

CLINICAL REVIEW

Clinical Review Section

preferred terms Some examples, include combining 1) initial insomnia, insomnia NEC, and insomnia aggravated as insomnia – 9 %, 2) Parkinson's Disease aggravated and parkinsonism as either term – 8 %, 3) all events representing pneumonia including aspiration pneumonia as pneumonia – 7 %, 4) administration site reactions as injection site reactions – 26 %, 4) dizziness/postural dizziness as the combined terms – 21 %, 5) all forms of heart failure as heart failure – 12 %, 6) preferred terms presented un the high level group term of depressed mood disorders and disturbances as this description – 10 %, and 7) hypotension, posutral hypotension, decreased blood pressure as the combination of terms – 11 %

As an alternative method of presentation, I propose presenting the TEAEs proposed to be presented in paragraph format instead in a table. In addition, I propose also adding TEAEs occurring on the day of in-office APM dosing and observation (presented in ISS Table 80 0) along with the TEAEs occurring in ≥ 5 % of patients in all phase 2/3 clinical trials. The TEAEs presented in Table 80 indicates a proximity with APM dosing and suggests a stronger possibility of causality related to APM treatment than TEAEs captured any time during participation in a trial. In some instances, a patient may not be actively dosing with APM but still the AE occurring during the overall treatment period would have been counted in incidence figures. I think that the information reflected TEAEs occurring on the day of in-office APM dosing observation provides complimentary information and should also be presented. Table 37 shows this combined table. **I further believe that Table 37 would be important to present in the label considering the fact that the safety experience collected under randomized, double-blinded, placebo-controlled conditions was so limited for APM compared to the usual safety experience collected for most approved drugs, especially drugs likely to be used by a significant number of patients. I suggest that the very limited, controlled conditions, safety experience collected for APM is relatively unique. I am not aware of another drug approved by DNDP that was based upon such a small safety experience collected under randomized, double-blinded, placebo-controlled conditions.**

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Table 37 Summary of Most Common Treatment-Emergent Adverse Events Occurring on Day of In-Office Apomorphine Dosing /Observation and Any Time During APM Treatment

Treatment-Emergent Adverse Events Occurring on Day of In-Office Apomorphine Dosing and Observation (≥ 1 % Incidence)	Percent Incidence N = 382 Patients	Treatment-Emergent Adverse Events Occurring Any Time During Apomorphine Treatment During Clinical Development Program (≥ 5 % Incidence)	Percent Incidence N = 550 Patients
Yawning	15	Nausea	31
Nausea	13	Fall	26
Dizziness/Postural Dizziness	12	Injection Site Reaction (Bruising – most common)	26
Somnolence	10	Dyskinesia	25
Hypotension/ Postural Hypotension/ Decreased Blood Pressure	8	Dizziness/Postural Dizziness	21
Dyskinesia	8	Somnolence	18
Injection Site Bruising	7	Hallucinations	16
Rhinorrhea	6	Yawning	16
Sweating Increased	5	Heart Failure	12
Vomiting	4	Hypotension/ Postural Hypotension/ Decreased Blood Pressure	11
Headache	3	Vomiting	11
Sedation	3	Arthralgia	10
Flushing	3	Depressed Mood Disorders and Disturbances	10
Pallor	3	Headache	9
Fatigue	3	Urinary Tract Infection	9
Weakness	2	Pain in Limb	8
Nasal Congestion	2	Parkinson's Disease/parkinsonism aggravated	8
Confusion	1	Pneumonia/Aspiration Pneumonia	8
Dyspnea	1	Confusion	7
Drooling	1	Rhinorrhea	7
		Dyspnea	6
		Fatigue	6
		Sweating Increased	6
		Ecchymosis	6
		Constipation	6
		Weakness	6
		Diarrhea	5
		Dehydration	5

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- Under the section Dosage and Administration, I recommend obtaining orthostatic blood pressures (supine and standing, up to at least — after APM because previous study showed that residual hypotensive effects are still evident at —. The sponsor had proposed the last blood pressure assessment at 60 minutes
- The sponsor changed the titration from DNDP's language recommending 1 mg APM increments every 1-2 weeks on an outpatient basis. Instead, the sponsor proposed titration in professional setting where blood pressure can be closely monitored and additional 1 mg increments in APM injection can be give at intervals of no less than 2 hours. Although this may have been done in some instances, I am not aware of data showing the safety of this relatively rapid titration schedule. **I think that such a rapid schedule could potentially result in patients using higher APM doses than are absolutely necessary. I have this concern particularly considering that the prescribing physician is not necessarily assessing a motor reponse with the motor scale of the UPDRS at particular times after APM injection and the data previously collected do not show that patients can reliably discern that they are significantly improved vis a vis motor function despite the fact that the UPDRS motor scale results are significantly better.** Although, I am not convinced that the very conservative schedule DNDP had proposed is necessary, it may be reasonable to consider a compromise and to shorten the titration proposed by DNDP but not nearly to as rapid a titration schedule as proposed by the sponsor. I raise the question whether it may be reasonable for the patient to assess the benefit of repeated APM injections at the dose level assessed to be reasonably tolerated and safe with regard to the lack of significant blood pressure lowering or orthostatic symptoms of concern. For example, if the patient tolerated 2 mg in the office, the patient would try this dose on repeat occasions over at least 2 days (or ? longer) at home and could then be instructed to increase the dose at the next 1 mg increment level, if the response at home is not considered adequate. This outpatient titration schedule could be repeated and dose adjustment (by 1 mg) could increase at ≥ 2 days intervals following repeat injections at home, or the dose could remain the same if a sufficient therapeutic response is perceived, or the dose could be decreased if the patient is experiencing adverse reactions. Thus, patients could dose escalate by 1 mg at intervals of ≥ 2 days on an outpatient basis interspersed by repeat treatments at home at the preceding dose level considered to be reasonably tolerated and safe for that patient.
- The sponsor has changed DNDP's language from noting that there is no evidence that doses above 6 mg show an increased effect to language indicating there this limited experience with doses above 6 mg. The sponsor has also deleted DNDP's recommendation against using APM doses > 6 mg. I strongly believe that the recommendation against using doses > 6 mg should be retained because there is relatively minimal safety experience with doses > 6 mg and there is not clear benefit that doses > 6 mg provide therapeutic benefit while there is clear data that increased adverse reactions occur at doses > 6 mg. This impression about the risk benefit ratio is primarily

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based upon the dose-dependent pharmacodynamic analyses conducted by the Biopharmaceutical reviewer, Dr J Duan in his original review

- The sponsor has added a sentence _____ This statement is based upon the results of one of many secondary efficacy endpoints in study APO202 and no statistical adjustment for multiplicity issues This statement is not appropriate here and should be deleted
- The sponsor has inserted additional language specifying the treatment of a particular "Off" episode The sponsor has also added caution about not repeating a second dose for the same "Off" if no response has occurred up to _____ (instead of 30-60 minutes as previously described) However, it does not seem like there is any clear advice to the prescriber about the shortest interval for repeating an injection of APM Although the sponsor has not presented a specific analysis from which one could assess a safe interval for repeating doses, a repeat injection was not supposed to be given within 120 minutes in the studies conducted by the sponsor Despite this plan, many patients repeated an injection at a shorter interval (i.e. < 120 minutes, and some patients repeated an injection of APM within minutes of a previous injection (up to 1 minute!)) I think that it would be desirable to make a clear statement about the shortest interval for repeating a dose It would seem reasonable to note that the shortest interval should be 120 minutes and then also offer a caution that this may be done only if there is no significant hypotension, dizziness, or chest pain

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Patient Package Insert

The Division of Surveillance, Research, and Communication Support (DSRCS) reviewed the sponsor's proposed patient information from a comprehensive perspective and the Division of Medication Errors and Technical Support (DMETS) reviewed the instruction for the patient information in an attempt to focus on safety issues to prevent possible medication errors in the administration of APM injection for the ampoule and the pen injector formulations. A consult was provided from these divisions along with comments to the Patients Package Insert that were bolded, underlined, and italicized as marked upon changes in the sponsor's proposed Patient Package Insert. I have reviewed these changes and have commented on my perception of the need or potential need for additional edits. I agree with comments and edits made by the DSRCS and DMETS and have focused on providing additional comments to be implemented or at least considered.

- Under the section providing instructions for using the ampoule formulation, the instruction to check for and get rid of air bubbles should be provided immediately prior to the instruction to instruction to adjust the syringe plunger to the desired dose. If this instruction is left where it is now (i.e. after the instruction to set the plunger at the desired dose), the dose administered after getting rid of any air bubble(s) could be less than the desired dose.
- It may be helpful to emphasize that the needle and syringe should be disposed together as one piece and to note parenthetically in bold type "**do not separate the needle from the syringe**".
- Under the section providing instructions for using the delivery pen, there is an instruction "to remove the needle from the pen after the injection is finished". This instruction violates "Universal Precautions" that recommends against recapping needles because of the increased risk of needle stick. If recapping of the needle is absolutely necessary (as it seems to be if one uses the delivery pen), then instruction should be given to 1) use a device to remove the needle such as a device that would hold the base of the needle while the pen is pulled up and away from the needle, or 2) remove the needle with a one-handed technique. I have concerns for patients who could sustain a needlestick injury if they attempt to remove the needle, particularly considering their difficulty with mobility and muscle control related to the Parkinson's Disease and the increased difficulty expected to do this maneuver when they are experiencing an "off" episode. In addition, the picture (e.g. # 13) should show the needle when recapping is recommended.
- A comment has been made regarding potential confusion regarding a patient administering a specific mg dose while ml designations are shown on the delivery pen. I would propose also considering that a table be inserted here showing the equivalence of mg doses with ml designations (e.g. 1 mg = 0.1 ml, 2 mg = 0.2 ml, up to 6 mg = 0.6 ml).
- Instruction is given regarding the possibility of having to refill the cartridge in the pen and administering a second injection if the patient attempts to administer a dose but there is an

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insufficient volume of APM remaining the cartridge to allow administration of the desired dose. It appears that it is not possible for a patient nor caregiver to know if there is a sufficient volume of APM left to give the full desired dose when the 3.0 ml cartridge has nearly been completely used. This is not a desirable situation considering the potential difficulty that may exist for a patient who is in an "off" state to self-administer a single injection let alone two injections. I question the possibility of a medication error manifested by administering an overdose. Furthermore, considering all the relatively fine motor movements required to refill the cartridge, it does not seem realistic nor practical to expect this to be accomplished with ease for a Parkinson's Disease patient let alone a patient who is in an "off" state and has markedly compromised motor abilities. I question how easily all these maneuvers can be accomplished for a Parkinson's Disease patient in an "off" state to administer the the desired dose safely via 2 separate injections separated by refilling the cartridge.

- It is not clear what the patient or caregiver should do with a needle after it has been used in a setting outside the home or access to a "sharps" container that a patient would not likely take with him/her when outside the home setting. Specific instruction should be given addressing this point.
- I have many comments regarding the Information for Patients and Caregivers. Most of these comments relate to making this document conform to information provided in the prescriber's label and presenting this information in a manner easily understood by a lay person.

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PREFACE

Although the same clinical reviewer is reviewing the efficacy and safety of NDA 21264 for apomorphine for the indication — the clinical reviews are being separated into an efficacy review and another review encompassing safety and other issues of clinical interest. This division into separate reviews is being done to help expedite the ability of the Clinical Team Leader to begin the efficacy review before the whole clinical review is completed. This is a priority review with a 6 month clock that is very short for an NDA that was expected to be complex for this new molecular entity. Separating the review of the whole NDA into at least two reviews will help supervisory personnel complete their reviews and memos in a more timely fashion. The review was submitted to FDA on 1/2/03 but it was not officially accepted for filing until nearly two months later. A decision for DNDP to file the review was not made until approximately 6 weeks after its receipt because there were concerns that the sponsor had not adequately addressed and submitted safety data as desired by DNDP. After discussion with the sponsor, DNDP eventually decided to file this NDA. Thus, this review will focus on the sponsor's 3 pivotal studies showing efficacy. I have discussed statistical issues with the Statistical reviewer and have incorporated some information, discussion, and feedback from this reviewer into my efficacy review.

The sponsor had never identified Study APO302 as a pivotal trial in the ISE nor in the Tabular Summary of Clinical Studies. However, I consider this trial also as a pivotal trial. APO302 was a prospective, multi-center, randomized, double-blinded, placebo-controlled, parallel group study that assessed the continued efficacy of APM in patients treated in two groups with active drug (i.e. APM) and two groups of placebo. Results from this study were submitted along with the Safety Update. I have reviewed this study at this end of this review.

I will not review two studies (APONIH and APO101) that were not conducted by the sponsor but were submitted by the sponsor as studies supporting the efficacy of apomorphine. We did not receive SAS transport files for these studies to be able to conduct independent statistical analyses as we were able to do for the 4 pivotal trials for which we received the efficacy datasets. APONIH was a retrospective analysis of efficacy of a study that was not primarily conducted to investigate the efficacy of APM. APONIH had many problems in conduct and design that did not make it a suitable study to review for this NDA. APO101 was conducted by another commercial sponsor to investigate another APM product. Neither will I review here the sponsor's Study 073 that is an open-label trial of 6 patients assessing pharmacokinetic and pharmacodynamic relationships of APM on efficacy. This study will be reviewed in detail by the Biopharmaceutical reviewer.

This review will not deal with any safety issues that will be reviewed separately by me in another review.

1 EXECUTIVE SUMMARY, CONCLUSIONS, RECOMMENDATIONS

Introduction

The sponsor is seeking approval of APM (2 formulations) administered as intermittent subcutaneous injections for the indication L

Although these patients supposedly were still having recurrent "off" episodes despite "optimal" oral antiparkinsonian medical therapy, it was not clearly shown that patients enrolled had been "optimally" treated. The disease characteristics of patients suggested that most patients appeared to have advanced Parkinson's disease. All patients were taking levodopa/dopa decarboxylase inhibitor. Essentially all patients (99 %) were taking a dopaminergic agonist and approximately 40 % had used a catechol-ortho-methyl transferase (COMT) inhibitor.

Study APO202

Study APO202 was a double-blind, placebo-controlled parallel group study of 29 patients (naive to APM) who were studied as inpatients over approximately 1 week followed by an outpatient phase over 4 weeks. Patients who enrolled in this study had to demonstrate levodopa responsiveness for improving UPDRS motor function scores. The dose of APM for each patient was selected as being "equivalent" to levodopa for improving UPDRS motor function scores. Patients from this study were allowed to enter an open-label, extension phase (Study APO401) to collect additional safety experience.

The following table shows the results of the primary analysis of the primary efficacy endpoint and that APM was highly effective.

Effect of Treatment on Response Ratio - % Response After Study Drug / % Response After Dopaminergic (Levodopa) Challenge

Variable		Apomorphine (n=20)	Placebo (n=9)	p-value**
UPDRS Motor Score	Mean (std error)	0.96 (0.06)	0.0 (0.08)	<0.0001
	Median	0.97	0.00	<0.0001

* N=20 for UPDRS Motor Score,

** p-values for the mean ratio were derived from the analysis of variance, p-values for the median ratio were derived from the Wilcoxon Rank Sum test.

Study APO301

Study APO301 was a double-blind, placebo-controlled cross-over study of 17 patients who were treated with a single injection of APM or placebo on 2 separate days. Prior to study enrollment, these patients had been treated chronically with intermittent injections of APM for a period of at least 3 months. These patients, who were studied in the U.K., did not have the opportunity of participating in Study APO401 to collect additional safety experience.

The following table shows the results of the primary efficacy endpoint using a non-parametric analysis that was appropriate because the assumption of normality of data was not satisfied. APM was highly effective in both periods of this cross-over design study.

Change from Pre-dose UPDRS Motor Score - Non Parametric Analysis

Time from Dosing	Sequence	Period 1 Median	Period 2 Median	Period1-Period 2 Median	p-value
20 minutes	APO/PL (n=8)	-23.5	1.5	-20.5	0.0019
	PL/APO (n=8)	-3.5	-22.5	17.5	

Study APO303

Study APO303 was a substudy of APO401 designed mainly to collect orthostatic vital sign (VS) and electrocardiographic (via Holter) data with respect to dosing in patients who were naive to APM. Patients received increasing single doses of APM (starting at 2 mg and escalating at 2 mg increments up to 10 mg, e.g. 2, 4, 6, 8, 10 mg) over several days as tolerated under open-label conditions except at the 4 mg level. The sponsor also incorporated a controlled, cross-over efficacy design evaluation in this trial by having patients receive either 4 mg APM or placebo on separate days under double-blinded conditions when patients were escalated to the 4 mg level. After collecting safety data at the 10 mg or highest tolerated level, patients (51) were then followed for a period up to 6 months to collect safety data before offered the opportunity of continuing to be followed in APO401 to collect additional safety experience. Patients were simultaneously enrolled in Study APO303 and APO401 and were followed in APO401 after completing APO303.

The following table shows the results of the primary analysis of the primary efficacy endpoint. Although APM appeared to be highly effective, there was a period/sequence effect in this study that uses a cross-over design. When data (APM vs placebo) were analyzed and compared only on Day 1 to avoid a period/sequence effect, there was no statistically significant effect of APM on the primary efficacy endpoint, the change in UPDRS motor score at 20 minutes after injection.

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Primary Efficacy Endpoint Effect of Apomorphine (4 mg) on Change in UPDRS Motor Score from Pre-dosing

Time from Dosing (min)	Placebo (N=51)		Apomorphine 4 mg (N=51)		p-values		
	Mean (SE)	Change from Pre-Dosing Mean (SE)	Mean (SE)	Change from Pre-Dosing Mean (SE)	[1]	[2]	[3]
0	42.5 (22.19)	----	42.7 (2.15)	-----			
20	39.8 (2.42)	-2.8 (1.15)	31.5 (2.13)	-11.2 (1.61)	0.0002	0.0038	0.1660

Note: one subject had visit TV2 but not TV3. For the ITT analysis, this subject's TV2 primary efficacy data were also used for TV3. LOCF was used for missing values.

[1] Repeated measures ANCOVA with the terms sequence, subject within sequence, pre-dose score, treatment and period

[2] p-value from sequence effect using subject within sequence MS as the error term

[3] ANOVA with the terms pre-dose score and treatment, using Day 1 data only

Study APO302

Study AP302 was a substudy of patients who had been treated in Study APO401 for at least 3 months. Study APO302 was a double-blinded, placebo-controlled parallel group study that evaluated the efficacy of APM or placebo treatment and also the effects of APM on 12 lead EKGs and orthostatic VS responses with respect to dosing in 4 groups of patients. Patients were randomized to receive either 1) their usual dose of an APM injection, 2) their usual dose of an APM injection + 2 mg up to a maximal dose of 10 mg, 3) the equivalent volume of placebo to their usual dose volume of an APM, or 4) the equivalent volume of placebo to their usual dose volume of an APM + 0.2 ml. Study APO302 was primarily designed to evaluate efficacy and safety parameters under double-blinded, placebo-controlled conditions of patients who had chronically been treated with APM for ≥ 3 months. There were some distinctive differences between studies APO302 and APO301 both of which were controlled studies assessing the ability of APM to provide benefit by reversing "Off" after prolonged period of repeated injections with APM. Study APO302 employed a parallel group study design instead a cross-over design used by Study 301. In addition, Study 302 investigated efficacy at both earlier (2.5 minutes) and later (90 minutes) timepoints than the earliest (10 minutes) and latest (60 minutes) timepoints evaluated in Study APO301.

The following table shows a therapeutic benefit of APM on the primary efficacy endpoint, change in UPDRS motor score.

Primary Efficacy Analysis of Change in UPDRS Motor Score from Pre-Dose for Pooled Apomorphine vs Pooled Placebo (ITT Population)

Time from dosing (min)	Pooled APM (n=35)			Pooled PL (n=27)			p-value	
	Mean (SE)	Change Mean (SE)	% Change Mean (SE)	Mean (SE)	Change Mean (SE)	% Change Mean (SE)	Change	%Change
0	42.0 (1.8)			40.6 (3.4)				
20	17.8 (1.9)	-24.2 (1.7)	-58.7 (3.8)	33.3 (4.4)	-7.4 (1.8)	-24.1 (5.6)	< 0.0001	< 0.0001

Secondary Efficacy Endpoints

Various secondary efficacy endpoints were assessed in these pivotal studies and results were analyzed with respect to nominal p-values without any correction/adjustment for making multiple comparisons (i.e. multiplicity). In many studies, the same efficacy parameters were assessed.

Diary data were collected for 4 weeks under randomized, double-blinded, placebo-controlled conditions in study APO202. APM successfully aborted 95% of spontaneously occurring "Off" episodes compared to 23% of episodes aborted by placebo treatment based upon diary data. Total daily "Off" hours were reduced by 1.7 hours in patients treated with APM vs no change with placebo treatment. This effect was not statistically significant but approached statistical significance ($p < 0.0880$).

The effect of APM at various timepoints was assessed relative to placebo treatment based upon analyses across studies. APM improved UPDRS motor function scores between 10 to 90 minutes after injection. In addition, motor function as assessed by Webster-Step Second testing usually improved after APM treatment.

There was no clear demonstration that patients were able to declare onset of relief from "Off" after injection at an earlier timepoint for APM treatment compared to placebo treatment. This effect was evaluated in studies APO301 and APO302.

APM resulted in increased dyskinesia but the change was relatively mild in most patients.

Dose-Response

The sponsor does not have any dose-response information based upon studies in which patients were randomized to fixed doses of APM. A range of doses often approximating 2 to 10 mg was frequently evaluated in the studies. Thus, it is not possible to make definitive statements on dose-response. However, some observations can be made. The most common doses of APM was 3 mg to 6 mg in studies evaluating its effect on a primary efficacy endpoint in a randomized, double-blinded, placebo-controlled study. There are no clear data that support 2 mg APM as an effective dose.

In study APO303, patients underwent a forced titration/escalation of APM from 2 mg up to 10 mg (in 2 mg increments) over several days. At the 4 mg level patients underwent a cross-over design and received either 4 mg APM or placebo in both sequences. All other dosing was under open-label conditions. Dose escalation was based upon APM tolerability and thus there is the potential for selection bias. UPDRS motor function scores were assessed at various intervals after injection. Based upon these results, it appeared that the maximal improvement (i.e. absolute score decrease from pre-dose) in UPDRS motor scores appeared with 6 mg of APM. There was no clear demonstration of additional therapeutic benefit with dosing above 6 mg based upon the absolute decrease in UPDRS motor score from pre-dose value. Considering that there was increased toxicity with APM dosing above 6 mg, 6 mg appears to be the maximal single dose that should be injected.

CONCLUSIONS

- APM shows highly statistically significant motor improvement or "rescue" from an "Off" state as reflected by substantial improvement in UPDRS motor function scores at or near 20 minutes after injection
- Although APM appeared to show an incremental benefit when added to a regimen of other anti-parkinsonian therapy (including levodopa/dopa decarboxylase inhibitor, oral dopaminergic agonists and occasionally a COMT or MAO-B inhibitor), it was not clearly documented how well each patient had received "optimized" anti-parkinsonian treatment prior to enrollment
- The suggestion of APM-induced efficacy in the outpatient setting supports the capability of patients or care-givers to administer APM effectively
- Although APM reverses/treats "Off" induced by withholding the patient's usual antiparkinsonian over night (based upon the primary statistical analysis of the primary efficacy endpoint , it is not clear if this is a surrogate for the spontaneously occurring end of dose wearing "Off"
- The effective dose range for approval appears to be 3 mg to 6 mg It is not possible to conclude that 2 mg APM is an effective dose because there were few patients who received this dose in pivotal studies
- Diary data collected during the outpatient-phase suggested that APM was effective in aborting most (95 %) spontaneously occurring "Off" episodes (compared to 23 % of spontaneously occurring "Off" episodes aborted by placebo) Although it might seem likely that many, if not most of the spontaneously occurring "Off" episodes that were aborted were end of dose wearing "off" episodes, the sponsor did not present any results indicating the type of "Off" episodes that were aborted
- APM is efficacious in treating/relieving "Off" events experienced by patients who have undergone repeated treatment of "Off" episodes over a prolonged period of at least 3 months
- Based upon analyses of secondary efficacy endpoints and nominal p-values (not corrected for multiplicity), APM is effective in improving motor function over a significant period ranging from 10 to 90 minutes Greatest improvement occurred between 20 to 40 minutes post injection
- It is not clear that patients can reliably discern the onset of relief from "Off" at an early timepoint after APM treatment
- Although APM clearly treats and reverses "Off" episodes, it is not possible to conclude that APM treats both end of dose wearing "off" and unpredictable ""On/Off" because we do not

know if the "Off" that was treated was a spontaneously occurring "Off" episode nor the type of "Off" episode that was treated

- APM treatment resulted in increased dyskinesia in some patients. Generally, increased dyskinesia from APM treatment was relatively mild in most patients and usually occurred at times when motor function was improved.

Overall Conclusion

Four pivotal clinical studies were included in this NDA submission. Three studies (APO2020, APO301, APO302) were positive for showing a statistically significant benefit of APM on the primary efficacy endpoint of treating "Off". The one study (APO303, cross-over design) that I do not consider positive showed a statistically significant benefit of APM on the primary efficacy endpoint but this effect was associated with a period/sequence effect. The result was not statistically significant ($p < 0.05$) when data from only Day 1 were compared. The statistical reviewer (Dr. Yan) has the same overall interpretations as mine regarding these 4 pivotal studies. Collectively, the four studies provide evidence that APM injection (recommended at final dosing ranging between 3 mg to 6 mg) is effective in treating "Off" events in late stage Parkinson's disease patients.

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RECOMMENDATIONS

1. The sponsor should reanalyze data in studies APO301, APO303, and APO302 separately to show the time of study medication injection relative to the last oral dosing of antiparkinsonian medication (including levodopa/dopa decarboxylase inhibitor) and the next dosing time that oral levodopa/dopa decarboxylase inhibitor should have been taken for each patient. These analyses would show the distribution of patients who experienced spontaneous "Off" and those who experienced an induced/drug withheld "off" because the next scheduled dosing of oral levodopa/dopa decarboxylase inhibitor was held until an "Off" episode had occurred, been treated, and the treatment response had been evaluated.
2. Study results for the primary efficacy endpoint should be reanalyzed with respect to whether the "Off" episode that was treated was spontaneously occurring or not. The sponsor should submit these reanalyses and provide its interpretation of results regarding the therapeutic benefit of APM.
3. The sponsor should analyze spontaneously occurring "Off" episodes that were treated in pivotal studies (APO301, 302, 303) to show whether the "Off" episode was an end of dose wearing "Off" or an unpredictable "On/Off". The sponsor should submit (to DNDP) an

analysis plan for determining the type of "Off" that was treated and obtain DNDP confirmation that the analysis plan is acceptable

- 4 The sponsor should reanalyze the data from pivotal studies with respect to whether the "Off" that was treated was an end of dose wearing "Off" or an unpredictable "On/Off". The sponsor should submit results to DNDP with the sponsor's interpretation of results with respect to the therapeutic benefit of APM for each type of "Off" episode

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2 INTRODUCTION AND BACKGROUND

2.1 Background and Rationale for Clinical Development of Apomorphine (APM)

Parkinson's disease (PD) is a neurodegenerative disorder of uncertain etiology. Hallmark characteristics include clinical symptoms of tremor, rigidity, and bradykinesia, and pathological evidence of degeneration of the dopaminergic nigrostriatal pathway, marked striatal dopamine deficiency, and the presence of laminated inclusions (Lewy bodies) in the neurons of the substantia nigra. Although incompletely understood, the pathophysiology of Parkinson's disease involves basal ganglia dysfunction. In Parkinson's disease, a decrease in dopaminergic stimulation of the striatum unbalances the complex electromechanics of motor function.

Pharmacological treatment of Parkinson's disease has been primarily directed towards striatal dopamine replacement. The oral administration of the dopamine precursor, levodopa (LD), remains the foundation for the current symptomatic treatment of Parkinson's disease. Early clinical results, especially in patients with advanced disease, were impressive, and at times dramatic. However, long-term use of LD has been associated with decreasing effectiveness and increase in adverse events.

Combined use of a peripheral dopa decarboxylase (e.g. carbidopa - CD) with LD provides additional therapeutic benefit by decreasing the peripheral degradation of LD. This pharmacological effect of CD results in increased plasma levels of LD and a longer half-life of plasma LD that ultimately increases the central delivery of LD to the brain and central dopamine levels. Levodopa/carbidopa (i.e. LD/CD) remains the mainstay of treatment for Parkinson's disease. However, approximately 10 percent of all subjects treated with LD will develop motor fluctuations per treatment year, so that approximately 50 percent are affected after five years of LD therapy. Although the pathophysiology of these "Off" episodes is not completely understood, it has been proposed that these episodes of hypomobility are the result of the pharmacokinetic and pharmacodynamic properties of LD. As the disease progresses and dopaminergic nerve terminals are lost, the buffering capacity of the striatum is lost because of the short plasma half-life of LD. The "efficacy half-life" becomes shorter and shorter. In the advanced stages of Parkinson's disease, the short duration of action of LD is thought to have secondary pharmacodynamic consequences resulting in complex patterns of drug response.

Apomorphine (APM) is a non-selective dopaminergic agonist with potent D₁ and D₂ pharmacological actions. There is a significant preclinical and clinical literature base demonstrating antiparkinsonian effects of APM. APM is the oldest and one of the most potent dopaminergic agonists. APM HCl is identified chemically as 4*H*-Dibenzo[de,g]quinoline-10,11-diol, 5,6,6a,7-tetrahydro-6-methyl-, hydrochloride, hemihydrate, and 6 α β -Aporphine 10,11-diol hydrochloride hemihydrate. APM HCl is manufactured as a sterile solution (10 mg/mL) in 2-mL ampoules and 3-mL cartridges (for manual injector pens) for subcutaneous injection using the following inactive ingredients: sodium metabisulphite, sodium hydroxide, hydrochloric acid, _____, and water for injection. Hydrochloric acid and sodium hydroxide are used

to adjust the pH of the final product between — Sodium metabisulphite is —
 — Benzyl alcohol is added to the cartridge as a preservative To further
 — , the ampoule headspace is filled with —

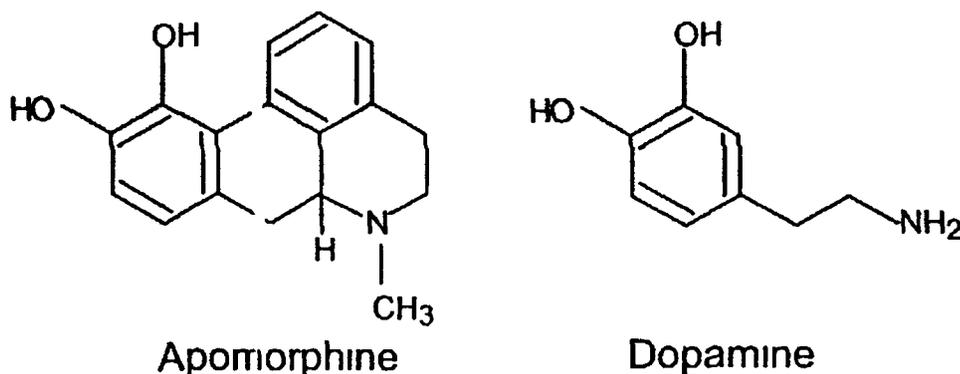


Figure 1 Chemical Structure of Apomorphine and Dopamine

Although known for decades to possess potential antiparkinsonian effects, APM has not been the subject of complete clinical development because subcutaneous injection of APM was inconvenient and because peripheral dopaminergic agonist activity, expressed as nausea/vomiting and hypotension (especially orthostatic), was considered to be inconsistent with practical clinical development. The successful development of newer oral dopamine agonists has demonstrated that peripheral dopamine agonist activity does not represent a significant limitation to practical therapy, possibly because of reduced sensitivity of peripheral dopamine receptors in patients receiving long-term dopaminergic therapy. Although new oral dopamine agonists might delay the onset of late stage motor fluctuations, it is estimated that approximately 50,000 U.S. patients suffer "Off" events despite administration of optimized regimens of available oral antiparkinson drugs. Under these circumstances, interest in APM was renewed specifically to take advantage of the rapid therapeutic response following subcutaneous administration.

2.2 "Off" in Parkinson's disease

A brief discussion of the nature of these motor fluctuations is helpful to understand the risk / benefit and efficacy of a medication such as APM for the treatment of Parkinson's disease. Two areas of particular concern are noted. The first is the characterization of the types of hypomobility states ("Off" episodes). The second is the clinical importance of these "Off" episodes.

Motor fluctuations, periods of hypomobility or immobility, can be divided into two major categories. The first category is termed "Wearing Off" or end of dose "Off" episodes. "Wearing Off" episodes are usually the first "Off" episodes encountered by Parkinson's disease in the course of their disease. These predictable fluctuations, as the name suggests, occur in association with the end of LD dosing intervals. They usually occur approximately three to five hours after each dose of LD. Initially these episodes can be treated by shortening the dosing interval and to

some extent by adding controlled release LD. The second category of motor fluctuations, random on-off fluctuations, are not predictable based on the LD dosing schedule. These "Off" episodes can occur abruptly and without warning and are also known as "On"/"Off".

Having discussed the types of "Off" episodes experienced by Parkinson's disease PD, it is important to consider the clinical significance of these events. The disability associated with these events can be characterized as direct and indirect. The direct impact depends on the degree of hypomobility associated with the individual "Off" episodes. The less severe episodes may be associated with the inability to perform basic hygiene, eat, or perform other activities of daily living. Symptoms associated with these "Off" periods can include sensory (pain) symptoms, autonomic symptoms and psychiatric symptoms. Some of these "Off" episodes are so pronounced as to result in complete immobility, which has resulted in the terms "Off" and "frozen" or "freezing" being used to describe these events. These episodes can be accompanied by fixed and painful dystonic posturing, profuse sweating, tachycardia, and panic. Perhaps equally debilitating are the indirect effects of "Off" episodes. Patients can become fearful of having an "Off" episode while away from home that they no longer leave their houses.

Recognizing that Parkinson's disease is that it is a progressive neurodegenerative disease, the quantity and quality of the episodes of hypomobility or immobility (e.g. "Off") typically increase as the disease progresses. Despite treatment with LD/CD and the more recently approved prophylactic treatments consisting of dopaminergic agonists, selegiline, and catechol-ortho-methyl transferase (COMT) inhibitors, and amantadine, which often reduce the amount of "Off" time per day, patients with Parkinson's disease, especially those with later stages of disease, often continue to experience "Off" episodes.

There currently is no approved medication to treat (i.e. abort) the symptoms of established "Off" episodes acutely. Such a treatment could possibly improve the quality of life for patients with late stage Parkinson's disease suffering debilitating "Off" episodes. The FDA has granted this application Fast Track status, a rolling submission and a 6 month priority review because APM was deemed potentially capable of providing a new treatment (i.e. acute treatment to reverse "Off").

APM by either intermittent subcutaneous injection or by continuous subcutaneous infusion is approved in the United Kingdom, France, and the Netherlands to control motor fluctuations. The current NDA focuses on the use of intermittent subcutaneous injections of APM as acute ("rescue") treatment of "Off" events in patients with more advanced Parkinson's Disease.

2.3 Pharmacokinetic and Pharmacodynamic Considerations

To appreciate the potential benefit of APM treatment it is helpful to understand some important pharmacokinetic (PK) and pharmacodynamic (PD) considerations. Absorption of APM after subcutaneous administration is relatively rapid and virtually complete with bioavailability approaching 100%. Based upon many studies in the literature and the sponsor's own PK studies, T_{max} reflecting C_{max} shows considerable variability and ranges in most patients from approximately 15 to 45 minutes with perhaps most patients showing T_{max} near 30 minutes.

Recognizing that that the PD effect of APM is relatively immediate and mindful of its Tmax, it is not surprising that significant PD effects are observed beginning at a few minutes after administration and peaking between 15 and 45 minutes in many patients. Thus, the PK/PD relationships support that potential for rapid onset of therapeutic benefit and somewhat sustained actions of APM after subcutaneous administration.

2.4 Intended Indication

The sponsor notes that this NDA presents data in support of the effectiveness of subcutaneous injections of APM for the following indication

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2.5 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.

2.6 Identification of Studies Supporting Effectiveness

This NDA submitted 4 pivotal studies to show efficacy of APM, but Table 1 only shows summaries of 3 pivotal studies. Studies APO202 and APO301 are two prospective multi-center randomized placebo-controlled pivotal trials that the sponsor proposes documents the efficacy of APM to reverse the hypomobility associated with "Off" episodes in APM-naive patients (APO202) and in patients receiving APM for at least 3 months (APO301). APO401 was designed as the main safety study to increase the U.S. experience in the long term use of APM and to assess the safety of outpatient self-administration of APM on a prospective basis. Patients enrolled in APO401 could also enroll in three companion sub-studies. Patients, naive to APM, were initially enrolled in APO303 (a substudy of APO401) and were studied under double-blinded, placebo controlled conditions using a cross-over design (4 mg vs placebo) to assess the efficacy of APM on reversing "Off". APO303 is also considered to be a pivotal study showing efficacy of APM. Patients enrolled in APO303 underwent a more controlled forced dose titration/escalation regimen than patients in APO401 in order to document orthostatic vital sign changes and potential electrocardiographic changes due to APM and to identify dose escalation methods that might acutely minimize adverse cardiovascular effects of APM. Patients enrolling in APOM-0073 participated in open-label pharmacokinetic and pharmacodynamic assessments to identify pharmacokinetic and pharmacodynamic relationships in APM's actions.

Results of pivotal study APO302 conducted by the sponsor were submitted with the Safety Update. Patients enrolling in APO302 (parallel group design), another substudy of APO401, participated in efficacy assessments in a randomized, double-blinded, placebo-controlled study to demonstrate the continued ability of APM to reverse "Off" events after at least three months' use of APM. In APO302 there was also collection of safety information, especially orthostatic vital sign changes and potential electrocardiographic changes timed to dosing. APO302 is not described in the tabular summary of trials (Table 1).

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] APO161 is a retrospective review of a safety experience of APM treatment in the United Kingdom. APO161 is briefly described in the tabular summary but did not contribute to information on effectiveness.

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3 TABULAR SUMMARY DESCRIPTION OF CLINICAL STUDIES

Studies APO202, APO301, and APO303 are pivotal studies conducted by the sponsor and shown in the Table 1. Another pivotal study APO302 that was not submitted in the original submission of clinical data is not shown in this tabular summary. APO302 results were submitted with the ISS Safety Update. APO401 was the main safety study (including long-term treatment) conducted by the sponsor. APO073 is a substudy of APO401 that was conducted by the sponsor and investigated acute pharmacokinetic and pharmacodynamic relationships of APM in a few patients with Parkinson's disease. APO073 is listed as a supportive study. APONIH and APO101 are considered supportive studies and were not conducted by the sponsor. APO161 is a retrospective review of a safety experience of APM treatment in the United Kingdom.

Table 1 Overview of Clinical Studies Conducted with Apomorphine HCl Injection

Study Type	Study No. (Ref No)	Study Title	Study Design	Drugs Dosage and Duration of Exposure	N A/P	Age Range (yr)	M/F	Results
<p>Abbreviations Used (S)AE = (serious) adverse event A/P= active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement NA = Data not available NS = Not Statistically Significant OP = outpatient P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic pharmacodynamic R = randomized SC = subcutaneous TV = Treatment Visit UPDRS(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover</p>								
PIVOTAL EFFICACY STUDIES								
Phase II Efficacy and Safety US Study 4 Sites	APO202	A Prospective Randomized Double-Blind Placebo-Controlled Parallel Groups Study Of The Safety And Efficacy Of Subcutaneous Injections Of Apomorphine In The Treatment Of "Off" Episodes In Patients With "On/Off" Or "Wearing Off" Effects Associated With Late Stage Parkinson's Disease	DB R PC PG	SC individualized based on LD response Avg Apo Dose = 5.4 mg Inpatient dose based on response to LD Outpatient DB R PC treatment duration was one month	29 20/9	45-80	69/31	Inpatient mean post injection UPDRS scores were reduced by 23.9 v 0.1 points by APO v P respectively (p < 0.0001). Dyskinesia was significant 20 minutes after dosing and was of a magnitude equal to that after oral LD. During the 1 month outpatient phase the mean % injections resulting in successful OFF was 95.7 and 23.4 for APO and PL (p = 0.0001). The outpatient response to APO is an independent substantiation of APO's efficacy. AEs recorded in 85% of APO patients included injection site reactions yawning drowsiness dyskinesia nausea vomiting dizziness rhinorrhea, hallucinations or confusion and chest pain.
<p>Abbreviations Used (S)AE = (serious) adverse event A/P= active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement NA = Data not available NS = Not Statistically Significant OP = outpatient P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic pharmacodynamic R = randomized SC = subcutaneous TV = Treatment Visit, UPDRS(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover</p>								
PIVOTAL EFFICACY STUDIES								
Phase III Efficacy and Safety Foreign Study 2 UK Sites	APO301 (APOS-001)	A Prospective Randomized Placebo-Controlled Crossover Study of the Safety and Effectiveness of Subcutaneous Injections of Apomorphine in the Treatment of "Off" Episodes in Patients With "On/Off" or "Wearing Off" Effects Associated With Late Stage Parkinson's Disease	DB R PC XO	SC individualized based on past history (at least 3 months) of APO Avg Apo Dose = 3.9 mg over the 2 dosing days	17 8 A/P 9 P/A	48-72	71/29	At the average dose of 3.91 mg mean post injection UPDRS scores at 20 minutes were reduced by 20.0 and 3.00 points by APO and P respectively (p < 0.0001). These results were corroborated by non-parametric analyses using the exact Wilcoxon Rank Sum Test (p=0.0005 for treatment effect, p=0.6058 for sequence effect). At 10 minutes and 60 minutes APO versus P changes in UPDRS motor scales were also significant (10 minutes 15.4 v 2.70 p = 0.0086 60 minutes 12.6 v -0.4 p=0.0009). AEs occurred in 3 of 17 (17.6%) patients during placebo testing 0 of 16 patients during APO testing and in 2 of 17 patients on non-treatment days. There were no deaths or SAEs.

CLINICAL REVIEW

Study Type	Study No. (Ref No)	Study Title	Study Design	Drugs, Dosage and Duration of Exposure	N	Age Range (yr)	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event, A/P = active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient, IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement, NA = Data not available NS = Not Statistically Significant OP = outpatient, P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic-pharmacodynamic R = randomized SC = subcutaneous TV = Treatment Visit UPDRS-(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
PIVOTAL EFFICACY STUDIES								
Phase III Primary Safety Efficacy Component US Study 22 US Sites	APO303 (sub-study of APO401)	Study of Orthostatic Changes upon Apomorphine Dose Initiation in Late Stage Parkinson's Disease Patients A Dose Escalation Study with a Double-Blind Placebo Controlled Efficacy Determination at 4 mg	IP Forced Titration Dose Initiation DB R PC XO 6 month open OP treatment at optimal dose 6 month OP Phase	SC IP forced titration dose introduction from 2 10 mg at 2 mg increments DB R PC XO at the 4-mg dose introduction level 6 month open OP treatment at optimal dose Ongoing Study (Data through January 2002 SAEs updated through March 2002)	56	46-82	59/42	56 patients enrolled 51 patients participated in the IP efficacy assessment The mean change in pre-dose UPDRS-MS was significantly greater after 4 mg APO v P at 20 (-11 v -3) 40 (-14 v -3) and 80 minutes (-5 v -2) Results were confirmed by non-parametric methods As of January 2002 8 subjects completed and 27 subjects continue OP therapy 96 % patients had at least 1 AE 15 patients discontinued due to AEs Common AEs included yawning dizziness nausea rhinorrhea sedation BP reduction and headache The incidence of AEs and orthostatic was related to dose One of 3 SAEs (sinus arrest syncope) was drug related One death was not considered drug related

Study Type	Study No. (Ref No)	Study Title	Study Design	Drugs, Dosage and Duration of Exposure	N	Age Range (yr)	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event, A/P = active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double blind IP = inpatient, IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement, NA = Data not available NS = Not Statistically Significant OP = outpatient, P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic-pharmacodynamic R = randomized SC = subcutaneous TV = Treatment Visit UPDRS-(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
KEY SAFETY STUDY								
Phase III Long Term Safety US Study 61 Sites	APO401 (parent study for APO303 and APOM-0073)	An Open Label Study to Evaluate the Long Term Safety and Effectiveness of Subcutaneous Injections of Apomorphine in the Treatment of "Off" Episodes in Patients With "On-Off" or "Wearing-Off" Effects Associated With Late Stage Parkinson's Disease	Open Titration to optimal dose	SC Titration to optimal dose Treatment for 1 year with optional extension Ongoing Study (Data through December 2002 SAEs updated through March 2002)	488	38-99	66/34	488 patients received APO 278 are active 129 on APO for at least 12 months Most patients withdrew because of AEs The average single dose for patients receiving APO for at least 12 months was 3.91 mg Ten deaths were reported—none attributed to APO Most AEs were mild to moderate and included dizziness nausea dyskinesia and orthostatic hypotension No clinically significant laboratory trends were observed Seven SAEs occurred that involved orthostasis or syncope-type episodes Two of these events occurred within 30 minutes of injection and within 60 The remaining events occurred greater than 2 hours after the last apomorphine dose

CLINICAL REVIEW

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs Dosage and Duration of	N A/P	Age Range	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event A/P= active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement NA = Data not available NS = Not Statistically Significant OP = outpatient P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic pharmacodynamic R = randomized SC = subcutaneous TV = Treatment Visit UPDRS-(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
SUPPORTIVE STUDIES								
Phase II Supportive Efficacy Clinical Pharmacology PK PD US Study 3 Sites	APOM-0073 (sub-study of APO401)	A Multiple Center Phase I Open Label Pharmacokinetic (PK) and Pharmacodynamic (PD) Study Following Subcutaneous Administration of Apomorphine HCl to Patients with Idiopathic Parkinson's Disease	Open 4 Treatment Visits All PD patients on stable APO dose	TV1 MD TV2/TV3 R between MD-2 mg and MD+2 mg TV4 MD every 90 min x 3 doses	6	57-73	67/33	The mean peak APO concentration occurred at 13.6 minutes after the SQ injection and declined with a half life of 43 minutes and with an elimination rate that appeared to obey first-order one compartment kinetics Indices of both efficacy (UPDRS MS and Webster step second scores) and safety (BP and DRS) correlated with APO plasma concentrations The correlation of plasma APO concentrations with parameters describing pharmacological outcome (both efficacy and safety) provides independent substantiation of drug effectiveness

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs Dosage and Duration of	N A/P	Age Range	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event A/P= active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement NA = Data not available NS = Not Statistically Significant OP = outpatient P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic pharmacodynamic R = randomized SC = subcutaneous TV = Treatment Visit UPDRS(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
SUPPORTIVE STUDIES								
Phase II Academic - Government Basic Science Study Retrospective Analysis of Efficacy and Safety Parameters US study 1 Site	APONIH	A Double-Blind Placebo Controlled Dose-Response Study Of Apomorphine In The Treatment Of "Off" Episodes In Parkinson's Disease Patients Grouped By Response to Levodopa / Carbidopa (based on data from a study conducted by the Experimental Therapeutics Branch National Institute of Neurological Disorders and Stroke National Institutes of Health) Apomorphine Responses In Parkinson's Disease And The Pathogenesis Of Motor Complications (Neurology 1997 48 369-372)	DB PC XO	SC individualized by titration on basis of Columbia Rating Scale Range 0 to 6mg Treatment duration was 2 weeks	34	32-74	68/32	Max % improvement in modified Columbia Rating Score produced by APO were 35 40 77 and 73% respectively (paired difference p<0.001 v PL) in each of four subgroups (LD naïve stable wearing off on/off) Responses of patients classified as "wearing-off" or "on-off" subsets were not significantly different from each other but were different from responses in patients at earlier stages of disease severity

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs Dosage and Duration of	N A/P	Age Range	% M/F	Results
Abbreviations Used (S)AE = (serious) adverse event A/P= active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement NA = Data not available NS = Not Statistically Significant OP = outpatient P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic pharmacodynamic R = randomized SC = subcutaneous TV = Treatment Visit UPDRS(MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover								
SUPPORTIVE STUDIES								
Supportive Phase II Efficacy and Safety Foreign Study	APO101	A Double-Blind Placebo Controlled Study With Apomorphine In A Pen Given To Parkinson's Patients With On-Off Phenomena Pen Injected Apomorphine Against Off Phenomena In Late Parkinson's Disease A Double Blind Placebo Controlled Study (J Neurol Neurosurg Psychiatry 1995 58 681 687)	DB PC XO	SC individualized by titration on basis of Columbia Rating Scale	22 XO	44-72	45/55	14 subjects completed the study 8 patients discontinued due to hypotension (3) unsatisfactory effect (2) exanthema (1) unclear "Off" periods (1) and lack of motivation (1). APO produced a statistically significant reduction in the mean daily duration and severity of "Off" periods. Efficacy and safety was demonstrated for two months under outpatient conditions

CLINICAL REVIEW

Study Type	Study No (Ref No)	Study Title	Study Design	Drugs, Dosage and Duration of Exposure	N A/P	Age Range (yr)	% M/F	Results
<p>Abbreviations Used (S)AE = (serious) adverse event, A/P = active to placebo ratio APO = apomorphine BID = twice daily BP = blood pressure DB = double-blind IP = inpatient, IV = intravenous infusion LD = levodopa MD = Maintenance Dose MPI = Maximum % Improvement, NA = Data not available NS = Not Statistically Significant, OP = outpatient, P = placebo PC = placebo controlled PD = Parkinson's Disease PG = parallel groups PK PD = pharmacokinetic-pharmacodynamic, R = randomized SC = subcutaneous TV = Treatment Visit, UPDRS (MS) = Unified Parkinson's Disease Rating Scale (Motor Scores) XO = crossover</p>								
SUPPORTIVE STUDIES								
Supportive Phase IV Safety Foreign Study	APO161 (APOD-401)	A Retrospective Safety Review of Subjects Treated with Apomorphine for Parkinson's Disease at One Centre Over a 13 Year Period (1986 to 1999) Middlesex Study	Retro spective Safety Review	Individualized dose SC intermittent SC continuous nasal IV and rectal	188	26-76	62/38	188 patients were reviewed with 159 summarized with complete CRF 60 deaths were documented with a mean of almost 6 years between APO introduction. Time of death and cause of death was similar to that expected of late stage Parkinson's disease. The most serious adverse events related to development of skin lesions and neuropsychiatric reactions that can require treatment discontinuation. Adverse events lack of effect and complexity of dosing contributed to discontinuation of therapy by 20% of patients within 1 year. Overall population median treatment duration is currently 70 months.

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4 Pivotal Studies Showing Efficacy

4.1 Study APO202 (Pivotal Study Showing Efficacy)

4.1.1 Summary Description of Protocol APO202

Title of Study A Prospective, Randomized, Double-Blind, Placebo-Controlled Parallel Groups Study of the Safety and Efficacy of Subcutaneous Injections of Apomorphine in the Treatment of "Off" Episodes in Patients with "On-Off" or "Wearing-Off" Effects Associated with Late-Stage Parkinson's Disease

Investigators [

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Study initiation (first patient enrolled) date 1/13/98

Study completion (last patient completed) date 7/15/98

Objectives

The primary objective was to examine the therapeutic response to apomorphine (APM) administration as a subcutaneous injection in the treatment of an induced "Off" state in Parkinson's disease patients

The secondary objective was to determine the effectiveness of APM in aborting "Off" phenomena during chronic administration and to determine APM's effect on total "Off" time during chronic administration

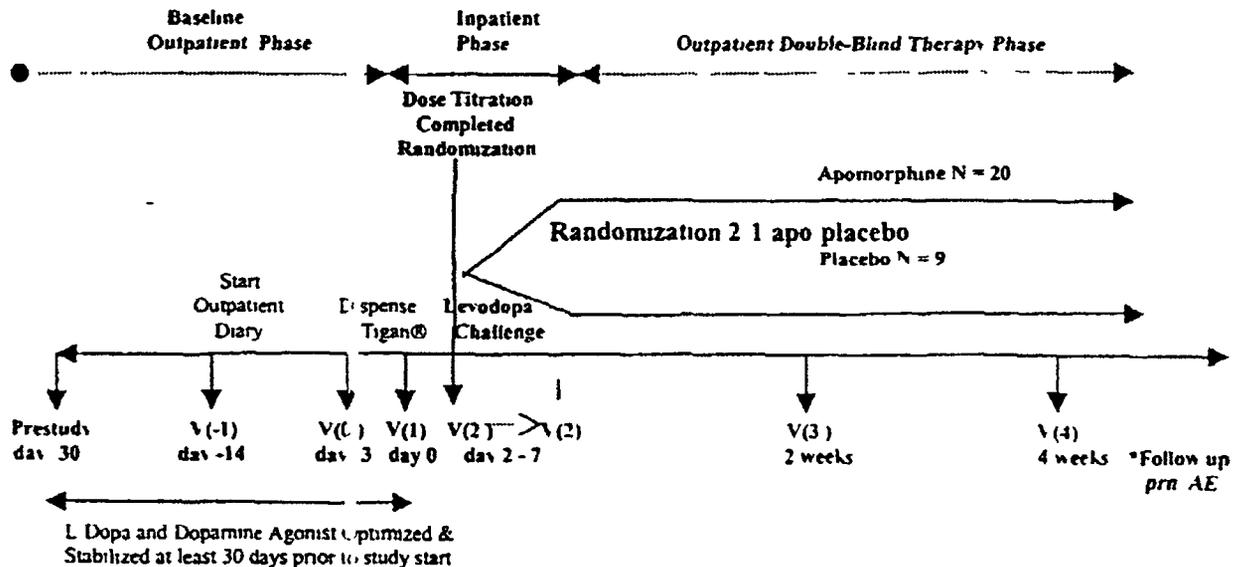
Study Design

This was a prospective, double-blind, randomized, parallel, multi-center study. Patients were considered to have refractory "Off" despite "optimal" anti-parkinson medical therapy based purely upon each investigator's individual judgement. After an initial outpatient baseline, this study involved two general phases, an inpatient phase and an outpatient phase. During the inpatient phase patients were admitted no later than 9 pm on the evening before Visit 1. "Off" states were induced by withholding morning doses of levodopa (LD) and dopamine agonists. With the exception of withholding the last doses before the morning doses for "brittle patients", no LD or dopaminergic agonist was to be given after midnight. Patients were to fast from midnight until lunch the next day. The patient was defined as dopamine "responsive" for inclusion in this trial when there was a $\geq 30\%$ improvement (i.e. decrease) in UPDRS motor score in response to the patient's usual LD dose after a "Off" induced by withholding LD. Motor function testing was to be performed once an "On" has occurred or between 60-120 minutes after LD (whichever comes first).

Visit 2 for titration of randomized study medication (i.e. APM or placebo) was conducted under double-blinded, placebo-controlled design and was supposed to occur during an interval ranging between 24 hours to 7 days after Visit 1. Each patient's "therapeutic" dose to study medication (i.e. APM or placebo) was determined by titrating the patient's motor function response to APM or placebo until a "therapeutic dose" was achieved. Titration involved administering increasing volumes of study medication starting at 0.2 ml (e.g. 2 mg of APM if randomized to APM) and using 0.2 ml increments up to a maximal volume of 1.0 ml (e.g. 10 mg of APM if randomized to APM). Motor function testing was to be performed once an "On" has occurred or within 10-15 minutes after APM (whichever comes first). The therapeutic dose was defined as the dose of APM that produced a UPDRS motor score that was $\geq 90\%$ of that demonstrated by the patient's usual LD dose after an induced "Off". The assessment of the primary efficacy endpoint was conducted by determining the change in UPDRS motor score from pre-dose up to 15 minutes after study medication at 2-hour intervals after the first dose. The protocol did not specify that a patient had to be "Off" or have a certain UPDRS motor score before administration of a repeat higher volume of study medication. Additional doses of study medication were to be administered at different sites in the abdomen. During these elicited "Off" states, response to study medication was recorded using UPDRS and other objective assessments.

During the 1-month outpatient phase, the blind was maintained and patients or caregivers administered subcutaneous treatment injections up to 5 times daily to treat spontaneously occurring "Off" episodes. Response to medication was assessed by daily patient diary. Investigators were allowed to make one dose change in the outpatient setting.

Figure 2 APO 202 Study Design



Treatment Duration 1 month

Key Inclusion Criteria

- All patients must have suffered refractory motor fluctuations associated with late stage Parkinson's disease and a minimum 2 hr daily average "Off" time
- All patients must have received pre-study therapy to include levodopa plus at least one oral dopamine agonist in an attempt to prevent immobility
- All patients must have exhibited at least 30% improvement in UPDRS score after dopaminergic challenge prior to randomization
- All patients must have been APM naive prior to study entry

Key Exclusion Criteria

- All patients taking dopamine antagonist or depleting drugs excluding clozapine, anticholinergics and/or antihistamines with anticholinergic effects
- All patients with signs or symptoms suggestive of clinically significant orthostatic hypotension, schizophrenia, dementia, "parkinson-plus" syndromes or unstable systemic disease

Efficacy Variables

Criteria of Evaluation / Parameters Evaluated Efficacy measurements and evaluations varied between the primary efficacy (i.e. efficacy evaluation of APM under inpatient conditions) and secondary efficacy (i.e. efficacy evaluation of APM during outpatient administration) objectives

Inpatient

Primary efficacy was to be evaluated after receiving at least one dose of randomized medication under inpatient conditions. The primary efficacy variable was the UPDRS motor examination score. This UPDRS scale (III) was to be assessed when the patient noted that he/she was "On" or up to 120 minutes during LD administration and up to 15 minutes after study medication (i.e. APM or placebo), whichever occurs first. The response ratio was calculated by determining the maximal percentage response (i.e. % decrease in UPDRS motor score) to study medication relative and dividing this response by the response (i.e. % decrease in UPDRS motor score) to LD. Response was then mathematically transformed by various methods allowing for multiple representation of the data including raw score change, % change relative to pre-dose score and, response ratio (% change test drug over % change oral levodopa). Determination of the response ratio was the primary efficacy analysis of the primary efficacy endpoint, as it simultaneously compared APM to placebo and APM to LD.

Other secondary efficacy variables that were to be evaluated included

- Hand-Tapping Test - The patient taps a set of counters 20.3 cm apart in succession for 60 seconds with one hand and then the other hand