

11.12 Electrocardiographic Analyses (ECGs)

11.12.1 Background

During the development of APM, DNDP recommended that the sponsor conduct studies to assess electrocardiographic effect of APM, especially effects on QTc and consider conducting clinical pharmacology studies for these evaluations. DNDP was particularly interested in potential dose-dependent effects of APM and effects on patients who were naive to APM and responses over increasing duration of treatment. The sponsor proposed and conducted various studies (APO303, APO302, and APO073) to assess electrocardiographic effects of APM with respect to dosing. Although the sponsor initially proposed studying all patients with standard 12 lead ECGs, it subsequently amended protocols APO303 and APO073 to evaluate electrocardiographic effects with Holter monitoring instead of standard ECGs. At the pre-NDA meeting (1/10/02) DNDP noted that the sponsor should address the validity of these findings because Holter monitoring is not recognized as a valid means of assessing QTc prolongation of drugs.

The clinical section of the NDA submitted in 9/02 did not contain electrocardiographic data. Consequently, DNDP informed the sponsor that the PDUFA clock would not start until these critically desired data were submitted and considered adequate with respect to recommendations provided to the sponsor at the pre-NDA meeting. An integrated ECG report was submitted with the Safety Update on 1/2/03. Initially, there was some dispute about whether the sponsor had provided an adequate submission, mainly for ECG data because the submission did not address issues identified and requests made at the pre-NDA meeting. The sponsor provided another submission (2/6/03 receipt) to address concerns noted by DNDP. Toward the end of February 2003, DNDP ultimately decided to file the NDA and to set the PDUFA clock as of the 1/2/03 date.

11.12.2 Sponsor's Approach to Analyzing Electrocardiographic Data Including QTc

Holter data Collection (APO303 and APO073)

The sponsor described the Holter data collection for studies APO303 and APO073. Holter electrocardiographic data were recorded at 500 samples/second with a 16-bit analog to digital converter. The data were recorded on a Digital Holter Monitor. The filter range on the monitor was 0.05 Hz and is supposed to be comparable to that used in 12-Lead digital ECGs. The monitor was pre-programmed to record 3 channels of continuous electrocardiographic recordings that approximate the V2, V4 and V6 ECG leads and the data were recorded on a Holter "Flashcard". Investigative site personnel recorded the pre-dose and dosing times, and the 20, 40 and 90 minutes post dosing time points onto the Holter Enrollment Form that accompanied each Flashcard when it was sent to the sponsor for processing. The investigative sites were also instructed on how to record a Holter "test strip" to evaluate the amplitude of the Holter ECG prior to the actual recording.

Upon receipt of a Holter Flashcard and Enrollment Form, the Cardiovascular Technologist assigned to the study uploaded the Holter data from the Flashcard onto the Holter Analysis System. The Holter ECG data was thoroughly evaluated for rate and rhythm, with all ectopic beats manually confirmed for accuracy. Representative Holter strips were "pulled" to document rate, rhythm and arrhythmias. At the predosing, dosing and 20-, 40- and 90-minute post-dosing timepoints, the Technologist selected a stable area to perform interval measurements. The digitized ECG was magnified, and on-screen electronic calipers were used to identify the onset and the offset of intervals, with the corresponding measurements expressed in milliseconds. A mean of five QRS complexes were evaluated in all three leads of ECG, with the mean of the means reported for the interval measurements.

The completed Holter scans were then immediately referred to the Cardiologists assigned to the study. The first Cardiologist provided a detailed interpretation of the data, including confirming the interval measurements from the selected timepoints. A second Cardiologist then also confirmed both the interpretation and the measurements.

A third reading of the data was conducted to identify the time to first events that discrete events such as ectopic beats or heart block and to enumerate discrete event occurrence for selected time intervals corresponding to drug administration.

12 Lead ECG Data Collection (APO302)

Standard 12-lead ECGs were collected by the site at pre-dose, and at 20 and 90 minutes post-dose. Central reading of the ECGs was performed by Interval measurements were read digitally and confirmed by a cardiologist.

General Methods of Analysis

Standard statistical methods were used to describe and analyze the interval measurements by APM dose, visit or randomized group. The intervals examined included the PR, QRS, QT, corrected QT, and RR. For the Holter data, discrete events that were also evaluated included ventricular and supraventricular isolated ectopic beats, ventricular and supraventricular ectopic couplets, ventricular and supraventricular runs, bradycardia and tachycardia. There were no other discrete events (e.g. complete heart block) observed during any of the studies.

For comparison of groups, ANOVA was used to compare group means. For analysis of concentration response linear regression was used. The rate of occurrence of each discrete event was computed for selected time intervals corresponding to drug or placebo administration. The time to first discrete event was described for all experience.

Controlling for Heart Rate in Analysis of QT data (i.e. QT Correction)

Initially, the sponsor used the Fredericia cube root correction ($QT/RR^{0.33}$) to correct the QT for heart rate unless there was evidence that the cube root did not correct the QT for heart rate. To check the validity of the cube root correction, linear regressions of the cube root corrected QT against RR were conducted using data from pre-dose and placebo. If necessary, a new exponent was defined that produced a "0" slope when the corrected QT (computed using this new exponent) was fit against RR in the same dataset. A "0" slope was defined as having an absolute value less than 0.001.

During the initial review of QTc analyses it became apparent that the sponsor had analyzed data using QT corrections that did not seem appropriate. For example, when a "0" slope was utilized, the data for this slope were derived from an experience during which the patient had been under treatment with the experimental drug of interest (e.g. APM). In addition, some subgroups (e.g. higher APM dose groups in study APO303) used a different correction exponent that had been used for other lower dose groups in the same study. Normally, the QT correction exponent is derived from data collected prior to ever receiving the experimental drug and/or from data of placebo treated patients who never received the experimental drug and the same QT correction is used for all patients within the same study. I discussed my concerns with Dr. Judy Racoosin (Safety Team Leader, DNDP) who agreed that we did not have experience with the methodological approach used by the sponsor's analyses. She concurred that there was reason for concern and agreed with my plan to ask the sponsor to re-analyze these QT data by determining an exponent based upon pre-treatment data prior to ever receiving any APM exposure. She also agreed that the same QT correction should be used for all patients analyzed within a single study.

I asked the sponsor to re-analyze the QT/QTc data with respect to my concerns described above and also to present the basis of the QT correction used for other studies (e.g. APO202, APO301, APO401) for which QTc analyses had been presented. The sponsor submitted re-analyses but had not re-analyzed the data as requested because data from many patients still utilized electrocardiographic results while a patient was intermittently receiving injections with the experimental drug for a significant period. The sponsor still used different QT correction analyses for higher dose groups. I then spoke to the sponsor to indicate that analyses had not been re-analyzed as desired and expected. Considering that it would be difficult to obtain adequate electrocardiographic data prior to APM exposure for determining a suitable QT correction, I then asked the sponsor to re-analyze all data according to the Bazett and Fredericia corrections for all patients in all studies as suggested by the FDA Preliminary Concept Paper (11/15/02) for evaluating QTc prolongation induced by drugs in clinical studies.

My review of effects of APM on QTc are therefore based upon QTc analyses of data received at FDA 5/28/03. The sponsor did not provide specific interpretations nor discussion of the results of these most recent re-analyses. However, the sponsor did provide several precautionary comments. There is a potential for bias if selecting an inappropriate QT correction, particularly if heart rate is affected. The sponsor further noted that the most common and

dramatic errors in QTc analyses have occurred using the Bazett square root correction. It was acknowledged, however, that bias can also occur with the Fredericia correction.

11.12.3 Electrocardiographic Data Timed to Apomorphine Dosing

Effect of Apomorphine on PR, QRS and RR Intervals

The sponsor noted that there did not appear to be any significant effect of APM on the PR or QRS intervals. There was a mild effect of APM on increasing the RR interval. This was expected considering that the RR interval reflects heart rate, and heart rate and RR interval are inversely related, and it was recognized in the studies of VS that APM decreases heart rate mildly. I agree with these interpretations and conclusions.

Sponsor's Conclusions About Effects of Apomorphine on QTc for Original Analyses

In view of the mild decrease in heart rate from APM treatment, APM caused a dose-related increase in uncorrected QT interval. Thus, it is necessary to correct the QT interval for heart rate (i.e. QTc). Although my review will focus on analyzing the most recent submission of results using the Bazett (QTcB) and Fredericia (QTcF) corrections for all results, I will briefly review the sponsor's conclusions derived from its review of the original analyses submitted. The sponsor noted that based upon the controlled study experience there was "no evidence that apomorphine increased the corrected QT." Despite the fact the APM resulted in a 4 msec QTc increment change from pre-dosing vs placebo at the 20 minute timepoint, this result "was not statistically compelling." The QTc increment in the usual dose APM group was more than that of the group receiving the usual dose + 2 mg, affirming the lack of a dose-response. In study APO303, "there were no numerical or statistical differences between 4 mg and placebo."

Reviewer's Approach to Reviewing QTc Data and Analyses

I have reviewed all of the sponsor's analyses and describe them in my review. More specifically, I reviewed the mean changes from baseline/pre-dosing at various times after dosing, the mean maximal change for any timepoint post-treatment, the categorical analyses of outliers, and considered treatment effect by adjusting for placebo response (and also oral medication in study APO303). I did not consider analyzing the "dosing" result data whereby Holter data were collected immediately at the time of injection because this is not a standard method for assessing QTc effects.

The sponsor's tables showed results of the Bazett and Fredericia corrections separately and each table was shown over several pages. In all instances, I created and have presented my own tables based upon data tabulated by the sponsor because I considered my own tables to be more informative particularly by showing results of QTc using the Bazett and Fredericia corrections simultaneously in the same table and on the same page. When considering treatment differences, I presented them based upon mean arithmetic differences rather than differences of least squared

means I did not focus on statistical analyses because these studies were not powered to show QTc differences based upon sample size estimation

Study APO303 Results

The sponsor proposed and conducted study APO303 (described earlier in section Vital Signs (VS) that was mainly an open-label study with a brief phase involving a randomized, double-blinded, placebo-controlled cross-over Study APO303 was also a substudy of APO401, the main safety study Study APO303 investigated effects of forced dose escalation of APM from 2 mg to 10 mg (in 2 mg increments) over several days When patients got to the level for 4 mg, they participated in the placebo-controlled, cross-over phase in which they were randomized to receive 4 mg APM and then placebo on different days or the reverse sequence After this forced titration phase, they continued taking APM for a period up to 6 months and then were followed in Study APO401 Responses to dosing with the patients' oral medications were also assessed prior to initiating APM for potential comparison

As patient escalated to higher APM doses, there was a progressive drop-out of this forced escalation phase because of adverse reactions Thus, the number of patients studied at higher doses for electrocardiographic effects of APM progressively decreased In addition, there were missing electrocardiographic results (sometime pre-dosing measurements because of technical problems) for some patients in various groups so that paired (pre-dosing and specific post-dosing measurements) were not always available for presentation **The sponsor calculated change data only when paired QT measurements for the same patient were available for the respective change comparison** For example, 14 patients advanced to the 10 mg level as shown for orthostatic VS measurement, but only 11 patients appeared have pre-dose QT measurements collected A pre-dose measurement was always a critical requirement for calculating a post-treatment change When treatment differences for the 10 mg exposure of the same patients were calculated relative to placebo and oral medication, there were only 7 - 8 paired post-treatment comparisons (20, 40, 90 minutes) for placebo adjustment and there were only 6 - 7 paired post-treatment comparisons (20, 40, 90 minutes) for oral medication adjustment

Table 55 shows effects of different doses of APM, placebo, and oral medication on QTc change from pre-dose and also on the maximal change (for any timepoint) from pre-dose Pre-dose mean absolute QTc values were similar across all treatments for respective QTcB and QTcF For QTcF, there was a suggestion of progressive dose-dependent mean QTc increments at the 40 minute timepoint These increments were higher at all APM doses relative to placebo and oral medication The dose-response curve appeared to be relatively shallow with similar increments occurring at the 4 and 6 mg doses and higher similar increments occurring at 8 and 10 mg doses Considering the QTcB changes, QTc prolongation was shown only at the 8 and 10 mg doses compared to all other treatments and the 10 mg increment was greater than that observed at 8 mg The mean maximal increments for QTcF and QTcB for the 10 mg dose were higher than those of all other treatments The mean maximal increments for both QT corrections for the 8 mg dose were greater than those for most APM treatments and other control treatments QTcB and QTcF

increments for the 8 mg dose were similar and were greater than respective increments of all other treatments including the 10 mg dose at 90 minutes post-treatment

Table 56 shows the mean treatment difference (i.e. mean treatment result - mean placebo result) for all treatments relative to placebo results in respective categories based upon paired comparisons. All QTcB and QTcF increments for the 8 mg dose were higher than all other treatments at all 3 timepoints (e.g. 20, 40, 90 minutes) except for the QTcB for 10 mg at 40 minutes. Most QTcF changes at 10 mg were similar to those of other treatments (except 8 mg). Mean maximal treatment difference increments for QTcB and QTcF for the highest APM doses (8 and 10 mg) were distinctly higher than those of all other treatments.

Table 57 shows results of the mean treatment difference (i.e. mean treatment result - mean oral medication result) for all treatments relative to oral medication results in respective categories based upon paired comparisons. QTcB and QTcF increments for the highest doses (8 and 10 mg) at 40 minutes were higher than respective QTc increments for all other treatments and the change for 10 mg was greater than the change for 8 mg suggesting a dose dependent effect. There was no suggestion of any other treatment effect differences including comparison of mean maximal increments.

Table 59 presents categorical outlier results including QTc increment ≥ 30 msec, QTc increment ≥ 60 msec, and QTc increment ≥ 500 msec. The number and percentage of patients with an outlier relative to the number of patients evaluated for that outlier at each timepoint and for the maximal increment for QTcB and QTcF are shown. There were no QTc increments ≥ 500 msec for placebo treatment. There were also some isolated QTc increments ≥ 500 msec for other APM doses and also a single similar outlier for oral medication but only for QTcB. There was no clear APM dose-dependent increase in the frequency of these various outliers.

Results were also analyzed to evaluate effects of APM on QTc changes relative to "baseline." Baseline was the mean of electrocardiographic data obtained during treatment with oral medication and at pre-dose prior to each patient's initial injection with APM (2 mg). Table 60 shows effects of different doses of APM, placebo, and oral medication on QTc change from pre-dose and also on the maximal change (for any timepoint) from baseline. Baseline mean absolute QTc values were similar across all treatments for respective QTcB and QTcF. In general, QTc changes for QTcB and QTcF for all timepoints at the 8 and 10 mg dose levels were usually greater in a positive direction than those of most lower APM dose changes and for placebo and oral medication. Overall, results for both corrections at the 40 minute timepoint for 8 mg and 10 mg doses appeared to show the most consistent difference from all other treatments. There did not appear to be a clear dose-dependent effect across all APM doses. However, if a dose-dependent effect existed, it appears to have a shallow slope. Neither was there a clear suggestion of a difference in the mean maximal QTc increments for QTcB and QTcF.

Table 61 shows the mean treatment difference (i.e. mean treatment result - mean placebo result) for all treatments relative to placebo results in respective categories for QTc change from baseline. In general, the QTcB and QTcF increments for the 8 mg dose at most timepoints is

higher than those for other treatments. The 10 mg dose only showed an isolated relatively large increment (5.8 QTcB) at 40 minutes. Mean maximal changes did not appear to be distinctly different.

Table 62 shows the mean treatment difference (i.e. mean treatment result - mean oral medication result) for all treatments relative to placebo results in respective categories for QTc change from baseline. The respective QTcB and QTcF increments for the 8 mg and 10 mg doses at the 40 minute timepoint appear to be greater than all other treatments. Mean maximal changes for the highest APM doses did not appear to be distinctly different from other treatments.

When data were analyzed for QTcB and QTcF changes according to the outlier categorical described earlier, there were several patients in the APM dose groups who exhibited various categorical abnormalities. However, there was no suggestion of any dose-dependence for APM effects.

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Table 55 Dose-Dependent Effects of Apomorphine on Time Course of QTc Changes (vs Pre-Dose) in Study 303

Rx Group	Oral Medication N = 44		Placebo N = 42		APM 2 mg N = 50		APM 4 mg N = 43		APM 6 mg N = 39		APM 8 mg N = 18		APM 10 mg N = 11	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
Pre-dose, Time 0	410.7	396.1	410.9	393.4	412.6	395.0	413.3	397.0	414.7	398.2	414.2	397.3	416.5	406.3
Δ at 20' after Pre-dose	2.9	2.3	0.6	1.8	0.6	3.2	-0.1	1.6	-0.4	2.3	3.0	6.4	1.7	-0.9
Δ at 40' after Pre-dose	2.1	0.7	2.0	2.0	-0.4	3.3	0.2	4.0	0.1	4.2	3.7	7.1	10.6	6.6
Δ at 90' after Pre-dose	1.3	2.4	0	1.8	0.3	1.6	-0.2	2.0	-0.5	2.1	3.2	4.4	-0.4	-1.7
Δ Maximal	8.2	8.7	8.4	8.8	9.8	10.9	6.7	9.1	9.2	10.3	10.5	12.2	15.4	11.7

Data Source: Sponsor's ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1.4.1XB and 1.4.1XF

Mean QTc Changes were calculated for paired data (i.e. pre-dose and post-dose) using the pre-dose QTc as reference

QTcB = Bazett correction QTcF = Fredericia correction

Δ Maximal = Maximal change from pre-dose considering any timepoint (e.g. 20, 40, or 90 minutes after injection/pre-dose)

Table 56 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Placebo) on Time Course of QTc Changes (vs Pre-Dose) in Study 303

Rx Group	Oral Medication – Placebo N = 44		APM 2 mg – Placebo N = 50		APM 4 mg – Placebo N = 43		APM 6 mg – Placebo N = 39		APM 8 mg – Placebo N = 18		APM 10 mg – Placebo N = 11	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
Δ at 20' after Pre-dose	1.9	1.0	-2.0	0	-0.4	0.1	-0.3	1.4	4.5	7.3	0.4	-2.4
Δ at 40' after Pre-dose	-0.9	-1.6	-2.1	1.9	-1.8	1.9	-2.1	1.5	6.2	8.6	8.3	4.6
Δ at 90' after Pre-dose	2.0	1.3	-0.4	0.1	-1.0	-0.6	0.5	1.5	5.9	7.3	2.1	-0.7
Δ Maximal	0.3	0.1	0.5	2.0	-1.7	0.2	0.1	0.6	6.1	7.7	11.0	7.6

Data Source Sponsor's ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1.4.2XB and 1.4.2XF

Treatment Difference = Active Treatment Change – Placebo Change

QTcB = Bazett correction QTcF = Fredericia correction

Δ Maximal = Maximal change from pre-dose considering any timepoint (e.g. 20, 40, or 90 minutes after injection/pre-dose)

Table 57 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Oral Medication) on Time Course of QTc Changes (vs Pre-Dose) in Study 303

Rx Group	Placebo - Oral Medication N = 42		APM 2 mg – Oral Medication N = 50		APM 4 mg – Oral Medication N = 43		APM 6 mg– Oral Medication N = 39		APM 8 mg– Oral Medication N = 18		APM 10 mg – Oral Medication N = 11	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
Δ at 20' after Pre-dose	- 2 3	- 0 5	- 3 9	- 1 4	- 1 7	0	- 3 2	0	- 0 4	1 6	1 0	1 1
Δ at 40' after Pre-dose	- 0 1	1 3	- 2 3	2 2	0 5	5 0	- 2 3	3 6	3 0	6 1	5 0	8 5
Δ at 90' after Pre-dose	- 1 3	- 0 6	0	- 0 1	- 1 4	0 1	- 3 6	0 2	1 3	2 3	- 7 1	- 2 8
Δ Maximal	0 2	- 0 1	- 0 3	0 8	- 0 7	1 7	0	1 8	2 0	1 7	- 0 6	- 0 6

Data Source Sponsor's ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1 4 3XB and 1 4 3XF

Treatment Difference = Treatment Change – Placebo Change

QTcB = Bazett correction QTcF = Fredericia correction

Δ Maximal = Maximal change from pre-dose considering any timepoint (e g 20, 40, or 90 minutes after injection/pre-dose)

Placebo change – oral medication change was no calculated by sponsor but by reviewer using mean differences

Table 59 Dose-Dependent Effects of APM on Time Course of Outlier Categorical QTc Changes (vs Pre-Dose) - Study 303

Rx Group	Placebo		APM 2 mg		APM 4 mg		APM 6 mg		APM 8 mg		APM 10 mg	
	N = 42		N = 50		N = 43		N = 39		N = 18		N = 11	
QTc Outlier Category	QTcB # (%)	QTcF # (%)										
QTc increment ≥ 30 msec above pre- dose 20 minutes	0	0	2 (4 0 %)	2 (4 0 %)	0	0	0	0	0	0	0	0
QTc increment ≥ 60 msec above pre- dose 20 minutes	0	0	1 (2 0 %)	0	0	0	0	0	0	0	0	0
QTc ≥ 500 msec 20 minutes	0	0	1 (2 0 %)	1 (2 0 %)	1 (2 0 %)	0	0	0	0	0	0	0
QTc increment ≥ 30 msec above pre- dose 40 minutes	1 (2 4 %)	0	0	1 (2 0 %)	1 (2 4 %)	1 (2 4 %)	1 (2 6 %)	2 (5 1 %)	0	0	1 (10 %)	1 (10 %)
QTc increment ≥ 60 msec above pre- dose 40 minutes	0	0	0	0	0	0	1 (2 6 %)	0	0	0	1 (10 %)	1 (10 %)
QTc ≥ 500 msec 40 minutes	0	0	0	0	0	0	1 (2 6 %)	1 (2 6 %)	0	0	0	0
QTc increment ≥ 30 msec above pre- dose 90 minutes	1 (2 4 %)	1 (2 4 %)	1 (2 1 %)	1 (2 1 %)	0	0	0	1 (2 7 %)	0	0	0	0
QTc increment ≥ 60 msec above pre- dose 90 minutes	0	0	0	0	0	0	1 (2 6 %)	0	0	0	0	0
QTc ≥ 500 msec 90 minutes	0	0	0	0	0	0	0	0	0	0	0	0
QTc increment ≥ 30 msec above pre- dose Maximal	2 (4 8 %)	1 (2 4 %)	3 (6 0 %)	4 (8 0 %)	1 (2 3 %)	1 (2 4 %)	1 (2 6 %)	2 (5 1 %)	0	0	1 (9 1 %)	1 (9 1 %)
QTc increment ≥ 60 msec above pre- dose Maximal	0	0	1 (2 0 %)	0	0	0	1 (2 6 %)	0	0	0	1 (9 1 %)	1 (9 1 %)
QTc ≥ 500 msec Maximal	0	0	1 (2 0 %)	1 (2 0 %)	0	0	1 (2 6 %)	1 (2 6 %)	0	0	0	0

Percentages based upon number of patients with abnormal categorical value/ number of patients assessed at that time
 Sponsor did not present categorical analysis for Oral Medication

Table 60 Dose-Dependent Effects of Apomorphine on Time Course of QTc Changes (vs “Baseline”) in Study 303

Rx Group	Oral Medication N = 47		Placebo N = 44		APM 2 mg N = 50		APM 4 mg N = 43		APM 6 mg N = 39		APM 8 mg N = 18		APM 10 mg N = 11	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
“Baseline”, Time 0	410.7	396.7	410.9	396.5	412.6	395.7	413.3	398.6	414.7	399.5	414.2	398.5	416.5	410.2
Δ at 20’ after Pre-dose	0	0.8	-1.3	-0.5	1.1	2.4	-1.3	-0.3	-0.7	1.0	1.6	-2.2	-2.3	-4.9
Δ at 40’ after Pre-dose	-0.1	-0.3	0.9	0	0.1	2.5	-1.0	2.0	-0.3	2.9	2.3	5.2	6.7	2.7
Δ at 90’ after Pre-dose	0	1.3	-1.0	-0.5	0.6	0.9	-1.4	0.2	-0.1	0.7	1.8	5.8	-4.4	-5.7
Δ Maxi- mal	6.5	7.2	6.5	6.1	10.2	10.2	6.0	7.6	8.9	9.0	9.1	10.9	11.4	7.7

Data Source: Sponsor’s ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1.4.1XB and 1.4.1XF
 Mean QTc Changes were calculated for paired data (i.e. baseline and post-dose) using the “baseline” QTc as reference
 “Baseline” is the mean of QTc data prior to ever receiving APM and during treatment with oral medication and “pre-dose” immediately prior to first APM (2 mg) injection

Table 61 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Placebo) on Time Course of QTc Changes (vs “Baseline”) in Study 303

Rx Group	Oral Medication – Placebo N = 47		APM 2 mg – Placebo N = 50		APM 4 mg – Placebo N = 43		APM 6 mg– Placebo N = 39		APM 8 mg– Placebo N = 18		APM 10 mg – Placebo N = 11	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
Δ at 20’ after Pre-dose	1.3	1.3	2.4	2.9	0	0.2	0.6	1.5	2.9	-1.7	-1.0	-4.4
Δ at 40’ after Pre-dose	-1.0	-0.3	0.1	2.5	-1.9	2.0	-1.2	2.9	1.4	5.2	5.8	2.7
Δ at 90’ after Pre-dose	1.0	0.7	1.1	1.9	-0.4	0.7	0.9	1.2	2.8	6.3	-3.4	-5.2
Δ Maximal	0	-3.0	4.1	3.7	-0.5	1.1	2.4	2.9	2.6	4.8	4.9	1.6

Data Source Sponsor’s ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1.4.2XB and 1.4.2XF

Treatment Difference = Mean Active Treatment Change – Mean Placebo Change calculated by reviewer (not calculated by sponsor)

QTcB = Bazett correction QTcF = Fredericia correction

Δ Maximal = Maximal change from baseline QTc considering any timepoint (e.g. 20, 40, or 90 minutes after injection/pre-dose)

Table 62 Dose-Dependent Effects of APM Treatment Difference (vs Oral Medication) on Time Course of QTc Changes (vs “Baseline”) in Study 303

Rx Group	Placebo - Oral Medication N = 44		APM 2 mg – Oral Medication N = 50		APM 4 mg – Oral Medication N = 43		APM 6 mg– Oral Medication N = 39		APM 8 mg– Oral Medication N = 18		APM 10 mg – Oral Medication N = 11	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
Δ at 20’ after Pre-dose	- 1 3	- 1 3	1 1	1 6	- 1 3	- 1 1	- 0 7	0 2	1 6	- 3 0	- 2 3	- 5 7
Δ at 40’ after Pre-dose	1 0	0 3	0 2	2 8	- 0 9	2 3	- 0 2	3 2	2 4	5 5	6 8	3 0
Δ at 90’ after Pre-dose	- 1 0	- 1 8	- 0 6	- 0 4	- 1 4	- 0 9	- 0 1	- 0 6	1 8	4 5	- 4 4	- 7 0
Δ Maximal	0	- 1 1	3 7	3 0	- 0 5	0 4	2 4	1 8	2 6	3 7	4 9	0 5

Data Source Sponsor’s ISS Safety Update Reanalyzed (5/27/03 submission) Tables 1 4 3XB and 1 4 3XF

Treatment Difference = Mean Treatment Change – Mean Placebo Change calculated by reviewer (not calculated by sponsor)

QTcB = Bazett correction QTcF = Fredericia correction

Δ Maximal = Maximal change from baseline QTc considering any timepoint (e g 20, 40, or 90 minutes after injection/pre-dose)

CLINICAL REVIEW

Table 63 Dose-Dependent Effects of APM on Time Course of Outlier Categorical QTc Changes (vs “Baseline”) -Study 303

Rx Group	Placebo		APM 2 mg		APM 4 mg		APM 6 mg		APM 8 mg		APM 10 mg	
	QTcB # (%)	QTcF # (%)										
QTc increment ≥ 30 msec above baseline 20 minutes	0	0	2 (4 0%)	3 (6 0%)	0	0	1 (2 6%)	0	1 (5 6%)	1 (5 6%)	0	0
QTc increment ≥ 60 msec above baseline 20 minutes	0	0	1 (2 0%)	0	0	0	0	0	0	0	0	0
QTc ≥ 500 msec 20 minutes	0	0	1 (2 0%)	1 (2 0%)	0	0	0	0	0	0	0	0
QTc increment ≥ 30 msec above baseline 40 minutes	1 (2 3%)	1 (2 3%)	0	1 (2 0%)	1 (2 4%)	1 (2 4%)	1 (2 6%)	1 (2 6%)	1 (5 6%)	1 (5 6%)	1 (10%)	1 (10%)
QTc increment ≥ 60 msec above baseline 40 minutes	0	0	0	0	0	0	1 (2 6%)	0	0	0	1 (10%)	1 (10%)
QTc ≥ 500 msec 40 minutes	0	0	0	0	0	0	1 (2 6%)	1 (2 6%)	0	0	0	0
QTc increment ≥ 30 msec above baseline 90 minutes	1 (2 3%)	1 (2 3%)	1 (2 1%)	1 (2 1%)	0	0	0	0	0	0	0	0
QTc increment ≥ 60 msec above baseline 90 minutes	0	0	0	0	0	0	0	0	0	0	0	0
QTc ≥ 500 msec 90 minutes	0	0	0	0	0	0	0	0	0	0	0	0
QTc increment ≥ 30 msec above pre-dose Maximal	2 (4 5%)	2 (4 5%)	3 (6 0%)	5 (10 0%)	1 (2 3%)	1 (2 3%)	2 (5 1%)	1 (2 6%)	1 (5 6%)	1 (5 6%)	1 (9 1%)	1 (9 1%)
QTc increment ≥ 60 msec above pre-dose Maximal	0	0	1 (2 0%)	0	0	0	1 (2 6%)	0	0	0	1 (9 1%)	1 (9 1%)
QTc ≥ 500 msec Maximal	0	0	1 (2 0%)	1 (2 0%)	0	0	1 (2 6%)	1 (2 6%)	0	0	0	0

Percentages based upon number of patients with abnormal categorical value/ number of patients assessed at that time

Sponsor did not present categorical analysis for Oral Medication

Study APO302

Patients, who had been treated for at least 3 months with APM were also studied under randomized, double-blinded, placebo-controlled, parallel treatment conditions. Patients were randomized to receive one of four parallel treatment groups including 1) their usual dose of an APM injection, 2) their usual dose of an APM injection + 2 mg (maximal dose allowed = 10 mg), 3) the equivalent volume of placebo to their usual dose volume of an APM, or 4) the equivalent volume of placebo to their usual dose volume of an APM + 0.2 ml. I will briefly describe results in these patients, who were studied for electrocardiographic effects at pre-dose, and at 20 and 90 minutes post injection. The average dose of APM was 4.6 mg (usual dose) and 5.8 mg (usual dose + 2 mg) in the two APM groups. The range of APM doses in each group is shown in Table 64. Most patients were using single APM doses that were ≤ 6 mg. Results of each of these groups and the pooled APM group were compared to the pooled placebo group.

Table 65 shows results for all 3 APM groups and the pooled placebo group based upon actual standard ECGs. Mean absolute respective QTcB and QTcF values were similar across treatment groups. Most QTc increments for each APM group (except QTcB at 20 minutes) were greater than respective QTc increments for pooled placebo. QTc increments associated with APM treatment at 90 minutes were also generally similar to those observed at 20 minutes and were greater than respective QTc increments for pooled placebo. Mean maximal increments for all APM QTc were higher than those for pooled placebo.

Table 66 presents results of mean treatment differences (relative to placebo) for each APM group. With the exception of the QTcB change at 20 minutes in the APM + 2 mg group that was negative, all QTc changes were positive treatment differences. The treatment differences were more frequent at the 90 minute timepoint than those observed at the 20 minute timepoint.

Table 67 shows outlier categorical analyses. The only outlier categorical changes that were observed in the pooled placebo group were for QTc increments ≥ 30 msec above pre-dose. In general, outlier categorical changes occurred for all categories except QTc increment > 60 msec at 90 minutes. These changes included 2 patients (1 in APM group, 514 msec at 20 minutes, 1 in APM + 2 mg group, 508 msec at 90 minutes) who showed post-treatment QTcB ≥ 500 msec. No patients showed this change for QTcF. There were no patients who showed QTc ≥ 500 msec at pre-dose "off" state. However, one patient (# 15/004) showing the post-treatment result of 508 msec also had a similar outlier (514 msec) value at pre-dose "On" state. This patient only showed a 14 msec increment at 90 minutes from pre-dose that was relatively high at 494 msec. The other patient (# 41/003) showed a 76 msec increment at 20 minutes to 514 msec and a 54 msec increment at 90 minutes to 492 msec. Both patients received a dose of 6 mg. The percentage frequencies of categorical outliers for QTc increments ≥ 30 msec and ≥ 60 msec was higher for APM treatment groups compared to placebo.

Table 64 Apomorphine Dose Ranges in Parkinson's disease Patients Investigated for 12 Lead ECG Changes with Respect to Dosing (e.g. 0, + 20 minutes, + 90 minutes) in Study 302

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

(Patients enrolled were not naive to apomorphine and had been treated previously with apomorphine for ≥ 3 months)

Table 65 Dose-Dependent Effects of Apomorphine on Time Course of Changes in QTc from Pre-Dose in Study 302

Treatment Group	Pooled Placebo N = 34		Pooled APM N = 27		APM N = 18		APM + 2 mg N = 16	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
"Baseline", Pre-dose, Time 0	402.5	389.7	408.6	391.9	408.5	391.6	408.6	392.2
Δ at 20' after Pre-dose	1.3	1.0	1.4	4.4	7.9	6.5	-5.5	2.1
Δ at 90' after Pre-dose	0.3	1.5	7.4	4.9	6.3	5.8	8.5	3.9
Δ Maximal	4.6	4.9	10.7	9.7	10.9	9.3	10.4	10.1

Table 66 Dose-Dependent Effects of Apomorphine Treatment Difference (vs Placebo) on Time Course of QTc Changes (vs Pre-Dose) in Study 302

Rx Group	Pooled APM – Pooled Placebo		APM – Pooled Placebo		APM + 2 mg – Pooled Placebo	
	QTcB	QTcF	QTcB	QTcF	QTcB	QTcF
Δ at 20' after Pre-dose	0 1	3 4	6 6	5 5	- 6 8	1 1
Δ at 90' after Pre-dose	7 1	3 4	6 0	4 3	8 2	2 4
Δ Maximal	6 1	4 8	6 3	4 4	5 8	5 2

Table 67 Dose-Dependent Effects of Apomorphine on Time Course of Outlier Categorical Changes in QTc from Pre-Dose QTc in Study 302

Treatment Group	Pooled Placebo N = 27		Pooled APM N = 34		APM N = 18		APM + 2 mg N = 16	
QTc Outlier Category	QTcB # (%)	QTcF # (%)	QTcB # (%)	QTcF # (%)	QTcB # (%)	QTcF # (%)	QTcB # (%)	QTcF # (%)
QTc increment ≥ 30 msec above pre-dose 20 minutes	1 (3 8 %)	0	2 (6 5 %)	3 (9 7 %)	2 (12 5 %)	2 (12 5 %)	0	1 (6 7 %)
QTc increment ≥ 60 msec above pre-dose 20 minutes	0	0	1 (3 2 %)	0	1 (6 3 %)	0	0	0
QTc ≥ 500 msec 20 minutes	0	0	1 (3 1 %)	0	1 (5 9 %)	0	0	0
QTc increment ≥ 30 msec above pre-dose 90 minutes	1 (3 8 %)	1 (3 8 %)	5 (14 7 %)	1 (2 9 %)	3 (16 7 %)	1 (5 6 %)	2 (12 5 %)	0
QTc increment ≥ 60 msec above pre-dose 90 minutes	0	0	0	0	0	0	0	0
QTc ≥ 500 msec 90 minutes	0	0	1 (2 9 %)	0	0	0	1 (6 3 %)	0
QTc increment ≥ 30 msec above pre-dose Maximal	2 (7 4 %)	1 (3 7 %)	5 (14 7 %)	3 (8 8 %)	3 (16 7 %)	2 (11 1 %)	2 (12 5 %)	1 (6 3 %)
QTc increment ≥ 60 msec above pre-dose Maximal	0	0	1 (2 9 %)	0	1 (5 6 %)	0	0	0
QTc ≥ 500 msec Maximal	0	0	2 (5 7 %)	0	1 (5 3 %)	0	1 (6 3 %)	0

Study APO073

Six patients who had been treated with APM in study APO401 enrolled in an open-label pharmacokinetic and pharmacodynamic study (APO073) One investigation in this study assessed the effects of repeat injections of APM at 90 minute intervals on QTc collected by Holter monitoring

Table 68 presents mean QTc results for change from pre-dose for QTcB and QTcF at various times over 270 minutes Some patients did not have samples collected at all times There was no suggestion of any QTc increment above the pre-dose There were no post-treatment QTc values that were ≥ 500 msec

Table 68 Effects of Repeat Injections of Apomorphine on Time Course of Change in QTc from Pre-Dose QTc in Study 073

QTc Change from Pre-Dose "Baseline" / Pre-dose / Time 0	APM Injection Every 90 minutes X 3 N = 6	
	QTcB	QTcF
+ 20 minutes	- 2.6	3.2
+ 90 minutes	- 2.1	5.6
+ 110 minutes	- 1.6	4.6
+ 180 minutes	5.7	10.0
+200 minutes	5.3	5.9
+ 270 minutes	2.6	8.9

Reviewer's Comments

I interpreted these QTc results from study 303 as suggestive of QTc prolongation Frequently, the increments were dose-dependent and most prominent at the highest doses of APM (e.g. 8 and 10 mg) Considering that Holter monitoring has not been shown to be a validated methodology for showing QTc prolongation from drugs, it is possible that these results underestimate the actual QTc prolongation The sponsor did not provide any evidence to support their Holter monitor results as a valid method for assessing possible QTc prolongation In fact, the sponsor provided a publication (Christiansen J L et al, Pace 19: 1296-1301, 1996) in which Holter monitor results were compared to standard ECG results The conclusion of the authors was "In the assessment of QT interval, potential sources of error of this magnitude could limit the clinical utility of ambulatory monitoring in detecting prolongation of the QT interval for diagnostic purposes "

Both QTcB and QTcF corrections were frequently associated with a QTc prolongation treatment difference (ranging from mean of ~ 5 – 8 msec) at various timepoints and regardless of whether QTc increments were compared to pre-dose or baseline and whether placebo or oral medication

was used to make an adjustment. Although the sponsor had cautioned about using QTcB, this correction may be more appropriate considering that APM decreases heart rate. The Bazett correction has been associated with artifact particularly when a drug increases heart rate. The Fredericia correction may bias results when heart rate is decreased.

Study 302 did use standard ECGs to evaluate QTc prolongation but did not collect samples at 40 minutes, a desirable time based upon T_{max} that usually occurs between 15 to 45 minutes and the slight pharmacodynamic delay that follows C_{max}/T_{max}. This study found QTc prolongation treatment effects that ranged between 4-8 msec and did not even study QTc at a time (e.g. 40 minutes) when APM effects on cardiac repolarization might be even greater.

In summary, I conclude that these results support a concern about potentially significant QTc prolongation and that these results may underestimate the QTc prolongation that actually occurs when sensitive methods are used to assess QTc.

Overall, the categorical analyses did not provide much useful information with the exception of the one patient who showed a 76 msec increment up to maximal value of 514 msec.

11.12.4 Electrocardiographic Data Not Timed to Apomorphine Dosing

Electrocardiographic results obtained in these studies were from ECGs that were analyzed at each site and not centrally.

Study 202 was a randomized, double-blinded, placebo-controlled, parallel group study of patients (naive to APM treatment) who were studied for < 1 week as inpatients and for 4 weeks as outpatients. This study collected a single ECG prior to treatment and a single ECG at the end of the study. There was no significant change in PR, QRS or QTc interval from baseline and no significant outlier results worthy of noting based upon APM treatment (vs placebo treatment).

Study 301 was a randomized, double-blinded, placebo-controlled, cross-over study of patients who were studied on separate days for a single administration of placebo or APM in both sequences. These patients had been treated with APM for at least 3 months. This study collected a single ECG prior to treatment and a single ECG at the end of the study. Results were not compared according to any treatment but were shown for all patients combined relative to change from screening. Thus, there is no basis for making any comparison of electrocardiographic data with respect to APM treatment because half of the patients who had an ECG at study exit had received placebo as the last treatment.

Study APO401 was an open-label safety without a control group for comparison. Changes for various electrocardiographic parameters were presented as change from baseline. There were no statistically significant changes, none worthy noting, and no outlier results that suggested a reason for concern.

11.13 Miscellaneous Safety Issues

11.13.1 Abuse Potential, Tolerance and Dependence

The sponsor has not conducted studies to evaluate the potential for tolerance, abuse, and/or dependence when APM is used as acute rescue treatment of "Off" episodes. Although APM is derived chemically from and is chemically similar to morphine, it does not appear to share direct pharmacological properties of morphine or the narcotic analgesics. APM is structurally similar to dopamine and acts nonselectively at the family subtypes of D₁ and D₂ receptors. Although APM does not act pharmacologically at opioid receptors, one study did show a reduction in APM-induced nausea and vomiting after intravenous infusion of naloxone but the mechanism for this effect is not clear.

According to the published literature, there are conflicting results as to the development of tolerance in animals and humans. Overall, there is a potential for some tolerance when APM is administered as continuous infusion. However, there does not appear to be significant tolerance to intermittent subcutaneous APM injections.

Abuse of subcutaneous APM injections is theoretically possible and there have been few reports of patients who abused APM. Some patients could want to avoid "Off" periods and therefore abuse APM inappropriately. Another form of abuse rarely seen is a psychosexual reaction related to APM's effects to produce penile erections and increase sexual desire. Four cases of patients with significant psychosexual disturbances were reviewed in the Periodic Safety Update for Britject (APM) 9/96-9/97. These patients self-administered increased doses and injections of APM relative to the daily recommendations. Psychological dependence might be more likely expected than physical dependence.

concluded that APM did not have a high abuse liability because the doses required to produce reinforcing response would also have an ability to induce an emetic response. This dual action was thought to limit inherently the abuse potential of APM.

However, there are many animal studies in the literature showing that dopaminergic stimulation, especially in the mesolimbic system can be involved in addiction and might predispose patients toward abuse. Considering this and that patients with Parkinson's disease may tolerate nausea and vomiting somewhat better than naive patients not taking any dopaminergic stimulation chronically (as do Parkinson's disease patients), and that the doses and routes are different, we have consulted this office to obtain their view on the addiction and abuse potential of this specific product and are awaiting the recommendation from that office.

11.13.2 Overdose

Animal studies show that overdose is associated with marked pharmacological effects of APM on the CNS. When animals are given very high doses, CNS stimulation (e.g. increased activity and nervousness and aggression) that is generally consistent with the known pharmacological effects of APM occurs. Rats treated with ≥ 40 mg/kg showed self-mutilation. Deaths of animals from overdose is not expected. The sponsor speculated that the risk of death from APM overdose would be "practically non-existent."

The ISS described 6 patients who were considered to have taken an overdose of APM. Some patients used subcutaneous infusions of APM and received a higher rate of administration without significant problems and others developed complications from intravenous infusion of APM.

- One patient received 35 mg as a subcutaneous infusion over 4 hours instead of 15 hours and did not experience any problems.
- One patient received 12 mg as a subcutaneous infusion over 1 hour instead of 12 hours and did not experience any problems.
- One patient, who was accidentally injected with 25 mg APM subcutaneously, exhibited nausea at 3 minutes and syncope for 20 minutes. When the patient became alert, the pulse was 40 and supine blood pressure was 90/50. Within 1 hour there was complete recovery.
- One patient "overmedicated" (amount not described) himself with a subcutaneous infusion pump and noted excessive sleepiness upon waking.
- Two patients received IV infusions (500 mg/d and 290 mg/d) of APM in excess total amounts, experienced thrombosis from APM and pulmonary embolism. APM formed a crystalline clot. Surgery was necessary to remove these clots. This is an unapproved use of APM and should be avoided.

Considering that patients still show therapeutic and hypotensive responses, and other adverse reactions after prolonged treatment, I would expect patients who receive an overdose of APM to exhibit severe examples of normal toxicity.

11.13.3 Human Reproductive Considerations

There were no pregnancies in the development program. The pharmacology/toxicology reviewer has concerns that the sponsor has not conducted appropriate reproductive toxicity studies. Although, many patients taking APM would be older and most females would be beyond their reproductive potential, it is possible that some younger women with reproductive potential could

use APM. Neither is it known what is the reproductive toxicity risk for men, who would have reproductive capacity much beyond that of females.

11.13.4 Interactions: Drug-Drug, Drug-Disease, and Drug-Demographic

Various potential interactions with APM relate particularly to hypotensive effects among others. The experience with sublingual APM

was that there was an increased risk for cardiovascular and hypotensive effects when patients took alcohol and vasodilators. The sponsor did not conduct any formal studies assessing drug-drug interactions (i.e., DDIs). However, when patients were taking a concomitant vasodilator, there was an increased frequency of SAEs for falls and injury and an increased frequency of non-serious hypotension as a TEAE. I would also expect a potential interaction with alcohol use and expect the same increased risk for an increased hypotensive/syncopal interaction observed when patients took sublingual APM in conjunction with nitrates (especially short-acting nitrates). Although the sponsor did not think that there was a relationship by which the vasodilator therapy increased the risks, I suspect that the falls and injuries were more common because of more hypotension/orthostatic hypotension.

The sponsor did not comment on the potential for drug-disease interactions. Patients with Parkinson's disease have an increased risk of orthostatic hypotension from autonomic dysfunction. Considering that hypotension/orthostatic hypotension is such a prominent risk with APM, I would expect patients with Parkinson's disease to exhibit higher risk than patients without Parkinson's disease.

Finally, elderly age itself is a risk factor associated with orthostatic hypotension. Thus, elderly patients might be more susceptible to APM's hypotensive actions. There were no results in the NDA that suggested specifically that there were more hypotensive TEAEs in elderly patients. However, data were not analyzed according to age to determine if age alters the incidence of various severities of orthostatic hypotension.

11.13.5 Review of Medical Literature

A review of the English literature found many publications on APM including results of over 159 trials investigating over 2700 patients worldwide. There is no information that emerges from the literature other than what has already been recognized with one exception. There is a recent report (Homann et al., *Wien Klin Wochenschr* 114: 430-431, 2002) that describes two patients who experienced sudden onset of sleep attacks with APM injection. The description of these cases suggests that they are good examples of sudden sleep attacks associated with APM therapy. Thus, APM appears to be similar to other dopaminergic agents that are associated with this risk.

11.13.6 Post-Marketing Experience

The post-marketing experience maintained by Britannia was provided in part as a Periodic Safety Update Review. Many cases described are similar to those observed in this NDA. However, there are some reports that suggest allergic reactions (urticarial rash, breathing difficulty and hives, etc.) In addition, there are brief descriptions of 6 serious spontaneous adverse event reports.

I had briefly reviewed the 2 cases of patients who developed venous thrombosis of crystalline APM and pulmonary embolism from off-label IV infusion of APM. The thrombosis extended from the venous system into the right atrium. Surgical removal of the thrombus occurred.

Another case described whereby a patient was inadvertently administered 75mg of APM as an intravenous infusion instead of a subcutaneous infusion. The patient developed pneumonia the next day and died. The coroner thought that this event was unrelated to APM.

Three other patients were administered subcutaneous APM infusions. One patient had visual hallucinations and formication. One had breathing difficulties that were considered not related to APM. The last patient reported that she began to lose her teeth after taking APM injections for 2 years and then starting a subcutaneous infusion.

11.13.7 Other Safety Experience Study 101 and Middlesex Retrospective Review

Study 101 used a formulation of 10 mg/mL APM in disposable pens in Parkinson's disease patients who were naive to APM treatment. The study design was randomized, double-blinded, placebo-controlled crossover study with 4 days placebo and 4 days APM during hospitalization and then an outpatient controlled period for 8 weeks (maintenance). There were no SAEs or deaths. The safety profile observed was similar to that which has been presented in this NDA. Of particular note, several patients experienced significant hypotension/orthostatic hypotension.

A retrospective analysis of the experience of Middlesex (that was sponsored by Britannia) was submitted. Patient used various doses of APM and various routes. Events in patients treated with intermittent subcutaneous injections of APM and subcutaneous infusion of APM were abstracted. Many of these patients were also treated with domperidone, a peripheral dopaminergic antagonist that is not approved in the U.S. to antagonize various adverse reactions. The only event of note observed in this development program that was not seen in the Bertek development program was necrosis at the injection site. It was not clear whether this occurred from continuous or intermittent subcutaneous administration.

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12 LABELING ISSUES

I have reviewed the sponsor's proposed label, have found several concerns/issues, and have summarized these concerns/issues and made some recommendations

Clinical Studies section

- This section should be rewritten to present primary efficacy data also at least in tabular format
- The sponsor presents results of many secondary efficacy endpoints that had nominal p values for statistical significance. There is no correction for multiplicity. Many of these presentations may not be appropriate at least not in the manner presented
- The dosing interval in study APO202 should be presented accurately as ≥ 2 hours
- It should be described that patients were dosed with APM to achieve a therapeutic response that was equivalent to levodopa

Indication section

- The sponsor did not distinguish whether end of dose wearing off or "on/off" was being treated. It may be appropriate to specify that the indication perhaps should be to treat end of dose wearing off or ask the sponsor to perform analyses to try to determine what type of "Off" was treated and what were the results. Conceivably, APM may be therapeutic solely or mainly for end of dose wearing off
- Considering the significant profile of toxicity for APM, it may be desirable to try to limit the indication to patients who have not been able to obtain improvement with maximized oral therapy. For example, the indication might be to restrict APM to patients who still experience "Off" episodes despite treatment with levodopa, a dopaminergic agonist, and one additional antiparkinsonian drug such as a COMT inhibitor or an MAO-B inhibitor

Warnings section

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- Falling Asleep during ADL should be a bolded warning

- The section on symptomatic hypotension should be rewritten to include some additional findings from studies of orthostatic VS indicating various severities of orthostatic hypotension

Precautions section

- This section might note the data on retinal toxicity (**Retinal pathology in albino rats**) of APM
- I am not sure if the sponsor is using updated figures for numbers of patients in the geriatric use section

Adverse Events section

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- The increased risk of fall/injury and hypotension with concomitant vasodilator use should be described

Dosage and Administration section

The sponsor has not specified most of these important parameters required for dosing The only specification by the sponsor is the recommended dose increment (i e 1 mg)

My recommendations

- The maximal single dose should be 6 mg based upon the exposure data
- The minimal dosing interval should not be less than 120 minutes if repeat dosing is recommended It is not even clear if repeat dosing should be recommended because in many, if not most instances, a repeat administration of APM might coincide with the next interval dosing of levodopa/dopa decarboxylase inhibitor Taking these drugs together could have the potential for increased toxicity from excessive dopaminergic stimulation
- The maximal number of daily injections should be 5

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- Although it may be desirable theoretically to try to recommend that the dose increments should be in steps of 0.5 mg rather than 1 mg, it is not clear that it is practical and achievable considering the error in drawing up such a small volume (e.g. 100 microliters for 1 mg or 50 microliters for 0.5 mg). Alternatively, if the person tries to measure 50 microliters for injection, considering error in APM volume withdrawal, it may be closer to 100 microliters

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- Supine and standing blood pressure and pulse should be measured immediately before injection, and at 20, 40, and 60 minutes later
- It may be desirable to initiate APM at 1 mg dose in the presence of significant renal impairment

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