

Reviewer's Comments, Discussion, and Conclusions

Because the sponsor did not present data nor analyses showing the variability of sleep times in the group of individuals who exhibited a mean sleep time of 6.5 hours, I do not know how much variability there is in sleep times amongst these patients. In addition, it should be kept in mind that the analyses of the type of "Off" treated were not based upon actual data from which individual dosing intervals were calculated based upon actual sleep times of individuals. The sponsor made assumptions that sleep times of individual patients studied in these pivotal trials were essentially similar to those determined from diary data in a subset of patients in open-label study APO401, especially when not only the mean sleep time (6.5 hrs) was considered but also when a shorter (6 hrs) and a longer sleep time (7 hrs) was applied to provide a bracket of sleep times for estimating individual patient dosing intervals.

I do not know how applicable the sponsor's assumptions of sleep times (derived from diary data of patients in open-label study APO401) are to the patients studied in the pivotal trials (APO301 and 302). However, the sponsor's approach does seem reasonable for calculating dosing intervals based upon the dosing during awake time (i.e. the complement of number of hours not presumed to be sleeping or 24 hrs - # sleep hrs). It would not have been possible to have conducted retrospective analyses of the type of "Off" episode treated without incorporation of some sleep time assumption to help calculate the dosing intervals. **Potentially different results may have been observed if the analyses of treatment of "Off" episodes were based upon calculating individual dose intervals based upon actual average sleep time of each individual patient who participated in these pivotal trials.**

Analyses of dosing intervals in these pivotal trials showed that the range of dosing intervals was between 1 and 9 hours, and that half of the patients used dosing intervals of approximately 3 to 6 hours with the remaining patients exhibiting some skewing toward longer dosing intervals.

I agree with the sponsor that all of the initial analyses based upon combined results of studies APO 301 and APO302 showed statistically significant treatment effects of APM vs placebo regardless of the iteration (e.g. sleep time assumption for calculating dosing interval or rule for categorizing the type of "Off" episode treated). However, as indicated in my request, I wanted to evaluate results of individual studies separately.

The separate analyses of study APO302 showed that APM was statistically superior to placebo for reducing UPDRS motor score for all analyses. The classification of type of "Off" treated revealed that approximately one fourth (15-17 patients depending on the specific analysis) of all patients (60) had been classified as having a spontaneous "Off" episode treated. Correspondingly, approximately 75% of all patients had "end of dose off" episodes treated. Respective UPDRS motor scores at pre-dose and post-treatment for all analyses were similar. This observation is indirectly reflected in Table 6 that shows that the treatment effect (mean APM UPDRS motor score reduction - mean placebo UPDRS motor score reduction) was similar for "spontaneous off" episodes (range 13.1 - 14.5) and for "end of dose off" episodes (range 18.8 - 19.1) for the various analyses. Of interest, the mean reduction in "end of dose off" episodes after APM treatment was greater than that for "spontaneous off" episodes. The statistical differences (Table

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6) for APM over placebo were also more highly significant for “end of dose off” episodes (all $p < 0.001$) than for “spontaneous off” episodes ($p < 0.0160 - p < 0.0337$)

Although many results in study APO301 were fairly similar to those observed in study APO302. There were some differences compared to results of study APO302. The majority (9-10 patients depending on specific analysis) of all patients (17) were categorized as having had a “spontaneous off” episode treated. In addition, there were no statistical differences for either type of “Off” episode that had been treated.

UPDRS motor scores at pre-dose and post-treatment in study APO301 were similar for all analyses as had been observed in study APO302. This observation is also indirectly reflected in Table 6 that shows that the treatment effect (mean APM UPDRS motor score reduction – mean placebo UPDRS motor score reduction) was fairly similar for “spontaneous off” episodes (range 13.5 - 13.8) and for “end of dose off” episodes (range 17.2 - 19.1). Similar to results in study APO302, the mean reductions in “end of dose off” episodes after APM treatment in study APO301 were greater than those for “spontaneous off” episodes. As can be seen in Table 6, the number of patients treated with APM (3) and placebo (4 or 5) for “end of dose off” episodes was relatively small. The number of patients treated with APM (5) and placebo (4 or 5) for “spontaneous off” episodes was also relatively small. Table 6 also shows the range of p values for “end of dose off” episodes ($p = 0.0513 - 0.1751$) and for “spontaneous off” episodes ($p = 0.1730 - 0.3698 - 0.0160$). **Of significant importance, the magnitude of the mean reductions in UPDRS motor score in study APO301 for both “spontaneous off” and “end of dose off” episodes is similar to the respective mean reductions in UPDRS motor score for both types of “Off” episodes in study APO302.** This observation is clearly seen in Table 6 when one compares treatment effects of APM across the various analyses. The magnitude of the mean reduction in UPDRS motor score after treatment (vs pre-dose) in study APO301 is also greater for treating “end of dose off” episodes as was also observed in study APO302.

There was a statistically significant difference (i.e. benefit of APM) between the two treatments for the change of UPDRS motor score at the 20 minute dose time point (from pre-dose) in study APO301 and the magnitude of the mean treatment effect (APM-placebo) of APM was larger in period 2 (-22.2) than that (-13.9) in period 1. The statistical review (Dr. S. Yan) of the original NDA 21264 noted that an evaluation of the normal assumption of the ANCOVA was not satisfied for data at 20 minutes post-dose analyzed by a parametric test (Shapiro-Wilks test), a non-parametric analysis of Wilcoxon Rank Sum test was applied on (Period 1 - Period 2) data as the primary efficacy analysis to examine the treatment difference further. A significant treatment difference in favor of APM was found **but there was no statistically significant period effect** based upon this non-parametric analysis of data from 16 patients who had received one treatment in each cross-over period. Neither was there a statistically significant carryover effect at 20 minutes post-treatment based upon an analysis of the primary efficacy endpoint from data (Period 1 + Period 2) using the non-parametric Wilcoxon Rank Sum test. I recognize that there was a relatively small sample size of 8 subjects receiving each treatment in each period/sequence and that a period effect may have existed but was not detected because this test for a period effect is not necessarily sensitive and is usually underpowered to detect a period effect.

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I agree with the sponsor's view that the likely reason that results of study APO301 are not statistically significant is related to the small numbers of patients compared in the analyses. Because there was no period effect, and because small number of patients analyzed only in period likely accounted for the lack of statistically significant differences in the sponsor's analyses, I think that it would be reasonable and appropriate to conduct additional analyses including results from both periods of study APO301. I recommended that the DNDP statistician (Dr S Yan) conduct additional analyses of results from both periods determine dosing intervals according to the various sleep time assumptions and apply both rules to categorize whether the "Off" is a "spontaneous off" or "end of dose off". These analyses combining both period results in the APO301 study did show statistically significant results as I had hypothesized (see Statistician's review, Dr Yan for details)

I conclude that

- 4) **APM is effective for treating both "spontaneous off" episodes and "end of dose off" episodes,**
- 5) **APM appears to show greater benefit for treating "end of dose off" episodes than "spontaneous off" episodes,**
- 6) **APM's efficacy for treating both types of "Off" episodes should be described in the label along with the assumptions inherent in these analyses**

2 Clinical Comment 2

FDA Comment 2

Clinical Trials In APO303, the between-group difference was 5 in the first period and 12 in the second period. This compares with a between-group difference of 24 in APO202, 18 in APO301, and 17 in APO302. We are less impressed by the results of APO303 because of this and therefore we do not believe the results should be described in labeling.

Bertek Response

APO303, a sub-study using patients enrolled in APO401 (the long-term open label safety protocol), was designed to assess adverse events during medically supervised dose titration in apomorphine-naïve patients. A placebo control group was included at the 4-mg dosing level to facilitate interpretation of both safety and efficacy, and because it was a common dose in previous clinical trials. However, 4 mg was not the most therapeutically effective dose in all APO303 patients. Indeed, the optimum therapeutic dose selected by study investigators for initial outpatient administration was greater than 4 mg in 24 of 51 (47%) patients who participated in the double blind crossover phase of APO303. Thus, it was not unexpected that the magnitude of the between-group treatment response was less than that observed in other trials in which the most therapeutically effective dose was determined and used for assessment.

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The Sponsor believes that the results of APO303 merit inclusion in the product label for a number of reasons

- APO303 provides controlled data obtained in apomorphine-naive patients who experienced spontaneous “Off” events
- The results of randomized, placebo-controlled, prospectively conducted Phase III trials are usually presented in labeling. The comparison at the 4-mg dosage group involved a double-blind randomized, parallel-groups, placebo controlled study design. Moreover, the “Off” episode that was treated was medically observed. We believe that it is essential for this study to be included in labeling.
- The results of APO303 support the efficacy of apomorphine in the acute treatment of “Off” events in patients with late-stage PD. Consistent with other studies in the NDA, APO303 employed the change in baseline UPDRS motor scores to document efficacy. Similar to other studies, the change from baseline UPDRS motor scores was statistically significantly lower in patients treated with apomorphine as compared to those treated with placebo.
- Physician-patient counseling requires an understanding of the pharmacodynamic response following subcutaneous apomorphine administration. Patients should be counseled that the onset of apomorphine effects may be as early as 7.5 minutes after the injection. Patients should be comfortable with the full effects of apomorphine before engaging in activities that could pose a threat to themselves or others should they experience postural hypotension or drowsiness.
- APO303 provides support for labeling instructions regarding repeated dosing in the office setting. Data obtained 90 minutes after dosing indicate that significant apomorphine treatment effects still persist. Therefore, repeated apomorphine doses should not be administered within 90 minutes of the first dose.

Revised prescribing information incorporating the data from APO303 is provided in Attachment 2. An annotated copy of the prescribing information noting the revisions made in the current labeling proposal from that provided by the FDA is provided in Attachment 3.

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The main problem is not that the beneficial effect of a 4 mg fixed dose of APM was less in study APO303 than effects observed in other studies in which patients received an “optimized” dose of APM. **The main problem with considering crossover study APO303 as a positive pivotal trial for description in the label was that APM was not statistically superior to placebo in both periods in study APO303. There was a period effect in which APM was statistically superior to placebo only in the second period in which the treatment effect (APO-placebo, -12) was much greater than the treatment effect (-5) in the first period. In this response, the**

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sponsor did not specifically address the period effect that it had found in its efficacy analysis and we had confirmed in our analysis

APO303 (double-blind, placebo-controlled study) provides data demonstrating the potential of APM for treating "spontaneous off" episodes in APM-naive patients. However, this study involving a cross-over design at 4 mg APM showed a statistically significant period effect. Although there was a statistically significant effect of APM on the primary efficacy endpoint in the second period, there was no statistically significant benefit of APM on the primary efficacy endpoint in the first period based upon the statistical analyses of the statistician, Dr. S. Yan. Thus, the conclusion of the DNDP was that 4 mg APM was not shown to be an effective dose for reversing "Off" as per improvement in the UPDRS motor function score at the 20 minutes timepoint (i.e. the primary efficacy endpoint). **DNDP did not consider this study (APO303) to be a positive pivotal trial demonstrating the efficacy of APM.** Phase 3 trials that are not positive (i.e. demonstrate a statistically significant effect according to an appropriate statistical analysis) are not typically presented in the drug's label. Furthermore, I find no compelling argument presented by the sponsor indicating why the sponsor thinks that "it is essential for this study to be included in labeling."

Although the results of study APO303, overall, may be supportive of the efficacy of APM for reversing "Off" episodes, the period effect and lack of efficacy in the first period precludes considering this a positive pivotal trial worthy of presentation in the label.

The sponsor talks about the onset of effects as early as 7.5 minutes after injection, but the analysis of the time course of a response was one of several secondary efficacy endpoints that had not undergone statistical correction for multiplicity (i.e. multiple comparisons). I am not sure what the sponsor means by the sentence: ↵

Advice about dosing can be provided in the section on dosing in the label without necessarily describing every dose in each specific study.

Information about the dosing interval can be provided in the dosing section of the label without necessarily describing study APO303 in the label.

I conclude that results of study APO303 are not appropriate for description in the Clinical Trials section of labeling because this pivotal study is not considered to be positive due to the period effect.

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FDA Comment 3

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QT Prolongation There appears to be an effect of apomorphine on the QTc interval, with doses of 8 – 10mg associates with a 2-8 msec prolongation in APO303. No cases of torsades were identified during the NDA review, but there were cases of syncope and sudden death (not unexpected in this patient population), and 3 patients experienced post-dose QTc interval of >500 msec. The effect on QTc interval will need to be described in labeling. We ask that you provide additional analyses from APO302, characterizing the effect of dose on QTc. If there is an adequate distribution of patients by dose, such analyses may support the QTc results obtained by 3-lead Holter in APO303. The data from APO303 suggests QTc prolongation at doses greater than 6mg. In any event, we believe you will need to perform a formal, randomized, placebo controlled trial to evaluate the effects of the full dose range of sc apomorphine on the QTc interval, this study may be performed after approval. We request that you submit all ECGs (for our review) conducted in patient # 41/003 who showed large QTc increments (including a QTc of 514 msec) after dosing of 6 mg apomorphine in study APO302.

Bertek Response

The Agency interpreted the QT data collected at 8 and 10 mg in the dose escalation period of APO303, the 3 patients that had post-dose QTCs of greater than 500 and the appearance of sudden deaths and syncope in the development program as providing enough evidence that apomorphine prolongs cardiac repolarization to describe this potential effect in the **WARNINGS** section of labeling. According to 21 CFR § 201.57, the **WARNINGS** section of labeling “shall describe serious adverse reactions and potential safety hazards as soon as there is reasonable evidence of an association of a serious hazard with a drug.” Bertek does not believe that the degree of evidence is significant enough to conclude that there is a reasonable likelihood that apomorphine prolongs cardiac repolarization.

In uncontrolled observations, isolated instances of QTc prolongation were observed that were not reproducible and were not dose-dependent. Preclinical studies support a lack of effect for apomorphine on the action potential duration, and an acceptable margin of safety in the hERG model (Attachment 13). There were no clinical signals in the Bertek apomorphine clinical development program reflective of an increased incidence of sudden death or syncope. A full discussion of the QTC prolongation potential of apomorphine supported by analysis of QTc data from APO302 and APO303 are provided in Attachment 33 along with all ECGs conducted in patient # 41/003.

The sponsor submitted a study report describing results of hERG channel inhibition studies of various concentrations of APM (0.03, 0.01, 0.3, 1 μ M), ropinirole (0.3, 1, 3, 10 μ M), and dopamine (0, 1, 100 μ M) compared to a positive control, haloperidol (0.1 μ M). There was no appreciable or significant hERG channel inhibition by dopamine, but APM and ropinirole showed significant inhibition and the IC₅₀ was 0.127 μ M and 1.214 μ M, respectively. The positive control (haloperidol) produced nearly complete inhibition (e.g. 92%) at 0.1 μ M.

The sponsor also submitted a study report describing results of studies of various concentrations of APM (0.01, 0.1, 1 μ M), ropinirole (0.1, 1, 10 μ M), and dopamine (0.01, 0.1, 1 μ M) on action

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potential duration in canine Purkinje fibers compared to effects of a positive control, sotalol (100 µM) The sponsor drew the following four conclusions

- 1) “Apomorphine did not cause statistically significant prolongation of APD₆₀ and APD₉₀ at 0.01, 1, and 1 µM concentrations and all three stimulus intervals (2, 1, and 0.5 s basic cycle lengths) except 0.1 µM apomorphine at 1 s BCL (basic cycle length) displayed significant shortening of APD₆₀ compared to vehicle control values ”
- 2) “ Dopamine did not cause statistically significant prolongation of APD₆₀ and APD₉₀ at 0.1, and 10 µM concentrations and all three stimulus intervals (2, 1, and 0.5 s basic cycle lengths) when compared to vehicle control values ”
- 3) “ Ropinirole did not cause statistically significant prolongation of APD₆₀ and APD₉₀ at 0.01, 1, and 1 µM concentrations and all three stimulus intervals (2, 1, and 0.5 s basic cycle lengths) when compared to vehicle control values Ropinirole at 10 µM induced a statistically significant prolongation of APD₆₀ and APD₉₀ at all three stimulus levels when compared to vehicle control values ”
- 4) “Under identical experimental conditions 100 µM sotalol significantly prolonged APD₆₀ by (Mean ± SEM) 67.5 ± 22.8 %, 50.6 ± 11.8 %, and 30.8 ± 4.3% at intervals of 2, 1, and 0.5 s basic cycle lengths, respectively , without significantly changing resting membrane potential, action potential amplitude and maximum rate of depolarization

In my review of human QT data, I will focus on QT correction (i.e. QTc) using the Bazett (QTcB) and Fridericia (QTcF) corrections rather than any “zero” slope exponent calculations My review (Safety NDA 21264 APM dated 6/20/03) outlined concerns in more detail about the most appropriate QT correction that should be applied The sponsor did not have sufficient data to determine a “zero” slope exponent based upon electrocardiographic data collected prior to APM treatment and wanted to use “pre-treatment” ECGs collected after exposure to APM **After much discussion with the sponsor, DNDP requested that all QT data be corrected using both QTcB (i.e. 0.50 exponent) and QTcF (i.e. 0.33 exponent)** Despite the fact that QTcB and QTcF can provide artefactual prolongation if a drug increases (QTcB) or decreases (QTcF) heart rate respectively, it is not clear that either correction is more appropriate because there is no clear evidence that APM significantly alters heart rate **It is also important to recall that electrocardiographic data collected in study APO302 were collected with standard 12 lead ECGs, that electrocardiographic data collected in study APO303 were collected with Holters, and that there are no data validating the Holter method for assessing drug-induced QTc prolongation** The FDA Draft White paper on this topic recommends against collecting QT data with Holter

The sponsor reviewed data from the controlled cross-over portion of study APO303 that showed that 4 mg APM did not show QTc prolongation relative to placebo The sponsor used a 0.477 exponent, an exponent similar to the QTcB I have not presented these data because they are similar to QTcB and QTcF data that did not suggest QTc prolongation with the 4 mg APM dose and that were reviewed previously in my Safety review

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The sponsor further noted that it “compared the change in QTc at the 20 minute time-point across doses in APO302 ” **However, the DNDP did not limit its request for additional analyses only to the 20 minute time-point** The sponsor presented a listing (Attachment 33 1) of predose and post-dose QTc (Bazett-QTcB and Fridericia-QTcF corrections) at 20 and 90 minutes according to treatment and APM dose **but did not calculate and provide QTc changes from pre-dose** The sponsor did present a listing (Attachment 33 2) of QTcB and QTcF for change from pre-dose **only for changes at 20 minutes but not for changes at 90 minutes** **It is important to note that the most impressive increments (vs placebo) in QTcB and QTcF that were noted in my previous analyses of study APO302 based upon data provided by the sponsor occurred at 90 minutes** Study APO302 did not collect data at 40 minutes post-treatment **It is also important and highly relevant to note that the 40 and 90 minute time-points were associated with overall the greatest QTcB and QTcF increments (vs placebo for 8 and 10 mg APM) in study APO303** Furthermore, prominent APM-induced blood pressure changes occurring at 40 and 90 minutes after APM injection support the importance of assessing pharmacodynamic actions (e g electrocardiographic) at more remote times after injection and after Cmax that generally ranges between 15 - 45 minutes

The sponsor presented APM 302 results (Table 7) using a QTc^{0.33} (i e QTcF) determined from placebo and pre-dose data Table 8, that I created in my Safety Review, shows both QTcB and QTcF results for the APM group, the APM + 2 mg group, and the pooled APM experience for both groups in study APO302 The sponsor noted that APM produced a small numerical increase in QTcF at + 20 minutes but that “the difference with placebo was not statistically compelling” and that the usual APM + 2 mg dose group response was smaller than that of the usual APM group

Table 7 Change from Predose QTcF After APM and Placebo in Study APO302

Treatment	Time point	Placebo		Apomorphine		(APO Change) - (Placebo Change)		P-value ^a
		N	Mean Change	N	Mean Change	Mean	Least Squares Mean (SE)	
APO	Predose	27		18				
	20 Min	26	1.0	16	6.5	5.5	5.8 (5.31)	0.2775
	90 Min	26	1.5	18	5.8	4.3	4.3 (4.55)	0.3456
APO+2 mg	Predose	27		16				
	20 Min	26	1.0	15	2.1	1.1	1.5 (5.42)	0.7873
	90 Min	26	1.5	16	3.9	2.4	5.5 (4.48)	0.6057

Population Safety

^a P-values are based on estimate statement in ANCOVA with the terms PREDOSE and treatment, based on least square means difference

Data extracted from Tables 1.6 and 1.10 of the Integrated ECG Report

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Table 8 Dose-Dependent Effects of Apomorphine Mean 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

The sponsor conducted and presented various analyses of QTcB and QTcF relative to APM dose. Figure 3 and Figure 4 show results of scatter plots of QTcB and QTcF **change from predose** at 20 minutes respectively relative to APM dose. APM had been administered at a concentration of 10 mg/ml, thus, 0.5 ml APM corresponds to a 5 mg dose. As can be seen in these figures that display the linear regression line mathematically derived from these data, there is no visually apparent slope positive slope of any significance suggesting a positive correlation between QTc and APM dose. The R values for Figure 3 and Figure 4 were ≤ 0.1 and thus do not suggest significant correlation between QTc change at 20 minutes and plasma APM. The sponsor also presented scatterplots of QTcB and QTcF at 20 minutes vs APM dose and the percent QTc change at 20 minutes from predose vs APM dose. I have not presented these scatterplots. None of these other scatterplots suggested a positive relationship between the QTc parameter and APM dose. Statistical analyses between each regression line and slope of zero were conducted and none of the p values, that ranged between 0.3568 and 0.7949, indicated a statistically significant difference. Thus, the sponsor's QTc analyses, that were limited to the 20 minute timepoint, did not suggest a positive correlation between APM dose and QTc at 20 minutes or QTc change from predose at 20 minutes.

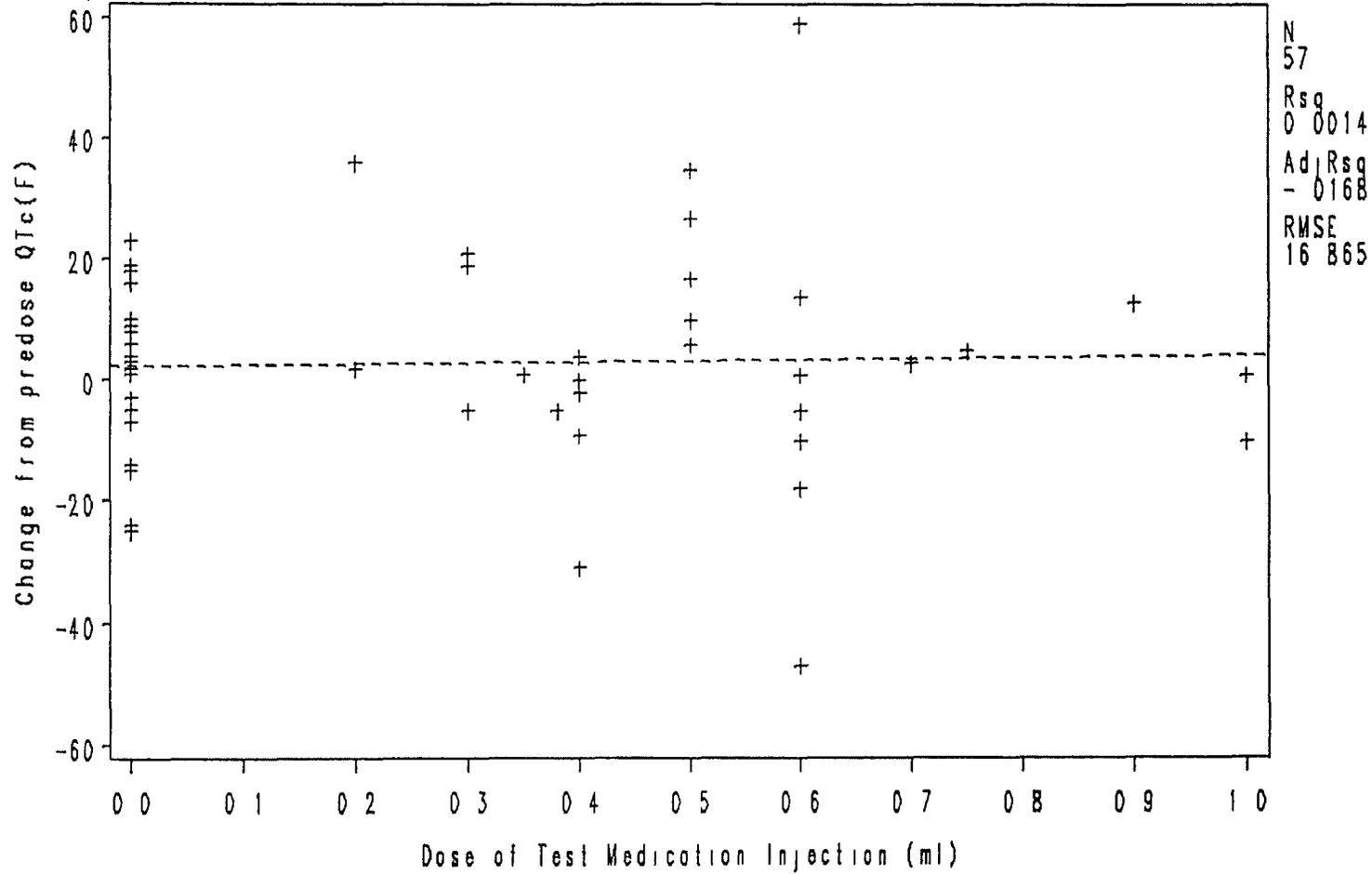
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Figure 3 Scatterplot of QTcF Change from Predose vs APM Dose in Study APO302

$$cfb_qtcf = 2.2796 + 2.0691 \text{ DOSE}$$

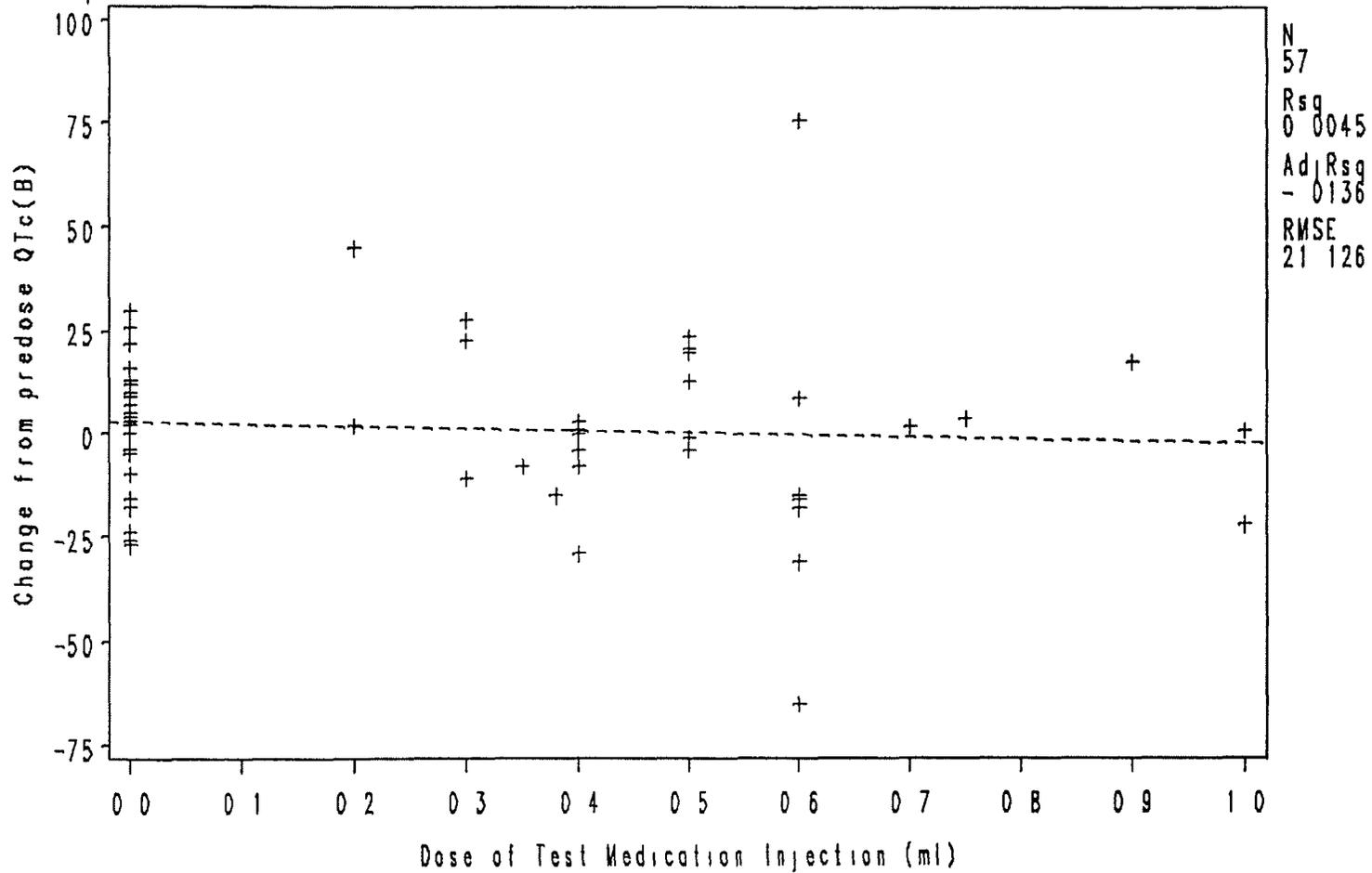


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Figure 4 Scatterplot of QTcB Change from Predose vs APM Dose in Study APO302

$clb_qtcb = 2.6676 - 4.6968 \text{ DOSE}$



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Table 9 Effect of Treatment on Mean QTc Change from Predose at 20 and 90 Minutes Post-Treatment in Study APO302

Post-Treatment Time-points	Placebo			APM 2- 6 mg					APM > 6 – 10 mg				
	N	QTcB	QTcF	N	QTcB	QTcB Rx Effect	QTcF	QTcF Rx Effect	N	QTcB	QTcB Rx Effect	QTcF	QTcF Rx Effect
20 minutes	26	1.3	0.3	27	1.7	0.4	4.8	4.5	5	0.6	0.3	2.4	2.1
90 minutes	26	1.0	1.5	29	6.7	5.7	4.1	2.6	5	10.8	9.8	3.8	2.3

Rx Effect = Mean APM result - Mean Placebo result

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The sponsor provided categorical analyses of centrally read QTc data for individuals in study APO302 who met safety criteria (e.g. QTc > 500 msec, QTc increment from predose > 500 msec, QTc increment from predose > 60 msec, etc.) These analyses were shown in Listings 4 and 5 for QTcB and QTcF, respectively. The sponsor also provided a listing (Attachment 33.8) of QTc results of the 3 patients (2 in study APO302 and 1 in study APO303) who exhibited QTc > 500 msec. The sponsor noted that one patient exhibited a QTcB increment from predose > 60 msec in study APO302. In this same study, these 2 patients exhibited a QTcB > 500 msec (patient APO401/15/004APO302A - 509 msec at predose "on" and 508 msec at 90 minutes after APM with predose of 494 msec, patient APO401/41/003APO302A - 514 msec at 20 minutes after APM with predose of 438 msec). Both patients who showed QTc > 500 msec had received 6 mg APM (one patient showed these categorical increments at both 2 and 6 mg APM).

One patient (APO401/04/016APO303) exhibited QTc > 500 msec in study APO303. QTcB and QTcF were 502 and 504 msec, respectively, immediately after injection of 6 mg APM. This same patient showed a QTcB increment of 92 msec from predose to a value of 552 msec at 20 minutes after 2 mg APM. QTcF was similarly markedly abnormal as reflected by a QTcF increment of 58 msec from predose to a value of 509 msec at 20 minutes after 2 mg APM. This patient further exhibited a QTc > 500 msec on a third occasion. There was a QTcB increment of 64 msec from predose to a value of 463 msec at 40 minutes after 6 mg APM. QTcF was again similarly markedly abnormal based upon a QTcF increment of 59 msec from predose to a value of 506 msec at 40 minutes after 6 mg APM. This patient was similarly studied on several repeat occasions while receiving various APM doses up to 10 mg and did not exhibit other QTc > 500 msec. Although most QTcB and QTcF values before and after APM for this patient ranged between 450 msec and < 500 msec, there was no clear reproducible increment in QTc after dosing on many other occasions. The sponsor argued that "inherent patient variability is again the most likely explanation for the observed increase in pre-dose corrected following the 6 mg dose."

Bertek does not consider the patients exhibiting QTcs > 500 msec to represent a signal of risk because the number of patients showing QTc increments after APM is small. **None of these analyses provided by the sponsor were new.** All this information had been submitted previously and is presented in my Safety review.

In response to our request, the sponsor provided electrocardiographic tracings of the results of patient showing QTc > 500 msec for our review. I reviewed photocopies of the actual 12 lead ECG tracings of this patient for predose off, and 20, and 90 minutes post-treatment, conducted my QT measurements with hand calipers (in conjunction with Dr. Shari Targum, a board certified cardiologist in DCRDP, HFD-110), and compared my readings with those of the central readings. Although the quality of the paper copy of tracings provided made it difficult to conduct the most accurate measurements, they were, nevertheless, measured. My QT calculations based upon 3 separate measurements of a rhythm strip were fairly similar to those of the central readings. For example, the sponsor's predose off, + 20 and + 90 minute post-treatment QT measurements were 408 msec, 436 msec, and 462 msec, respectively. My predose off, + 20 and + 90 minute post-treatment QT measurements were 423 msec, 427 msec, and 477 msec, respectively. It should also be noted that this patient had a pacemaker.

The sponsor reviewed and presented the uncontrolled, high APM dose (8 mg and 10 mg) experience of APM naive patients who were evaluated in study APO303. Briefly, patients had baseline electrocardiographic data collected at baseline before and after oral anti-Parkinson's Disease medication (i.e. "oral medication") and then underwent gradual APM titration from 2 mg to 10 mg APM at 2 mg increment at intervals of ≤ 3 days. When patients arrived at the 4 mg level, they were randomized to receive either 4 mg APM or placebo under double-blinded conditions. Patients subsequently underwent progressive APM titration as tolerated under open-label conditions.

Of the 18 patients with valid Holter data after 8 mg APM, 14 also had baseline data collected with oral medication and 15 had QTc data collected after placebo. "Baseline" is the mean of QTc data prior to ever receiving APM and during treatment with oral medication and the "pre-dose" ECG collected immediately prior to each patient's initial 2 mg APM injection. Treatment effects (i.e. APM result – placebo result or APM result – oral medication result) at similar pre- and post-APM treatment times were presented only for paired responses when a patient had data collected after APM and placebo or after APM result and oral medication. Although the sponsor included analyses showing absolute QTcB and QTcF data at different times relative to 8 and 10 mg APM, **I have focused on presenting the sponsor's analyses of QTcB and QTcF changes from predose or baseline**.

Table 10 and Table 11 summarize analyses of the **change from predose** for QTcB and QTcF respectively at dosing (immediately after APM injection), 20, 40, and 90 minutes after APM for patients who achieved the 8 mg dose. These analyses show results for APM, placebo, oral medication, and treatment effects of APM vs placebo and APM vs oral medication. The sponsor noted that QTcB and QTcF changes from predose were small and the difference was always < 10 msec. The only comparison that reached statistical significance was that with placebo at 40 minutes.

Table 12 and Table 13 summarize similar analyses of the **change from baseline** for QTcB and QTcF respectively as was presented for QTc change from predose. The sponsor acknowledged that there was little change from baseline in QTcB and a small increase in QTcF. When comparing the QTc change from baseline observed with placebo, there were no "statistically compelling" results at any time point and the size of the difference for QTcF was ≤ 5 msec. The sponsor also commented that although Table 12 and Table 13 showed a QTc change from baseline analysis for oral medication, the findings may not be that helpful because the baseline for oral medication is the oral medication experience plus the experience at pre-dose before the first APM injection.

In summary, the sponsor noted that the only statistically compelling finding occurred in the analysis of the QTc increment from pre-dose at 40 minutes. This finding had occurred in the context of 4 time points, 2 comparisons (placebo and oral medication) plus another set of comparisons for change from baseline. Hence, considering the multiple comparisons, observing one statistically significant finding would not be unusual. In addition, the largest effect size observed was always < 10 msec.

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The uncontrolled experience in APO303 at 10 mg was derived from 14 patients who had been treated with 8 mg APM and went on to receive 10 mg. Of these 14 patients, 11 had valid Holter data. During review of various analyses of these patients, the sponsor noted that one patient (40/028) who exhibited a marked QTc increment at 40 minutes after the initial study of 10 mg APM did not show similar, marked QTc increment following repeat study of 10 mg (Figure 5). Thus, the sponsor also conducted and presented analyses excluding results of this patient (40/028).

Table 14 and Table 16 summarize analyses of the **change from predose** for QTcB and QTcF respectively at dosing (immediately after APM injection), 20, 40, and 90 minutes after APM for patients who achieved the 10 mg dose. **Table 15 and Table 17 summarize similar analyses of the change from predose for QTcB and QTcF with the exception that data from patient 40/028 have been excluded.** The sponsor commented that the most apparent finding was that observed at the 40 minute time point at which both QTcB and QTcF were significantly increased after 10 mg APM relative to pre-dose or baseline, or to the corresponding values with oral medication or placebo. The sponsor also pointed out that, except for QTcF for oral medication, the 40 minute time point was also the largest value within a group of QTc data for oral medication and for placebo groups.

The sponsor noted that analyses (Table 14 and Table 16) of the change from predose including patient 40/028 confirmed an increase in QTcB and QTcF at 40 minutes after 10 mg APM. When compared with the change from pre-dose observed with oral medication or placebo, the effect size was always < 10 msec and was never "statistically compelling." When patient 40/028 was removed and excluded from these analyses, there was no increase in QTcB or QTcF from pre-dose (Table 15 and Table 17). The sponsor also commented that similar findings were observed in the analyses of QTc change from baseline shown in Table 18 - Table 21. The sponsor emphasized that there were no statistically compelling QTc changes with the 10 mg experience and that the increments in QTcB and in QTcF that had been observed at 40 minutes were due to the experience of a single patient.

Patient 40/028 went on to receive 10 mg in the outpatient phase of APO303. The sponsor presented a table (not presented) showing electrocardiographic parameters for all of this patient's experience during APO303. Figure 5 visually shows QTc data (squares = QTcB and circles = QTcF) with respect to APM administration at various specific time points over time. The large increment (112 msec-QTcB, 79 msec-QTcF) seen at the initial 10-mg APM dose was not reproducible during outpatient therapy. The sponsor further commented that there appeared to be a consistent trend toward greater QTc intervals at 40 minutes after dosing throughout this patient's evaluation in APO303.

Based upon these data, that demonstrated minimal to no QTc prolongation after 8 - 10 mg APM, the sponsor concluded "that there is no evidence to support a WARNING label regarding APM's effect on the corrected QT interval or a position of concern."

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While the sponsor acknowledges "that there are some findings of concern occurring in the context of a small database with 8 and 10 mg, the concern does not raise to the level of a **WARNING**" Instead, Bertek proposed the following statement

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In addition to adding a labeling statement about potential QT effects, the Agency proposed that Bertek conduct " a formal, randomized, placebo controlled trial to evaluate the effects of the full dose range of sc apomorphine on the QTC interval" after approval Bertek believes that it is not possible to conduct a randomized study that does not have some degree of selection bias There is no experience in administering large doses of apomorphine without titration to naive patients due to the pronounced nausea and hypotensive effects that could occur In fact, Bertek is not aware of any patient that received an initial apomorphine doses greater than 4 mg Hence, any randomized study of large dose would have to include a run-in period Even then, there would be a significant loss of patients at higher doses In APO303 where doses were titrated to tolerance, only about 45 % reached 8 mg and about 25 % reached 10 mg

Since there will be concerns about selection bias irrespective of the study design, Bertek proposes post approval that it studies patients who are prescribed higher doses by their physician This study would be based upon a large group of investigators who agree to enroll patients who need doses higher than 6 mg Twelve-lead ECG data would be collected at pre-dose and post-dose Patients would remain in the study for 30 days and we would follow their use of doses greater than 6 mg

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Table 10 QTcB Change from Predose Versus Placebo or Oral Medication Dosing in Patients Who Reached 8 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	1.7 (18)	(-2.7, 6.1)	2.1 (14)	(-2.7, 6.9)	0.9 (15)	(-3.6, 5.5)	0.4 (14)	(-7.0, 7.8)	1.2 (15)	(-6.2, 8.5)
20'	3.0 (18)	(-2.9, 8.9)	4.5 (14)	(-0.2, 9.3)	-1.6 (15)	(-7.6, 4.4)	-0.4 (14)	(-6.5, 5.8)	4.5 (15)	(-5.2, 14.2)
40'	3.7 (18)	(0.5, 7.0)	-0.8 (14)	(-8.1, 6.6)	-3.0 (15)	(-9.6, 3.5)	3.0 (14)	(-4.3, 10.2)	6.2 (15)	(-1.2, 13.5)
90'	3.2 (18)	(0.0, 6.4)	2.0 (12)	(-8.1, 12.0)	-2.3 (14)	(-10.5, 5.3)	1.3 (12)	(-10.1, 12.5)	5.9 (14)	(-3.5, 15.3)

Table 11 QTcF Change from Predose Versus Placebo or Oral Medication Dosing in Patients Who Reached 8 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	-0.9 (18)	(-5.5, 3.6)	1.9 (14)	(-1.1, 4.8)	0.9 (15)	(-2.5, 4.4)	-3.0 (14)	(-9.4, 3.4)	-1.4 (15)	(-7.6, 4.8)
20'	6.4 (18)	(0.7, 12.2)	4.8 (14)	(0.4, 9.2)	-0.4 (15)	(-5.8, 5.0)	1.6 (14)	(-6.4, 9.6)	7.3 (15)	(-2.6, 17.3)
40'	7.1 (18)	(2.7, 11.4)	-1.5 (14)	(-7.0, 4.0)	-1.3 (15)	(-6.5, 4.0)	6.1 (14)	(-1.2, 13.4)	8.6 (15)	(3.2, 13.9)
90'	4.4 (18)	(0.4, 8.4)	2.6 (12)	(-5.5, 10.8)	-1.2 (14)	(-7.4, 5.0)	2.3 (12)	(-7.6, 12.2)	7.3 (14)	(-0.5, 15.2)

Table 12 QTcB Change from Baseline Versus Placebo or Oral Medication Dosing in Patients Who Reached 8 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	0.3 (18)	(-4.2, 4.8)	0.8 (16)	(-7.5, 4.0)	3.0 (15)	(-1.9, 7.8)	-0.9 (16)	(-6.1, 4.2)	-2.8 (15)	(-11.4, 4.9)
20'	1.6 (18)	(-6.0, 9.2)	2.4 (15)	(-0.3, 5.2)	0.4 (15)	(-3.7, 4.6)	-0.1 (15)	(-8.7, 8.4)	0.6 (15)	(-10.1, 11.4)
40'	2.3 (18)	(-3.3, 8.0)	-2.6 (15)	(-5.3, 0.1)	-0.4 (16)	(-4.9, 4.0)	4.3 (15)	(-2.7, 11.3)	1.1 (16)	(-5.3, 7.5)
90'	1.8 (18)	(-2.0, 5.6)	0.8 (13)	(-4.5, 6.1)	-0.2 (15)	(-5.4, 5.1)	1.6 (13)	(-5.4, 8.5)	1.5 (15)	(-5.1, 8.1)

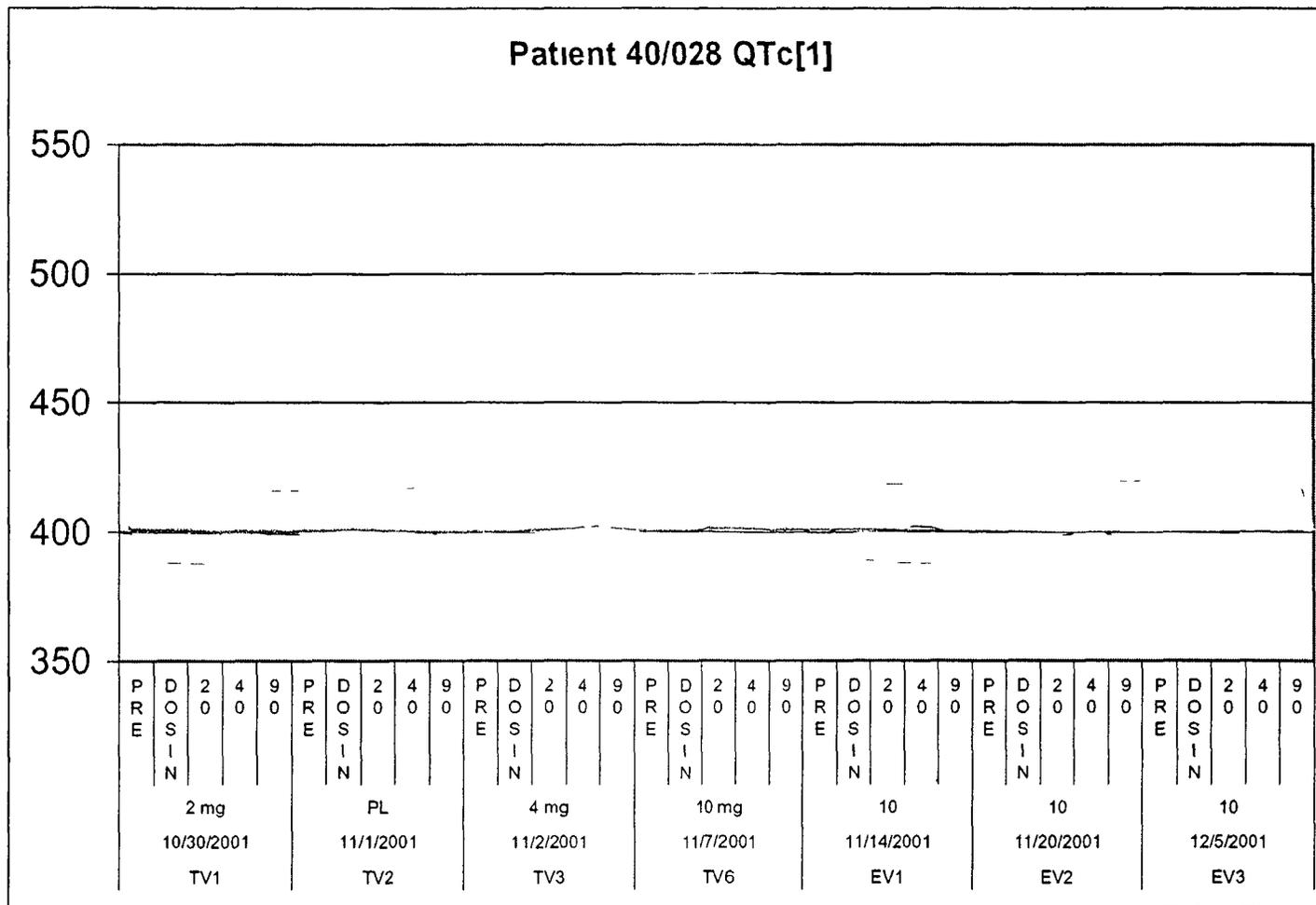
Table 13 QTcF Change from Baseline Versus Placebo or Oral Medication Dosing in Patients Who Reached 8 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	-2.2 (18)	(-7.9, 3.5)	0.6 (16)	(-1.8, 3.0)	1.8 (15)	(-4.0, 7.5)	-3.8 (16)	(-10.2, 2.5)	-3.7 (15)	(-11.3, 3.5)
20'	5.2 (18)	(-2.0, 12.3)	2.8 (15)	(-0.4, 6.0)	0.4 (15)	(-4.1, 4.9)	2.4 (15)	(-5.2, 10.0)	5.0 (15)	(-4.8, 14.7)
40'	5.8 (18)	(-0.6, 12.2)	-3.0 (15)	(-5.4, -0.5)	-0.5 (16)	(-4.7, 3.6)	7.9 (15)	(-0.0, 15.8)	4.9 (16)	(-1.1, 10.8)
90'	3.2 (18)	(-1.2, 7.5)	2.1 (13)	(-3.3, 7.5)	-1.5 (15)	(-7.1, 4.2)	3.0 (13)	(-5.4, 11.4)	4.7 (15)	(-0.7, 10.2)

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Figure 5 Predose and APM Post-treatment QTcB (squares) and QTcF (circles) Results Over Time of Patient 40/028 Who Exhibited Marked Increment in QTc (40 minutes) After 10 mg APM at TV6 Visit



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Table 14 QTcB Change from Predose Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	1.9 (10)	(-2.0, 5.7)	1.2 (7)	(-5.2, 7.6)	-1.1 (7)	(-9.4, 7.1)	2.1 (7)	(-8.9, 13.1)	3.6 (7)	(-7.8, 14.9)
20	1.7 (11)	(-5.2, 8.6)	0.8 (7)	(-8.6, 10.1)	0.3 (8)	(-7.3, 8.0)	1.0 (7)	(-8.4, 10.4)	0.4 (8)	(-15.1, 5.9)
40	10.6 (10)	(-16.3, 6.8)	-2.7 (6)	(-12.6, 8.8)	6.6 (7)	(1.0, 14.2)	5.0 (6)	(-10.2, 0.0)	8.3 (7)	(-29.4, 5.6)
90	-0.4 (11)	(-4.6, 3.9)	6.8 (6)	(-5.6, 19.1)	-1.8 (7)	(-14.1, 0.6)	-7.1 (6)	(-20.5, 5.9)	2.1 (7)	(-14.1, 8.5)

Table 15 QTcB Change from Predose Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM Excluding Patient 40/028 from APM Data

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	2.1 (9)	(-2.3, 6.5)	2 (7)	(-5.2, 7.6)	-0.3 (6)	(-10.9, 9.6)	2.1 (7)	(-8.9, 13.1)	3.1 (6)	(-11.1, 17.2)
20	0.1 (10)	(-6.6, 6.9)	0.8 (7)	(-8.6, 10.1)	1.2 (7)	(-7.6, 10.0)	1.0 (7)	(-8.4, 10.4)	-2.8 (7)	(-19.1, 3.4)
40	-0.7 (9)	(-7.6, 6.1)	-2.7 (6)	(-12.6, 8.8)	4.8 (6)	(-2.9, 12.6)	5.0 (6)	(-10.2, 0.0)	-6.2 (6)	(-21.8, 7.7)
90	-1.4 (10)	(-5.5, 2.7)	6.8 (6)	(-5.6, 19.1)	-0.9 (6)	(-16.1, 4.3)	-7.1 (6)	(-20.5, 5.9)	-0.4 (6)	(-19.1, 18.4)

Note: Patient 40/028 was excluded from the analysis

Table 16 QTcF Change from Predose Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	1.0 (10)	(-2.9, 4.9)	0.9 (7)	(-1.6, 3.4)	-1.0 (7)	(-7.5, 5.6)	1.4 (7)	(-6.3, 9.1)	1.6 (7)	(-9.0, 12.2)
20	-0.9 (11)	(-6.4, 4.6)	1.1 (7)	(-8.0, 10.2)	1.1 (8)	(-7.5, 9.7)	1.1 (7)	(-9.7, 11.9)	-2.4 (8)	(-18.1, 3.0)
40	6.6 (10)	(-14.2, 6.8)	-4.4 (6)	(-10.1, 6.6)	4.7 (7)	(-3.0, 12.3)	8.5 (6)	(-4.7, 21.6)	4.6 (7)	(-28.3, 6.6)
90	-1.7 (11)	(-8.5, 5.0)	7.5 (6)	(-3.6, 18.6)	-0.1 (7)	(-11.1, 10.3)	-2.8 (6)	(-11.5, 5.8)	-0.7 (7)	(-20.1, 18.9)

Table 17 QTcF Change from Predose Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM Excluding Patient 40/028 from APM Data

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	1.1 (9)	(-3.3, 5.6)	0.9 (7)	(-1.6, 3.4)	-0.8 (6)	(-8.9, 7.3)	1.4 (7)	(-6.3, 9.1)	1.5 (6)	(-12.1, 4.7)
20	-0.6 (10)	(-6.8, 5.5)	1.1 (7)	(-8.0, 10.2)	2.3 (7)	(7.4, 12.0)	1.1 (7)	(-9.7, 11.9)	-3.2 (7)	(-21.1, 5.0)
40	-1.5 (9)	(-11.8, 4.4)	-4.4 (6)	(-10.1, 6.6)	3.9 (6)	(5.3, 13.0)	8.5 (6)	(-4.7, 21.6)	-6.2 (6)	(-30.1, 8.0)
90	-1.3 (10)	(-8.8, 6.2)	7.5 (6)	(-3.6, 18.6)	-0.1 (6)	(-13.1, 12.9)	-2.8 (6)	(-11.5, 5.8)	0.2 (6)	(-24.2, 24.4)

Note: Patient 40/028 was excluded from the analysis

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Table 18 QTcB Change from Baseline Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	-0.6 (10)	(-7.0, 5.8)	0.1 (7)	(-7.6, 7.9)	2.1 (8)	(-9.1, 4.9)	-0.0 (7)	(-14.1, 3.5)	-0.3 (8)	(-7.1, 6.4)
20	-2.3 (11)	(-10.5, 5.5)	-0.3 (7)	(-6.0, 5.4)	0.0 (9)	(-6.4, 6.5)	-1.1 (7)	(-13.1, 1.0)	-5.5 (9)	(-16.5, 5.1)
40	6.7 (10)	(-17.3, 0.0)	-1.6 (6)	(-6.3, 3.1)	4.1 (9)	(-1.9, 10.1)	1.0 (6)	(-8.1, 10.2)	2.7 (9)	(-22.2, 7.7)
90	-4.4 (11)	(-11.2, 2.5)	5.1 (6)	(-2.9, 13.2)	-3.0 (9)	(-12.6, 6.3)	-9.1 (6)	(-22.4, 4.1)	-3.5 (9)	(-17.9, 5.5)

Table 19 QTcB Change from Baseline Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM Excluding Patient 40/028 from APM Data

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	1.2 (9)	(-4.3, 6.8)	0.1 (7)	(-7.6, 7.9)	-0.8 (7)	(-8.3, 6.7)	-0.0 (7)	(-14.1, 3.5)	0.5 (7)	(-7.3, 8.2)
20	-2.6 (10)	(-11.6, 6.3)	-0.3 (7)	(-6.0, 5.4)	1.3 (8)	(-5.3, 8.0)	-1.1 (7)	(-13.1, 1.0)	-7.5 (8)	(-19.3, 3.7)
40	-3.2 (9)	(-11.4, 8.8)	-1.6 (6)	(-6.3, 3.1)	3.1 (8)	(-3.4, 9.5)	1.0 (6)	(-8.1, 10.2)	-7.3 (8)	(-18.3, 6.6)
90	-4.1 (10)	(-12.3, 6.6)	5.1 (6)	(-2.9, 13.2)	-1.8 (8)	(-12.8, 5.5)	-9.1 (6)	(-22.4, 4.1)	-4.6 (8)	(-19.1, 10.3)

Note: Patient 40/028 was excluded from the analysis.

Table 20 QTcF Change from Baseline Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	-2.7 (10)	(-6.5, 1.1)	0.3 (7)	(-5.2, 5.9)	2.6 (8)	(-12.7, 4.4)	-4.9 (7)	(-13.3, 3.1)	-1.1 (8)	(-8.5, 6.3)
20	-4.9 (11)	(-11.0, 0.9)	0.5 (7)	(-5.1, 6.1)	-0.4 (9)	(-8.2, 7.4)	-5.2 (7)	(-14.3, 3.1)	-5.5 (9)	(-17.6, 2.2)
40	2.7 (10)	(-18.2, 3.3)	-3.2 (6)	(-7.2, 0.8)	1.3 (8)	(-4.7, 9.5)	0.1 (6)	(-10.1, 10.2)	-0.1 (9)	(-23.2, 2.5)
90	-5.7 (11)	(-12.1, 0.0)	1.1 (6)	(-1.8, 16.0)	-3.0 (9)	(-14.3, 9.9)	-9.4 (6)	(-18.0, 0.7)	-1.4 (9)	(-15.1, 2.6)

Table 21 QTcF Change from Baseline Versus Placebo or Oral Medication Dosing in Patients Who Reached 10 mg APM Excluding Patient 40/028 from APM Data

Session (Min)	APO		Oral Med		Placebo		APO-OM		APO-PL	
	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI	Mean (N)	95%CI
DOSING	-2.8 (9)	(-7.1, 1.5)	0.3 (7)	(-5.3, 5.9)	-2.9 (7)	(-15.8, 8.9)	-4.9 (7)	(-13.3, 3.1)	-1.1 (7)	(-9.9, 7.8)
20	-4.8 (10)	(-11.1, 6.6)	0.5 (7)	(-5.1, 6.1)	0.2 (8)	(-8.8, 9.1)	-5.2 (7)	(-14.3, 3.1)	-6.2 (8)	(-20.7, 2.2)
40	-5.6 (9)	(-15.3, 8.8)	-3.2 (6)	(-7.2, 0.8)	1.3 (8)	(-6.4, 9.0)	0.1 (6)	(-10.1, 10.2)	-8.4 (8)	(-22.5, 5.6)
90	-5.5 (10)	(-13.1, 9.9)	7.1 (6)	(-1.8, 16.0)	-3.8 (8)	(-16.1, 1.2)	-9.4 (6)	(-18.0, 0.7)	-0.4 (8)	(-16.1, 15.7)

Note: Patient 40/028 was excluded from the analysis.

Reviewer's Comments, Discussion, and Conclusions

- The sponsor had noted that preclinical studies support a lack of effect for APM on the action potential duration, and an acceptable margin of safety in the hERG model. My comments are based upon my review of these in vitro studies and brief discussion of my review with the Pharmacology/Toxicology reviewer (Dr P Roney). The sponsor interpreted the results of APM as negative for showing a prolongation of action potential duration as positive for showing some inhibition of hERG channels.

I have reservations about the sensitivity of the sponsor's study design for determining in vitro drug effects of APM, ropinirole, dopamine, and sotalol on action potential duration in a canine Purkinje fiber assay system. The sponsor had noted that it had selected drug concentrations of APM and ropinirole by studying the lowest concentration that approximated therapeutic levels and higher concentrations that were 10 and 100-fold multiples of therapeutic levels. The sponsor's study report noted that results of various concentrations of APM (0.01, 0.1, 1 μ M), ropinirole (0.1, 1, 10 μ M), and dopamine (0.01, 0.1, 1 μ M) on action potential duration in a canine Purkinje fiber assay system were compared to effects of a positive control, sotalol (100 μ M).

I think that it is important to recognize that the sponsor did not select the highest APM dose to be studied appropriately. Considering that the mean C_{max} for the highest APM dose (10 mg) is approximately 50 ng/ml (~0.2 μ M), following the sponsor's rationale for highest dose selection, the highest APM dose (e.g. 100 fold over the therapeutic level) studied in the Purkinje fiber assay should have been ~20 μ M rather than only 1 μ M. It may also be relevant to note that the concentration of sotalol, the positive control, that clearly prolonged action potential duration was 100 fold greater than the highest concentration of APM studied and 10 fold greater than the highest concentration of ropinirole studied. However, sotalol is a relatively weak positive control for this assay system compared to dofetilide, that is a very potent positive control. Regardless of the positive control used, I am not certain that it is necessarily appropriate to limit the study even to 100 fold of the therapeutic level of the drug because one does not know how the sensitivity of the canine model system for responding to a drug translates to the human sensitivity for responding to a drug. I would think that it would have been more reasonable to study **at least equimolar concentrations** to assess if there is any effect on action potential duration and **may have been reasonable to study several fold higher concentrations of the experimental drugs under evaluation relative to the positive control.** In contrast, the sponsor studied molar concentrations of the positive control (sotalol) that was 100 fold greater than the highest concentration of APM evaluated and 10 fold greater than the highest concentration of ropinirole evaluated. I question what results this model system would have shown if the sponsor had studied $\geq 100 \mu$ M APM, ropinirole, and dopamine? **Thus, it is difficult to escape the conclusion that these studies may have been conducted with an insensitive study design for showing prolongation of action potential by these drugs. I am not convinced that these results for APM represent a true negative in terms of its effects on action potential duration.**

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Furthermore, even if the study design of the Purkinje fiber system was appropriate and the results did suggest a true negative, I would not necessarily attribute much significance to the absence of significant effects of APM in Purkinje fiber studies assessing effects on action potential duration. **Thus, a negative result in the Purkinje fiber system for assessing effects of APM on action potential duration is not necessarily reassuring for diminishing the risk of QTc prolongation because this model system is not considered to be a sensitive, screening method for suggesting drugs with a significant risk of human QTc prolongation and Torsades de pointes.** I also note that in vivo preclinical studies of effects of APM on QTc in dogs were not conducted with a sensitive design for demonstrating effects on QTc prolongation because the time of electrocardiographic assessment was much later after administration of APM at a time when plasma APM levels would be expected to be very low, if measurable.

I was not involved with the NDA review of ropinirole and thus am not familiar with risks of ropinirole for QTc prolongation from preclinical studies and human studies. However, results reported by the sponsor show appreciably significant hERG channel inhibition (i.e. $IC_{50} = 1 \mu M$), making ropinirole also a candidate for risk of QTc prolongation and arrhythmia (e.g. Torsades de pointes). Ropinirole is indicated for treatment of early and advanced Parkinson's Disease. ☐

☐ I searched the label for ropinirole and noted that in the adverse events section of clinical trials that events with $\geq 2\%$ incidence and $>$ placebo were noted for extrasystoles, palpitation, tachycardia, syncope, hypotension, and dizziness. The "laundry list" of adverse events also notes that cardiac arrest and tachycardia were infrequent and that ventricular tachycardia was rare. It is conceivable that some of these adverse events may have represented Torsades de pointes that was not diagnosed. I also searched PUBMED today for paired searches of ropinirole and several separate terms/phrases including sudden death, cardiac arrest, Torsade de pointes, ventricular arrhythmia, ventricular tachycardia, and ventricular fibrillation and did not find any relevant publications. Nevertheless, I believe that this hERG channel result for ropinirole raises the question whether ropinirole could also be associated with a previously unrecognized risk for human QTc prolongation and Torsades de pointes.

The sponsor presented new, recent results in a hERG channel assay system prompting significant concern for the potential of human QTc prolongation and Torsades de pointes. APM produced significant inhibition ($0.127 \mu M = IC_{50}$) during in vitro studies of hERG channels in mammalian cells supporting a serious potential for QTc prolongation in humans. An IC_{50} result of $\leq 1 \mu M$ is considered to be a relatively good surrogate for suggesting a potential concern of a risk for human QTc prolongation and Torsades de pointes. This concern is based upon the facts that most drugs shown to be associated with human QTc prolongation and Torsades de pointes showed similar results (i.e. $IC_{50} \leq 1 \mu M$) in the hERG channel assay (Table 22). These results based upon a somewhat limited but still substantial dataset were provided by Dr. John Koerner (Pharmacologist/Toxicologist in DCRDP, HFD-110), who is an expert at FDA/CDER on this

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Table 23 Sensitivity and Specificity of IC₅₀ hERG Channel Assay Result (i.e. $\leq 1 \mu\text{M}$) for Drugs Associated with Proarrhythmia (e.g. Torsades de pointes) and Human QTc Prolongation or Human QTc Prolongation

Associated with Proarrhythmia (e.g. Torsades de pointes)		Associated with Human QTc Prolongation (Regardless of Presence or Absence of Proarrhythmia such as Torsades de pointes)	
Sensitivity	Specificity	Sensitivity	Specificity
69 % (20/29)	79 % (15/19)	71 % (22/31)	88 % (15/17)

Sensitivity = # drugs associated with the a specific outcome described and showing the “positive”, defined abnormal test result (e.g. $\leq 1 \mu\text{M}$ IC₅₀ in hERG channel assay) / # drugs associated with a specific outcome described and showing any IC₅₀ test result in hERG channel assay,

Specificity = # drugs **not** associated a specific outcome described and showing a “negative” test result (e.g. $> 1 \mu\text{M}$ IC₅₀ in hERG channel assay) / # drugs **not** associated with a specific outcome described and showing any IC₅₀ test result in hERG channel assay,

topic For purposes of discussion, it should be noted that drugs reported to be associated with Torsades de pointes in humans were also associated with QTc prolongation in humans. Of 24 drugs that exhibited an IC₅₀ $\leq 1 \mu\text{M}$ in a hERG channel study, 20 (83 %) were reported to be associated with Torsades de pointes (Table 22). When 24 drugs with the same categorical result (i.e. IC₅₀ $\leq 1 \mu\text{M}$ in a hERG channel study) were assessed for the frequency of being associated with human QTc prolongation with or without Torsades de pointes, 22 drugs (92 %) were considered to be associated with human QTc prolongation. The corresponding **true positive rate** for finding “potent” inhibition in a hERG assay (i.e. IC₅₀ $\leq 1 \mu\text{M}$, that predicted an association with Torsades de pointes (and QTc prolongation) and with human QTc prolongation (regardless of the presence or absence of Torsades de pointes), was 69 % (20/29) and 71 % (22/31), respectively. The corresponding **false positive rate** for finding “potent” inhibition in a hERG assay (i.e. IC₅₀ $\leq 1 \mu\text{M}$, that predicted an association with Torsades de pointes (and QTc prolongation) and with human QTc prolongation (regardless of the presence or absence of Torsades de pointes), was 21 % (4/19) and 12 % (2/17), respectively. Table 23 presents results shown in Table 22 with respect to sensitivity and specificity of a hERG channel IC₅₀ result of $\leq 1 \mu\text{M}$. **Overall, the sensitivity of relatively “potent” inhibition in a hERG channel result (i.e. IC₅₀ $\leq 1 \mu\text{M}$) for Torsades de pointes or human QTc prolongation was moderately good. The specificity of such a result for Torsades de pointes or human QTc prolongation was quite substantial and even higher than the sensitivity.** Finally, considering a different perspective of these hERG channel results, only 9 drugs (9/24 - 38 %) were reported to be associated with Torsades de pointes or human QTc prolongation when a hERG channel IC₅₀ result was $> 1 \mu\text{M}$.

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It is worthy to note that the APM results in the hERG assay reported by the sponsor indicate an element of specificity for hERG channel inhibition by dopaminergic agonists. The sponsor had studied different concentrations of dopaminergic agonists, including dopamine (0, 1, 100 μM), APM (0.03, 0.01, 0.3, 1 μM), ropinirole (0.3, 1, 3, 10 μM) and a positive control, haloperidol (0.1 μM). Whereas there was no appreciable or significant hERG channel inhibition by dopamine, the IC_{50} for APM and ropinirole was 0.127 μM and 1.214 μM , respectively showing greater potency of APM over ropinirole. The positive control (haloperidol) produced nearly complete inhibition (e.g. 92%) at 0.1 μM . These results show that the IC_{50} for APM for hERG channel inhibition was approximately 10 fold more potent than that of ropinirole, a dopaminergic agonist presently approved in the U.S. and throughout the world for Parkinson's Disease. Although an IC_{50} for hERG channel inhibition by haloperidol, the positive control, was not provided because only a single concentration was studied, the inhibition produced by 1 μM APM (92%) was identical to that produced by 0.1 μM haloperidol. While haloperidol was clearly more a more potent hERG channel inhibitor than APM, inhibition by APM was clearly significant.

- As I reviewed additional QTc analyses in the sponsor's submission, I became aware of additional detailed information relevant to the collection of predose QT data for studies APO302 and APO303. Predose "off" QT data collected by standard 12 lead ECGs in APO302 had been obtained over a relatively long period (ranging from 1 to 59 minutes) prior to administration of randomized treatment. In many instances the interval was > 30 minutes. Considering that QT can spontaneously vary over time, assessing QTc changes from a single value **collected at a more remote time from treatment administration** contributes to "noise" in the data analyses and makes it more difficult to assess treatment effects accurately, particularly if the treatment effects are not dramatic but relatively small or modest. Thus, this design issue or design "flaw" of the reference QTc value used for comparison of APM treatment effects further clouds the reliability of APO302 results and argues for additional study of APM on QTc.

This concern about selecting an appropriate reference QTc value used for assessing APM treatment effects is somewhat lessened for data collected in study APO303. In this study's evaluation of QTc effects of APM with Holter methodology, almost all patients received the treatment injection within 20 minutes of collection of predose "off" QT measurement. Although a considerable number of patients received a treatment injection between 10 and 20 minutes after measurement of predose "off," many patients received an injection within 10 minutes of collection of predose "off" QT. Because it is not clear that the collection of "baseline" QT/QTc data was necessarily more appropriate for use in comparing effects of APM treatment, I have put more weight on the results of QTc analyses relative to the predose comparator based upon a QT measured just before the treatment injection. Although I recognize the potentially problematic nature of comparing post-treatment effects at different times in reference to a single pre-treatment comparator, the treatment effects of 8 mg APM also suggest QTc prolongation when change from baseline (including more pre-treatment QT measurements from different time) is assessed.

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- **In this submission, the sponsor did not conduct and present comprehensive analyses of QTc changes from predose according to dose at all timepoints available for study APO302** The sponsor had noted that it “compared the change in QTc at the 20 minute time-point across doses in APO302 ” **However, the DNDP had not limited its request for additional analyses only to the 20 minute time-point** The sponsor presented a listing (Attachment 33 1) of predose and post-dose QTc (Bazett-QTcB and Fridericia-QTcF corrections) at 20 and 90 minutes according to treatment and APM dose **but did not calculate and provide QTc changes from pre-dose in this submission** The sponsor did present a listing (Attachment 33 2) of QTcB and QTcF for change from pre-dose **but only for changes at 20 minutes (but not for changes at 90 minute)** **It is important to note that the most impressive increments (vs placebo) in QTcB and QTcF that had been noted in my analyses of study APO302 results provided by the sponsor (presented in my original Safety Review of NDA 21264 dated 6/20/03) occurred at 90 minutes** Study APO302 did not collect data at 40 minutes post-treatment It is also important and highly relevant to recall that my Safety Review (dated 6/20/03) had noted that the 40 and 90 minute post-treatment time-points were associated with overall the greatest QTcB and QTcF increments (vs placebo for 8 and 10 mg APM) in study APO303 It is also of interest and relevant to study APO302 results to recall that my Safety Review illustrated and described prominent pharmacodynamic actions of APM at 40 and 90 minutes with some hypotensive blood pressure effects most prominent at 40 minutes **Altogether these results suggested the importance of also assessing effects of APM on QTc at "later" timepoints (e g 40 and 90 minutes post injection)**

I do not know why the sponsor did not present and discuss QTcB results of either APM group or the pooled APM experience that shows appreciable QTc increments above placebo for study APO302 in which electrocardiographic data were characterized with standard 12 lead ECGs Although the APM + 2 mg group showed a treatment effect (i e APM – placebo) for QTcB that was greater than the APM group at 90 minutes (Table 8), a similar effect was not observed at the 20 minute time-point However, the absence of a QTc significant difference between APM groups is not necessarily surprising considering that the difference between the mean APM dose in each group (mean APM = 4.6 mg, mean APM + 2 mg = 5.8 mg) was very small, only approximately 1 mg (Table 24) Furthermore, the absence of “statistically compelling” differences is of no value considering that these results were not necessarily designed nor powered to show any statistical differences for QTc, let alone “statistically compelling” treatment differences for QTc Overall, I interpret these results of both QTcB and QTcF, that show similar effects, as suggesting the possibility APM prolongs QTc at 90 minutes and that the effect at 40 minutes is not known because this time-point was not evaluated in this study

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Table 24 Apomorphine Dose Ranges in Parkinson's disease Patients Investigated for Standard 12 Lead ECG Changes with Respect to Dosing (e.g. Pre-dose, + 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)

It is not clear why the sponsor did not conduct analyses assessing a possible relationship between APM dose and QTc at 90 minutes. I created Table 9 based upon QTcB and QTcF changes from predose at 20 and 90 minutes based upon the sponsor's listing of data (Listing 2 in Attachment 33.1). Overall, there is no significant suggestion that either APM dose category (i.e. 2-6 mg or > 6-10 mg per injection) prolongs QTcB or QTcF assessed at 20 minutes after treatment injection. In contrast, data assessed at 90 minutes after treatment injection suggest that APM prolongs QTcB or QTcF (Table 9). Whereas, these mean QTc results suggest APM dose-dependent QTcB prolongation (e.g. QTcB itself or QTcB treatment effect after correction from placebo), analogous mean QTcF results do not suggest progressive APM-induced QTcF prolongation. However, it should be noted that the data for the high dose category are based upon a very small number of patients. **There was no good distribution of APM doses (N = 35) in study APO302 over a wide range of doses of 2-10 mg (Table 24).** For example, 86% (30/35) of patients used APM ≤ 6 mg injections, 80% (28/35) used > 2 – 6 mg per injection and only 14% (5/35) were randomized to receive > 6 - 10 mg per injection (e.g. 2 received usual APM dose, 3 received usual APM dose + 2 mg). **My overall assessment of QTc results from study APO302 is that there is a distinct possibility of APM-induced QTc prolongation and that characterization or exclusion of QTc prolongation by APM clearly requires additional study, particularly at "high" doses (> 6 mg/injection).**

- My review of the ECGs (predose, and + 20 and 90 minute post-treatment) of patient 41/003, who showed large increments (QTcB - 76 msec, QTcF - 59 msec) from predose at + 20 minutes to peak values of 514 msec (QTcB) and 487 msec (QTcF) confirmed that the QT/QTc measurements appeared to be real. Furthermore, I also obtained similar QTc measurements at + 90 minutes, the timepoint for which significant, identical increments from predose were also reported for QTcB (+ 54 msec) and QTcF (+ 54 msec). Thus, these

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measurements did not appear to be based upon an artefactual reading. There was no value in reviewing other ECG tracings for this same patient provided by the sponsor because these tracings were not centrally read and information about the time relationship of these ECGs to APM injection was not known.

- Overall, I interpret the results of study APO303 as suggestive of possible QTc prolongation from high doses (> 6 mg injections) of APM. The mean treatment effect (APM - placebo) of the 8 mg dose shows significant QTc increments (~ 5 - 9 msec) from predose for both QTcB and QTcF with the largest increment occurring at 40 minutes for both corrections (Table 10 and Table 11). Although the mean 8 mg treatment effect relative to oral medication (i.e. APM - oral medication, another type of control) for QTc change from predose is less than for each corresponding timepoint and correction relative to placebo, there are still small treatment effects and the treatment effect at 40 minutes for QTcF is considerable at 6 msec (Table 10 and Table 11).

The sponsor's QTc analyses in this submission focused on results for the 8 and 10 mg APM dose groups relative to placebo or oral medication results and relative to QTc change from "pre-dose" or from "baseline." For potential easy reference to compare high dose APM (i.e. 8 and 10 mg) results also with those of low dose APM (≤ 6 mg), I have included my tables (from my Safety Review dated 6/20/03) showing various analyses of APM treatment effects on QTcB and QTcF. Table 25 and Table 26 show treatment effects (relative to predose) of APM on QTc results compared to placebo and oral medication, respectively. Table 27 and Table 28 show APM treatment effects (relative to baseline) on QTc results compared to placebo and oral medication, respectively. Although APM-related QTc changes (e.g. increment) from predose were occasionally similar to the QTc changes from baseline, QTc increments for these different reference comparators were not always similar. Thus, I have presented analyses with respect to both QTc reference comparators (i.e. predose and baseline QTc) as did the sponsor in analyses provided in this submission. Whereas, these results overall do not suggest a QTc prolonging effect of APM at doses ≤ 6 mg per injection, these results overall suggest or at the very least raise questions about QTc prolongation at 8 and 10 mg doses.

The greatest treatment effect relative to placebo (i.e. APM - placebo) for QTc changes from baseline at any time were approximately 2 and 5 msec for QTcB and QTcF (Table 12 and Table 13). The greatest treatment effect relative to oral medication (i.e. APM - medication) for QTc changes from baseline at any time was approximately 2 and 8 msec for QTcB and QTcF (Table 12 and Table 13), respectively. I consider the QTc change from predose as potentially more relevant for assessing APM treatment effects than the QTc change from

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Table 25 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)