

Study AP302 was a substudy of patients who had been treated in Study APO401 for at least 3 months. Study APO302 was a double-blinded, placebo-controlled parallel group study that evaluated the efficacy of APM or placebo treatment and also the effects of APM on 12 lead EKGs and orthostatic VS responses with respect to dosing in 4 groups of patients. Patients were randomized to receive either 1) their usual dose of an APM injection, 2) their usual dose of an APM injection + 2 mg up to a maximal dose of 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. Study APO302 was primarily designed to evaluate efficacy and safety parameters under double-blinded, placebo-controlled conditions of patients who had chronically been treated with APM for ≥ 3 months. There were some distinctive differences between studies APO302 and APO301 both of which were controlled studies assessing the ability of APM to provide benefit by reversing "Off" after prolonged period of repeated injections with APM. Study APO302 employed a parallel group study design instead a cross-over design used by Study 301. In addition, Study 302 investigated efficacy at both earlier (2.5 minutes) and later (90 minutes) timepoints than the earliest (10 minutes) and latest (60 minutes) timepoints evaluated in Study APO301.

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Table 7 Schedule of Events for Open-Label Safety Study APO401

PROCEDURE	BASELINE		ACTIVE APOMORPHINE THERAPY PHASE			
	Baseline Visit 1	Baseline Visit 2	Dose Adjustment (PRN)	Routine 1 month	Routine Every 4 months	Exit Procedures
Medical Records Review	•					
Drug History/Diet Review	•					
Concomitant Medications	•	•	•	•	•	•
Informed Consent	•					
Update Consent Yearly						
Diary Instructions	•	•	•	•	•	
Dispense Diary	•	•		•	•	
Diary Review		•		•	•	•
Record Diary ³	•			•	•	•
Investigator Survey of Patient Apomorphine Dosing Frequency			• (In-office visit only)	•	•	•
Complete Physical Exam	•					•
Review of Systems				•	•	
12-Lead ECG ⁵	•				•	•
Fasting Labs/Blood Urine ¹	•				•	•
Serum Pregnancy Test ²	•				•	•
Coombs Test ¹	•				•	•
Vital Signs	•	•	•	•	•	•
Orthostatic Monitoring ⁴	•	•	•	•	•	•
Dispense Trimethoprim	•			•	•	
Apomorphine Dose Titration		•	•	•	•	
Dispense Study Medication		•		•	•	
Hoehn and Yahr Stage	•			•	•	•
UPDRS	•			•	•	•
Adverse Event Assessment		•	•	•	•	•

¹Repeat labs once if necessary
²For women of childbearing potential practicing a medically supervised form of birth control
³Record diary for at least 3 days between Visit 1 and Visit 2. Record diary 2 days prior to and 2 days after routine visits. Record 2 days prior to (only) exit visit.
⁴Supine and standing systolic and diastolic blood pressure and pulse measurements. Orthostatic monitoring performed before and after apomorphine titration to occur at Baseline visit 2, any visit where titration occurs, or when it is clinically relevant.

The bulk of the prospectively collected safety experience is derived from open-label, uncontrolled study conditions. The extent of study under double-blind, placebo-controlled conditions is relatively small as can be seen in Table 8. Controlled safety experience was

collected only for approximately 732 patient-days for APM and only for approximately 375 patient-days for placebo

Table 8 Summary of Number of Patient Days During Which Safety Experience Was Collected in Double-Blind, Placebo-Controlled Conditions

Study	Double-Blind, Placebo-Controlled Treatment		# Treatment Days	# Patient Days Studied ^b	
	APM	Placebo		APM	Placebo
APO202	18 ^a	8 ^a	35 ^b	630	280
APO301	16	17	1	16	17
APO303	51	51	1	51	51
APO302	35	27	1	35	27
Total	120	103		732	375

a Not including 3 patients (2 APM , 1 placebo) treated only during in-patient phase for few days

b Approximate number under double-blinded, placebo-controlled conditions

11.3 Summary of Process for Collecting and Analyzing Adverse Events (AEs)

Investigators were supposedly instructed to consider any event (sign, symptom, or disease) that developed during the study as a treatment-emergent-adverse event (TEAE) An AE occurring up to 30 days after study discontinuation was considered to be a TEAE Diagnoses and symptoms that were present at baseline were defined as TEAEs only when they increased in severity Investigators were supposed to record the start time, ending time, duration, severity, and assessed causality on case report forms (CRFs) During the development program, standard data collection was modified for serious adverse events (SAEs) to include information on the timing of the event relative to the last APM dose and the sponsor queried sites when this information was missing Any ongoing adverse event (AE) at study exit was supposed to have a 30 day follow-up TEAEs were supposed to be followed until resolution of at least stability of the TEAE For patients who were studied in an outpatient setting, TEAEs were discovered not only passive reporting by patient or patient care-giver but also observation of some patients after dosing in the office

Investigators were supposed to classify AEs with regard to the potential causality (i.e attribution) of the AE to study medication according to one of 5 categories

- Definitely related temporally associated, observation can be related to known pharmacological effects(s) of the drug, relationship very likely, no obvious alternative etiology
- Probably drug-related temporally associated and relationship likely
- Possibly drug-related temporally associated, no obvious alternative etiology

- Remotely drug-related not temporally associated, alternative etiology possible
- Definitely not drug-related not temporally associated, alternative etiology probable

AEs were recorded on CRFs for reporting to the sponsor. For analyses of AEs, verbatim terms were coded according to a MeDRA version 2.4 dictionary to high level group and preferred terms.

The sponsor presented various subgroup analyses of all AEs according to any APM exposure, treatment in a controlled trial, age, gender, APM dose, frequency of dosing, duration of APM treatment and types of concomitant medications (i.e. dopaminergic agonist, COMT inhibitor, vasodilator). To assess the frequency of APM dosing, all investigators were surveyed in 11/01 to note the average frequency of APM use for the previous month. I have presented information selectively from these subgroup analyses when there is a point to be made.

In Study APO401 (the main study for collecting safety data), physicians were instructed to count recurrent or episodic events that occurred during the study as AEs even if the patient had a history of such events at baseline/pre-treatment. Investigators had the option of coding episodic events AEs that occurred ≥ 3 times in a patient as "intermittent" not entering a new AE for the same AE unless it changed in severity. However, Bertek discovered during the study that some investigators were not considering episodic events (e.g. falling) to be AEs if the patient had a history of such events at baseline/pre-treatment. The sponsor then informed investigators to count such events as AEs if the patient had a history of such events at baseline. The sponsor noted that "the sites were required to check source documents to identify any falls that may not have been reported. The sites then reported these events as treatment emergent events."

This appeared to be a deviation from the standard approach of considering any increased frequency or severity of an event present at baseline/pre-treatment as a TEAE in addition to considering any newly developing untoward event as an AE. This deviation could have resulted in missing events as TEAEs. Consequently, I asked the sponsor: How could it provide assurance that AEs not initially recorded by some investigators were comprehensively recalled by the investigator and comprehensively captured in the database? The sponsor responded that investigators had been instructed to report events present at baseline or in the past if they demonstrated an increased frequency or severity. The sponsor further noted that it became concerned that investigators ought to be capturing events such as falls occurring with increased frequency routinely, but they might be attributing the falls to the patient's background condition rather than possibly to study medication. This practice could result in under-reporting the incidence rate of recurring events such as falls. Finally, the sponsor concluded that by bringing this to the attention of investigators it was the sponsor's belief that it had captured prospectively and retrospectively all available data from source documents on CRFs. Despite this response, I still believe that it is difficult to know how comprehensively events recurring with increased frequency or severity during study were captured as adverse events, particularly those that had occurred before investigators were notified and reminded about this issue.

11.4 Baseline Demographic and Parkinson's disease Characteristics of Patients in Safety and Efficacy Populations

There were 536 patients in the clinical studies. More than half of the patients in the trials were male and (97 %) of all patients were Caucasian. Only 10 % of patients used a tobacco product and approximately 97 % reported their alcohol use as none or rare. The sponsor also provided additional information in the ISS about particular concomitant medication use at baseline. Almost all patients (532, 99 %) had a dopaminergic agonist prescribed. The percentage of patients using a catechol-ortho-methyl transferase (COMT) inhibitor was 42 % (225) and the percentage of patients using a vasodilator (including Viagra/sildenafil) was 17 % (93).

I asked the sponsor to provide specific baseline information on demographic and disease characteristics of all patients treated with APM and patients treated in pivotal trials. At the time of the request we had not recognized that Study 302 should be considered a pivotal trial because the sponsor had never specifically identified this trial as a pivotal one for efficacy in the NDA. All the sponsor's mention of "pivotal" trials within the NDA only referred to studies 202, 301, and 303. Thus, the sponsor's recent submission (end of 5/03) of the requested information for pivotal trials only includes data on patients in studies 202, 301, and 303. The sponsor will eventually amend these data to include information on patients in study 302.

The requested information is shown in Table 9 and Table 10. As can be seen in these tables, the average patient had late stage Parkinson's disease that had been present for 11 years and was associated with significant dysfunction (e.g. UPDRS scores, total "Off" hours, % of daily "Off"). The characteristics of patients in the pivotal trials appeared to be similar to the characteristics of all APM-treated patients in any trial. There did not appear to be a significant or notable change in these characteristics of all patients or of patients in pivotal trials according to the duration of treatment. Thus, the profiles appeared to remain relatively constant regardless of the duration that patients participated in trials.

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Table 9 Baseline Disease and Demographic Characteristics of All APM-Treated Patients

Parameter	Any Treatment	Treatment >= 3 months	Treatment >= 6 months	Treatment >= 12 months
Boehr & Yahr Stage				
N	52 000	375 000	308 000	190 000
Mean	3 01	2 985	2 971	2 895
25th Percentile	2 000	2 000	2 000	2 000
Median	3 000	3 000	3 000	3 000
75th Percentile	3 000	3 000	3 000	3 000
Maximum				
Age				
N	536 000	378 000	311 000	192 000
Mean	65 174	64 534	64 193	64 370
Minimum	38 000	38 000	38 000	39 000
25th Percentile	58 000	57 000	57 000	57 000
Median	66 000	65 000	66 000	66 000
75th Percentile	73 000	72 000	71 000	71 000
Maximum	99 000	99 000	99 000	99 000
UPDRS total (ON)				
N	422 000	1 000	253 000	150 000
Mean	53 296	52 131	51 542	49 967
Minimum				
25th Percentile	3 000	36 000	36 000	36 000
Median	53 000	51 000	48 000	47 000
75th Percentile	67 000	65 000	64 000	63 000
Maximum				
UPDRS total (OFF)				
N	83 000	62 000	55 000	40 000
Mean	63 163	64 694	63 964	66 150
Minimum				
25th Percentile	46 000	49 000	42 000	52 000
Median	61 000	64 000	64 000	66 000
75th Percentile	82 000	83 000	83 000	8 000
Maximum				
UPDRS Section III (ON)				
N	437 000	315 000	255 000	152 000
Mean	27 547	27 043	26 459	25 342
Minimum				
25th Percentile	17 000	7 000	16 000	17 000
Median	20 000	25 000	24 000	24 000
75th Percentile	36 000	35 000	35 000	32 500
Maximum				
UPDRS Section II (OFF)				
N	104 000	69 000	61 000	44 000
Mean	37 135	37 043	36 672	38 818
Minimum				
25th Percentile	26 000	27 000	26 000	27 000
Median	36 500	35 000	35 000	35 500
75th Percentile	47 000	47 000	47 000	50 000
Maximum				
Years with PD				
N	36 000	378 000	311 000	192 000
Mean	1 216	1 239	11 465	11 875
Minimum	0 000	0 000	0 000	0 000
25th Percentile	7 000	7 000	7 000	8 000
Median	11 000	0 000	1 000	11 000
75th Percentile	14 000	14 000	5 000	15 000
Maximum	38 000	38 000	38 000	38 000
Daily OFF (hrs)				
N	102 000	67 000	54 000	24 000
Mean	6 72	6 773	6 947	6 817
Minimum				
25th Percentile	4 724	4 800	4 000	4 000
Median	6 300	6 000	6 500	6 800
75th Percentile	8 500	8 023	8 500	9 250
Maximum				
Daily % OFF of waking hrs				
N	102 000	67 000	54 000	24 000
Mean	39 53	8 659	40 399	37 003
Minimum				
25th Percentile	28 402	29 412	31 250	22 785
Median	36 600	5 294	7 457	34 471
75th Percentile	5 000	45 714	49 101	49 550
Maximum				

Note 1 includes Studies APO202, APO30, APC3C2, APO303, and APO401.
 Note 2 Four patients in APO202 and 1 patient in APO301 never received Amonorphine and are not included in this table.
 Note 3 For patients in both APO202 and APO401 the APC2C2 baseline data was used.
 Note 4 Total UPDRS (ON or OFF) was only collected in study APO401.
 Note 5 Daily OFF (hrs) and Daily % OFF of waking hrs were derived from patient diaries.

Baseline data were not collected for patients in APO301 or for patients in APO401 (or substudies APO302 or APO303) prior to protocol amendment 4012.
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Table 10 Baseline Disease Characteristics of Patients in Pivotal Trials

Parameter	Any Treatment	Treatment >= 3 months	Treatment >= 6 months	Treatment >= 12 months
Hoehn & Yahr Stage				
N	85 000	51 000	41 000	9 000
Mean	3 141	3 098	3 46	2 778
Minimum	2 000	2 000	2 000	000
25th Percentile	3 000	2 000	2 000	2 000
Median	3 700	3 000	3 000	2 000
75th Percentile	4 000	4 000	4 000	4 070
Maximum				
Age				
N	97 027	51 000	41 000	9 000
Mean	65 74	64 529	65 244	65 000
Minimum	45 000	50 000	50 000	54 000
25th Percentile	59 000	58 000	59 000	62 000
Median	65 000	64 000	6 000	64 700
75th Percentile	72 000	73 000	4 000	68 000
Maximum	82 000	82 000	82 000	79 0 0
UPDR Total (ON)				
N	63 000	47 000	37 000	7 000
Mean	4 556	55 000	53 649	47 286
Minimum	0 000	0 000	0 000	0 000
25th Percentile	36 000	3 000	33 000	31 000
Median	54 000	54 000	48 000	48 000
75th Percentile	66 000	72 000	69 000	57 000
Maximum				
UPDRS Total (OFF)				
N	6 000	4 000	4 000	2 000
Mean	75 333	77 7 0	77 750	65 500
Minimum	0 000	0 000	0 000	0 000
25th Percentile	64 000	65 500	65 500	64 000
Median	74 500	76 000	6 000	65 500
75th Percentile	85 000	90 000	90 000	67 000
Maximum				
UPDRS Section III (ON)				
N	0 000	0 000	0 000	0 000
Mean	24 808	27 182	25 437	0 000
Minimum	0 000	0 000	0 000	0 000
25th Percentile	14 000	14 0 0	13 000	9 000
Median	22 500	25 0 0	22 000	20 000
75th Percentile	32 000	35 000	35 000	23 000
Maximum				
UPDRS Section III (OFF)				
N	47 000	1 000	10 000	6 000
Mean	0 000	0 000	0 000	0 000
Minimum	1 000	1 000	2 000	21 700
25th Percentile	36 000	40 000	40 000	28 700
Median	41 000	42 000	41 000	43 000
75th Percentile	47 000	46 000	46 000	47 000
Maximum				
Years with PD				
N	97 00	5 000	41 000	9 000
Mean	1 165	9 961	10 366	6 5 6
Minimum	0 000	0 000	0 000	0 000
25th Percentile	7 000	6 000	7 0 0	5 000
Median	1 000	9 000	0 000	7 000
75th Percentile	15 000	14 000	14 000	9 000
Maximum	26 000	25 000	25 00	11 000
Daily OFF (hrs)				
N	0 000	75 000	20 000	7 000
Mean	6 206	6 248	6 000	6 000
Minimum	0 000	0 000	0 000	0 000
25th Percentile	4 595	4 800	4 673	4 000
Median	5 922	6 500	5 922	5 375
75th Percentile	7 750	7 500	7 765	8 029
Maximum				
Daily % OFF of waking hrs				
N	44 000	25 000	20 000	7 000
Mean	36 443	30 923	36 870	33 098
Minimum	0 000	0 000	0 000	0 000
25th Percentile	28 090	3 952	30 694	21 858
Median	33 973	37 519	33 118	32 7 7
75th Percentile	43 308	42 373	45 37	49 101
Maximum				

Note Includes Studies APO202 APO301 and APO303
 Note Four patients in APO202 and 1 patient in APO301 never received Apomorphine and are not included in this table
 Note Total UPDRS (ON or OFF) was only collected in study APO401
 Note Daily OFF (hrs) and Daily % OFF of waking hrs were derived from patient diaries. Baseline diaries were not collected for patients in APO301 or for patients in APO401 for substudies APO302 or APO303 prior to protocol amendment 401 02

11.5 Deaths

There were 10 deaths reported in the ISS and an additional 4 deaths reported in the ISS Table 12 is a listing of all these deaths All deaths occurred in open-label, study APO401 None of the deaths were considered by the investigator sponsor to be related to study medication Many deaths occurred well after the last dose of study medication Important details about APM dosing were missing from some cases

11.5.1 Tabular Listing of Deaths

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Table 12 Listing of Deaths

Pt ID	Age/ Sex	Adverse Event	Onset ^a (days)	Study Days ^b	Time from last APM dose to AE ^c	APM Dose (mg)	Investigator Relatedness Assessment	Reviewer's Comments
Original NDA								
APO401/ 01/004* APO202 *	82/F	death	0	554	8 days	2.5	definitely not/ Unlikely	Death was believed to be due to natural causes Unlikely accident caused by APM considering long interval after APM injection
APO401/ 01/008	69/M	feet fractures, respiratory and renal failure leading to death	25	589	few weeks	5.0	remote	There was no description of how the patient had sustained the fractures Neither was there any description of how respiratory and renal failure that contributed to death had occurred Without knowing details how feet fractures occurred and relationship to last APM injection it is difficult to exclude a possible contributory role of APM. Conceivably APM could have caused orthostatic hypotension that resulted in the accident and feet fractures
APO401/ 05/004	83/F	pneumonia (possible aspiration), cardioresp- iratory failure leading to death	4	161	11 days	not spec- ified	definitely not	No pertinent negatives of no nausea and vomiting to exclude possible aspiration of emesis with last APM and that treatment could have resulted in aspiration pneumonia.
APO401/ 13/005	52/M	cardiac arrest leading to anoxic encephalo- pathy and death	9	207	6 weeks	2	definitely not	Patient died in hospital from complications of cardiac arrest experienced at home Unlikely accident caused by APM considering long interval after APM injection
APO401/ 31/004	76/F	pneumonia complicat- ed by pneumo- thorax and death from respiratory arrest	21	41	1 day	4.0	not related	No pertinent negatives of no nausea and vomiting to exclude possible aspiration of emesis with last APM and that treatment could have resulted in aspiration pneumonia

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Pt ID	Age/ Sex	Adverse Event	Onset ^a (days)	Study Days ^b	Time from last APM dose to AE ^c	APM Dose (mg)	Investigator Relatedness Assessment	Reviewer's Comments
Original NDA								
APO401/ 37/004	60/M	motor vehicle accident leading to death	10	161	28 days	4 0	definitely not	Details not provided how motor vehicle accident occurred Unlikely accident was caused by APM considering long interval after APM injection
APO401/ 38/007 APO303	72/F	pneumonia leading to death	4	63	not speci- fied	4 0	definitely not	No pertinent negatives of no nausea and vomiting to exclude possible aspiration of emesis with last APM and that treatment resulted in aspiration pneumonia
APO401/ 43/005	79/M	aspirated meat developed collapsed left lung and multiple medical complicat- ions leading to death	6	81	not speci- fied	1 5	definitely not	In the absence of details about APM use prior to aspirating the meat, it is difficult to exclude the possibility that APM played a role in this aspiration. Conceivably the patient could have experienced hypotension and/or a cardiac arrhythmia that prompted the aspiration that ultimately led to death
APO401/ 54/006	63/F	death	0	107	17 hours	2 0	definitely not	Investigator speculated death may have been caused by cardiac arrest or pulmonary embolism. Unlikely death was caused by APM considering long interval after APM injection
APO401/ — 007	75/M	death	0	150	4 hours	4 0	definitely not	Unlikely death was caused by APM considering relatively long interval after APM injection. Furthermore, there is no mention that the patient had been having any problems while his wife was with the patient
Safety Update								
APO401/ 13/011	74/F	death	0	363	13 days	0	definitely not	It was speculated that patient died in hospice setting of cardiac arrest secondary to end-stage Parkinson's disease Unlikely death was caused by APM considering long interval after APM injection

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Pt ID	Age/ Sex	Adverse Event	Onset ^a (days)	Study Days ^b	Time from last APM dose to AE ^c	APM Dose (mg)	Investigator Relatedness Assessment	Reviewer's Comments
APO401/ 23/012 APO302 P	71/M	aspiration pneumonia	5	680	1 day	2 0	remote	No pertinent negatives of no nausea and vomiting to exclude possible aspiration of emesis with last APM and that treatment resulted in aspiration pneumonia.
APO401/ 28/001	57/M	cardiac arrest, death	28	41	2 5 hours	4 0	definitely not	The general timeframe for considering toxic pharmacodynamic actions is ≤ 2 hours. However, it seems that it is not possible to exclude an effect from APM given the relatively close onset of cardiac arrest. This patient had experienced severe peri-operative blood loss and could have developed hepatic and/or renal insufficiency. Conceivably, the patient could have experienced decreased clearance of APM and thus higher than usual plasma levels of APM leading to the arrest.
APO401/ 36/008	72/F	death	0	393	12 hours	4 0	definitely not	Unlikely death was caused by APM considering relatively long interval after APM injection.

^a Number of days from onset of AE associated with or leading to death until death

^b Study days = AE onset - date of first APM dose + 1

^c Time from last APM dose until onset of AE

11.5.2 Narrative Description of Deaths

I have reviewed all the sponsor's narrative descriptions of deaths and have provided narrative summaries here:

Patient APO/401/004*APO202*A was an 82-year-old woman who was enrolled in the open-label safety study (APO401) after participating in the controlled study APO202 and who died at her home of presumably natural causes. She had a history of atrial fibrillation, orthostatic hypotension, pedal edema, and hypothyroidism. Her last dose (2.5 mg) of APM was 8 days prior to her death. There was no autopsy. This patient had been using an average dose of 2.4 mg of APM with a frequency of 3.3 times daily and had been in study APO401 for 554 days. During the study, she had experienced an SAE consisting of a fall resulting in a hip fracture 4 hours after APM and went on to have surgical repair several months earlier. She also had SAEs of rectal bleeding and a feeding tube becoming dislodged. Concomitant medication at the time of death included Sinemet IR and CR, pramipexole, ASA, conjugated estrogens, levothyroxine, bisacodyl,

hydrocodone, zalepon, and milk of magnesia. Her death was considered not related to study medication

Reviewer's Comment Unlikely accident caused by APM considering long interval after APM injection

Patient APO401/01/008 was a 69 year-old man who was enrolled in the open-label safety study (APO401) and who died of respiratory and renal failure approximately 3 weeks after sustaining a left ankle and right foot fracture that resulted in hospitalization. He had a history of type 2 diabetes mellitus, obstructive and central sleep apnea, pulmonary hypertension, congestive heart failure and hypertension. Details were not known about how the patient sustained both fractures. This patient was not considered to be a candidate for surgical repair of his fractures. His last dose of APM was a few weeks prior to his death but it was not specified when his last dose of APM was relative to sustaining the fractures. This patient had been using an average dose of 4.8 mg of APM with an average frequency 3 times daily and had been in study APO401 for 589 days. He had an SAE consisting of a basal cell carcinoma of the ear. Concomitant medications at the time of death included Sinemet IR and CR, ropinirole, Vasotec, Celebrex, coumadin, Nitro patch, Calan SR, and allopurinol. His death was considered remotely related to study medication.

Reviewer's Comment Without knowing details how feet fractures occurred and relationship to last APM injection, it is difficult to exclude a possible contributory role of APM. Conceivably, APM could have caused orthostatic hypotension that resulted in an accident and feet fractures.

Patient APO401/05/004 was an 83 year-old woman who was enrolled in the open-label safety study (APO401) and who died from cardiorespiratory failure and pneumonia. She had a history of mitral and aortic valvular insufficiency, osteoporosis with spinal compression fracture, falling, anemia, S/P skin cancer resection, S/P hysterectomy and ectopic pregnancy, and S/P cataract surgery. The patient was rushed to the hospital with severe dyspnea believed due to respiratory failure from congestive heart failure and possible aspiration pneumonia. The chest X-ray showed right upper lobe pneumonia. The patient was intubated and admitted to an ICU where she received mechanical ventilation. She died after mechanical ventilation was removed 4 days after admission. Her last dose of APM was 11 days prior to her death. This patient had been using an average dose of 4.3 mg of APM with average frequency of 0.5 times daily and had been in study APO401 for 83 days. Concomitant medications at the time of death included Sinemet IR and CR, pergolide, Ismo, metoprolol, Prilosec, acetaminophen, and vitamin E. Her death was considered not related to study medication.

Reviewer's Comment In the absence of details about the patient's last APM use and why it was discontinued, it is difficult to know if APM played any role in the complications that eventually resulted in death. For example, it is possible that the patient could have experienced nausea and vomiting from APM use prior to its discontinuation and could have aspirated. However, it seems unlikely that the patient would have been home for 11 days with a pneumonia from aspirating.

emesis without needing to seeking medical help during that whole time

Patient APO401/13/005 was a 52 year-old man who was enrolled in the open-label safety study (APO401) and who died from complications of a cardiac arrest at home. He had a history of left pallidotomy and left subthalamic brain stimulation. His last dose (2 mg) of APM was approximately 6 weeks prior to his death because he ran out of study drug. After suffering an apparent cardiac arrest at home, he was admitted to a hospital with asystole. He exhibited anoxic encephalopathy with deep coma, fevers, and died 9 days after admission. This patient had been using an average dose of 2 mg of APM with an unknown daily average frequency of injection and had been in study APO401 for 207 days. Concomitant medications at the time of death included Sinemet, pergolide, metamucil, and trimethobenzamide. His death was considered not related to study medication.

Reviewer's Comment Unlikely accident caused by APM considering long interval after APM injection

Patient APO401/13/011 was a 75 year-old woman who was enrolled in the open-label safety study (APO401) and who died in a hospice of cardiorespiratory arrest secondary to her end stage Parkinson's disease. There was no autopsy. She had a history of systolic orthostatic hypotension, slight glucose intolerance, monoclonal gammopathy of unknown significance, rheumatoid arthritis, possible scleroderma, anxiety/depression, S/P hysterectomy for endometriosis, fibroids, and dysmenorrhea, bladder polyps, and asthma (no recent attacks). Her last dose of APM was 13 days prior to her death. APM had been discontinued because it no longer seemed helpful. This patient had been using an average dose of 1.9 mg of APM with average frequency of 7 times daily and had been in study APO401 for 334 days. Concomitant medications at the time of death included Sinemet, ropinirole, diazepam, sertraline, atenolol, glycerine suppository, acetaminophen, milk of magnesia, and estrogen. Her death was considered not related to study medication.

Reviewer's Comment It was speculated that patient died in hospice setting of cardiac arrest secondary to end-stage Parkinson's disease. Unlikely death was caused by APM considering long interval after APM injection.

Patient APO401/37/004 was a 60 year-old man who was enrolled in the open-label safety study (APO401) and who died in a motor vehicle accident that "was not his fault." There was no history of significant medical problems. The patient was in a motor vehicle accident 28 days after the last injection of APM. He was found unresponsive, admitted to a hospital with multiple injuries and died 10 days later from hemodynamic instability, sepsis, and acute renal failure. This patient had been using an average dose of 5.7 mg of APM with average frequency of 4.1 times daily and had been in study APO401 for 121 days. He had discontinued from study due to AEs of delusions and increasing agitation. Concomitant medications at the time of death included Sinemet, ropinirole, selegiline, Buspar, Seroquel, and ibuprofen. His death was considered not related to study medication.

Reviewer's Comment Unlikely accident was caused by APM considering long interval after APM injection

Patient APO401/38/007(APO303) was a 72 year old woman who was enrolled in the open-label safety study (APO401) and who died 4 days after hospitalization for pneumonia. She had a history of S/P pallidotomy, hypothyroidism, urinary incontinence, insomnia, "arthritis," and blurred and double vision. The patient was hospitalized for cough, congestion, and shortness of breath and was diagnosed with pneumonia with infiltrates on her chest X-ray. She was treated with oxygen, and antimicrobial therapy and placed on a mechanical ventilator on the next day. The patient asked to come off the ventilator because she was doing better and did not like it and was removed from the ventilator. Later in the day the patient deteriorated but the family decided not to reintubate the patient and place her on the ventilator again. She was also noted to have a hemoglobin of 7.5 that prompted treatment with packed RBCs. Her condition continued to deteriorate and she died 4 days after admission. Her APM dosing history in the immediate period prior to admission was not specified. However, she continued to receive APM in the hospital for until 2 days prior to her death. The final cause of death was noted to be pneumonia, *Staphylococcus capitis*, and Parkinson's disease. This patient had been using an average dose of 4 mg of APM with average frequency of 4.8 times daily and had been in study APO401 for 60 days. Concomitant medications at the time of admission included Sinemet, IR and CR, entacapone, and pramipexole. Her pneumonia and death were considered definitely not related to study medication.

Reviewer's Comment In the absence of details about the patient's last APM use and why it was discontinued, it is difficult to know if APM played any role in the complications that eventually resulted in death. For example, it is possible that the patient could have experienced nausea and vomiting from APM use and could have aspirated.

Patient APO401/43/005 was a 79 year-old man who was enrolled in the open-label safety study (APO401) and who died apparently from aspirating a piece of meat while eating. He had a history of intermittent falls, symptomatic orthostatic hypotension, urinary incontinence, benign prostatic hypertrophy, macular degeneration, claustrophobic depression, and "arthritic" symptoms in the shoulder and hands. There was no specification of when the last dose of APM was administered prior to his event or death nor if APM was given in the hospital. The patient was intubated in the ER and his chest X-ray showed complete atelectasis of the left lung consistent with obstruction. The patient also had copious pharyngeal secretions. During bronchoscopy the meat was visualized, was removed and the patient showed improvement. The patient subsequently experienced complications including bilateral pneumonia, possible pleural effusion, episodes of atrial fibrillation, with rapid ventricular response, hypotension, subdural hematoma and prerenal azotemia, and died 6 days after admission. This patient had been using an average dose of 1.5 mg of APM with average frequency of 1.2 times daily and had been in study APO401 for 75 days. Concomitant medications at the time of admission included Sinemet IR and CR, pergolide, and Flornef. His death was considered not related to study medication.

Reviewer's Comment In the absence of details about APM use prior to aspirating the meat, it is difficult to exclude the possibility that APM played a role in this aspiration. Conceivably, the patient could have experienced hypotension and/or a cardiac arrhythmia that prompted the aspiration that ultimately led to death.

Patient APO401/54/006 was a 63 year-old woman who was enrolled in the open-label safety study (APO401) and who died unexpectedly from an unknown cause. The investigator speculated the cause of death was cardiac arrest or pulmonary embolism. She had a history of "low B-12", degenerative joint disease, polyneuropathy and depression. Her last dose of APM was at noon on 9/24/01, approximately 17 hours prior to her death. There was no autopsy. This patient had been using an average dose of 2 mg of APM with average frequency of 2 times daily and had been in study APO401 for 105 days. She had also previously experienced SAEs of pneumonia (3 months earlier), and severe anemia (Hgb 5.7 and Hct 18). Although the patient had been hospitalized 8 days prior to her death for the anemia and received blood transfusion, a specific cause of the anemia was not identified. Concomitant medications at the time of death included Sinemet IR and CR, ropinirole, tolcapone, prednisone, Celexa, cyclobenzaprine, Celebrex, Neurontin, trimethobenzamide, Pepcid, Xanax, and Demerol. Her death was considered not related to study medication.

Reviewer's Comment Unlikely death was caused by APM considering long interval after APM injection.

Patient APO401/ — 007 was a 75 year-old man who was enrolled in the open-label safety study (APO401) and who died unexpectedly at home. He had a history of hypertension, intermittent "orthostasis", falls, psoriasis, nocturnal incontinence, and bilateral knee "arthritis" and carpal tunnel syndrome. His last dose of APM was 4 hours prior to his death. The patient's wife was sitting with the patient and after she left the room and returned, the patient had "passed away". The coroner's report indicated that the patient had arrested en route to the hospital. The autopsy report noted that the probable cause of death was cardiac arrhythmia due to extensive fibrotic myocarditis of uncertain etiology with mild non-specific pulmonary congestion and edema. This patient had been using an average dose of 3.2 mg of APM with average frequency of 1.4 times daily and had been in study APO401 for 149 days. Concomitant medications at the time of death included pergolide, metoprolol, Sinemet, and trimethobenzamide. His death was considered not related to study medication.

Reviewer's Comment Unlikely death was caused by APM considering relatively long interval after APM injection. Furthermore, there is no mention that the patient had been having any problems while his wife was with the patient just prior to death.

Patient APO401/23/012*APO302*P was a 73 year-old man who was enrolled in the open-label safety study (APO401) and who died from aspiration pneumonia and deterioration of Parkinson's disease manifested by poor responsiveness to usual medications. He had a history of exertional dyspnea, S/P left shoulder surgery, urinary frequency, "clogged" artery left leg, constipation, heartburn, and ulcer. Ten days prior to the patient's death, the patient was

hospitalized for vertigo and treated. The patient was then transferred on the next day to a skilled nursing where he continued to receive APM 2 mg 2-3 times daily. One day after the last dose of APM, the patient was hospitalized for increased, dyspnea, cough, increased difficulty swallowing and hypoxemia. The patient was treated for possible aspiration pneumonia. Eventually his chest X-ray showed bilateral pneumonia. His overall condition deteriorated rapidly as he became poorly responsive to his usual Parkinson's disease medications. The patient also developed complications of right leg deep venous thrombosis, possible pulmonary embolism, and post-obstructive, acute renal insufficiency. The patient died 5 days after admission that was one day after last APM injection. This patient had been using an average dose of 2 mg of APM with average frequency of 1.9 times daily and had been in study APO401 for 672 days. Concomitant medications at the time of death included Sinemet IR and CR, Lodosyn, selegiline, entacapone, amantadine, ASA, Benedryl, Detrol, and Ditropan. His death was considered remotely related to study medication.

Reviewer's Comment In the absence of details about the patient's last APM use, it is difficult to know if APM played any role in the complications that eventually resulted in death. For example, it is possible that the patient could have experienced nausea and vomiting from APM use and could have aspirated. There were no pertinent negatives such as no nausea or vomiting with his most recent APM use. However, it is also possible that the patient had swallowing problems from Parkinson's disease that could have increased the risk of aspiration.

Patient APO401/28/001 was an 58 year-old man who was enrolled in the open-label safety study (APO401) and who died of cardiac arrest on the second post-operative day from spinal surgery (spinal fusion and laminectomy). He had a history of eczema, insomnia, and constipation. The perioperative period was complicated by major blood loss (~ 6 liters) requiring transfusions of RBCs, plasma, and platelets and the patient was transferred to an ICU. Two days after surgery the patient received his last dose (2 mg) of APM. The patient was transferred out of the ICU approximately 90 minutes after the APM and approximately 1 hour later (i.e. ~ 2.5 hours after APM) the patient suddenly became pulseless and unresponsive. After cardiopulmonary resuscitation, the patient exhibited a sinus rhythm. A cardiology consult suspected a primary pulmonary event such as pulmonary embolism or aspiration. The exact cause of the cardiac arrest was not determined. The patient had experienced a hypoxic encephalopathy and was eventually transferred to a nursing facility (with DNR order). The patient died 28 days after the cardiac arrest. An autopsy showed necrotizing bronchopneumonia involving all lung lobes with polymicrobial bacterial overgrowth, consistent with aspiration pneumonia. Describe death event and any previous SAE. This patient had been using an average dose of 2.8 mg of APM with average frequency of ~ 2 times daily and had been in study APO401 for 581 days. Concomitant medications at the time of hospital admission included Sinemet, entacapone, pramipexole, amantadine, and trimethobenzamide. His death was considered not related to study medication.

Reviewer's Comment It may be purely coincidental, but it is not possible to exclude that APM contributed in some way to the cardiac arrest considering the relatively close temporal sequence (i.e. ~ 2.5 hours after the last APM). There were no pertinent negatives such as no specification of no nausea or vomiting with his most recent APM use. Considering that the patient appeared to

develop a severe aspiration pneumonia that resulted in death, one can only speculate whether it may have occurred before or after the cardiac arrest

Patient APO401/31/004 was a 76 year-old woman who was enrolled in the open-label safety study (APO401) and who developed pneumonia shortly after starting APM and died. This patient had a history of asthma (no recent attacks), S/P cataract surgery, degenerative joint disease, and S/P facelift. She was admitted to a hospital 19 days after starting APM injections and had received the last injection one day prior to admission. During her hospital stay she developed a collapsed lung and expired from a respiratory arrest 21 days after admission. It was not specified whether APM was continued during the hospitalization. Approximately 1 week after the patient's death, the patient's son notified the investigator about his mother's death. The cause of death was listed as collapsed lung and respiratory arrest. This patient had been using an average dose of 4 mg of APM but the average frequency of daily injections was unknown. She had been in study APO401 for a total of 40 days from the first APM until her death. There were no recorded AEs for nausea or vomiting. Concomitant medications at the time of death included Sinemet IR and CR, bromocriptine, and Pamelor. Her death was considered not related to study medication.

Reviewer's Comment There were no pertinent negatives such as no specification of no nausea or vomiting with his most recent APM use. In the absence of this negative history for nausea and vomiting, it seems that taking a most conservative approach, that one cannot exclude the possibility that the patient may have developed an aspiration pneumonia from vomiting from APM and ultimately the patient died as a complication of this event.

Patient APO401/36/008 was a 72 year-old woman who was enrolled in the open-label safety study (APO401) and who was found dead while sitting in a chair. She had a history of congestive heart failure, chest pain, hypercholesterolemia, S/PD left pallidotomy, insomnia, constipation, and chronic urinary tract infections, and hypothyroidism. Her last dose of APM was on the previous evening approximately 12 hours prior to her death. The patient had awakened at 5 am to do something in the kitchen and was found dead in the chair at 6 am by a family member. The narrative notes that the patient's primary care physician attributed the death to congestive heart failure. This patient had been using an average single dose of 4.2 mg of APM with average frequency of 2.5 times daily (although the narrative notes taking APM 10 x daily most recently) and had been in study APO401 for 331 days. There were no AEs worthy of note within a month of the patient's death. Concomitant medications at the time of death included Sinemet, pramipexole, trimethobenzamide, Synthroid, amantadine, Zocor, Restoril, ASA and multivitamins. Her death was considered not related to study medication.

Reviewer's Comment Unlikely death was caused by APM considering relatively long interval after APM injection.

11.5.3 Reviewer's Comments on Deaths

The sponsor and investigators had thought that none of the 14 deaths were at least possibly related to APM treatment. However, there are seven cases (e.g. 1 cardiac arrest, 1 feet fractures

leading to death, 4 pneumonias, 1 meat aspiration) where there are insufficient details about the timing of APM dosing and the lack of other important details and pertinent negatives to exclude the possibility that APM play a role in an event that ultimately led to a patient's death. I do not have good reasons to suspect that APM contributed to death and I tend to agree with the sponsor that APM was not a likely contributor to a patient's death, I cannot exclude APM's potential role in several cases when I take a conservative approach because of limited or missing information about APM dosing related to the event of death or leading to death.

11.6 Serious Adverse Events (SAEs)

11.6.1 Definition of Serious Adverse Events (SAEs)

A serious adverse event (SAE) was defined as any untoward medical occurrence that during treatment

- Resulted in death
- Was life threatening
- Required in-patient hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability/incapacity
- Was a congenital anomaly/birth defect
- Was an otherwise significant event

There were 159 patients who participated in the randomized, double-blinded, placebo-controlled trials. Most of these patients (121) received APM. Some patients treated with APM in a cross-over study also may have received placebo and 38 patients received only placebo. There were no SAEs reported in patients treated with APM. I pointed out earlier (Table 8) that the safety experience collected under randomized, double-blinded, placebo-controlled study conditions was very limited and consisted of only 732 patient-days for APM and 375 patient-days for placebo. Most patients were exposed to APM or placebo for a single treatment on 1 day and only 18 patients received APM over an extended period (e.g. ~ 35 days). Thus, it is not surprising that there were no SAEs associated with this extremely limited total number of patient-days under placebo-controlled conditions.

The sponsor presented a narrative summary for each patient experiencing an SAE. In addition, the sponsor gave special attention to certain SAEs (e.g. falls, cardiovascular events including arrhythmias, heart failure, coronary artery disorder, syncope, hypotension, and those occurring in close proximity to APM injection) in the ISS. I reviewed all these narrative descriptions of SAEs and will present selected narrative summaries that I deem worthy of interest after the presentation of tabulated SAE results. All narrative summaries that I have deemed worthy of interest for presentation here were considered to be at least possibly caused by APM by the investigator, sponsor and/or myself.

11 6 2 Review of Serious Adverse Events (SAEs) in All Patients in All Controlled and Open-Label Clinical Studies

The primary organ systems involved with SAEs are shown in Table 14. The most common organ system/categories in descending order were general, infections and infestations, cardiac disorders, injuries, nervous, psychiatric, respiratory, gastrointestinal, and vascular. There were no SAEs in APM-treated patients in the placebo-controlled trials. Table 15 shows the total number of each SAE according to the preferred term and the number and percentage of patients with each SAE for all APM-treated patients. There were a total of 227 SAEs in 103 patients or approximately 20 % of patients treated with APM. As can be seen, many of the specific SAEs observed were similar to those reported in the literature and were thus not unexpected with APM treatment. There were a variety of different types of SAEs, many of which were not expected. The two most common SAEs were pneumonia NOS (not otherwise specified) and falls that occurred in 3 % and 2 % of patients, respectively. After these SAEs others were categorized as occurring in ≤ 1 % of patients. In general, the total number of SAEs is similar to the number of patients who experienced the SAE. Thus, it appears that SAEs were not usually recurrent in the same patient.

If one reviews Table 15 carefully to consider the specific breakdown and description of SAEs by preferred terms, it is apparent that this analysis categorizes some medical events that seem to be or may be similar extremely specifically. Such an analysis with such fine splitting of preferred terms could potentially underestimate the frequency of similar SAEs, especially if the preferred terms assigned are not unequivocally established or confirmed by appropriate medical evidence. For pneumonia for example, there were 4 different preferred terms (e.g. NOS, aspiration, lobar, bacterial). When I reviewed the narrative summaries for pneumonia, it was not necessarily clear that there was clear evidence to distinguish that these pneumonias were different. If one combines all these cases, there were 24 SAEs of pneumonia in 23 different patients providing an incidence of 4.3 %, somewhat higher than the incidence for the most common form (e.g. pneumonia NOS) shown to occur in 3 % of patients. From a pharmacological perspective of APM's actions, there is no reason to expect that APM would increase the susceptibility of patients to develop community acquired pneumonia. However, there are reasons to consider aspiration pneumonia in these patients. APM frequently causes nausea and vomiting and patients could aspirate their emesis. In many cases, the narrative summaries and Medwatch reports do not provide pertinent negatives such that the patient was not experiencing nausea and vomiting within a reasonable temporal timeframe prior to the event to help diminish the likelihood that the patient could have been at increased risk for aspirating because of vomiting. Furthermore, patients with Parkinson's Disease may have swallowing difficulties and could have an increased risk of aspirating from the oropharyngeal cavity. In view of these observations, it is possible that many if not most of these cases represent aspiration pneumonia. It is also possible that APM increased the risk of aspiration pneumonia because of APM-induced vomiting that was not identified within a reasonable timeframe prior to the recognition of the SAE.

A similar argument can be mounted for combining the preferred terms of fall, various specific fractures, and injury to consider that patients sustained an accident or injury. Combining such

preferred terms in Table 15 for fall, fracture of the hip, clavicle, fibula, and rib, compression fracture, and head injury results in 29 SAEs for 26 patients. Patients who experience these accidents/injuries could do so as a result of orthostatic hypotension, that was not identified at the time of the accident/injury. In most of the narrative summaries of these cases, there is no mention of a pertinent negative that the patient did not experience light-headedness around the time of the accident/injury, especially after standing up from a sitting or lying position. Neither are details usually provided that leads a reader to think that some other reason was responsible for the accident/injury. In many cases, details about the time of the last APM injection prior to the event are not provided. Specifying that the last injection was several hours or longer prior to the accident/injury would make it unlikely that APM played a role or contributed to the SAE.

Finally, I would suggest considering combining SAEs for certain cardiovascular events that seem to be of a similar nature. Atrial fibrillation, atrial flutter, cardiac arrest, sinus arrest, bradycardia, and ventricular tachycardia (not Torsades de pointes) are all cardiac arrhythmias but when coded separately, the incidence of each is < 1 %. Combining these preferred terms would show that there were 11 SAEs of cardiac arrhythmia occurring in 11 patients with an overall incidence of 2.1 %. However, it is not clear whether many, most, or all of these SAEs considered under the more general category of cardiac arrhythmia are caused by APM. In addition, there is little distinction in considering hypotension and postural hypotension separately when they may both be caused by hypotensive effects of APM. But combining these terms does not substantively change their incidence that still remains < 1 % despite representing 4 SAEs in 4 patients.

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Table 14 Treatment-Emergent Serious Adverse Events (SAEs) By Decreasing Frequency of Primary Organ Class System for All Apomorphine Treated Patients in All Trials

Primary Organ System	Total # of SAEs	# Patients (%)^a with SAE
Any SAE	227	103 (19 %)
General Disorders and Administration Site Conditions	33	30 (6 %)
Infections and Infestations	38	30 (6 %)
Cardiac Disorders	30	23 (4 %)
Injury and Poisoning	21	19 (4 %)
Nervous System Disorders	12	12 (2 %)
Psychiatric Disorders	21	12 (2 %)
Respiratory, Thoracic, Mediastinal Disorders	12	11 (2 %)
Gastrointestinal Disorders	13	10 (2 %)
Vascular Disorders	8	8 (2 %)
Musculoskeletal, Connective Tissue, Bone Disorders	8	7 (1 %)
Neoplasms, Benign and Malignant	7	7 (1 %)
Metabolic and Nutritional Disorders	5	5 (1 %)
Renal and Urinary Disorders	6	4 (1 %)
Blood and Lymphatic System Disorders	3	3 (1 %)
Reproductive System and Breast Disorders	3	3 (1 %)
Investigations	2	2 (< 1 %)
Surgical and Medical Procedures	2	2 (< 1 %)
Ear and Labyrinth Disorders	1	1 (< 1 %)
Hepato-biliary Disorders	1	1 (< 1 %)

^a Incidence (1 e %) counts each patient once regardless of the number of episodes of TEAE

Table 15 Treatment-Emergent Serious Adverse Events (SAEs) By Decreasing Frequency of Preferred Term for All Apomorphine Treated Patients in All Trials

Preferred Term	Total # SAEs	# Patients (%) a with SAE (N = 536)
Any SAE	227	103 (19 %)
Pneumonia NOS	16	16 (3 %)
Fall	15	13 (2 %)
Hip fracture	8	7 (1 %)
Myocardial Infarction	6	6 (1 %)
Urinary tract infection NOS	6	6 (1 %)
Dehydration	5	5 (1 %)
Pneumonia aspiration	5	4 (1 %)
Atrial fibrillation	4	4 (1 %)
Cardiac failure congestive	4	4 (1 %)
Angina unstable	4	3 (1 %)
Hypotension	3	3 (1 %)
Coronary artery disease NOS	3	3 (1 %)
Chest pain NEC	3	3 (1 %)
Hallucination NOS	3	3 (1 %)
Dyspnea NOS	3	3 (1 %)
Fecal impaction	3	3 (1 %)
Parkinson s disease aggravated	3	3 (1 %)
Cardiac arrest	2	2 (< 1 %)
Syncope	2	2 (< 1 %)
Bradycardia NOS	2	2 (< 1 %)
Road traffic accident	2	2 (< 1 %)
Bronchitis acute NOS	2	2 (< 1 %)
Lobar Pneumonia NOS	2	2 (< 1 %)
Anxiety NEC	2	2 (< 1 %)
Delusion NOS	2	2 (< 1 %)
Depression NEC	2	2 (< 1 %)
Drug induced psychosis	2	2 (< 1 %)
Respiratory failure	2	2 (< 1 %)
Dysphagia	2	2 (< 1 %)
Abdominal pain NOS	2	2 (< 1 %)
Rectal bleeding	2	2 (< 1 %)
Diarrhea NOS	2	2 (< 1 %)
Back pain	2	2 (< 1 %)
Basal cell carcinoma	2	2 (< 1 %)
Urinary retention	2	2 (< 1 %)
Calculus renal NOS	2	2 (< 1 %)
Anemia NOS	2	2 (< 1 %)
Benign prostatic hyperplasia	2	2 (< 1 %)
Arthritis infective NOS	1	1 (< 1 %)
Bonchitis NOS	1	1 (< 1 %)
Bonchitis chronic NOS	1	1 (< 1 %)
Atrial flutter	1	1 (< 1 %)
Lethargy	1	1 (< 1 %)
Cellulitis	1	1 (< 1 %)
Osteomyelitis acute NOS	1	1 (< 1 %)
Sepsis NOS	1	1 (< 1 %)
Spinal cord abscess NOS	1	1 (< 1 %)
Gastroenteritis clostridial	1	1 (< 1 %)

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Preferred Term	Total # SAEs	# Patients (%) a with SAE (N = 536)
Gastroenteritis helicobacter	1	1 (< 1 %)
Pneumonia bacterial NOS	1	1 (< 1 %)
Fungemia	1	1 (< 1 %)
Vaginal candidiasis	1	1 (< 1 %)
Sinus arrest	1	1 (< 1 %)
Ventricular tachycardia	1	1 (< 1 %)
Edema peripheral	1	1 (< 1 %)
Pulmonary edema	1	1 (< 1 %)
Clavicle fracture	1	1 (< 1 %)
Compression fracture	1	1 (< 1 %)
Fibula fracture	1	1 (< 1 %)
Rib fracture	1	1 (< 1 %)
Spinal compression fracture	1	1 (< 1 %)
Arthropod bite	1	1 (< 1 %)
Collapse of lung	1	1 (< 1 %)
Gall bladder perforation	1	1 (< 1 %)
Head injury	1	1 (< 1 %)
Hepatic hematoma	1	1 (< 1 %)
Subcutaneous hematoma	1	1 (< 1 %)
Dysarthria	1	1 (< 1 %)
Loss of consciousness NEC	1	1 (< 1 %)
Speech disorder NEC	1	1 (< 1 %)
Parkinsonism aggravated	1	1 (< 1 %)
Lumbar spinal stenosis	1	1 (< 1 %)
Radiculopathy NOS	1	1 (< 1 %)
Cerebrovascular accident NOS	1	1 (< 1 %)
Agitation	1	1 (< 1 %)
Anxiety aggravated	1	1 (< 1 %)
Obsessive-compulsive disorder	1	1 (< 1 %)
Depressed mood	1	1 (< 1 %)
Confusion	1	1 (< 1 %)
Delirium	1	1 (< 1 %)
Hypomania	1	1 (< 1 %)
Mood disorder NOS	1	1 (< 1 %)
Personality disorder NOS	1	1 (< 1 %)
Suicidal ideation	1	1 (< 1 %)
Bronchospasm NOS	1	1 (< 1 %)
Pleural effusion	1	1 (< 1 %)
Colitis NOS	1	1 (< 1 %)
Intestinal obstruction	1	1 (< 1 %)
Postural hypotension	1	1 (< 1 %)
Phlebitis NOS	1	1 (< 1 %)
Thromboembolism NOS	1	1 (< 1 %)
Venous thrombosis deep limb	1	1 (< 1 %)
Transient ischemic attack	1	1 (< 1 %)
Musculoskeletal pain	1	1 (< 1 %)
Neck pain	1	1 (< 1 %)
Intervertebral disc degeneration NOS	1	1 (< 1 %)
Intervertebral disc prolapse	1	1 (< 1 %)
Aseptic necrosis bone	1	1 (< 1 %)
Muscle weakness NOS	1	1 (< 1 %)
Malignant melanoma of skin stage unspecified	1	1 (< 1 %)
Skin carcinoma NOS	1	1 (< 1 %)

CLINICAL REVIEW

Preferred Term	Total # SAEs	# Patients (%) a with SAE (N = 536)
Squamous cell carcinoma of skin	1	1 (< 1 %)
Colon cancer NOS	1	1 (< 1 %)
Bladder cancer adenocarcinoma recurrent	1	1 (< 1 %)
Hypokalemia	1	1 (< 1 %)
Hydronephrosis	1	1 (< 1 %)
Renal atrophy	1	1 (< 1 %)
Secondary anemia	1	1 (< 1 %)
Cervical stricture	1	1 (< 1 %)
Electrocardiogram abnormal NOS	1	1 (< 1 %)
Hematuria	1	1 (< 1 %)
Device expulsion	1	1 (< 1 %)
Life support	1	1 (< 1 %)
Vertigo NEC	1	1 (< 1 %)
Cholecystitis NOS	1	1 (< 1 %)

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

There were 15 SAEs for 13 various types of events occurring in 103 patients that were considered to be at least possibly related to study medication by the investigator. The preferred terms for these events were atrial fibrillation, bradycardia NOS, sinus arrest, cardiac failure congestive, fall, lethargy, confusion, delirium NOS, hallucination NOS (2), mood disorder NOS, drug-induced psychosis (2), hypotension NOS, and postural hypotension NOS. Despite these attributions of causality for APM, a better means of suggesting which SAEs are likely caused by APM is to show an increased frequency of SAEs in the APM group in a considerable number of patients in randomized, double-blinded, placebo-controlled studies conducted for longer periods of exposure. Thus, the relatively minimal exposure of patients to APM for prolonged periods and comparison to a placebo control group is a significant shortcoming in this development program. This shortcoming makes it difficult to suggest which SAEs are likely to be caused by APM.

11.6.3 Sponsor's Review of Serious Adverse Events (SAEs) of Special Interest

The sponsor reviewed certain SAEs (e.g. SAEs suggestive of falls, cardiovascular events including hypotension and syncope) of special interest that might be considered to have been precipitated by APM treatment. The sponsor noted that it reviewed CRFs suggestive of the aforementioned events of interest and narratives for these events that occurred in close temporal relationship to APM administration. Considering the temporal relationship of APM use and APM's pharmacological hypotensive actions, it categorized these cases as "likely" to have been caused by APM, "unlikely", or of "uncertain" relationship to APM use and did not use the investigator's assessment of causality to study medication. The sponsor presented very brief summaries of the cases.

SAEs Suggestive of Falls

There were 15 patients who had events suggestive of falls. These patients had been classified as experiencing a fall according to the preferred term or "bone and joint injuries" with or without fall as a preferred term. Many of these patients sustained a fracture. For all these cases, the

sponsor considered that APM was an unlikely cause of the event or that its potential causality was uncertain

I used a conservative perspective in reviewing these cases and tried to assess if I could reasonably exclude APM as a contributor to the event. Considering APM's variability in terms of pharmacokinetic and pharmacodynamic relationship, I took the position that APM could have potential deleterious effects if administered within 2 hours of the event and also looked for details (especially pertinent negative) that might help in a causal assessment. Although I did not conclude that APM was a likely cause of any of these events, my view was that there were insufficient details to exclude APM as a cause in the majority of these cases. As an example, there was one case of a 75 year old woman with a history of orthostatic hypotension and adrenal insufficiency who fell while getting out of a chair and fractured her clavicle. Although it was noted that APM was taken 1 hour prior to the event, the sponsor considered that APM was an unlikely cause. I think that it is possible that the patient experienced orthostatic hypotension that led to the fall and fracture and APM could have contributed to the orthostatic hypotension. I will present summaries of narratives later for selected, representative cases of SAEs of interest.

Cardiovascular SAEs

These SAEs focused on cardiac arrhythmia events, heart failure events, coronary artery disorder events, syncope, and hypotension. There were 17 patients who experienced many of these cardiovascular SAEs. There were five patients (1 %) who experienced an event consistent with syncope. The sponsor considered it likely that APM caused syncope and sinus arrest in one patient who developed these SAEs 2 minutes after the initial APM injection (2 mg). The sponsor also considered APM as causal of hypotension and bradycardia 30 minutes after the initial APM (2 mg) treatment. I concur with these assessments. In the remaining cases, the sponsor's assessment was that APM was an unlikely or uncertain cause of these SAEs. In contrast, my assessment after reviewing the sponsor's brief summaries of these cases was that it was not reasonable to exclude APM as a possible causal contributor based upon information provided and missing information not provided.

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

The sponsor conducted various subgroup analyses of SAEs 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 (1 e 99 %) were using a dopaminergic agonist. Race was not analyzed because most patients were Caucasian.

Age

More patients (23 %) in the older group (i.e. ≥ 65 years old) experienced SAEs than patients (15 %) in the younger group (i.e. < 65 years old). Not surprisingly, the frequency of certain SAEs or categories of SAEs were higher in the elderly. Differences worthy of noting include cardiac disorders in general (5 % vs 3 %), coronary artery disorder (3 % vs < 1 %), GI disorders (3 % vs < 1 %), fall (3 % vs < 1 %), and bone and joint injuries (4 % vs < 1 %).

Gender

There did not appear to be any significant difference in the frequency of specific SAEs according to gender.

Concomitant Medications

There did not appear to be any obvious or appreciable difference in the incidence of any specific SAE with respect to use of COMT inhibitors. There was a higher incidence of falls (5 % vs 2 %) and bone and joint injuries (6 % vs 1 %) in patients taking a vasodilator than in those who were not taking such a drug. The sponsor noted this difference but commented that there was no "definite orthostatic episode leading to a fall or fracture" and of those with timing information, none occurred within 2 hours of apomorphine. The sponsor's conclusion was that the increased frequency of vasodilator use in these cases was a chance event or that vasodilator use identified a subgroup of patients who were more likely to fall irrespective of APM use. I differ from the sponsor and think that this observation is likely to be real and suggestive of the possibility that patients on vasodilating drugs are at increased risk for such events while using APM. It is not reasonable to expect evidence for a "definite orthostatic episode" because no one is evaluating the patient for orthostatic hypotension when the event occurs. Furthermore, often timing information is not provided to help make a reasonable assessment of APM's possible contributory role or to help exclude it as a factor.

Apomorphine Dosing

There was no suggestion that the APM dose (i.e. 0, > 0 and < 4 mg, ≥ 4 mg) at the time of an SAE nor average daily frequency of APM injection (i.e. < 4 , ≥ 4) correlated with the occurrence of specific SAEs.

The sponsor noted that Table 53.0 summarizes SAEs by time since starting APM therapy but also commented that one should not simply compare incidences of specific SAEs of the differences because of differences in person-years of APM exposure for the different periods. The sponsor did not provide a table allowing for such a comparison of the frequency of SAEs and patients with such events based upon duration of APM exposure. However, the sponsor did provide Table 35.0 that shows the number of person-years of APM use for various periods since starting APM therapy. The sponsor did not make any specific comment about the rates of any

SAE, any specific SAE, or patients experiencing any SAE after adjustment of APM exposure for certain periods since initiating APM treatment

I created Table 16 that integrates information from the sponsor's Tables 35 0 and 53 0 and shows the frequency of number of any type SAE and the number of patients experiencing any SAE per patient-year of APM therapy relative to the time since starting APM therapy Thus, Table 16 presents rates of any SAE and patients experiencing any SAE adjusted for patient exposure to APM for different periods following the initiation of treatment The pattern for these rates shows that 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) The rate of developing any SAE and the rate of a patient experiencing an SAE adjusted for patient years of exposure for various time periods (e g day 1-7, day 8-30, day 31-180 Day 181-365, and \geq day 366) appears to be relatively constant Although I did not calculate rates of each specific SAE that occurred, there was no general suggestion of a difference for any specific SAE when the incidence of specific SAEs was reviewed and the approximate number of patients-years of APM exposure for the different periods was kept in mind

Table 16 Frequency of SAEs 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 SAE	4	17	80	63	62	226
# Pts with SAE(s) (%)	2 (< 1 %)	10 (2 %)	25 - 45 ^a (6 - 12 %)	34 (11 %)	31 (17 %)	103
Rate # SAEs/P-Y	0 4	0 6	0 5	0 5	0 6	0 6
Rate # patients with SAE/P-Y	0 2	0 3	0 2 - 0 3 ^a	0 3	0 3	0 2

Data Source ISS Safety Update Tables 35 0 and 53 0

^a Uncertain of precise number because of possible overlap in patient number between day 31-90 and day 91-180

11 6 5 Reviewer's Selected Treatment-Emergent SAE Narrative Summaries

I have reviewed all narrative descriptions of SAEs and will present selected narrative summaries that I deem worthy of interest All narrative summaries that I have deemed worthy of interest for

presentation here were considered to be at least possibly caused by APM by the investigator, sponsor and/or myself

SAEs Related to Accidental Injury, Trauma, Falls, Fracture

Patient AP0401/O1/O06 was a 66 year-old man with hypertension who experienced two falls resulting in hip fractures (right and left hip) The first fall and hip fracture occurred after 679 days of APM treatment and the second fall and fracture occurred 6 months later (after the 31 December 2001 cut-off date for Study APO401) His medications included the vasodilators Cardiazem ER and Terazosin The date and time of the last dose of APM in relation to the first fall and hip fracture was unknown The second fall and hip fracture occurred 12 hours after his last APM dose The patient continued to use APM during and following his last hip fracture hospitalization

Reviewer's Comment Without information of timing of APM dosing it is difficult to exclude APM treatment as a possible cause of this patient's first fall resulting in hip fracture

Patient APO401/05/004 was an 82 year-old woman with a history of falls and mitral ,and aortic valvular insufficiency who fell and fractured her fibula She had been on APM treatment for 77 days and her medications included the vasodilator Isordil The event was reported as being "non-syncopal due to advanced Parkinson's Disease" The date and time of the last dose of APM prior to the fall is unknown She continued in Study APO401 for approximately 2 more months She died 10 days after discontinuing study medication (see death section)

Reviewer's Comment Without information of timing of APM dosing it is difficult to exclude APM treatment as a possible cause of this patient's fall and fracture

Patient APO401/58/002 was a 75 year-old woman with hypertension who fell and fractured her hip 2 hours after her last dose of APM She had been taking APM for 15 days and her medications included the vasodilator Doxazosin She continued in Study APO401 following the fracture

Reviewer's Comment It is certainly possible that this patient fell because of hypotension/orthostatic hypotension There were not pertinent negatives about the lack of light-headedness, dizziness to help make exclude the likelihood of a contributory role from APM The timeframe (although perhaps near the end of what might be considered a reasonable window) is certainly consistent with a contributory role from APM

Patient AP0401/04/O07 was a 75 year-old woman with congestive heart failure, hypertension and a pacemaker who fractured her hip when she fell getting back into her chair and missed its location She had been on APM treatment for nearly two years and her medications included the vasodilator Imdur The study drug was stopped permanently while the patient was in the hospital