CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202049Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 12, 2008, 2-3:30pm
Meeting Location:	White Oak Building, Room 1415
Application Number:	70277
Product Name:	Aridol
Received Briefing Package	February 14, 2008
Sponsor Name:	Pharmaxis Ltd.
Meeting Requestor:	Pauliana Hall, President, PCH Integrated Regulatory Services, Inc.
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D., Division Director
Meeting Recorder:	Miranda J. Raggio, RN, BSN, MA, RPM
Meeting Attendees:	
FDA Attendees:	Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products
	Lydia Gilbert-McClain, M.D., Medical Team Leader, Division of Pulmonary and Allergy Products
	Carol Bosken, M.D., Medical Reviewer, Division of Pulmonary and Allergy Products
	Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer, Division of Pulmonary and Allergy Products
	Wei Qiu, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II, Office of Clinical Pharmacology
	Qian Li, Sc.D., Biostatistics Team Leader, Division of Biometrics II
	Miranda Raggio, Regulatory Project Manager, Division of Pulmonary and Allergy Products

Sponsor Attendees:

Pauliana Hall, RAC, US Agent and Regulatory Consultant for Pharmaxis, Ltd., President, PCH Integrated Regulatory Services, Inc.

Brett Charlton, M.D., Ph.D., Medical Director, Pharmaxis, Ltd.

Ron Sinani, BPharm, Regulatory Affairs Manager, Pharmaxis, Ltd.

(b) (4)

Background

PCH Integrated Regulatory Services, Inc. (PCH), on behalf of Pharmaxis Ltd, requested a Type B, Pre-NDA meeting in a correspondence dated January 16, 2008, received January 17, 2008. The purpose of this meeting was to discuss the necessary clinical/nonclinical data to support the NDA filing and ensure all the clinical issues are addressed in the NDA. The meeting briefing package was submitted to the Division on February 14, 2008. Upon review of the briefing package, the Division provided responses to PCH for Pharmaxis, Ltd. via a telephone facsimile on March 6. 2008. The content of telephone facsimile is printed below, with the Division's responses (in ***bold italics***) to the Pharmaxis questions. On March 11, 2008, Pauliana Hall, on behalf of Pharmaxis, Ltd, let the Division know that they would like to discuss the clinical/nonclinical 2, 8, and 10 at the meeting. Summary comments of the meeting discussion related to these questions are found in *italics* at the end of this document. A powerpoint presentation document which was presented and distributed to the meeting attendees by Pharmaxis, Ltd. is attached.

Questions and Responses

Question 1. The Agency informed Pharmaxis at the pre-IND meeting (held July 19, 2004) that a PK study was required to demonstrate that inhaled mannitol was not accumulating in the airways. A bioavailability study was conducted following further discussion on the design and conduct of such a study (Bronchiectasis Type B meeting) and submission of the study protocol to the Agency for review.

Based on the data presented in this Pre-NDA Clinical/Nonclinical Meeting Package, does the Agency agree that the biopharmaceutical aspects of Aridol have now been satisfactorily addressed?

Division Response: ***The Bioavailability study (DPM-A-101) synopsis included in this submission is acceptable for NDA review. Whether biopharmaceutical aspects of Aridol have been satisfactorily addressed or not is a review issue.***

Discussion: No further discussion occurred.

Question 2. The Agency informed Pharmaxis at the pre-IND meeting (held July 19,

2004) that the Phase 3 clinical trial that was ongoing outside the United States (Australia) at the time (Study DPM-A-301) was not sufficient to establish the efficacy of Aridol in the proposed indication. Therefore, a second Phase 3 clinical trial was conducted in the United States (Study DPM-A-305) following the Agency's recommendations, investigated Aridol's use in subjects with suspected asthma rather than subjects with known asthma and healthy volunteers (study population for Study DPM-A-301). Although the second Phase 3 trial (Protocol No. DPM-A-305) investigated the "target" population, Pharmaxis contends that true sensitivity and specificity cannot be measured in such a population and therefore requests the Agency to consider both trials as pivotal clinical trials to support the proposed indication for Aridol.

Does the Division agree that substantial clinical evidence for safety and efficacy can be established based on the results from Protocol Nos. DPM-A-301 and DPM-A-305?

Division Response: ***We are uncertain if substantial evidence of efficacy can be established based on the results from Protocol DPM-A-301 and DPM-A-305 for the proposed indication of detection of bronchial hyperresponsiveness. The deficiencies of the development program of Aridol as a bronchoprovoactive agent have been previously discussed in various communications (see minutes of the July 19, 2004 pre-IND Meeting; FDA comments dated April 25, 2005). The design of your studies DPM-A-301 and DPM-A-305 do not address:***

(a) Sensitivity and specificity of Aridol in a random population of patients with hyperresponsiveness (refer to comment # 16 of FDA comments dated April 25, 2005). Since the most common clinical indication for a bronchial challenge is to evaluate the likelihood of asthma in patients in whom the diagnosis is suggested by current symptoms but is not obvious, it is important to test your product in patients who are likely to be subjected to the test, such as patients with non-asthmatic conditions that are also associated with hyperresponsiveness, and subjects who are relatively healthy.

(b) Comparison of subjects with a known range of sensitivity to methacholine to their responsiveness to mannitol. This would require complete characterization of the bronchial response curves (sensitivity and specificity) to mannitol and methacholine and not just the qualitative analysis.

To define sensitivity and specificity of the test you may also need to test the performance of the Aridol test in a normal population (i.e. patients with normal spirometry, non-smokers, with no history or symptoms of asthma or any other lung disease, no family history of asthma, and no symptoms of allergy). Although protocol DPM-A-301 was conducted in asthmatic (n =557) and "non-asthmatic" (n =97) subjects, it is not clear what population constitutes the "non-asthmatics."

For a diagnostic test you will need to target for an acceptable level of sensitivity and specificity of the test. The thresholds generally expected will be above 85%. If your product has a lower threshold of sensitivity and specificity you will need to justify the lower thresholds.

You state in your briefing package (page 69) that in the pivotal study DPM-A-305, some subjects enrolled in this study likely had other diagnoses such as de-conditioning. Both studies DPM-A-301 and 305 contain ambiguities in the patient population that would need to be sorted out in order for these studies to be reviewed in support of your proposed indication. The final study report for both studies must include the following detailed information on the patient population:

1) ***Methods used for screening the patients for enrollment,***
2) ***Description of specific signs and symptoms considered to be suggestive of asthma,***
3) ***Pulmonary function test results,***
4) ***Response to beta agonists if reversibility testing was performed,***
5) ***Asthma diagnostic standards used for patients diagnosed with asthma,***
6) ***Characterization of severity for patients diagnosed with asthma,***
7) ***Listing of concomitant medications for each patient and a summary of concomitant medications for the study population, and***
8) ***The diagnosis of each patient with a negative mannitol bronchoprovocation test.***

Regarding safety, we concur that there is enough safety information to support an NDA for the proposed indication of diagnosis of bronchial hyperresponsiveness.

(b) (4)

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Highlights of this discussion are provided below:

1. *The FDA stated that pivotal trials require a greater variety in the patient population selected than Pharmaxis has selected. Studies must look across a group of patients with a diagnosis associated with hyperresponsiveness, not just those with asthma, and should include healthy subjects.*
2. *The FDA stated that tests performed on these study subjects must be able to discriminate between those patients with asthma and those with other diseases which present in a similar manner.*
3. *The FDA noted that it is vital that at the end of the trial study investigators are able to make a determination as to which patients definitively have asthma, without unblinding the study population.*
4. *The FDA asked Pharmaxis for a clarification as to what constitutes a healthy volunteer in study A-301. Pharmaxis responded that the healthy volunteer group is comprised of patients with no history of smoking, no family history of diseases which cause bronchial hyperresponsiveness, and no clinical signs or symptoms of hyperresponsive reactions. Pharmaxis further clarified that their criteria for non-asthmatics includes those patients who have never had a clinical diagnosis of asthma nor experienced signs and symptoms suggestive of asthma.*
5. *Pharmaxis stated that the Aridol kit is not meant to be used as a definitive diagnostic procedure for asthma. They described the distinctions between an indirect challenge test and a direct challenge test with regards to lower thresholds for sensitivity and specificity and the justification for these thresholds.*
6. *The FDA and Pharmaxis discussed the concept of bronchoprovacation tests, including the methachloline challenge. Pharmaxis stated that the methacholine challenge was too sensitive for the purpose of excluding subjects from the military and other activities because it identified individuals as abnormal who will never develop asthma. Pharmaxis wants to develop a test that when positive one could be sure that the subject had asthma.* (b) (4) [redacted]. *The FDA also noted that some of the differences in test performance were related to the cutoffs that were chosen to distinguish between normal and abnormal. In order to evaluate the usefulness of the mannitol challenge test the reviewers will require enough data to assess the entire range of mannitol and comparator reactivity.*
7. *The FDA stated that in the NDA Pharmaxis must present clear justification for the cut-offs and thresholds. Pharmaxis confirmed that this data would be in the NDA submission.*
8. *The FDA recommended that Pharmaxis look at the differences in the clinical tests performed and the outcomes of these tests with regard to the various diseases studied.*
9. *Pharmaxis confirmed that they would submit all study data, not just summary data, with the NDA so that the FDA can perform an independent analysis.*

Question 3. Considering the indication for use, the benign safety profile and low potential risk associated with the mannitol dry powder inhaler, does the Division agree that postmarketing pharmacovigilance activities will be adequate to minimize the potential risk associated with the use of Aridol (mannitol) dry powder inhaler for detection of bronchial hyperresponsiveness in patients with suspected asthma?

Division Response: This is a review issue.

Discussion: No further discussion occurred.

Question 4. The safety of mannitol has been well established through its use as a food ingredient and a pharmaceutical excipient. During the Pre-IND Meeting on July 19, 2004, the Agency requested that Pharmaxis conduct a further nonclinical toxicology study in non-rodents in addition to the studies completed in rats. Pharmaxis has completed a 2-week study in dogs, a 3-month study in rats, and a 6-month study in dogs, (b) (4) The Agency has confirmed that the current nonclinical safety data package is adequate to support the Phase 3 clinical studies (b) (4). Pharmaxis is not planning to do any additional nonclinical inhalation toxicology study to support the Aridol NDA submission.

Does the Division agree that no additional toxicology study is required to support the Aridol NDA filing?

Division Response: Yes, we agree.

Discussion: No further discussion occurred.

Question 5. Pharmaxis plans to combine the safety data from Study Nos, DPM-A-301 and DPM-A-305 for the purpose of an integrated safety analysis. The full details of the safety data from the supportive, published clinical trials are not available to Pharmaxis. The NDA will contain a summary of the safety results reported in the publications for these supportive trials, but this will not be included in the formal ISS. In addition, the NDA will contain any relevant safety information from multiple-dose Phase 2 and 3 studies being run for separate uses of inhaled mannitol in the management of bronchiectasis and cystic fibrosis. However, it will not be formally analyzed as part of the ISS. Some proposed mock-up tables for the ISS are provided in Appendix 8.7. Potential additional safety factors to tabulate include maximum fall in FEV_1 and recovery time after challenge.

Does the Division concur that the Integrated Summary of Safety will include only safety data from DPM-A-301 and DPM-A-305, and that the supportive safety data from other sources will be presented as narrative summaries?

Division Response: This is acceptable. However, see our response to Question 2.

Discussion: No further discussion occurred.

Question 6. Does the Agency agree that the Integrated Summary of Efficacy will include an **integrated analysis** of the effectiveness data, i.e., test sensitivity and specificity, from the two pivotal trials (Studies Nos, DPM-A-301 and DPM-A-305)? (emphasis added)

Division Response: No, we do not agree. The data should be presented separately. See our response to Question 2.

Discussion: No further discussion occurred.

Question 7. Pharmaxis is planning to submit the Aridol NDA as an eCTD. The planned publisher of the eCTD has previously published eCTDs which have been submitted to the FDA. Does the Division wish to obtain a sample eCTD?

Division Response: We do not need to see a sample eCTD.

Discussion: No further discussion occurred.

Question 8. The proposed PI for Aridol is presented in Appendix 8.9. The content of the Aridol proposed PI is based on the Australian PI for Aridol (March 22, 2006). The format is based on FDA's "Requirements on Content and Format of Labeling for Human Prescribing Drug and Biological Products; Final Rule and Draft Guidance," published January 26, 2006.

In general, does the Division agree with our approach to the Aridol labeling?

Division Response: We note that your label does not entirely conform to the Physician's Labeling Rule (PLR) format. The label must conform to all the requirements of the Final Rule. Be advised that any agent approved for bronchoprovocation testing will have a boxed warning similar to the current boxed warning for Provocholine®. You may use the currently approved Provocholine® label as a guide in drafting a boxed Warning for Aridol. We note that section 14 (Clinical Studies) lacks patient population information that must be included to comply with the Physician Labeling Rule. Refer to the draft "Guidance for Industry on the Clinical Studies Section of the Label" for further guidance in completing this section of the label. Refer to CMC response to Question 7 for additional comments on Aridol labeling.

Discussion: It was decided that Question 8 would be discussed at the CMC meeting on March 13, 2008.

Question 9: The clinical study report for the pivotal clinical study (Protocol No, DPM-A-305) will be written according to the ICH E3 Guidance, with all appendices included in the NDA submission. A draft table of contents is provided in Appendix 8.10,

Does the Division have any comments on the structure of the pivotal clinical study report (Protocol No. DPM-A-305) outlined in the study report TOC (Appendix

8.10)?

Division Response: The outline of the structure of the study report TOC is acceptable. However, see our response to Question 2 for additional information that must be included in the content of the study report.

Discussion: No further discussion occurred.

Question 10: We will have clinical studies in cystic fibrosis and bronchiectasis patients in progress during the Aridol NDA review. We propose excluding these studies from the NDA Safety Update because they are for different indications, with very different dosages - Bronchitol™ (same active ingredient) can be administered for up to 6 months to cystic fibrosis (b) (4) patients, whereas Aridol is indicated only for a single use for diagnostic purposes.

Does the Division agree with our proposed NDA Safety Update plan?

Division Response: No, we do not agree. Summary tables of adverse events reported in patients treated with mannitol for other indications should be included.

(b) (4)

Question 11. Pharmaxis is an Australian company with an operation in the United States. We are currently employing fewer than 500 full-time-equivalent employees and have no marketed products in the United States. Aridol is our first NDA submission to the FDA. We are planning to submit a request to waive the User Fees 3 months before the NDA submission.

Does the Agency agree that we are eligible for the User Fees Waiver?

Division Response: The Division does not make the decision about user fees. Contact the Office of Regulatory Policy for further information.

Discussion: No further discussion occurred.

Question 12. Does the Agency agree that our current clinical data package can be considered for the Pediatric Research Equity Act of 2007 (PREA) requirements and no additional Phase 4 pediatric effectiveness and safety study should be required?

Division Response: A request and justification for a waiver should be included in the NDA, and a decision will be made during the review.

Discussion: No further discussion occurred.

ADDITIONAL COMMENTS

Pharmacology/Toxicology

1. ***Address the safety qualification of drug impurities and degradation products according to the ICH Guidances Q3A and Q3B.***

2. ***Address the safety qualification of any extractable/leachables from the device.***

Discussion: No further discussion occurred.

Clinical

1. ***In the summary for protocol DPM-A-305 305 a positive response to mannitol is defined in two ways: When the FEV_1 falls 15% from baseline OR 10% from the previous FEV_1. However, in the proposed Aridol label, a positive test is defined as a 15% fall in FEV_1 from baseline. In order to support the label, the definition of a positive test used in the study must be the same as that proposed for the label.***

2. ***Throughout your briefing package, multiple inconsistencies are noted, leading to assumptions about the meaning of many statements. Such inconsistencies in an NDA submission could result in numerous information requests for clarification which may hinder the efficiency of the review process. Please ensure that your NDA submission is carefully edited. Refer to the "Guidance for Review Staff and Industry - Good Review Management Principles and Practices for PDUFA Products."***

Discussion: No further discussion occurred.

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Linked Applications	Sponsor Name	Drug Name
IND 70277	PHARMAXIS LIMITED	ARIDOL

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/s/

MIRANDA B RAGGIO
03/19/2008

Memorandum of Telephone Facsimile Correspondence

Date: April 4, 2006

To: Austin Brewin, M.D.
President, Piedmont Consulting

Fax: 650-523-8557

From: Christine Yu, R.Ph.
Regulatory Project Manager

Subject: IND 70,277 Bronchitol (mannitol) in patients with cystic fibrosis
Minutes of EOP2 meeting on February 15, 2006

Reference is made to the meeting/teleconference held between representatives of your company and this Division on February 15, 2006. Attached is a copy of our final minutes for that meeting/teleconference. These minutes will serve as the official record of the meeting/teleconference. If you have any questions or comments regarding the minutes, please call me at (301) 796-2300.

Thank you.

MEETING MINUTES

DATE:	February 15, 2006
TIME:	12:30 - 2:00 PM (scheduled)
LOCATION:	White Oak Conference Room 1539
APPLICATION:	IND 70,277
DRUG NAME:	Bronchitol (mannitol) for inhalation
TYPE:	End of Phase 2 (EOP2) meeting
IMTS:	16967
SPONSOR:	Pharmaxis, Ltd.

Participants: Present in person:

Brett Charlton, MBBS, Ph.D., Medical Director, Pharmaxis, Ltd.
Ron Sinani, Regulatory Affairs Manager, Pharmaxis, Ltd.
Douglas Francis, Ph.D., Manager - Product Development, Pharmaxis, Ltd.
Moira Aitken, M.D., Professor of Medicine, University of Washington Medical Center
(b) (4)

The following from the Cystic Fibrosis Therapeutics Development Network Coordinating Center (CF TDN) joined by phone from the Children's Hospital and Regional Medical Center in Seattle, Washington:

Bonnie W. Ramsey, M.D., Director, CF TDN, and Endowed Chair in Cystic Fibrosis, University of Washington
Nicole Mayer Hamblett, PhD, CF TDN Statistical Analysis Unit, and Assistant Professor, Department of Pediatrics, University of Washington
Peter Cornelisse, MS, CF TDN Statistical Analysis Unit

The following joined by phone from Pharmaxis Ltd in Frenchs Forest, Australia:

John Crapper, BSc, MBA, Chief Operations Officer (including manufacturing)
Hester Slade, BSc, Quality Assurance Manager (for manufacturing operations)
Edward Vaiciurgis, BAppSci (App. Chem.), Quality Control Supervisor (for manufacturing operations)
Laurence Garceau, Regulatory Affairs Manager (recently joined Pharmaxis Ltd)

FDA: Division of Pulmonary & Allergy Products, unless noted otherwise

Participants: Alan Schroeder, Ph.D., CMC Reviewer
Eugenia Nashed, Ph.D., Pharmaceutical Assessment Lead, Acting
Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer
Timothy McGovern, Ph.D., Supervisory Pharmacologist
Sayed (Sam) Al Habet, R.Ph., Ph.D., Clinical Pharmacology & Biopharmaceutics (CPB) Reviewer
Amjad Iqbal, B.S., Pharm.D., R.Ph, Post-Doctoral Fellow
Tayo Fadiran, R.Ph., Ph.D., CPB Team Leader

James Gebert, Ph.D., Biometrics Reviewer
Ruthanna Davi, M.S., Biometrics Team Leader
Carol Bosken, M.D., Medical Reviewer
Lydia Gilbert-McClain, M.D., Medical Team Leader
Peter Starke, M.D., Medical Team Leader
Eugene Sullivan, M.D., Deputy Director
Badrul Chowdhury, M.D., Ph.D., Director
Christine Yu, R.Ph., Regulatory Project Manager

BACKGROUND:

Pharmaxis submitted an EOP2 meeting request to discuss Bronchitol (mannitol) for inhalation in patients with cystic fibrosis. They submitted a briefing package received January 17, 2006, which contained a list of questions to be discussed at this meeting. Upon review of the briefing package, the Division responded to their questions via fax on February 14, 2006. The content of that fax is printed below.

FORMAT OF MINUTES:

After receipt of the Division's fax, Pharmaxis notified the Division that they would like to clarify and further discuss responses to questions 1c, 4, 7,9, Additional Clinical comment c, 11, 15, 21, 26, and Additional CMC comments h, i, l, v. Discussions during the meeting are captured directly under the relevant original faxed responses, including any changes in our original position. Pharmaxis' questions are in ***bold italics***; FDA's faxed responses are in *italics*; discussions during the meeting are in normal font.

MINUTES:

Question 1

Is the single PK study as outlined in the briefing package sufficient for supporting the approval of mannitol for inhalation for (b) (4) ***(Aridol challenge and Bronchitol*** (b) (4) ***CF)?***

a. *To allow appropriate labeling for the product, multiple-dose pharmacokinetic (PK) parameters are needed. You may consider obtaining this PK information in a subset of patients in the proposed Phase 3 study.*

Pharmaxis replied that they will consider conducting a multiple dose (MD) study, as recommended, and asked if the population pharmacokinetic (pop PK) method may be utilized.

The Division responded that the pop PK method is acceptable, but the drug has a short half-life. Therefore, Pharmaxis should select adequate time points for PK sampling. The draft protocol may be submitted to the IND for comment. The Division also expressed concern about ten capsules of Bronchitol being administered one after another, as well as about the potential variability in the time it takes for the subjects to administer ten capsules. They asked about whether the 10 mg capsules are distinguishable from the 40 mg capsules.

Pharmaxis responded that there is no distinguishing difference between the 10 and 40 mg capsules.

b. *We strongly recommend that you use more than 6 subjects in the proposed single dose PK study to obtain interpretable data.*

The Division noted that there is high variability in the data and recommended that the study be conducted using at least 12-24 subjects so that the resulting data will be interpretable. This is generally the accepted minimum number of subjects for this type of PK study. Additionally, based on the known and expected variability in the data, consult your statistician for the optimal number of subjects for the study.

c. *Use a washout period of longer than 48 hours between treatments in the proposed single dose PK study. The washout period should be long enough to avoid any pharmacodynamic carryover effects.*

The Division indicated that a 1-week washout period may be sufficient.

Question 2

Is the proposed format and duration of treatment in the two phase III trials suitable to demonstrate efficacy and safety?

The appropriate duration of the trial depends upon the primary outcome. If maintenance of pulmonary function, as determined by spirometry, is the outcome, then studies of several years duration would be required. If Bronchitol is to be administered chronically, then you will need a 1-year safety study at some time during the development program. Also see responses to questions 9 and 10.

Question 3

Is the control of a sub therapeutic dose of Bronchitol (50 mg twice daily) acceptable for the studies?

Assuming that the capsules are indistinguishable from the active treatment, this is acceptable.

Question 4

Is FEV_1 a suitable primary endpoint? Would Quality of Life be a suitable co-primary endpoint.

The efficacy results obtained in phase II trials should inform the selection of the most appropriate efficacy endpoints for phase III trials. The FEV_1 is a standard and validated measure of function in subjects with obstructive lung disease. However, because Bronchitol is not expected to act as a bronchodilator, small changes in FEV_1 over short periods of time would not, by themselves, be sufficient to support approval. Additional co-primary or secondary outcomes would be required. Quality of life (QOL) questionnaires may be acceptable secondary or co-primary outcome measures. However, these questionnaires must be carefully validated, and a clinically meaningful change must be predetermined prior to using these questionnaires as important efficacy endpoints in pivotal studies.

Pharmaxis noted that they would like to use QOL SF36 as a secondary endpoint (not a co-primary endpoint), but have questions about powering the two phase 3 trials. They proposed analyzing the primary efficacy variable, a measure of FEV_1, separately for each study. For analysis of the secondary endpoint they asked if it would be appropriate to pool the data from both trials. Pharmaxis stated that this is approach is being proposed because of the larger sample size that is required for a quality of life endpoint when the size of the treatment effect is close to the clinically meaningful difference. (b) (4)

(b) (4)

Pharmaxis' plan to pool the data would not provide the necessary independent substantiation of the claim.

The Division commented that although allowable under regulations, uncontrolled studies to assess safety are difficult to interpret, e.g., with the absence of a control arm, all adverse events are attributed to the drug. The Division advised that the company obtain safety data using a controlled study design if feasible.

Question 5

Is exacerbation frequency a suitable secondary endpoint?

Exacerbation frequency is a suitable endpoint, however, the study should include a precise definition of exacerbations and a description of the mechanisms in place to ascertain them.

Question 6

Is comparison of the improvement in FEV_1 with that achieved in the pivotal Pulmonzyme trial suitable to demonstrate significant benefit as a first line therapy?

No, you must have concurrent controls.

Question 7

Does the protocol design and analysis support an application for the indication of both first line and add on therapy (with Pulmozyme) in CF?

If you think that there is a significant number of subjects who would benefit from Bronchitol and who would not be taking Pulmozyme, then you must test Bronchitol in a manner that can assess the effects in both subject groups.

The Division asked if the intent of the study was to show overall benefit or additive effect.

Pharmaxis stated that they plan to conduct a subgroup, exploratory analysis (b) (4)

Question 8

Do the inclusion/exclusion criteria allow sufficient heterogeneity for registration application?

Yes.

Question 9

Is the proposed dosing of 400 mg twice daily acceptable?

The first requirement for drug doses used in clinical trials is that the dose be supported by preclinical safety data. Once that has been demonstrated, the dose and dosing interval for phase III trials should be determined by the results of well designed phase II dose ranging trials.

The Division noted that there were adverse event reports of bronchial irritation and suggested that a blinded study using lower doses may be more appropriate.

Pharmaxis stated that they were half way through the dose ranging study and expressed concern about using a lower dose for the phase 3 trials if 400 mg would be statistically more effective than a lower dose, and the lower dose would not show efficacy.

The Division commented that although it is generally better to have data to support the proposed dose(s) by the EOP2 meeting, it is acceptable to go into phase 3 trials with two proposed doses. Additionally, a longer study may be necessary to support decrease in exacerbations whereas a shorter study may support a claim in FEV1 improvement.

The Division also noted that Pharmaxis used different devices in the studies, including the (b) (4) which is not approved in the United States. Since device changes may have significant clinical impact, the Division recommended that the phase 3 trials be conducted using the to-be-marketed device and drug product. Although providing a comprehensive table comparing the devices used during phases of development would be helpful, bridging studies may still be needed.

Question 10

Are the proposed patient numbers sufficient for safety evaluation?

Although this is not a new molecular entity, the route of administration is novel and the primary safety concern is the safety effects in the lung with chronic administration in this population. Therefore the extent of exposure should be as described in the ICH E1A Guidance for Industry, "The extent of population exposure to assess clinical safety: For drugs intended for long-term treatment of life-threatening conditions." At least 300 patients should be treated for 6 months and 100 patients treated for at least 1 year. If possible, the 1-year safety study should also include a comparator. A total of 1500 subjects overall should have been exposed to mannitol via inhalation to support the NDA. Specific safety findings that may arise during the course of development could increase the size of the necessary safety database. Note that adverse events occurring during long-term safety studies may be difficult to interpret in the absence of an appropriate control group. In the absence of a control group, observed adverse events will be attributed to study drug.

Additional Clinical comments:

a. *The protocol should include criteria for individual subject withdrawal and for study termination.*

b. *Treatment with 10 capsules twice daily may become tedious, and measures should be included to assess subject compliance with the regimen.*

Pharmaxis noted that on the average it takes about 3 minutes to dose 10 capsules and that compliance is a concern that has been noted and needs to be addressed.

c. *The use of a beta-agonist prior to treatment with study drug might improve delivery of the study drug deep into the lung and may also provide prophylaxis against treatment-induced bronchospasm. The previous Bronchitol protocol included pre-treatment with beta-agonist. The current protocol requires withholding beta-agonists unless the subject suffers chest pain, wheezing, or shortness of breath after the Bronchitol treatment. This stipulation should be justified, and a plan for emergency treatment of respiratory distress throughout the treatment period should be elaborated.*

The Division stated that how the study is conducted will determine labeling, therefore, it is advisable to carefully consider beta-agonist pretreatment. There is a general safety concern with administering any irritant to CF patients (with or without beta-agonist pretreatment), so a black box may be warranted if the drug is to be administered without beta-agonist pretreatment.

d. *The protocol should include plans for the management of concomitant therapy and/or the inclusion of these variables in the analysis phase.*

e. *The proposed protocol includes bronchoprovocation testing using Aridol in order to determine eligibility. This will be problematic in the event that Aridol for bronchoprovocation testing is not approved at the time this NDA is considered. In that case, it would be very difficult to appropriately label Bronchitol.*

f. *Durability of the device should be explored in the phase III program. Subjects should be instructed to report and return devices suspected of malfunctioning. Returned devices should be appropriately evaluated. In addition, a subset of apparently normally functioning devices should be collected and evaluated after a period of use.*

g. *All applications for new active ingredients, new dosage forms, new indications, new routes of administration and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric studies unless this requirement is waived or deferred. The decision to waive or defer pediatric studies is made when the NDA is received. At the current time your drug development program describes studies to be conducted in patients 8 years of age and older. You will need to outline your plan for addressing the requirement for pediatric studies for patients under 8 years of age.*

Question 11

At a meeting held on June 16, 2005 for IND 70,277, the Agency requested that an additional twenty-six week inhalation study be completed to support the registration of inhaled D-mannitol (up to 800 mg per day) for chronic administration. The study is to be carried out using the "most appropriate" species, and "Rationale for Use Rats in 26-Week Study" provides arguments for the choice of rats.

Taking into consideration the justification provided in the "Rationale for Use of Rats in 26-Week Study" document, is the rat an appropriate species in which to conduct the 26-week repeat dose inhalation toxicity study, and is the study design acceptable?

The available evidence is insufficient to justify that the rat is the species of choice for the 6-month inhalation toxicity study of mannitol. We defer the decision until the completion of our review of the completed 2-week inhalation toxicity study in dogs and the 13-week inhalation toxicity study in rats. Submit study reports for the dog study to the Agency for review. Since differences were observed in the doses administered and findings noted in the 2-week rat and dog studies as well as the 13-week rat study, a 13-week inhalation toxicity study in dogs might be useful in determining the most appropriate species for the 6-month inhalation toxicity study.

The Division defers commenting on the proposed protocol of the 6-month inhalation toxicity study of D-mannitol in rats until the species of choice is selected for the 6-month study.

Pharmaxis reiterated their position that the rat is the species of choice for the 26-week D-mannitol inhalation toxicity study. They stated that the results of the 13-week inhalation study in rats submitted to the Agency after the submission of the briefing package further confirmed their interpretations. Pharmaxis believed that additional inhalation toxicity studies in dogs were not needed.

The Division stated that their comments were based on the submitted summary and **preliminary** review of the study report for the 13-week inhalation rat study, received approximately 1 week prior to this meeting. (The Division has not yet conducted a detailed review of the report.) Furthermore, the Division has not received the report of the 2-week dog

study. Based on review of completed studies, the Division may have a different interpretation of the data. At this time, the Division could not concur with Pharmaxis with the selection of the rat as the species of choice for the 6-month inhalation toxicity study. Pharmaxis should submit reports of all completed studies and other available information. After complete review of that data, including data from the 13-week rat study, the Division can then make a determination about the need for additional studies, the most appropriate species for the 26-week study, and whether findings in rats are relevant to humans.

Question 12

Are the Sponsor derived respiratory and ECG data together with the widespread human and animal exposure (as below) sufficient to meet the pre-clinical safety pharmacology requirements to support registration of Bronchitol?

Yes, the available data are sufficient to address the nonclinical safety pharmacology requirement for the product registration of D-mannitol.

Question 13

Are the Sponsor-derived toxicokinetic, BAL and accumulation data for inhaled D-mannitol together with published systemic ADME data sufficient to meet the pre-clinical toxicokinetic and pharmacokinetic requirements to support registration of Bronchitol?

Yes, the available data are sufficient to address the nonclinical pharmacokinetic and toxicokinetic requirements for the product registration of D-mannitol.

Question 14

Do the Sponsor derived ocular studies satisfy the pre-clinical safety issues that would arise from the accidental ocular exposure to mannitol for inhalation?

Yes, the available data are considered sufficient to address the nonclinical safety concerns that would arise from the accidental ocular exposure to mannitol for inhalation.

Question 15

Are the Sponsor derived single and repeat dose inhalation studies (up to twenty-six weeks of exposure) together with published long-term systemic exposure studies (as below) sufficient to support registration of Bronchitol?

There is insufficient information to make such a determination at the present time. However, a 6-month inhalation toxicity study of D-mannitol in a most appropriate species that provides an adequate safety margin for the maximum proposed clinical dose would be sufficient to support registration if the Division determines that a to-be-completed 6-month inhalation toxicity study is valid and the study does not reveal any safety concerns.

As discussed at the June 16, 2005 meeting, the current available nonclinical data does not appear to support the safety of the proposed clinical dosing of up to 800 mg mannitol/day due to the lack of adequate safety margins. Usually, a safety margin of 10 or above, on a mg/kg/day basis, would be considered adequate. Note that the safety margins are calculated using estimated pulmonary deposited doses in animals and the proposed nominal dose in humans. A preliminary review of the available nonclinical data indicates that the data would support a top clinical mannitol dose of approximately 60 mg/patient/day for repeated inhalation exposure. This estimate is based on an assumed No-Observed-Adverse-Effect Level (NOAEL) of 12.4 mg/kg/day (estimated pulmonary

deposit) in the 13-week inhalation toxicity in rats and a body weight of 50 kg in a patient [62 mg/day/patient = 12.4 mg/kg/day ÷ 10 (safety factor) x 50 kg/patient]. A final determination will be made when we complete review of all relevant nonclinical data.

Of note, in the absence of an adequate 6-month inhalation toxicity study of D-mannitol in the most appropriate species, proposed clinical trials should be supported by inhalation toxicology studies of an appropriate duration in two species.

Also, consider lowering the mass mean aerodynamic diameter (MMAD) of the inhaled particles in the inhalation toxicity studies. The completed 13-week inhalation toxicity study of D-mannitol in rats used MMADs of (b) (4) *. Such MMADs are larger than an ideal range of* (b) (4) *in the tested species. A decrease in MMAD will increase the efficiency of pulmonary deposition. Small particles are even more desirable given the difficulty of reaching high aerosol mannitol concentrations.*

Pharmaxis stated that they are continuing their attempts to decrease the mannitol particle-sizes for future studies. Pharmaxis was able to decrease the MMAD in rats to about (b) (4) in their recent work and increase the top dose in rats to approximately 1,000 mg/kg/day. As for the (b) (4) study, the NOAEL dose provides an approximate 7-fold safety margin based on 100% dose deposition in humans and 20% deposition in dogs. It will be difficult to achieve a ten-fold safety factor to support the proposed high clinical dose, but they will try to maximize exposure/duration to the extent possible.

The Division responded that they will consider these concerns raised by Pharmaxis as they evaluate the data. They reminded Pharmaxis that the clinical dose still needs to be determined.

Pharmaxis asked if it would be acceptable to submit draft toxicity study reports. The Division replied that draft reports are acceptable, but the final report must be available within 120 days after submission of the draft report. Line listings should be included in the draft study reports. Pharmaxis inquired whether it is acceptable to submit the 2-week dog study without data for toxicokinetics and bronchoalveolar lavage fluid. The Division stated that such an approach was acceptable for draft report, but the final report must include these data.

Pharmaxis continued discussions with a question to the Division about supporting clinical trials with inhalation toxicity studies in one animal species. For example, could a single 13-week inhalation toxicity study in rats be used to support a 13-week clinical trial? The Division stated that one 13-week inhalation toxicity study in the most appropriate species would suffice for compounds such as D-mannitol for which extensive information for other routes of administration is available. However, the most appropriate species for D-mannitol inhalation toxicity studies has not yet been determined at this time.

Pharmaxis asked whether it would be appropriate to submit interim non-clinical data to support initiation of a clinical study (with subsequent submission of complete nonclinical study results) so that the trial can proceed (staggering nonclinical and clinical development).

The Division stated that submission of complete non-clinical data supporting a proposed clinical study is preferable before the clinical study is conducted. However, if Pharmaxis would like to stagger their non-clinical and clinical development, they can submit a rationale to the IND for doing so, but the company assumes the risk to their product development as safety concerns from the nonclinical study could lead to termination of the on-going clinical trial.

Question 16

Do the published genotoxicity and carcinogenicity data provide sufficient evidence that long-term use of inhaled D-mannitol will not induce respiratory or systemic tumors bearing in mind its long history and incident free exposure?

No, the published genotoxicity and carcinogenicity data at the present time do not provide sufficient evidence to address the carcinogenicity potential of inhaled D-mannitol since the potential of D-mannitol to induce tumors in the lung following inhalation administration is unknown. However, the lack of any pre-neoplastic changes in the respiratory system in the to-be-completed 6-month inhalation toxicity would be considered sufficient to evaluate the local carcinogenic potential of Bronchitol®. Findings of pre-neoplastic changes associated with D-mannitol in the respiratory system may make it necessary to assess the carcinogenic potential of inhaled D-mannitol in a complete carcinogenicity study.

Question 17

Does the published literature showing that the in vivo fetal exposure to D-mannitol's rapid and complete excretion, support the use of Bronchitol in pregnant women?

Yes, the published literature is considered sufficient to address the reproductive and developmental toxicity of D-mannitol and to support the use of Bronchitol in pregnant women.

Question 18

Does the published data indicating that alveoli numbers do not change after the age of six and the alveoli are mature beyond the age of two years (bow) combined with the Sponsor derived long-term repeat dose studies (above) support the use of Bronchitol in children over the age of six years?

From a nonclinical standpoint, the available literature data are considered sufficient to support the use of Bronchitol in the intended pediatric population.

Question 19

(This question pertains to the (b) (4) analysis.) The spiking and recovery method required by Ph. Eur. are carried out with the ICP-OES method. Is this adequate?

This is a review issue. The change in methods may be acceptable if appropriately validated.

Question 20

(This question pertains to microbial limits.) Since the capsule shells constitute a substantial part of the finished product, we cannot apply stricter limits than those applied by our supplier. Does the Agency concur?

This is acceptable. Methods are to be at least equivalent to USP <61> methods and indicated objectionable microorganisms are to be absent.

Question 21

(This question pertains to the Agency's request that drug product specifications include acceptance criteria for foreign particulates and crystal morphology.) If sufficient and reproducible data can be obtained for the NDA, we do not see the necessity of carrying out these studies on an ongoing basis and propose light microscopy examination for the purpose of release for both crystal morphology and control of foreign particles. Is this acceptable?

This is a review issue. The method used at release should be adequate to control foreign particulates and crystal morphology.

Pharmaxis noted that the amorphous content was below level of detection (LOD) in the stability studies that have been conducted. As per the draft guidance, if they are able to demonstrate that there were no changes in the amorphous form during stability, then would it be acceptable not to control or monitor them during release?

The Division responded that a decision regarding this issue will be based on supportive data. With the to-be marketed product, Pharmaxis may start with monitoring and controlling for them. If adequate methods are used and no changes are observed, then a request to drop the controls can be submitted in the future.

Pharmaxis asked about the difference between the terms crystal "shape" and "habit" used in the guidance.

The Division stated that different terms may have been used in the guidances, but both terms are essentially the same.

Question 22

(This question pertains to stability testing acceptance criteria for related substances and degradation products and for uniformity of emitted dose.) Given the nature of the dosing regimen, tightening the specifications for single 40 mg capsules is unlikely to be of any benefit. Does the Agency agree to maintain the current compendial limits?

a. *Evaluation of acceptance criteria is a review issue.*

b. *Our recommendations for requirements for emitted dose uniformity are unchanged but will be evaluated against your future NDA stability data.*

c. *Specifications should be in place for both emitted dose uniformity and dose uniformity of the capsule content.*

Question 23

(This question pertains to the method for determining the average content of active (mannitol) by (b) (4) ***Does the Agency agree with this approach?***

This approach may be adequate as long as hygroscopicity is not a problem for mannitol over a reasonable range of ambient humidities.

Question 24

(This question pertains to a reduction in sample size for content of active during stability testing. (b) (4) ***Is this acceptable?***

This is a review issue, and adequacy will be determined based upon the validation of the method.

(Post meeting note: the legal compendia in the U.S. are USP/NF.)

Question 25

Is the study investigating dose uniformity and aerodynamic particle size distribution at different flow rates and volumes sufficient to address the issue of variation in intended patient population?

a. *This is a review issue. Appropriate in vitro performance testing should be provided, along with data on patient capabilities, for whatever device is to be used. We recommend that this testing be repeated with the* (b) (4)

b. *Ensure that the flow rates and volumes which you use for routine performance testing are meaningful relative to patient capability.*

Question 26

Are the studies investigating respirable gelatin content adequate to address the issue of effect of moisture on brittleness of the Bronchitol capsules?

a. *This is a review issue. We recommend that you include as a part of stability testing, direct measurement of capsule brittleness after low humidity storage since capsule disintegration may affect the dose and particle size distribution of drug delivered to the patient.*

b. *Brittleness of packaged product should be evaluated after long term storage at very low humidity.*

Pharmaxis noted that the capsules would be in foil packaging (aluminum laminate on both sides), but not overwrapped. They asked if 25 degrees C/40% humidity would be acceptable testing conditions.

The Division responded that results of testing conducted under extreme testing conditions (worst case scenario) would provide more useful information. The concern that needs to be addressed is about what happens to the capsule when the patient puts it in the device to administer the medication. The packaging to be tested should be the to-be-marketed packaging, with data bridging it to the packaging used for clinical trial batches. The Division recommended direct measurement of capsule brittleness, but Pharmaxis can submit a rationale for other approaches selected.

Pharmaxis stated that they will work on selecting a direct method of measuring capsule brittleness.

Question 27

(This question pertains to a change in the capsules between those used in the clinical trial compared to those intended for marketing. An abbreviated stability protocol is proposed.) Is this sufficient to avoid the necessity of carrying out a further study to show equivalence between the two capsules?

a. *Provide the protocol for the abbreviated stability study with drug product for clinical trials, for our evaluation.*

b. *Indicate whether the two capsules (for clinical studies and for commercial product) are from the same source and have the same test properties (e.g., moisture content, brittleness).*

Question 28

(This question pertains to the possibility that two DPI devices which differ in flow resistance may be used, e.g. for different subsets of patients.) Please note that relevant product testing (e.g. dose

uniformity) will be carried out on the final chosen device(s). Does the Agency have a concern about this possibility?

Full testing should be performed with the drug product using the device or devices to be used in the clinical studies, at release as well as on stability.

Additional Chemistry, Manufacturing and Controls (CMC) Comments

See our recommendations in our draft "Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing and Controls Documentation." Comments below are not meant to provide full guidance. These comments are directed towards your future NDA.

a. *Container closure materials of construction (including critical components of the device, i.e., those that contact the patient's mouth and/or the drug, and the blister packaging) should preferably be listed in the Agency's food additive regulations, and be compliant with USP <87> and <88> biological reactivity testing for critical components.*

b. *This drug product is considered to be a drug/device combination in the U.S.*

c. *Characterize and control the extractable profile in critical device components and blister packaging.*

d. *Provide your acceptance specifications for the device. Ensure that flow resistance is characterized and controlled.*

e. *Clarify which device (low and/or high resistance* (b) (4) *) was used to provide the drug product data.*

f. *Provide the Drug Master File (DMF) number for the* (b) (4) *. Provide letters of authorization for all supporting DMFs (e.g., device, mannitol, blister packaging).*

g. *Changes in the device during or after phase 3 trials are not recommended.*

h. *Characterize the flow rates that may be achieved by patients through the drug product (for both devices, with capsule in place).*

See the Division's response to question 25 for discussion points raised here.

i. *We recommend aerodynamic particle size distribution (APSD) specifications based upon the* (b) (4) *as we previously indicated.*

Pharmaxis stated that they have (b) (4)

The Division responded that it is important to get mass balance measurements of what comes out of the devices, limit losses and control mass balance. The amount of drug lost on the walls should be reported separately since the particle sizes will be unknown. Specify conditions and provide initial data.

j. *Specific acceptance criteria are a review issue.*

k. *Provide individual* (b) (4) *and component data. Propose* (b) (4) *to control the APSD, not merely a single "fine particle dose."*

l. *Provide a stability protocol for primary NDA stability batches. Specify the intended batch scale for stability batches and for commercial product. Stability batches should include multiple batches of the device(s).*

When asked if two device batches would be sufficient, the Division responded that 2 batches could be adequate if batch-to-batch variability is not high. Additional batches may be need if high variability is observed.

m. *Batch scale for stability batches is recommended to be not less than* (b) (4) *the scale intended for commercial batches.*

n. *Ensure that all potential drug substance impurities are characterized and controlled, based upon ICH Q3A reporting and identification thresholds.*

o. *We recommend that you include USP monograph tests for the mannitol drug substance which currently are not being conducted (e.g., specific rotation).*

p. *Clarify all differences between Bronchitol and Aridol, besides those of* (b) (4), *and clarify any resulting differences in drug product performance and stability.*

q. *Describe the* (b) (4) *processes and their controls. Clarify the reason for* (b) (4).

r. *Add drug product specifications for foreign particulates, and solid state characteristics (e.g., polymorphic form,* (b) (4) *content, shape, crystal habit). Provide a mean dose content uniformity specification (e.g., +/-* (b) (4) *% of label claim).*

s. *Provide with your NDA, stability summaries organized by test parameter, in tabular and graphical format. Include both individual and mean data in both formats, and include various limits on the dose content uniformity (DCU) graphs (e.g., +/-* (b) (4) *%,* (b) (4) *%,* (b) (4) *%,* (b) (4) *% of label claim).*

t. *The NDA specification sheet should specify how many capsules are tested for each test.*

u. *Provide clear documentation that the gelatin for the gelatin capsules meet FDA recommendations relative to* (b) (4) *concerns.*

v. *We recommend not more than* (b) (4) *L total volume of air be specified for dose content uniformity testing of the drug product.*

w. *Clarify which tests you perform in accepting the mannitol, device and packaging. If you rely on certificates of analysis (COAs), indicate that you perform as a minimum, identity testing, as well as periodic validation of the information on the COAs.*

x. *Clarify whether mannitol is produced as a drug substance, as an excipient, or as a food additive. If not manufactured as a drug substance, show what processing is performed to ensure its quality as a drug substance.*

y. *We remind you of CMC comments previously sent for this IND (see letters and meeting minutes).*

Discussions concluded at this time, and the meeting was adjourned.

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/s/

Christine Yu
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