CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,384 Serial #039

Acadia Pharmaceuticals INC.
Attention: Hilde Williams, Director, Regulatory Affairs
3911 Sorrento Valley Blvd.
San Diego, CA 92121

Dear Ms. Williams:

Please refer to the teleconference between representatives of your firm and FDA on September 25, 2006. The purpose of this meeting was to provide guidance regarding proposed phase IIb/III clinical design and the adequacy of the phase III clinical and preclinical program for registration.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Keith Kiedrow, Pharm.D., Regulatory Health Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING
IND 68,384, ACP-103
Acadia Pharmaceuticals INC.
Type B meeting / EOPII
September 25, 2006

Participants –

FDA

Robert Temple, MD	Director, Office of Drug Evaluation 1
Thomas Laughren, MD	Director, Division of Psychiatry Products
Ni Aye Khin, MD	Medical Team Leader, Division of Psychiatry Products
Earl Hearst, MD	Medical Reviewer, Division of Psychiatry Products
Marc Walton, MD	Deputy Director, Division of Neurology Products
Russell Katz, MD	Director, Division of Neurology Products
John Feeney III, MD	Medical Team Leader, Division of Neurology Products
Leonard Kapcala, MD	Medical Reviewer, Division of Neurology Products
Peiling Yang, PhD	Statistics Team Leader
Yeh-Fong Chen, PhD	Biostatistics Reviewer
Barry Rosloff, PhD	Supervisory Pharmacologist
April Robison	Pharmacy Student Intern
Keith Kiedrow, PharmD	Regulatory Project Manager

Attendees Representing the Sponsor

Marylynn Cain	Manager, Regulatory Affairs
David Furlano, PhD	Vice President, Regulatory Affairs
Roger Mills, MD	Executive Vice President, Development
Dan van Kammen, MD, PhD	Vice President, Clinical Development
Kim Vanover, PhD	Director, Clinical Operations
Hilde Williams	Director, Regulatory Affairs

(b) (4)

Background:

ACP-103 is an inverse agonist of 5HT2A and 5HT2C receptors that the sponsor is developing for the treatment of Parkinson's disease psychosis (PDP). We have had several meetings with the sponsor, including: (1) a 7-2-03 preIND meeting (under IND (b) (4); (2) an 11-12-03 telcon under IND 68,384; and (3) a 6-29-06 meeting during which we reached agreement on a number of issues pertinent to the development of this product for this indication. [See minutes for each of these meetings for additional background for this meeting.]

The sponsor is planning a 6-week phase IIb/III study (ACP-103-012) that will compare 2 dose levels of ACP-103 (10 and 40 mg/day) vs placebo in patients with PDP. Dose justification is based on experience from study 006 and PET receptor occupancy studies. Patients must be on stable anti-Parkinson's therapy with no changes within 1 week prior to starting, and must have an MMSE of $\geq$ 21. The entry criteria for PDP are expected to be in line with the anticipated diagnostic criteria for PDP coming out of the recent NINDS meeting. As indicated in the 6-29-06 telcon, the primary assessment will be the combined hallucinations and delusions domains of

the SAPS. The study will be powered to detect a difference on the SAPS as well as a 5 point margin of difference between drug and placebo on the key secondary endpoint, i.e., the UPDRS Parts II and III. However, the sponsor apparently does not plan to formally assess noninferiority on this endpoint, but rather, provide only "descriptive statistics."

The sponsor expects to begin a second trial in phase 3, i.e., Study ACP-103-014. This study would include patients with Parkinson's disease with or without psychosis. For this trial, the primary endpoint would be UPDRS Parts II and III, with a key secondary for assessing psychosis improvement (i.e., SAPS hallucinations and delusions). This would be a 6-month study comparing up to 2 ACP-103 dose arms vs placebo. The primary hypothesis would be a non-inferiority hypothesis, i.e., that ACP-103 is no worse than placebo by some margin. The sponsor is requesting accelerated approval of ACP-103 under 21CFR314.520 (Subpart H), based on the rationale that PDP is a serious illness for which there are no approved treatments. Thus, they would hope to gain approval based on Study 012 alone, with a commitment to complete Study 014 post-approval.

If permitted to develop ACP-103 under Subpart H, the sponsor would expect to have approximately 1000 exposed patients at the time of initial NDA submission, including approximately 100 for 6 months but no more than 25 for > 6 months.

Questions:

Clinicl/Biopharmaceutical Questions

Endorsement of PDP as an indication for ACP-103

Question 1 background; supporting info found in briefing document Section 3; P. 21, Appendix 1; P. 94: As discussed in the Type C teleconference held with the Agency on 29 June 2006, the development of psychotic features in PD patients is likely a result of Parkinson's disease progression and other PD-related factors, possibly in combination with anti-Parkinson's treatment. The National Institute on Neurological Disorders and Stroke (NINDS) consensus meeting attended by the Division and industry representatives last November concluded that PDP was a discrete indication which could be clinically distinguished from other forms of psychosis (including drug induced psychosis). Publication of diagnostic criteria by an independent working group established out of the NINDS Workshop is forthcoming. (As discussed at the Type C teleconference, ACADIA intends to use the NINDS draft criteria to determine study eligibility for psychotic symptoms in its Phase IIb/III study.)

1. In light of this developing framework, does the Division agree that treatment of PDP is an indication for which ACADIA can seek registration/labeling?

   Preliminary Comments: Yes, we are in agreement that PDP is a legitimate clinical target for drug development. However, as noted in our 6-29-06 telcon, it will be important to have specific and widely-accepted diagnostic criteria for selecting patients for any future studies.

   Discussion at Meeting: There was no further discussion at the meeting.

Question 2 background; supporting info found in briefing document Section 3; P. 21, Section 5.1.1.1; P. 58: ACADIA intends to seek approval for ACP-103 in the first-line treatment of PDP. In the absence of any approved treatments in the United States (U.S.), first-line management of PDP sometimes involves dose-adjustment or even cessation of anti-Parkinsonian therapy. However, this approach typically worsens Parkinsonism and does not improve the

patient's psychiatric condition. Although off-label use of currently available antipsychotics have been employed in the treatment of PDP, most have not consistently demonstrated efficacy or an acceptable safety profile (e.g., 'black box' in this and other patient populations). Within this framework, there continues to be a need for proven safe and effective antipsychotic therapy that does not require pre-adjustment of anti-Parkinsonian treatment. Hence, for the proposed Phase IIb/III program, entry of PDP patients into ACP-103 trials will not be limited to those with previous adjustments of their dopaminergic therapy. Patients with and without prior reductions in L-dopa will be allowed to enroll, assuming they meet all other entry criteria.

2. If ACP-103 is demonstrated to be effective in improving psychotic symptoms while preserving motor function in patients with PDP, would the Division agree that a first-line label claim for ACP-103 may be endorsed without recommendations for prior adjustment of anti-Parkinsonian treatment?

   Preliminary Comments: ***As indicated in our 6-29-06 telcon, we would not require patients having had prior adjustment of anti-Parkinsonian treatment, providing that ACP-103 can be shown not to worsen Parkinsonian symptoms. However, we will ask that patients be carefully characterized with regard to adjustments in anti-Parkinson's drug treatments in the period preceding entry into your trials, so that treatment response can be explored in the 2 subgroups, i.e., those with and those without adjustment of their anti-Parkinson's drug treatments.***

   Discussion at Meeting: ***The sponsor agreed to collect information regarding adjustments in anti-Parkinson's drug treatments in the period preceding entry into their trials, so that treatment response can be explored post hoc in the 2 subgroups, i.e., those with and those without adjustment of their anti-Parkinson's drug treatments. They indicated their expectation was that a majority of patients would have had prior dosage adjustments. They then requested confirmation that this approach would suffice for gaining an indication without constraints on prior dose adjustments. We agreed in principle that their proposed approach should suffice, however, we cautioned that it would be a review issue and, in addition, any future NDA would very likely be presented to the PDAC. In addition, we asked that they provide preliminary data on the proportion of the first 50 patients who fell into each of these 2 subgroups. They agreed to provide this information.***

The adequacy of the Phase IIb/III study design for NDA filing and registration of ACP-103 for treatment of PDP

Questions 3, 4, and 5 supporting info found in briefing document Section 5.1.1.1; P. 58

3. Is the population, as proposed in the Phase IIb/III protocol synopsis, appropriate for NDA filing/registration to support the intended indication?

   Preliminary Comments: ***The population described generally appears to be appropriate, however, we would like clarification that a clearly defined set of diagnostic criteria will be in place at the time the trial is started and that patients will be expected to satisfy these criteria. In general, we want better characterization of the patients you intend to recruit for your trials. It is our expectation that most patients will have advanced Parkinson's disease, and we would like confirmation on this point. In addition, we recommend that the minimum MMSE score be set at 24, rather than 21.***

Discussion at Meeting: ***The sponsor indicated that they do intend to use the NINDS Workshop criteria for PDP, and they agreed to submit to us within the next month a draft publication discussing these criteria. They did ask for confirmation that we would not require a particular threshold of severity of Parkinson's disease for entry into their trials, and we agreed. They did confirm, nevertheless, that they expect a majority of patients in these trials will have advanced Parkinson's disease. Finally, they argued that requiring an MMSE score of $\geq$ 24 rather than $\geq$ 21 would be too restrictive, and we agreed to accept 21 as a threshold score.***

4. Based on the proposed study design as outlined in the protocol synopsis, is the proposed Phase IIb/III trial of sufficient duration to support the intended indication?

Preliminary Comments: ***Six weeks should be of sufficient duration to establish short-term antipsychotic efficacy.***

Discussion at Meeting: ***The sponsor wanted confirmation that 2 positive studies of 6 weeks duration would be sufficient to support an antipsychotic claim that is not restricted regarding duration. We clarified that 2 such studies would support a general antipsychotic claim in PDP, however, labeling would also note that longer-term efficacy (i.e., beyond 6 weeks) had not yet been established.***

5. The proposed Phase IIb/III study will be powered to demonstrate superiority against placebo on the primary endpoint (mean combined Scale for the Assessment of Positive Symptoms [SAPS] hallucinations and delusions scores). The size of the proposed study (N = 280, with 2 active and 1 placebo arms), and specifically the number of patients per arm (n = ~80), was calculated (assuming a 10% drop out rate) to be able to detect a difference of 4.75 points on this endpoint at $\alpha = 0.05$ using a 2-sided test with 90% power.

This proposed sample size is also sufficient to ensure non-inferiority with 90% power on the key secondary endpoint, Unified Parkinson's Disease Rating Scale (UPDRS) Parts II and III scores, based on a 5-point non-inferiority margin with a 90% 2-sided CI on the treatment difference. Effects on this secondary endpoint will be reported using descriptive statistics.

a) Does the Division agree that for the primary endpoint, a difference of 4.75 points in mean combined SAPS scores between placebo and ACP-103 is an appropriate margin for use in the Phase IIb/III program?

Preliminary Comments: ***Yes.***

Discussion at Meeting: ***There was no further discussion at the meeting.***

b) Does the Division agree that the study will be sufficiently powered to support approval for the intended indication?

Preliminary Comments: ***The power calculations seem reasonable, however, since the true effect size is not known, there is no guarantee the study will be sufficiently powered. We also notice that there are two doses of ACP-103 included in study 012 in comparison with placebo, but your sample size calculation did not take the multiple comparisons into consideration.***

Discussion at Meeting: ***The sponsor proposed that the multiplicity issues would be handled using a Bonferroni adjustment or a stepdown approach, and we agreed that their proposed approaches were acceptable, but the explicit approach needs to be pre-specified in the protocol or SAP.***

c) Does the Division agree with the proposal to use descriptive statistics to evaluate the key secondary endpoint, UPDRS Parts II and III scores?

Preliminary Comments: ***Given the very wide margin for non-inferiority, we would expect that the non-inferiority hypothesis would be satisfied. If not, there would be concern that ACP-103 may not be an acceptable treatment because of a significant worsening of the Parkinsonian symptoms. Thus, we consider this critical information in our evaluation of any future NDA that must be evaluated along with the efficacy data before reaching a judgment about risk and benefit. Furthermore, this should be a 2-sided test using a 95% CI on the difference, because it is our understanding that you intend to consider both inferiority and superiority of ACP-103 to placebo on this outcome. Please send the statistical analysis plan to the FDA for review as early as possible prior to data unblinding to allow a sufficient time to finalize it.***

Discussion at Meeting: ***The sponsor agreed to a 2-sided test using a 95% CI on the difference between drug and placebo. They asked if submitting a final SAP as late as a month before unblinding would be acceptable. We expressed reservations about such a late SAP. We asked that the protocols for their studies include sufficient detail about the planned analyses that it would not be necessary to make major changes late in the study.***

The adequacy of the overall clinical plan for ACP-103 to support a marketing application for the proposed indication of PDP

6. Is the clinical program, as proposed in the briefing package, for ACP-103 in PDP adequate for filing/registration? Specifically,
   a. Will the Phase IIb/III study, as outlined, provide adequate and well-controlled evidence of safety and efficacy in the PDP population? (background info Section 5.1.1.1; p.58)

Preliminary Comments: ***We have several comments:***
-For Study 012, we strongly recommend that you include an active control group, e.g., quetiapine, even though there are no drugs approved for this indication. Having quetiapine as a control would help in the interpretation of both the efficacy benefit as well as any effect on motor function.
-Study 012 by itself will not be sufficient as a source of efficacy and safety data, even if it is positive on the efficacy outcome and meets the noninferiority hypothesis. We do not accept your argument for a Subpart H filing, thus, you must have evidence from 2 trials.

Discussion at Meeting: ***The sponsor argued strongly against having an active control arm, and we agreed that this would not be a requirement, but rather, was a suggestion to help in interpretation of the findings from their studies. We explained our basis for rejecting a Subpart H filing, and also the alternative of 1 positive study plus confirmatory evidence. The sponsor asked if two placebo-controlled 6-week studies***

would suffice, and we indicated our agreement. We strongly encouraged them to utilize fixed dose designs in both studies.

b. Given that PDP is a serious and life-shortening (if not life-threatening) condition without adequate treatment options, would the Division endorse accelerated approval under 21 CFR 314.520 (Subpart H), based on this single Phase IIb/III study, if the results are sufficiently robust? (background info Section 5.3.1; p.64)

Preliminary Comments: ***As noted for question a, we do not agree with a Subpart H filing.***

Discussion at Meeting: ***See 6a.***

c. A second adequate and well-controlled study is proposed in patients with Parkinson's disease patients with or without psychosis. The primary endpoint is UPDRS Parts II and III (i.e., motor function) with a key secondary endpoint for assessing psychosis (i.e., SAPS Hallucinations and Delusions Total Score). (background info Section 5.1.2; p.62)

Assuming that this second study is initiated prior to NDA submission, would FDA accept study completion and submission of the data as a post-marketing commitment based on accelerated approval per 21 CFR 314.520 (Subpart H) with a single pivotal trial? (background info Section 5.3.1; p.64)

Preliminary Comments: ***As noted for question a, we do not agree with a Subpart H filing.***

Discussion at Meeting: ***See 6a.***

d. Is the proposal for conducting drug-drug interaction studies, as outlined in Section 5.2.3, adequate for NDA filing/approval? (background info Section 5.2.3; p.64)

Preliminary Comments: ***More information is needed about the range of likely co-administered drugs in this population before we can reach a judgment on this issue. We ask that you provide such information.***

Discussion at Meeting: ***The sponsor provided a list of drugs expected to be coadministered with ACP-103, and indicated that they will study the interaction of ACP-103 and L-DOPA. In addition, they indicated that, based on the results of in vitro metabolism studies, they will likely study other interactions in vivo as well.***

e. Will a QT study, conducted as per ICH E14 Guidance to Industry, provide adequate assessment of the risk for QT prolongation for ACP-103? Is the study adequate for NDA filing/approval? (background info Section 5.2.2; p.64)

Preliminary Comments: ***A thorough QT study meeting ICH E14 standards should be capable of adequately addressing this question.***

Discussion at Meeting: There was no further discussion at the meeting.

f. Is the plan for conducting studies in other special populations, as outlined in Section 5.2.2, adequate for NDA filing/approval? (background info Section 5.2.2; p.64)

Preliminary Comments: Your plans to conduct special safety studies in the elderly, in hepatically impaired patients, in renally impaired patients, and a thorough QT study may be adequate, however, a final judgment on this issue must await review of emerging data from your development program.

Discussion at Meeting: There was no further discussion at the meeting.

g. Are the adsorption, distribution, metabolism, and excretion (ADME) studies, as proposed in Section 5.2.1, adequate for NDA filing/approval? (background info Section 5.2.1; p.64)

Preliminary Comments: On face, the planned clinical pharmacology program appears to be adequate, however, a final judgment on what specific studies are needed will have to depend on emerging data from your development program.

Discussion at Meeting: There was no further discussion at the meeting.

h. Are there any other special or supportive clinical safety studies that the Division will require at time of NDA filing? (background info Section 5.2; p.64)

Preliminary Comments: We have no specific advice to offer on this question at this early stage of development, however, a final judgment on what specific additional studies may be needed will have to depend on emerging data from your development program.

Discussion at Meeting: There was no further discussion at the meeting.

7. (b) (4) (b) (4) The safety database can be updated with additional exposures at the time of the 120-day update and further safety experience may be garnered in postmarketing studies. Given that patients with PDP are underserved by currently available treatment options and the population is inherently small (U.S. estimates range from <200,000 [Noyes, 2006] to 600,000 [Marsh, 2005]), ACADIA requests comment from the Division as to the adequacy of the projected safety database for NDA filing and approval.

Preliminary Comments: ACP-103, if approved, would be a chronically used drug, and the NDA should meet ICH exposure criteria for such drugs.

***Discussion at Meeting*: The sponsor argued that PDP is a serious condition with substantial morbidity and is also hard to study because it is difficult to recruit patients.** (b) (4)

(b) (4) (b) (4) (b) (4)

that one factor in deciding how much exposure data might be acceptable would be the size of the treatment effect demonstrated by their studies. A very substantial benefit might well be an argument in favor of compromising somewhat on the total safety database.

Nonclinical

The adequacy of the nonclinical plan for ACP-103 to support a marketing application for the proposed indication of PDP

1. Is the proposed nonclinical program to NDA adequate for filing/registration? (background info Section 6.2; p.88)

***Preliminary Comments*: The nonclinical program is adequate in form but we, of course, will need to review the data. There is always the possibility that additional studies may be needed based on the results of the ongoing animal and human studies. In addition, you will need to characterize the in vivo metabolism of ACP-103 in rats and monkeys as well as in humans. Human metabolites which are not well covered in the animal toxicity studies may need further evaluation.**

***Discussion at Meeting*: There was no further discussion at the meeting.**

2. Question background; supporting info found in briefing document Section 6.1.5.3; P. 86: Dose and duration-dependent phospholipidosis (PL) has been observed in toxicity studies of ACP-103 at doses of 90 mg in the rat (subchronic 3-month study) and ≥25 mg in the monkey (subchronic 3-month study). Drug-induced PL is considered an adaptive response to compounds like ACP-103 with a cationic amphiphilic structure (CADs), and its clinical significance is unknown. The PL observed in rat and monkey subchronic toxicity studies has demonstrated partial or complete reversibility following 4-week recovery periods. To date, the absence of PL has been used to define no-observed-effect levels (NOELs) in the subchronic toxicity studies.

   a. Does the Division agree that doses of ACP-103 which result in PL (but demonstrate reversibility and occur in the absence of any persistent histopathological correlates) may be considered no-observed-adverse-effect levels (NOAELs) in these studies and that a reversible profile of PL is not of great clinical concern?

***Preliminary Comments*: The Division cannot comment on this issue prior to our evaluation of the data in the 3, 6, and 12 month toxicity studies. If we concur that the PL is reversible and occurs in the absence of any persistent histopathological correlates, we would likely agree.**

Discussion at Meeting: There was no further discussion at the meeting.

b. The 6- and 12-month chronic toxicity studies with ACP-103 in rats and monkeys are currently ongoing. The designs of these studies include an extended treatment period for the monkey study and extended post-treatment recovery phase (3 and 4 months for rats and monkeys, respectively) for all treatment groups in both the rat and monkey studies. These additions to the standard chronic design were incorporated to provide a clearer occurrence and reversibility profile of PL in these studies. Does the Division agree with this approach to chronic toxicity assessments, and that no additional studies would be necessary to further characterize PL?

Preliminary Comments: The Division cannot concur prior to our evaluation of the results of these studies. There is one concern with regard to the dose selection for the 6 month rat study. You state that an extended post-treatment recovery phase of up to 3 months in rats was "incorporated to provide a clearer occurrence and reversibility profile of PL..". However, the high dose in this study is 30 mg/kg which is the NOEL for phospholipidosis based on the results of the three month rat study; thus the proposed study may not be adequate to evaluate reversibility.

Discussion at Meeting: The sponsor argued that duration of exposure was an important factor as well as dose in the development of PL, and that based on effects in shorter term rat studies PL is likely to become evident by 6 months of treatment at the 30 mg/kg dose. We agreed with this reasoning, but noted that this would still be a review issue.

3. ACADIA intends to conduct 2-year bioassays in rats and mice to assess the carcinogenic potential of ACP-103. Given the age of the population, the seriousness of the disease and the lack of other approved treatment options, would FDA accept ongoing carcinogenicity studies at time of accelerated approval and submission of the study reports as a post-approval commitment? (background info Section 6.2.3; p.89)

Preliminary Comments: The Division believes that submission of the 2-year carcinogenicity study in rats and mice after submission of the NDA is not warranted.

Discussion at Meeting: There was no further discussion at the meeting.

Question 4 background; supporting info found in briefing document Section 6.2.4; p.89: In light of the general use of dopaminergic therapy in Parkinson's patients, FDA noted the need to conduct nonclinical ACP-103/Sinemet interaction studies during the Pre-IND meeting. ACADIA is currently planning to perform an evaluation of tolerability, pharmacokinetics, and toxicity of ACP-103 in combination with a fixed dose of L-dopa:carbidopa. This evaluation will be performed in two stages: (1) Initial studies in both rat and monkey will be designed to evaluate pharmacokinetics and determine the maximum tolerated dose of ACP-103 in combination with L-dopa:carbidopa; (2) A definitive 13-week study will then be conducted in rats, the most sensitive toxicology species to ACP-103.

4. Acadia's proposal to pursue a single subchronic bridging study to support adjunctive use of ACP-103 in Parkinson's patients is consistent with the Agency's recent Guidance for Industry entitled Nonclinical Safety Evaluation of Drug or Biologic Combinations (issued in March 2006). Is this proposal for non-clinical evaluation of potential ACP-103/Sinemet interactions acceptable to FDA?

Preliminary Comments: ***The proposal for non-clinical evaluation of potential ACP-103/Sinemet interactions is acceptable.***

Discussion at Meeting: ***There was no further discussion at the meeting.***

Conclusions:
Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Acadia Pharmaceuticals Inc. is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

Keith Kiedrow, Pharm.D.
Regulatory Project Manager

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/s/

Thomas Laughren
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