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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 22, 2010
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-368
Applicant	Pharmaxis, Ltd.
Date of Submission	April 7, 2010
PDUFA Goal Date	October 7, 2010
Proprietary Name / Established (USAN) names	Aridol/mannitol inhalation powder
Dosage forms / Strength	Inhalation powder/0, 5, 10, 20, and 40 mg hard gelatin capsules
Proposed Indication(s)	1. The assessment of bronchial hyperresponsiveness in patients > 6 years of age who do not have clinically apparent asthma.
Recommended:	Approval

1. Introduction

Pharmaxis, Ltd. submitted a 505(b)(1) new drug application (NDA 22-368) on February 27, 2009, for the use of Aridol (mannitol bronchial challenge test) as a single-use product for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma. While the data submitted with the original NDA submission was adequate to support the efficacy and safety of Aridol as a bronchial challenge test, due to GMP violations seen in three drug testing sites, the recommendation from the Office of Compliance was to withhold approval until the GMP violations were resolved. The Division's Complete Response letter, dated December 23, 2009, listed the GMP product quality as the single outstanding issue that precluded approval. Pharmaxis in a submission dated April 7, 2010, has responded to the Complete Response letter of December 23, 2009. This review will focus on the new information submitted by the Applicant to resolve the GMP deficiency as well as the safety update submitted with the Complete Response. For the purpose of this review, discipline-specific sections below in which previous reviews have recommended approval of the Aridol bronchial challenge test are designated as not applicable (N/A). For a complete discussion of the drug development program see the reviews of the initial NDA submission from each specific discipline and/or the CDTL review dated December 16, 2009, and Division Director summary review dated December 23, 2009. The PDUFA due date for this application is October 7, 2010.

2. Background

N/A

3. CMC/Device

Due to GMP violations observed during inspections at the time of the first review cycle, the Office of Compliance recommended to withhold approval pending resolution of the deficiencies at the following manufacturing sites:

(b) (4)

The Applicant has addressed the product quality deficiencies noted in the Complete Response letter. Specifically, reinspections have been completed and found acceptable for (b) (4) on February 22, 2010. (b) (4) has been replaced with Pharmaxis (acceptable cGMP status).

In addition to the above GMP deficiencies that have been resolved, based on the initial review of the CMC team, Pharmaxis Inc. has not fully characterized foreign particulate matter and aerodynamic particle size distribution to set final release specifications. The Applicant in submissions dated November 13 and December 4, 2009 agreed to revise these specifications when more data become available post-approval. Specifically, the Applicant agreed:

1. To test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Subsequently the Applicant should submit a changes-being-effected supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalize the test specification.
2. To review/revise the current interim APSD specifications based on the first 10 Aridol (mannitol inhalation powder) U.S. commercial batches by means of a prior approval supplement (PAS).

4. Nonclinical Pharmacology/Toxicology

N/A

5. Clinical Pharmacology/Biopharmaceutics

N/A

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

N/A

8. Safety

As set forth in 21 CFR 314.50(d)(5)(vi)(b), a safety update covering the period from July 1 to December 31, 2009, was submitted (structured as a revision of the previous 120-day safety update submitted on August 31, 2009) in this complete response by the Applicant. Of note is that since the time of the previous safety update there are no new safety data from Pharmaxis-sponsored studies on the use of the Aridol bronchial challenge test in the indicated population (patients with symptoms suggestive of asthma. However, several multiple-dose studies investigating the use of chronically administered inhaled mannitol (Bronchitol) in patients with cystic fibrosis and bronchiectasis have been completed or are ongoing. In studies for this chronic use indication, a mannitol bronchial challenge test is administered under

medical supervision prior to the start of chronic dosing as a screening tool to help exclude patients from the trials who have excessive bronchoconstriction responses to inhaled mannitol.

Specifically, the Phase 2 or 3 studies for cystic fibrosis included in the safety update are:

- Non-US Study DPM-CF-203: A Cross-Over Comparative Study of Inhaled Mannitol, Alone and in Combination with Daily RhDNase, in Children with Cystic Fibrosis
- Non-US Study DPM-CF-301: Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis – A Safety and Efficacy Study
- US Study DPM-CF-302: Long-term Administration of Inhaled Mannitol in Cystic Fibrosis – A Safety and Efficacy Study

A Phase 3 (study DPM-B-305) Multicenter, Randomized, Parallel Group, Controlled, Double Blind Study to Investigate the Safety and Efficacy of Inhaled Mannitol over 12 Months in the Treatment of Bronchiectasis was initiated on November 9, 2009. As of the December 31, 2009 safety update cut-off date, 30 patients had been screened with the mannitol bronchial challenge test. Of these patients, one had a positive challenge that resulted in a decrease in oxygen saturation to 88% and one 43 year old female patient withdrew due to an SAE of hemoptysis that occurred 10 days after the mannitol challenge test. She was noted to have blood streaked sputum, hospitalized and treated with IV antibiotics (ceftazidine and aztreonam) for Pseudomonas aeruginosa in her sputum.

In the safety update Pharmaxis has also submitted safety data from three other studies in their bronchiectasis program with data on 375 patients with bronchiectasis who had received a mannitol bronchial screening test prior to chronic dosing with inhaled mannitol.

Of note is that for the purpose of the use of inhaled mannitol as a bronchial challenge test for the cystic fibrosis and bronchiectasis populations, safety data were reported from the time the patient was administered the screening mannitol bronchial challenge test until they were randomized and began chronic dosing with inhaled mannitol. This time period could be up to 4 weeks duration in some of the studies. In contrast, for the Aridol development program as a bronchial challenge test in patients with suspected asthma, the safety reporting period was limited to the actual testing period and 24 hours thereafter.

Following is a table which compares the incidences of the more common and potentially significant adverse reactions observed across the different patient populations. There are no new safety concerns observed in these other patient populations that would impact or change the safety determination for the Aridol bronchial challenge test in the proposed indicated population (patients with suspected asthma).

Incidences of the more common adverse reactions reported in association with the mannitol bronchial challenge test across different patient populations

	Cystic Fibrosis N=879 n (%)	Bronchiectasis N=375 n (%)	Suspected asthma/asthma* N=1046 n (%)
MedDRA Preferred Term			
Headache	14 (1.6)	29 (7.7)	59 (5.6)
Pharyngolaryngeal pain	5 (0.6)	6 (1.6)	25 (2.4)
Nausea	6 (0.7)	3 (0.8)	19 (1.8)
Throat irritation	1 (0.1)	1 (0.3)	19 (1.8)
Cough	41 (4.7)	5 (1.3%)	17 (1.6)
Wheezing	7 (0.8)	-	8 (0.8)
Bronchospasm#	5 (0.6)	1 (0.3)	-
Hemoptysis	4 (0.5)	5 (1.3)	-

* the population in which Aridol is indicated
# this is the incidence of bronchospasm reported as an adverse reaction. It should be noted that the mannitol test is meant to cause bronchospasm in susceptible patients/subjects.

Postmarketing Experience

As of December 31, 2009, the mannitol bronchial challenge test (Aridol, Osmohale) has been approved for use in 19 countries and the commercial product has been administered to approximately (b) (4) patients. Since the previous safety update cut-off of June 30, 2009 and December 31, 2009, two post-marketing adverse reaction reports have been submitted. Both reactions were for nausea and dizziness in a 46 year old male and 59 year old female that occurred during the conduct of the bronchial challenge. Both were non-serious in severity and resolved upon stopping the test.

Safety Summary

In summary, the safety data submitted in the safety update, despite being in patient populations (CF, bronchiectasis) which in some ways are more fragile than the proposed indicated population, do not raise any new concerns over the safety of Aridol as a bronchial challenge test when administered by a trained health care provider in a setting where medications and equipment to deal with respiratory adverse reactions such as severe bronchoconstriction are available.

9. Advisory Committee Meeting

The advisory committee meeting for the Aridol program was held on November 20, 2009. After commenting on the evidence to support the safety and efficacy of Aridol as a bronchial challenge test, the Committee voted on the following question:

Do the data provide substantial and convincing evidence to support the use of the mannitol bronchial challenge test to assess bronchial hyperresponsiveness to aid in diagnosing patients who have symptoms of asthma or symptoms that are suggestive of asthma?

a) In patients 18 years of age and older
If not, what additional data should be obtained?
b) In patients 12 to 17 years of age
If not, what additional data should be obtained?
c) In patients 6 to 11 years of age
If not, what additional data should be obtained?

The committee voted that the data presented did provide substantial and convincing evidence in favor of Aridol as a bronchial challenge test to assess bronchial hyperresponsiveness for all three subject populations outlined. The voting was 12 yes, 3 no with 1 abstention for patients 18 years of age and older; 14 yes and 2 no for patients 12 to 17 years of age; and 11 yes and 5 no for patients 6 to 11 years of age. The committee also discussed the lack of safety data in adults greater than 50 years of age, especially those who may have other significant medical conditions (COPD, cardiac disease, etc.).

10. Pediatrics

N/A

11. Other Relevant Regulatory Issues

DMEPA and DDMAC were consulted at the time of the original NDA submission with regard to the proposed name "Aridol" and found it acceptable.

Re-review of the proprietary name, Aridol, by DMEPA during this review cycle did not identify any additional names thought to look or sound similar to the proposed name. Thus, the name remains acceptable.

12. Labeling

Several major content-related label issues were addressed with the Applicant during the first review cycle. During this review cycle, there have been issues related to the lack of the label being in the correct PLR format. The Highlights section has been edited substantially, wording changed for consistency and some additional data requested to provide context to statements made. A labeling teleconference has been scheduled with the Applicant for July 26, 2010 to finalize labeling the changes.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The Applicant (Pharmaxis) has adequately addressed the product quality GMP deficiencies noted in the Complete Response letter dated December 23, 2009. Reviews of the initial NDA submission have determined that there is adequate safety and efficacy data to support approval

of Aridol as a bronchial challenge test. Therefore, the recommended action on this application is for Approval.

- Risk Benefit Assessment

The risk benefit assessment supports the approval of Aridol as a bronchial challenge test. Previous reviews of two clinical studies (DPM-A-301 and DPM-A-305) demonstrated that Aridol (mannitol inhalation powder) administered as a single use bronchial challenge test demonstrated acceptable efficacy as a test to assess bronchial hyperresponsiveness. As a single use diagnostic test, the safety profile of mannitol inhalation powder was also acceptable.

- Recommendation for Postmarketing Risk Management Activities

There are no specific postmarketing risk management activities that are recommended. While there is a risk of excessive bronchoconstriction in subjects receiving Aridol, it will be administered only by health care professionals trained in its use and only in facilities that are equipped to emergently treat subjects who may develop severe bronchoconstriction as a result of the bronchial challenge test.

- Recommendation for other Postmarketing Study Commitments

The older (> 50 years) population enrolled in the clinical trials generally lacked many of the co-morbidities that the elderly frequently possess (chronic respiratory diseases, cardiac risk factors, etc.). As result, and consistent with discussion held at the Aridol PADAC advisory committee meeting, the following postmarketing requirement was discussed with and agreed to by the Applicant during the first review cycle:

1. Conduct a clinical trial with Aridol in subjects/patients older than 50 years of age who have significant co-morbidities common in an elderly population (e.g., COPD, obesity, cardiac risk factors, etc.) or reanalyze the data from completed clinical trials in which Aridol was administered to an elderly population with co-morbidities. A substantial number of the total population should be 65 years of age or greater. The trial should include the following objectives: 1) evaluate the degree of bronchoconstriction defined as a fall in FEV1 in the older subject/patient population and 2) evaluate the overall adverse event profile in subjects over 50 years of age.

As noted in Section 3 above, the Applicant has also agreed to revise the foreign particulate matter and aerodynamic particle size distribution release specifications post-marketing after more data become available

- Recommended Comments to Applicant

No additional comments are recommended to be conveyed to the applicant.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

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/s/

ANTHONY G DURMOWICZ
07/27/2010

Cross-Discipline Team Leader Review

Date	December 14, 2009
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-368
Applicant	Pharmaxis, Ltd.
Date of Submission	February 27, 2009
PDUFA Goal Date	December 27, 2009
Proprietary Name / Established (USAN) names	Aridol/mannitol inhalation powder
Dosage forms / Strength	Inhalation powder/0, 5, 10, 20, and 40 mg hard gelatin capsules
Proposed Indication(s)	1. The assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma.
Recommended:	Approval

1. Introduction

Pharmaxis, Ltd. submitted a 505(b)(1) new drug application (NDA 22-368) on February 27, 2009, for the use of Aridol (mannitol bronchial challenge test or MBCT) as a single-use product for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma. Currently there is one product approved by FDA as a bronchial challenge test, Provocholine (methacholine chloride powder), approved on October 31, 1986. The MBCT was developed under IND# 70,277 with the original filing date of November 22, 2004. The proposed bronchial hyperresponsiveness testing regimen is for a patient to serially inhale mannitol powder supplied in hard gelatin capsules at doses of 0, 5, 10, 20, 40, 80, 160, 160, and 160 mg. Spirometry is performed immediately after each serial inhalation. Dosing is stopped (test is positive) when either forced expiratory volume measured in one second (FEV1) decreases 15% or more from baseline or decreases ≥ 10% from the value obtained following the immediate previous dose. Testing is negative if all doses of mannitol are inhaled (635 mg total) without decreases in overall FEV1 ≥ 15% or a decrease ≥ 10% from the value obtained following the immediate previous dose. The PDUFA due date for this application is December 27, 2009. The mannitol bronchial challenge test is currently marketed in at least 15 other countries including the UK and Australia under the names Aridol and Osmohale inhalation powder. This review will provide an overview of the application with a focus on the clinical program conducted to support the use of the MBCT as a test to assess for bronchial hyperreactivity.

2. Background

Mannitol is a well known, naturally occurring sugar alcohol found in most vegetables and is generally recognized as safe when ingested. The MBCT, developed as a test with which to assess for bronchial hyperreactivity in this NDA, consists of a series of capsules containing increasing doses of mannitol powder for inhalation. There is currently one other FDA approved drug for use as a means to assess for bronchial hyperreactivity, Provocholine® (methacholine chloride). An important safety concern with regard to tests for bronchial hyperreactivity is the potential for severe bronchoconstriction in susceptible subjects being tested such as those with asthma or other respiratory diseases/conditions. Therefore these tests are to be performed only by trained health care providers in a setting where the skill and equipment necessary to treat individuals who experience severe bronchoconstriction are present. Due to these safety concerns, the label of the FDA approved bronchial challenge test, Provocholine®, contains a boxed warning instructing that the test should be performed only under the supervision of a physician trained in and thoroughly familiar with management of respiratory distress.

The MBCT is currently approved for marketing in at least 15 countries (10 under the name “Aridol” and 5 under the name “Osmohale”) and is being marketed in 10 of these countries (Australia, Sweden, Denmark, The Netherlands, Ireland, Portugal, the United Kingdom, Greece, Finland, and Norway) for use in identifying bronchial hyper-responsiveness. Mannitol inhaled on a chronic basis is also being studied for other indications (enhance mucociliary clearance in patients with bronchiectasis, cystic fibrosis, and COPD).

A Pre-IND meeting (IND# 70277) was held July 19, 2004 during which the design and results of Study DPM-A-301, the pivotal study used for approval in Australia and other countries, was discussed with the Applicant. Pharmaxis asked whether that single phase 3 study was adequate to support an NDA filing. FDA responded by stating that while a single pivotal study may be adequate to support filing an NDA, Study 301 was not adequately designed to meet its objectives. We noted that:

1. Hypertonic saline, an active comparator bronchial challenge test used in Study 301, was not the gold standard for the detection of bronchial hyperresponsiveness and is not approved for use as a bronchial challenge test in the United States.
2. The sensitivity and specificity of the mannitol provocation test in a group of subjects with a known diagnosis of asthma (as was determined in Study 301) may not be indicative of the performance of the test in a group of subjects with suspected asthma but whose diagnosis is not established. Since the latter is the group is more likely to receive the diagnostic test, examination of the sensitivity and specificity in that type of a patient group would be necessary.
3. As designed, the study would provide point estimates of the sensitivity and specificity of the mannitol provocation test; however, because these estimates can be affected by the spectrum of the study subjects' disease, it will be necessary to consider these performance measures relative to those of another diagnostic procedure, such a methacholine challenge. Therefore, an appropriate study design for evaluation of a diagnostic test should include a statistical comparison of the sensitivities and specificities of each of the diagnostic procedures (mannitol challenge and methacholine challenge, for example) where the sensitivity and specificity of each challenge can be calculated relative to some gold standard.
4.

As a result of these discussions, on November 19, 2004, IND# 70277 was opened in which a protocol for a second phase 3 study, Study 305, that incorporated many of the above recommendations, was submitted and, subsequently, conducted.

3. CMC/Device

Mannitol is the drug substance and is used neat in the drug product. It is a white or almost white, crystalline powder or free flowing granules. It is freely soluble in water and very slightly soluble in alcohol. The drug product is a standardized test kit consisting of 5 strengths: 0 mg, 5 mg, 10 mg, 20 mg and 40 mg of hard gelatin capsules containing mannitol (the 0 mg capsules are empty) and a hand held dry powder inhaler, the RS01 Inhaler Model 7 device. The device is a (b) (4) marketed outside the United States. It appears physically and functions similarly to other devices used as the delivery devices for other approved single-dose dry powder medications. The mannitol obtained from the company, (b) (4) is (b) (4) by Pharmaxis Inc. Australia, to give the specific properties desired for the inhalation grade of mannitol.

The regulatory specifications on the drug product include purity of mannitol and testing for related substances, identification by infrared, (b) (4) (b) (4) appearance (of capsules, capsule contents, blisters and packs), bacterial endotoxins, microbial limits, aerodynamic particle size distribution, and uniformity of delivered dose. All methods and acceptance criteria were found acceptable except for the Uniformity of Dosage Content acceptance criterion. A comment was forwarded to the Applicant to tighten the acceptance criterion for Uniformity of dosage content and comply with the USP criterion which they agreed to in a communication dated December 11, 2009.

A review of the safety of impurities, extractables and leachables in the mannitol powder capsules did not reveal any concerns

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The applicant proposes a shelf life of 12 months which is supported by stability data.

From a CMC perspective, the recommendation is for approval pending acceptable cGMP recommendation from the Office of Compliance.

The CMC team also recommends two post-approval CMC commitments which have been discussed with the Applicant:

1. To test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and evaluate the (b) (4) (b) (4) (method used for foreign particulate testing) results on completion of this testing. Subsequently the Applicant should submit a changes-being-effected supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalize the test specification.
2. The Applicant will review/revise the current interim APSD specifications based on the first 10 Aridol (mannitol inhalation powder) U.S. commercial batches by means of a prior approval supplement (PAS).

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team has concluded that the application has adequately evaluated the toxicity profile of inhaled mannitol. Mannitol is non-mutagenic, non-carcinogenic and non-teratogenic. Because of the extensive clinical and nonclinical data available on mannitol, the toxicology program focused on effects of inhaled mannitol, particularly its effect on the respiratory system. The program included inhalation toxicity studies up to 3 and 6 months in rats and dogs, respectively. The studies identified the respiratory tract as the target organs of toxicity of inhaled mannitol with increased incidences of macrophage aggregation and alveolitis in the 3 month rat study and coughing, laryngeal ulceration and sinus histiocytosis in the 6 month dog study. The no observed adverse effect level (NOAEL) in the 6 month dog study was 43 mg/kg/day.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology team reviewed the clinical pharmacology information submitted under NDA 22-368 on February 27, 2009 and finds it acceptable from the clinical pharmacology perspective. The MBCT is to be used as a tool to identify and quantify bronchial hyperresponsiveness (BHR). The MBCT is postulated to be an "indirect" test of BHR. The Applicant has proposed that the mechanism of action of inhaled mannitol is that it increases the osmolarity of the airway surface, resulting in the release of mediators such as histamine, prostaglandins and leukotrienes which act on bronchial smooth muscle to cause contraction and consequent narrowing of the airways. The airway response is then measured by assessing for a decrease in forced expiratory volume in 1 second (FEV1).

At the July 19, 2004 Pre-IND meeting it was decided that no formal pharmacokinetic or bioavailability studies were necessary. The justification was because safety profiles of large intravenous (IV) and oral doses on mannitol have been well established and that the MBCT would not be used chronically but only as a single use product as a diagnostic test.

However, the Agency asked the sponsor conduct a PK and bioavailability (BA) study to determine the absolute BA of mannitol powder for inhalation compared to mannitol administered intravenously and the relative bioavailability of mannitol powder for inhalation compared to mannitol administered orally. The study was an open-label, randomized, three-way cross over study design in 18 healthy male subjects aged 18-65 years old. Each subject received three treatments: 635 mg mannitol powder for inhalation using a drug powder inhaler, 500 mg mannitol powder administered orally, and mannitol 500 mg in a commercial formulation for intravenous use. The results indicate that the absolute bioavailability of inhaled mannitol in comparison to intravenously administered mannitol was 0.59 and the relative bioavailability of inhaled mannitol in comparison to orally administered mannitol was 0.96. The time to reach the mannitol peak plasma concentration (Cmax) was similar; 1.5 hour for inhaled and 1.4 hour for oral administration as was the mean terminal half-life of mannitol of 5 hours regardless of route of administration.

6. Clinical Microbiology

This section is not applicable as mannitol is not an antimicrobial product.

7. Clinical/Statistical- Efficacy

Overview of the clinical program:

The relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following Section 8.

Table 1. Relevant Clinical Studies with Inhaled Mannitol Powder

Type of Study	ID	Treatment Groups	Objective	Design	Number of Subjects	Duration of Treatment
Human PK Study						
PK	DPM-PK-101	Normal Subjects	Bioavailability of mannitol, IV, oral, and inhaled	3-way crossover	15 adults	24 hours
Device Usability Study						
Device usability	OSM-401	Asthma and Normal Subjects	Assess inspiratory flow rates/volumes	Open, observational	34 adults	No active treatment
Phase 3 Pivotal Study						
Efficacy and Safety	DPM-A-305*	Asthma-like symptoms, no clinical diagnosis	Sensitivity, specificity of mannitol and methacholine to detect EIB as manifestation of BHR	Crossover, mannitol, methacholine, exercise	509 6-50 years	Single test
Phase 3 Supportive Study						
Efficacy and Safety	DPM-A-301#	Asthma and Normal Subjects	Sensitivity, specificity of mannitol vs 4.5% saline	Crossover, mannitol, 4.5% saline	654 6-83 years	Single test

* Study DPM-A-305 was conducted entirely in the United States during 2005-06
\# Study DPM-A-301 was conducted in Australia during 2003-2004
EIB = exercise induced bronchospasm; BHR = bronchial hyperreactivity

Design and conduct of the studies:

Study DPM-A-305:

Study DPM-A-305 (study 305) was a multicenter, randomized, blinded study in 509 subjects 6- 50 years of age with symptoms of or suggestive of asthma but without a definitive diagnosis of asthma. Subjects with chronic respiratory diseases (COPD, pulmonary fibrosis, emphysema, etc.), recent surgery, a history of heart disease that would be felt to increase the risk of the exercise, methacholine or mannitol challenge tests, and those with a ≥ 10 pack year smoking history were among those excluded. As part of this study, subjects were independently determined as having a positive or negative bronchial challenge test using a methacholine challenge test (with methacholine positivity defined as the provoking concentration causing a 20% fall in FEV1 being than or equal to 16 mg/mL (ATS guidelines)) and the MBCT (with positivity defined as a 15% fall in FEV1 at any provoking dose of mannitol until the maximum dose had been given or a between-dose drop of ≥ 10% in FEV1 was observed). Subjects were also required to undergo two exercise challenge tests for diagnosis of exercise-induced bronchospasm (with exercise positivity defined as ≥10% fall in FEV1 after either of two standardized treadmill runs) to act as the standard of truth for calculation and comparison of the sensitivity and specificity of the methacholine and mannitol diagnostic tests. The primary objectives of the study were:

1. To accurately estimate sensitivity and specificity of MBCT to detect bronchial hyperresponsiveness (BHR), as manifested by a positive exercise challenge, i.e., within a 10% margin of the point estimates
2. To demonstrate that MBCT sensitivity for BHR is significantly greater than 60%
3. To demonstrate that MBCT specificity is significantly greater than that seen with methacholine challenge to detect BHR.

From the statistical analysis perspective, the intent-to-treat (ITT) group was protocol-defined as all subjects who received at least one dose of methacholine or mannitol. The per-protocol population was defined as all subjects with no major protocol violations that complete all of the required challenge tests, including methacholine and MBCT challenges. Missing results for the mannitol or methacholine challenges were to be imputed using a worst-case approach as follows: missing MBCT results were assumed to be negative if the subject was exercise positive and positive if the subject was exercise negative while missing methacholine results were assumed to be positive if the subject was exercise positive and negative if the subject was exercise negative.

Study DPM-A-301:

Study 301 was a multicenter, open-label, operator-blinded, randomized, crossover study in 654 subjects 6-83 years of age (557 with asthma (428 adult, 129 children), 97 normal subjects (82 adult, 15 children). The ITT population included 646 subjects. The design of the study was such as to allow comparison of inhaled mannitol and hypertonic saline, an approved bronchoprovocation agent in Australia, in terms of safety and efficacy in well-defined subject populations who either carried a definitive diagnosis of asthma or do not have asthma. Subjects with asthma were to have an FEV1 > 70% predicted and to have active signs and symptoms of asthma. Any subjects with chronic respiratory disease other than asthma, uncontrolled hypertension, or a myocardial infarction or cerebral vascular accident in the six months prior to enrollment were excluded. After screening and randomization the subjects underwent the first bronchial challenge test (either with mannitol or 4.5% saline). The second challenge was conducted 1 week later. Subjects returned for a follow up visit, including spirometry one week after the second challenge test was performed. At this visit, a respiratory physician who was not aware of the subjects' asthma status would determine the asthma status of the subject using a combination of history, physical exam, and the results of the 4.5% saline challenge.

The primary efficacy endpoint was to estimate and compare the sensitivity and specificity of the mannitol challenge with respect to the 4.5% saline challenge. Subjects were considered positive to either test if at least a 15% reduction in FEV1 from baseline occurred. Because the use of 4.5% saline as a bronchoprovocation test has not been evaluated by the FDA, this endpoint is not relevant to this application. However, data relevant to the performance of the MBCT were obtained. In my opinion the secondary endpoint of determining the efficacy of the mannitol challenge compared to standard clinical assessment in discriminating between those with and without active asthma is a relevant endpoint for review as the ability to distinguish between patients with definite asthma and normal individuals (while not the specific indicated population in which the study will be utilized) should be viewed as a prerequisite for any further consideration of efficacy of the test. This viewpoint differs somewhat from the opinion outlined in the statistical review which discounts the ability of Study 301 to assess the usefulness (efficacy) of the MBCT due to lack of an appropriate active comparator bronchial challenge test as a benchmark for efficacy (see the statistical review by Ruthanna Davi).

Efficacy findings:

As the two Phase 3 studies conducted to support the use of the MBCT were of different design in different populations, the results of the studies will be discussed separately below.

Study DPM-A-305
A total of 509 subjects were screened for enrollment in the study. Seventy three were not enrolled due to events occurring prior to randomization leaving 436 in the all-randomized/safety analysis group. An additional 16 subjects were excluded from the efficacy analyses post-randomization [withdrew consent (5), took prohibited drug (2), excess FEV1 variability (1), adverse event (2), and enrollment closed (2)] leaving 420 (96%) in the "intent-to-treat plus" (ITT plus) population. This ITT plus population included 29 subjects not included in the Applicant's ITT population whose exercise challenges were both negative but were considered inadequate. However, as the protocol had originally defined the ITT population as all subjects who received at least one dose of methacholine or mannitol, the ITT plus population seems to most closely represent this definition. Thus the primary FDA analysis used the ITT plus population. An additional 16 subjects are excluded from the ITT group to create the per protocol (PP) population with 375 (86%) subjects.

In the study population 54% of subjects were female, 74% were Caucasian, 9% Hispanic and 9% Black. The mean age was 25 years and the mean body mass index (BMI) was 24. No subjects older than 50 years of age were enrolled in the study. Subjects had near normal baseline spirometry results, with a mean pre-bronchodilator FEV1 of 3.27 L or 93% of the predicted value. They also had low NAEPPII asthma scores, with a mean of 1.2. Most, 78.2% were atopic, however few, 7.5%, responded positively (increase in FEV1 $\geq$ 12% and 200 mL) after administration of a short-acting bronchodilator.

The analyses of the sensitivity and specificity of the MBCT necessary to address the primary efficacy objectives are shown in Table 2 below. These include the sensitivities and specificities (calculated relative to exercise challenge) and the associated 95% confidence intervals for the MBCT and methacholine as well as the differences in these measures between the MBCT and methacholine and the associated 95% confidence intervals. These results are primarily derived from FDA statistical reviewer analyses. Selected similar analyses submitted by the Applicant which differ by a small amount are included for comparison. These small differences are likely the result of the Applicant using different statistical analyses [Markov Chain Monte Carlo simulation (MCMC)] than the FDA. The FDA analyses were undertaken to confirm that the qualitative conclusions with the normal approximation methods would be similar to those of the MCMC results. More detailed analyses can be found in the statistical and primary clinical reviews by Ruthanna Davi and Anya Harry, respectively).

Table 2. By-Treatment Group Comparisons of Sensitivity & Specificity (Calculated Relative to Exercise Challenge) for MBCT and Methacholine for Assessment of the Primary Efficacy Objectives

Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
FDA Analysis Group	**Methacholine Cutoff**	**Missing Data**	**MBCT**	**Methacholine**	**Difference**	**MBCT**	**Methacholine**	**Difference**
ITT plus	16	Worst Case	58% (50%, 65%)	53% (46%, 61%)	5% (-4%, 13%)	63% (57%, 69%)	68% (62%, 73%)	-5% (-12%, 3%)
ITT plus	16	Ignored	58% (51%, 66%)	54% (46%, 61%)	5% (-4%, 13%)	64% (58%, 70%)	68% (62%, 73%)	-4% (-11%, 3%)
PP	16	Worst Case	58% (51%, 66%)	55% (48%, 63%)	3% (-6%, 12%)	65% (58%, 71%)	69% (63%, 75%)	-4% (-12%, 3%)
Applicant Analyses*								
ITT	16	Worst Case	58% (50%, 65%)	53% (46%, 61%)	5% (-4%, 13%)	69% (63%, 76%)	64% (58%, 71%)	-5% (-13%, 2%)
ITT	16	Ignored	58% (51%, 65%)	54% (46%, 61%)	5% (-4%, 13%)	65% (59%, 71%)	69% (63%, 75%)	-4% (-12%, 3%)
PP	16	Worst Case	58% (51%, 66%)	55% (48%, 63%)	3% -6%, 12%)	65% (58%, 71%)	69% (62%, 75%)	-4% (-12%, 3%)

Source: FDA statistical reviewer analyses
* Applicant analyses utilized a Markov Chain Monte Carlo (MCMC) simulation; 95% credible intervals calculated Adapted from Tables 11-9, 11-10, and 11-11 Study DPM-A-305 Study Report

As illustrated by both the lower and upper confidence interval limits for the sensitivity and specificity of the MBCT being within 10 percentage points of the point estimates, the analyses confirm the Applicant's first study objective in all cases presented. However, the second study objective was not confirmed for any case presented as illustrated by the lower confidence interval limit for the MBCT sensitivity being less than 60%. Additionally, the third study objective was also not confirmed for any case presented as illustrated by the lower confidence interval limit for the difference in the MBCT specificity and the methacholine challenge specificity being less than zero. While the primary efficacy analyses presented in Table 2 do not support the efficacy of the MBCT, it could be argued that the primary efficacy objectives defined for this study are not the most relevant in terms of assessing the efficacy of the MBCT. This argument should include the notion that the exercise challenge-induced BHR to which the sensitivity and specificity of the MBCT and methacholine were compared should be viewed more as a model of demonstrating BHR so that comparisons between MBCT and methacholine can be made rather than as a "gold standard" to assess BHR.

At the pre-IND meeting held July 19, 2004, the FDA believed that an appropriate study design for evaluation of a diagnostic test should include a statistical comparison of the sensitivity and specificity of the new diagnostic procedure with an established/FDA-approved diagnostic procedure (methacholine challenge, for example) where the sensitivity and specificity of each challenge are calculated relative to some "gold standard", in this case ECT-induced BHR. In doing so, the new diagnostic procedure should perform better than chance alone, that is, the sensitivity and specificity and the new diagnostic procedure compared to ECT-induced BHR should exceed 50%. This was demonstrated for the MBCT as the lower confidence interval limits for the sensitivities and specificities for the MBCT were greater than 50%. Additionally, while the study was not designed to assess for non-inferiority, from a clinical viewpoint the MBCT performed similarly to that of the FDA-approved bronchial challenge test, methacholine.

Another way to assess the efficacy of the MBCT and assess the similarities in sensitivity and specificity between the MBCT and methacholine would be to use the blinded physician likely diagnosis of asthma as the common comparator or standard of truth rather than the results of the exercise challenge tests (Table 3). In this comparison the physician diagnosis of "probably", "possible", "very likely", and "extremely likely or definite" for asthma were considered positive diagnoses of asthma and "unlikely but not excluded" and "very unlikely or excluded" were considered negative diagnoses for purposes of this analyses. One can see from Table 3 that the nominal values for the sensitivity and specificity of the MBCT compared to blinded physician diagnosis are greater than 50%. While the lower limits of the confidence intervals for the sensitivity of the MBCT are 48-49%, the sensitivity of the MBCT relative to blinded physician diagnosis appears to perform nominally better than the approved methacholine challenge test.

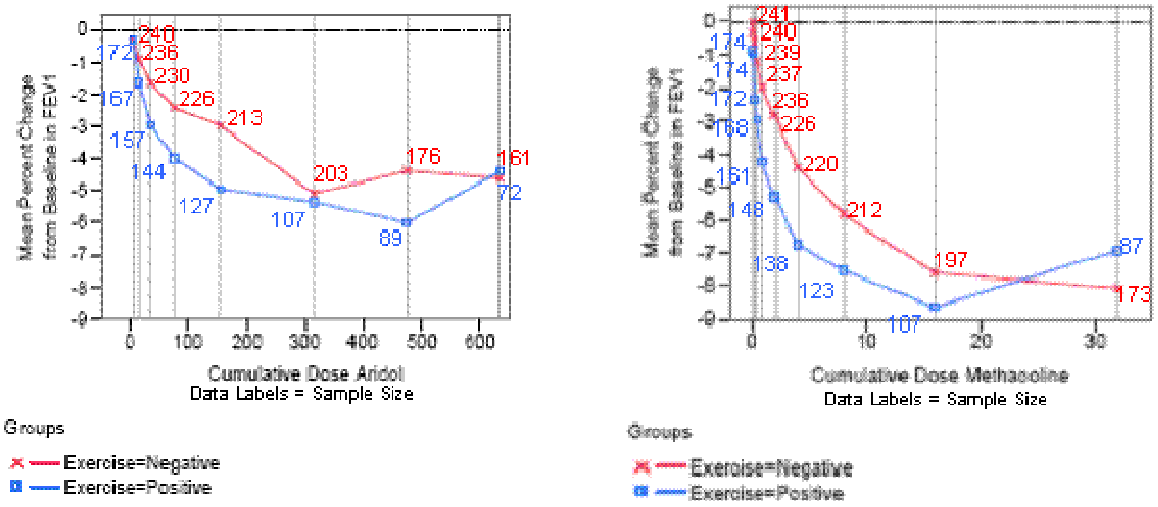
Table 3. By-Treatment Group Comparisons of Sensitivity & Specificity (Calculated Relative to Blinded Physician Diagnosis from Visit 5) for MBCT and Methacholine

Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst Case	54% (48%, 60%)	50% (44%, 56%)	4% (-3%, 11%)	69% (62%, 76%)	72% (65%, 79%)	-3% (-12%, 6%)
ITT plus	12	Worst Case	54% (48%, 60%)	45% (39%, 51%)	9% (2%, 16%)	69% (62%, 76%)	75% (68%, 81%)	-6% (-25%, 5%)
PP	16	Worst Case	55% (49%, 61%)	51% (45%, 57%)	4% (-3%, 11%)	73% (65%, 80%)	75% (67%, 82%)	-2% (-11%, 7%)
PP	12	Worst Case	55% (49%, 61%)	46% (40%, 52%)	9% (2%, 16%)	73% (65%, 80%)	77% (70%, 84%)	-4% (-13%, 4%)

Source: FDA statistical reviewer analyses

Another method to assess the performance of the MBCT relative to methacholine would be to construct plots of the cumulative dose of mannitol or methacholine by the mean percent change from baseline in FEV1 for the exercise positive and exercise negative strata as is demonstrated in Figure 1. The graphs are intended to illustrate that the fall in FEV1 associated with administration of mannitol is greater in the exercise positive subjects that in the exercise negative subjects and that this relationship is similar to that when methacholine is administered. While there is generally no statistically significant difference between the exercise positive and exercise negative groups in the mean percent change from baseline in FEV1 for either mannitol or methacholine, numerically, it does appear that the exercise positive subjects do experience a larger mean drop in FEV1 than exercise negative subjects with administration of either product as evidenced by the blue lines generally falling below the red lines in the Figure. Note that since subjects with the greatest falls in FEV1 at the lower cumulative doses do not proceed to the higher cumulative doses (as they are diagnosed as positive and dosing stops), the impact of missing data on the mean fall in FEV1 becomes more pronounced for the higher cumulative doses. That is the likely explanation for the change in the slope of the blue line (exercise positive subjects) in both the MBCT and methacholine test groups below.

Figure 1. Mean Percent Change from Baseline in FEV1 with MBCT or Methacholine by Exercise Stratum (ITT plus analysis group)



Source: FDA statistical reviewer analyses

Results in Special Populations

Pediatrics

The primary efficacy analyses divided by age subgroups for Study 305 are given in Table 4. While there were no statistically significant differences in the sensitivity and specificity of the MBCT relative to exercise challenge among the different age subgroups (6-11 years, 12-17 years, and > 17 years), the specificity of the MBCT (as well as methacholine) appears to decrease in the younger age groups, 47%, 62%, and 65% for the 6-11, 12-17, and >17 year old groups, respectively.

Table 4. By-Treatment Group Comparisons of Sensitivity & Specificity (Calculated Relative to Exercise Challenge) by Age

Ages 6 to 11 Years								
Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst Case	67% (47%, 87%)	71% (52%, 91%)	-5% (-29%,20%)	47% (21%, 72%)	33% (9%, 57%)	17% (-29%, 62%)
ITT plus	12	Worst Case	67% (47%, 87%)	67% (47%, 87%)	0% (-26%,26%)	47% (21%, 72%)	40% (15%, 65%)	7% (-32%, 46%)
Ages 12 to 17 Years								
Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst Case	55% (37%, 72%)	65% (48%, 81%)	-10% (-32%,13%)	62% (46%, 77%)	64% (49%, 79%)	-3% (-24%, 19%)
ITT plus	12	Worst Case	55% (37%, 72%)	65% (48%, 81%)	-10% (-32%,13%)	62% (46%, 77%)	74% (61%, 88%)	-13% (-32%, 6%)
Ages 17 Years and Above								
Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst	57%	47%	10%	65%	71%	-6%

		Case	(48%, 65%)	(38%, 55%)	(1%, 20%)	(58%, 71%)	(65%, 77%)	(-14%, 1%)
ITT plus	12	Worst Case	57% (48%, 65%)	44% (35%, 52%)	13% (3%, 23%)	65% (58%, 71%)	74% (68%, 80%)	-10% (-17%, -2%)

Source: FDA statistical reviewer analyses

In addition, treatment groups were compared by gender and race (Caucasian/Noncaucasian). There were no differences in the sensitivity or specificity calculated relative to exercise challenge of the MBCT noted based on gender or race (see primary clinical review for specific data).

In summary, the study failed to meet two of three proposed primary objectives. However, these objectives were not necessarily the most relevant in determining the usefulness of the MBCT as an assessment of bronchial hyperreactivity. The study did demonstrate that the MBCT performed similarly to the methacholine challenge test with regard to detection of exercise induced bronchoconstriction as a measurement of bronchial hyperreactivity, with regard to a blinded physician's clinical diagnosis of asthma, and with regard to cumulative dose response. These positive outcomes, in my opinion, support the utility of the MBCT as a test for bronchial hyperreactivity.

Study 301 Results

Study Results

A total number of 654 subjects were enrolled in the study: 557 with asthma and 97 subjects without asthma. Eight withdrew before receiving study medication (6 with asthma and 2 without asthma), leaving 646 in the ITT and safety populations. In the safety population, there were 301 (47%) males and 345 (53%) females. The ages ranged from 6 to 83 years with a mean age of 35 years. There were 627 subjects who underwent the mannitol challenge of whom 14 (2%) did not complete it. There were 551 (85%) subjects with asthma and 95 (15%) subjects without asthma. The mean FEV1 in the subjects with asthma was 3.0 L (95% predicted) compared to 3.2 L (95% predicted) for subjects without asthma.

MBCT Compared to Clinical Diagnosis of Asthma

As stated above, the main usefulness, with regard to efficacy, of this supportive study was to ensure that the MBCT was capable of differentiating between patients with asthma and normal individuals without asthma. These data are presented below.

- **Mannitol vs Clinical Diagnosis in Subjects with Asthma**

The sensitivity of the MBCT in subjects with asthma at study entry was 58% (54%, 62%, 95th CI), with 291 mannitol positive subjects of 501 subjects with asthma. The sensitivity of the clinical diagnosis in the same population was 97% (95%, 98%) with 485 of 501 subjects with asthma being identified by the blinded investigator as having asthma. The difference in sensitivity of these two parameters was 39% (35%, 43%) indicating a statistically significant difference between the sensitivity of the MBCT to detect an asthmatic subject compared with that of the clinical diagnosis.

- **Mannitol vs Clinical Diagnosis in Subjects without Asthma**

For the subjects without asthma, the specificity of mannitol was 95% (90%, 99%) with 86 of the 91 subjects without asthma being mannitol negative while the specificity of the clinical diagnosis was 98% (95%, 100%) with 89 of the 91 subjects without asthma being identified by the blinded investigator as without asthma. The difference between mannitol and the clinical diagnosis in identification of subjects without asthma was 3.3% (-1%, 8%) indicating no significant difference in specificity between mannitol and physician diagnosis in determining subjects without asthma.

As noted above, the specificity of the MBCT in identifying subjects in Study 301 without asthma was very similar to that of a physician's diagnosis. Thus, the data are supportive such that a negative MBCT correlates well with the "gold standard" of a physician's conclusion that a subject does not have asthma.

The Applicant suggested that the low sensitivity with respect to clinical diagnosis was affected by the use of systemic or inhaled corticosteroids. In post-hoc analyses in which the subjects with asthma who were mannitol negative but were known to be receiving inhaled corticosteroid therapy were excluded (159 subjects) an increase in sensitivity to 88% was noted. While it is reasonable and likely that the use of inhaled corticosteroids may influence the results of the MBCT, the post-hoc analyses conducted by the Applicant likely overestimate this effect.

8. Safety

Safety data from studies DPM-A-301 and DPM-A-305 form the clinical trial safety data base for this application.

It is of note that the two trials had different active comparators. Study 301 compared the MBCT against inhaled hypertonic saline, a bronchial challenge test commonly used outside the United States, while the active comparators for Study 305 were exercise testing and a methacholine challenge test, which is the only bronchial challenge test approved in the United States (Provocholine, NDA 19-193, approved October 31, 1986) to aid in establishing a diagnosis of asthma. Since the safety of the hypertonic saline bronchial test has not been assessed by FDA, it is difficult to draw conclusions about the safety of MBCT using hypertonic saline as a comparator. Thus, the primary active comparator to act as a benchmark for safety will be the methacholine challenge test.

Neither study investigated the long-term effects of inhaled mannitol or the effects of inhaled mannitol on blood chemistry, hematology, or urinalysis parameters. This was considered appropriate given that mannitol is considered safe for use as a dietary supplement in doses much larger than those administered during the pivotal studies.

It is also of note that Study 305 excluded enrollment of subjects > 50 years of age due to the physical demands of the exercise challenge. While this decision was arguably appropriate, it does limit the size of the safety database for older subjects who may have co-morbid conditions such as cardiovascular disease or other chronic respiratory diseases.

The safety database included 1,082 subjects with asthma, symptoms suggestive of asthma, and healthy subjects of which 1,046 received at least one dose on mannitol in the two Phase 3 trials. Other than the differences in study population already described (definite asthma vs symptoms suggestive of asthma) the demographic and baseline characteristics of subjects in Studies 301 and 305 were similar (Table 5).

Table 5. Demographic and Other Baseline Characteristics in Subjects in Studies 301 and 305, Safety Population

Parameter		DPM-A-301 N = 646	DPM-A-305 N = 436
Age, years	N	646	436
	Mean	34.8	24.5
	Minimum-maximum	6.4-83.1	6-50
Sex	Male, n (%)	301 (46.6%)	204 (46.8%)
	Female, n (%)	345 (53.4%)	232 (53.2%)
Race	Caucasian, n (%)	588 (91.0)	328 (75.2%)
	African descent, n (%)	2 (0.3%)	0
	Aboriginal/Torres Strait Islander, n (%)	1 (0.2%)	0
	Asian, n (%)	32 (5.0%)	23 (5.3%)
	Black, n (%)	0	38 (8.7%)
	Hispanic, n (%)	0	40 (9.2%)
	Other, n (%)	23 (3.6%)	7 (1.6%)
BMI, kg/m^2	N	646	434
	Mean	25.5	24.4
	Minimum-maximum	14.5-52.1	13.4-34.9
Height, cm	N	646	436
	Mean	164.2	167.3
	Minimum-maximum	116-200	118.0-204.5
Weight, kg	N	646	436
	Mean	70.2	68.9
	Minimum-maximum	20-140	20.0-135.2
Smoking pack-years	N	Not reported (NR)	49
	Mean	NR	2.9
	Minimum-maximum	NR	0-9
FEV_1, L	N	646	434
	Mean	2.97	3.3
	Minimum-maximum	1.26-6.03	1.15-5.62
FEV_1, L, for asthmatic/symptomatic Subjects	N	551	N/A
	Mean	3.0	N/A
	Minimum-maximum	1.3-6.0	N/A
FEV_1, L, for non-asthmatics	N	95	N/A
	Mean	3.2	N/A
	Minimum-maximum	1.5-5.7	N/A
% Predicted FEV_1	N	646	434
	Mean	94.9	93.7
	Minimum-maximum	64-139	59.1-195.2
% Predicted FEV_1 for asthmatics	N	551	N/A
	Mean	95.0	N/A
	Minimum-maximum	64.0-139.0	N/A

No deaths occurred in association with the use of the MBCT in the clinical program and one serious adverse event (SAE) occurred, a case of appendicitis in Study DPM-A-305 eight days after methacholine challenge, but before the MBCT.

A total of 11 subjects withdrew from the studies as a result of adverse events after bronchial challenges, 7 in Study 301, and 4 in Study 305. Seven of the subjects discontinued after receiving the MBCT (decreased lung function, throat irritation, sore throat, fall, feeling jittery, retching, and cough) , 3 after receiving hypertonic saline (sciatica, influenza, and chest infection), and one after methacholine (dizziness).

Common Adverse Events

The most common AEs associated with the MBCT were headache, pharyngolaryngeal pain, nausea, throat irritation, and cough. The most common AEs noted for methacholine were dyspnea and chest discomfort. Of note is that combined gastrointestinal AEs (nausea, retching, and vomiting) were higher in the MBCT group. Adverse events occurring during or within a day of the challenge tests with an incidence ≥ 1% patient are shown in Table 6 below.

Table 6. Adverse Events with an Incidence ≥ 1% During or Within a Day After Challenge: Studies 301 and 305, Safety Population

	Study DPM-A-301		Study DPM-A-305		Total,
MedDRA Preferred Term	Mannitol BCT (N = 627) n (%)	Saline Challenge (N = 636) n (%)	Mannitol BCT (N = 419) n (%)	Methacholine Challenge (N = 420) n (%)	Mannitol BCT (N = 1,046) n (%)
Headache NOS	54 (8.6%)	51 (8.0%)	5 (1.2%)	4 (1.0%)	59 (5.6%)
Pharyngolaryngeal pain	19 (3.0%)	9 (1.4%)	6 (1.4%)	0	25 (2.4%)
Nausea	14 (2.2%)	9 (1.4%)	5 (1.2%)	0	19 (1.8%)
Throat irritation	7 (1.1%)	1 (0.2%)	12 (2.9%)	1 (0.2%)	19 (1.8%)
Cough	8 (1.3%)	8 (1.3%)	9 (2.1%)	8 (1.9%)	17 (1.6%)
Rhinorrhoea	8 (1.3%)	2 (0.3%)	8 (1.9%)	0	16 (1.5%)
Dyspnoea NOS	3 (0.5%)	1 (0.2%)	12 (2.9%)	21 (5.0%)	15 (1.4%)
Chest discomfort	0	0	13 (3.1%) [a]	18 (4.3%) [a]	13 (1.2%)
Wheezing	2 (0.3%)	2 (0.3%)	6 (1.4%)	7 (1.7%)	8 (0.8%)
Fatigue	7 (1.1%)	1 (0.2%)	0	0	7 (0.7%)
Feeling jittery	0	0	6 (1.4%)	2 (0.5%)	6 (0.6%)
Retching	2 (0.3%)	0	4 (1.0%)	0	6 (0.6%)
Vomiting NOS	6 (1.0%)	3 (0.5%)	0	0	6 (0.6%)
Dizziness	0	0	5 (1.2%)	13 (3.1%)	5 (0.5%)
Hyperhidrosis	0	0	4 (1.0%)	0	4 (0.4%)

Source: Clinical Summary of Safety, Table 2 7 4 7

Specific Safety Concerns

Severe Bronchoconstriction

A major safety concern with the use of a bronchial challenge test is a severe loss of lung function as a result of bronchospasm. Table 7 shows the number and per cent of subjects who had excessive decreases in FEV1 (defined as a fall in FEV1 ≥ 30%) during bronchial

challenges. In general the MBCT appeared to result in fewer episodes of excessive decreases in FEV1 during the clinical program. Three subjects who received methacholine challenges had decreases in FEV1 ≥ 60% while the maximal decrease in FEV1 observed in a subject receiving the MBCT was 46%. Of note is that 23 of the 26 subjects who had decreases in FEV1 ≥ 30% after mannitol had confirmed asthma.

Table 7. Incidence in the Fall in FEV1 ≥ 30% in Studies 301 and 305 Combined, All Exposed Subjects

Challenge	Number Exposed	Number (%) with Fall in FEV1 ≥ 30%
Exercise	435	27 (6%)
Mannitol	1043	26 (3%)
Methacholine	420	51 (12%)

Source: Clinical Summary of Safety, Tables 2 7 4 26 and 2 7 4 27

Cough
Cough occurred in the large majority of subjects who received the MBCT (85% in Study 301 and 93% in Study 305). Cough was severe enough to result in stopping the challenge in 17 of 1046 (1.6%) of subjects exposed to the MBCT in the two studies. This compares to 0.8% of subjects who received hypertonic saline challenges in Study 301. No analysis was performed for the incidence of cough after methacholine in Study 305.

Recovery to Baseline Pulmonary Function
For Study 301, the mean time for recovery to baseline pulmonary function in subjects who had a positive test (within 5% of pre-challenge FEV1) was approximately 19 minutes for both the MBCT and hypertonic saline groups. The maximum time for recovery for a subject receiving the MBCT was 65 minutes. For Study 305, the mean recovery times were 22 minutes for both the MBCT and methacholine groups. The maximum time for recovery was 67 and 50 minutes following the MBCT and methacholine, respectively.

Albuterol/Salbutamol Use
Albuterol/salbutamol was given to subjects following positive challenges in both Studies 301 and 305. Additional rescue medication could be administered if needed, until the subject's FEV1 returned to within 5% of pre-challenge FEV1. Subjects with negative challenges could be given rescue medication at the discretion of the investigator. For Study 301, a total of 344 (55%) subjects received a 200 mcg dose of salbutamol for recovery after the MBCT. A second salbutamol 200 mcg dose was given to 46 (7.3%) subjects after MBCT and additional medical treatment was required to return the subject to within 5% of pre-challenge FEV1 in 6 (1.0%) subjects following the mannitol BCT. These treatments were additional doses of short-acting beta agonists (albuterol/salbutamol, terbutaline).

Pediatrics
Overall, the types and severities of adverse events in children were similar to those observed in the adult population. As in the adult population, the AEs of headache, pharyngolaryngeal pain, and nausea were the most common. There were also no major differences in the types of AEs observed in children 6-11 years of age compared to adolescents 12-17 years old.

No deaths or other SAEs were reported in the pediatric population. Two withdrawals due to AEs were reported in the pediatric population one in Study 301 and one in Study 305; withdrawal following throat infection and influenza in an 11 year old in Study 301 and withdrawal due to retching in a 14 year old in Study 305. An AE of mild hemoptysis was also reported in a 16 year old in Study 301.

Table 8 shows the incidence of decreases in FEV1 ≥ 30% for pediatric subjects who underwent the MBCT and methacholine and exercise challenges. Note that they are similar to those observed in the adult population (Table 7).

Table 8. Incidence in the Fall in FEV1 ≥ 30% for Pediatric Subjects in Studies 301 and 305 Combined, All Exposed Subjects

Challenge	Number Exposed	Number (%) with Fall in FEV1 ≥ 30%
Exercise	108	10 (9%)
Mannitol	241	26 (5%)
Methacholine	107	16 (15%)

Source: Clinical Summary of Safety, Tables 2 7 4 54 and 2 7 4 56

Postmarketing Experience

The MBCT has been approved for use in identifying bronchial hyperreactivity in at least 15 countries with a total cumulative commercial exposure to date (22 March-2006 to 20 April 2009) is estimated (b) (4) subjects. During the safety reporting period, there were no reports that raised any new safety concerns. Two spontaneous adverse reaction reports from healthcare professionals were reported: one in a 63 year old woman with a history of chronic cough who had an FEV1 drop by 48% after administration of the placebo (baseline) dose containing no mannitol. She was treated with a salbutamol and fully recovered. The second report was of a 19 year old man who developed excessive thirst and dry throat after inhaling 635mg of mannitol (negative challenge).

Safety Summary

The relative safety of the MBCT (including pediatrics) is supported by the submitted clinical study data. Safety data showed that the MBCT was most commonly associated with headache, pharyngolaryngeal pain, nausea, and throat irritation. The incidence of these AEs was greater in number than for the comparator bronchial challenge test, methacholine. The MBCT also appeared to have more gastrointestinal system AEs (nausea, vomiting, retching and in children upper abdominal pain). It is possible this may be the result of the osmotic load and laxative effect of mannitol. The active comparator, methacholine was noted to have an increased incidence of the AEs dyspnea and chest discomfort compared to the MBCT.

The most concerning events for a bronchoprovocation test is severe bronchoconstriction. It is notable that both adults and children who received MBCT had one third to one fourth the incidence of excessive decreases in FEV1 than were reported for methacholine. The size of the safety database is adequate for this type of challenge test, including pediatrics with pediatric subjects making up about 23% of the safety population. Given the inherent potential for severe bronchoconstriction with a bronchial challenge test, the safety profile of the MBCT is

acceptable for use as a bronchial challenge test when administered by a trained health care professional.

9. Advisory Committee Meeting

The advisory committee meeting for the Aridol program was held on November 20, 2009. The Committee addressed the following issues:

1. Please comment on the evidence to support the use of the mannitol bronchial challenge test to assess bronchial hyperresponsiveness to aid in diagnosing patients who have symptoms of asthma or symptoms that are suggestive of asthma. Specifically address the evidence in patients 50 years of age and older and patients < 18 years of age.
2. Please comment on any safety concerns with use of the mannitol bronchial challenge test.
3. Do the data provide substantial and convincing evidence to support the use of the mannitol bronchial challenge test to assess bronchial hyperresponsiveness to aid in diagnosing patients who have symptoms of asthma or symptoms that are suggestive of asthma? [voting question]
    a) In patients 18 years of age and older
        If not, what additional data should be obtained?
    b) In patients 12 to 17 years of age
        If not, what additional data should be obtained?
    c) In patients 6 to 11 years of age
        If not, what additional data should be obtained?

The advisory committee discussed the evidence submitted to support the usefulness and safety of Aridol as a bronchial challenge test for subjects ≥ 6 years of age. For Question 3 above, the committee voted that the data presented did provide substantial and convincing evidence in favor of Aridol as a bronchial challenge test to assess bronchial hyperresponsiveness for all three subject populations outlined. The voting was 12 yes, 3 no with 1 abstention for patients 18 years of age and older; 14 yes and 2 no for patients 12 to 17 years of age; and 11 yes and 5 no for patients 6 to 11 years of age. The committee also discussed the lack of safety data in adults greater than 50 years of age, especially those who may have other significant medical conditions (COPD, cardiac disease, etc.). The adequacy of the pediatric data were also discussed.

10. Pediatrics

Pediatric efficacy and safety data are presented in Sections 7 and 8, respectively. The size of the pediatric safety database is adequate with pediatric subjects making up about 23% of the safety population. A total of 246 pediatric subjects were evaluated in Phase 3 clinical trials. This total includes 82 subjects 6-11 years of age and 56 subjects 12-17 years old in Study 301 and 36 subjects 6-11 years of age and 72 subjects 12-17 years old Study 305.

The pediatric data presented were not a response to a written request. The Applicant submitted a request for a waiver for pediatric studies for children < 6 years of age based on the inability of children less than 6 years of age to perform the Aridol bronchial challenge test adequately

(children at this young age are not generally able to perform serial spirometry assessments reproducibly). The Division agreed that a waiver in children < 6 years of age was reasonable. The request was discussed at the Perc meeting on October 7, 2009, during which the committee also agreed that a waiver was appropriate.

11. Other Relevant Regulatory Issues

The Applicant states that no debarred investigators participated in the study, and all studies were conducted under Good Clinical Practices. No significant financial conflicts of interest for investigators in the clinical program were identified. DSI audits were conducted at two clinical sites (Kenneth Rundell, PhD/Site #152300 and Paul Ratner, MD/Site #29 in the United States that enrolled relatively large numbers of subjects in study DPM-A-305 as well as at Pharmaxis office at 403 Gordon Drive, Exton, PA. No significant regulatory violations were noted.

DMEPA and DDMAC were consulted with regard to the proposed name for the MBCT "Aridol". DMEPA found the proposed name, Aridol, acceptable in OSE Review #2008-1631, dated March 13, 2009. On October 16, 2008, DDMAC reviewed the proposed name and had no concerns regarding the proposed name from a promotional perspective.

12. Labeling

A proposed label and carton were submitted by the Applicant in PLR format which were reviewed in detail. Highlights of significant label issues identified are outlined below:

- The label will include a boxed warning similar to that of the Provocholine (methacholine chloride) label to warn that use of the Aridol bronchial challenge test may result in severe bronchoconstriction in susceptible subjects who receive it.
- The indication for the Aridol test will be modified to be more consistent with that of the approved bronchial challenge test, methacholine.
- The risk of excessive bronchoconstriction will also be added to the Warnings and Precautions section.
- Caution regarding the use of Aridol in subjects with Co-morbid conditions (ventilatory impairment, spirometry-induced bronchoconstriction, pneumothorax, recent abdominal or thoracic surgery, recent upper or lower respiratory tract infection, etc.) will be added to the Warnings and Precautions section.
- The Clinical Studies section requires substantial revision.
- Since Study DPM-A-301 utilized hypertonic saline as the comparator, a bronchoprovocation agent not approved in the US, the section describing it will not be included in the Clinical Trials section of the label.
- Specific directions regarding the conduct of the bronchial challenge test will be given in a separate instructions document rather than in the body of the label.
- Promotional language throughout the label will be removed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The Applicant (Pharmaxis) has submitted adequate safety and efficacy data to support approval of Aridol as a bronchial challenge test indicated for the assessment of bronchial hyperresponsiveness in subjects 6 years of age and older who do not have clinically apparent asthma. The recommended action on this application is for Approval.

- Risk Benefit Assessment

The risk benefit assessment supports the approval of Aridol as a bronchial challenge test. The clinical studies DPM-A-301 and DPM-A-305 demonstrated that the proposed serial increasing doses of Aridol (mannitol inhalation powder) administered as a single use bronchial challenge test provides acceptable data for use as a test to assess bronchial hyperresponsiveness. The statistical analyses were carried out in comparison to other diagnostic challenge tests that assess bronchial hyperreactivity, specifically, the approved bronchial challenge agent, Provocholine (methacholine chloride) and exercise. As a single use diagnostic test, the safety profile of mannitol inhalation powder is also acceptable. In the clinical studies conducted for this application, there were no serious adverse events temporally related to administration of Aridol. Aridol demonstrated a predictable adverse event profile (decrease in pulmonary function) that was consistent with and possibly improved over that which is observed with other bronchoprovocation tests (Provocholine and exercise) that was reversible after administration of a short-acting beta-2 agonist.

- Recommendation for Postmarketing Risk Management Activities

There are no specific postmarketing risk management activities that are recommended. Aridol is a single use bronchial challenge test used to assess for bronchial hyperreactivity. While there is a risk of excessive bronchoconstriction in subjects receiving Aridol, it will be administered only by health care professionals trained in its use and only in facilities that are equipped to emergently treat subjects who may develop severe bronchoconstriction as a result of the bronchial challenge test.

- Recommendation for other Postmarketing Study Commitments

While the safety profile of older subjects who received Aridol in the clinical program did not appear to differ significantly from that of the general population the older population enrolled in the clinical trials generally lacked many of the co-morbidities that the elderly frequently possess (chronic respiratory diseases, cardiac risk factors, etc.). As result, and consistent with discussion held at the Aridol PADAC advisory committee meeting, the following postmarketing requirement is recommended by the clinical team:

1. Conduct a clinical trial with Aridol in subjects/patients older than 50 years of age who have significant co-morbidities common in an elderly population (e.g., COPD, obesity, cardiac risk factors, etc.) or reanalyze the data from completed clinical

trials in which Aridol was administered to an elderly population with co-morbidities. A substantial number of the total population should be 65 years of age or greater. The trial should include the following objectives: 1) evaluate the degree of bronchoconstriction defined as a fall in FEV1 in the older subject/patient population and 2) evaluate the overall adverse event profile in subjects over 50 years of age.

Additional postmarketing clinical studies in children were considered but as the safety profile in children was very similar to that in the adult population, there were no statistical differences in efficacy compared to adults, and the pediatric program was robust (it encompassed 23% of the overall study population), postmarketing commitments were not felt to be necessary.

This submission fulfills the PREA requirements for Aridol as indicated.

The following postmarketing CMC Commitments are also recommended to which the Applicant has agreed:

1. The Applicant (Pharmaxis) commits to test foreign particulate matter for the first 6 commercial batches as part of a post-approval commitment and will evaluate the optical microscopy (method used for foreign particulate testing) results on completion of this testing. Pharmaxis further proposes to submit a changes-being-effected (CBE) supplement to the NDA to provide the data from the 6 commercial batches (assuming the data meets the proposed specification) to either remove or finalize the test specification.

2. The proposed specifications for Aerodynamic particle Size Distribution (APSD) are interim and the applicant will review/revise the APSD specifications based on the first 10 Aridol (mannitol inhalation powder) U.S. commercial batches by means of a prior approval supplement (PAS).

- Recommended Comments to Applicant

No additional comments are recommended to be conveyed to the applicant.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22368	ORIG-1	PHARMAXIS LTD	ARIDOL POWDER FOR INHALATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY G DURMOWICZ
12/18/2009