CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22368Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22,368
Priority or Standard	Standard
Submit Date(s)	April 7, 2010
Received Date(s)	April 7, 2010
PDUFA Goal Date	October 7, 2010
Division / Office	DPARP
Reviewer Name(s)	Anya C. Harry
Review Completion Date	July 27, 2010
Established Name	Mannitol
(Proposed) Trade Name	Aridol
Therapeutic Class	Sugar alcohol
Applicant	Pharmaxis Ltd.
Formulation(s)	Dry powder inhalation
Dosing Regimen	Challenge increasing concentration
Indication(s)	Assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma.
Intended Population(s)	Patients with signs or symptoms suggestive of asthma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The data submitted in the complete response submission for the New Drug Application (NDA) 22,368 for the diagnostic test Aridol to assess for bronchial hyperresponsiveness (BHR) has addressed the outstanding product quality issues and an approval action is therefore recommended. Pharmaxis submitted adequate data to support efficacy and safety of the Aridol bronchial challenge test as a single use diagnostic test in subjects 6 years of age and older in the original NDA 22,368 submitted on February 27, 2009. The Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was held on November 20, 2009 for the Aridol bronchial challenge test. The Committee voted with an overall majority that the submitted data provided substantial and convincing evidence to support approval of Aridol for testing of bronchial hyperresponsiveness. The Committee commented that the data for patients aged 50 years and older was limited, but recommended that the Aridol bronchial challenge test be made available for patients 6 years of age and older. However, the application received a Complete Response action on December 23, 2009 due to cGMP violations seen in three testing sites:

(b) (4)

In response, the Complete Response NDA resubmission dated April 7, 2010 addressed the violations by replacing (b) (4) (b) (4) with Pharmaxis which has acceptable cGMP status and specifications were changed under the drug substance section to include a new method for testing (b) (4) (b) (4) In addition, the remaining two sites resolved the deficiencies identified during inspection. The updated information has been evaluated and found to be adequate by the CMC reviewer Dr. D. Arora [Review dated June 15, 2010] and the recommendation is now for an Approval action.

1.2 Risk Benefit Assessment

The new safety data submitted in the NDA Safety Update (clinical studies of the inhaled mannitol product, Bronchitol™, that involve a mannitol tolerance test (MTT) as part of the screening process to be used to clear mucous more effectively in patients with Cystic Fibrosis or bronchiectasis) continue to support a beneficial risk benefit assessment. Common adverse events (cough, head ache, pharyngolaryngeal pain, and nausea) remained consistent with that seen in the data submitted for the original NDA and were self limited. The overall AE profile remained predictable including those

findings expected in the Cystic Fibrosis and bronchiectasis patient population. Still, the major safety concern for this bronchoprovocation test is the potential for acute bronchospasm during the test, which will be reflected as a boxed warning. The Aridol test will only be performed by trained professionals under the supervision of physicians familiar with all aspects of bronchial challenge test.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Mannitol is categorized as GRAS when administered orally or intravenously and has demonstrated an acceptable safety profile when inhaled for use as a bronchoprovocation test. Given the relatively low doses utilized in this single use diagnostic test, the consistent safety profile demonstrated in this program and the limitation that it will be administered by a trained health care professional at a site equipped to deal with rapid acute decreases in pulmonary function, there is no recommendation for a postmarketing risk evaluation and mitigation strategy (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

Pharmaxis had agreed to conduct a required post-marketing study to assess the safety of Aridol in subjects 50 years of age and older who have significant comorbid conditions common in the 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 as a postmarketing requirement (PMR). 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 well, 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 to either remove or finalize the test specification. Pharmaxis has also proposed interim specifications in an amendment to the application and will review the Aerodynamic particle Size Distribution (APSD) specifications based on the first 10 Aridol U.S. commercial batches by means of a prior-approval supplement (PAS). For any confirmed out-of-specification (OOS) result in marketed drug product, Pharmaxis has committed to submit a Field Alert report to FDA.

7 Review of Safety

Safety Summary

The relative safety of the Aridol bronchial challenge test was supported by the original submitted clinical study data. In the interval of time (up to December 2009) during the resubmission there were no new Pharmaxis sponsored studies on the use of the Aridol bronchial challenge test in patients with symptoms suggestive of asthma or COPD. However the MTT, which is an abbreviated version of the Aridol bronchial challenge test, was used as a screen in studies on the use of Bronchitol in patients with CF or bronchiectasis. Therefore, the NDA Safety Update included the AEs associated with this use of the MTT as a screen. The AEs found with the greatest incidence listed in the NDA Safety Update include: headache, lower respiratory tract infection, nasopharyngitis, cough, condition aggravated, CF lung and pharyngolaryngeal pain. These findings were consistent with those from the original submission: headache, pharyngolaryngeal pain, nausea and throat irritation with the exception of the expected AEs associated with the different population of patients with CF and bronchiectasis. Still, the most concerning event for a bronchoprovocation test is severe bronchoconstriction. In the bronchiectasis studies use of the MTT resulted in 1 episode of desaturation, 1 episode of reduction in FEV1, one episode of bronchospasm and 2 episodes of dyspnea of the 375 patients. In summary, the additional safety information obtained since the last data cut-off (July 1, 2009 to December 31, 2009) and presented in the NDA Safety Update has not changed the safety profile of the Aridol bronchial challenge test.

7.7 Additional Submissions / Safety Issues

There were no new safety data from Pharmaxis-sponsored studies on the use of the Aridol bronchial challenge test in patients with symptoms suggestive of asthma or in studies in patients with COPD. However, as requested by the Division, new safety data from Pharmaxis-sponsored multiple dose Phase 2 and 3 studies in bronchiectasis and cystic fibrosis (CF) using the MTT as a screening test were submitted in the NDA Safety Update. The purpose of the mannitol inhalation powder as a MTT which is different than the ARIDOL bronchial challenge test in these studies is to screen out patients who would not be tolerant of long term treatment with inhaled mannitol (Bronchitol™). The MTT is different from the Aridol bronchial challenge test in that the starting and/or total cumulative doses are different. The starting dose is 40 mg and the maximum cumulative dose is 400 mg. The Aridol bronchial challenge starting dose is 0 mg followed by 5mg with sequential increasing doses until the cumulative dose of 635 mg is given. For the MTT airway reactivity is also defined differently, a positive MTT is defined as a reduction in FEV1 of ≥ 20% where as a positive Aridol bronchial challenge test is defined as the dose of provoking stimulus causing a 15% reduction in FEV1 at any dose until the maximum dose had been given or a between-dose drop of ≥ 10% in FEV1 was

observed). As part of screening, the MTT could be administered up to 2 or 4 weeks prior to randomization to treatment regimen.

The compiled adverse events (AEs) that occurred during or after the screening MTT, but before receiving subsequent study medication was obtained from Phase 2 and 3 studies that were ongoing or completed as of the cut off date December 31, 2009. These studies include:

- Completed Phase 2, DPM-B-201, Bronchitol in Bronchiectasis Study, a Phase 2 Study to Determine the Safety and Efficacy of Inhaled Dry Powder Mannitol in Patients with Bronchiectasis
- Completed Phase 2, DPM-B-202, Mancot Study, a Phase 2 Randomised, Placebo-controlled, Blinded, Crossover Study to Determine the Safety and Efficacy of Dry Powder Mannitol in Bronchiectasis
- Completed Phase 2, DPM-B-301, A Phase 2 Multicenter, Randomised, Parallel, Placebo-Controlled, Double Blind Study to Investigate the Safety and Efficacy of Dry Powder Mannitol in the Symptomatic Treatment of Bronchiectasis
- Ongoing Phase 3, US 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
- Completed Phase 2, DPM-CF-201, A Phase 2 Study to Determine the Safety and Efficacy of Inhaled Dry Powder Mannitol in Cystic Fibrosis
- Completed Phase 2a, DPM-CF-202, A Phase 2a Randomised, Open Label, Dose Response Study to Determine the Optimum Dose of Dry Powder Mannitol Required to Generate Clinical Improvement In Patients with Cystic Fibrosis
- Completed Phase 2, 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
- Completed Phase 3, non-US Study DPM-CF-301, Long Term Administration of Inhaled Dry Powder Mannitol in Cystic Fibrosis – A Safety and Efficacy Study
- Ongoing Phase 3, US study DPM-CF-302, Long-term Administration of Inhaled Mannitol in Cystic Fibrosis

The data reviewed was for all subjects enrolled in Phase 3 trials, DPM-CF-301 and DPM-CF-302 but only for the Safety Population, defined as all patients who received at least one dose of randomized treatment, in Phase 2 trials (where are these studies coming from) DPM-CF-201, DPM-CF-202 and DPM-CF-203. The AE information is available only for the Safety Population in the bronchiectasis trials.

Reviewer's Comment:
As expected in patients with bronchiectasis or CF, who have significant pre-existing impairment of lung function, the AEs in the weeks following the MTT were on occasion more severe than would be expected in patients with suspected asthma.

Safety in Bronchiectasis Studies

At the request of the Division on January 14 and 19, 2010, the studies investigating the use of Bronchitol in patients with bronchiectasis used to compile AEs included: completed Studies DPM-B-201, DPM-B-202, and DPM-B-301 and the ongoing Study DPM-B-305 up to the cut off date of December 31, 2009. The AEs presented occurred during or after the screening MTT, but before receiving subsequent study medication, this could be up to 2 weeks post MTT. The AE information is available only for the Safety Population which included all patients who received at least one dose of post MTT study treatment in these trials. There were no AEs during this period in Studies DPM-B-201 and DPM-B-202. However, three AEs occurring during or after the MTT but prior to study treatment were reported for the 30 patients enrolled in Study DPM-B-305 as of December 31, 2009. These were: oxygen desaturation to 88%, hemoptysis, and condition aggravated. There have been no deaths in Pharmaxis sponsored studies in patients with bronchiectasis. Four SAEs were noted in 2 (1.1%) of 375 subjects prior to the start of randomized study treatment: infective exacerbation of bronchiectasis and 2 separate events of hemoptysis and condition aggravated. Both patients withdrew as a result of their SAEs. See table 1 to review the AEs with an incidence >1% compiled across the bronchiectasis studies.

Table 1

Incidence of AEs >1% Across Bronchiectasis Studies DPM-B-201, DPM-B-202, DPM-B-301, DPM-B-305 Prior to Commencement of Bronchitol Treatment but After MTT as of December 31, 2009

MedDRA term SOC	Preferred term	N = 375 %
Gastrointestinal	Diarrhea	1.1
General disorders, administration site conditions	Chest discomfort	1.3
	Condition aggravated	2.1
Infections and infestations	Lower respiratory tract infection	3.2
	Upper respiratory tract infection	1.6
	Nasopharyngitis	2.1
Musculoskeletal and connective tissue disorders	Back pain	1.9
Nervous system	Headache	7.7
	Sinus headache	1.6
Respiratory, thoracic and mediastinal disorders	Cough	1.3
	Hemoptysis	1.3
	Pharyngolaryngeal pain	1.6

Safety in Cystic Fibrosis Studies

The studies for the CF indication that were used to compile AEs up to the December 31 cut off date include: completed Phase 2 Studies DPM-CF-201, DPM-CF-202, and DPM-CF-203 and Phase 3 Study DPM-CF-301 and ongoing Phase 3 Study DPM-CF-302. Like the bronchiectasis safety data, the AEs presented for the CF safety data occurred during or after the screening MTT, but before receiving subsequent study medication. However, randomization was allowed up to 4 weeks post MTT screening. The AE information was available only for the Safety Population in Phase 2 Studies DPM-CF-201, DPM-CF-202, and DPM-CF-203 and Phase 3 Study DPM-CF-301 however for Study DPM-CF-302 the AEs were obtained from the All Enrolled Patients Population in these studies. The following AEs each occurred in at least 1% of subjects: cough (41 [4.7%]), condition aggravated (28 [3.2%]), headache (14 [1.6%]), and cystic fibrosis lung (28 [3.2%]). “Condition aggravated" and "cystic fibrosis lung" are the MedDRA coded preferred terms for an exacerbation of cystic fibrosis. There have been no deaths in Pharmaxis-sponsored studies involving administration of an MTT to a total of 879 cystic fibrosis patients.

Preliminary safety data for the ongoing CF study DPM-CF-302 as of December 31, 2009 included 341 enrolled subjects of which 26 (7.6%) had positive MTTs, 315 (92.4%) had negative MTTs, and 8 (2.3%) had incomplete screening MTTs. Two patients withdrew due to AEs during or following the MTT but prior to receiving randomized treatment due to cough and productive cough. Of note, a Phase 1 pharmacokinetic trial in 18 CF patients is still ongoing, Study DPM-PK-102. Five AEs were reported in four patients in this trial, including headache, cannula site pain, nausea, rotavirus infection, and vitamin D deficiency.

There have been no deaths in cystic fibrosis patients in Pharmaxis sponsored studies involving administration of an MTT to a total of 879 cystic fibrosis patients. The rate of SAEs following the MTT but prior to the start of randomized treatment has been low 24 (2.7%). The types and incidences of AEs occurring during MTT and before randomization to study medication have been consistent with that expected from the CF study population using a bronchoprovocation test. See table 2 for review of the AEs occurring with an incidence of greater than 1% during or after the MTT utilized in studies in investigating the use of Bronchitol™ in CF patients. Also of note, a Phase 1 pharmacokinetic trial in 18 CF patients continues in progress, Study DPM-PK-102. Five AEs were reported in four patients in this trial, including headache, cannula site pain, nausea, rotavirus infection, and vitamin D deficiency.

Table 2

Adverse Events With Incidence >1% During or After the MTT but Before Receiving Subsequent Medication for the Studies in Cystic Fibrosis Patients, All Enrolled Subjects or Safety Populations, as of December 31, 2009

MedDRA System Order Class	Preferred Term	DPM-CF-201 N = 49	DPM-CF-202 N=85	DPM-CF-203 N = 26	DPM-CF-301 N = 378	DPM-CF-302 N = 341
Blood and lymphatic system disorders	Lymphadenopathy		1.2			
Congenital, familial and genetic disorders	Cystic Fibrosis Lung			11.5		7.3
Eye disorders	Eye edema		1.2			
	Ocular hyperemia			3.8		
Gastrointestinal disorders	Abdominal pain		1.2			
	Diarrhea		1.2			0.9
	Dyspepsia		1.2			
	Nausea	4.1			1.1	
	Oral pain			3.8		
General disorders and administrative site conditions	Asthenia		1.2			
	Chest discomfort				1.6	
	Chest pain		1.2			
	Peripheral edema			3.8		
	Pyrexia	2				
Infections and infestations	Bronchitis					1.5
	Respiratory tract infection					1.2
	Upper respiratory tract infection				0.3	1.2
Injury, poisoning and procedural complications	Limb injury		2.4			
	Procedural vomiting			3.8		
Investigations	Bacteria sputum identified		1.2			
Musculoskeletal and connective tissue disorders	Musculoskeletal chest pain		1.2			
	Pain in extremity		1.2			
Nervous system disorders	Headache		3.5	3.8	0.3	0.8
Reproductive system and breast disorders	Breast mass		1.2			

	Penile pain		**1.2**			
Respiratory, thoracic and mediastinal disorders	**Bronchospasm**			**3.8**	**0.8**	
	Cough			**7.7**	**5**	**4.1**
	Epistaxis		**2.4**			
	Nasal congestion					**1.2**
	Nasal discomfort			**3.8**		
	Nasopharyngitis		**1.2**			
	Productive cough			**3.8**		**0.6**
	Wheezing				**1.3**	**0.6**
Skin and subcutaneous tissue disorders	**Allergic dermatitis**			**3.8**		
	Rash		**1.2**			

8 Postmarket Experience

Up to December 31, 2009, over 44,000 subjects and patients had been administered the mannitol inhalation powder to test for airway responsiveness, commercially and in clinical trials. This includes 1,046 subjects who received Aridol as part of the two Phase 3 studies sponsored by Pharmaxis, 3,607 additional subjects in the mannitol inhalation powder clinical development program, approximately 2,386 subjects in investigator sponsored clinical trials, and more than (b) (4) patients exposed to Aridol through commercial use outside of the U.S. A total of 246 pediatric subjects have been evaluated in Phase 3, well-controlled clinical trials of Aridol in patients 6 years of age or older. However, new safety data from Pharmaxis-sponsored studies in bronchiectasis and cystic fibrosis (CF) are available and have been summarized in this NDA Safety Update.

A total of 246 pediatric subjects have been 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 DPM-A-301 (Safety Population), and 36 subjects 6-11 years of age and 72 subjects 12-17 years old in Study DPM-A-305. In addition, 130 subjects ≥ 50 years of age and 25 subjects ≥ 65 years of age were exposed to ARIDOL in the non-US registration Study DPM-A-301. As well, up to the cut off date of Dec 31, 2009, (b) (4) patients had received Bronchitol™ under the Special Access Scheme in Australia, Named Patient Supply in New Zealand and the Compassionate Use Scheme in the United Kingdom, Argentina and Hong Kong.

The Mannitol inhalation powder has never been withdrawn from marketing outside the U.S. for safety reasons. As of December 31, 2009, it has been approved for use in identifying BHR in 19 countries, including Australia, South Korea, Malaysia, and Singapore, as well as the following European countries: Sweden, Denmark,

Netherlands, Ireland, Portugal, the United Kingdom, Greece, Finland, Norway, Germany, France, Spain, Italy, Belgium, and Switzerland.

9 Appendices

9.2 Labeling Recommendations

The original submission required substantive changes to the label which were addressed by Pharmaxis. The revised label included in the CR submission was not in the required PLR format and specific recommendations were sent to the Applicant on June 17, 2010. As well, significant changes were recommended to the Highlights of Prescribing Information, Warnings and Precautions, Adverse Reactions and Use in Specific Populations sections and minor changes were made to the Bronchial Challenge Test Instructions sheet which will be finalized with the next label review.

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/

ANYA C HARRY
07/27/2010

ANTHONY G DURMOWICZ
07/27/2010

SUMMARY REVIEW OF REGULATORY ACTION

Date:	December 23, 2009
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary and Allergy Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	22-368
Applicant Name:	Pharmaxis Ltd
Date of Submission:	February 27, 2009
PDUFA Goal Date:	December 27, 2009
Proprietary Name:	Aridol
Established Name:	Mannitol Inhalation Powder
Dosage form:	Inhalation powder in gelatin capsules, and inhaler device
Strength:	0, 5, 10, 20, and 40 mg gelatin capsules
Proposed Indications:	Assessment of bronchial hyperresponsiveness
Action:	Complete Response

1. Introduction

Pharmaxis Ltd submitted this 505(b)(1) application for use of Aridol (mannitol inhalation powder) in a single patient use inhaler as a single use product for the assessment of bronchial hyperresponsiveness in subjects 6 years of age and older. Assessment of bronchial hyperresponsiveness is usually done as an aid in the diagnosis of asthma. The proposed testing regimen is for a patient to serially inhale mannitol powder supplied 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 and the test is called positive when either 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 application is based on clinical efficacy and safety study. This review will provide an overview of the application with a focus on the clinical program.

2. Background

There is currently one other FDA approved drug for use for assessment bronchial hyperresponsiveness. The product is Provocholine (methacholine chloride), which was approved in 1986. A mannitol test for assessment of bronchial hyperresponsiveness is currently approved for marketing in at least 15 countries under the trade name Aridol or Osmohale. Mannitol inhaled on a chronic basis is also being studied to enhance mucociliary clearance in patients with bronchiectasis, cystic fibrosis, and chronic obstructive pulmonary disease (COPD).

3. Chemistry, Manufacturing, and Controls

The product is a single use test kit consisting of 5 strengths of mannitol: 0 mg, 5 mg, 10 mg, 20 mg, and 40 mg, in hard gelatin capsules, and a hand held dry powder inhaler. The inhaler is similar to other marketed single dose dry powder inhaler devices. To deliver a dose of mannitol, the health care provider will placed one capsule in the chamber of the inhaler device, press the push buttons to pierce the capsule on each end, and ask the patient to breathe in rapidly and deeply through the mouthpiece.

The drug substance is manufactured by (b) (4) and the finished product is manufactured by Pharmaxis Inc in Australia. The inhaler device is manufactured by (b) (4) Pharmaxis has submitted adequate stability data to support expiry of 12 months. All Drug Master Files (DMFs) associated with this application were also found to be acceptable.

The overall recommendation from Office of Compliance is a withhold recommendation due to some GMP violations seen in three testing sites

(b) (4)

Based on this recommendation from the Office of Compliance, CMC is recommending a Complete Response action pending an acceptable overall recommendation from the Office of Compliance for all manufacturing and testing sites listed in the application.

Based on limited data available in the application, Pharmaxis Inc. has not fully characterized foreign particulate matter and aerodynamic particle size distribution to set final release specifications. Post approval agreements are in place to address these two issues. These by themselves do not preclude approval and will be noted as agreements in the action letter.

4. Nonclinical Pharmacology and Toxicology

The nonclinical program for the application focused on the effect of inhaled mannitol on the respiratory system because the toxicological profile of mannitol for non-inhalation use has been well established. Mannitol is non-carcinogenic, non-genotoxic, and non-teratogenic; and it is considered to be generally safe when given orally. Pharmaxis submitted reports of up to 3 and 6 months inhalation toxicology studies in rats and dogs, respectively. The studies showed toxicities in the respiratory system, which included increased incidence of alveolitis and macrophages accumulation in the lung in rats, and laryngeal ulceration in dogs. However, these findings in animals had acceptable safety margins to support the proposed human dosage, hence, are not of concern for the intended Aridol use in humans.

5. Clinical Pharmacology and Biopharmaceutics

The clinical pharmacology program submitted was limited because Aridol will be used only as a single dose use product and not chronically, and mannitol is considered to be generally safe when given orally. This limited program is acceptable. Pharmaxis conducted a study in 18 healthy male subjects to compare the bioavailability of mannitol powder administered by inhalation route to mannitol administered intravenously and orally. The relative bioavailability of inhaled mannitol compared to orally administered mannitol was 96%.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of 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.

Table 1. Relevant clinical studies with indacaterol maleate

ID	Study type	Study duration	Patient Age, yr	Test groups	N (ITT)	Study Year#	Countries
301	crossover	Single test	6-83	Mannitol inhalation 4.5% saline inhalation	509	2004	Australia
305	crossover	Single test	6-50	Mannitol inhalation Methacholine inhalation Exercise challenge	654	2006	USA
# Year study subject enrollment ended							

b. Design and conduct of the studies

Study 301 was a multi-center, open-label, operator-blinded, randomized, crossover in design conducted in patients who either carried a definitive diagnosis of asthma or do not have asthma. After screening and randomization, study subjects underwent either a mannitol or 4.5% saline challenge test 1 week apart. Subjects were considered positive to either test if at least a 15% reduction in FEV1 from baseline occurred. 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. Safety assessments were limited to physical examination and recording of adverse events.

Study 305 was a multi-center, open-label, operator-blinded, randomized, crossover in design conducted in patients with symptoms suggestive of asthma but without a definitive diagnosis of asthma. During the course of the study subjects underwent three types of bronchial challenge tests utilizing exercise, Aridol, and methacholine. A positive

exercise test was defined as a decrease in FEV1 ≥ 10%, a positive Aridol test was defined by either a decrease in FEV1 by ≥ 15% from baseline or a between-dose fall in FEV1 ≥ 10%, and a positive methacholine response was defined as a decrease in FEV1 ≥ 20% after breathing methacholine at a concentration less than or equal to 16 mg/mL. The sensitivity and specificity of Aridol and methacholine challenges were assessed relative to exercise testing which served as a common comparator. The objectives of the study were to : (1) Estimate sensitivity and specificity of Aridol to detect bronchial hyperresponsiveness, as manifested by a positive exercise challenge, i.e., within a 10% margin of the point estimates. (2) Demonstrate that Aridol challenge test sensitivity for bronchla hyperresponsiveness is significantly greater than 60%; and (3) Demonstrate that Aridol specificity is significantly greater than that seen with methacholine to detect bronchial hyperresponsiveness. Safety assessments were limited to physical examination and recording of adverse events.

c. Efficacy findings and conclusions

The submitted clinical studies are adequate to support the use of Aridol for assessment of bronchial hyperresponsiveness in subjects 6 years of age and older.

Study 301 allowed estimation of sensitivity and specificity of Aridol with respect to physician diagnosis of asthma. The sensitivity of Aridol in subjects with a physician diagnosis of asthma was 58% [(54%, 62%, 95th CI)] compared to a sensitivity of the physician diagnosis in the same population of 97% [(95%, 98%, 95th CI)]. The specificity of Aridol in subjects without asthma was 95% [(90%, 99%, 95th CI)] compared to the physician diagnosis in the same population of 98% [(95%, 100%, 95th CI)]. Comparative data to 4.5% saline is of no utility because it is not recognized as a bronchial challenge test in the United States.

Study 305 was conducted by Pharmaxis at the Division's request to provide data in patients with symptoms suggestive of asthma but without a definitive diagnosis of asthma, because this is the population on which the test will be performed if approved. Pharmaxis included exercise challenge test as a common denominator to compare mannitol and methacholine because exercise challenge is a recognized test in patients with asthma. Results of the study are shown in Table 1 and Figure 1 below.

The sensitivity and specificity of Aridol and methacholine were comparable in this study population, and both were statistically significantly higher than 50% for the overall study population, a level of success that could be achieved by chance alone (Table 2). The fall in FEV1 associated with administration of increasing dose of mannitol is greater in the exercise positive subject that in the exercise negative subjects and this relationship is similar to that of methacholine (Figure 1). This analysis further supports efficacy.

Table 2. Comparison of sensitivity and specificity (calculated relative to exercise challenge) for Aridol and methacholine (Study 305)

Population	Treatment	Sensitivity % (95% CI)	Specificity % (95% CI)
Overall (n=419)	Aridol	58 (50, 65)	63 (57, 69)
	Methacholine	53 (46, 51)	68 (62, 73)
	Difference	5 (-4, 13)	-5 (-12, 3)
Age 6-11 years (n=36)	Aridol	67 (47, 87)	47 (21, 72)
	Methacholine	71 (52, 91)	33 (9, 57)
	Difference	-5 (-29, 20)	17 (-29, 62)
Age 12-17 years (n=70)	Aridol	55 (37, 72)	62 (46, 77)
	Methacholine	65 (48, 81)	64 (49, 79)
	Difference	-10 (32, 13)	-3 (-24, 19)

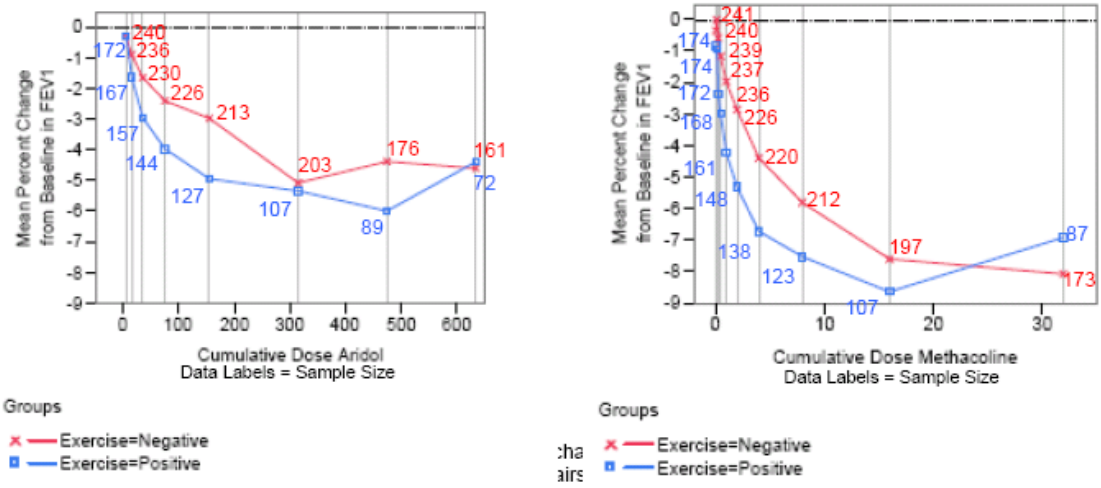

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Figure 1. Mean percent change from baseline in FEV1 with Aridol or methacholine by exercise stratum

8. Safety

a. Safety database

The safety assessment of Aridol is based on studies shown in Table 1. The primary safety database is comprised of the two pivotal studies that consist of 1082 unique subjects (577 females and 505 males). The safety database is adequate and typical for other similar applications.

b. Safety findings and conclusion

The safety data do not raise any obvious safety concern for Aridol that will preclude approval. The studies did not investigate the long-term effects of Aridol, or the effects of Aridol on blood chemistry, hematology, urinalysis, or ECG parameters. This is appropriate because mannitol is considered generally safe when given orally and the dose given by inhalation route for bronchial hyperresponsiveness test is much smaller considered the amount generally used orally.

There were no deaths in the clinical program. There was one serious adverse event of appendicitis in the program that was considered unrelated to the study drug. Common adverse events were related to the respiratory tract, which is expected of the drug and the study population. A major safety concern of bronchial hyperresponsiveness testing is large decrease in FEV1 during the test. Frequency of subjects with decreases in FEV1 ≥30% was 6% for Aridol compared to 12% for methacholine. Aridol will have a boxed warning regarding the potentials for bronchospasms and recommendations on safe administration of the test.

One limitation of the safety database is paucity of data in older subjects, an age group where co-morbid conditions such as cardiovascular and chronic respiratory disease other than asthma is common. Study 305 excluded enrollment of subjects 50 years of age and older due to physical demands of the exercise challenge. If the application was approved in this review cycle, this limitation could be addressed as a post-marketing study. Pharmaxis had agreed to conduct a required post-marketing study to assess the safety of Aridol in older subjects. Since the application will not be approved, Pharmaxis will be given the option of addressing this requirement in their response to the action.

c. REMS/RiskMAP

There are no substantial safety concern that would require REMS and RiskMAP. The major safety concern with Aridol is large decrease in FEV1 during the test, which will be reflected as a boxed warning. Aridol test will only be performed by trained professionals under the supervision of physicians familiar with all aspects of bronchial challenge test.

9. Advisory Committee Meeting

An advisory committee for Aridol was held on November 20, 2009. The Committee voted with an overall majority that the submitted data provide substantial and convincing evidence to support approval of Aridol for testing of bronchial hyperresponsiveness. The Committee commented that the data for ages 50 years and older was limited, but recommended that Aridol be made available for patients 6 years of age and older. The Committee commented on the low sensitivity of Aridol as well as methacholine for diagnosis of asthma, but noted that neither Aridol nor methacholine is a diagnostic test for asthma. The Committee stated that in some situations Aridol will provide useful information that will help clinicians make a diagnosis of asthma. The Committee did not want the Aridol test to be overused as a screening test for asthma.

10. Pediatric

Pharmaxis submitted a request for a waiver for studies for children below 6 years of age based on the inability of children below 6 years of age to perform serial spirometry reliably, which is required for the Aridol bronchial challenge test. The Division agreed that a waiver in children below 6 years of age is reasonable. The request was discussed at the PERC meeting on October 7, 2009, during which the committee also agreed that a waiver is appropriate.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two sites that enrolled large number of patients in study 305. Audit of the sites did not reveal any major irregularities. During review of this application the clinical team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. None of the investigators had significant equity interest in Pharmaxis.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Aridol was reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

Pharmaxis submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. The labeling contains a Boxed Warning for bronchospasm. The label was reviewed by various disciplines of this Division, DRISK, DMEPA, SEALD, and by DDMAC. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to health care providers. The Division and Pharmaxis have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, OBP, and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

There is no patient labeling and medication guide. Aridol test will only be performed by trained professionals under the supervision of physicians familiar with all aspects of bronchial challenge test.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Pharmaxis has submitted adequate data to support efficacy and safety of Aridol in a single patient use inhaler as a single use product for the assessment of bronchial

hyperresponsiveness in subjects 6 years of age and older. However, the application cannot be approved because the Office of Compliance has made a withhold recommendation due to violations seen in the testing sites (see section 3 above). Based on this recommendation from the Office of Compliance, CMC is recommending a Complete Response action pending an acceptable overall recommendation from the Office of Compliance for all manufacturing sties listed in the application. Therefore, the action on this application will be Complete Response.

b. Risk Benefit Assessment

An overall risk and benefit assessment of this application cannot be made because as noted in section 3 and section 13a the Office of Compliance has identified violations in the drug product testing site. This deficiency will preclude approval. From a pure clinical standpoint, the submitted data otherwise would have supported approval of Aridol for the assessment of bronchial hyperresponsiveness in subjects 6 years of age and older. The submitted clinical studies demonstrate that the proposed serial increasing dose of Aridol provides acceptable data as a test of bronchial hyperresponsiveness. The safety profile of Aridol as a single use product is also acceptable. The adverse event profile was predictable and not of concern. The major safety concern with Aridol is acute bronchospasm during the test, which will be reflected as a boxed warning. Aridol test will only be performed by trained professionals under the supervision of physicians familiar with all aspects of bronchial challenge test.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

Pharmaxis had agreed to conduct a required post-marketing study to assess the safety of Aridol in subjects 50 years of age and older as discussed in section 8b above. Since the application will not be approved in this review cycle, Pharmaxis will be given the option of addressing this requirement in their response to the action.

Pharmaxis has not fully characterized foreign particulate matter and aerodynamic particle size distribution to set final release specification. Post approval agreements are in place to address these two issues. These by thmeselves do not preclude approval and will be noted in the action letter.

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/

BADRUL A CHOWDHURY
12/23/2009

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22,368
Priority or Standard	Standard
Submit Date(s)	February 27, 2009
Received Date(s)	February 27, 2009
PDUFA Goal Date	December 27, 2009
Division / Office	DPAP
Reviewer Name(s)	Anya C. Harry
Review Completion Date	November 18, 2009
Established Name	Mannitol
(Proposed) Trade Name	Aridol
Therapeutic Class	Sugar alcohol
Applicant	Pharmaxis Ltd.
Formulation(s)	Dry powder inhalation
Dosing Regimen	Challenge increasing concentration
Indication(s)	Assessment of bronchial hyperresponsiveness to aid in the diagnosis of Patients ≥ 6 years old with symptoms of or suggestive of asthma
Intended Population(s)	Patients with signs or symptoms suggestive of asthma

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, the data submitted in New Drug Application (NDA) 22,368 for the diagnostic test, Aridol to assess for bronchial hyperresponsiveness (BHR) provides support for **approval** with revisions to the proposed label. The adequate and well-controlled clinical studies demonstrated that the proposed serial increasing doses of inhaled mannitol dry powder administered as a single use diagnostic challenge test provides acceptable statistical data to aid in the diagnosis of bronchial hyperresponsiveness. The primary assessment of the diagnostic efficacy was based on commonly used statistical endpoints of sensitivity and specificity with corresponding 95% confidence intervals. The statistical analyses were carried out in comparison to other diagnostic challenge tests that assess bronchial hyperreactivity, specifically using hypertonic saline, Provocholine (methacholine chloride) and exercise and all were evaluated against physician diagnosis.
As a single use diagnostic test, the safety profile of mannitol dry powder for inhalation is acceptable. In the clinical studies conducted for this application, mannitol dry powder demonstrated a predictable adverse event profile consistent with what is observed with other bronchoprovocation tests (decrease in pulmonary function) that was reversible and arguably, better than that of the approved bronchoprovocation product, Provocholine. The safety of mannitol dry powder is also supported by the Agency's previous finding of generally recognized as safe (GRAS) for mannitol administered orally or intravenously.

Of note is that subjects greater than 50 years of age were not enrolled in the pivotal clinical trial. The lack of data for subjects > 50 years of age will be a discussion point at a Pulmonary and Allergy Advisory Committee meeting on November 20, 2009. The committee will discuss whether safety and efficacy in this population would be expected to be different than younger subjects and, if so, what additional data would be necessary to support approval.

1.2 Risk Benefit Assessment

The risk benefit assessment supports approval of the mannitol bronchial challenge test (MBCT) for the assessment of BHR.

The efficacy results provided primarily in the pivotal Study DPM-A-305 and selected data from the supportive Study DPM-A-301 support the efficacy of the MBCT. The sensitivity and specificity of the MBCT relative to a positive exercise challenge test are 58% (50%, 65%) and 63% (57%, 69%) respectively (95% confidence intervals in parentheses). While these results are not robust they may be valuable in aiding a

physician in the determination of airway hyperreactivity as part of a comprehensive clinical diagnostic evaluation for asthma and are very similar to the results obtained with the approved bronchoprovocation test product, Provocholine.

The safety results also support a beneficial risk benefit assessment. There were no deaths and only one serious adverse event (appendicitis) in the program. Common adverse events (cough, head ache, pharyngolaryngeal pain, nausea were self limited. The most concerning events for a bronchoprovocation test is severe bronchoconstriction. In this regard the MBCT had had a decreased incidence (one third to one fourth) of excessive decreases in pulmonary function (FEV1) than that for the approved bronchoprovocation drug, Provocholine. 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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Mannitol is categorized as GRAS when administered orally or intravenously and has demonstrated an acceptable safety profile when inhaled for use as a bronchoprovocation test. Given the relatively low doses utilized in this single use diagnostic test, the safety profile demonstrated in this program, and the fact that it will be administered by a trained health care professional at a site equipped to deal with rapid acute decreases in pulmonary function, there is no recommendation for postmarket risk evaluation and mitigation strategies (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

Pending discussion of the adequacy of the data to support the use of the MBCT in subjects greater than 50 years of age, a post-marketing commitment may be forthcoming to further study the safety of the MBCT in this older population.

2 Introduction and Regulatory Background

2.1 Product Information

The established name for the proposed product is mannitol and the proposed trade name is Aridol. The abbreviation “MBCT” will generally be used in this review to refer to the product.

D-Mannitol is a well known, naturally occurring sugar alcohol found in most vegetables. The MBCT, developed as a diagnostic agent in this NDA consists of a series of capsules containing increasing doses of mannitol powder for inhalation. The

test kit includes the capsules in blister packaging and a dry powder inhaler (Osmohaler, (b) (4)). The MBCT is administered by sequential inhalations of 0, 5, 10, 20, 40, 80, 160, 160, 160 mg of dry powder mannitol using the dry powder inhaler contained in hard gelatin capsules through a single dose dry powder inhaler. The capsules for inhalation contain 0, 5, 10, 20, and 40 mg of mannitol. Therefore, doses of 80 and 160 mg are delivered by rapidly inhaling the contents of two and four 40 mg capsules, respectively. 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 proposed indication for the MBCT is for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, Provocholine® (methacholine chloride, NDA 19-193) is the only drug approved in the United States (October 31, 1986) for the indication of “diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma”.

2.3 Availability of Proposed Active Ingredient in the United States

The MBCT is currently not marketed in the United States. Mannitol administered either intravenously or orally is currently marketed for multiple medical indications including as a diuretic and laxative. It is also used as an excipient in many products and is available as a dietary supplement.

2.4 Important Safety Issues With Consideration to Related Drugs

The principle safety issue for both the MBCT and the approved bronchoprovocation agent, Provocholine® (methacholine chloride) is the potential for bronchoconstriction in patients with underlying bronchial hyperreactivity. The Provocholine® label 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 warning also contains the need of emergency equipment and medication to be immediately available to treat acute respiratory distress.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A Pre-IND meeting (IND# 70277) was held July 19, 2004 during which Study 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 (Study 301) 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 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. The proposed study protocol indicated that the primary efficacy analysis will include the subset of randomized subjects who satisfy all inclusion and exclusion criteria and complete both challenges. We stated that we would also consider the efficacy results of the intent-to-treat (ITT) group, which includes all patients who were randomized. For subjects in the ITT group with missing efficacy data, a worst-case approach would be used for imputation of their results. If the diagnosis according to the mannitol (or comparator) challenge is not available for this analysis, that subject should be considered to have been incorrectly diagnosed by the mannitol (or comparator) test.

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.

2.6 Other Relevant Background Information

The mannitol bronchial challenge test 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. It is approved for use in adults and children ≥ 6 years in Australia and South Korea, and currently for adults only in Europe. Mannitol

inhaled on a chronic basis is also being studied for other indications (enhance mucociliary clearance in patients with bronchiectasis, cystic fibrosis, and COPD).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA is an electronic submission and is adequately organized to permit clinical review.

3.2 Compliance with Good Clinical Practices

The Applicant states that no debarred investigators participated in the study, and all studies were conducted under Good Clinical Practices.

The Division requested audits by the Division of Scientific Investigations (DSI) for this NDA since MBCT is proposed for a relatively novel indication and the data for efficacy are is based on the results of a single study (305).

3.3 Financial Disclosures

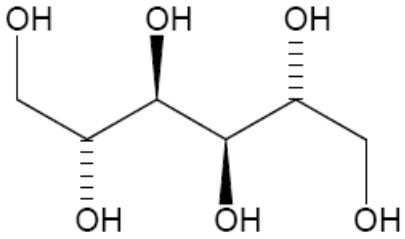
The Applicant certifies that it did not enter into financial arrangements with any investigator whereby the value of compensation could be affected by the outcome of the study (Category 1), that no investigator received significant payments (Category 2), that none of the investigators disclosed a proprietary interest in the product (Category 3), or possessed a significant equity interest in the Applicant (Category 4) as defined in 21 CFR 54.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

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. There are three morphic forms of mannitol denoted as α, β, δ-mannitol. The structural formula is depicted in Figure 1 below:

Figure 1 : Mannitol Molecular Structure



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 and a hand held dry powder inhaler, the RS01 Inhaler Model 7 device. No excipients are included in the contents of the capsules (the 0 mg capsules are empty). The device is (b) (4) marketed outside the US for many years. It appears physically and functions similarly to other devices used as the delivery devices for other approved single-dose dry powder medications such as (b) (4) Evaluation of the robustness of the device included dropping the inhalers under specified orientations onto a hard surface and inspecting for damage (b) (4) (b) (4) (b) (4) all damage sustained was immediately recognizable, and it will be primarily handled by a health professional trained in its use, it is acceptable.

A review by Dr Luqi Pei of the safety of impurities, extractables and leachables in the mannitol powder capsules did not reveal any concerns.

4.2 Clinical Microbiology

This section is not applicable for this NDA as the drug is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

Mannitol is used as a nutrient and/or dietary supplement and as an ingredient in numerous drug products. As a dietary supplement, mannitol is considered generally recognized as safe [GRAS, 21CFR§582.5470].

The mannitol toxicology by non-inhalation use is well understood. Mannitol is non-mutagenic, non-carcinogenic and non-teratogenic. The National Toxicology Program evaluated carcinogenicity and mutagenicity of D-mannitol. It concluded that F344/N rats

and B6C3F1 mice fed with up to 5% D-mannitol in diet for 103 weeks did not reveal any evidence of tumorigenicity. Mannitol was non-genotoxic in a bacterial mutation assay, an in vitro mouse lymphoma cell assay, an in vivo mouse micronucleus assay and other assays. The Joint FAO/WHO Expert Committee on Food Additives Monograph on Mannitol considered D-mannitol non-teratogenic.

The application has adequately evaluated the toxicity profile of inhaled mannitol. 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. For additional pharmacology/toxicology information, see the Pharmacology/Toxicology review by Dr. Luqi Pei.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The MBCT is to be used as a tool to identify and quantify BHR. The presence of BHR is a clinical finding in several pulmonary diseases but appears to be most pronounced in those with the diagnosis of asthma. The MBCT is postulated to be an “indirect” test of BHR. Indirect agents are believed to cause bronchoconstriction by acting on cells other than smooth muscle cells such as inflammatory cells, epithelial cells, vascular smooth muscle cells and nerves. Stimulation of these cells leads to release of mediators or neurotransmitters that provoke smooth muscle contraction. Agents such as mannitol are postulated to increase the osmolarity of the airway surface, resulting in the release of mediators such as histamine, prostaglandins and leukotrienes. These mediators then act via specific receptors 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).

4.4.2 Pharmacodynamics

Please refer to the pharmacodynamic and pharmacokinetic data reviewed by Dr. Ying Fan. As described above, upon inhalation, mannitol induces an increase in osmolarity in the airways which is associated with the release of mediators that lead to bronchoconstriction. When the mediators bind to their receptors on bronchial smooth muscle this leads to contraction with resulting airway narrowing. This airway response is

more pronounced in those with BHR. The safety concerns associated with bronchoconstriction are discussed in further detail in Section 7.3.5.

4.4.3 Pharmacokinetics

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 to provide information on the fate of the drug in the lungs after inhalation. Thus, a PK and BA study (study DPM-PK-101) was conducted to determine: 1) the absolute BA of mannitol powder for inhalation compared to mannitol administered intravenously; 2) the relative bioavailability of mannitol powder for inhalation compared to mannitol administered orally; 3) the pharmacokinetic parameters of systemically available mannitol after inhalation.

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 (5 ml of Osmitrol 10% solution), and mannitol 500 mg (5 ml of Osmitrol intravenous infusion 10%) 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. 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.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant has conducted 8 clinical studies with mannitol. These studies include one pharmacokinetic trial in healthy volunteers, one device usability study, 2 studies in subjects with asthma, symptoms suggestive of asthma, or subjects without asthma, and 4 studies in patients with bronchiectasis, cystic fibrosis, or COPD in which mannitol was inhaled chronically as an agent to enhance mucous clearance.

To support the efficacy and safety of the MBCT for the proposed indication, the Applicant is relying primarily on the results of Study 305 in subjects with asthma-like symptoms but without a clinical diagnosis of asthma. Supportive data were supplied

from Study 301, conducted in subjects with a definite diagnosis of asthma and subjects definitely without asthma. This study was used for approval of the mannitol bronchial challenge test (Aridol, Osmohale) in at least 15 countries outside the United States but is primarily useful for supplying additional safety data in subjects known to have asthma.

The table below provides the pivotal and supportive clinical studies to support the application. Studies that have been conducted for the chronic use indications (cystic fibrosis, bronchiectasis, COPD) are also included for completeness but are not directly relevant to this application.

Table 1 Mannitol Challenge Test Clinical Development Program

Type of Study	Identifier	Treatment Groups	Objective	Design	Number of Subjects	Duration of Treatment
Human PK Study						
PK	DPM-PK-101	No asthma	Bioavailability of mannitol inhaled powder vs. i.v.	OL, R, three-way crossover	15	24 hours
Device Usability Study						
Device usability	OSM-401	Asthma, No asthma	Inspiratory flow rates/volumes using Osmohaler	Open, observational	34	24 hours
Phase 3 Pivotal Study						
Efficacy and Safety	DPM-A-305	Asthma-like symptoms, no clinical diagnosis	Estimate sensitivity, specificity of mannitol to detect EIB as manifestation of BHR	MC, OL, R, crossover	509	varies
Phase 3 Supportive Study						
Efficacy and Safety	DPM-A-301	Asthma, No asthma	Safety profile and sensitivity, specificity of mannitol BCT vs. 4.5% saline	MC, OL, R, crossover	654	3 weeks
Studies Conducted for Chronic Use Indications						
Efficacy and Safety	DMP-B-201/202	Bronchiectasis	Data from both studies combined to assess changes in SGRQ, lung function	Phase 2, MC, R, PC, DB, crossover	60	2 weeks
Efficacy and Safety	DPM-B-301	Non-CF bronchiectasis	Assess effects of inhaled mannitol on QOL, and mucous clearance	DB, R, PC, P	440	Phase 1: 13 weeks Phase 2: 52 weeks
Efficacy and Safety	DPM-COPD-201	Mild, moderate COPD	Compare effect of 12 wks treatment ICS on FEV1 between mannitol BCT + and – COPD pts	MC, OL	79	12 weeks
Efficacy	DPM-CF-201	CF	Prediction of treatment response to ICS by mannitol BCT	R, MC, DB, C, crossover	39	Two weeks

Source: Adapted from Table 5.2.1 in CTD Module 5.2

5.2 Review Strategy

The two Phase 3 studies (DPM-A-305 and DPM-A-301) provide the primary safety and efficacy data for the application. DPM-A-305 is the pivotal study whereas DPM-A-301 is a non-US registration, supportive study. Both are presented and discussed in detail in Section 5.3 below. Both studies included bronchial challenge tests as active comparators, methacholine in Study 305, and hypertonic saline in Study 301. Because the safety and efficacy of the hypertonic saline bronchial challenge test has not been assessed in the United States by FDA, the presentation of the efficacy data for Study 301 will focus on the sensitivity and specificity of the MBCT challenge relative to a physician's diagnosis of asthma. Reviews of the studies are based primarily on the original protocols and statistical analysis plans. All summary data tables submitted by the Applicant as well as relevant Case Report Forms (CRFs) were also reviewed. Meetings with the statistical team were held to review the analyses performed by the Applicant as well as the reanalyses performed by the statistics review team.

5.3 Discussion of Individual Studies/Clinical Trials

This section presents an overview of efficacy data from pivotal Study 305 and supportive non-IND Study 301 that was used for approval in Australia and other countries. A detailed discussion of safety results can be found separately in the safety section.

While the general objectives of Studies 301 and 305 were similar; to examine the sensitivity and specificity of the MBCT compared to an approved drug active comparator as a bronchoprovocation agent to assess BHR, both the study populations and comparator drugs were different between the two studies. The subjects in Study 301 had either a clear diagnosis of asthma or have never had a diagnosis of asthma. This design using distinct populations of symptomatic subjects with asthma and subjects without asthma allowed the quantitation of the sensitivity and specificity of the mannitol challenge in relation to hypertonic saline (not approved in the United States as a bronchial challenge agent) and allowed for evaluation of the suitability and validity of the MBCT to aid in the diagnosis of patients with BHR in groups of well-defined subjects with and without asthma. However, Study 301 was insufficient to establish the efficacy of the MBCT for the proposed indication because the sensitivity and specificity of the MBCT in a group of subjects with a known diagnosis of asthma 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 it is the latter group that is likely to receive the diagnostic test, examination of the sensitivity and specificity in that type of a patient group was needed. Therefore, Study 301 provides safety data and provides data on whether the MBCT can differentiate between patients with asthma and normal individuals without asthma. Study 305 was therefore conducted to establish the sensitivity and specificity of the MBCT compared to methacholine and exercise

challenge test (ECT) in assessing BHR in a group of subjects with symptoms suggestive of asthma but without a definitive diagnosis of asthma. Evaluation of this population was expected to more accurately represent the clinical utility and reproducibility of the MBCT than using a population of patients with known asthma.

Reviewer's Comment:
As per discussions during both PIND and Pre-NDA meetings, it was necessary to have some standard by which to measure the response to mannitol. Methacholine is the standard for bronchial challenge test (BCT) in the US and there is a great deal of clinical experience with its use. By comparing the response after mannitol to the response after methacholine and the clinical diagnosis of asthma, the Applicant would accomplish two goals. They would provide comparative sensitivity and specificity for mannitol and methacholine, and they could also demonstrate the superior correlation between mannitol responsiveness and the diagnosis of asthma as compared to methacholine responsiveness and the diagnosis of asthma. There was also a need to calculate the sensitivity and specificity of mannitol and methacholine relative to some common standard for which the population of patients displaying increased BHR to exercise was utilized.

5.3.1 Study DPM-A-305

Title
A Phase 3 Multicenter Study to Demonstrate the Sensitivity and Specificity of Aridol (Mannitol) Challenge as Compared with Methacholine Challenge to Predict Bronchial Hyperresponsiveness as Manifested by a Positive Exercise Challenge in Subjects Presenting with Signs and Symptoms Suggestive of Asthma but without a Definitive Diagnosis.

Study design and conduct
This was a multicenter, randomized, blinded, Phase 3 study in subjects with symptoms of or suggestive of asthma but without a definitive diagnosis of asthma. 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 either 12 mg/mL (defined in the statistical analysis plan (SAP)) or 16 mg/mL (ATS guidelines)) and the MBCT (with positivity defined as the dose of provoking stimulus causing a 15% fall in FEV1 at any dose 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 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.

The secondary objectives were:

1. To estimate the sensitivity, specificity, and positive and negative predictive values of the MBCT and methacholine with respect to EIB as a manifestation of BHR
2. To estimate the sensitivity, specificity, and positive and negative predictive values decision theory properties of the MBCT and methacholine with respect to physician-diagnosed asthma
3. To compare correlations among the MBCT, methacholine, and exercise challenges when PD15FEV1, PC20FEV1, and fall in FEV1 after exercise (largest fall in FEV1 and average fall in FEV1 for the two exercise challenges), respectively, are compared.

The study was conducted at 25 sites across the United States with a study period from November 15, 2005 to August 31, 2006. The study duration for each participant ranged from 5 to 20 days which included 5 scheduled visits.

Inclusion Criteria:

- Complete informed consent
- Ages 6-50 years, male and female
- On effective birth control if female of childbearing potential
- Have current symptoms suggestive of asthma according to the National Institutes of Health (NIH) Questionnaire but without a definitive clinician diagnosis or an exclusion of the diagnosis of asthma or had at least Step 1 symptoms according to the National Asthma Education and Prevention Program (NAEPPII) asthma severity grading
- Have not used medications 6 weeks before the Screening Visit or during the study that would interfere with bronchial provocation challenge testing (including but not limited to corticosteroid use within 4 weeks of the Screening Visit)
- Have a skin test negative to seasonal and perennial allergens that were present in the environment during the time that the subject was enrolled in the study, or if the skin test positive to these aeroallergens, the subject must not have reported worsening of symptoms when exposed to these aeroallergens during the time that the subject was participating in the study
- Have FEV1≥ 70% of the predicted value at Screening Visit baseline and remained ≥ 70% of the predicted value and within 15% of the Screening Visit baseline value at all subsequent visit baselines

Exclusion Criteria:

- Currently using a cholinesterase-inhibitor medication
- Upper or lower respiratory tract infection within the previous 4 weeks
- Had a medical condition that in the opinion of the Investigator would impair the ability of the subject to participate
- Diagnosis of aortic or cerebral aneurysm, cirrhosis or portal hypertension, cardiac ischemia, malignant arrhythmias, uncontrolled hypertension, orthopedic limitations
- Had other chronic restrictive or obstructive pulmonary diseases (cystic fibrosis, COPD, bronchiectasis, chronic bronchitis, emphysema, tuberculosis, pulmonary carcinoma, pulmonary fibrosis, pulmonary hypertension, hypercapnia)
- Recent major surgery
- Recent cataract surgery
- History of heart disease that would increase the risk of performing exercise, methacholine or MBCT
- Smoked within the past year (average > 1 cigarette per week), or had a ≥ 10 pack year smoking history
- Inability to perform spirometry of acceptable quality
- Intolerant to MBCT, methacholine or albuterol
- Pregnant or lactating
- Participated in any other investigative drug study parallel to, or within 4 weeks of study entry
- BMI ≥ 35
- Been diagnosed at Screening Visit (Visit 1) as definitively having or not having asthma; patients that were not to continue in the study included those given the following diagnosis: asthma is extremely likely or definite (95 to 100% likelihood) or asthma is very unlikely or excluded (0 to < 5% likelihood)
- Previously received a MBCT
- Clinically significant abnormal CXR or ECG

After review of the patient eligibility, an initial assessment for asthma and severity was evaluated by a respiratory physician using the NIH Questionnaire and the NAEPP II grading, respectively. Based on the screening assessments conducted during Visit 1, the physician assigned a likelihood of a diagnosis of asthma on to one of six categories: asthma is extremely likely or definite (95%-100% likelihood); asthma is very likely (72.5 to <95%); asthma is probable (50 to <72.5%); asthma is possible (27.5 to <50%); asthma is unlikely but cannot be excluded (5 to 27.5%); and asthma is very unlikely (0-<5%). The categories of extremely likely and very unlikely were excluded from the study. Also performed during Visit 1 was beta agonist reversibility testing according to the ATS criteria for a significant response of ≥ 12% improvement in FEV1 and an absolute improvement of ≥ 200 mL.

Subjects were to undergo an exercise challenge test for diagnosis of exercise induced bronchospasm at both visits 2 and 3. Visit 2 was to occur 1 to 4 days after the screening visit and visit 3 was to occur 1 to 4 days after visit 2, each at a recommended starting time within ±2 hours of the starting time of the screening visit. Subjects with a positive outcome for at least one of two exercise challenge tests were considered "exercise positive" for purposes of the standard of truth for this study and were therefore to be used in the calculation of the sensitivities of interest. Subjects with a negative outcome on both exercise challenge tests were considered "exercise negative" for purposes of the standard of truth for this study and were therefore to be used in the calculation of specificities of interest.

Exercise Challenge: Exercise was performed by running on a motorized treadmill while breathing medical grade dry air (20-25ºC) from a Douglas Bag and spirometry assessment was in accordance with American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines. Briefly, exercise was ramped up over 2 minutes to 80-90% predicted heart rate (220 minus age) and then sustained for 6 minutes. The highest FEV1 was measured before and at 5, 10, 15, and 30 minutes after exercise. The % fall in FEV1 was calculated by subtracting the lowest value recorded after exercise (best of two acceptable attempts at each time point) from the value measured immediately before exercise and expressing it as a percentage of the pre exercise value. A subject was designated as having a positive exercise challenge if there was a fall in FEV1 of at least 10% on at least 1 of 2 tests.

The MBCT and methacholine challenge were each to be administered at visit 4 or 5. Visit 4 was to occur 1 to 4 days after the visit 3 and visit 5 was to occur 1 to 4 days after visit 4, each at a recommended starting time within ±2 hours of the starting time of the screening visit. Randomizations of the order of administration of the MBCT and methacholine challenge test were 1:1 and were completed separately for the exercise positive and exercise negative groups. To maintain blinding, the MBCT and methacholine challenges were performed by personnel separate from the screening assessment team and respiratory physician. The results of the challenge tests were not disclosed to the assessment team or the respiratory physician.

MBCT: The MBCT was administered as a diagnostic test for BHR. The total dose administered ranged from 0 mg to 635 mg, depending on airway response. MBCT was given sequentially as follows: 0 mg, 5 mg, 10 mg, 20 mg, 40 mg, 80 mg, 160 mg, 160 mg, and 160 mg (Table 2). At the end of 60 seconds post inhalation, the FEV1 was measured in duplicate. Each dose followed the previous dose until the FEV1 fell by ≥ 15% from baseline, a between-dose fall in FEV1 was ≥ 10%, or the cumulative dose of 635 mg had been administered. The provoking dose of mannitol to induce the 15% fall in FEV1 (i.e., PD15) was calculated by linear interpolation from the curve relating the percent fall in FEV1 from the post 0 mg capsule baseline value for FEV1 to the cumulative dose of mannitol delivered (e.g., 5 mg, 15, mg, 35 mg, 75 mg, 155 mg, 315 mg, 475 mg, or 635 mg). For purposes of this study, MBCT positivity was defined as

the PD15 being achieved by the maximum dose or a between-dose drop of ≥ 10% in FEV1 was observed.

Table 2 Dose Steps for the Mannitol Challenge Test

Dose #	Dose (mg)	Cumulative dose (mg)	Capsules per dose
1	0	0	1
2	5	5	1
3	10	15	1
4	20	35	1
5	40	75	1
6	80	155	2x40 mg
7	160	315	4x40 mg
8	160	475	4x40 mg
9	160	635	4x40 mg

Source: Section 9.4.5, Clinical Study Report, DPM-A-305

Methacholine Challenge: The methacholine challenge was administered as a diagnostic test for BHR. Methacholine was given sequentially as follows: 0.0312 mg/mL, 0.0625 mg/mL, 0.125 mg/mL, 0.25 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 4 mg/mL, 8 mg/mL, and 16 mg/mL. Each dose followed the previous dose until the FEV1 fell by ≥ 20% from baseline or until all doses had been administered. The provoking concentration of methacholine to induce the 20% fall in FEV1 (i.e., PC20) was calculated by linear interpolation from the curve relating the percent fall in FEV1 from the baseline value for FEV1 to the cumulative dose of methacholine delivered. For purposes of this study, methacholine positivity was defined as the PC20 being less than or equal to either 12 mg/mL (SAP defined) or 16 mg/mL (ATS guidelines)).

Also at visit 5, a respiratory physician, a clinician, diagnosed the subjects (by examining the subject and reviewing the subject's study record including any relevant diagnostic information available at the time of this visit except the methacholine or MBCT). Subjects were classified into one of the following categories:

- asthma is extremely likely or definite (95 to 100% likelihood)
- asthma is very likely (72.5 to <95% likelihood)
- asthma is probable (50 to 72.5% likelihood)
- asthma is possible (27.5 to <50% likelihood)
- asthma is unlikely but cannot be excluded (5 to <27.5% likelihood)
- asthma is very unlikely or excluded (0 to <5% likelihood)

The Applicant chose to analyze results for both a 12 mg/mL and 16 mg/mL cutoff dose of methacholine as the positive level. According to the ATS Guidelines for Methacholine and Exercise Challenge Testing-1999, Table 3 shows the categorization of BHR as relates to the dose of methacholine causing a 20% drop in FEV1.

Table 3 Categorization of Bronchial Responsiveness

PC 20 (mg/ml)	Interpretation*
> 16	Normal bronchial responsiveness
4- 16	Borderline BHR
1- 4	Mild (positive test)
< 1	Moderate to severe BHR

*Before applying this interpretation scheme, the following must be true: 1. baseline airway obstruction is absent; 2). Spirometry quality is good; 3). There is substantial post-challenge FEV1 recovery.
[Source: ATS Guidelines for Methacholine and Exercise Challenge Testing, Crapo RO et al., Am J Respir Crit Care Med, 2000: 161; 309-29.]

Statistical Considerations:

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. The primary efficacy analysis was to be conducted in both the ITT and PP groups. 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.

The primary efficacy analysis specified in the statistical analysis plan was to calculate 95% confidence intervals for the sensitivities and specificities of the MBCT and methacholine challenges using normal approximations for the binomial distribution. In addition, 95% confidence intervals for the differences between the MBCT and methacholine in sensitivity and specificity were to be calculated using normal-approximations for the binomial distribution.

Each of the three efficacy objectives stated above for this study would then have been considered successfully achieved if the following criteria were met:

1. Both the lower and upper confidence interval limits for the sensitivity and specificity of MBCT challenge should be within a 10% points of the point estimates
2. The lower confidence interval limit for the MBCT challenge sensitivity should be greater than 60%
3. The lower confidence interval limit for the difference in MBCT challenge specificity and the methacholine challenge specificity is greater than zero.

The statistical analysis plan noted that if the distributions are visibly non-normal, then tests for the primary objectives would be conducted through Markov Chain Monte Carlo

(MCMC) simulation. The MCMC simulation was conducted by the Applicant rather than using the binomial method. The FDA statistical team reanalyzed the data using the standard binomial method and that analysis represents the data on which FDA conclusions on efficacy are based. No correction for multiplicity was planned for the three primary objectives as success with all three was to be required for successful demonstration of the efficacy of the MBCT.

Safety Assessments:
The primary safety evaluations included assessments of ECGs, adverse events, vital signs and spirometry. General laboratory data were not obtained, as mannitol is generally regarded as safe as an excipient in the United States for food substances at doses of up to 20 g/day and the exposure to mannitol in this trial was much lower than these limits. Several safety analyses were also conducted post hoc, these include: adverse events in the pediatric population, analysis of spirometry findings (FEV1, FVC, and FEF25-75) for each of the exercise challenges; maximum fall and percentage fall in FEV1 for subjects with positive challenges and cough during mannitol challenges.

Study Results

Demographics:
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 whose exercise challenges were both negative but were considered inadequate. As the protocol had originally defined the ITT population as simply 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. The Applicant also defined an ITT population excluding these 29 subjects from the 420 in the ITT plus population leaving 391 (90%) subjects. An additional 16 subjects are excluded from the ITT group to create the per protocol (PP) population with 375 (86%) subjects.

The PP population included 111 pediatric subjects ages range from 6 to 17 years old and 264 adults age ranges from 18 to 50 years old; 53.6% were female, 74.1% were Caucasian, 9.4% Hispanic and 9.2% Black. The mean age was 24.9 years and the mean body mass index (BMI) was 24.4. 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 ≥ 12% and 200 mL) after administration of a short-acting bronchodilator.

Efficacy Analyses:

The analyses necessary to address the primary efficacy objectives for this study are included in Table 4. 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. More detailed analyses can be found in the statistical summary briefing document.

The results presented in Table 4 are primarily derived from FDA statistical reviewer analyses using the ITT plus population as described above. 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 the MCMC simulation (in lieu of the more traditional use of the normal approximation methods) while FDA statistical analyses used the more traditional normal approximation methods. 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. In addition, with the large size of this study, the normality assumption is less critical and given the traditional wide-spread use of the normal approximation methods and the fact that these were the primary methods specified for the efficacy analysis in the protocol and statistical analysis plan, the normal approximation methods are preferred by FDA. Of note is that the qualitative conclusions resulting from the two approaches are largely the same.

Table 4 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%)
ITT plus	12	Worst Case	58% (50%, 65%)	50% (43%, 58%)	7% (-2%, 16%)	63% (57%, 69%)	72% (67%, 78%)	-9% (-16%, -2%)
ITT plus	4	Worst Case	58% (50%, 65%)	35% (28%, 43%)	22% (14%, 31%)	63% (57%, 69%)	84% (79%, 89%)	-21% (-27%, 14%)
PP	16	Worst Case	58% (51%, 66%)	55% (48%, 63%)	3% (-6%, 12%)	65% (58%, 71%)	69% (63%, 75%)	-4% (-12%, 3%)
PP	12	Worst Case	58% (51%, 66%)	52% (44%, 60%)	6% (-3%, 15%)	65% (58%, 71%)	74% (68%, 80%)	-9% (-16%, -2%)
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%	54%	5%	65%	69%	-4%

			(51%, 65%)	(46%, 61%)	(-4%, 13%)	(59%, 71%)	(63%, 75%)	(-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 Tables11-9, 11-10 and 11-11 DPM-A-305 Study Report.

Since it was unclear in the protocol whether the ITT plus or PP group was considered primary, analyses in both groups are presented. Analyses implementing cutoffs for the methacholine challenge of 16 mg/mL, the standard published in the ATS guidelines, 12 mg/mL, as specified in the Applicant's statistical analysis plan, and 4 mg/mL due to FDA interest are presented. In general, a worst case approach was used for addressing missing data as follows: missing MBCT diagnoses were assumed to be negative if the subject was exercise positive and positive if the subject was exercise negative while missing methacholine diagnoses were assumed to be positive if the subject was exercise positive and negative if the subject was exercise negative. Given the very conservative nature of this missing data imputation, an analysis ignoring the missing data is also presented to illustrate whether the missing data imputation was severely affecting the overall conclusions of the analyses. As is shown in the table, with the exception of the case where a methacholine cutoff of 4 mg/mL was used, none of these criteria dramatically altered the results of the analyses.

To reiterate, the Applicant's primary objectives for this study were to:

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

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 in Table 6 confirm the Applicant's first study objective in all cases presented. However, the second study objective was not confirmed for any case presented in Table 6 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 in Table 5 as illustrated by the lower confidence interval limit for the difference in MBCT specificity and the methacholine challenge specificity being less than zero.

While the primary efficacy analyses presented in Table 6 do not appear to support the efficacy of the MBCT, it could be argued that the primary efficacy objectives defined as part of 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%. Additionally, the new diagnostic procedure must be shown to possess sensitivity and specificity similar to that of an FDA-approved procedure. While not achieving its primary objectives, the study design for study 305 allows such post-hoc comparisons. For instance, referring to Table 6, the lower confidence interval limits for the sensitivities and specificities for the MBCT being greater than 50% illustrate that the first of these post-hoc objectives is achieved. The second objective, showing the new diagnostic procedure possesses sensitivity and specificity similar to that of an FDA-approved procedure (methacholine challenge), as the study was not designed with this type of noninferiority objective in mind and would therefore require some definition of the clinical meaning of similarity in sensitivity and specificity between the MBCT and methacholine. In the absence of such documentation such as a noninferiority margin, we can use the confidence interval data for the differences between the MBCT and methacholine in sensitivity and specificity in Table 6 to illustrate the degree to which the two diagnostic tests are the same and leave to clinical judgment whether this level of precision is acceptable in order to conclude that the two procedures are providing analogous levels of information. Taking the first case from Table 6 (i.e., ITT plus, methacholine cutoff of 16 mg/mL, and worst case missing data imputation) as an example, the sensitivity of the MBCT is demonstrated to be no more than 4 percentage points worse (and may be up to 13 percentage points better) than the sensitivity of methacholine while the specificity of the MBCT is demonstrated to be no more than 12 percentage points worse (and may be up to 3 percentage points better) than the specificity of methacholine. With the exception of the case where a methacholine cutoff of 4 mg/mL was used, the results of the other cases are generally comparable to this.

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 5 below). In this comparison the physician diagnosis of "probably", "possible", "very likely", and "extremely likely or definite" 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. These analyses can be interpreted in the same way as

described above for the analyses provided in Table 4. For the first post-hoc analysis described above (the sensitivity and specificity and the new diagnostic procedure now compared to blinded physician diagnosis should exceed 50%), one can see from Table 7 that while the nominal values for sensitivity and specificity is greater than 50% under all conditions analyzed, the lower limits of the confidence intervals for the sensitivity of the MBCT are 48-49%. Of interest, however, is that the sensitivity of the approved methacholine challenge test relative to blinded physician diagnosis appears to perform nominally worse than the MBCT.

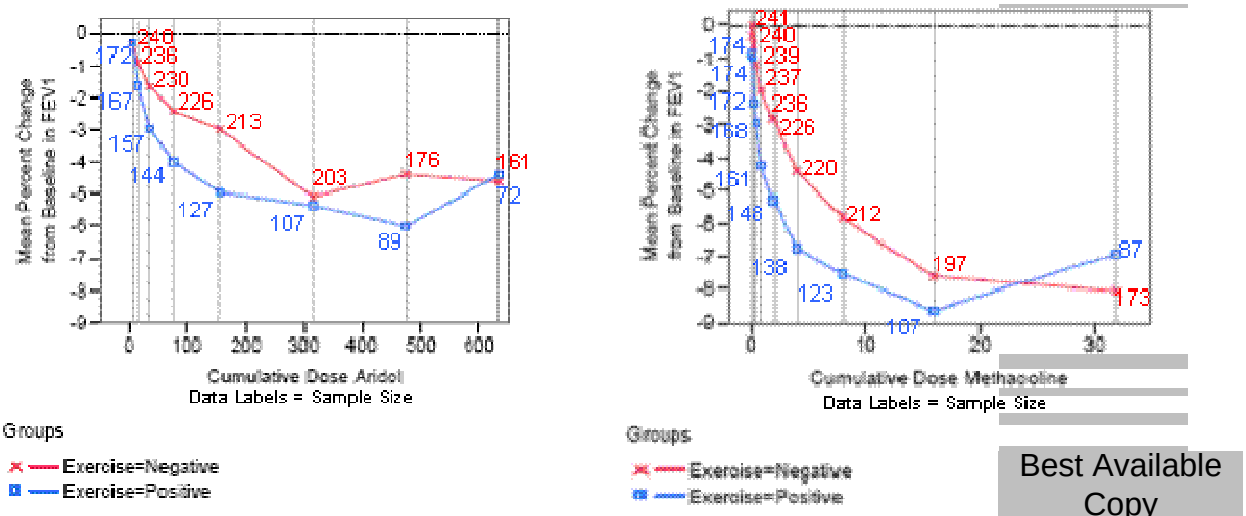
Table 5 By-Treatment Group Comparisons of Sensitivity & Specificity (Calculated Relative to Blinded Physician Diagnosis from Visit 5) for MBCT and Methacholine

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

A 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 2. 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. Note that 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 Figure 2. However, it should be noted that the mean result may not be a good indicator for what will happen to a typical individual subject in which the test results will be interpreted as either positive or negative. Also, 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 2 : Dose vs. mean percent change from baseline in FEV1



Best Available Copy

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 6. 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 6 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	Methacholine	Missing	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference

Group	Cutoff	Data						
ITT plus	16	Worst Case	57% (48%, 65%)	47% (38%, 55%)	10% (1%, 20%)	65% (58%, 71%)	71% (65%, 77%)	-6% (-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, specifically caucasian or noncaucasian (Table 7). There were no differences in the sensitivity or specificity calculated relative to exercise challenge of the MBCT noted based on gender or race.

Table 7 By-Treatment Group Comparisons of Sensitivity & Specificity (Calculated Relative to Exercise Challenge) by Gender, and Race (Caucasian/Noncaucasian)

Males								
Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst Case	58% (47%, 68%)	47% (36%, 58%)	10% (-3%, 22%)	62% (54%, 71%)	69% (61%, 78%)	-7% (-17%, 3%)
ITT plus	12	Worst Case	58% (47%, 68%)	46% (35%, 57%)	11% (-2%, 24%)	62% (54%, 71%)	71% (63%, 79%)	-9% (-19%, 2%)
Females								
Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst Case	59% (49%, 68%)	59% (49%, 68%)	0% (-12%, 12%)	64% (55%, 72%)	66% (58%, 74%)	-2% (-13%, 8%)
ITT plus	12	Worst Case	59% (49%, 68%)	54% (44%, 64%)	4% (-8%, 17%)	64% (55%, 72%)	73% (66%, 81%)	-9% (-19%, 0%)
Caucasian								
Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst Case	58% (50%, 67%)	57% (48%, 65%)	2% (-8%, 12%)	63% (56%, 70%)	67% (60%, 74%)	-4% (-12%, 4%)
ITT plus	12	Worst Case	58% (50%, 67%)	52% (43%, 61%)	6% (-4%, 17%)	63% (56%, 70%)	73% (66%, 79%)	-10% (-17%, -2%)
Non-Caucasian								
Conditions			Sensitivity (95% CI)			Specificity (95% CI)		
Analysis Group	Methacholine Cutoff	Missing Data	MBCT	Methacholine	Difference	MBCT	Methacholine	Difference
ITT plus	16	Worst Case	57% (42%, 71%)	46% (31%, 60%)	11% (-6%, 28%)	64% (51%, 76%)	69% (57%, 81%)	-5% (-21%, 11%)
ITT plus	12	Worst Case	57% (42%, 71%)	46% (31%, 60%)	11% (-6%, 28%)	64% (51%, 76%)	71% (59%, 82%)	-7% (-23%, 10%)

Source: FDA statistical reviewer analyses

Conclusions

The study failed to meet two of three proposed primary objectives. The results demonstrated that the sensitivity and specificity of the MBCT in detecting EIB as a manifestation of BHR was able to be accurately measured (objective #1), however, the MBCT did not have an acceptable sensitivity in detecting EIB as a manifestation of BHR

(objective #2) nor was the specificity of the MBCT superior to the methacholine challenge test (objective #3). The MBCT did appear to perform similarly to the approved bronchial challenge agent, methacholine.

Study DPM-A-301

The supportive study, Study 301, is titled, "A Phase 3 Study to Determine the Safety and Efficacy of Inhaled Dry Powder Mannitol as a Bronchial Provocation Test for Airway Hyperresponsiveness". As part of this study, known subjects with asthma and known subjects without asthma were enrolled and independently diagnosed as positive or negative using the MBCT and by the respiratory physician using the hypertonic saline comparator challenge as well as the subject's respiratory and medical history (excluding the results of the MBCT). As part of the inclusion and exclusion criteria, subjects with asthma were required to have active signs and symptoms of asthma (as defined by Asthma Management Handbook 2002 pg 4) and subjects without asthma were required to have never had a clinical diagnosis of asthma nor experienced signs and symptoms suggestive of asthma. From the FDA perspective, in addition to safety, the efficacy objective of interest (secondary objective #1) was to describe the sensitivity and specificity of the MBCT relative to the standard of truth, the respiratory physician diagnosis (which was based on the saline challenge as a bronchial provocation test and the respiratory and medical history).

Title
A Phase 3 Study to Determine the Safety and Efficacy of Inhaled Dry Powder Mannitol as a Bronchial Provocation Test for Airway Hyperresponsiveness

Study design and conduct
Study 301 was a multicenter, open-label, operator-blinded, randomized, crossover study in 654 subjects (557 with asthma (428 adult, 129 children), 97 normal subjects (82 adult, 15 children). The ITT population included 646 subjects.

The primary objectives were:

1. To describe the safety profile of dry powder mannitol as a bronchial provocation test for assessing airway hyperresponsiveness.
2. To describe the sensitivity and specificity of a dry powder mannitol challenge compared to 4.5% saline challenge as a bronchial provocation test in people with signs and symptoms of asthma.

The secondary objectives were:

1. To determine the efficacy of a dry-powder mannitol challenge compared to a reference (standard clinical assessment) in discriminating between those with and without active asthma.
2. To determine the variation in dose-response associated with a positive mannitol challenge.

3. To examine the mannitol challenge with respect to simplicity, safety, subject and health care convenience.

The study was conducted at 12 sites across Australia with a study period from November 21, 2003 to August 21, 2004. The challenges performed at Visit 1 and Visit 2 were 7 days apart but could be delayed by up to 7 additional days if respiratory symptoms were present. Visit 3 was to be 7 days following Visit 2 and could also be delayed by up to 7 days if respiratory symptoms were present.

Inclusion Criteria: Subjects without asthma

- Age 6 or older
- Never given diagnosis of asthma nor experienced signs and symptoms suggestive of asthma
- Capable and willing to:
    - Use the study diary
    - Perform all of the techniques necessary to measure lung function
- Complete informed consent

Inclusion Criteria: Subjects with Asthma

- Age 6 or older
- Active signs and symptoms of asthma (defined by Asthma Management Handbook 2002)
- Capable and willing to:
    - Use the study diary
    - Perform all of the techniques necessary to measure lung function
- Complete informed consent

Exclusion criteria

- Subjects whose baseline FEV1 as measured at visit 1 is less than 70% of normal predicted values for asthmatic subjects OR less than 80% of normal predicted values for non asthmatic subjects.
- Subjects with an active upper or lower respiratory tract infection severe enough to require a medical consultation
- Subjects with other acute or chronic pulmonary disorder including: cystic fibrosis, chronic obstructive pulmonary disease, bronchiectasis, chronic bronchitis, emphysema, tuberculosis and carcinoma
- Uncontrolled hypertension – systolic BP > 160 and or diastolic BP greater than 90, known aortic aneurysm
- Myocardial infarction or cerebral vascular accident in the six months prior to enrollment.
- Abdominal or ocular surgery in the three months prior to enrolment
- Subjects who are breast feeding or pregnant

- Subjects who have participated in another investigative drug study parallel to, or within 4 weeks of study entry
- Known intolerance to mannitol or salbutamol
- Previous admission to Intensive Care for asthma, in the two years prior to study entry
- Subjects taking oral/parental corticosteroids in the two weeks prior to study enrollment

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. The subjects with asthma were required to have active signs and symptoms of asthma according to the National Asthma Council of Australia Asthma Management Handbook Guidelines 2002. The normal subjects were required to have never had a clinical diagnosis of asthma or experienced signs and symptoms suggestive of asthma. At Visit 1, after screening and randomization the subjects underwent the first bronchial challenge test. The second challenge was scheduled 1 week later at Visit 2, and the study was completed a week when subjects returned for a follow up visit, including spirometry. At this visit, the respiratory physician would determine the asthma status of the subject.

The MBCT was conducted in an identical manner as in Study 305 described above with one exception. For Study 301 if the FEV1 fell by ≥ 10% after any one dose of mannitol, then that same dose was repeated while in Study 305 dosing would have been stopped without repeating it. As in Study 305, the dose of mannitol (mg) or saline (mL) to provoke a 15% fall in FEV1 (PD15) was calculated by linear interpolation from the curve relating the % fall in FEV1. For mannitol this was from the post 0 mg capsule baseline value for FEV1 to the cumulative dose of mannitol delivered (e.g., 5 mg, 15 mg, 35 mg, 75 mg, 155 mg, 315 mg, 475 mg, 635 mg).

Efficacy was analyzed using sensitivity and specificity of the mannitol challenge with respect to the 4.5% saline challenge and the clinical assessment. Subjects were considered positive to a test if at least a 15% reduction in FEV1 from baseline occurred. Subjects who reached the end of a challenge with <15% reduction in FEV1 were considered to have a negative response.

Efficacy Endpoints
The efficacy endpoints included estimating the sensitivity and specificity of the mannitol challenge with respect to both the 4.5% saline challenge and the clinical assessment of asthma. Subjects were considered positive to a test if at least a 15% reduction in FEV1 from baseline occurred. Subjects who reached the end of a challenge with <15% reduction in FEV1 were considered to have a negative response.

Safety Endpoints

The safety endpoints include: spirometry to assess lung function performed prior to each challenge; at challenge completion and recovery, monitoring for adverse events during clinical procedures by study staff and between visits, and vital signs measured prior to each challenge; at challenge completion and at recovery.

Study Results

Demographics
A total number of 654 subjects were enrolled in the study: 557 with asthma (428 adult, 129 children) and 97 subjects without asthma (82 adult, 15 children). Eight withdrew before receiving study medication, 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.

Efficacy: 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%, 95^{th} 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.

The Applicant suggested that the low sensitivity with respect to clinical diagnosis was affected by the use of systemic or inhaled corticosteroids. The Applicant therefore conducted a post-hoc analysis in which the subjects with asthma who were mannitol negative but were known to be receiving inhaled corticosteroid therapy were excluded (159 subjects). Subsequent analysis demonstrated an increase in sensitivity to 88%.

- **Comparison of the MBCT to inhaled hypertonic saline**

While the safety and efficacy of inhaled hypertonic saline as a bronchoprovocation agent has not been evaluated by the FDA, the comparison data shown below is included for completeness.

The sensitivity, defined as the probability of a positive test result with the MBCT, given a positive saline result (Pr[M+|S+] = 260/322), was 80.7%, with a 95% CI of 76.4%, 85.1%. Specificity, defined as the probability of a negative test result with the MBCT, given a negative saline result (Pr[M−|S−] = 234/270), was 86.7%, with a 95% CI of 82.6%, 90.7%. The sensitivity and specificity for the MBCT to identify responsiveness to hypertonic saline in both the PP as well as ITT population are given in Table 8.

Table 8 Summary of Primary Efficacy Analyses: Study DPM-A-301

Analysis	Comparison	Sensitivity %, (95% CI)	Specificity %, (95% CI)
Primary, PP15	Mannitol vs Saline	80.7 (76.4,85.1)	86.7 (82.6,90.7)
Primary, ITT, PD15	Mannitol vs Saline	73.3 (68.7, 77.9)	80.7 (76.1, 85.2)

[Source: Table 2.7.3.8 Section 2.7.3.2.1.4 Summary of Clinical Efficacy, CTD Module 2.7.3]

The sensitivity of the MBCT appeared to increase and the specificity to decrease with increasing severity of asthma in the adult PP15 population, from 71.4% and 87.0% for the mild asthma category to 93.3% and 50.0% for the severe category.
Positive and negative predictive value did not follow either trend. This is presented in Table 9.

Table 9 Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value of Mannitol vs Hypertonic Saline, by Severity of Asthma: Study DPM-A-301, Adult PP15 Population

Efficacy Parameter	Value
Mild (n = 191)	
Sensitivity [Pr(M+/C+)]	71.4%
Specificity [Pr(M-/C-)]	87.0%
Positive Predictive Value [Pr(C+/M+)]	83.3%

Negative Predictive Value [Pr(C-/M-)]	77.0%
Moderate (n = 151)	
Sensitivity [Pr(M+/C+)]	81.0%
Specificity [Pr(M-/C-)]	82.9%
Positive Predictive Value [Pr(C+/M+)]	94.0%
Negative Predictive Value [Pr(C-/M-)]	56.9%
Severe (n = 36)	
Sensitivity [Pr(M+/C+)]	93.3%
Specificity [Pr(M-/C-)]	50.0%
Positive Predictive Value [Pr(C+/M+)]	90.3%
Negative Predictive Value [Pr(C-/M-)]	60.0%

Source: Table 4.7, ISE, CTD Module 5.3.5.3.1

In summary, the MBCT appears to perform very similarly as a bronchoprovocation test as the unapproved test agent, hypertonic saline.

6 Review of Efficacy

Efficacy Summary

Because of differences in the study populations and study designs including the primary objectives it is not possible to conduct an integrated review of efficacy for this NDA. Following is a brief summary of the efficacy results for the pivotal and supportive trials. The complete reviews of efficacy for the pivotal Study DPM-A-305 and the supportive Study DPM-A-301 can be found in Section 5.3.

Study 305 Efficacy Results

A total of 436 subjects were randomized in the study and comprised the safety population. The mean age was 24.9 years; 53.6% were female, 74.1% were Caucasian, 9.4% Hispanic and 9.2% Black. No subjects enrolled were over the age of 50 years. 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 ≥ 12% and 200 mL) to administration of a short-acting bronchodilator.

The analyses necessary to address the primary efficacy objectives are shown in the table 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 then FDA.

Table 10 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.

Overall, the sensitivity and specificity of the MBCT and methacholine with respect to EIB as a manifestation of BHR were similar.

Study 301 Efficacy Results

A total number of 654 subjects were enrolled in the study; 557 with asthma (428 adult, 129 children) and 97 subjects without asthma (82 adult, 15 children). Eight withdrew before receiving study medication, leaving 646 in the ITT and safety populations. The mean age was 34.8 years; 53.4% were females with the great majority of subjects being Caucasian. Twenty-five subjects were ≥ 65 years of age. 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.

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.

The Applicant suggested that the low sensitivity with respect to clinical diagnosis was affected by the use of systemic or inhaled corticosteroids. The Applicant therefore conducted a post-hoc analysis in which the subjects with asthma who were mannitol negative but were known to be receiving inhaled corticosteroid therapy were excluded (159 subjects). Subsequent analysis demonstrated an increase in sensitivity to 88%.

Pediatric Efficacy

The primary efficacy analyses divided by age subgroups for Study 305 are given in the table below. 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 11 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%)

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%)
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 Case	57% (48%, 65%)	47% (38%, 55%)	10% (1%, 20%)	65% (58%, 71%)	71% (65%, 77%)	-6% (-14%, 1%)

Source: FDA statistical reviewer analyses

Geriatrics

No subjects older than 50 years of age were enrolled in the pivotal study (Study 305), presumably because of risks associated with exercise challenge tests in an older population. Therefore data are lacking in this population.

7 Review of Safety

Safety Summary

The relative safety of the MBCT is supported by the submitted clinical study data. Safety data showed that the MBCT is most commonly associated with headache, pharyngolaryngeal pain, nausea, and throat irritation. The incidence of these AEs is greater in number than for the comparator bronchial challenge test, methacholine. The MBCT also appears 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. However, methacholine is 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 as defined as those ≥ 30% from baseline 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.

In summary, on evaluation of the overall safety data the clinical review believes that the safety profile for the proposed serial doses for the Aridol diagnostic test would be acceptable.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from study DPM-A-301 conducted for marketing approval outside the United States and from Study DPM-A-305 form the clinical trial safety data base for this application.

Due to differences in study design between the 2 phase 3 studies, some data are difficult to integrate and are presented for each individual study individually. These differences include different study designs, comparators, and subject populations that are briefly outlined below and discussed in the individual study descriptions in more detail. In addition to different study designs, Studies 301 and 305 differ somewhat in their definition of adverse events (AEs) and the duration of time adverse events are reported. In Study 301 an adverse event was defined as any untoward medical occurrence in a subject administered a pharmaceutical product, including the comparator hypertonic saline for inhalation without regard to the possibility of a causal relationship. In order to allow collection of safety data from the exercise challenge tests performed in Study 305, the definition of and adverse event was extended to include unfavorable or unintended changes to the structure, function, or chemistry of the body for both pharmaceutical product and study procedure.

In addition, AE data for Study 301 were collected over the entire duration of the study time between challenges and for 7 days following the second challenge, whereas AE data for Study 305 were limited to collection on the day of and day after each of the bronchial challenge tests. While this practice is acceptable to this type of diagnostic test drug product, it does make it more difficult to interpret integrated safety data for the two trials. As a way to be able to assess integrated AE safety data, the Applicant has conducted post-hoc analyses of selected safety data limiting the reporting of AEs for Study 301 to those reported within the same time frame as Study 305.

The two trials also had different 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 an exercise challenge test and methacholine, which is the only inhalation test approved in the United States (Provocholine, NDA 19-193, approved October 31, 1986) as a bronchial challenge test 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.

Study 305 excluded enrollment of subjects > 50 years of age due to the physical demands of the exercise challenge but did evaluate limited electrocardiogram (ECG) data in subjects who had received the MBCT.

7.1.2 Categorization of Adverse Events

The applicant's categorization of AE data by system, organ, class and preferred term, according to the MedDRA were appropriately coded. The specific safety assessments for DPM-A-301 included: baseline profile, spirometry, AE, study diary, vital signs and time to recovery. Specifically, the subject's baseline profile included a medical history and respiratory history questionnaire at Visit 1. Subjects also completed a respiratory symptom questionnaire at each subsequent visit. Spirometry was performed on all subjects at Visit 1 (first bronchial challenge) and Visit 2 (second bronchial challenge), prior to start of the challenge, as well as at completion, and recovery to baseline was assessed following each challenge. Spirometry was also performed during follow-up at Visit 3. To evaluate AE in between visits, a study diary was distributed to all subjects. Study drug reactions were monitored during clinical procedures. Respiratory symptoms, AE, and concomitant medications were recorded on a daily basis during the study period. Vital signs including blood pressure, respiratory rate, and oxygen saturation were monitored prior to, during, and after completion of each bronchial provocation challenge, as well as after recovery. The time to reversibility of FEV1 to within 5% of pre-challenge levels was also assessed. In addition, subject and operator satisfaction questionnaires completed at the end of each challenge were assessed for relevance to safety.

The following primary safety endpoints were assessed for DPM-A-305: physical examination (PE) at start of study at Visit 1; drug-related AE reported by subject by severity and drug at Visit 4 and 5 for both methacholine and Aridol; comparison of the severity of device drops in FEV1 after MBCT as compared with methacholine challenge at Visit 4 or 5; the change from baseline to the end of MBCT in vital signs and oxygen saturation at Visit 4 or 5 and the change from baseline to the end of mannitol BCT in ECG values at Visit 4 or 5. In addition, the following safety analyses were conducted post hoc: analyses of safety parameters in the pediatric and geriatric in DPM-A-301 only populations; analyses of safety data by racial/ethnic group DPM-A-305 only and by gender; analyses of retrospectively defined potentially clinically significant abnormalities in QTcB and QTcF results; analyses of data from manual reading of ECGs; analysis of

spirometry findings (FEV1, FVC, and FEF25-75) for each of the exercise challenges; maximum fall and percentage fall in FEV1 for subjects with positive challenges and cough during mannitol challenges.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from Studies 301 and 305 were appropriately pooled to allow for estimation of the incidence of adverse events directly related to the bronchial challenge tests in those studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety database included 1,046 subjects with asthma, symptoms suggestive of asthma, and healthy subjects in the two Phase 3 trials. Each subject was to complete one each of a battery of bronchial challenge tests; responses to mannitol, exercise, and methacholine in Study 305 and to mannitol and hypertonic (4.5%) saline in Study 301. The actual dose of each study drug depended on the pulmonary response as determined by decrease in FEV1. For mannitol, the maximal inhaled dose that a subject would be exposed to was 635 mg (a subject with a negative challenge). The demographic and baseline characteristics of subjects in Studies 301 and 305 can be found in Table 12 below.

Table 12 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

Further age subdivision can be seen in the table below. Pediatric subjects ≥ 6 years of age were enrolled in both phase 3 trials. The safety data gathered for pediatric subjects (6-18 years of age, n = 246) represent approximately equal numbers of young children (ages 6-11, n=118) and adolescents (ages 12-17, n=128) and comprise about 23% of the total study population.

Regarding elderly subjects, allegedly due to the physical demands of the exercise challenge in Study 305 subjects > 50 years of age were excluded from that trial. This limited the number of elderly subjects (≥ 65 years of age) to a total of 25, all from Study 301. Because of this low number, differences in safety between elderly (who would have age-related co-morbidities) and younger patients is not able to be fully addressed. Refer to Table 13 for the age distribution for both Phase 3 studies.

Table 13 Age Distribution of Subjects in Studies 301 and 305, Safety Population

Age	DPM-A-301 N = 646 N (%)	DPM-A-305 N = 436 N (%)
6-9 years	41 (6.3%)	14 (3.2%)
10-11 years	41 (6.3%)	22 (5.0%)
12-17 years	56 (8.7%)	72 (16.5%)
18-30 years	148 (22.9%)	221 (50.7%)
31-50 years	224 (34.7%)	107 (24.5%)
51-64 years	111 (17.2%)	0
≥ 65 years	25 (3.9%)	0

Source: Table 2.7.4.4 Summary of Clinical Safety

7.2.2 Explorations for Dose Response

The premise of the MBCT itself is a for a differential dose response in subjects who have bronchial hyperreactivity. The majority of MBCT positive subjects received between 75 and 315 mg of mannitol. This correlates with administration of the 5^{th} to 7^{th} mannitol doses (of maximum of 8). Data in younger children (ages 6-11) and the elderly (≥ 65 years) are more variable.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or preclinical testing was performed for this application. Adequate preclinical testing was performed to explore potential adverse reactions and is briefly summarized in Section 4.3. For a complete description of the preclinical program , refer to the Pharmacology/ Toxicology reviewer, Dr. Luqi Pei's review.

7.2.4 Routine Clinical Testing

The effects of inhaled mannitol on blood chemistry, hematology, or urinalysis parameters were not assessed in the MBCT program. 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.

7.2.5 Metabolic, Clearance, and Interaction Workup

The pharmacokinetics and bioavailability of inhaled mannitol are described briefly in Section 4. No formal drug-drug interaction studies were included in this program.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

A safety concern specific to a provocation test designed to evaluate bronchial hyperresponsiveness is an early exaggerated response in the fall of FEV1. These results are presented in more detail in Sections 7.3.5.

7.3 Major Safety Results

7.3.1 Deaths

No deaths have been reported in association with the use of the mannitol BCT, either in clinical studies or in postmarketing use.

7.3.2 Nonfatal Serious Adverse Events

One serious adverse event (SAE) occurred in the clinical development program for the mannitol BCT, a case of appendicitis in Study DPM-A-305 8 days after methacholine challenge, but before the mannitol BCT. The subject recovered following appendectomy and completed the trial.

7.3.3 Dropouts and/or Discontinuations

A total of 11 subjects (out of 1,046) 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).

7.3.4 Significant Adverse Events

For adverse events deemed serious or potentially serious, refer to above Section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

Excessive Bronchoconstriction

The major safety concern with the use of a bronchial challenge test is a severe loss of lung function as a result of bronchospasm. The table below shows the number and per cent of subjects who had excessive decreases in FEV1 during bronchial challenges. Three subjects who received methacholine challenges had decreases in FEV1 ≥ 60%. The maximal decrease in FEV1 observed in a subject receiving the MBCT was 46%.

Table 14 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

Of note is that 23 of the 26 subjects who had decreases in FEV1 ≥ 30% after mannitol had confirmed asthma.

Hypoxia

Severe bronchoconstriction may also lead to hypoxia. Oxygen saturation was assessed at baseline and at the end of the bronchial challenges. The mean changes in oxygen saturation for the MBCT and hypertonic saline were < 1% in study 301 with a maximum decrease of 5%.

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 intended to be 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, and 370 (58%) after receiving hypertonic saline. A second salbutamol 200 mcg dose was given to 46 (7.3%) subjects after MBCT, and 38 (6.0%) after the saline challenge. 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 and 2 (0.3%) following hypertonic saline. These treatments were additional doses of short-acting beta agonists (albuterol/salbutamol, terbutaline). Data for subjects who required greater than one dose of albuterol after a positive bronchial challenge in Study 305 were not summarized.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

- Adults:

Some points to consider when evaluating the AE pooled from the two clinical studies are reviewed first. The clinical study reports (CSRs) for the two Phase 3 studies differed in their mode of presentation of AEs. The CSR for Study DPM-A-301 reports each AE in terms of the number (%) of subjects reporting each AE. Study DPM-A-305, in contrast, reports the total number of times each AE was reported, but does not present in summary form the number (%) of subjects reporting each AE.

The two Phase 3 studies also varied in terms of delay between challenges. In Study DPM-A-301, the second drug challenge was to occur 7 to 14 days after the first drug challenge however, in Study DPM-A-305, the delay was to occur only 1 to 4 days after the first drug challenge. Therefore, of note, AEs were collected over substantially longer

periods of time post-challenge for some subjects than for others. The Applicant attempted to compensate for these between-study differences by examining the incidence of treatment emergent adverse events (TEAEs) commencing within approximately 1 day following each challenge in both Phase 3 studies. These temporally associated TEAE data are post hoc analyses for both studies and are summarized by number (%) of subjects reporting each TEAE in table 15 below.

Overall, the AEs were similar qualitatively and quantitatively to those seen with the hypertonic saline and methacholine challenges and are those that would be expected to occur during a bronchoprovocation challenge. There were no SAEs or deaths seen in DPM-A-301/305.

Only three TEAEs had an incidence in either study ≥ 3% for the MBCT: headache, with an incidence of 8.6% in Study DPM-A-301; chest discomfort, with an incidence of 3.1% in Study DPM-A-305 and pharyngolaryngeal pain, with an incidence of 3.0% in Study DPM-A-301.

Table 15 TEAEs with an Incidence ≥ 1% During or Within a Day After Challenge in Any Mannitol BCT Group: Studies DPM-A-301 and DPM-A-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%)	6 (1.4%)	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%)

Abbreviation: NOS, not otherwise specified.
[a] Most AEs of chest discomfort were categorized in the General SOC. However, one AE of chest discomfort following the mannitol BCT and one following the methacholine challenge were categorized in the Respiratory SOC.
REF: *Post hoc* analyses of data in CSR for DPM-A-301, Listing 16.2.7.1.2, and CSR for DPM-A-305, Listing 16.2.7.1
[Source: Table 6.3 Section 6.2 ISS, CTD Module 5.3.5.3.2]

- Pediatrics:

The mot common AEs in the pediatric population were similar to the adult population including dyspnea, headache, pharyngolaryngeal pain and nausea, summarized in tables 16 and 17. There were no deaths or SAEs reported in children.

The incidence of maximum % falls ≥30% or ≥60% was also analyzed for the pediatric population, with slightly higher percentages among children than among the overall population. Of the pediatric subjects exposed, 16 of 107 (15.0%) had a fall ≥30% in FEV 1 after methacholine, compared to only 2 of 107 (1.9%) after mannitol, whereas 10 of 108 (9.3%) had a fall ≥30% in FEV 1 after exercise. One pediatric subject experienced a fall in FEV1 ≥60%, following exposure to methacholine. In the overall population, 6.2% had a fall ≥30% in FEV 1 after exercise, 12.1% after methacholine, and only 0.7% after the mannitol challenge, with 3 subjects (0.7%) experiencing a fall ≥60%. A total of 246 children 6 years of age and older were studied in the two large Phase 3 clinical trials, DPM-A-301 and Study DPMA-305. There were no notable differences in the mean and median percentage fall in FEV1, the incidence of AEs, in time to recovery, or in vital signs between the pediatric population and the population as a whole.

Table 16 Most Common TEAEs (≥5% Incidence in Either Group): Overall vs. Pediatric Safety Population, Study DPM-A-301

	Overall Population		All Children, 6-17 years	
Parameter	After Mannitol BCT (N = 627) n (%)	After Saline Challenge (N = 636) n (%)	After Mannitol BCT (N = 134) n (%)	After Saline Challenge (N = 138) n (%)
Headache NOS	108 (17.2%)	121 (19.0%)	20 (14.9%)	27 (19.6%)
Pharyngolaryngeal pain	32 (5.1%)	19 (3.0%)	11 (8.2%)	3 (2.2%)
Nausea	27 (4.3%)	19 (3.0%)	8 (6.0%)	6 (4.3%)
Abdominal pain upper	12 (1.9%)	9 (1.4%)	7 (5.2%)	4 (2.9%)

REF: CSR for DPM-A-301. Table 12.2.1.1 and *post hoc* analyses
[Source: Table 12.17 Section 12.3.1.3 ISS, CTD Module 5.3.5.3.2]

Table 17 Most Common TEAEs (≥5% Incidence in Either Group): Overall vs. Pediatric Safety Population, Study DPM-A-305

	Overall Population		All Children, 6-17 years	
Parameter	After Mannitol BCT (N = 419) n (%)	After Metha-choline (N = 428) n (%)	After Mannitol BCT (N = 107) n (%)	After Metha-choline (N = 107) n (%)
Dyspnea	12 (2.9%)	21 (5.0%)	5 (4.7%)	6 (5.6%)

REF: CSR for DPM-A-305, Table 12-5 and Table 12-6 and *post hoc* analyses

[Source: Table 12.18 Section 12.3.1.3 ISS, CTD Module 5.3.5.3.2]

7.4.2 Laboratory Findings

Clinical laboratory assessments were not conducted in the MBCT program.

7.4.3 Vital Signs

Routine vital sign assessment was performed at baseline, post-challenge, and recovery in Study 301 and at baseline and post-challenge in Study 305. In Study 305 there were predictable increases in heart rate, respiratory rate, and blood pressure following the exercise challenge. There were no clinically meaningful differences from baseline in mean vital signs for the methacholine and mannitol challenges.

7.4.4 Electrocardiograms (ECGs)

Except for an ECG at screening, ECGs were performed only in Study 305 and were performed immediately before and after the MBCT only. Changes from baseline in mean ECG parameters were not significant except for RR intervals and QT intervals corrected for heart rate in subjects with positive mannitol challenges. This population subgroup showed a decrease in RR interval of -24.04 ($p = 0.021$) and corresponding increases in mean QTcB and QTcF values of 7.26 ms and 5.24 ms ($p < 0.0001$ for both), respectively. These statistically significant increases following positive challenges were most likely due to the protocol defined administration of albuterol, which is known to be associated with QTc increases.

7.4.5 Special Safety Studies/Clinical Trials

No unexpected safety issues arose during the clinical investigations with MBCT for its intended indication or use as the mannitol tolerance test in clinical studies in other indications. Therefore, no special safety trials were conducted for the Aridol NDA.

7.4.6 Immunogenicity

Not applicable for this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The maximum dose of mannitol that could be inhaled was 635 mg. Subjects who had positive challenges by definition had decreases in FEV1 ≥ 15% at doses less than 635 mg. There is some evidence that AEs specifically associated with mannitol (pharyngolaryngeal pain and throat irritation) may occur in subjects who receive the maximal inhaled dose of 635 mg (negative challenge).

7.5.2 Time Dependency for Adverse Events

The MBCT is a single use one time test to assess bronchial hyperreactivity. Adverse events associated with the test generally occur in the time frame immediately after the test.

7.5.3 Drug-Demographic Interactions

There were no significant differences in the safety profile of the MBCT between male and female subjects. A total of 246 children 6 years of age and older were studied in two large, well-controlled, Phase 3 clinical trials of Study DPM-A-301 and Study DPMA-305. There were no major differences in the safety profile of the MBCT between the pediatric population and the population as a whole in these trials. For the geriatric population, a total of 25 subjects 65 years of age and older, most of whom had a prior history of asthma, were studied in Study 301. While there were no apparent differences in incidence of adverse events, the number of elderly subjects studied was not sufficient to determine if there were any differences in the safety between elderly and younger subjects.

7.5.4 Drug-Disease Interactions

Individuals with bronchial hyperreactivity will, by definition, have an increased response (decrease in FEV1) to the MBCT which may be severe.

7.5.5 Drug-Drug Interactions

Use of inhaled corticosteroids reduces the airway sensitivity to the MBCT. This was demonstrated in Study 301 in which the primary analysis demonstrated that MBCT had a 58% and 95% sensitivity and specificity, respectively, in identifying subjects with asthma compared to a physician's clinical diagnosis. However, when subjects who had a negative MBCT that were receiving inhaled corticosteroids were excluded from the analysis, sensitivity increased to 89% while specificity remained the same (95%). The Applicant has supplied literature which suggests that other asthma medications (anti-histamines, leukotriene modifiers, mast cell stabilizers) may also blunt the airway response to the MBCT.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies were performed for this NDA. However, mannitol is non-carcinogenic based on 2 year dietary carcinogenicity studies conducted by the National Toxicology Program.

7.6.2 Human Reproduction and Pregnancy Data

Mannitol is non-teratogenic according to the Joint FAO/WHO Expert Committee on Food Additives Monograph. However, a serum pregnancy test was performed during screening. There have been no spontaneous (postmarketing) reports regarding the use of the MBCT during pregnancy or lactation.

7.6.3 Pediatrics and Assessment of Effects on Growth

No formal studies in pediatrics on growth were conducted for this Aridol NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no known pharmacological or psychological potential for abuse of MBCT. However, susceptible persons may suffer severe bronchospasm following any dose of inhaled mannitol.

7.7 Additional Submissions / Safety Issues

There was a periodic safety update report submitted covering the time from April 21, 2008 to April 20, 2009 that was amended on July 22, 2009. During this reporting period, no fatal or life-threatening SAEs and no cardiac events involving mannitol were received. As well, no important safety concerns related to mannitol were made available. Therefore no changes in the safety profile of the mannitol BCT was required.

8 Postmarket Experience

The MBCT has been approved for use in identifying bronchial hyperreactivity in at least 15 countries. Total cumulative commercial exposure to date (22 March-2006 to 20 April 2009) is estimated a (b) (4) subjects. During the safety reporting period, there were two spontaneous adverse reaction reports from healthcare professionals: 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). No further details were offered.

9 Appendices

9.1 Literature Review/References

The Applicant provided 199 literature references with electronic copies regarding bronchial hyperresponsiveness, asthma, challenge tests to evaluate pulmonary mechanics, bronchoprovocation agents and respiratory function tests. Selected reports were reviewed briefly and did not suggest additional safety concerns.

9.2 Labeling Recommendations

(b) (4)

9.3 Advisory Committee Meeting

The advisory committee meeting is scheduled for November 20, 2009. The Committee will be asked to address 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?

Pending the outcome of the discussion at the advisory committee meeting, additional safety and or efficacy data in specific populations may be required.

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/

ANYA C HARRY
11/30/2009

ANTHONY G DURMOWICZ
11/30/2009

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 22-368	TRADE NAME:	Aridol™
APPLICANT/SPONSOR:	Pharmaxis Ltd.	USAN NAME:	mannitol
MEDICAL OFFICER:	Anya C. Harry, M.D., Ph.D.		
TEAM LEADER:	Anthony Durmowicz, M.D.	CATEGORY:	Hyperosmotic bronchial irritant
DATE:	April 30, 2009	ROUTE:	Oral inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
February 27, 2009	February 27, 2009	NDA	Electronic NDA submission

RELATED APPLICATIONS

Document Date	Application Type	Comments
July 19, 2004	PIND 70,277	Pre-IND meeting minutes
November 19, 2004	IND 70,277	Initial IND

REVIEW SUMMARY:

This is a 45-day filing and planning review of NDA 22-368 Aridol (mannitol bronchial challenge test). This NDA supplement is submitted in support of the use of mannitol for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma. The sponsor is Pharmaxis Ltd.

The clinical program for this NDA consists of two studies: two Phase 3 trials, one pivotal and one supportive and referenced literature.

- Study DPM-A-305 a clinical safety and efficacy trial to assess the sensitivity and specificity of Aridol to detect exercise induced bronchospasm as a manifestation of bronchial hyperresponsiveness.
- Study DPM-A-301 a clinical safety and efficacy non IND trial to determine the sensitivity and specificity of Aridol compared to hypertonic (4.5%) saline challenge as a bronchial provocation test to asses airway hyperresponsiveness.

The submission appears complete to allow for a further more complete review, and is therefore considered "fileable." The Division will plan to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee as this NDA is for a drug to be used in a novel format as a diagnostic test. Audits by the Division of Scientific Investigations will be requested.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS:	FILABLE	X	NOT FILABLE
OTHER ACTION:	COMMENTS FOR SPONSOR		

I. GENERAL INFORMATION

Drug Substance

Trade Name:	Aridol
US Adopted Name:	Mannitol bronchial challenge test
International Non-proprietary Name:	Mannitol bronchial challenge test
Molecular Formula:	$C_6H_{14}O_6$
Molecular Weight:	182.17
Manufacturer:	Pharmaxis Ltd.

This NDA supplement is submitted in support of the use of Mannitol (Aridol™) oral inhalation for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma. Dry powder mannitol was included as an inactive ingredient in the formulation of inhaled insulin that was approved for oral inhalation use January 27, 2006 (NDA 21-868, Exubera®). Under the same IND (70,277) as the current mannitol bronchial challenge test (BCT) program, dry-powder mannitol is also being developed as a chronic treatment (b) (4)
Both products employ a drug-device combination consisting of hard gelatin capsules containing spray-dried mannitol and a proprietary dry powder inhaler. As of November 11, 2008, mannitol BCT has been approved in 10 countries as Aridol™ (proposed proprietary name), and in 4 countries as Osmohale™. Mannitol is a Generally Recognized as Safe (GRAS) excipient in the US for food substances at intakes of up to 20 g/day without additional labeling for oral, intravenous and ocular products.
The Aridol™ package contains capsules of dry-powder Mannitol that are administered by oral inhalation via a single-use disposable device, the RS01 Inhaler Model 7, (b) (4) marketed outside the US for many years. Each Aridol™ test kit contains 19 capsules, and a proprietary dry-powder inhaler to be used on one patient.
The clinical program for this NDA consists of two Phase 3 clinical studies, one pivotal and one supportive. The pivotal study DPM-A-305 is a clinical safety and efficacy trial to assess the sensitivity and specificity of Aridol™ to detect exercise induced bronchospasm as a manifestation of bronchial hyperresponsiveness. The primary endpoint of sensitivity was not met with a lower 95% confidence limit of 0.509 with a goal ≥ 0.60. The supportive study DPM-A-301 is a clinical safety and efficacy non IND trial conducted outside of the U.S. to determine the sensitivity and specificity of Aridol™ compared to hypertonic (4.5%) saline challenge as a bronchial provocation test to assess airway hyperresponsiveness. The Mannitol PD15 had a sensitivity of 81% and specificity of 87% with respect to PD15 for 4.5% saline. In addition to the two Phase 3 studies, referenced literature is included for support of NDA 22-368.
The submission appears complete to allow for a further more complete review, and is therefore considered "fileable." The Division will plan to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee as this NDA is for a drug to be used in a novel format as a diagnostic test. Audits by the Division of Scientific Investigations will be requested.

II. BACKGROUND AND RATIONALE

Mannitol is a naturally occurring product found in plants, algae, fungi and some bacteria; also, it is endogenous in humans. D-Mannitol/ Mannitol has been used for many years as a food additive as well as pharmaceutical excipient and active ingredient in oral, ophthalmic and injectable products. When inhaled, mannitol induces an increase in osmolarity in the airways similar to that induced by other bronchial provocation tests, such as hypertonic saline, exercise, and the hyperpnea of dry air. The increase in osmolarity is associated with the release of a wide variety of mediators of bronchoconstriction from inflammatory cells within the airways. These mediators then act via specific receptors on bronchial smooth muscle to cause contraction and consequent narrowing of the airways. The airway response is most pronounced (hyperresponsive) in patients with asthma and exercise-induced asthma.

III. REGULATORY AND FOREIGN MARKETING HISTORY

A. Regulatory History

- Initial P-IND (70,277) for Aridol powder was submitted on July 18, 2004 as a bronchial provocation test for assessing airway hyperresponsiveness. In this study, DPM-A-301 patients with asthma and normal volunteers were given Mannitol challenge tests without a comparator drug. The response to Mannitol was compared to a clinical diagnosis. The FDA response to this protocol was to suggest: (1) study patients with a range of diagnoses and pulmonary functions (2) include a comparator drug such as methacholine, US standard.
- The original IND was submitted in November, 2004 with a substantially modified protocol. The protocol enrolled subjects with signs and symptoms of asthma who have not been formally diagnosed. The subjects had a series of additional tests in addition to a Mannitol challenge and then treatment with ICS for 6 weeks. The Mannitol challenge was repeated at the end of the 6 week trial. (b) (4)

  Evaluation of the Mannitol challenge was conducted by comparing the results of the challenge with the diagnosis of asthma. The Division suggested: subjects without a diagnosis of asthma should not be treated with ICS, methacholine challenge should be included as a comparator and that the definition of asthma should be specified prospectively.
- An amended protocol was submitted on July 4, 2005, DPM-A-305 where exercise challenge and methacholine challenge were included as comparators however, the inclusion criteria did not allow for subjects with lung diseases other than suspected asthma. Each subject was to be characterized as being exercise, methacholine, Aridol and asthma positive or negative. The Sponsor chose exercise testing rather than methacholine as the primary comparator because they stated that exercise has higher specificity than methacholine for identifying bronchoreactivity. The clinical diagnosis from visit 3, using all the data other than the Aridol response was to be used. The primary analysis was to compare the Aridol and exercise challenge test response. The primary objective would be met if Aridol could be shown to have sensitivity of 0.65 or greater and a specificity of 0.75 or greater when compared to the response to

exercise. The secondary endpoint was Aridol challenge response to be compared with the asthma diagnosis and the methacholine challenge response.

- In the interim, the original (preIND) asthma protocol DPM-A-301 was completed in Australia and protocol DPM-A-305 was completed in the US. These two studies and references to studies in the published literature form the basis of the proposed NDA application.
- A preNDA meeting package was reviewed in February 2008 where studies DPM-A-301 and DPM-A-305 were reviewed. In the study DPM-A-301 patients with a diagnosis of asthma, 74.5% of whom were treated with ICS prior to enrollment, were compared to normal subjects with no history or symptoms of asthma. Of the subjects with asthma, 59.8% had a positive Mannitol challenge test compared to 65.1% with a positive response to hypertonic saline. The specificity was 95.2% in for both challenges. The sponsor attributed the low degree of responsiveness to the large number of subjects that were treated with ICS at the time of the study. In a post-hoc analysis where the subjects treated with ICS were excluded the sensitivity of the Mannitol was 70%. For the study DPM-A-305 not all results were presented at the time; the sponsor indicated that the Mannitol challenge is equivalent to the methacholine test in predicting bronchial hyperresponsiveness to exercise. The Division expressed that: We are uncertain if substantial evidence of efficacy can be established based on the results from Protocols DPM-A-301 and DPM-A-305 for the proposed indication of detection of bronchial hyperresponsiveness. Highlights of the Divisions comments include: the design of the two studies do not address the sensitivity and specificity of Aridol in a random population of patients with hyperresponsiveness, we require a complete characterization of the bronchial response curves (sensitivity and specificity) to Mannitol and methacholine, and to define sensitivity and specificity of the test you may also need to test the performance of the Aridol test in a normal population.

B. Foreign Marketing History

Aridol was first approved in Australia on the 22nd March, 2006 for the indication of *'Identifying bronchial hyper-responsiveness to assist in the diagnosis of asthma'*. Aridol was also approved in Sweden on the 20th October, 2006 for the indication of ' Identifying bronchial hyperresponsiveness and in the diagnosis and control of asthma'. There have been no Regulatory Authority or Marketing Authorization Holder (MAH) actions taken for safety reasons during the reporting period, and there have been no changes to reference safety information during the reporting period. During the reporting period, an approximate total of (b) (4) patients were exposed to Aridol. Of these, (b) (4) patients were exposed to Aridol through commercial sales, and 1,553 patients were exposed through clinical trials. During the safety reporting period, no serious adverse events or important safety concerns related to Aridol have arisen.

IV. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS

A. Necessary Elements (21 CFR 314.50)

The table below lists the necessary elements for an NDA and their location within the electronic submission.

Type	Status	Location (Item #: Folder from Main Table of Contents)
Application Form (FDA 356h):	Present	Module 1.1.2 \356h.pdf
Investigator Debarment Certification:	Present	Module 1.3.3 \debar-cert.pdf
Financial Disclosure:	Present	Module 1.3.4 \financial-cet-disclosure.pdf
Statements of Good Clinical Practice:	Present	Individual study reports
Environmental Assessment:	Present	Module 1.12.14 \environmental-assessment.pdf
Proposed label:	Present	Module 1.14.1 labeling\proposed.pdf
Integrated Summary of Efficacy	Present	Module 2.7.3 summary-clin-efficacy.pdf
Integrated Summary of Safety:	Present	Module 2.7.4 summary-clin-safety.pdf
Integrated Summary of Benefits and Risks:	Present	Module 2.5 summary-clinical.pdf
Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures:	Present	Individual study reports
Statistical Analyses:	Present	Module 2.7.3 summary-clin-efficacy.pdf
Pediatric Use Section:	Present	Pediatric indication < 6 years old request a waiver
Case Report Tabulations:	Present	Module 5.3.1.1.21 16-2-6-ind-efficacy-response.pdf
Case Report Forms (for patients who died or did not complete study):	Present	Module 5.3.1.1.16 16-2-1-discontinued.pdf
Patent Information:	Present	Module 1.3.5.1 us-patent-5817028.pdf

B. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

V. PRELIMINARY REVIEW OF PACKAGE INSERT

The label was converted to the PLR format.

Reviewer: Inclusion of warning similar to Provocholine is necessary.

VI. CLINICAL STUDIES

DPM-A-305

509 subjects with current symptoms suggestive of asthma but without a definitive clinician diagnosis of asthma ages 6 – 50 year olds given ascending doses sequentially either Aridol or Methacholine, each dose following previous dose until fall in FEV1 or all doses given

- Compared Aridol with Methacholine Challenge to predict BHR as manifested by a positive exercise challenge
- Hypothesis: Aridol challenge sensitivity is significantly greater than 0.6 at the 0.025 level, one sided, to detect BHR as manifested by a positive exercise challenge in subjects presenting with signs and symptoms suggestive of asthma but without a definitive diagnosis and Aridol challenge specificity is significantly greater than that seen with methacholine challenge to detect BHR

Main inclusion criteria: Ages 6–50 years, male and female, have current symptoms suggestive of asthma but without a definitive clinician diagnosis of asthma or an exclusion of the diagnosis of asthma, have not used medications that would interfere with bronchial provocation challenge testing (including ICS), be skin test negative to seasonal and perennial aeroallergens that were present in the environment during the time that the subject was enrolled in the study, have FEV1 ≥ 70% of the predicted value at Screening Visit (Visit 1) baseline

- Primary Endpoint: sensitivity and specificity of Aridol and methacholine with respect to EIB as a manifestation of BHR
  - Aridol positivity defined as PD15FEV1 at any dose until the maximum dose had been given or between-dose drop of ≥10% in FEV1)
  - methacholine positivity-PC20FEV1 less than or equal to either 12 mg/ml or 16 mg/ml [ATS defined])
  - exercise positivity defined as > 10 % fall in FEV1 after either of two standardized treadmill runs
- The gold standard for the primary analyses was one or more positive exercise challenges
- The primary objective of acceptable sensitivity would have been met if the lower confidence limit for mannitol sensitivity equaled or exceeded 0.60. The observed lower endpoint was 0.509, thus the primary endpoint for sensitivity was not met.

- The primary objective of superiority for specificity would have been met if the specificity of mannitol was > methacholine at the 0.025 level. Estimated mannitol specificity was lower than methacholine specificity (0.652 vs. 0.690). Thus, the primary objective of superiority of mannitol for specificity was not met.
- Secondary Endpoint: sensitivity and specificity of Aridol and methacholine with respect to physician-diagnosed asthma and correlations among Aridol (PD15FEV1), methacholine (PC20FEV1) and exercise (fall in FEV1), respectively
- Safety endpoints
  - Pre/post challenge ECG, AEs, vital signs, pulse oximetry and spirometry
  - Lab data not obtained as mannitol is characterized as a GRAS excipient for food substances at doses up to 20 g/day
- The sensitivity and specificity of mannitol ($PD_{15}FEV_1$) and methacholine ($PC_{20}FEV_1$ at 16 mg/mL) with respect to physician-diagnosed asthma at Visit 5 were 55.4% and 72.8% for mannitol and 49.8% and 75.0% for methacholine (NS), showing mannitol and methacholine to be highly comparable and consistent.

DPM-A-301

Non-IND safety and efficacy clinical study, R, MC, OLD, operator-blinded, X-over trial to investigate the safety and efficacy of dry-powder mannitol as a BPT for airway hyperresponsiveness in 646 subjects, ages 6 to 83 years, with (n = 551) and without (n = 95) signs and symptoms of asthma.

- Primary Objective: to determine the sensitivity and specificity of the mannitol challenge compared to hypertonic (4.5%) saline challenge as a bronchial provocation test for assessing airway hyperresponsiveness

- Results:
  - Per-Protocol Population analyzed for PD15 was 592 subjects. The mannitol BCT was positive in 296 subjects (50%).
  - With respect to the 4.5% saline challenge, the sensitivity of the mannitol challenge PD15 was 81%, and the specificity was 87%.
  - When the overall diagnosed asthmatic/non-asthmatic group was analyzed, the sensitivity of the mannitol challenge PD15 with respect to the clinical diagnosis was 60%, with a specificity of 95%
    - Use of ICS was shown to reduce the response to the mannitol challenge. When subjects taking ICS were removed from the analysis, sensitivity improved to 70%, with specificity remaining at 95%
- Study DPM-A-301, the mannitol PD15 had a sensitivity of 81% and specificity of 87% with respect to PD15 for 4.5% saline.
- A positive mannitol test cut-off of a 15% fall in FEV1 (PD15) provided appropriate sensitivity and specificity with respect to clinical diagnosis of asthma even when the patient's baseline FEV1 was within the normal range.

- Based on an analysis of patients with a clinical diagnosis of asthma, and excluding those with a negative test result and on current corticosteroid therapy, mannitol PD15 had a sensitivity of up to 89% to detect the presence of asthma and specificity of 95% for clinical diagnosis of asthma.

VII. ADVISORY COMMITTEE MEETING

Request for Pulmonary Allergy Drugs Advisory Committee meeting will be made.

VIII. DSI REVIEW / AUDIT

The Applicant states that no debarred investigators participated in the study. Preliminary review of the data does not show any treatment-center effects. Because there are no financial conflicts with investigators or treatment-center effects, A DSI audit is recommended for the study sites which enrolled the most patients in Study DPM-A-305 (Ratner, Texas, 40 subjects; LaForce, North Carolina, 43 subjects; and Rundell, Pennsylvania, 36 subjects.

IX. SUMMARY

This is a 45-day filing and planning review of NDA 22-368 Aridol (mannitol bronchial challenge test). This NDA supplement is submitted in support of the use of mannitol for the assessment of bronchial hyperresponsiveness to aid in the diagnosis of patients ≥ 6 years of age with symptoms of or suggestive of asthma. The sponsor is Pharmaxis Ltd.

The clinical program for this NDA consists of two studies including two Phase 3 trials, one pivotal and one supportive and referenced literature.

- Study DPM-A-305 a clinical safety and efficacy trial to assess the sensitivity and specificity of Aridol to detect exercise induced bronchospasm as a manifestation of bronchial hyperresponsiveness.
- Study DPM-A-301 a clinical safety and efficacy non IND trial to determine the sensitivity and specificity of Aridol compared to hypertonic (4.5%) saline challenge as a bronchial provocation test to asses airway hyperresponsiveness.

The submission appears complete to allow for a further more complete review, and is therefore considered “fileable.” The Division will plan to present this NDA to the Pulmonary-Allergy Drugs Advisory Committee as this NDA is for a drug to be used in a novel format as a diagnostic test. An audit by the Division of Scientific Investigations will be requested.

X. REVIEW TIMELINE

Milestone	Target date for completion
Filing and planning meeting	April 13, 2009
74-day letter	May 12, 2009
Midcycle review meeting	August 3, 2009
Label	September 28, 2009
Wrap-up meeting	October 27, 2009
PDUFA Action date (10 months)	December 27, 2009

XI. REVIEWER COMMENTS

The application is fileable from a clinical standpoint. No clinical comments will be conveyed to the Applicant at this time.

Reviewed by:

_____
Anya C. Harry, M.D., Ph.D.
Medical Officer, Division of Pulmonary and Allergy Products

_____
Anthony Durmowicz, M.D.
Medical Team Leader, Division of Pulmonary and Allergy Products

ADDENDUM

NDA/BLA Number: 22368 **Applicant: Pharmaxis** **Stamp Date: February 27, 2009**

Drug Name: Aridol **NDA/BLA Type:**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	x			

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 DPM-A-305 Indication: Dx of asthma Pivotal Study #2 DPM-A-301 Indication: Dx of asthma				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	x			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver for < 6 years of age
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?				
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

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

/s/

Anya Harry
5/11/2009 11:43:20 AM
MEDICAL OFFICER

Anthony Durmowicz
5/11/2009 11:47:46 AM
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