Reviewer's Comment Because the date and time of last dose of APM prior to the fall is unknown, it is difficult to exclude APM as a potential contributory factor for the fall and fracture

Patient APO401/10/015 was a 72 year-old woman on APM treatment for 82 days, who tripped, fell and fractured her hip while doing housework The date and time of the last dose of APM prior to the fall is unknown She is continuing in Study APO401 and had completed 248 days of APM treatment

Reviewer's Comment Because the date and time of last dose of APM prior to the fall is unknown, it is difficult to exclude APM as a potential contributory factor for the fall and fracture

Patient APO401/33/002 was a 62 year-old man with hypertension who fell off his horse fracturing his ribs and contusing his liver He had been on APM treatment for 271 days and his medications included the vasodilator doxazosin He reportedly did not have neurological symptoms contributing to his fall The date and time of last dose of APM prior to the fall is unknown He was continuing in Study APO401 after 370 days of APM treatment

Reviewer's Comment Because the date and time of last dose of APM prior to the fall is unknown, it is difficult to exclude APM as a potential contributory factor for the fall and fracture Note there was no specification of no lightheadedness or dizziness as opposed to just no neurologicl symptoms I am not certain if that statement means no dizziness/lightheadedness

Patient APO401/23/016 was an 80 year-old man with hypertension who fell and suffered a vertebral compression fracture He had been on APM for 68 days and his medications included the vasodilator Doxazosin The patient is reported to have a history of postural instability His last dose of APM was on the day prior to the fall He discontinued from Study APO401 due to this event

Reviewer's Comment It is certainly consistent that APM caused postural hypotension and this contributed to his fall and fracture Other details about timing of last APM dose are lacking to make a better assessment

Patient APO401/10/018 was a 69 year-old woman who slipped and fell on ice fracturing her hip 30 minutes after her last APM injection

Reviewer's Comment It is difficult to exclude the possibility of a contributory role from APM such as causing orthostatic hypotension The timing of APM use relative to the event is consistent with some causal role There were no pertinent negatives of no dizziness/lightheadedness

Patient APO4OL — 01O*APO202*P was a 65 year-old man who fell after 113 days on APM treatment He was reported to have postural hypotension after 152 days on APM treatment He was continuing in APO401

Reviewer's Comment It is certainly consistent that APM caused postural hypotension and this contributed to his fall Other details are lacking to make a better assessment

Cardiovascular SAEs including Cardiac Arrhythmias, Chest Pain/Angina/Myocardial Infarction, Syncope, Hypotension/Orthostatic Hypotension

Patient APO401/27/011 (APO303) was a 68 year-old man who experienced about a 16 second sinus arrest associated with syncope (brief loss of consciousness) 16 minutes following his initial 2 mg apomorphine dose in APO303 The lowest heart rate was 32 Within 2 minutes following syncope, the patient's heart rate increased to near pre-dose intervals At 60-minutes following the event, the patient was in stable condition with the signs and symptoms returned to baseline He did not receive any other APM doses

Reviewer's Comment APM seems clearly to be the cause of this event

Patient APO401/30/005 was a 62 year-old man who had bradycardia and hypotension 30 minutes following his initial 2 mg APM dose in APO401 The pre-dose BP was 130/80 and 30 minutes post dose it was 60/40 The patient had orthostatic symptoms An ambulance was called and the patient apparently stabilized in the office He was then transferred to the emergency room for observation and subsequently released He had no further exposure to APM

Reviewer's Comment APM seems clearly to be the cause of this event

Patient APO401/05/008(APOM0073) was a 71 year-old woman who experienced dizziness, lightheadedness and chest tightness about 15 minutes after injection She took another injection on the same day and one the following morning Because her symptoms were continuing, she went to her physician and was diagnosed with atrial fibrillation with rapid ventricular response and was admitted She was discharged the next day on Lopressor and was continuing in APO401 after 495 days of APM treatment and had no additional symptoms similar to these

Reviewer's Comment APM could have been the cause of the precipitation of atrial fibrillation The rapid ventricular response could have induced angina in a patient with known or unknown coronary disease The strong temporal relationship to the event suggests the likelihood of a contributory role from APM

Patient APO401/08/007 was an 83 year-old male in APO401 After about 8 months of APM use, he was diagnosed with sick sinus syndrome that consisted of bradycardia, atrial fibrillation and near syncope A permanent pacemaker was inserted He continued APM treatment for about 8 months

Reviewer's Comment Sufficient details about APM use relative to the events are lacking to exclude a contributory role of APM to the near syncope and/or arrhythmias

Patient APO401/11/005 was a 58 year-old male with a history of shortness of breath prior to

initiating APM treatment He was hospitalized with a diagnosis of congestive heart failure, and atrial fibrillation 3 days after he had been discontinued from APM Heart failure symptoms had developed 2 months after starting APM and the diagnosis of CHF was approximately 3 months later When diagnosed with CHF, the ECG indicated that the patient was in atrial fibrillation He restarted APM several weeks later despite the fact that the investigator considered the events possibly related to APM

Reviewer's Comment It is difficult to know whether APM played a role in precipitating the atrial fibrillation or heart failure

Patient APO401/30/001 was a 78 year-old man hospitalized with chest pain and found to have significant coronary artery disease The timing of APM to the onset of chest pain is unknown He underwent a PTCA He continued on APM after the event and completed study participation

Reviewer's Comment It is difficult to exclude a contributory role from APM

Patient APO401/61/001 was a 69 year-old man who had symptoms of chest pain and left arm numbness 1 day after initiating apomorphine treatment and was diagnosed with a myocardial infarction His symptoms began 2 or 3 hours after the last APM injection He stopped APM 11 days after the symptoms started but then restarted APM 3 months later

Reviewer's Comment It is difficult to exclude a contributory role from APM

Patient APO401/08/008 was a 69 year-old man with a history of coronary artery disease who was on APM for over 12 months He presented to the emergency room on three occasions over

the course of 6 days with complaints of shortness of breath and back pain The second episode occurred 1 hour after an APM injection On the final visit and three days after discontinuation of apomorphine treatment he was admitted with a diagnosis of non-Q wave myocardial infarction confirmed by cardiac enzymes His hospital course was complicated by hypertension, acute renal failure, aspiration pneumonia, and anemia

Reviewer's Comment It is difficult to exclude a contributory role from APM The timing of one episode1 hour after APM is certainly consistent with a causal/contributory role

Patient APO401/56/007 was a 57 year-old female who had a fall after losing consciousness The timing of APM to the event could not be determined after multiple queries to the site The patient appears to have stopped using APM around the time of the event

Reviewer's Comment It is difficult to exclude a contributory role from APM without knowing the timing of APM use relative to the event

Patient APO401/55/004 was a 69 year-old woman with a history of diabetes, CABG x 3,

hypertension, and dyslipidemia who experienced lethargy and increased slurred speech on 2 occasions Twelve days after starting the study she had chills and slurred speech after taking an injection of APM (timing of injection to onset of event unknown) Six days later, within one hour of an APM injection she developed lethargy and an episode of hypotension (BP 101/44 mmHg, HR 30s) Blood pressures recorded shortly thereafter were normal Because she continued to have lethargy and slurred speech, she was admitted for further evaluation and APM was discontinued During the hospitalization she continued to have slurred speech, lethargy and vital sign fluctuations Follow-up 11 months after the event, indicates that the lethargy and slurred speech have continued The episode of hypotension is likely to have been caused by APM However, we are missing information on the details of her hospitalization and do not know whether the patient had a CVA There is also some information stating that the patient had slurred speech at baseline

Reviewer's Comment The episode of hypotension is likely to have been caused by APM It is difficult to exclude a contributory role from APM without knowing the timing of APM use relative to the event, that may have been a stroke

Patient APO401/58/05 was a 77 year-old woman with hypertension and coronary artery disease who had a myocardial infarction 1 hour after a 4 mg APM injection She had a 100 % stenosis of her right coronary artery and underwent stent placement with good results Whether the patient had orthostatic hypotension prior to the event is unknown The patient discontinued APM because of the event

Reviewer's Comment The temporal relationship strongly suggest a causal role in precipitating the event

Patient APO401/40/010 was a 73 year-old man with coronary artery disease status post coronary artery bypass surgery and stent placement who had a myocardial infarction 2 hours after his last APM dose On cardiac catheterization he was found to have severe significant coronary occlusions and underwent angioplasty APM was resumed on discharge from the hospital

Reviewer's Comment The temporal relationship strongly suggest a causal role in precipitating the event

Patient APO401/25/005 was a 59 year-old man who was admitted with symptoms of unstable angina 3 5 hours after his last apomorphine injection He was found to have a 90% lesion of the right coronary artery and a stent was placed APM was continued during the hospital stay

Reviewer's Comment The temporal relationship suggests a possibly contributory role for APM in precipitating the event Note that the admission occurred 3 5 hours after the APM It is not clear how soon the angina began after the injection Presumably it was occurring for some time prior to the admission thereby making the injection have a closer relationship to the onseet of the angina

SAEs Related to Pneumonia

Patient APO401/13/003 was a 69 year-old man who was admitted with symptoms of pneumonia approximately 1 day after his last apomorphine injection He was treated with antibiotics and resumed apomorphine treatment

Reviewer's Comment Pertinent negatives were not provided regarding nausea and vomiting Conceivably the patient could have been experiencing vomiting and aspirated emesis to cause an aspiration pneumonia that cannot be excluded

Patient APO401/41/002 was an 85 year-old woman who was admitted for pneumonia, after a 3 to 4 week history of shortness of breath, cough and wheezing 2 hours after her last APM injection The timing of this event to her last apomorphine injection is unknown She was treated with antibiotics and continued APM in the hospital

Reviewer's Comment It is difficult to exclude that the patient developed an aspiration pneumonia some time relatively soon before the admission There were no pertinent negatives that the patient did not experience vomiting

Patient APO401/57/004 was a 59 year-old woman who was admitted for pneumonia The timing of her last dose of APM to the event is unknown She discontinued APM treatment

Reviewer's Comment Details are insufficient to exclude any role from APM It is difficult to exclude that the patient developed an aspiration pneumonia some time relatively soon before the admission There were no pertinent negatives that the patient did not experience vomiting

Patient APO401/01/015 was a 75 year-old male admitted for pneumonia He continued using APM during hospitalization

Reviewer's Comment It is difficult to exclude the possibility that the patient developed an aspiration pneumonia before the admission There were no pertinent negatives that the patient did not experience vomiting

Neuropsychiatric SAE

Patient APO401/57/003 was a 48 year-old woman with a history of depression who was admitted for worsening psychiatric symptoms She was diagnosed with paranoid delusions, paranoid psychosis, and organic psychosis APM was discontinued

Reviewer's Comment It is difficult to exclude that the patient developed these symptoms from some causal role from APM The timing of APM injection is not provided to help decrease the likelihood of a contributory role from APM APM treatment is consistent with producing this reaction

11.7 Dropouts, Study Discontinuations/Withdrawals due to Adverse Events and Overall Disposition of Patients

11 7 1 Disposition of Patients

Table 17 shows the patient disposition in the randomized double-blinded, placebo-controlled studies Only 3 APM-treated patients withdrew from all these studies during the controlled phase and all discontinuations occurred in the longest, controlled study 202 One APM-treated withdrawal occurred during the in-patient phase for nausea and vomiting, one discontinuation occurred during the outpatient phase for chest pain, and the third patient withdrew because of a scheduling conflict Placebo patients rarely withdrew but when they did, the usual reason was lack of effect or "other" (e g some reason other than adverse event, lack of effect, or lost to follow-up)

Table 17 Disposition of Patients . Randomized Double-blinded, Placebo-controlled Studies

Study	Status	APO-Treated	Placebo
APO202 (N=29)	Completed outpatient dosing	*17/20 (85%)*	*8/9 (89%)*
	Discontinued prior to first outpatient dose		
	Patient terminated early due to adverse event	1/20[1]	
	Patient terminated early due to lack of effect		1/9[2]
	Discontinued during outpatient phase		
	Patient terminated early due to adverse event	1/20[3]	
	Patient terminated – not due to adverse event(s)or lack of effect	1/20[4]	
		APO/Placebo	Placebo/APO
APO301 (N=17)	Completed Study	8/8 (100%)	8/9 (89%)
	Discontinued		
	Patient terminated early – not due to adverse event(s) or lack of effect		1/9[5]
		APO/Placebo	Placebo/APO
APO303 (N=51)	Completed double-blind, placebo controlled, crossover phase	30/30 (100%)	20/21 (95%)
	Discontinued		
	Patient terminated – not due to adverse event(s)or lack of effect		1/21[6]
		APO-Treated	Placebo
APO302 (N=62)	Completed Study	*35/35 (100%)*	*25/27 (93%)*
	Discontinued		
	Patient terminated early – due to lack of effect		2/27[7]

Note Study APO303 was predominantly an open label dose escalation study with a double-blind placebo controlled, randomized crossover component at TV2 and TV3

[1]Patient APO202/1 — 003 discontinued during dose titration due to adverse events of nausea and vomiting

[2]Patient APO/ — 004 discontinued during the dose titration phase due to lack of effect

[3]Patient APO202 — 014 reported chest pain with left arm numbness during the first week of outpatient use of apomorphine at a dose of 4 mg The onset was within one hour of dosing and duration was two hours. The patient discontinued study due to this event Subsequent exercise stress testing with dobutamine challenge and dobutamine thallium scans were normal with no clear indicators of ischemia

[4]Patient APO202/ — /001 discontinued the outpatient phase at 3 weeks because of a visit scheduling conflict

[5]Patient APO301/01/005 a 52 year-old female suffered severe off pain after placebo injection and was unable to continue with required UPDRS and Dyskinesia evaluations beyond 10 minutes on Day 1 and withdrew from the study

[6]Patient APO401/04/017(APO303), a 57 year-old female suffered severe off symptoms during placebo injection and was unable to continue with the cross-over phase of Study APO301 She continued in the outpatient phase of Study APO301

[7]Patient APO401/04/002(APO302)P a 46 year-old female, experienced considerable discomfort post injection and was nearly immobilized She was given Sinemet and Comtan at 50 minutes post-dose Patient APO401/10/004 APOM0073/APO302)P a 63 year-old female developed an intolerable OFF episode 20 minutes after injection and the study was stopped Both patients continued in study APO401

Disposition of Patients · All Studies

The overall disposition of patients in all clinical trials of Parkinson's Disease patients is shown in Table 18 Not surprisingly there were no patient discontinuations from studies 301 and 302 that involved only a single dosing of APM There were significant numbers of patient discontinuations in longer studies (202, 303, 401) involving multiple dosings and the most common reason was treatment-emergent adverse event (TEAE)

Table 18 Number and Percentage of Apomorphine-Treated Patients Discontinuing from Study and Reason for Study Discontinuation [ab]

Study #	202 N = 20 (Completed 17)	301 N = 16 (Completed 16)	302 N = 35 (Completed 35)	303[c] N = 56 (Completed 32)	401 N = 508 (Ongoing)
Reason for Study Discontinuation					
Any	3 (15 %)	0 (0 %)	0 (0 %)	24 (43 %)	250 (49 %)
Adverse Event	2 (10 %)	0 (0 %)	0 (0 %)	17 (30 %)	118 (23 %)
Lack of Effect	0 (0 %)	0 (0 %)	0 (0 %)	1 (2 %)	34 (7 %)
Lost to Follow-Up	0 (0 %)	0 (0 %)	0 (0 %)	2 (4 %)	14 (3 %)
Other [d]	1 (5 %)	0 (0 %)	0 (0 %)	4 (7 %)	84 (17 %)

a Data Source ISS Safety Update Table 14 0
b Only 5 placebo patients (1–APO 202, 1-APO301, 1-APO303, 2-APO302) discontinued and reason was lack of effect or other
cAll dropouts occurred during in the open-label phase
d Not due to adverse event, lack of effect, or lost to follow-up

11 7 2 Dropouts, Study Discontinuations / Withdrawals Due to Treatment-Emergent Adverse Events (TEAEs) in All Patients in All Controlled and Open-Label Clinical Studies

Table 19 shows the most common TEAEs prompting study discontinuation in all APM–treated patients from all trials The overwhelming majority of patients whose data are presented were in the long-term, open-label safety study (APO401) Almost one-quarter of all patients withdrew for a 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 are considered to be TEAEs typically associated with the safety/toxicity profile of APM Table 20 shows the most common TEAEs that were considered at least possibly related (i e causally assessed as possibly, probably, or definitely related) to study medication and that caused study discontinuation Most TEAEs included in Table 19 were also included in Table 20 indicating that investigators also frequently considered that these most common TEAEs prompting study discontinuation were related to APM treatment

Table 19 Treatment-Emergent Adverse Events (TEAEs) Causing Study Discontinuation in All Apomorphine Treated Patients in All Trials . Presented by Decreasing Frequency of Preferred Terms and Occurring in ≥ 5 Patients (≥ 0 9 %) [a]

Preferred Term	Total # TEAEs	# Patients (%) [a] with TEAE (N = 536)
Any TEAE	238	120 (22 4 %)
Nausea	18	16 (3 0 %)
Dyskinesia NEC (not elsewhere classified)	12	11 (2 1 %)
Vomiting NOS (not otherwise specified)	11	11 (2 1 %)
Dizziness (excluding vertigo)	11	9 (1 7 %)
Death NOS	9	9 (1 7 %)
Somnolence	8	8 (1 5 %)
Hallucinations	6	6 (1 1 %)
Back pain	6	5 (0 9 %)
Hypotension NOS	5	5 (0 9 %)

a Incidence (i e %) counts each patient once regardless of the number of episodes of TEAE
Data Source ISS Safety Update Table 63 0

Table 20 Frequency of TEAE (Preferred Term) Causing Study Discontinuation and Considered at Least Possibly Related to Study Medication by Investigator in ≥ 3 Patients in All Apomorphine Treated Patients

TEAE causing study discontinuation	Number of Patients
nausea	16
vomiting NOS	10
dyskinesia NEC	9
dizziness (excluding vertigo)	8
somnolence	8
hypotension NOS	5
postural hypotension	3
hallucination NOS	3
confusion	3
sedation	3
chest pain NEC	3
edema lower limb	3

Source of Data Sponsor's ISS Safety Update Table 63 1

11 7.3 Subgroup Analyses of All Apomorphine-Treated Patients with Respect to Age, Gender, Concomitant Medication, and Apomorphine Dosing

The sponsor conducted various subgroup analyzes of TEAEs causing study discontinuation for age, gender, concomitant medication (e g dopaminergic agonist, COMT inhibitor, vasodilator) and dosing parameters Although analysis was conducted for patients taking and not taking a dopaminergic agonist, this analysis did not seem useful considering that virtually all patients (i e 99 %) were using a dopaminergic agonist Race was not analyzed because most patients were Caucasian

Age

There did not appear to be any significant difference in the frequency of specific TEAEs associated with study discontinuation according to age (e g patients $\geq$ 65 years old vs patients , 65 years old)

Gender

The frequency of study discontinuation because of death in females (3 9 %) was approximately 2 fold that of males (2 0 %) The sponsor recognized this but also noted that none of the deaths were considered related to study drug The sponsor also commented that the incidence of dyskinesia causing dropout was higher in females (3 %) than in males (1 %) There were no other gender differences that seem striking or worthy of comment for TEAEs causing study discontinuation

Concomitant Medications

There did not appear to be any obvious or appreciable difference in the incidence of any specific TEAE causing study discontinuation with respect to use of COMT inhibitor or vasodilator It was not possible to analyze for dopaminergic agonist use because essentially all patients had been using such a drug

Apomorphine Dosing

When TEAEs are analyzed relative to APM dosing parameters, there are some interesting observations I created Table 21 from data in ISS Safety Update Tables 35 0 and 69 0 that analyzed the number of patient treatment years experience and TEAEs associated with patient dropout relative to the time since start of APM treatment Table 21 shows the frequency of TEAEs and patients associated with study discontinuation (i e dropout) relative to various lengths of time since the patient began treatment with APM before dropping out of a study The bulk of the experience in patient years occurred in patients treated for $\geq$ 31 days The number of

TEAEs associated with a patient discontinuing for a TEAE is highest in the initial dosing period of 1-7 days Analogously, the rate for the number of TEAEs associated with patient dropout /patient-years of treatment and the rate for the number of patients dropping out/patient-year of treatment are also highest for this period These rates are inversely related to the duration of APM treatment and decrease over time as the duration of treatment increases The differences in rates are quite striking The rate of the number of TEAEs (associated with patient dropout)/patient-years of treatment for patients discontinuing from study in the first week is approximately 40 and 80 fold higher than the respective rates for patients who dropped out between 6-12 months and after 12 months following initiation of treatment The rate for the number of patients dropping out/patient-year of treatment is 38 fold greater than the rate for 6-12 months and > 12 months of treatment Progressive decrements in these rates appear to level off after 6 months of APM treatment Most common TEAEs associated with dropout early in therapy include nausea and vomiting, cardiovascular AEs (e g cardiac arrhythmias, hypotension/postural hypotension) and CNS AEs (e g dizziness, somnolence, dyskinesia)

Based upon data in Table 21, it is clear that the highest risk of developing a TEAE sufficient enough to prompt study discontinuation is highest within the first 7 days of treatment 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

Table 21 Frequency of TEAEs Associated with Patients Dropping Out of Study Relative to Time Since Starting Treatment with APM

Parameter	Day 1-7 N = 536	Day 8-30 N = 505	Day 31- 180 N = 390	Day 181- 365 N = 321	Day ≥ 366 N = 186	Total Any Duration N = 536
# APM Rx PatientYears (P-Y)	10 0	30 7	151 8	128 1	98 1	418 7
# Any TEAE associated with dropout	80	43	64	21	27	235
# Pts with TEAE(s) (%)associated with dropout	38 (7 %)	26 (5 %)	43 (8 %)	13 (4 %)	13 (7 %)	133
Rate # TEAEs/P-Y (patients with TEAE causing study dropout)	8 0	1 4	0 4	0 2	0 1	0 6
Rate # patients with TEAE/P-Y (patients with TEAE causing study dropout)	3 8	0 8	0 3	0 1	0 1	0 3

Data Source ISS Safety Update Tables 35 0 and 69 0

When the initial dose of APM is considered, it is apparent that the occurrence of TEAEs and TEAEs associated with patient dropout is dose-related particularly with initial prescribed APM doses that are ≥ 6 mg (Table 30 shown in section 11 8 4) However, there did not appear to be a clear trend across dose groups correlating the occurrence of a TEAE with the APM dose used at the time a patient discontinued from study because of a TEAE Neither did there appear to be an increase in the frequency of TEAEs prompting study discontinuation associated with patients who injected themselves more frequently (e g > 4 injections/day) on an average daily basis These latter observations suggest perhaps that patients adapt somewhat to the potential for adverse reactions related to dose after continued use and/or that there is a selection of patients who can use somewhat higher doses without increased risk or perhaps with less risk for adverse reactions

Finally, there did not appear to be any suggestion of increased risk for developing a TEAE that caused study dropout in patients taking dopaminergic agonist, COMT inhibitors, or vasodilators

I did not have any essential disagreements with comments or interpretations presented by the sponsor in the ISS section dealing with patient discontinuations for any reason including TEAE

11.8 Treatment Emergent Adverse Events (TEAEs)

11 8 1 Approach to Treatment Emergent Adverse Events (TEAEs) in Patients

The sponsor analyzed and presented data regarding TEAEs for all patients exposed to APM in the phase 2/3 clinical trials including a separate presentation of TEAEs for each of the 4 randomized, double-blinded, placebo-controlled trials The sponsor also conducted and presented the subgroup analyses for TEAEs according to age, gender, concomitant medication use, relationship to study drug and various dosing parameters as previously done for SAEs and TEAEs causing study discontinuation Data from the sponsor's PK studies involving healthy volunteers, subjects with renal or hepatic impairment, and a few Parkinson's Disease patients who were not incorporated in the ISS but were analyzed separately by the sponsor These data will be presented separately as TEAEs for patients in clinical pharmacology trials

I was unable to find a definition for AE in the protocols except for study 301 Typically patients were asked an open ended questions if they had any adverse reaction/experience Thus, it did not appear that laboratory abnormalities would necessarily be considered a TEAE Without a definition of AE/TEAE, it would seem that the reporting of some events such as laboratory abnormalities would be left to the experience and discretion of each investigator I asked the sponsor to clarify if there was a definition for AE in the protocol that I had missed but had not yet received a response as of 6/13/03

Incidence of TEAEs was the focus of the ISS and was defined as the number of patients in the exposed population who experienced a TEAE In general, a patient was counted once among all the patients treated if the patient experienced one or more AEs at that level Incidence of TEAEs were analyzed and presented according to 3 levels of MeDRA 2 4 coding terms including primary system organ class, high level group term, and preferred term I have focused on presenting TEAEs by the preferred terms

11 8 2 Review of Treatment-Emergent Adverse Events in Clinical Trials

Treatment-Emergent Adverse Events Randomized, Double Blind, Placebo Controlled Studies

The sponsor presented TEAEs for each of the pivotal, controlled studies Table 22 shows results of the most common TEAEs in the parallel group study that involved the longest treatment, period ($\leq$ 5 weeks including an inpatient phase up to 1 week and an outpatient phase up to 4

weeks These patients were naive to APM therapy The overall incidence of any TEAE and injection site complaint was similar in the APM and placebo groups However, 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 It would be better if specific terms were combined only when they reflected the same adverse reaction as might be expected for drowsiness or somnolence Although chest pressure and angina might be synonymous terms reflecting the same phenomenon, other combined terms (e g hallucinations and confusion) are different events and should be presented separately to present a more accurate picture of adverse reactions It would also be of interest to know the frequency of these events after initial, early treatment in the inpatient phase compared to later treatment in the outpatient phase

Table 22 Treatment-Emergent Adverse Events in Double Blind Placebo Controlled Study APO202 (Parallel Group Design) for All Patients Treated for Any Time

Summary o	Study APO202 Adverse Events Occurring in Two or More Patients			
Adverse Event	Apomorphine		Placebo	
	N = 20	%	N = 9	%
Any Adverse Reaction	17	85	8	89
Injection Site Complaint	9	45	5	56
Yawning	8	40	0	0
Dyskinesias	7	35	1	11
Drowsiness or Somnolence	7	35	0	0
Nausea or Vomiting	6	30	1	11
Dizziness or Postural Dizziness	4	20	0	0
Rhinorrhea	4	20	0	0
Chest Pain / Pressure / Angina	3	15	1	11
Hallucination or Confusion	2	10	0	0
Edema / Swelling of Extremitie	2	10	0	0

In-patient phase was typically ≤ 1 week and out-patient phase was ≤ 4 weeks In the out-patient phase 18 patients were treated with APM and 8 patients were treated with placebo

Table 23 shows the experience in the controlled, cross-over study involving a single treatment with APM and placebo in patients who had been treated with APM for at least 3 months There were no TEAEs in patients treated with APM in this study conducted in conjunction with another sponsor (Britannia Pharmaceuticals) in the United Kingdom Despite the fact that each patient had a single exposure to APM and this study was conducted under Good Clinical Practice (GCP) conditions, this adverse reaction experience contrasted markedly with the experience observed in studies APO302 and 303 in which patients also received a single exposure to APM in studies conducted in the U S and experienced TEAEs Conceivably, this observation may be related to the fact that the study was conducted in Europe where some consider the frequency of recording/reporting adverse reactions to be less than the experience generally found in studies conducted in the U S

Table 23 Treatment-Emergent Adverse Events in Double Blind Placebo Controlled Cross-Over Study APO301

	Study APO301			
	Apomorphine		Placebo	
	N = 16	%	N = 17	%
Any Adverse Reaction	0	0	3	18
Pain at Injection Site	0	0	2	11 8
Dry Skin	0	0	1	5 9

Patients received a single treatment with APM and placebo (both sequences) on different days

Table 24 reflects the adverse reactions observed in APO303, the cross-over study in which patients were randomized to receive either APM and then placebo or placebo and then APM on consecutive days This randomized treatment occurred after patients who were naive to APM treatment had received a single exposure to 2 mg of APM within 3 days The overall incidence of any TEAE as well as each of the specific adverse reactions was higher with APM treatment compared to placebo treatment Many of the TEAEs (e g injection site complaint, nausea, vomiting, dizziness, dyskinesia, somnolence, rhinorrhea) observed in this study were the same as many of those observed in study APO202 Whereas the overall incidence of any TEAE was much lower than during APM treatment, the incidence of specific TEAEs was much lower than those seen with APM

Table 24 Treatment-Emergent Adverse Events in Double Blind Placebo Controlled Cross-Over Study APO303

Study APO303 Doul le-blind, Placebo Controlled, Crossover Phase Summary c· Adverse Events Occurring in Two or More Patients				
	Apomorphine		Placebo	
	N =51	%	N =51	%
Any Adverse Event	30	59	12	24
Yawning	13	26	3	6
Nausea	9	18	1	2
Dizziness	8	16	2	4
Sedation	7	14	2	4
Dyskinesia	6	12	0	0
Sweating Increased	5	10	0	0
Somnolence	4	8	0	0
Headache	4	8	0	0
Vomiting	3	6	0	0
Rhinorrhoea	3	6	0	0
Flushing	3	6	0	0
Pallor	3	6	0	0

Patients received a single treatment with APM and placebo (both sequences) on different days

Table 25 shows the results from study APO302, the parallel group, controlled, study involving a single treatment with the patient's usual APM dose, the usual APM dose + 2 mg, and the pooling of the 2 placebo groups (the patient's usual APM volume or their usual APM volume + 0 2 ml) These patients had been treated repeatedly with APM for at least 3 months prior to randomization There was a higher incidence of any TEAE and of yawning, somnolence, and dizziness in either APM group compared to the incidence for each with placebo treatment There was a suggestion of dose-dependent effect of APM because the incidence for each event was higher in the group receiving an additional 2 mg of APM above the patient's usual dose vs results for patients receiving only their usual APM dose In addition, this higher dosed treatment group also showed rhinorrhea and nausea vs the other 2 groups

Table 25 Treatment-Emergent Adverse Events in Double Blind Placebo Controlled Study APO302 (Parallel Group Design)

Study APO302 Double-blind Placebo Controlled Parallel Groups Summary of Adverse Events Occurring in Two or More Patients								
	Apomorphine						Placebo	
	Apomorphine Total		Maintenance Dose		Maintenance Dose + 2 mg			
	N=35	%	N=19	%	N=16	%	N=27	%
Any Adverse Event	16	46	8	41	8	50	9	33
Yawning	8	23	3	16	5	31	2	7
Somnolence	6	17	3	16	3	19	0	0
Dizziness	4	11	2	10	2	13	1	4
Rhinorrhoea	3	9	0	0	3	19	0	0
Nausea	2	6	0	0	2	13	0	0

Patients received a single treatment with their usual APM dose, their usual dose + 2 mg (maximal dose = 10 mg), their usual treatment volume as placebo, or their usual treatment volume + 0 2 ml as placebo

The sponsor did not integrate the TEAE experience across all randomized, double-blinded, placebo-controlled studies However, I combined results from all these separate presentations into a single presentation of TEAEs as shown in Table 26 for patients treated with any dose of APM and any placebo treatment The incidence of any TEAE in the combined experience was almost twice as frequent with APM vs placebo treatment Furthermore, the incidence of each TEAE shown in Table 26 was higher with APM treatment For many TEAEs the difference in the incidence between treatment groups was quite striking The most common TEAEs (in terms of decreasing order of frequency) were drowsiness/sedation/somnolence, nausea/vomiting, dizziness/postural dizziness, yawning, dyskinesia, and rhinorrhea

Previously, I had noted (see Table 8) that a shortcoming of this development program was the very limited experience of APM treatment under randomized, double-blinded, placebo-controlled conditions Although the incidence for particular TEAEs in Table 26 was technically reported in association with APM or placebo treatment, this table combines the experience from very diverse trials designs Most patients whose experience is presented in this tabulation received a single treatment on 1 day Their data are combined with the data from a relatively small number of

patients who received APM ((N = 18) or placebo (N = 8) for a longer period up to 5 weeks Thus, there is a significant difference in the number of patient days of treatment exposure among patients Whereas there were some patients who had been treated only with APM or placebo on a single day in a parallel design study, there were others who had received a single exposure to both treatments on separate day single day and were subject potentially to carry over effects of the preceding treatment In addition, patients treated with both sequences under controlled conditions in study APO303 also had received open-label treatment with a single dose of 2 mg of APM immediately before the randomized cross-over phase

Table 26 Summary of Most Common Treatment-Emergent Adverse Events by Preferred Term in Patients in All Randomized, Double-Blinded, Placebo-Controlled Studies

TEAE	Apomorphine N = 122	Placebo N = 104
Any TEAE	63 (51 7 %)	32 (30 8 %)
Drowsiness and/or Somnolence and/or Sedation	24 (19 7 %)	2 (1 9 %)
Nausea and/or Vomiting	20 (16 4 %)	2 (1 9 %)
Dizziness and/or Postural Dizziness	16 (13 1%)	3 (2 9 %)
Yawning	16 (13 1%)	5 (4 8 %)
Dyskinesia	13 (10 7 %)	1 (1 0 %)
Rhinorrhea	10 (8 2 %)	0 (0 %)
Injection Site Complaint	9 (7 4 %)	7 (6 7 %)
Sweating Increased	5 (4 1%)	0 (0 %)
Headache	4 (3 3 %)	0 (0 %)
Chest Pain and/or Chest Pressure and/or Angina	3 (2 5 %)	0 (0 %)
Pallor	3 (2 5 %)	0 (0 %)
Flushing	3 (2 5 %)	0 (0 %)
Hallucination and/or Confusion	2 (1 6 %)	0 (0 %)
Edema and/or Swelling of Extremities	2 (1 6 %)	0 (0 %)
Dry Skin	1 (0 8 %)	0 (0 %)

Experience is derived from combining Studies APO202, 301, 302, and 303 that involved cross-over and parallel group designs, patients who were APM naïve and previously treated with APM, and patients randomized to a single treatment assignment on 1 day treated under controlled conditions or treatment over many days up to approximately 5 weeks

It may be possible to reanalyze the combined safety experience (Table 26) of patients in the cross-over studies only on the first day by comparing results of half of the patients in both sequences (e g compare APM to placebo only on day 1) It may also be important to consider the interval between the last open-label APM treatment in these patients to control for potential carry over effects on the development of TEAEs Finally, consideration should also be given to the fact that many patients in this tabulation had been exposed repeated to APM treatment for a period of at least 3 months (and often much longer) and that others were naive to APM treatment If there

is any patient adaptation that occurs and decreases the risk of adverse reactions with increasing duration of treatment, then one could potentially present a misleading picture of the risk of TEAEs and thereby underestimate the risk of adverse reactions if you combine results from patients who have been treated for a long time with those who are naive to APM therapy

Recognizing that patients are at the greatest risk for exhibiting TEAEs during the earliest phase (i e days 1-7) after initiating treatment (see Table 21), it is possible that combined data from all these patients may be misleading because the safety experience is different in the early phase of treatment compared to later phase after longer term treatment Conceivably, some patients may become relatively "tolerant" toward the development of TEAEs and undergo some "adaptation" with prolonged repeat treatments It is also possible that there may be a selection process whereby patients with the greatest susceptibility to develop TEAEs cease treatment and the relatively less susceptible or more tolerant patients continue treatment It certainly seems like patients who continued with APM dose escalation up to 10 mg in Study 303 were an example of a selection bias process because the number of patients progressively decreased with progressive dose increments (e g N = 44 at 6 mg, N = 25 at 8 mg, N = 14 mg at 10 mg) Under such circumstances, one could potentially underestimate the risk for various TEAEs by showing the safety experience of predominantly patients who have undergone long-term treatment with APM Considering these observations, I think that the safety experience in patients who were naive to APM may be the most relevant for presentation of the safety risks in patients who initiate APM therapy in product labeling It would also be desirable to look at the TEAE experience of patients in study 202 by separating the TEAEs to in-patient phase and out-patient phase Finally, it would be interesting to combine the in-patient phase safety experience from study APO202 with experience from APM naive patients undergoing the forced dose titration/escalation phase in study 303 However, most of this phase for study APO303 was conducted as open-label treatment

Treatment-Emergent Adverse Events in All Apomorphine-Treated Patients

Table 27 shows the most common organ system classes for the specific TEAEs The top 2 organ systems involved in TEAEs were the nervous and gastrointestinal systems as might be expected

Table 27 Most Common (> 15 % Patients) Primary Organ Class System Involved in Treatment-Emergent Adverse Events By Decreasing Frequency for All Apomorphine Treated Patients in All Trials

Primary Organ Class System	Total # of TEAEs	% Patients[a] with TEAE N = 536
Nervous System Disorders	898	60 %
Gastrointestinal Disorders	571	46 %
Respiratory, Thoracic, Mediastinal Disorders	387	33 %
Psychiatric Disorders	331	32 %
Musculoskeletal, Connective Tissue, Bone Disorders	285	29 %
Infections and Infestations	234	27 %
Administration Site Conditions	185	25 %
General Disorders	402	25 %
Vascular Disorders	154	19 %
Cardiac Disorders	150	17 %

a Incidence (i e %) counts each patient once regardless of the number of episodes of TEAE

The most common specific TEAEs occurring in 10 % of more of all APM-treated patients in descending order were nausea, fall, dyskinesia, dizziness (excluding vertigo), somnolence, yawning, injection site bruising, hallucinations, and vomiting (Table 28) I suspect that the preferred term "dizziness" commonly represents light-headedness which is not a specific preferred term provided and perhaps also includes orthostatic light-headedness from APM-induced decrements in blood pressure Many of the most frequently occurring specific TEAEs shown in Table 28 are also shown as the most common adverse reactions for patients in the APM arm of the randomized, double-blinded, placebo-controlled studies (Table 22, Table 24, Table 25, Table 26) I interpret this overlap as evidence suspporting the view that these TEAEs (most of which occurred in open-label safety study APO401) were likely due to APM treatment This specific safety profile of adverse reactions associated with APM use is not unexpected

I would also like to point out that some reactions (e g dizziness, hypotension, orthostatic/postural hypotension) that have been presented separately may actually be underestimates of the same pathophysiological adverse event This may be true because of the coding "splitting" process and/or the fact that other phenomena associated with the event may not have had the opportunity to be captured For example, a patient who experienced light-headedness/dizziness upon standing because of orthostatic hypotension may not have had a blood pressure check to document orthostatic hypotension and therefore only dizziness was recorded In addition, a patient with hypotension captured as an adverse event while in a hospital setting may not have had the opportunity to develop dizziness because the patient was confined to bed and

did not have the opportunity to exhibit orthostatic hypotension because the patients was not allowed to stand up and have blood pressure checked relative to a supine or sitting position

Table 28 Most Common Treatment-Emergent Adverse Events Presented By Descending Frequency of Preferred Term in All Apomorphine-Treated Patients in All Trials and Occurring in ≥ 4 % Patients

Preferred Term	Total # TEAEs	# Patients (%) a with SAE (N = 536)
Any TEAE	4329	471 (88 %)
Nausea	255	161 (30 %)
Fall	232	117 (22 %)
Dyskinesia NEC	155	110 (21 %)
Dizziness (excluding vertigo)	155	89 (17 %)
Somnolence	137	98 (18 %)
Yawning	163	83 (15 %)
Injection site bruising	97	82 (15 %)
Hallucination NOS	78	66 (12 %)
Vomiting NOS	77	56 (10 %)
Arthralgia	54	47 (9 %)
Depression NEC	48	44 (8 %)
Pain in limb	48	40 (7 %)
Edema lower limb	44	39 (7 %)
Rhinorrhea	64	37 (7 %)
Urinary tract infection NOS	49	37 (7 %)
Back pain	45	37 (7 %)
Skin appendage conditions	50	36 (7 %)
Parkinson's disease aggravated	39	36 (7 %)
Confusion	43	33 (6 %)
Sweating increased	44	32 (6 %)
Ecchymosis	41	31 (6 %)
Fatigue	36	31 (6 %)
Dyspnea NOS	33	31 (6 %)
Constipation	30	28 (5 %)
Diarrhea NOS	31	27 (5 %)
Hypotension NOS	26	23 (4 %)
Pneumonia NOS	29	22 (4 %)
Postural hypotension	27	21 (4 %)
Muscle cramps	23	20 (4 %)
Injection site granuloma	22	20 (4 %)
Abrasion NOS	24	19 (4 %)
Cough	19	19 (4 %)
Neck pain	19	19 (4 %)

11 8 3 Review of Sponsor's Treatment-Emergent Adverse Events (TEAEs) of Special Interest

The sponsor combined similar AE coding terms and reviewed certain TEAEs (e g TEAEs suggestive of falls, possible orthostatic hypotension, postural dizziness) of special interest that might be considered to have been precipitated by APM treatment The sponsor presented very brief narrative summaries of selected cases Some of these cases that were SAEs are reviewed earlier in my narrative summaries (see Reviewer's Selected Treatment-Emergent SAE Narrative Summaries)

TEAEs Suggestive of Falls

Based upon Table 93 0 of the ISS Safety Update, there were 128 patients who experienced 323 events suggestive of falls There were a total of 3 patients who discontinued from study because of one or more of these events and there were 25 SAEs, two of which led to study discontinuation AE terms used to obtain this compilation included fall, abrasion, laceration, and fracture The sponsor did not make any comments here about causality of the 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

TEAEs Suggestive of Orthostatic Hypotension

The sponsor combined AE terms for hypotension, postural hypotension, decreased blood pressure, and/or syncope to assess events possibly suggestive of orthostatic hypotension When these terms were combined, there were 53 patients who experienced 70 events possibly suggestive of orthostatic hypotension There were a total of 11 patients who discontinued from study because of one or more of these events and there were 6 SAEs, two of which led to study discontinuation Correspondingly, 9 TEAEs leading to study discontinuation were non-serious TEAEs according to the regulatory definition of serious 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 event sor 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 coming to the visit Although 2 patients had TEAEs coded with the preferred term of syncope, 8 patients (1 %) treated with APM had events that could essentially be considered as syncope

TEAEs Suggestive of Postural Dizziness

The sponsor's ISS Safety Update Table 94 0 provided a listing of patients suggestive of postural dizziness in the clinical studies AE terms that were combined to form this list of patients included dizziness (excluding vertigo), vertigo, postural dizziness, impaired balance, and feeling

drunk There were125 patients who experienced 203 events possibly suggestive of postural dizziness There were a total of 13 patients who discontinued from study because of one or more of these events and there was only 1 SAE All TEAEs that led to study discontinuation were considered non-serious according to the regulatory definition 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

TEAEs Observed at In-Office Dosing Visits

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

More than three hundred fifty patients had a visit in which in-office dosing after Amendment 2 Approximately 40 % of patients had at least 1 TEAE The pattern of TEAEs was similar to that observed previously before in-office dosing began The most common TEAEs that occurred with in-office dosing were cardiovascular TEAEs particularly those related to heart rate and blood pressure (e g arrhythmias, hypotension, postural hypotension), nausea, vomiting, dykinesia, dizziness, sedation, somnolence, syncope, confusion, and hallucinations I believe that many of these TEAEs were likely related to APM administration

11 8 4 Subgroup Analyses of All Apomorphine-Treated Patients with Respect to Age, Gender, Concomitant Medication, and Apomorphine Dosing

The sponsor conducted various subgroup analyzes of TEAEs causing study discontinuation for age, gender, concomitant medication (e g dopaminergic agonist, COMT inhibitor, vasodilator) and dosing parameters Although analysis was conducted for patients taking and not taking a dopaminergic agonist, this analysis did not seem useful considering that virtually all patients (i e 99 %) were using a dopaminergic agonist Race was not analyzed because most patients were Caucasian

Age

The sponsor commented that TEAEs for hallucinations and confusion were more frequent in patients ≥ 65 years old vs those < 65 years old Hallucinations (16 %) and confusion (12 %) appeared to be relatively common TEAEs that also appeared to be appreciably more likely in elderly patients If one considers TEAEs occurring in at least 10 % of patients and at least 2 fold more frequent as a criterion for comment, falls also achieve this criterion for an age difference Falls were 2 fold more frequent in patients ≥ 65 years old (28 %) compared to younger patients (14 %) below 65 years

Gender

There were no gender differences in frequency of specific TEAEs that seemed striking or worthy of comment

Concomitant Medications

There did not appear to be any significant differences in the occurrence of TEAEs related to the presence of a COMT inhibitor The sponsor noted that there were small increments in the percentage of patients experiencing hypotension, decreased blood pressure or syncope while taking a vasodilator at baseline I did not consider the difference in incidence to be notable for syncope (2 % vs 1 %) and decreased bl ood pressure (11 % vs 7 %) but I did consider the difference in hypotension (9 % vs 3 %) to be notable for patients with a recorded use of a concomitant vasodilator medication

Apomorphine Dosing

The sponsor noted that there did not appear to be any consistent or large difference across groups in terms of frequency of experiencing specific TEAEs based upon the dose of APM at the time of the TEAE or the average frequency of daily injection I concur with the sponsor's views

The sponsor noted that Table 86 0 summarizes TEAEs by time since starting APM therapy but also commented that one should not simply compare incidences of specific TEAEs of the differences in exposure based upon person-years Although the sponsor did not provide a table allowing for such a comparison of the frequency of TEAEs and patients with such events based upon duration of APM exposure, it did note that there was an increased rate of occurrence of certain TEAEs shortly after starting APM These adverse reactions are cardiovascular events including hypotension, syncope, nausea and vomiting, dyskinesia, somnolence, dizziness, confusion, hallucinations, and injection site bruising

I created Table 29 to show the frequency of all types of TEAEs in patients/patient year of APM therapy relative to the time of starting APM therapy This presentation shows rates of TEAEs and

patients experiencing TEAEs adjusted for patient exposure to APM for different periods following the initiation of treatment This presentation is similar to those shown for the development of TEAEs causing study discontinuation and of SAEs 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 (Table 21) These rates are highest during the first 7 days since starting APM and progressively decrease over time and seem to plateau after 30 days since starting APM This plateauing may occur a few months earlier than the plateauing of rates (e g $\geq$ 6 months) that seems to occur for TEAEs prompting patients to drop out of a trial This pattern for these rates contrasts with the pattern observed for SAEs that developed since time of starting APM where both rates did not appear to change over time but rather appeared to be relatively constant since the time APM treatment was started (Table 16)

Table 29 Frequency of TEAEs in Patients Relative to Time Since Starting Treatment with APM

Parameter	Day 1-7 N = 536	Day 8-30 N = 505	Day 31- 180 N = 390	Day 181- 365 N = 321	Day $\geq$ 366 N = 186	Total Any Duration N = 536
# APM Rx PatientYears (P-Y)	10 0	30 7	151 8	128 1	98 1	418 7
# Any TEAE	901	590	1039	699	644	3873
# Pts with TEAE(s) (%)	265 (49 %)	236 (47 %)	221 - 390 [a] (57 - 100 %)	206 (64 %)	131 (70 %)	471 (88 %)
Rate # TEAEs/P-Y	90 1	19 2	6 8	5 5	6 6	9 3
Rate # patients with TEAE/P-Y	26 5	7 7	1 5 – 2 6 [a]	1 6	1 3	0 3

Data Source ISS Safety Update Tables 35 0 and 86 0
a Uncertain of precise number because of possible overlap in patient number between day 31-90 and day 91-180

An analysis was also conducted to evaluate the effect of the specifics of dosing and the setting for initiating APM dosing on adverse reactions within the first 30 days after initiating treatment More specifically, this analysis investigated some APM dosing parameters relative to the development of an SAE or any TEAE within the first 30 days of dosing and the risk of dropping out of a study within the first 30 days after initiating treatment

The initial prescribed dose was ≤ 2 mg in 44 % of patients and > 2 mg up to 4 mg in 34 % of all patients treated The most common initial dose administered was 2 mg Some patients received higher doses ranges initially such as > 4 mg up to 6 mg (15%), > 6 mg up to 8 mg (4 %) and > 8 mg up to 10 mg (2 %) It was not clear why some patients would have started on these relatively high doses (e g > 4mg) There did not appear to be any difference in the distribution of the initial outpatient dose by age (≥ 65 vs < 65) or gender

I created Table 30 which shows the frequency of experiencing a serious adverse event, any adverse event, or an adverse event causing study discontinuation within 30 days of initiating treatment with APM These frequencies are shown relative to the initial dose, the dosing pattern of receiving a single or multiple doses of APM under observation, or starting APM without observation The sponsor's only comment for these data was that there appeared to be tendency to prescribe larger outpatient dose when patients had received multiple doses under observation for the initial dosing

I believe that the data in Table 30 provide some interesting observations Based upon these data of adverse outcomes (e g study discontinuation, SAE, TEAE) in the first 30 days, there did not appear to be a clear overall advantage of administering initial dosing under observation vs not under observation nor of administering a single dose vs multiple doses initially under observation However, the risk for adverse outcomes within the first 30 days of dosing appeared to be a dose-dependent and vary directly with the dose Whereas all these 3 adverse outcomes increased with APM dose when the response to a single dose was observed, there was a dose-dependent risk for developing a TEAE when multiple doses were administered under observation, and a dose-dependent risk for dropping out of the study when initial dosing did not occur under observation In addition, all 3 adverse outcomes were more frequent when the frequency risk for each adverse outcome was averaged across all 3 initial dosing settings The risk for these adverse outcomes overall was lowest in patients initially dosed with < 4 mg APM In general, patients prescribed lower doses initially were more likely to increase their dose later and patients prescribed higher doses initially were more likely to decrease their dose later

Table 30 Frequency of Experiencing Serious Adverse Event, Any Adverse Event, or Adverse Event Causing Study Discontinuation Within 30 Days of Initiating Treatment with Apomorphine Relative to Initial Dose, Dosing Pattern, and Observation Status

Apomorphine Treated Patients in APO401 (N = 508)							
Observation category at initiation visit	Initial Outpatient Dose	# Pts (%) for each observation category	# Dropouts (%) within 30 days	# Pts (%) with SAE within 30 days	# Pts (%) with any AE within 30 days	# Pts (%) with dose decrease within 30 days	# Pts (%) with dose increase within 30 days
Single dose observed at initiation visit N = 139	No outpt dose	1 (1 %)	0 (0 %)	0 (0 %)	1 (100 %)	0 (0 %)	0 (0 %)
	< 4 mg	114 (82 %)	11 (10 %)	2 (2 %)	63 (55 %)	5 (4 %)	36 (32 %)
	4 – < 6 mg	16 (12 %)	3 (19 %)	0 (0 %)	9 (56 %)	1 (6 %)	1 (6 %)
	≥ 6 mg	8 (6 %)	2 (25 %)	1 (13 %)	7 (88 %)	2 (25 %)	1 (13 %)
	Any dose	139 (100%)	16 (12 %)	3 (2 %)	79 (57 %)	8 (6 %)	38 (27 %)
Multiple doses observed at initiation visit N = 105	< 4 mg	30 (29 %)	5 (17 %)	0 (0 %)	17 (57 %)	0 (0 %)	7 (23 %)
	4 – < 6 mg	51 (49 %)	7 (14 %)	3 (6 %)	32 (63 %)	10 (20 %)	12 (24 %)
	≥ 6 mg	24 (23 %)	3 (13 %)	1 (4 %)	18 (75 %)	4 (17 %)	5 (21 %)
	Any dose	105 (100%)	15 (14 %)	4 (4 %)	67 (64 %)	14 (13 %)	24 (23 %)
Dosing not observed at initiation visit N = 264	No outpt dose	5 (2 %)	0 (0 %)	1 (20 %)	3 (60 %)	0 (0 %)	0 (0 %)
	< 4 mg	146 (55 %)	12 (8 %)	1 (1 %)	96 (66 %)	11 (8 %)	73 (50 %)
	4 – < 6 mg	70 (27 %)	4 (6 %)	2 (3 %)	47 (67 %)	15 (21 %)	11 (16 %)
	≥ 6 mg	43 (16 %)	9 (21 %)	0 (0 %)	28 (65 %)	11 (26 %)	8 (19 %)
	Any dose	264 (100 %)	25 (9 %)	3 (1 %)	171 (65 %)	37 (14 %)	92 (35 %)

Percentage are rounded to nearest integer
Data source Sponsor's ISS Safety Update Table 45 1

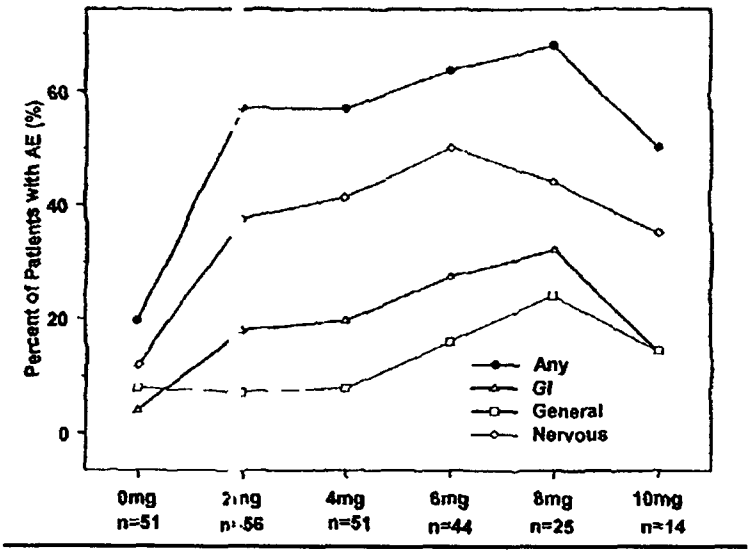
Patients in studies APO202 and APO401 (including substudy APO303) were allowed the option to repeat an injection of APM if a patient had not experienced an adequate therapeutic response by at least 20 minutes after injection I reviewed previously (see section 10 EXPOSURE AND DOSING FOR APOMORPHINE) my concerns about repeat dosing of APM at "short" intervals Allowing patients to repeat dosing at "short" intervals could be unnecessary in some patients if done before 60 minutes and could be associated with significant toxicity that was not captured or appreciated because of the way the sponsor collected and/or presented information Furthermore, data from the trials do not clearly show that patients can easily perceive that they are "On" and that "Off" has resolved after APM treatment despite the fact the UPDRS motor score function testing shows numerically significant and statistically significant changes from baseline Thus, if patients repeated a dose because they did not think that they were yet "On", they could be unnecessarily repeating a dose and exposing themselves to significant toxicity when in fact they would appear to be "On" according to UPDRS motor score function testing It does not seem that the results of UPDRS motor score function testing correlate well with a patient's perception that he or she is "On" and that "Off" has resolved

It would be helpful to know what TEAEs occurred and how frequently in patients who repeated dosing at "short" intervals because of an inadequate therapeutic response to a previous injection It is important to establish what the "safe" minimal dosing interval should be so that this can be described in the dosing section of the label The sponsor did not specify a minimal dosing interval in its proposed label

11 8 5 Dose-Dependent Effect of APM Treatment on TEAEs

There was no PK sampling in patients in the clinical studies Thus, it is not possible to evaluate relationships between plasma APM levels and TEAEs However, patients who were naive to APM treatment were titrated at 2 mg increments (at intervals of 3 days or less) to a single exposure to doses ranging between 2 and 10 mg in study APO303 During this forced titration, many patients experienced TEAEs The dose-dependent frequency of any TEAE and TEAEs of a general nature, and associated with the CNS and gastrointestinal systems is shown in Figure 2 There was a dose-dependent increase in TEAEs that was generally progressive up to 8 mg The frequency of TEAEs then decreased somewhat for patients treated with 10 mg vs 8 mg APM Of interest, the number of patients in each dose group progressively decreased during forced titration exposure from 2 to 10 mg Patient dropout was especially striking at escalation from the 8 mg and 10 mg treatment It is not only theoretically possible but probably the case that patients who dropped out of the dose escalation/titration phase had done so because of the development of TEAEs These patients then proceeded to Evaluation Visit 1 where they would be followed for several months during treatment with an "optimal" dose of APM

Figure 2 Dose-Dependent Effect of Apomorphine on Frequency of Treatment-Emergent Adverse Event in Study APO303



Changes in UPDRS motor function score from pre-dose score were assessed at each dose over time (0, 20, 40, and 90 minutes) under open-label conditions (Figure 3) (except for the 4 mg dose level studied as randomized, double-blinded, placebo-controlled cross-over) Although the mean maximal decrement in UPDRS motor score for the 10 mg group is slightly greater than those for the 6 mg and 8 mg groups, the mean maximal change for the 6 mg group is slightly greater than that for the 8 mg group Overall, the responses to APM at each timepoint appear to be essentially equivalent for the 6 mg and 8 mg groups It is not clear that the overall response of the patients given 10 mg is actually greater than those of patients in the 6 mg and 8 mg dose groups Considering these data, it appears that a 6 mg dose may produce a maximal effect on the percentage decrease in UPDRS motor score (i e motor function improvement) and that higher single doses (e g > 6 mg) may solely or predominantly increase the risk for toxicity with perhaps no or minimal additional therapeutic benefit

The Biopharmaceutical reviewer (Dr John Duan) used the UPDRS motor function score data in a program simulating pharmacodynamic effects Figure 4 presents the results of entering data collected under open-laabel conditions from study APO073 into this program to assess the shape of the dose-response curve for efficacy As can be seen, APM doses ≥ 6 mg appear to produce a similar maximal effect on the absolute decrease in UPDRS motor function score Thus, based upon results in this simulated model, there seems to be no additional benefit of injecting a single dose above 6 mg to achieve the maximal decrease in UPDRS motor fiction score However, this model does suggest that the duration of the decrease in UPDRS motor score is dose-dependent for all single doses between 1 to 9 mg It is then debatable from a risk benefit prespective to ask how much additional therapeutic benefit is gained in terms of obtaining a longer duration of motor function improvement relative to the risk of increased dose-dependent toxicity by using single doses of APM above 6 mg Extrapolations from this simulation would suggest that the duration of motor function improvement is relatively small (e g several minutes) compared to the potential risk of increased toxicity with doses above 6 mg