıc hypotensıon Some patıents showed persıstent orthostatıc hypotensıon of varıous severıtıes and others who showed orthostatıc hypotensıon at baselıne dıd not exhıbıt orthostatıc hypotensıon durıng ın-office dosıng It was not specıfied how many assessments of orthostatıc hypotensıon were evaluated at baselıne and post-treatment Some patıents also showed sıgnıficant ıncrements or decrements ın pulse after standıng

I consıder that these orthostatıc VS assessments performed wıth APM dosıng ın and out of the office are lıkely to be underestımates of the true ıncıdence of orthostatıc hypotensıon because neıther set of assessments was necessarıly optımally tımed to look at VS wıth respect to pharmacokınetıc and pharmacodynamıc consıderatıons Consıderıng that there appears to be a slıght delay of approxımately 10 mınutes (mean) for a maxımal pharmacodynamıc effect (e g based upon UPDRS motor functıon) after Tmax, and that hypotensıve effects ın study APO303 were greatest at 40 mınutes, I suggest that 40 mınutes would be an excellent tıme to evaluate for orthostatıc effects on a routıne basıs

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Table 50 Occurrence (% of Patients) of Orthostatic Hypotension or Vital SignThreshold Change While Changing from Supine to Standing At Baseline and After Apomorphine Treatment (47 Patients, Dosed In Office)

	New Onset	Persistent	Not Occurring	Not Persistent
Orthostatic VS Threshold				
SBP decrease ≥ 20 mm Hg	6 4 %	25 5 %	55 3 %	12 8 %
SBP decrease ≥ 40 mm Hg	8 5 %	2 1 %	83 0 %	6 4 %
SBP decrease ≥ 30 mm Hg to ≤ 90 mm Hg	6 4 %	2 1 %	91 5 %	0 %
DBP decrease ≥ 10 mm Hg	17 0 %	14 9 %	59 6 %	8 5 %
DBP decrease ≥ 20 mm Hg	4 3 %	6 4 %	85 1 %	4 3 %
DBP decrease ≥ 20 mm Hg to ≤ 50 mm Hg	4 3 %	0 %	95 7 %	0 %
Pulse increase ≥ 15	10 6 %	4 3 %	74 5 %	8 5 %
Pulse decrease ≥ 15	4 3 %	0 %	93 6 %	2 1 %

Timing of collection of post-treatment VS was optional and not specified in protocol
New Onset = Not present at baseline but observed with APM treatment
Persistent = Present at baseline and observed with APM treatment
Not Occurring = Not present at baseline nor observed with APM treatment
Not Persistent = Present at baseline but not observed with APM treatment
SBP = systolic blood pressure and DBP = diastolic blood pressure
Patients are counted once during treatment regardless of number of times achieving the threshold change

Table 51 shows similar analyses of patients who were assessed for orthostatic hypotension while changing from supine to standing but who were dosed with APM prior to arriving at the office These analyses showed considerable percentages (21 6 % and 18 %) of patients who manifested the minimal criteria for new onset of systolic and diastolic orthostatic hypotension respectively after initiating treatment with APM Small percentages of patients also showed the new development of severe levels of systolic and diastolic orthostatic hypotension Although most patients did not ever manifest any level of orthostatic hypotension, others showed that it was either persistent or not persistent Small percentages of patients also showed significant pulse increments and decrements

Table 52 presents these same data from a somewhat different perspective The frequency of various levels of orthostatic hypotension was shown at baseline and during treatment for patients who were evaluated with dosing in the office and for patients who were evaluated in the office without APM dosing in the office (but at some interval prior to arriving at the office) These latter patients had not necessarily administered a dose within a "short" time prior to their office visit Thus, this analysis does not necessarily indicate that APM is the cause of the higher frequency of orthostatic hypotension during the APM treatment period However, it is certainly possible that APM played some causal role in the increased frequency of orthostatic hypotension during the treatment phase I have indicated in bold type in the table instances that I consider to show appreciable increments in the frequency of various levels of orthostatic hypotension Increments in patients who were not dosed in the office seem overall more impressive than those of patients who were dosed in the office It is conceivable that investigators assessed orthostatic VS when motor function improvement was most obvious, and possibly at a time when blood pressure changes were not maximal There were appreciable increments in the frequency of patients exhibiting intermediate severities of orthostatic hypotension during the APM treatment phase

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Table 51 **Occurrence (% of Patients) of Orthostatic Hypotension or Vital SignThreshold Change While Changing from Supine to Standing At Baseline and After Apomorphine Treatment (268 Patients, Not Dosed In Office)**

	New Onset	Persistent	Not Occurring	Not Persistent
Orthostatic VS Threshold				
SBP decrease ≥ 20 mm Hg	21 6 %	6 3 %	66 8 %	5 2 %
SBP decrease ≥ 40 mm Hg	6 7 %	1 1 %	90 7 %	1 5 %
SBP decrease ≥ 30 mm Hg to ≤ 90 mm Hg	2 6 %	0 4 %	95 5 %	1 5 %
DBP decrease ≥ 10 mm Hg	18 0 %	7 9 %	68 4 %	5 6 %
DBP decrease ≥ 20 mm Hg	6 4 %	0 4 %	92 1 %	1 1 %
DBP decrease ≥ 20 mm Hg to ≤ 50 mm Hg	0 8 %	0 4 %	98 9 %	0 %
Pulse increase ≥ 15	10 2 %	2 3 %	82 2 %	5 3 %
Pulse decrease ≥ 15	2 3 %	0 %	95 8 %	1 9 %

Dosing was administered at unspecified times prior to office visit
New Onset = Not present at baseline but observed with APM treatment
Persistent = Present at baseline and observed with APM treatment
Not Occurring = Not present at baseline nor observed with APM treatment
Not Persistent = Present at baseline but not observed with APM treatment
SBP = systolic blood pressure
DBP = diastolic blood pressure
Patients are counted once during treatment regardless of number of times achieving the threshold change

Table 52 Occurrence (% of Patients) of Orthostatic Hypotension or Vital SignThreshold Change While Changing from Supine to Standing At Baseline and During Apomorphine Treatment for Patients Dosed In Office and Patients Not Dosed In Office

	47 Patients, Dosed In Office		268 Patients, Not Dosed In Office	
Orthostatic VS Threshold	Baseline	During APM Rx	Baseline	During APM Rx
SBP decrease ≥ 20 mm Hg	38 3 %	31 9 %	11 5 %	**27 9 %**
SBP decrease ≥ 40 mm Hg	8 5 %	10 6 %	2 6 %	**7 8 %**
SBP decrease ≥ 30 mm Hg to ≤ 90 mm Hg	2 1 %	**8 6 %**	1 9 %	3 0 %
DBP decrease ≥ 10 mm Hg	23 4 %	**31 9 %**	13 5 %	**25 9 %**
DBP decrease ≥ 20 mm Hg	10 7 %	10 7 %	1 5 %	**6 8 %**
DBP decrease ≥ 20 mm Hg to ≤ 50 mm Hg	0 %	**4 3 %**	0 4 %	0 8 %
Pulse increase ≥ 15	14 9 %	17 0 %	7 6 %	**12 5 %**
Pulse decrease ≥ 15	2 1 %	4 3 %	1 9 %	2 3 %

<u>Baseline %</u> was derived from and for each respective group by adding % in "Persistent" and "Not Persistent" columns because these columns included patients showing the categorical threshold change at baseline

<u>During APM Rx %</u> was derived from and for each respective group by adding % in " New Onset" and "Persistent" columns because these columns included patients showing the categorical threshold change during APM Rx

SBP = systolic blood pressure

DBP = diastolic blood pressure

Percentages shown in bold indicate an "appreciable" % increase from baseline of ≥ 4 % as arbitrarily designated by the Clinical Reviewer In office dosing was performed without specific regard to time of dosing

Baseline Prevalence of Orthostatic Hypotension in All Apomorphine-Treated Patients and Patients in Pivotal Trials

I asked the sponsor to show the prevalence of patients who demonstrated orthostatic hypotension at baseline prior to being treated in any clinical, trial Requested analyses used the minimal standard criteria for systolic and diastolic orthostatic hypotension and showed the prevalence of isolated systolic or diastolic orthostatic hypotension or both changes (mutually exclusive categories) These analyses also showed the percentage of patients in these various categories relative to the duration of treatment in a trial for all trials and for pivotal trials These data were requested to determine whether there might be a selection process whereby patients with orthostatic hypotension at baseline prior to initiating APM treatment might progressively dropout of studies

Table 53 shows a considerable number of patients in each of the 3 categories of orthostatic hypotension assessed during supine and standing positions There was a progressive decline in the number of patients in each category over time Few patients appeared to have been assessed for orthostatic hypotension by evaluation changes from sitting to standing There was also a progressive decline in patients who did not exhibit orthostatic hypotension at baseline but it was not apparent whether there was a disproportionate drop-out of patients with baseline orthostatic hypotension Overall, I interpreted these data as showing that there was not an abrupt drop-out of patents who had orthostatic hypotension at baseline and began APM treatment

Table 54 shows numbers of patients in similar categories of orthostatic hypotension for pivotal trials according to the duration of treatment in a study Overall, there was a distinct but relatively minimal decline in a relatively small numbers of patients in different categories over 6 months It would not be unexpected for patients to drop-out over time I interpret these data also similarly as I did in Table 53 as showing that there was not an abrupt drop-out of patients who enrolled in pivotal trials Overall, these tables show that considerable numbers of patients with baseline orthostatic hypotension were able to tolerate APM for relatively long-term treatment

Initially, I had requested only results for pivotal trials APO202, 301, and 303 because the sponsor had not identified study APO302 as a pivotal trial The sponsor is supposed to update these data to include patients from study APO302

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Table 53 Baseline Prevalence of Orthostatic Hypotension in All Apomorphine-Treated Patients in All Trials According to Duration of Treatment

Orthostatic Hypotension Threshold and Positional Changes	Apomorphine-Treated Patients (N=536)			
	Any Rx	Rx > 3 Months	Rx > 6 Months	Rx > 12 Months
Systolic orthostatic hypotension alone (supine to standing)	28 (9%)	13 (8%)	8 (5%	4 (7%)
Diastolic orthostatic hypotension alone (supine to standing)	31 (10%)	21 (9%)	18 (13%)	5 (8%)
Systolic and diastolic orthostatic hypotension (supine to standing)	24 (8%)	20 (9%)	6 9%)	7 (11%)
Systolic orthostatic hypotension alone (sitting to standing)	1 (33%)	[illegible] 33%)	(33%)	1 (33%)
Diastolic orthostatic hypotension alone (sitting to standing)	0	0	0	0
Systolic and diastolic orthostatic hypotension (sitting to standing)	0	0	0	0

Note All blood pressure measurements that were collected at a predose or non-dose timepoint at a baseline visit are considered to be baseline measurements Patients can have more than one baseline assessment They are counted only once within each row but can fulfill the necessary criteria for more than one row

Note Systolic orthostatic hypotension is defined as a >= 20 mm Hg decrease while changing from supine to standing or sitting to standing positions Diastolic orthostatic hypotension is defined as >= 10 mm Hg decrease while changing from supine to standing or sitting to standing positions

Note Systolic orthostatic hypotension alone is defined as having orthostatic hypotension for the systolic value but not for the diastolic value (rows 1 and 4 of the table) Diastolic orthostatic hypotension alone is defined as having orthostatic hypotension for the diastolic value but not for the systolic value (rows 2 and 5 of the table) Systolic and diastolic orthostatic hypotension is defined as having orthostatic hypotension for the systolic and diastolic values (rows 3 and 6 of the table)

Note Percentages are based on the number of patients in each duration category with a baseline visit that has a pair of blood pressure values to calculate the orthostasis criteria A pair of values is defined as those collected at supine and standing or sitting and standing

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Table 54 Baselıne Prevalence of Orthostatıc Hypotensıon ın Patıents ın Pıvotal Trıals Accordıng to Duratıon of Treatment

Orthostatic Hypotension Threshold and Positional Changes	Patients Who Participated in Apomorphine Pivotal Trials (202 301 303) (N=97)			
	Any Rx	Rx > 3 Months	Rx > 6 Months	Rx > 12 Months
Systolic orthostatic hypotension alone (supine to standing)	2 (3%)	2 (5%	1 (3%)	0
Diastolic orthostatic hypotension alone (supine to standing)	7 (12%)	4 (9%)	4 (12%)	0
Systolic and diastolic orthostatic hypotension (supine to standing)	5 (8%)	5 (12%)	4 (12%)	0
Systolic orthostatic hypotension alone (sitting to standing)	0	0	0	0
Diastolic orthostatic hypotension alone (sitting to standing)	0	0	0	0
Systolic and diastolic orthostatic hypotension (sitting to standing)	0	0	0	0

Note Only patients who participated in an Apomorphine pivotal trial (APO202 APO301 or APO303) are included in this summary Orthostatic measurements were not performed in APO202 or APO301

Note All blood pressure measurements that were collected at a "predose" or non-dose timepoint at a baseline visit are considered to be baseline measurements Patients can have more than one baseline assessment They are counted only once within each row but can fulfill the necessary criteria for more than one row

Note *Systolic orthostatic hypotension is defined as a >= 20 mm Hg decrease while changing from supine to standing or sitting to standing positions* Diastolic orthostatic hypotension is defined as >= 10 mm Hg decrease while changing from supine to standing or sitting to standing positions

Note Systolic orthostatic hypotension alone is defined as having orthostatic hypotension for the systolic value but not for the diastolic value (rows 1 and 4 of the table) Diastolic orthostatic hypotension alone is defined as having orthostatic hypotension for the diastolic value but not for the systolic value (rows 2 and 5 of the table) Systolic and diastolic orthostatic hypotension is defined as having orthostatic hypotension for the systolic and diastolic values (rows 3 and 6 of the table)

Note Percentages are based on the number of patients in each duration category with a baseline visit that has a pair of blood pressure values to calculate the orthostasis criteria A pair of values is defined as those collected at supine and standing or sitting and standing

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