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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-264

Medical Review(s)

Clinical NDA Review of Sponsor's Response to Approvable Letter

Brand Name **APOKYN**

Generic Name **apomorphine**

Sponsor **Bertek Pharmaceuticals**

Indication **⌈**

1

NDA Number **21264**

Original Receipt Date: **10/20/03**

Clinical Review Author : **Leonard P. Kapcala, M.D.**

Review Completed: **3/1/04**

CLINICAL REVIEW

Clinical Review Section

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1. EXECUTIVE SUMMARY, CONCLUSIONS, RECOMMENDATIONS

Background and Introduction

The sponsor submitted (1/2/03) NDA 21264 for subcutaneously administered apomorphine (APM), a non-selective dopaminergic agonist, for the indication:

This NDA was reviewed in the DNDP (HFD-120) and the Agency issued an approvable letter on 7/2/03. Many issues of concern and requiring a response were specified for all disciplines including Chemistry, Clinical, Pharmacology/Toxicology, and Biopharmaceutics/Clinical Pharmacology. On 10/20/03, the Agency received the sponsor's Response to the Approvable Letter, that is the subject of my review.

Indication APOKYN™ (apomorphine hydrochloride) (APM) is indicated for the acute, intermittent treatment of hypomobility ("Off") episodes in Parkinson's disease. APOKYN™ has been studied as an adjunct to other Parkinson's medications.

This Executive Summary specifies the Clinical Comments to the sponsor and my conclusions based upon my review of the sponsor's responses to these clinical comments. In addition, I have also summarized my conclusions regarding other important issues.

CLINICAL COMMENTS

The approvable letter contained 8 clinical comments. The sponsor responded to each of DNDP's clinical comments. I have provided my conclusions based upon my review of the sponsor's responses.

FDA Comment 1

Indication You are seeking a claim for the treatment of two types of Off periods: end-of-dose wearing Off and spontaneous Off. In the initial phase of APO202, you induced Off periods by withholding PD medication overnight. Such induced Off periods may be more complex, given that they occur unrelated to time of dosing. In APO301 and APO302, patients received their morning doses of PD medication and were followed until their first Off of the day (at least 1 hour post dosing). Whether the results of APO301 and 302 address the efficacy of apomorphine for spontaneous Off periods depends on the distributions of time-to-Off in those studies. If many studied Off periods occurred well before the end of the usual dosing interval, the results would bear on spontaneous Off periods. If, however, the great majority of Off periods occurred close to the end of the usual dosing interval, then the results bear more on end-of-dose Off. We therefore ask you to examine APO301 and APO302 to determine each patient's time-to-apomorphine-dosing and compare this to the patient's usual dosing interval. Please categorize patients based on whether the treated Off period best represents end-of-dose wearing Off or spontaneous Off.

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I conclude that

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

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.

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

FDA Comment 3

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.

I conclude that

- 1) **preclinical in vitro hERG channel results for APM support a serious potential risk of APM for Torsades de pointes and human QTc prolongation,**

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- 2) preclinical in vitro Purkinje fiber assay results investigating the effect of APM on action potential duration were not performed appropriately in a most sensitive manner and thus the negative result reported by the sponsor is of indeterminate significance,
- 3) a description of a potential risk of QT/QTc prolongation from APM and the potential clinical significance of this QTc prolongation is warranted in the WARNINGS section of the label based upon the totality of information available and summarized in my assessment,
- 4) the sponsor should conduct a randomized, double-blinded, placebo-controlled study to evaluate the effects of the full dose range (up to 10 mg) of subcutaneous APM on the QTc interval

FDA Comment 4

Concomitant Tigan The exposure to Tigan in the NDA needs to be fully characterized prior to approval While we know that essentially all patients received Tigan we do not know how Tigan was used over time Please provide information bearing on this issue It would be helpful to break down the apomorphine exposure into time with and without Tigan Specifically, determine the number of patients who were able to successfully taper off of Tigan and continue apomorphine Once off Tigan, did patients need to resume Tigan?

I conclude that the sponsor has reasonably addressed DNDP's inquiries and presented information that provides a better understanding of how Tigan was used in conjunction with APM

FDA Comment 5

The dose of Tigan used in the apomorphine development project was 250mg tid This dose is no longer marketed in this country, the marketed dose is 300mg It will be a matter of judgment as to whether the 50mg increment could interfere with the efficacy of apomorphine at the approved doses or alter the safety profile seen in the NDA We ask you to explain why you believe a 50mg increment in dosing for Tigan will not significantly alter the experience with apomorphine

I conclude that

- 1) it remains unknown whether the 300 mg formulation of Tigan is associated with a different efficacy or safety profile than the profiles characterized during the concomitant use of the 250 mg formulation of Tigan because data are not available for analysis of this issue,

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- 2) **answers regarding safety questions can be derived from future analyses of safety experience resulting from a planned, randomized, double-blind, placebo-controlled study assessing the need to use 300 mg Tigan tid and future analyses from ongoing open-label APO401 study in which patients are being switched to the 300 mg Tigan,**
- 3) **insight as to whether the 300 mg Tigan formulation might alter the efficacy of APM might be obtained from the planned pharmacokinetic study addressing whether the 300 mg Tigan affects the APM pharmacokinetic profile differently than the 250 mg Tigan,**

FDA Comment 6

After approval, you should conduct a randomized, parallel group, placebo-controlled trial to investigate the actual necessity for the use of concomitant Tigan to decrease nausea and vomiting in patients who initiate and continue treatment with apomorphine. While we are describing the concomitant use of Tigan in our version of labeling, we believe that more definitive evidence of the benefit of Tigan should be accrued.

I conclude that the sponsor's response to commit to a randomized, parallel group, placebo-controlled trial to investigate the actual necessity for the use of concomitant Tigan to decrease nausea and vomiting in patients who initiate and continue treatment with APM after APM approval is reasonable and adequate at this time.

FDA Comment 7

Please address the capability of the intended patient population to self-administer apomorphine by subcutaneous injection. We recognize that patients have been supplied with ampules/syringes in your studies to date, but we are interested in knowing whether self-administration or administration by a caregiver was usual. Please address the capability of patients with advanced Parkinson's disease to use the dosing pen.

I conclude that

- 1) **there are significant concerns that patients with Parkinson's Disease can safely administer APM with the pen delivery system without possibly sustaining needle injuries from recapping the needle, and without overdosing themselves (because this pen device does not inform the patient if the cartridge has sufficient volume of APM for a single injection) due to the occasional necessity of administering the desired APM treatment as 2 injections,**
- 2) **demonstration of the safety of using the APM pen should be based upon the presentation of analyses showing the experience of the pen based upon actual use in**

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patients involving administration both by patients and caregiver and should not be based upon less compelling, indirect or theoretical information,

- 3) a safety experience with the pen can be collected in patients, analyzed in comparison with the safety profile of the ampoule formulation, and these data and analyses can be submitted to support an approval of the pen formulation,**

FDA Comment 8

Please justify the use of the benzyl alcohol formulation, you have presented no data about the safety of this formulation other than single 2 mg doses in normal volunteers

I conclude that

- 1) there are no actual data that support the safe use of the APM pen formulation containing 0.5 % benzyl alcohol because the sponsor has not presented any use data from patients treated with the benzyl alcohol formulation but has only presented the minimal experience of single injections of low dose (2 mg with 0.5 % benzyl alcohol) APM given to healthy volunteers,**
- 2) the sponsor has not adequately justified the safe use of the APM formulation containing 0.5 % benzyl alcohol, particularly with respect to DNDP's concern about increased local toxicity at the injection site,**
- 3) actual pen use data of APM containing 0.5 % benzyl alcohol (derived from patients who self-administer APM and who receive it from a caregiver) should be submitted for DNDP review to support the safe use of the APM pen,**

Safety Update #2 (SU2)

This current Safety Update (SU2) summarizes the safety experience of 550 patients (vs 536 patients in SU1). On average, these patients were 65 years of age, had Parkinson's disease for 11 years, and had "Off" episodes for a significant portion of their hours awake. SU2 provides data for 535 patient-years of treatment with APM in the Bertek clinical development program, representing data from 14 new patients enrolled in APO401 since SU1 and a total increase of 116 patient-years of exposure to APM (28 % increase above SU1 APM exposure).

I conclude that there is no substantive change in the safety profile of APM related to the safety experience of APM presented in SU2 and in the updated reported foreign post-marketing experience of APM compared to the safety profile that I had assessed during my review of the safety experience in the ISS and SU1 and reported foreign post-marketing experience of APM

Drug Interaction Studies Related to Hypotension

Drug-drug interaction studies investigating potential interactions of APM with alcohol and APM with vasodilators (short-acting and long-acting nitrates) had been recommended in the Clinical Pharmacology and Biopharmaceutics section of the approvable letter. The sponsor argued against the need for these drug-drug interaction studies based upon pharmacokinetic interactions but did not address the need for such studies relative to potential pharmacodynamic interactions. The biopharmaceutical reviewer (Dr J Duan) agrees that these studies are not needed because of pharmacokinetic interactions. **However, the biopharmaceutical reviewer recommends that these drug interaction studies be conducted to address potential safety concerns relative to pharmacodynamic interactions on lowering blood pressure.**

I noted in my review of SU2 that patients taking vasodilating medications (including non-nitrate drugs used to treat hypertension) exhibited an increased association of serious adverse events such as falls, bone and joint injuries, myocardial infarction, and pneumonia and non-serious adverse events such as hypotension, and lethargy. **Considering the well recognized hypotensive effects of APM and the hypotensive effects of many of these vasodilating medications, I think that it is quite reasonable to expect that an increased occurrence of many, if not perhaps all these events, might be related to increased hypotension associated with the concomitant use of these vasodilating medications and APM.**

Previous drug-drug interaction studies between sublingual APM and alcohol, APM and nitrates showed clearly increased safety risks associated with increased hypotension and events (e.g. syncope) related to hypotension. Placebo-controlled studies showed significant pharmacodynamic interactions between APM and alcohol or nitrates (short-acting and long-acting) with respect to hypotension and hypotensive-related adverse reactions of significant concern including syncope.

There were no clear pharmacodynamic interactions between sublingual APM (5 mg) and non-nitrate antihypertensive drug groups (ACE inhibitors, beta blockers, diuretics, calcium channel blockers, alpha₁ blocker) in a placebo-controlled study to address this issue. However, it is critical to recall the limited bioavailability (10%) of sublingual APM and the essentially complete (100%) bioavailability of subcutaneously injected APM. Thus, 5 mg of sublingual APM would be equivalent to < 1 mg injection of APM. **Considering that doses of injectable APM (i.e. APOKYN) to be used would likely range from 2-6 mg per injection (and patients could potentially use up to 10 mg APM off-label), the interaction studies between non-nitrate antihypertensive drugs and sublingual APM are of no real relevance to concerns about the risk of hypotension and hypotension-related adverse events from pharmacodynamic interactions between APOKYN and many anti-hypertensive drugs.**

There is an additional scenario whereby the concomitant use of APM and anti-hypertensive drugs could be problematic. It is potentially relevant to note that some patients experience vasovagal reactions with APM administration and that the normal physiological adaptive

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response to any hypotensive experience is for heart rate/pulse to increase. However, patients experiencing a vasovagal effect from APM would not be expected to be able to mount a normal physiological adaptive response of increased heart rate/pulse to hypotensive effects of other drugs, and thus, this phenomenon could result in increased hypotension and adverse reactions.

I believe that it is also important to note that the European label recommends caution about taking injectable APM with vasoactive drugs such as antihypertensive drugs, or taking APM in patients with postural hypotension or with cardiac disease, and that there is a potential for APM to potentiate antihypertensive and cardiac active drugs. **Thus, considering all these observations outlined, I conclude that it is important that the sponsor be required to commit to phase 4 studies investigating these potential, hypotensive pharmacodynamic interactions between APM and other agents including 1) alcohol, 2) nitrates (short-acting and long-acting nitrates), and 3) various categorical types of anti-hypertensive drugs.**

Serious Adverse Events Related to Drug Interaction Between APM and Ondansetron

On 3/31/04, the sponsor contacted DNDP to ask if the Agency still has "concerns about the use of ondansetron with apomorphine that should be provided in the labeling." This topic had arisen after an internal review of Bertek's development program for APM. In 1997, Mylan Pharmaceuticals (Bertek) was informed that it could not conduct studies to compare the ability of ondansetron to prevent APM-induced nausea and vomiting with the ability of trimethobenzamide to do the same because the Agency was aware of a serious problem when APM and ondansetron were used in combination. Mylan was not informed of the nature of the serious adverse reaction. There is no information to indicate that Mylan investigated this drug interaction in animal studies nor that it attempted to see if this issue could be addressed in humans.

On 3/13/97, DNDP received reports that 3 healthy volunteers had experienced serious adverse reactions consisting of severe hypotension, syncope/loss of consciousness, and bradycardia and one subject experienced seizure activity. These adverse reactions occurred within a half hour of administration of 10 mg Zydys apomorphine after 3 days of oral ondansetron 8 mg every day (including administration 30 minutes prior to Zydys APM). This experience was observed under IND [redacted] and occurred in 3 of 12 subjects studied and prompted a CLINICAL HOLD for studying additional humans with Zydys APM and ondansetron. All 3 subjects recovered (additional details regarding this experience are described in my review of Labeling Issues). These most serious adverse reactions were suspected as being related to a drug interaction between ondansetron and APM because similar reactions did not occur with the use of ondansetron. Neither did such dramatic adverse reactions appear to occur in subjects administered single doses of Zydys APM at 10 mg or higher (up to 30 mg) in the absence of ondansetron. Nevertheless, the nature of the suspected drug interaction was never characterized. IND [redacted] was subsequently withdrawn.

This suspected drug interaction between ondansetron and APM is most serious, of great concern, and should be described in the APOKYN label by making ondansetron a contraindication and cross-referencing this information in the Drug Interactions section. I question whether this suspected drug interaction might even occur with other 5HT₃ antagonists so that this adverse

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reaction could potentially be a result of a drug interaction between APM and the class of other similar drugs that act as 5HT₃ antagonists (e.g. granisetron, dolasetron, alosetron)

I have serious concerns that serious reactions, potentially life-threatening, could occur if patients used APM in conjunction with ondansetron, and possibly even other 5HT₃ antagonists. Such potential drug interaction use with ondansetron and APOKYN would likely be associated with much higher plasma levels of both drugs. The C_{max} for 10 mg Zydys APM is ~ 3 ng/ml, much lower than the mean C_{max} expected with use of the lowest dose (2 mg) of APOKYN recommended for use in the label. It is important to recall that the mean C_{max} for the highest recommended dose (6 mg) of APOKYN would be ~ 30 ng/ml and that patients could potentially use a higher than recommended dose (e.g. 10 mg) off-label that would have a mean C_{max} of ~ 50 ng/ml. In addition, the normal daily use of ondansetron is 8 mg BID or TID. Thus, it seems clear that if such drug interactions occurred after approval of APOKYN, these drug interactions would likely be accompanied by much higher levels of both drugs and one would expect even more severe adverse reactions than those previously observed.

I also believe that there is a reasonable possibility that some patients might use APOKYN in combination with ondansetron or other similar 5HT₃ antagonists. First, some physicians might opt for the off-label chronic use of ondansetron or a related drug to prevent or minimize nausea and vomiting instead of the recommended anti-emetic, trimethobenzamide that is also being used in an off-label indication. Second, some patients might be treated with these 5HT₃ antagonists to prevent nausea and vomiting for chemotherapy or radiation therapy if some patients also require treatment for a cancer. Some could also receive these drugs for the prevention of post-operative nausea and vomiting. Finally, a search of the literature revealed publications describing the use of ondansetron for the treatment of hallucinations in Parkinson's Disease or drug-induced psychosis in Parkinson's Disease. Thus, there seems to be a reasonable possibility that patients could use APOKYN and ondansetron or one of the other 5HT₃ antagonists.

Given the potential for this serious drug interaction between APOKYN and ondansetron or other 5HT₃ antagonists, I consider it critical that such information must be contained in the APOKYN label. ☐

☐ If this information cannot be included in the APOKYN label, then NDA 21264 should receive another approvable letter

Carcinogenicity

The approvable letter had noted that the sponsor needed to address the carcinogenicity potential of APM by conducting its own appropriate studies. ☐

☐

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In the response to the Approvable Letter, the sponsor noted [

[

[

] At the time, the

sponsor was unable to provide any information []
would look into the matter and respond to DNDP. As of 4/7/04, DNDP has not yet received a response to DNDP's request []

I consider that it is important to include information in the APOKYN label about a potential risk for injection site cancer following chronic, intermittent APOKYN use. I would consider it unethical not to inform (in the label) users about this potential risk of which we are aware. I consider this to be a similar issue as informed consent in terms of informing humans subjects about potential safety risks when they enroll in experimental studies. **If the carcinogenicity findings cannot be described in the APOKYN label now, then I would conclude that an approvable action would be appropriate for APOKYN at this time.** The sponsor must consider conduct its own carcinogenicity studies and these studies should be initiated as soon as possible []
(started soon)

Need for Studies of Metabolism

The Approvable Letter noted that metabolic studies in animals and humans must be conducted prior to approval. My original safety review made this same recommendation. Subsequent to the approvable letter, the DNDP and sponsor discussed this issue at a teleconference (8/7/03) and the DNDP said that the sponsor could make an argument to conduct metabolic studies post-approval as a phase 4 commitment. Based upon internal discussions within the DNDP among other disciplines (Clinical, Biopharmaceutics, Pharmacology/Toxicology, I can accept these studies being conducted post-approval as a phase 4 commitment.

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Labeling Issues

I have many concerns about labeling. These concerns have been outlined at the end of my review. My most important labeling concerns are to describe **1) the potential risk for QTc prolongation and the potential significance of QTc prolongation vis a vis Torsades de pointes (and possible cardiac arrest or sudden death) clearly and adequately in the Warning section of the label, 2) the potential safety risk of injection site sarcomas based upon the animal carcinogenicity findings in rodents, and 3) the potential serious drug interaction (e.g. severe hypotension and loss of consciousness) from taking APM with ondansetron and possibly other 5HT₃ antagonists and to contraindicate the concomitant use of these drugs**

I recommended that the sponsor conduct a randomized, placebo-controlled, parallel group fixed dose study characterizing the effect of the full range of APM doses (2 – 10 mg) prior to approval in my original safety review (6/20/03) of this NDA. The approvable letter noted that such a study must be conducted but could be conducted as a phase 4 commitment approval of APM. I believe that I can accept this change in the timing of this requirement as long as the effect of APM on QTc is clearly and adequately described in the Warning section of the label.

1.1. Overall Conclusions and Recommendations

Action Recommendations

- 1) **I consider this application to be conditionally worthy of an approval for the ampoule formulation of APM (APOKYN) as safe and effective for the indication of acute, intermittent treatment of hypomobility (“Off”) episodes associated with advanced Parkinson’s disease only if particular safety concerns can be adequately presented in the label**. The conditions that I require to recommend approval of the ampoule formulation of APM are to describe **1) the potential risk for QTc prolongation and the potential significance of QTc prolongation vis a vis Torsades de pointes (and possible cardiac arrest or sudden death) clearly and adequately in the Warning section of the label, 2) the potential safety risk of injection site sarcomas based upon the animal carcinogenicity findings in rodents, and 3) the potential serious drug interaction (e.g. severe hypotension and loss of consciousness) from taking APM with ondansetron and possibly other 5HT₃ antagonists in the Warning section and to contraindicate the concomitant use of these drugs**

I further define adequate description of the QTc prolongation section of the Warnings as including the following elements: 1) labeling the section as QTc prolongation and some additional phrase to put the QTc prolongation into perspective (e.g. QTc Prolongation and Proarrhythmia Effects or

2) a summary of the main QTc prolongation findings outlined in my review, 3) a description that QTc prolongation is considered to be a surrogate for Torsades de Pointes (i.e. polymorphic ventricular tachycardia) and potential clinical manifestations of Torsades de pointes, 4) a description of factors that

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can increase the risk for Torsades de pointes in the setting of QTc prolongation, 5) at the least a caution (if not contraindication) about using APOKYN with other drugs known to prolong QTc and the description of the possibility for additive effects on QTc prolongation, 6) a contraindication about using APOKYN in patients with a history of congenital long QT syndrome, and 7) cross-referencing this Warning with other appropriate sections (e.g. Drug Interaction, Contraindication) in the label

If all 3 of these safety risks cannot be adequately described in the label, then I recommend an approvable action at this time The sponsor should then do whatever is necessary to address these safety concerns by 1) [

1) adding ondansetron and APM drug interaction in the label, and 2) conducting its own studies addressing the injection site sarcomas in carcinogenicity studies, and the ondansetron and APM drug interaction as necessary, and the placebo-controlled QTc study (to characterize the risk of QTc prolongation more accurately) that has been recommended

- 2) I cannot recommend an approval of the APM formulation containing benzyl alcohol that is administered by the pen until the sponsor submits data showing the safety of this formulation with respect to my safety concerns outlined in my review

Phase 4 Requirements Based Upon Clinical Concerns

- 1) The sponsor should conduct a randomized, double-blinded, placebo-controlled study to evaluate the effects of the full dose range (up to 10 mg) of subcutaneous APM on the QTc interval at various times after injection. I recommend that DNDP provide recommendations to the sponsor regarding important features to incorporate into this study. The rationale for the importance of conducting this study has been outlined in my review.
- 2) The sponsor should conduct a randomized, double-blind, placebo-controlled study assessing the need to use concomitant 300 mg Tigan tid to decrease nausea and vomiting in patients who initiate and continue treatment with APM. The sponsor has already committed to conduct this type of study but has not yet submitted specific information about its design.
- 3) The sponsor should conduct a study investigating pharmacodynamic interactions of injecting APM in close temporal relationship to the separate administration of alcohol, nitrates (short and long-acting), and anti-hypertensive drugs for effects on orthostatic (i.e. supine and standing) blood pressure and pulse.
- 4) The sponsor should conduct metabolism studies in humans and animals. I also recommend that the sponsor conduct human studies using a "high" dose (e.g. 6 mg) of APM to characterize the metabolic profile and metabolic pathways using the highest recommended dose so that potentially relevant pathways and metabolites could be

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defined. If subjects are studied with the lowest recommended dose (e.g. 2 mg), it is possible that somewhat different results could be obtained because higher APM doses show a different metabolic profile related to saturation of some metabolic pathways. The previous information derived from the study of human metabolism of APM in the (sublingual APM) involved plasma levels of APM that would be much lower than those experienced by patients treated with APOKYN. Studying APOKYN to detect the possible characterization of metabolites not previously shown at low levels of APM exposure could provide important metabolic information and would be an improvement adding to our knowledge base regarding the human metabolism of APM.

- 5 The sponsor should conduct reproductive toxicity studies as required by the pharmacology/toxicology reviewers.

Other Recommendations

- 1 The sponsor should adopt DNDP's recommendations for revising the label (including the patient information/package insert) or negotiate deviations with the DNDP.
- 2 The sponsor should analyze results from ongoing open-label APO401 study in which patients are being switched to the 300 mg Tigan for the safety experience relative to the safety experience observed in patients treated with 250 mg Tigan and reported in the NDA, SU1 and SU2.

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2. INTRODUCTION, BACKGROUND, REGULATORY HISTORY

Mylan Pharmaceuticals Inc (Mylan), (a wholly-owned subsidiary of Mylan Laboratories Inc , the Sponsor) currently holds IND #52,844 that details the investigation of APM HCl injection in the acute symptomatic (rescue) treatment of "Off" episodes in patients with "On/Off" or "Wearing-Off" effects associated with late stage Parkinson Disease Bertek Pharmaceuticals (another wholly-owned subsidiary of Mylan Laboratories) is Mylan's marketing division for branded products and would be the sponsor's marketing organization for the product in this NDA should the application be approved This NDA is being re-submitted by Bertek Pharmaceuticals after it was initially submitted by Mylan in 2000 but it was not accepted for filing (i e Refuse to File) Mylan and Bertek are used interchangeably throughout the application in referring to the sponsor

In April 1993, _____ received Orphan Designation for the use of APM in the above indication This designation was subsequently transferred to Mylan In a January 1999 meeting with the Agency, the Sponsor presented its plans for NDA submission after the completion of study APO202 demonstrated the significant treatment effects of APM to reverse induced "Off" episodes under medically observed conditions and those occurring in patients during one month of _____ use (i e outpatient conditions) During a discussion with Dr Robert Temple (ODE 1 Office Director), Mylan learned that the NDA could not be approved without evidence of effectiveness after continual use (defined as at least 3 months in duration), which could be conducted in patients already receiving APM Although the sponsor understood that additional toxicology and safety data would be required prior to approval, the sponsor originally believed that this information could be provided as amendments to the NDA Thus in April 2000, Mylan Pharmaceuticals Inc submitted an NDA (assigned NDA #21-264 to the DNDP) for Apomorphine Hydrochloride Injection, 10 mg/mL However, the FDA notified the sponsor that it refused to file NDA #21-264 on grounds of inadequate pharmacology/toxicology, and clinical safety information

DNDP held several meetings (face to face or teleconferences) subsequently to help the sponsor address shortcomings identified in the 2000 NDA submission DNDP gave the sponsor significant feedback particularly about collecting safety data desired by DNDP prospectively In addition, DNDP recommended collecting particularly adequate safety data assessing the effects of APM on orthostatic hypotension and potential adverse events related to APM's potent effects on the cardiovascular and central nervous system More specifically, DNDP recommended studying patients who were naive to APM from immediately prior to APM administration up until at least 1 hour later and to assess the effect of administration of APM initially, after a relatively short repeated treatment period (e g weeks), and after more prolonged treatment (months) DNDP also recommended that the sponsor collect 12 lead ECG data to exclude or at least characterize potential QTc prolongation, at various times shortly after dosing

On 1/10/02 DNDP held a pre-NDA meeting with the sponsor to plan for the NDA resubmission During subsequent discussions that outlined the requirements for NDA filing the FDA offered the option of a rolling submission Bertek formally accepted the offer of a rolling submission in December 2001 The FDA also granted NDA #21-264 Fast Track status on June 27, 2001

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The sponsor submitted (1/2/03) NDA 21264 for subcutaneously administered APM for the indication

This NDA was reviewed in the DNDP (HFD-120) and the Agency issued an approvable letter on 7/2/03. Many issues of concern and requiring a response were specified for all disciplines including Chemistry, Clinical, Pharmacology/Toxicology, and Biopharmaceutics/Clinical Pharmacology.

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3. CLINICAL COMMENTS

The format of the Clinical Comments section shows each specific FDA comment and then each Bertek Response. Much or most of the sponsor's responses that I have provided in my review is frequently a verbatim or virtually verbatim copy of the text of the response submitted by the sponsor. Following each Bertek response, I have provided a section termed **Reviewer's Comments, Discussion, and Conclusions**.

1 Clinical Comment 1

FDA Comment 1

Indication You are seeking a claim for the treatment of two types of Off periods: end-of-dose wearing Off and spontaneous Off. In the initial phase of APO202, you induced Off periods by withholding PD medication overnight. Such induced Off periods may be more complex, given that they occur unrelated to time of dosing. In APO301 and APO302, patients received their morning doses of PD medication and were followed until their first Off of the day (at least 1 hour post dosing). Whether the results of APO301 and 302 address the efficacy of apomorphine for spontaneous Off periods depends on the distributions of time-to-Off in those studies. If many studied Off periods occurred well before the end of the usual dosing interval, the results would bear on spontaneous Off periods. If, however, the great majority of Off periods occurred close to the end of the usual dosing interval, then the results bear more on end-of-dose Off. We therefore ask you to examine APO301 and APO302 to determine each patient's time-to-apomorphine-dosing and compare this to the patient's usual dosing interval. Please categorize patients based on whether the treated Off period best represents end-of-dose wearing Off or spontaneous Off.

I have provided synopses of the study designs of study APO301 and APO302 for reference with respect to the requested analyses for these efficacy studies.

Synopsis of APO301 Study Design

Patients who had been receiving repeated injections with subcutaneous APM for ≥ 3 months were randomized to a single injection of placebo or their usual dose of APM on 2 consecutive days in a double-blind, cross-over study. Patients were treated with both sequences (i.e. placebo and then APM or APM and then placebo). Experimental drug is to be administered in response to a significant "Off" event (in 75% of patients it is expected that pre-dose UPDRS score will measure ≥ 32).

On observation days 1 and 2, each patient is to receive a subcutaneous injection of double-blinded supplies of APM or placebo, according to the randomized crossover assignment. The volume of the injected dose in mL is to be set equal to that typically used by the patient prior to study entry. No other medications are to be used within one hour of this dose of test medication.

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On each observation day, the patient's usual anti-parkinsonian medications are to be taken in the manner typically used during outpatient pre-study use until arrival at the clinic. Following arrival at the clinic, no further non-study APM will be used. Patients are to be observed for the first significant "Off" event which occurs at least one hour after morning dosing.

Efficacy response to dosing will be assessed by capturing (1) the repeated measurement UPDRS motor scores and dyskinesia scores over a 60-minute interval, and (2) the interval (in minutes) between injection and the time of patient declaration of the first perception of significant relief of immobility. Time course of dose response was to be determined by measuring the UPDRS motor score pre-dose and at 10, 20, and 60 minutes post dosing.

Upon completion of the 60-minute observations, resumption of normal medications is allowed for the remainder of the day. The patient needed not be confined to an inpatient environment. Observation of response to test medication was to be conducted on separate days, which were typically to be scheduled sequentially, but might be separated by up to one week. Study exit was to occur after completion of the observation of drug effect on the second observation day.

Patients continued to be treated with an anti-emetic, domperidone, if they had been taking this drug prior to enrollment in this study.

Treatment Duration For 2 days of treatment on dosing days 1 and 2, each patient was to receive either subcutaneous APM HCl (subject's usual dose, up to a maximum of 10 mg), or matched placebo. Patients receiving APM HCl on day 1 would receive placebo on day 2. Patients receiving placebo on day 1 would receive APM HCl on day 2.

Synopsis of APO302 Study Design

Patients who had been receiving repeated injections with subcutaneous APM for ≥ 3 months were to be randomized in a 2:2:1:1 ratio respectively to 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. Patients were supposed to take their typical morning oral anti-parkinsonian medical therapy and were to receive an injection of experimental medication to treat the first "Off" that occurred at least 1 hour after this typical morning regimen. No other anti-parkinsonian medical therapy was allowed until the onset of an "Off" and the completion of the 90 minute evaluation period after treatment injection. Patients were allowed to use COMT and/or MAO-B-B inhibitors. An anti-emetic was allowed (e.g. trimethobenzamide) if it had been used prior to enrollment.

Efficacy response to dosing was to be assessed by capturing: 1) the repeated measurement of UPDRS motor scores and dyskinesia scores at various times over a 90-minute interval, 2) the interval (in minutes) between injection and the time of patient declaration of the first perception

of significant relief of immobility, and 3) onset of drug response by repeated administration of a modified Webster Step-Seconds test

Upon completion of the 90-minute observations, resumption of normal medications was allowed for the remainder of the day. The patient did not need to be confined to an inpatient environment

Treatment Duration 1 day

Bertek Response

Analysis plans to describe the type of "Off" were discussed with the Division during an August 7, 2003 telephone conference and a subsequent telephone conference with Dr. Feeney. Bertek's minutes for the August 7th telephone conference are provided in Attachment 26. The following analysis plans were agreed upon:

APO301 and APO302 were studies designed to evaluate the continued efficacy of apomorphine to abort "Off" episodes in patients with idiopathic Parkinson's disease (PD) who had received apomorphine for at least three months before the study in addition to multiple oral drug therapy to control PD symptoms. In both studies, the times of the morning dose of oral PD medication, of the subsequent in-office "Off" episode and of apomorphine administration were documented on the case report forms.

It was agreed to classify the in-office "Off" episode for analysis in two ways:

- The "1 hour rule" if the time of the in-office "Off" episode was within 60 minutes of the time for the next dose of conventional oral PD medication, then the "Off" episode was considered to be an "end-of-dose Off". Otherwise, the "Off" would be classified as "spontaneous."
- The "75% rule" if the "Off" episode occurred during the first 75% of the dosing interval, the "Off" would be considered spontaneous. Otherwise, the "Off" would be classified as "end-of-dose." This "75% rule" was suggested by the Division during a subsequent telephone call with Dr. Feeney also on August 7, 2003.

Both algorithms rely on a determination of the time to the next dose of conventional oral PD medication, specifically Sinemet. Although instructions for use of conventional oral PD medication were documented in the Case Report Forms, some standardization was employed to ensure consistent interpretation of the dosing instructions for analysis. For example:

- Patients did not take oral medication during sleep. Based on diary card assessment of a subset of patients in open-label study APO401, the average sleep time was 6.54 hours. For the purposes of determining a dosing interval, sleep time for all patients in these efficacy studies was assessed as 6, or 6.5 or 7 hours to bracket the average sleep time determined in APO401.

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- Patients took their first dose of conventional oral PD medication upon arising, and the remaining doses were to have been taken during the awake time (i.e., 18, 17.5 and 17 hours awake time for 6, 6.5 and 7 hours of sleep time, respectively)
- If specific Instructions for use were described (e.g., every X hours, or at specific times during the day), the dosing interval was defined by the instructions for use
- If the instructions for use simply gave a frequency, (e.g., 5 times daily or QID), the dosing interval was determined by dividing the remaining doses (which would equate to the number of daily doses minus 1, since the first dose was taken upon waking) into the awake time
- Based on the August 7, 2003 teleconference with the DNDP, the instructions for use for Sinemet® or (levodopa/benserazide for some of the UK patients) was used to determine the next dosing interval

All patients from APO301 and APO302 that contributed efficacy data for each study were used in the current analysis and a listing of dosing interval times was presented in an attachment (31.1). As would be expected, the dosing interval range shortened as sleep time increases, however, indices of centrality (i.e., mean and median dosing intervals) were only slightly affected and were submitted. An example of the dosing interval data based upon the 6.5 hrs sleep assumption is shown in Figure 1. The boxes represent the middle quartiles (i.e. quartile 2 representing 25%ile to 50%ile, and quartile 3 representing 50%ile to 75%ile, and the lines outside the boxes represent the range of quartile 1 and quartile 4 illustrating the "outside" quartiles and the minimal and maximal dosing intervals. Figure 2 depicts these same data and shows the cumulative distribution of dosing intervals (based upon 6.5 hr sleep assumption). The Y-axis indicates the cumulative distribution such that 0.2 density represents 20% of patients.

I created

Table 1 from the sponsor's separate tabulations (Attachment 31.2) that show mean and various percentiles of dosing intervals related to calculation of interval using different sleep time assumptions. Using the 6.5 hr sleep assumption, the mean and median dosing intervals were 4.9 and 4.5 respectively and the range was 1-9

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Table 1 shows that there was relatively little change in these quantitative representations of the distribution of dosing intervals related to using different sleep times assumptions

Figure 1 Quartile Distribution of Dosing Intervals in Patients in Studies APO301 and 302 Based upon 6.5 Hour Sleep Assumption

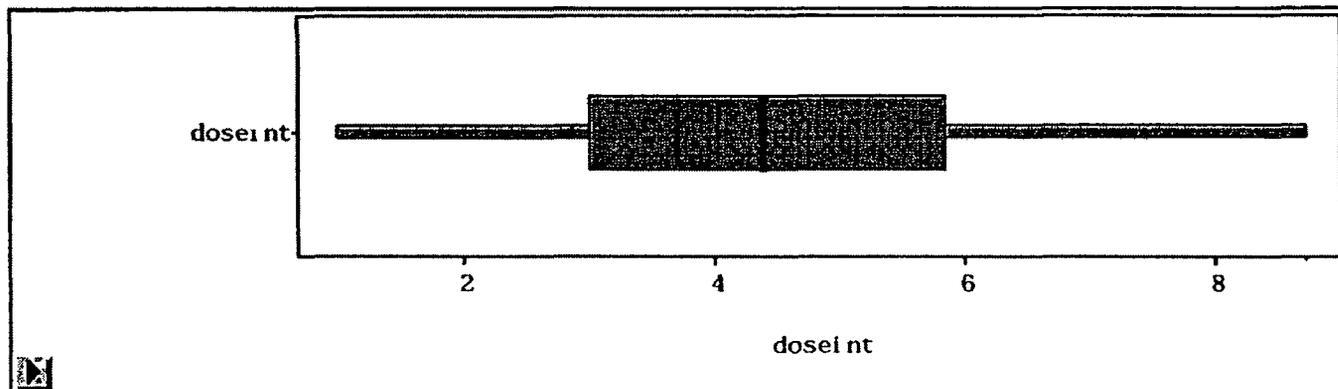
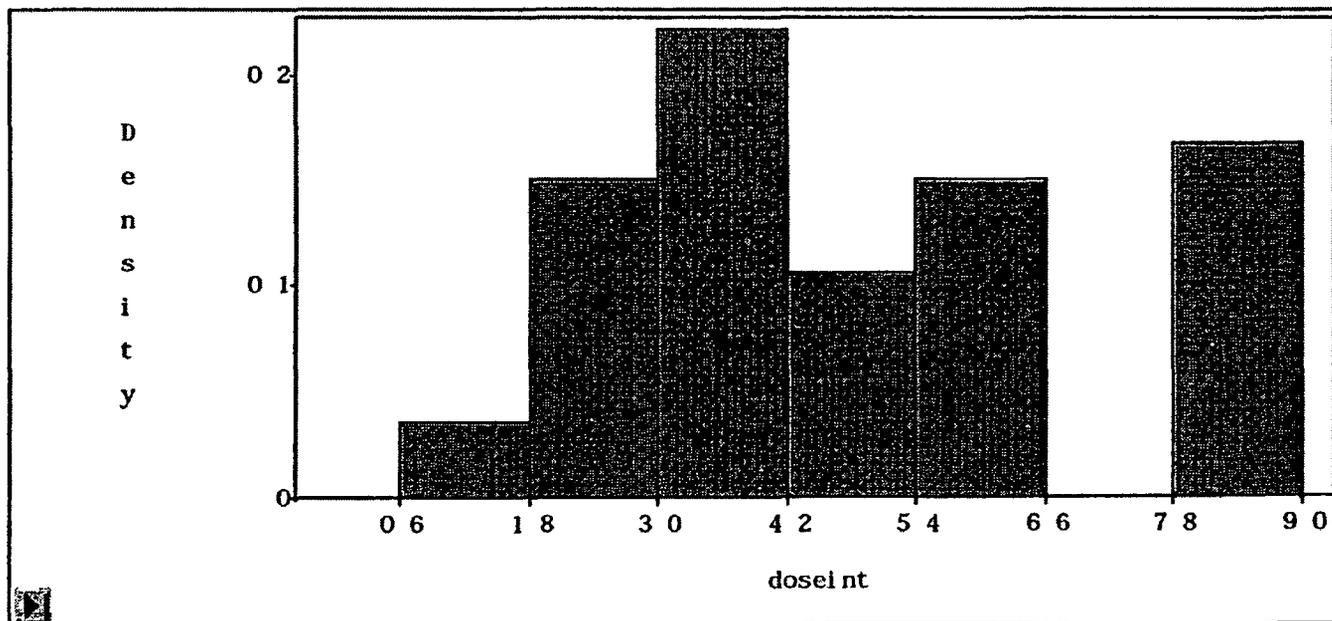


Figure 2 Cumulative Distribution of Dosing Intervals in Patients in Studies APO301 and 302 Based upon 6.5 Hour Sleep Assumption



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Table 1 Quantitative Presentation of Dosing Intervals Related to Different Sleep Assumptions

Parameter	6 hrs sleep assumption	6.5 hrs sleep assumption	7 hrs sleep assumption
N	94	94	94
Mean	4.90	4.78	4.67
Standard deviation	2.43	2.35	2.27
Skewness	0.61	0.61	0.62
100 %ile (quartile 4 /maximum)	9.0	8.75	8.5
75 %ile (quartile 3)	6.0	5.83	5.67
50 %ile median (quartile 2)	4.5	4.38	4.25
25 %ile (quartile 1)	3.0	3.0	3.0
1 %ile	1.0	1.0	1.0

The primary efficacy variable in both APO301 and APO302 was the change from predose UPDRS Motor Scores at 20 minutes after injection of study medication. **Whereas all results from APM and placebo treated patients in study APO302 (parallel group study design) were presented, only results from period 1 of cross-over study APO301 were analyzed and presented.** The sponsor applied the algorithms described previously and categorized each patient as being treated for a "spontaneous off" or an "end of dose off". Statistical analyses of results based upon the type of "Off" treated with placebo and APM were conducted using sleep times of 6, 6.5 and 7 hours with "Off" episodes also classified by both the 1-hour and 75% rules. In all analyses, the reduction UPDRS motor scores was statistically significantly lower for patients who received APM as compared to those who received placebo injection to treat the medically observed "Off" episode. An example of combined study results for the 6.5 hr sleep assumption is shown with respect to the 1 hour rule (Table 2) and the 75 % rule (Table 3). Results (not shown) based upon analyses using 6 and 7 hrs sleep assumptions for calculating dosing interval and categorizing type of "Off" were similar to those shown in Table 2. The sponsor concluded that these results clearly indicate that apomorphine is effective in the acute treatment, intermittent treatment of both spontaneous and end-of-dose hypomobility ("Off") episodes associated with advanced Parkinson's disease.

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Table 2 Primary Efficacy Endpoint (Mean Change in UPDRS Motor Score at 20 Minutes from Pre-Dose) for “Spontaneous Off” and “End of Dose Off” in Combined Analyses of Patients in Studies APO301 and APO302 Based Upon Calculation of Dosing Interval Using 6.5 Hour Sleep Assumption and 1 Hour Rule

Spontaneous OFF?	Time	Apomorphine-				Placebo				p value
		n	Mean	(Std)	Range	n	Mean	(Std)	Range	
N	Pre dose	25	44.4	(9.99)	(27.74)	26	41.0	(17.29)	(18.91)	< .0001
	20 minutes	25	17.2	(11.18)	(2.44)	26	32.9	(21.89)	(7.108)	
	Change from pre dose	25	27.2	(9.26)	(46.5)	26	8.1	(8.93)	(26.17)	
Y	Pre dose	17	38.4	(10.77)	(23.61)	9	38.0	(13.59)	(9.56)	0.0080
	20 minutes	17	20.6	(12.38)	(4.49)	9	34.9	(18.59)	(2.72)	
	Change from pre dose	17	17.8	(13.48)	(43.17)	9	3.1	(9.44)	(19.16)	

Note: P values are from ANCOVA with the terms pre dose score and treatment

Note: Data used is from APO302 (parallel groups design) and APO301 (crossover design) period 1 data only

Note: APO301 subject 01/005 had only a pre dose value. The 20 minute value was carried forward from pre dose

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Table 3 Primary Efficacy Endpoint (Mean Change in UPDRS Motor Score at 20 Minutes from Pre-Dose) for “Spontaneous Off” and “End of Dose Off” in Combined Analyses of Patients in Studies APO301 and APO302 Based Upon Calculation of Dosing Interval Using 6.5 Hour Sleep Assumption and 75% Rule

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Spontaneous OFF?	Time	Apomorphine			Placebo			p value		
		n	Mean	(Std)	Range	n	Mean		(Std)	Range
N	Pre-dose	27	43.8	(9.92)	(27.74)	25	40.4	(17.33)	(18.91)	< 0001
	20 minutes	27	16.6	(10.92)	(2.44)	25	31.9	(21.78)	(7.108)	
	Change from pre-dose	27	27.1	(9.06)	(46.5)	25	8.4	(8.95)	(26.17)	
Y	Pre-dose	15	38.7	(11.37)	(23.61)	10	39.9	(14.15)	(9.57)	0.0092
	20 minutes	15	22.1	(12.50)	(4.49)	10	37.1	(18.87)	(2.72)	
	Change from pre-dose	15	16.7	(13.84)	(43.17)	10	2.8	(8.95)	(19.16)	

Note: P values are from ANCOVA with the terms pre-dose score and treatment

Note: Data used is from APO302 (parallel groups design) and APO301 (crossover design) period 1 data only

Note: APO301 subject 01/005 had only a pre-dose value. The 20 minute value was carried forward from pre-dose

I requested that the sponsor conduct analyses of each study separately because we do not normally pool results from pivotal studies. The following request was sent to the sponsor:

Please reanalyze your spontaneous "Off" (for 1 hour rule and 75 % rule separately) and induced "Off" data (attachment 31.3) to show results of studies APO301 and APO302 separately (without pooling as you have done). In these reanalyses of each study separately please also reanalyze data among groups of patients by pooling responses of patients without regard to the average time of sleep. For example, results of patients with an average of 6, 6.5, or 7 hours would be pooled.

BERTEK RESPONSE

In both studies (APO301 and APO302), the times of the morning dose of oral Sinemet, the subsequent in-office "Off" episode and APM administration were documented on the case report form. Sleep Time was not captured on the Case Report Form, and was not part of any primary data set. Rather, it was derived from a subset of patients in APO401 who had diary cards that indicated the average Sleep Time in APO401 was 6.54 hours.

Thus, the sponsor clarified that calculation of dosing interval in individual patients was not based upon applying actual sleep times (derived from individual patient diary results) of patients in the pivotal studies. Although the sponsor had conducted multiple analyses based upon dose interval calculation using sleep time assumptions of 6, 6.5 or 7 hours to bracket the various sleep times of individual patients, the sponsor did not present data or analyses showing the variability of sleep times in the group of individuals who exhibited a mean sleep time of 6.5 hours.

The sponsor conducted separate study analyses of the primary efficacy endpoint (change from predose UPDRS Motor Scores at 20 minutes after injection of study medication) based upon dosing interval calculation and application of various sleep time (6, 6.5, 7 hrs) assumptions described previously. More specifically, the same dosing interval data as used in the combined

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study analyses were used in the separate study analyses. As before, all patients from APO301 and APO302 that contributed efficacy data for each study were used in the current analyses.

Results for each study using 6, 6.5 and 7 hours of Sleep Time assumption and both classification methods (i.e. 1 hour rule or 75 % rule) were presented. Results for APO302 (the larger study) were statistically significant for both types of "Off" in all iterations. Because of the small sample size, the results for APO301 did not reach statistical significance in any of the comparisons, however, the trend and the magnitude of the change from pre-dose in UPDRS motor scores was similar to that seen for APO302. Using the 6.5 hour sleep assumption for calculating dosing interval, an example of separate study results is shown in Table 4 for the 1 hour rule and in Table 5 for the 75 % rule. I created Table 6 based upon results presented in 6 tables (Attachment 2) submitted by the sponsor in response to my request. Table 6 shows the treatment effect (i.e. APM – placebo) for the primary efficacy endpoint in all these reanalyses.

The sponsor concluded that these results, as with the previous analyses with the combined data set, demonstrate the efficacy of APM in the acute treatment (rescue) of both spontaneous and end of dose "Off" episodes.

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Table 4 Primary Efficacy Endpoint (Mean Change in UPDRS Motor Score at 20 Minutes from Pre-Dose) for “Spontaneous Off” and “End of Dose Off” in Separate Analyses Studies APO301 and APO302 Based Upon Calculation of Dosing Interval Using 6 5 Hour Sleep Assumption and 1 Hour Rule

Study	Spontaneous OFF?	Time	-----Apomorphine-----			-----Placebo-----			p-value		
			n	Mean	(Std)	Range	n	Mean		(Std)	Range
APO301	N	Pre-dose	3	44.3	(8.50)	(36.53)	5	40.6	(11.59)	(29.57)	0.0513
		20 minutes	3	17.7	(7.37)	(12.26)	5	33.0	(15.92)	(16.57)	
		Change from pre-dose	3	-26.7	(5.51)	(-32.21)	5	-7.6	(10.45)	(-26.0)	
	Y	Pre-dose	5	42.0	(14.40)	(30.61)	4	37.8	(5.85)	(31.44)	
		20 minutes	5	27.0	(15.83)	(7.49)	4	36.3	(5.25)	(33.44)	
		Change from pre-dose	5	-15.0	(23.10)	(43.17)	4	1.5	(3.42)	(-6.2)	
APO302	N	Pre-dose	22	44.4	(10.35)	(27.74)	21	41.1	(18.62)	(18.91)	< 0.001
		20 minutes	22	17.1	(11.73)	(2.44)	21	32.9	(23.42)	(7.108)	
		Change from pre-dose	22	-27.3	(9.75)	(46.5)	21	-8.2	(8.81)	(-24.17)	
	Y	Pre-dose	12	36.9	(9.22)	(23.55)	5	38.2	(18.54)	(9.56)	
		20 minutes	12	18.0	(10.30)	(4.35)	5	33.8	(25.83)	(2.72)	
		Change from pre-dose	12	-18.9	(8.10)	(-32.7)	5	4.4	(12.84)	(-19.16)	

Note P-values are from ANCOVA with the terms pre-dose score and treatment

Note Data used is from APO302 (parallel groups design) and APO301 (crossover design) period 1 data only

Note APO301 subject 01/005 had only a pre-dose value The 20 minute value was carried forward from pre-dose

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Table 5 Primary Efficacy Endpoint (Mean Change in UPDRS Motor Score at 20 Minutes from Pre-Dose) for “Spontaneous Off” and “End of Dose Off” in Separate Analyses Studies APO301 and APO302 Based Upon Calculation of Dosing Interval Using 6.5 Hour Sleep Assumption and 75% Rule

Study	Spontaneous OFF?	Time	----- Apomorphine -----				----- Placebo -----				p-value
			n	Mean	(Std)	Range	n	Mean	(Std)	Range	
APO301	N	Pre-dose	3	44.3	(8.50)	(36.53)	4	36.5	(8.19)	(29.45)	0.1751
		20 minutes	3	17.7	(7.37)	(12.26)	4	27.0	(9.90)	(16.40)	
		Change from pre-dose	3	-26.7	(5.51)	(-32.21)	4	-9.5	(11.03)	(-26. -3)	
	Y	Pre-dose	5	42.0	(14.40)	(30.61)	5	41.6	(9.99)	(31.57)	
		20 minutes	5	27.0	(15.83)	(7.49)	5	40.4	(10.33)	(33.57)	
		Change from pre-dose	5	-15.0	(23.10)	(-43.17)	5	-1.2	(3.03)	(-6.2)	
APO302	N	Pre-dose	24	43.7	(10.24)	(27.74)	21	41.1	(18.62)	(18.91)	< 0.001
		20 minutes	24	16.5	(11.40)	(2.44)	21	32.9	(23.42)	(7.108)	
		Change from pre-dose	24	27.2	(9.49)	(-46. -5)	21	-8.2	(8.81)	(-24.17)	
	Y	Pre-dose	10	37.1	(10.00)	(23.55)	5	38.2	(18.54)	(9.56)	
		20 minutes	10	19.6	(10.56)	(4.35)	5	33.8	(25.83)	(2.72)	
		Change from pre-dose	10	17.5	(7.66)	(-31. -7)	5	-4.4	(12.84)	(-19.16)	

Note P-values are from ANCOVA with the terms pre-dose score and treatment

Note Data used is from APO302 (parallel groups design) and APO301 (crossover design) period 1 data only

Note APO301 subject 01/005 had only a pre-dose value The 20 minute value was carried forward from pre-dose

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Table 6 Mean Treatment Effect (APM - Placebo) for Primary Efficacy Endpoint (Change in UPDRS Motor Subscale-III at 20 minutes after APM)

Mean Sleep (Hrs)	Rule for Assessing Type of "OFF"	Study 301				Study 302				Study 301 and 302			
		APM + Placebo = Total N	EODO ^a	SO ^b	p value	APM + Placebo = Total N	EODO	SO	p value	APM + Placebo = Total N	EODO	SO	p value
6	1 Hr	3+4=7	- 17.2		0.1751	22+21=43	- 19.1		<0.0001	25+26=51	- 19.1		<0.0001
6	1 Hr	5+5=10		- 13.8	0.1730	12+5=17		- 14.5	0.0160	17+9=26		- 14.7	0.0080
6	75 %	3+4=7	- 17.2		0.1751	23+21=44	- 18.8		<0.0001	25+26=51	- 18.6		<0.0001
6	75 %	5+5=10		- 13.8	0.1730	11+5=16		- 14.4	0.0224	17+9=26		- 14.8	0.0056
6.5	1 Hr	3+5=8	- 19.1		0.0513	22+21=43	- 19.1		<0.0001	25+26=51	- 19.1		<0.0001
6.5	1 Hr	5+5=10		- 13.5	0.3698	12+5=16		- 14.5	0.0160	17+9=26		- 14.7	0.0080
6.5	75 %	3+4=7	- 17.2		0.1751	24+21=45	- 19.0		<0.0001	27+25=52	- 18.7		<0.0001
6.5	75 %	5+5=10		- 13.8	0.1730	10+5=15		- 13.1	0.0337	15+10=25		- 13.9	0.0092
7	1 Hr	3+5=7	- 19.1		0.0513	22+21=43	- 19.1		<0.0001	25+26=51	- 19.1		<0.0001
7	1 Hr	5+4=9		- 13.5	0.3698	12+5=17		- 14.5	0.0160	17+9=26		- 14.7	0.0080
7	75 %	3+4=7	- 17.2		0.1751	24+21=45	- 19.0		<0.0001	27+25=52	- 18.7		<0.0001
7	75 %	5+5=10		- 13.8	0.1730	10+5=15		- 13.1	0.0337	15+10=25		- 13.9	0.0092

a EODO = End of Dose Off

b SO = Spontaneous Off