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RESEARCH**

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2) Resubmission after RTF
Application Number	NDA 205,555
Reference NDAs	NDA 20,587 (Bryan) NDA 21,388 (Bryan)
Priority or Standard	Standard
Submit Date	April 14, 2016
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Division / Office	DOP1/OHOP
Reviewer Name(s)	Nancy S. Scher, MD Laleh Amiri-Kordestani, MD
Review Completion Date	January 16, 2017
Established Name	Talc powder
(Proposed) Trade Name	STERITALC®
Therapeutic Class	Sclerosing agent
Applicant	Novatech S.A.
Formulations	2, 3, and 4 g, single-dose vial
Dosing Regimen	2-5 g intrapleurally (Malignant Pleural Effusion) (b) (4) 2 g intrapleurally (Pneumothorax)
Proposed Indications	Malignant pleural effusion Pneumothorax
Intended Population	Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The FDA Microbiology Team determined that the applicant has not provided adequate controls for endotoxin, precluding approval at this time. This is a 505(b)(2) application referencing two approved talc products and providing substantial evidence of safety and efficacy based on clinical data from the published literature. In addition to the unresolved issues with regard to Microbiology requirements, there are unresolved issues with regard to compliance with the recently implemented International Council on Harmonization (ICH) Q3D Guidance on Elemental Impurities. The 510k clearance for Novatech's Talcair device for talc poudrage for the pneumothorax indication is also pending.

When the Microbiology and Elemental Impurity issues are resolved, based on the clinical data, NDA 205,555 should be granted full approval for the following indications:

- Steritalc is indicated to decrease the recurrence of malignant pleural effusions (MPE) in symptomatic patients following maximal drainage of the pleural effusion.
- Steritalc is indicated in adults to decrease the recurrence of (b) (4) pneumothorax (b) (4)

1.2 Risk Benefit Assessment

This is a 505(b)(2) application referencing two approved asbestos-free talc products and providing substantial evidence of safety and efficacy based on clinical data from the published literature for both (b) (4) indications. The application references two Bryan Corporation products, Sclerosol® (NDA 20,857), approved in 1997, and Sterile Talc Powder (NDA 21,388), approved in 2003, for (b) (4) of malignant pleural effusion (MPE). Sclerosol is administered intrapleurally as an aerosol. Sterile Talc Powder is administered as an aqueous slurry into a thoracostomy tube. Both products were 505(b)(2) applications, referencing the published literature, and Sterile Talc Powder also referenced Sclerosol for safety and efficacy. No clinical trials were conducted for the Bryan applications, nor were any trials conducted by Novatech for Steritalc.

Steritalc is marketed in more than 50 countries around the world and has been marketed in Europe since at least 1999 for pleurodesis. The published literature includes data on more than 900 patients treated with Steritalc in Europe and elsewhere for the pneumothorax indication and more than 700 patients treated for malignant pleural effusion. Talc is an effective sclerosing agent, and has been used for both MPE

and pneumothorax. Steritalc is asbestos-free, graded talc, with smaller particles selectively removed, compared with the current US-approved talc products, which are considered “mixed” talc. The literature supports a superior safety profile for Steritalc regarding the potential for hypoxemic pulmonary toxicity. Carcinogenicity is not a serious concern if talc is asbestos-free. Long-term studies have shown good preservation of pulmonary function many years after talc pleurodesis for pneumothorax.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The clinical team does not recommend REMS or Medication Guide for marketing of Steritalc

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team does not recommend any Postmarketing Requirements (PMR) or Postmarketing Commitments (PMC).

2 Introduction and Regulatory Background

Introduction

Therapeutic pleurodesis is commonly used to prevent recurrence of symptomatic malignant pleural effusions for cancers not readily responsive to systemic therapies and to treat recurrent or complicated pneumothorax. Pleurodesis may be achieved by surgical abrasion or by the instillation of a sclerosing agent into the pleural cavity to promote adherence of the visceral to the parietal pleura. This pleural symphysis obliterates the potential pleural space in order to prevent re-accumulation of fluid or air following evacuation of fluid/air from the space and to permit expansion of the lung. A sclerosing agent may be instilled into the pleural cavity by a surgical approach such as video-assisted thoracoscopic surgery (VATS) or at the bedside via a thoracostomy tube. A variety of sclerosing agents have been used to treat symptomatic MPE and pneumothorax (see section 2.2).

- Malignant pleural effusion (MPE) is a common cause of morbidity in patients with advanced cancer. Symptoms include progressive dyspnea, cough, and chest pain. Effusion is caused by direct pleural tumor invasion. The most common primary sites are lung cancer and breast cancer. MPE has been estimated to affect at least 150,000 people each year in the US (Clive 2016). Bethune (1935) introduced thoracoscopic talc poudrage in 1935 as a method to induce pleural adhesions to facilitate lobectomy. In 1958, Chambers reported the use of talc slurry administered by a chest tube to treat MPE in 1958. Talc powder is frequently administered intraoperatively by open surgical or thoracoscopic

insufflation. Talc may also be administered bedside, following drainage of pleural fluid, as an aqueous slurry through a percutaneously placed chest tube.

Compounded US Pharmacopeia talcs were used in the US prior to the approval of Bryan Steritalc in 1997 (administered by aerosol during open thoracotomy or by thoracoscopy) and Bryan Sterile Talc Powder in 2003 (administered as aqueous slurry by chest tube).

- Pneumothorax is the presence of air in the pleural space with secondary lung collapse. The spectrum of severity may vary between asymptomatic and hemodynamically compromised. Pneumothorax may be “spontaneous,” with no antecedent event or secondary to trauma. Spontaneous pneumothorax may be further classified into primary or secondary. Primary spontaneous pneumothorax (PSP) most often occurs in healthy young people, especially males, without an apparent lung disorder. However, smoking is a risk factor, and patients with apparent PSP could have unrecognized lung disease, such as pleural blebs, with pneumothorax resulting from rupture of a bleb. Secondary spontaneous pneumothorax (SSP) is associated with known underlying lung disease, particularly chronic obstructive pulmonary disease (COPD) with bullous disease. The estimated incidence of PSP is 7.4 cases per 100,000 (men) and 1.2 cases/100,000 (women) in the US. PSP has a recurrence range from 25 percent to more than 50 percent, with most recurrences seen within the first year (UpToDate 2016).

Since recurrences of PSP progressively increase after a second or third episode (How 2013), management of recurrent pneumothorax often includes pleurodesis after drainage. Both surgical and chemical methods have been used. In 2001, the American College of Chest Physicians (ACCP) commissioned the development of practice guidelines for the management of PSP (Baumann et.al. 2001). A literature search from 1967 to 1999 obtained 9 articles, which included 8 randomized trials and 1 practice guideline. For pneumothorax recurrence prevention, the ACCP guidelines recommend that except for patients with persistent air leaks (defined as air leaks persisting beyond 4 days); procedures to prevent the recurrence of a PSP should be reserved for the second occurrence (85% of panel members). Thoracoscopy was preferred and instillation of a sclerosing agent through a chest tube was acceptable. Success rates with chemical pleurodesis are reported as 78-91%, for a variety of sclerosing agents, compared with 95-100% for surgical intervention. However, in a randomized trial, Tschopp et al (2015) report a success rate for talc pleurodesis of greater than 95%, which is comparable to that for surgical abrasion. For patients with SSP, 81% of panel members recommended an intervention after the first pneumothorax because of the potential lethality of recurrence in patients with underlying lung disease.

In 2015, the European Respiratory Society’s (ERS) Task Force published recommendations on treatment of PSP (Tschopp et al 2015) based on a

systematic literature search of publications from 1993 to 2014. They cite recurrence rates for PSP of 17-54% in the first year following pneumothorax. ERS summarizes the indications for definitive management of PSP to include a second episode, persisting air leak (>3-5 days), hemopneumothorax, bilateral pneumothorax, and professions at bariatric risk. Talc is cited as the most commonly used agent in Europe, administered as poudrage by thoracostomy, with a success rate of 93-97%. **Novatech Steritalc** 2-4 g is specifically cited in this reference, and mention is made of the improved safety of “graded talc” with no incidences of adult respiratory distress syndrome reported in European series compared with North American series after “talc poudrage using only American Food and Drug Administration approved talc,” which is “ungraded,” containing some particles of smaller size.

Regulatory Background

This New Drug Application (NDA) is submitted under the Federal Food, Drug and Cosmetic Act (“the Act”) section 505(b)(2). The application is a resubmission following issuance of a Refuse to File (RTF) Letter on May 3, 2013. FDA cited 67 deficiencies. Some of the deficiencies include unsatisfactory organization and incompleteness of the application, illegible information, incomplete translation to English, inaccurate description of the proposed Reference Listed Drugs (RLDs), incomplete specifications for drug substance (DS), no documentation of bioequivalence of active ingredient to a reference drug or request for a waiver. Since [REDACTED] (b) (4) is not an FDA-approved indication [for previous talc products], the application could not rely on prior findings of safety and effectiveness, and the application did not discuss how references from the literature support effectiveness and safety of Steritalc for [REDACTED] (b) (4) of pneumothorax. There was no integrated summary of effectiveness or safety for the clinical indications.

The application references two Bryan Corporation approved talc products, Sclerosol® (NDA 20,857) and Sterile Talc Powder (NDA 21,388). They were both 505(b)(2) applications, referencing the published literature, approved in 1997 and 2003, respectively. On December 14, 1995, the Oncology Drug Advisory Committee (ODAC) had recommended approval of Sclerosol under section 505 (b)(2), based on evidence from the medical literature of efficacy and safety from 9 controlled and 24 uncontrolled published trials in patients with MPE using various talc products. For Sterile Talc Powder NDA, Bryan referenced the safety of Sclerosol and also submitted data from 5 controlled trials and 13 single-arm trials from the literature of talc slurry administered intrapleurally via chest tube to patients with MPE to support efficacy and safety. No clinical trials were conducted to support either of the Bryan talc products. The indications for the RLDs are as follows:

- Sclerosol® Intrapleural Aerosol, administered by aerosol during thoracoscopy or open thoracotomy, is indicated to prevent recurrence of malignant pleural effusion in symptomatic patients.
- Sterile Talc Powder, administered intrapleurally as a slurry through a chest tube, is indicated to decrease the recurrence of malignant pleural effusion in symptomatic patients following maximal drainage of the pleural effusion.

The proposed indications for Steritalc are listed in the next section, below. In the cover letter to the NDA, Novatech indicates they are “relying on the published literature, as well as the Agency’s findings of safety and efficacy” for Sclerosol and Sterile Talc Powder. The proposed dosage of Steritalc for the malignant pleural effusion indication does not match the RLDs. Also, the Steritalc pneumothorax indication is an unapproved indication for a talc product in the U.S.

2.1 Product Information

Steritalc® is an asbestos-free talc powder (hydrate magnesium silicate) for intrapleural administration as a sclerosing agent. It is approved as a medical device in Europe and many countries throughout the world. Korea is the only country in which Steritalc is approved as a pharmaceutical (Nov 16, 2015). Novatech’s talc product was approved in Europe initially in 1989 (b) (4) in 1995, the product name changed to Steritalc. In 1996, Novatech developed Steritalc as the same (b) (4) talc powder in vials, (b) (4) Steritalc in vials has been marketed in Europe since 1999. Steritalc is currently approved in 28 countries of the European Union (EU), 4 non-EU European countries, 7 countries in Latin America, 7 countries in the Middle East, 5 countries in Asia, 2 African countries, and Australia.

The proposed indications are:

Steritalc is a sclerosing agent indicated:

- (b) (4) To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximal drainage of the pleural effusion
- (b) (4) pneumothorax.

Steritalc will be supplied in 3 presentations, all containing only (b) (4), asbestos-free, USP grade talc powder, without excipients:

- Steritalc (b) (4) (2 g/vial)
- Steritalc (b) (4) (4 g/vial)
- Steritalc (b) (4) (3 (b) (4) g/vial).

Steritalc (b) (4) and (b) (4) can be used as a suspension (slurry in saline solution) or as poudrage. Steritalc (b) (4) is intended to be used for the administration of talc poudrage in combination with Novatech’s pulverization kit, Novatech Talcair device. The device is a

powder blower comprised of an insufflation cannula, and insufflation bulb and connecting pieces, to attach the device to a vial. The Talcair device is FDA 510(k) cleared (clearance number, K151832) for the following indication:

- Treatment of malignant pleural effusion by insufflation of medical grade talc following drainage of pleural fluid.

The proposed doses of Steritalc for the indications are:

- Malignant pleural effusion (MPE), 2-5 grams intrapleurally
- Pneumothorax (PNX), (b) (4) 2 grams intrapleurally

For both indications, the applicant proposes “discretion” in dosing to the physician, “but a cumulative dosage of 10 g should not be exceeded.”

2.2 Tables of Currently Available Treatments for Proposed Indications

For both indications, initial treatment may include simple aspiration, tube drainage, and chemical sclerosis of the pleura. Long-term indwelling pleural catheters have been used for palliation of symptoms in patients with MPE (Davies 2012). Pleurodesis may be attempted by physical methods only, such as insertion of a chest tube or direct surgical abrasion of the pleural surface. For MPE, a variety of chemical irritants have been used to cause pleurodesis. No products are approved for (b) (4) pneumothorax, although talc is commonly used both for (b) (4) recurrent pneumothorax (PNX), and for malignant pleural effusion (MPE). Quinacrine hydrochloride was used at one time, but it is no longer marketed. Tetracycline hydrochloride for intravenous (IV) administration was commonly used for chemical pleurodesis for both recurrent PNX and MPE until it was taken off the market due to its sclerosing properties (as an IV antibiotic). The tetracycline derivatives, such as doxycycline and minocycline, are less efficacious. Povidone-iodine has been administered through tube thoracostomy or thoracoscopy to treat MPE and PNX with efficacy of approximately 90% reported in a meta-analysis of observational studies (Agarwal 2006). The following table lists treatments that are currently approved in the U.S. to treat or decrease recurrence of MPE.

Table 1: FDA Approved Sclerosing Agents for (b) (4) Malignant Pleural Effusion (Reviewer Table)

DRUG	INDICATION	BASIS for Approval
*Sclerosol Intrapleural Aerosol 1997	To prevent recurrence of malignant pleural effusions in symptomatic patients	505(b)(2) referencing medical literature , controlled (9) and uncontrolled (24) trials
Sterile Talc Powder 2003	To decrease recurrence of malignant pleural effusions in symptomatic patients following maximum drainage of the pleural	505(b)(2) referencing safety of Sclerosol, and medical literature, controlled (5) and uncontrolled (13) trials

	effusion	
Bleomycin sulfate	Sclerosing agent for treatment of malignant pleural effusion and prevention of recurrent pleural effusions	Randomized trial, 30-day recurrence rate 36% for bleomycin vs. 67% for tetracycline IV
Thiotepa for Injection, USP	For controlling cavitory effusions secondary to diffuse or localized neoplastic diseases of various serosal cavities	Not provided in product label
Mustargen (mechlorethamine HCl) for Injection	Intrapleurally, intraperitoneally, or intrapericardially, for palliative treatment of metastatic carcinoma resulting in effusion	Not provided in product label

*The December 14, 1995, Oncology Drug Advisory Committee (ODAC) recommended approval of Sclerosol based on evidence from the medical literature of efficacy and safety of talc under section 505 (b)(2) of the Food, Drug and Cosmetic Act.

Anti-neoplastic agents would be contraindicated for off-label use for patients with non-neoplastic disease (recurrent pneumothorax). Mechlorethamine is rarely used to treat MPE because of severe pain associated with administration. The efficacy of talc administered by poudrage or chest tube slurry is $\geq 90\%$, with a low incidence of serious adverse events, resulting in talc being commonly used in the US and internationally for treatment of MPE.

2.3 Availability of Proposed Active Ingredient in the United States

There are two approved talc products marketed in the United States, both by the Bryan Corporation, Woburn, MA.

- Sclerosol® Intrapleural Aerosol, administered by aerosol during thoracoscopy or open thoracotomy, is indicated to prevent recurrence of malignant pleural effusion in symptomatic patients.
- Sterile Talc Powder, administered intrapleurally as a slurry through a chest tube, is indicated to decrease the recurrence of malignant pleural effusion in symptomatic patients following maximal drainage of the pleural effusion.

2.4 Important Safety Issues with Consideration to Related Drugs

Adult Respiratory Distress Syndrome (ARDS) has been reported in the literature with talc, and in the FDA Adverse Event Reporting System (FAERS) for the approved Bryan products in patients with MPE. The literature suggests an association of ARDS with the administration of higher doses of talc such as 10 g (Rinaldo 1983). The literature also suggests that acute pneumonitis/ARDS may be associated with talc products with smaller median particle size, due to systemic absorption of talc (Ferrer 2001, Janssen 2007, Gonzalez 2010, Bridevaux 2011). It has been suggested that conducting mechanical abrasion of the pleura and/or biopsy at the time of talc instillation may also

facilitate absorption of talc particles into the circulation by disrupting pleural capillaries. (Aelony 2011, Rehse 1999).

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The following table summarizes important pre-submission regulatory activity for this application.

Table 2: Regulatory History (Reviewer Table)

Date	Meeting or Event
December 8, 1997	Orphan Drug Status granted for malignant pleural effusion (MPE) (#97-1067)
December 8, 1997	Orphan Drug Status granted for pneumothorax (#97-1092)
February 17, 2009	Type B pre-IND (#104,068)/pre-NDA meeting between Novatech and FDA/Division of Drug Oncology Products (DDOP) regarding Steritalc (sterile talc powder). FDA responded that an NDA submission under section 505(b)(2) of the Act, referencing published literature, might be acceptable. FDA responded to Novatech's questions about user fees and establishment fees. Novatech inquired about providing Steritalc to physicians under an Emergency/Treatment IND. FDA advised this was not appropriate, and Novatech should initiate and enroll patients in a clinical trial under an IND.
March 1, 2013	NDA submitted to FDA/Division of Oncology Products 2 (DOP2)
May 3, 2013	DOP2 issued a Refuse to File (RTF) Letter (67 deficiencies)
June 27, 2013	Type A meeting between Novatech and DOP2 to discuss RTF Letter
March 31, 2016	Talcair powder blower for talc insufflation FDA cleared (K151832) for the MPE indication
April 15, 2016	Novatech resubmits NDA to FDA/Division of Oncology Products 1 (DOP1)

On June 23, 2016, DOP1 issued a Letter to Novatech that the application was sufficiently complete to be filed.

2.6 Other Relevant Background Information

Steritalc is marketed in many countries in Europe, Asia, Latin America, and in Australia. Novatech has marketed Steritalc as a powder contained in vials in Europe since 1999, and prior to that, from 1989, the same (b) (4) talc was packaged as a (b) (4) (b) (4) (b) (4) in 1995, the product name was changed to Steritalc. The following table, provided by the Applicant, summarizes the countries in which Steritalc is marketed and the year of authorization. It should be noted that Steritalc is marketed as a device, not a drug, in all of these countries, with the exception of South Korea, where it is marketed as a drug. Specifically, the Steritalc (b) (4) presentation is available in South Korea.

Table 3: Countries in which Steritalc is Marketed and Year of Authorization (Applicant Table)

Country	Year of approval	Country	Year of approval
European Union		Latin America	
France	1999	Chile	2013
Italy	1999	Costa Rica	2014
Germany	1999	Argentina	2013
UK	1999	French Guyana	2015
Spain	1999	Jamaica	2015
Belgium	1999	Cameroun	2011
Bulgaria	2007	Trinidad/Tobago	2012
Slovakia	2004		
Netherlands	1999	Australia	
Poland	2004	Australia	2007
Portugal	1999		
Greece	1999	Africa	
Hungary	2004	South Africa	2011
Sweden	1999	Kenia	2015
Romania	2005		
Slovenia	2004	Middle East	
Finland	1999	Iran	2015
Ireland	1999	Israel	2009
Denmark	1999	Sudan	2016
Estonia	2004	Turkey	2015

Croatia	2011	UAE	2008
Latvia	2004	Pakistan	2013
Lithuania	2004	Morocco	2001
Luxemburg	1999		
Malta	2004	Asia	
Austria	1999	Hong Kong	2005
Czech Republic	2004	Thailand	2013
Cyprus	1999	Korea	2015
		India	2016
Europe (non EU)		Malaysia	2015
Switzerland	1999		
Norway	1999		
Iceland	1999		
Lichtenstein	1999		

In response to FDA inquiry, the Applicant provided all known safety reports (23 from 2005 to 2014). None of these were clinical and were generally of the nature, “Hole in the pouch” or other packaging concern, consistent with the device designation of the product. In South Korea, where Steritalc is authorized as a drug, it is exempted from safety reporting, as is its (Bryan) competitor. The Applicant indicates that they are in contact with the Korean distributor and “there are no known safety issues since the product is on the market.”

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The organization of the eCTD submission is satisfactory. The sponsor has referenced the previous FDA reviews for the two Bryan talc products and conducted an updated review of the medical literature to support the safety and efficacy of talc for (b) (4) malignant pleural effusion and for the new indication, (b) (4) pneumothorax.

3.2 Compliance with Good Clinical Practices

No clinical trials were conducted by the applicant.

3.3 Financial Disclosures

No financial disclosures have been submitted. No clinical trials were conducted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Steritalc is composed of asbestos-free sterile talc powder. Talc is a hydrated magnesium silicate ($\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$). The composition of talc ore and related impurities vary depending on the geographic location in which the talc is mined. For detailed discussion of CMC issues, please see the separate reviews of Haripada Sarker, Ph.D. (Drug Substance), Nina Ni, Ph.D. (Drug Product), and Gerlie Gieser, Ph.D. (Biopharmacology Reviewer).

In 2011 the applicant purchased (b) (4) Steritalc. The applicant considers this asbestos-free and sized talc to be (u) (4) for Steritalc. FDA considers this to be Drug Substance (DS). (b) (4) , when FDA conducted inspections during the week of Oct. 28, 2016, there was no fully-operational DS facility to inspect. It appears that FDA may agree to consider the (b) (4) and bess pro gmbh (Germany) facilities both as being DS manufacturing sites.

The FDA Office of Testing and Research (OTR) conducted comparative testing of Steritalc and the 2 Bryan Reference Listed Drugs (RLDs), Sclerosol Intrapleural Aerosol and Sterile Talc Powder. Dr. Akhtar Siddiqui, OTR/Division of Product Quality and Research (DPQR) evaluated Particle Size Distribution (PSD) for the 3 products and *in vitro* permeation. The testing was conducted because of clinical concerns that differences in particle size could affect product safety (See discussion review section 7.2.3).

4.2 Clinical Microbiology

For details of the clinical microbiology issues with the application, please see the separate review of Yarery Smith, Ph.D. The Microbiology team has concerns about Novatech's plan for testing for bacterial endotoxin, container closure integrity testing, and depyrogenation of glass vials. The sponsor submitted a Major Amendment to address these issues on January 6, 2017 (received January 9).

4.3 Preclinical Pharmacology/Toxicology

The applicant did not perform preclinical studies to support the NDA. One review concern was that the applicant's proposed specification for lead per gram of Novatech talc may exceed that recommended in the International Council on Harmonization (ICH) Q3D Guidance on elemental impurities, based on acceptable limits for lead exposure in children. Preliminary testing on a single batch of Steritalc also suggested possibly higher than recommended levels for (b) (4).

To comply with the Q3D Elemental Impurities FDA Guidance for Industry, the applicant has yet to provide all required data. Although the lead level for the Permitted Daily Exposure (PDE) was elevated, for a one or two time usage in a rare disease, FDA has determined that Steritalc for intrapleural use would be acceptable for the MPE indication for adults and children, and only for adults for the pneumothorax indication. In addition, single assessments for other elements have shown the level of (b) (4).

. It may be possible to justify the levels, but the applicant needs to provide the results of testing for a total of 3 lots before FDA can make a determination.

Please see the separate review of George Ching-Jey Chang, Ph.D, for further details.

4.4 Clinical Pharmacology

Novatech has requested a waiver of the requirement for evidence of *in vivo* bioavailability, based on medical literature and on the Agency's review of Clinical Pharmacology and Biopharmaceutics for Sterile Talc Powder (NDA 21,388) and Sclerosol (NDA 20,587). The Clinical Pharmacology Reviewer is Xianhua Cao, Ph.D.

4.4.1 Mechanism of Action

Talc is a Sclerosing agent. When introduced into the pleural cavity, talc is believed to induce an inflammatory reaction, which promotes adherence of the visceral to the parietal pleura, obliterating the (potential) pleural space, which may prevent re-accumulation of pleural fluid or pleural air.

4.4.2 Pharmacodynamics

Talc is administered directly into the pleural cavity and measurement of talc blood levels is not feasible.

4.4.3 Pharmacokinetics

Talc is administered directly into the pleural cavity and measurement of talc blood levels is not feasible.

4.5 Devices and Companion Diagnostic Issues

Novatech submitted (K170030) on Jan. 3, 2017, to request clearance for their Talcair device for the pneumothorax indication since the Talcair device is only cleared for talc poudrage for malignant pleural effusion. There is no device currently cleared in the US for the pneumothorax indication. The Center for Devices and Radiological Health (CDRH) reviewer has indicated that they may be able to complete their review and issue a 510K clearance for the NDA Action Date.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The NDA is a 505(b)(2) application referencing the efficacy and safety of two Bryan talc products, Sclerosol and Sterile Talc Powder, which were 505(b)(2) applications, and for which no clinical trials were conducted. Sclerosol, an aerosol formulation of talc, administered during open thoracotomy or by thoracoscopy, was approved by the FDA for (b) (4) of symptomatic MPE in 1997, based on the published literature for talc. Sterile Talc Powder, administered as an aqueous slurry by chest tube, was approved by the FDA in 2003, referencing the safety of Sclerosol, and the medical literature for safety and efficacy of talc. No clinical trials were conducted for the referenced NDAs or for the current NDA. A variety of talcs were utilized in the published literature. See section 6 (Efficacy) and section 7 (Safety) of this review for discussion of clinical trial data from the published literature.

5.2 Review Strategy

The medical officer reviewed the following materials:

- The regulatory history of the application and related (pre)IND 104,068
- Oncology Drugs Advisory Committee minutes Dec. 14, 1995 (Sclerosol)
- Clinical Review of NDA 20-587 (Bryan Sclerosol Intrapleural Aerosol)
- Clinical Review of NDA 21,388 (Bryan Sterile Talc Powder)
- Electronic submissions of the NDA
- Relevant published literature
- Electronic labeling proposal for Steritalc and approved labels for Sclerosol and Sterile Talc Powder
- Consultation from Lydia Gilbert-McClain, MD, FCCP, Deputy Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
- Consultation from Jitendra Virani, MS, General Surgery Devices, Branch 2, Center for Devices and Radiologic Health (CDRH)
- Consultation from Regina Lee, PharmD, and Afrouz Nayernama, PharmD, review of FDA Adverse Event Reporting System (FAERS) post-marketing reports for US-approved talc products, Sclerosol and Sterile Talc Powder

- FDA response to two Citizen Petitions regarding cosmetic talc products (see review section 7.6.1) and personal communication from Nakissa Sadrieh, Ph.D., Director, Cosmetics Division, Center for Food Safety and Applied Nutrition (CFSAN)

Materials related to the Bryan NDAs were reviewed for regulatory content and evidence of efficacy and safety of talc for the malignant effusion and pneumothorax indications. Since the Bryan RLDs are approved only for the MPE indication, Novatech was required to conduct a literature review as the basis for approval of the new indication for this application, (b) (4) pneumothorax. The medical reviewer conducted an independent literature search, as well, to verify that the sponsor had captured all key data. Of particular interest are new randomized controlled trials (RCT) not previously reviewed for the Bryan applications, especially for the pneumothorax indication, clinical reviews/meta-analyses, and new safety data regarding use of talc. Clinical trials from the published literature which identify their talc source as Steritalc are particularly important.

5.3 Discussion of Individual Studies/Clinical Trials

See section 6 (Efficacy) and section 7 (Safety) of this review for discussion of data from the published literature to support the indications. Several template headings have been deleted from sections 6 and 7. These headings do not pertain to a 505(b)(2) application based on efficacy and safety of two approved talc products and, for the pneumothorax indication, also based on literature review

6 Review of Efficacy

Efficacy Summary

Efficacy of talc as a sclerosing agent is well established. Efficacy depends on the same principle, to achieve pleurodesis, to obliterate the potential pleural space to prevent re-accumulation of fluid or air, respectively, whether the indication is malignant pleural effusion (MPE) or pneumothorax (PNX). As a 505(b)(2) application, the efficacy of the Reference Listed Drugs (RLDs) support efficacy for Novatech Talc. All 3 products are talc in powder form intended for intrapleural use as a sclerosing agent. The applicant has provided an analysis of the relevant published literature to provide support for both indications.

For MPE, the applicant has referenced the NDA clinical reviews for the 2 previously approved talc products. The applicant has also conducted an updated literature review to provide adequate and well-controlled trials from the published literature with supportive single arm trials to demonstrate the efficacy of talc for the indication. There are published efficacy data for more than 250 patients treated with a talc product clearly identified as Steritalc for the MPE indication.

For PNx, the applicant has provided adequate and well-controlled trials from the literature with supportive single arm trials to demonstrate the efficacy of talc for the indication. There are data from the literature for more than 800 patients treated with Steritalc for PNx. The applicant has also submitted several systematic treatment reviews from the literature which support efficacy. FDA identified and reviewed published consensus guidelines for treatment of primary spontaneous PNx (PSP) from the European Respiratory Society (Tschopp 2015) and the American College of Chest Physicians (Baumann 2011). In general, the guidelines recommend a procedure (surgical or chemical) after the second occurrence of uncomplicated PSP or after the initial episode of secondary SP. Pleurodesis with talc by poudrage or slurry are both effective options to decrease recurrence of PNx.

For the MPE indication, the RLD Bryan Sclerosol is labeled at a dose of 4-8 g for poudrage and the RLD Sterile Talc Powder is labeled at a dose of 5 g for use as a slurry administered via chest tube. For MPE, Novatech Steritalc proposes dosing at 2-5 g either by poudrage or slurry, and this appears to be supported by the literature. For the PNx indication, the proposed dose is (b) (4) 2 g. The dose supported in the published literature for the PNx indication is 2 g.

There are difference in particle size distribution (PSD) between Steritalc and the RLDs, with Steritalc having a lower percent of small particles. Based on literature review, the difference in PSD appears to favor Steritalc, with implications for safety.

6.1 Indication (1)

Steritalc is a sclerosing agent indicated:

- (b) (4). To decrease the recurrence of malignant pleural effusions in symptomatic patients following maximum drainage of the pleural fluid.

6.1.1 Methods

For efficacy, the applicant references the FDA Approval Summaries for Sclerosol (NDA 20,587, approved Dec. 24, 1997) and for Sterile Talc Powder (NDA 21,388, approved Dec. 15, 2003). The applicant also conducted a literature search in PubMed to obtain the literature reports of trials that FDA had considered to be adequate and well-controlled as discussed in the FDA Approval, and searched PubMed by “malignant pleural effusion” and talc pleurodesis” to obtain additional references. The applicant abstracted 32 publications, 2 of which are systematic reviews of efficacy of talc in MPE, 17 are prospective, randomized and controlled to support the use of both talc slurry and talc poudrage in treatment of MPE. Thirteen additional publications are prospective and non-comparative or retrospective, 4 of which use talc slurry. To assess the completeness of the applicant’s submitted database, the clinical reviewer conducted an independent literature search, with focus on references published subsequent to

approval of the RLDs. The search terms were “Malignant Pleural Effusion” and “Talc”. The databases searched were PubMed, EMBASE and Cochrane from 1990 through July 2016. There was extensive overlap of the applicant and FDA databases. However, the Novatech database did not reference the systematic review of the literature and meta-analysis for MPE (1888 records, 62 randomized trials, 3428 patients) published by Clive and colleagues (2016).

Efficacy of Talc by Poudrage for Malignant Pleural Effusion (MPE)

NDA 20,587 for (Bryan) Sclerosol Intrapleural Aerosol was approved in 1997 as a 505(b)(2) application, with demonstration of efficacy and safety for (b) (4) of MPE based on the analysis of reports of controlled (9) and uncontrolled (24) trials published in the medical literature. Sclerosol is an aerosol formulation for administration of talc powder during thoracoscopy or open thoracotomy. When the findings were presented to the Oncology Drugs Advisory Committee (ODAC), chaired by Paul Bunn, MD, on Dec. 14, 1995, the Committee and FDA agreed that articles by Sorensen 1984, Fentiman 1986, Fentiman 1983, and Hamed 1989 were the best representation of “adequate and well controlled trials” in the literature. They were prospectively conducted, randomized trials, and provided a definition of success which included objective measures. The safety profile of a single administration of 4 to 8 g of talc was considered acceptable based on the entirety of the available medical literature (comparator and non-comparator trials). Please see the Clinical Review for NDA 21,388 for additional details.

The following table is taken from the Novatech submission. It includes information about 9 randomized controlled trials of talc powder administered as poudrage vs. control to patients with MPE following drainage of pleural fluid. The list includes 3 of the 4 references from the literature with “adequate and well controlled trials” cited by ODAC, Fentiman 1986 and 1983, and Hamed 1989. The 4th trial, Sorensen 1984 is not referenced by Novatech to support poudrage, presumably because the talc arm utilized slurry and the comparator was chest tube drainage. However, the prospectively conducted, randomized trial does demonstrate the efficacy of talc as a sclerosing agent. The additional 6 trials in the table below, are prospective, randomized trials that support efficacy of talc administered as poudrage in symptomatic patients with MPE. These trials were published subsequent to the approval of Sclerosol. The 9 trials have defined an objective measure of success, usually based on decreased fluid reaccumulation over time. The “success” rate across the trials ranged from 84 to 100%. The exact dose of talc administered by poudrage was not provided in all the trials. For the remaining trials, the dose of talc administered was 5 g in 3 trials, 4 g in 1 trial, and 3g in 1 larger trial (Stefani et al) which included 72 patients in the poudrage treatment arm.

Table 4: Randomized Controlled Studies of Talc Poudrage vs. Control for MPE (Applicant Table)

Investigator, Publication	Treatment	Response Rate in Evaluable Patients
Agarwal, Respir 2011; 16: 1064-1069 ^a	5 g cosmetic talc Vs. 20 mL 10% iodopovidone in 80 mL NS	84.2% (16/19) Vs. 78.9% (15/19)
Diacon, Am J Respir Crit Care Med 2000; 162: 1445-1449,	5 g talc + 20-30 mL lidocaine* Vs. 60 IU bleomycin in 100 mL of NS + 20 mL lidocaine 1%	87% (13/15) Vs. 59% (10/17)
Fentiman, Eur J Cancer Clin Oncol 1986; 22: 1079-1081	Talc (exact dosage not given) Vs. 500 mg TCN in 50 mL NS	91.7% (11/12) Vs. 47.6% (10/21)
Fentiman, Cancer 1983; 52: 737-739	Talc (exact dosage not given) Vs. 15 mg mustine in 50 mL NS	90% (18/20) Vs. 52.9% (9/17)
Hamed, et al Br J Surg 1989; 76: 1266-1267	Talc (exact dose not given) Vs. 1 mg/kg bleomycin in 50 mL NS	100 % (10/10) Vs. 33.3% (5/15)
Kuzdzal, Med Sci Monit, 2003; 9(6): PI72-77	10 g Talc Vs. 500 mg doxycycline in 25 mL NS	100% (18/18) Vs. 46.6% (7/15)
Mohsen, Eur J Cardiothorac Surg 40 (2011) 282-286 Metastatic Breast Cancer	4 g Talc (STERITALC®) Vs. 20 mL povidone-iodine in 30 mL NS	91 % (20/22) Vs. 85% (17/20)
Stefani et al., Eur J Cardiothorac Surgery 2006; 30: 827-832	3 g Talc (STERITALC®) Vs. 6 g Talc in 200 mL saline	87.5% (63/72) Vs. 73% (27/37)
Terra, Chest 2009;136;361-368	5 g Talc via VATS Vs. 5 g in 50 mL NS + 5 mL 2% lidocaine	100% (30/30) Vs. 90% (27/30)

* Plus sedatives (midazolam) and analgesics (pethidine)

*In Table 4, above, there is an error: The correct dose for Stefani, above dose is 6 g Steritalc (not 3).

Table 6, later in this review, summarizes randomized controlled trials to support the MPE indication for talc slurry, from the 2003 Clinical Review of NDA 21,388. Table 8 lists additional randomized controlled trials, published after 2003, including trials by Dresler 2005, Mourad 2004, and Yim 1996. These trials use talc insufflation/poudrage as the comparator arm to talc slurry. Both methods are efficacious in these trials.

The sponsor has also identified 5 retrospective published literature series that demonstrate efficacy of poudrage when dosed at 2-8 g. One of these trials, Koschmann 2005 utilized Steritalc 8 g administered by thoracoscopy with success in 76/85 (89%) patients. Milanez de Campos 2001 reported success with 2 g by thoracoscopy in 371/393 (94%) of patients. The following table shows the prospective single arm trials of talc poudrage identified by Novatech from the published literature.

Table 5: Prospective Uncontrolled Talc Poudrage Trials for MPE (Applicant Table)

Investigator, Publication	Dose per Pts	Success (%)
Aelony Y. et al., Ann. Intern. Med. 1991; 115: 778-792	2.5 g Talc powder	82% (23/28)
Aelony Y. et al., Chest 1998; 113:1007-1012	2.5 – 5 g Talc powder	88% (22/25)
Reddy C et al., Chest 2011; 139(6): 1419-23.	5 g Talc powder	92% (24/26)
Ishida A et al., Interact Cardiovasc Thorac Surg 2011;12:667-670	4 g STERITALC® powder	88.9% (8/9)
	Range: 2.5 – 5 g Talc powder	Total: 87.5% (77/88)

These uncontrolled, prospective clinical trials of talc poudrage from the published literature also appear to demonstrate efficacy. The Ishida trial used Steritalc powder at a dose of 4 g. The trials conducted by Aelony, show similar efficacy, using a lower dose of talc (2.5 g) for poudrage.

See section 6.1.8, “Analysis of Clinical Information Relevant to Dosing Recommendations.”

Efficacy of Talc Slurry for MPE

NDA 21,388 for (Bryan) Sterile Talc Powder was approved as a 505(b)(2) application, referencing Sclerosol Intrapleural Aerosol, and an analysis of clinical trials from the published literature. For Sterile Talc Powder, there were 5 randomized trials of talc administered as an aqueous slurry for MPE from the medical literature that were deemed adequate and well-controlled. An additional 14 single-arm trials from the literature with talc slurry administered intrapleurally via chest tube to patients with MPE, following maximal drainage of fluid, supported efficacy and safety for NDA 21,388.

The following table from the 2003 FDA Clinical Review for NDA 21,388 summarizes data from the 5 randomized controlled clinical trials with talc slurry administered to decrease recurrence of MPE in symptomatic patients. For 3 trials, bleomycin was the comparator; in 1 trial (Sorensen 1984) the comparison was between talc and chest tube drainage without addition of a chemical sclerosant; for the fifth trial, the comparison was between talc slurry and talc powder insufflation (Yim 1996).

Table 6: Randomized Controlled Trials of Talc Slurry as Sclerosing Agent for Malignant Pleural Effusion (Reviewer Table)

REFERENCE	TREATMENT	RESPONSE RATE EVALUABLE PTS ^a p value*	RESPONSE RATE ALL PTS p value*	MINIMUM DURATION OF RESPONSE
Sorensen et al. Eur J Respir Dis. 1984;65:131-5	Talc Slurry 10g /250 ml NS vs. Chest Tube drainage	100% (9/9) vs. 58% (7/12) p = 0.04	64% (9/14) vs. 41% (7/17) p= 0.29	3 months (Median duration = 10 months)
Noppen et al. Acta Clin Belg 1997; 52:258-62	Talc Slurry 5g /50 ml NS vs. Bleomycin 1mg/kg /50 ml NS	79% (11/14) vs. 75% (9/12) p = 1.00	79% (11/14) vs. 75% (9/12) p = 1.00	Not given
Zimmer PW et al. Chest 1997; 112(2):430-434	Talc Slurry 5g /50 ml NS ^c vs. Bleomycin 60U /50 ml NS ^c	90% (17/19 ^b) vs. 79% (11/14 ^b) p = 0.63	Not given	Not given
Ong KC et al. Respirology 2000; (5):99-103	Talc Slurry 5g /150 ml NS ^d vs. Bleomycin 1 U/kg /150 ml NS ^d	89% (16/18) vs. 70% (14/20) p = 0.24	64% (16/25) vs. 56% (14/25) p = 0.77	1 month
Yim AP et al. Ann Thorac Surg 1996; 62:1655-8	Talc Slurry 5g /50ml NS, lidocaine 2% 10ml vs. Talc Insufflation 5g powder	90% (26/29) vs. 96% (27/28) p = 0.61	90% (26/29) vs. 96% (27/28) p = 0.61	Not given

*Two-sided p-value based on Fisher's exact test

^aPatients were evaluable if chest x-rays were done to assess response per protocol. Sorensen study, patients also excluded if incomplete lung re-expansion post drainage.

^bData per procedure (33 procedures per 29 evaluable patients, 3 patients with bilateral effusions)

^cPlus lidocaine 1% 20ml

^dPlus lidocaine 1% 10ml

The information for the next table is also taken from the 2003 Clinical Review for NDA 21,388. The table summarizes the 14 single-arm clinical trials deemed supportive of efficacy for talc slurry for the MPE indication. It should be noted that there was significant variation among the trials as to the definition of "response" or "success," and in some trials there was no definition. In both series, doses of 5 or 10 grams were usually administered. In 2 single-arm trials, the dose was 4 grams and in 1 trial, the dose was 3 grams. Please see the Clinical Review for NDA 21,388 for additional details.

Table 7: Single Arm Trials of Talc Slurry for MPE (Reviewer Table)

Reference	Design	Treatment	Response Rate	Age, Mean (Range)	M/F
Adler et al, 1976	Retrospective	Talc 10 gm ^a /250 ml NS	(41/44) 93%	(17-81)	Not given
Webb et al, 1992	Prospective	Talc 5 gm + 3 gm thymol iodide/50 ml NS + lidocaine 1% 20 ml	(28/28) 100%	50 (26-88)	Not given
Kennedy et al, 1994	Retrospective	Talc 10gm / 150-250 ml NS	(38/47) 81%	54.4 (32-84)	40/56 pts (56/73 procedures)
Miller et al, 1994	Retrospective	Talc 2 gm / 50 ml NS	(8/8) 100%	Not given	Not given
Turler et al, 1997	Prospective	Talc 5gm + 3gm thymol iodide/80 ml NS + lidocaine 1% 0.5 ml/kg	(36/39) 92%	63.8 (35-84)	17/26
Jacobi et al, 1998	Prospective	Talc 5gm + 3gm thymol iodide/30 ml NS + lidocaine 1% 0.5ml/kg	(31/33) 94%	60.1 ^b (34-81)	24/26 ^b
Thompson et al, 1998^c	Prospective	Talc 5 gm + 3 gm thymol iodine/100ml NS + lidocaine 2% 20 ml	(14/17) 82%	66 (42-78)	4/11
Bloom et al, 1999^k	Retrospective	Talc 5 gm/100 ml NS +/- lidocaine 1% 20 ml	(6/8) 75%	(22-81)	1/7
Marom et al, 1999^d	Prospective	Talc 5 or 10 gm ^e /100 ml NS + lidocaine 1% 10 ml	(27/32) 84%	64 (26-82) ^f	16/16 ^f
Saffran et al, 2000^g	Prospective	"Talc slurry" 4 gm +lidocaine 1% 50 ml	(6/8) 75%	55 (41-79)	0/10
Sahin et al, 2001^h	Prospective	Talc 5 gm /50 ml NS+ lidocaine 2% 5 ml	(16/19) 84%	56.4 (43-66)	11/13
Prevost et al, 2001	Prospective	Talc 4 gm/30 ml NS+ lidocaine 2% 10 ml on 2 successive days	(22/27) 81%	62.4	9/22
Marom et al, 2002ⁱ	Retrospective	Talc 5 or 10 ^j gm/ 100 ml NS +lidocaine 1% 10ml	11/(13) 85%	63	0/25

^aDose reduced ½ to 2/3s if patient "small or frail"

^bDemographic data includes 14 patients with benign disease, 36 malignant

^cSmall-bore pigtail catheter; 15 patients, 17 procedures; 5 treated previously; 11 loculated

^{d, i, k} Small-bore pigtail catheter

^e 23/60 patients received talc 10 gm; 37 patients 5 gm; 11/32 evaluable patients received 10 gm, 21/32 received 5 gm; evaluable patients are alive at 30 days and had for x-ray

^f Demographic data for evaluable patients (32/60); alive at 1 month and had x-ray

^g Small-bore pigtail catheter to gravity-drainage; outpatient feasibility study

^h Small-bore catheter

^j 3/25 patients received 10 gm; 22/25 patients received 5 gm

From their literature review for the MPE indication, Novatech found 4 additional randomized controlled trials to support the efficacy of talc administered as a slurry. These studies, conducted by Dresler C et al (2005), Haddad FH et al (2004), Mourad J et al (2004), and Terra R et al (2009), were all published subsequent to the approvals of the Bryant talc NDAs. The next table summarizes the findings from these additional trials.

Table 8: Additional Prospective Randomized Controlled Trials of Talc Slurry for MPE (Reviewer Table)

Reference	Treatment	Response Rate (Evaluable Patients)
Dresler, Chest 2005	4-5 g Talc in 100 mL NS ^a Vs. 4-5 g Talc <i>powder</i>	(92/130) 71% Vs. (119/152) 78%
Haddad, World J Surg 2004	4 g Talc in 100 mL NS Vs. 60 units Bleomycin	90.2% Vs. 87.6%
Mourad, JEgypt NCI 2004	5-10 g Talc in 100 mL NS Vs. 5-10 g Talc <i>powder</i> Vs. 20-25 mg/kg Tetracycline in 50 mL NS	(15/20) 75% Vs. (17/20) 85% Vs. (12/20) 60%
Terra, Chest 2009	5 g Talc in 50 mL NS + 5 mL 2% lidocaine Vs. 5 g Talc via VATS ^b	(27/30) 90% Vs. (30/30) 100%

^a NS=Normal Saline

^b VATS=Video-Assisted Thoracoscopy

In the Dressler and Terra trials, and for one arm of the Mourad trial, the comparator to talc slurry was talc powder administered as poudrage. For Dresler, lung expansion >90% was assessed at 1 month. For Haddad, success was no recurrence of effusion on follow-up, or, lack of symptoms with a small effusion and no requirement for re-treatment. Median follow-up and median survival were 2.5 months in this trial of patients with advanced cancer. For the Mourad study, a good response was no pleural fluid recurrence during follow-up, or asymptomatic small recurrence not requiring aspiration for 1 month. For the Terra trial, treatment was considered a failure if a new pleural procedure was required any time during follow-up. Again, there are variations in design and treatment in the trials, and definitions of “response,” but all the trials demonstrate efficacy for talc.

Systematic Review of the Literature and Meta-analysis

A comprehensive systematic review of the literature and meta-analysis for MPE (1888 records, 62 randomized trials, 3428 patients through May 2015) published by Clive and colleagues (2016) provides further support to the efficacy of talc. The authors concluded, based on the rate of pleurodesis failure in randomized controlled trials of intrapleural interventions for adults with symptomatic MPE, that talc poudrage appears to be the most effective method to prevent fluid recurrence. However, they “could not say definitely that it is better than ...giving talc or doxycycline through a chest drain.”

6.1.2 Demographics

The following table shows patient gender and malignancy type for patients in the randomized controlled trials (RCTs) provided to support efficacy for MPE, treated with either talc poudrage or talc slurry. The mean age was 58.6 years. There were 759 females and 452 males, reflecting the common occurrence of malignant effusion in patients with advanced breast cancer. Thirty-nine % of patients in the RCTs had breast cancer and 33% had lung cancer.

Table 9: Gender, Malignancy in MPE Randomized Controlled Trials (Applicant Table)

Investigator, Publication	Gender	Malignancy type		
		Breast	Lung	Other*
TALC SLURRY				
Dresler, Chest 2005; 127: 909-915	F:269 M: 213	115	182	185
Haddad, World J. Surg. 2004; 28: 749-754	F: 57 M: 14	33	12	26
Mourad, J of the Egyp Nat Cancer Inst. 2004; 16: 188-194 ^a	F: 26 M: 34	-	-	-
† Noppen M et al., Acta Clin Belg. 1997; 52(5): 258-62	-	-	-	-
Ong KC Respirology 2000; 5:99-103	F: 21 M: 17	10	19	9
† Sorensen Eur J Respir Dis. 1984: 65(2):131-5	-	-	-	-
Terra, Chest 2009; 136: 361-368	F: 45 M: 15	34	17	9
Yim AP et al., Ann Thorax Surg. 1996; 62:1655-8	F: 37 M: 20	15	33	9
Zimmer, Chest, 1997; 112: 430-434	F: 22 M: 11	5	13	15
TALC POWDER				
Agarwal, Respir 2011; 16: 1064-1069 ^b	F: 17 M: 56	4	23	11
Diacon, Am J Respir Crit Care Med 2000; 162: 1445-1449,	F: 21 M: 15	15	15	6
Fentiman, Eur J Cancer Clin Oncol 1986; 22: 1079-1081	F: 42 M: 0	42	0	0
Fentiman, Cancer 1983; 52: 737-739	F: 46 M: 0	46	0	0
Hamed, et al Br J Surg 1989; 76: 1266-1267	F: 29 M: 0	29	0	0
Kuzdzal, Med Sci Monit, 2003; 9(6): PI72-77	F: 27	16	8	9

Investigator, Publication	Gender	Malignancy type		
		Breast	Lung	Other*
	M: 6			
Mohsen, Eur J Cardiothorac Surg 40 (2011) 282-286 Metastatic Breast Cancer	F: 42 M: 0	42	0	0
Stefani et al., Eur J Cardiothorac Surgery 2006; 30: 827-832	F: 58 M: 51	28	49	32
Total^d	F: 733 M: 418	434 (39%)	371 (33%)	311 (28%)

:- Not given

^a Patients have not been included in total since data on malignancy type was not provided for study

^b 35 patients had pneumothoraces in this study, these 35 patients have not been included in the total M/F tally.

^c Patients not included in total tally for M/F since gender was not specified.

^d The percentages were calculated based on a total of 1151 patients – 35 patients = 1116 patients. Thirty-five of these patients had pneumothoraces in the Agarwal et al., 2011 study. These 35 patients are included in the Total M:F Gender ratio total but not the total malignancy type.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

In Dec. 1995, when ODAC reviewed the NDA for Sclerosol, administered by poudrage, to decrease recurrence of MPE, they determined that the safety profile of a single administration of 4 to 8 g of talc was acceptable based on the entirety of the available medical literature (comparator and non-comparator trials). This is the dose for which Sclerosol is labeled. When Sterile Talc Powder was approved for administration as an aqueous slurry for MPE, the labeled dose was determined to be 5 g, based on the available literature and concerns about potential pulmonary toxicity associated with higher doses. Therefore, Sterile Talc Powder, administered as a slurry, is labeled for a 5 g dose for MPE. The sponsor proposes a dose of 2-5 g for MPE, which agrees with the European label for Steritalc. In randomized controlled trials from the literature, 4-5 g is the dose most frequently used, but there are multiple trials showing efficacy with lower doses for MPE, especially for poudrage. It should be noted that the literature for efficacy of talc for the pneumothorax indication most frequently reports a dose of 2 g. The following applicant tables summarize the doses of talc used in literature reports of controlled trials for MPE.

Table 10: Talc Poudrage Dose in Literature Controlled Trials for MPE (Applicant Table)

Investigator, Publication	Dose of Talc Slurry Used
Agarwal, Respir 2011; 16: 1064-1069 ^a	5 g cosmetic talc
Diacon, Am J Respir Crit Care Med 2000; 162: 1445–1449,	5 g talc + 20-30 mL lidocaine*
Fentiman, Eur J Cancer Clin Oncol 1986; 22: 1079-1081	Talc (exact dosage not given)
Fentiman, Cancer 1983; 52: 737-739	Talc (exact dosage not given)
Hamed, et al., Br J Surg 1989; 76: 1266-1267	Talc (exact dose not given)
Kuzdzal, Med Sci Monit, 2003; 9(6): PI72-77	10 g Talc
Mohsen, Eur J Cardiothorac Surg 40 (2011) 282-286 Metastatic Breast Cancer	4 g Talc (STERITALC [®])
Stefani et al., Eur J Cardiothorac Surgery 2006; 30: 827-832	3 g Talc (STERITALC [®])
Terra, Chest 2009;136;361-368	5 g Talc via VATS

*Stefani, above: The correct dose is 6 g Steritalc (not 3)

Table 11: Talc Slurry Dose in Literature Controlled Trials for MPE (Applicant Table)

Investigator, Publication	Dose of Talc Slurry Used
Dresler, Chest 2005; 127: 909-915	4-5 g/100 mL NS
Haddad, World J. Surg. 2004; 28: 749-754	4 g/100 mL NS
Mourad, J of the Egyp Nat Cancer Inst. 2004; 16: 188-194	5-10 g/100 mL NS
Noppen M et al., Acta Clin Belg. 1997; 52(5): 258-62	5 g/50 mL NS
Ong KC Respiriology 2000; 5:99-103	5 g/150 mL NS, lidocaine 1% 10 mL
Sorensen Eur J Respir Dis. 1984; 65(2):131-5	10 g/250 mL NS
Terra, Chest 2009; 136: 361-368	5 g/60 mL NS
Yim AP et al., Ann Thorax Surg. 1996; 62:1655-8	5 g/50 mL NS, lidocaine 2% 10 mL
Zimmer, Chest, 1997; 112: 430-434	5 g/50 mL NS, lidocaine 1%, 20 mL

Also, see Table 5 (above), which lists the administered dose of talc for prospective, uncontrolled trials of talc poudrage in MPE. These trials appear to demonstrate efficacy for lower doses of talc than the doses used in the controlled trials. Aelony (1991, 1998) administered effective poudrage with talc 2.5 g. In a retrospective, uncontrolled trial, Milanez de Campos (2001) reported successful poudrage in 94% of MPE patients with a dose of 2 g (371/393).

Reviewer Comment: A labeled dose of 2-5 g for MPE, as proposed by the applicant, appears acceptable, particularly for poudrage. Also, see section 9.2 of this review.

6.2 Indication (2)

Steritalc is a sclerosing agent indicated:
(b) (4) of pneumothorax.

6.2.1 Methods

The applicant references the FDA Approval Summary for Sclerosol (NDA 20,587, approved Dec. 24, 1997) and for Sterile Talc Powder (NDA 21,388, approved Dec. 15, 2003). The applicant also conducted a literature search in PubMed by “pneumothorax” and “talc pleurodesis” to support efficacy and safety for the pneumothorax (PNX) indication. The applicant identified 21 individual published studies to support efficacy and 3 systematic reviews (How 2013, Kennedy 1994, and Sepehripour 2011). Among the 21 studies, 7 are comparative, with 4 prospectively controlled, and 3 of these are randomized. Three of the comparative studies are retrospective, historically controlled trials. The 14 remaining publications include a case study, 5 prospective non-comparative studies, and 8 retrospective non-comparative studies. The sponsor additionally references the data on the efficacy of talc in treatment of MPE to support the efficacy of talc as a sclerosing agent to treat PNX.

To assess the completeness of the applicant’s submitted database, the clinical reviewer conducted an independent literature search. The search terms were “Pneumothorax” and “Talc”. The databases searched were PubMed, EMBASE and Cochrane from 1990 through July 2016. There was extensive overlap of the applicant and FDA databases. However, the Novatech database did not reference the European Respiratory Society’s published guidelines on treatment of Primary Spontaneous Pneumothorax (PSP) published in 2015 (Tschopp) or the American College of Chest Physicians (ACCP) guidelines for management of PSP, published in 2011 (Baumann).

Efficacy of Talc for Pneumothorax

The efficacy of talc for the pneumothorax indication is supported by the efficacy of talc in (b) (4) MPE. For both indications, talc is a sclerosing agent. By inducing an inflammatory reaction, talc causes symphysis of the visceral and parietal pleura, obliterating the (potential) pleural space, and therefore, decreasing the possibility of recurrence of air or fluid.

See section 2 of this review for the clinical context and an overview of treatment options for pneumothorax. As discussed, management of recurrent pneumothorax often includes pleurodesis after drainage, and may include surgical and/or chemical approaches. For pneumothorax recurrence prevention, the 2001 American College of Chest Physicians (ACCP) guidelines were based on a formal literature search (Baumann 2001) and recommend, except for patients with persistent leaks, procedures to prevent recurrence of (uncomplicated) primary spontaneous pneumothorax (PSP)

should be reserved for the second occurrence (85% of panel members). For secondary spontaneous pneumothorax (SSP), the panel recommended treatment to prevent recurrence at the time of first occurrence. The European Respiratory Society (ERS) Task Force recommendations were published by Tschopp in 2015, based on a systematic literature search. They cite recurrence rates of 17-54% in the first year after initial PSP, and recommend a definitive procedure after the second episode in most (uncomplicated) circumstances. Whereas the ACCP guidelines appear to prefer talc slurry to talc poudrage, the ERS guidelines appear to have a slight preference for poudrage over slurry. Both groups agree on the efficacy of talc pleurodesis, regardless of the mode of administration. The ERS cites talc as the most commonly used sclerosing agent in Europe, with a success rate of 93-97%, by poudrage via thoracostomy. The ERS guidelines specifically recommend Novatech Steritalc 2-4 g, and the improved safety of “graded” compared with FDA approved “ungraded” talc.

The applicant identified 7 comparative trials from the literature utilizing talc for pneumothorax. Four of these comparative trials were prospectively controlled, of which 3 were randomized, and 3 were retrospective, historically controlled trials. The applicant identified an additional 14 publications to support the efficacy of talc to treat pneumothorax. These non-comparative references include 5 prospective studies and eight retrospective studies. The next table summarizes these 7 comparative trials identified from the published literature utilizing talc in the management of pneumothorax. The design for each of these trials, treatment administered, and success (lack of recurrence of pneumothorax) are provided. Additional demographic information regarding these trials is contained in section 6.2.2 of this review.

Table 12: Comparative Trials of Talc for Pneumothorax (Applicant Table)

Investigator, Publication	Design	Treatment	Dosage	Success
Agarwal R et al., <i>Respir</i> 2011; 16: 1064-1069	Prospective, randomized	Drainage output < 150 mL/day, cosmetic talc	5 g cosmetic talc	Pnx: 14/14 -100%
	Active concurrent control	Drainage until output < 150 mL/day, 10 % iodopovidone	20 mL of 10% iodopovidone in 50 mL NS	Pnx: 20/20 -100%
Almind M et al., <i>Thorax</i> 1989;44:627-630	Prospective randomized	Talc pleurodesis	5 g in 250 mL NS	22/24 (91.66%)
	Active concurrent control	Simple Drainage	NA	16/25 (64%)
	Active concurrent control	Tetracycline pleurodesis	550 mg tetracycline in 20 mL sterile water	21/24 (87.5%)
Kim SJ et al., <i>Korean J Thorac Cardiovasc Surg</i> 2011;44:225-228	Retrospective	Conventional treatment (chest tube insertion and chemical (talc) pleurodesis)	Not given	27/39 (69%) (Recurrence: 12/39 (31%))
	Historic controlled	Video-assisted thoracoscopic Surgery (VATS) with Talc	2 g talc	21/22 (95.5%) (Recurrence: 1/22 (4.5%))
Moreno-Merino, <i>Interactive CardioVascular and Thoracic Surgery</i> 0 (2012) 1-5	Retrospective	Talc poudrage, via insufflating (Group B)	2-3 g STERITALC [®]	395/399 (98.99%) (Re-intervention in 4 cases, 4 cases of recurrence (1.01%))
	Historic controlled	Pleural abrasion (Group A)	NA	382/399 (96%) (Re-intervention in 17 (4.3%) patients, 11 due to recurrence)
Ng CK et al., 2010 <i>Int J Tuberc Lung Dis</i> 14(10): 1342-1346	Multicenter Retrospective	Talc Pleurodesis: Talc slurry via the intercostal tube	2.5 – 5.0 g in 100 mL NS	Immediate Success: 46 (71.9%)
	Historic Controlled	Minocycline	300 mg in 100 mL NS	Immediate Success: 95 (78.5%)
Noppen M et al., <i>Eur Respir J</i> 1997; 10: 412-416	Prospective	Thoracoscopic talcage in patients with PSP	2 g talc (insufflated)	29/31 (93.5%) (Recurrence: 2/31 (6.5%))
		Thoracoscopic talcage in patients with SSP	2 g talc (insufflated)	21/23 (91.3%) (Recurrence: 2/23 (8.7%))
Tschopp, <i>Eur Respir J</i> 2002; 20: 1003-1009	Multicentre Prospective Randomized	Simple thoracoscopic talcage (TT) w/ local anesthesia	2 g talc + 1 % lignocaine	60/61 (98.4%) (Immediate recurrence: 1/61 (1.6%)) 56/59 (95%) Recurrence after 5 years: 3/59 (5%)
				37/47 (78.7%) (Immediate recurrence: 10/47 (21.3%)) 31/47 (66%) (Recurrence after 5 years: 16/47 (34%))
	Active Concurrent Control	Pleural drainage (PD) via chest tube	NA	

The 3 randomized, controlled trials from the literature of talc for pneumothorax are the publications by Agarwal 2011, Almind 1989, and Tschopp 2002. The largest of these trials is the Tschopp trial, comparing talc by medical thoracoscopy vs. simple chest tube

drainage of PSP after failure of treatment by simple aspiration. The Almind trial randomized patients with their first episode of PSP to either simple drainage, or drainage plus tetracycline pleurodesis or drainage with talc pleurodesis (5 g). The fourth prospective trial was conducted by Noppen, in which there were 2 parallel cohorts each treated by thoracoscopic talcage with 2 g of talc. One cohort consisted of patients with P(rietary)SP and one cohort consisted of patients with S(econdary)SP. The table in review section 6.2.2 provides demographic information about patients in the comparator trials, including the number of patients with PSP vs. SSP. In the Almind and Tschopp trials, both randomized trials, all patients had PSP. In the remaining prospective randomized trial, Agarwal, there were 10 patients with PSP and 25 with SSP. The Agarwal trial was a subset of a larger trial that also randomized patients with MPE, following drainage to either 5 g cosmetic talc or iodopovidone administered by tube thoracostomy. The definition of “success” varied but in general was defined around rate of recurrence of pneumothorax following treatment. (See table below for definitions of “success” for the comparative trials). The comparative trials showed efficacy for talc pleurodesis in decreasing recurrence of pneumothorax, for PSP and for SSP, and whether talc was administered as poudrage or by slurry via chest tube.

Table 13: Definitions of "Success" for the Comparative Trials of Talc in Pneumothorax (Applicant Table)

Compared Studies	
Agarwal, Respir 2011; 16: 1064-1069	Pneumothorax: criterion for failure was any recurrence of pneumothorax during follow up period
Almind M et al., Thorax 1989;44:627-630	Success was defined as no recurrence.
Kim SJ et al., Korean J Thorac Cardiovasc Surg 2011;44:225-228	Success was defined as to which method has low recurrence rate, less hospitalization time, and morbidity and mortality rate.
Moreno-Merino, Interactive CardioVascular and Thoracic Surgery 0 (2012) 1-5	Complete lung re-expansion was observed. The variables studied were recurrence, surgical time, morbidity and in-hospital length of stay.
Ng CK et al., 2010 Int J Tuberc Lung Dis 14(10): 1342-1346	This study compared the immediate sclerosing efficacy in prevention on SSP recurrence. Immediate failure was defined as having recurrence of pneumothorax within the same hospitalisation after the pleurodesis.
Noppen M et al., Eur Respir J 1997; 10: 412-416	Study endpoints (Macroscopic thoracoscopic findings, duration of the procedure, perioperative complications, postoperative pain and fever, duration of chest tube drainage, hospital stay and recurrence rate) were compared between the two groups.
Tschopp JM, Eur Respir J 2002; 20: 1003-1009	Recurrence of SP was defined as a relapse of pneumothorax requiring any further intervention, either immediately or during a second hospitalisation. Side-effects, recurrence rate and pain felt by the patient during and after each procedure were prospectively assessed, and the costs of the two procedures was calculated as precisely as possible.

The remaining 3 comparative studies, Kim 2011, Moreno-Merino 2012, and Ng 2010, were all retrospective evaluations with historical controls.

Kim (2011) compared VATS + talc pleurodesis vs. chest tube insertion + talc pleurodesis for secondary spontaneous pneumothorax (SSP) in an elderly population (n=61) with underlying lung disease. The dose of talc was 2 g in the VATS group and not clearly specified in the (chest tube) control group. Selection for VATS was biased in favor of patients with good clinical condition (to permit a surgical procedure), and persistent air leak for > 5 days, inadequate lung expansion, and/or presence of multiple

bullae on CAT scan. The chest tube patients ceased to have an air leak after “one or two episodes of chemical pleurodesis.”

Reviewer comment: *In the Kim trial, the recurrence rate was lower for the VATS (Video-Assisted Thoracoscopic Surgery) plus talc treatment arm compared with talc alone, for these patients who all had underlying lung disease. This is not a useful comparison regarding efficacy of talc because there were necessary baseline differences in the two treatment groups. Patients in both treatment arms received talc pleurodesis. The VATS group also may have had surgical therapy (e.g. excision of bullae, etc.) in addition to talc pleurodesis.*

Moreno-Merino (2012) was a retrospective comparative study of talc poudrage versus pleural abrasion for treatment of primary spontaneous pneumothorax (PSP). The majority of patients were male and the majority had been smokers. The mean ages were similar for the 2 treatment groups. From 1992 to 2010, 787 patients were treated for PSP at the University Hospital in Seville, Spain. Group A (n=399) was treated with mechanical pleural abrasion and Group B (n=388) was treated with talc pleurodesis. All patients underwent videothoracoscopy and selective bronchial intubation, maintaining collapse in the affected lung during the procedures. Talc poudrage was performed by insufflating 2-3 g of sterile asbestos-free talc (Novatech, **STERITALC**). The authors concluded that both techniques were effective. The recurrence rate and need for re-intervention was 2.76% in the surgical abrasion group and 1.03% in the talc group, not a significant difference. The authors also concluded that talc poudrage was associated with less morbidity.

Ng (2010) was a retrospective analysis of patients with secondary spontaneous pneumothorax (SSP) who underwent chemical pleurodesis in 2004 at 12 hospitals in Hong Kong with either minocycline or talc slurry. The primary goal was to compare the immediate sclerosing efficacy of intrapleural minocycline versus talc slurry in prevention of SSP recurrence. There were 121 patients treated with minocycline and 64 treated with talc slurry. Minocycline 300 mg was diluted in 100 mL of Normal Saline (NS) and talc 2.5 to 5.0 g was suspended in 100 mL NS. Each treatment was administered via intercostal tube. The authors report the rate of immediate procedural failure was similar, 21.4% for minocycline and 28.1 % for talc (P=.31). (This is less than the usual literature reports of success rates of 93-100% for talc.) The sponsor comments “it was impossible to ensure the uniform distribution of talc slurry onto pleural surfaces with direct visualization through thoracoscopy” [which] “might explain inferiority compared to talc poudrage.

Reviewer comment: *It should be noted that the Ng population consisted of patients with underlying lung disease (SPS), so the success rates would be lower than for patients with PSP. Also, treatment did not include a thoracoscopic approach that might permit concomitant bullectomy, etc. as may be conducted in concert with poudrage.*

The following table summarizes 13 non-comparative studies from the literature in which talc is used to prevent recurrence of pneumothorax. (The 14th non-comparative reference, a single case report, is not included in the table.) Success is usually defined as lack of recurrence.

Table 14: Published Non-Comparative Trials of Talc for Pneumothorax (Reviewer Table)

Reference	Design	Treatment	Dose	Success %
Cardillo 2006	Prospective, follow-up 861 PSP	VATS ^a +/- stapling blebs + talc	2 g	97.2-98.6
Casaz 2011	Retrospective 130 PSP	VATS +/- resection + talc	3 g Steritalc	97% at 10 months
de Campos 2001	Retrospective 49 PSP	Thoracoscopy (+/- resection) + talc	2 g	100%
Dubois 2010	Prospective 72 PSP ^b	VATS apical bullectomy +talc	5 g (Bryan)	100%
Gyorik 2007	Prospective follow-up, 59 of 112 PSP	Thoracoscopy + talc	French - dose?	95% long-term (median 10Y)
Lange^c 1988	Retrospective 114 PSP, lung function	Tube drainage +/- talc	?	Drain only 63% Talc 97.5%
Milanez 1994	Prospective, 18 recurrent PSP	Thoracostomy + talc	2 g (Brazil)	94.4%
Nandi 1980	Retrospective, 24 recurrent or chronic SP	Talc poudrage	"4-6 oz."	91.7%
Pletinckx 2005	Retrospective, 20 (15 PSP, 5 SSP)	Thoracoscopic talc +/- bullectomy	8 g Steritalc	100%
Ramos-Izquierdo 2010	Retrospective 124 PSP	VATS + talc	2 g French	97%
Tschopp 1997	Prospective, 89 complicated SP	VATS + talc	"3-5 mL pure talc"	97% immediate, 95% at 5 years
Weissberg 1980	Retrospective ,127 mixed diagnoses	Talc insufflation via mediastinoscope	2 g	(8/8) 100% recurrent PNX
Weissberg 2000	Retrospective 1199 pneumothorax	111 thoracostomy+talc;	2 g	Expansion + adhesions, 86%

^a VATS = Video-Assisted Thoracoscopic Surgery

^b Pulmonary Function tests pre-op, 6 and 12 months

^c22-35 year follow-up lung function after 1st pneumothorax; no mesothelioma

For the non-comparative trials summarized in Table 14 above, the study design, the patient populations, the details of therapy differ. A variety of doses and different

sources of talc were administered. The definition of success usually was lack of recurrence over time (or requirement for surgery), but in some cases, there may not have been long term follow-up and success may have referred to full lung expansion at time of hospital discharge. However, the information that is available for the large number of patients evaluated in these trials is supportive of efficacy for talc in preventing recurrence of pneumothorax. Several investigators utilized (Novatech) Steritalc brand of talc in their trials, although no trials have been conducted by Novatech for this application. The patients in the Casas and Pletinckx studies were treated with Steritalc. The Gyorik and Ramos-Izquierdo studies both used talc, described in the reports as “French sterile, asbestos-free graded talc, 50% particles > 10 µm,” which appears to match the description of (b) (4) talc (Novatech). The Dubois study used Bryan talc.

Two of the larger uncontrolled studies, listed in the table above, which demonstrate efficacy of talc for the pneumothorax indication include the published references of Cardillo (2006) and Weissberg (2000). A third large trial, not referenced by the applicant for efficacy but referenced for safety is Bridevaux (2011), which utilizes Steritalc. Following is a brief discussion of each of these 3 larger trials, one of which utilized Steritalc to treat PNx.

Cardillo (2006) evaluated short-term and intermediate term results with 861 patients with recurrent and complicated PSP treated with VATS and talc poudrage from Sept. 1995 through Jan. 2004. There were 578 men, 283 women, mean age 28.6 years, and 59% were smokers. Asbestos-free sterilized talc selected according to Italian pharmacopeia standards was used at a dose of 2g. Chest X-ray and clinical evaluation were conducted at 1 month, 3 months, and every 12 months through Nov. 2004. 26 patients were followed for more than 5 years. After a mean follow-up of 52.5 months, 14 patients (1.73%) recurred. *Pulmonary function tests remained within normal range for the 26 patients with long-term follow-up.* The authors conclude, “VATS to be an excellent technique for treatment of recurrent and complicated PSP and talc poudrage to be the preferred tool for inducing pleurodesis.”

Weissberg (2000) conducted a retrospective review of experience in treatment of 1119 patients with pneumothorax from 1980 to 1997 at a university-affiliated medical center in Israel. There were 865 male patients and 334 female patients. There were 723 cases of spontaneous pneumothorax (218 primary and 505 secondary), 403 cases of pneumothorax due to trauma, and 73 cases of pneumothorax due to iatrogenic causes. A total of 166 cases had a pleuroscopy procedure for recurrent or persistent PNx, and 111 had talc insufflation. The talc used was sterile asbestos-free talc, and the dose used was 2 g.

Bridevaux (2011) conducted a prospective, multicenter, uncontrolled trial in 418 patients with recurrent PSP from 2002 to 2008 in 9 centers in Europe and South Africa.

STERITALC 2 g (Novatech) was used for pleurodesis administered by video-thoracoscopic insufflation. There were 4 cases of pleurodesis failure (<1%), with

persistent leaks for > 2 days, requiring a surgical procedure. During the 30-day period after poudrage patients were followed primarily for safety. The study showed that there were no cases of ARDS or respiratory distress. The authors concluded that “thoracoscopic talc poudrage using larger particle talc to prevent recurrence of PSP can be considered safe.”

The applicant additionally cited the findings of 3 systematic review of talc treatment for PNx to further support efficacy. These are the published literature reviews authored by How (2013), Kennedy (1994), and Sepehrpour (2011).

How (2013)

This article reviewed treatment options for pleurodesis for SP. The most common sclerosing agent used in the US, UK, Canada, Australia, and New Zealand is talc. The author concludes that talc is effective therapy for PSP and SSP, with decreased recurrence to 0-9%.

Kennedy (1994)

The purpose of this reference was to review the chemical properties, efficacy, and safety of talc as a pleurodesis agent, including PNx and MPE. The review summarizes 22 English literature publications reporting the use of talc in the treatment of pneumothorax (PSP, SSP, and Iatrogenic). The overall success rate was 91% (620/684) for PNx, with most authors using recurrence of PNx as the definition of failure. The review includes studies in which talc is administered by poudrage and as slurry, with doses of “2 to 10 g being most common.” The publication addresses potential safety issues with talc, which will be discussed in section 7 (Review of Safety).

Sepehrpour (2011)

This was a literature review (Medline search 1948-2011) with the goal to determine if the outcome is superior for mechanical pleurodesis (parietal pleurectomy, pleural abrasion) or chemical pleurodesis for patients undergoing VATS procedures for recurrent PSP. A total of 542 papers were found, of which 6 represented best evidence to answer the question. The authors concluded the outcome was similar for mechanical and chemical pleurodesis, “with modest evidence suggesting lower rates of recurrence with chemical talc pleurodesis.”

6.2.2 Demographics

The following applicant table provides demographic information regarding participants in the comparative trials from the literature submitted by the applicant, to support efficacy for the PNx indication.

Table 15: Comparative Clinical Trials: Gender, Age, and Pneumothorax Type (Applicant Table)

Investigator, Publication	Gender	Age, median (range or SD)	Pneumothorax	
			Primary	Secondary
Agarwal R et al., Respir 2011; 16: 1064-1069 ^a	F: 17 M: 56	54.4 (SD 14.3)	10	25
Almind M et al., Thorax 1989;44:627-630	F: 38 M: 58	18 – 88	96	0
Kim SJ et al., Korean J Thorac Cardiovasc Surg 2011;44:225-228	F: 5 M: 56	Conventional treatment ^b : 71.8 ± 9.6 VATS: 61.3 ± 8.46	0	61
Moreno-Merino, Interactive CardioVascular and Thoracic Surgery 0 (2012) 1–5	F: 12 M: 775	Pleural abrasion group: 25.2 Talc poudrage group: 29.4	787	0
Investigator, Publication	Gender	Age, median (range or SD)	Pneumothorax	
			Primary	Secondary
Ng CK et al., 2010 Int J Tuberc Lung Dis 14(10): 1342–1346	F: 12 M: 173	Tal group: 71 (63-75) Minocycline group: 73 (66-77)	0	185
Noppen M et al., Eur Respir J 1997; 10: 412–416	F: 18 M: 30	PSP: 27±8 (16-56) SSP: 43±21 (17-74)	28	20
Tschopp, Eur Respir J 2002; 20: 1003–1009	F: 33 M: 75	Thoroscopic talcage: 28±8 Pleural drainage: 27±7	108	0
Total	F: 135 M: 1223	Average age across all groups ^c : 46.5	1029	291

^a Only 35 of the 73 patients in this study had a pneumothorax. Genders were not specified for individuals with pneumothoraces.

^b Conventional treatment: air leak through chest tube and chemical pleurodesis (talc).

^c Almind et al (1989) was not included in the average age across all groups because only a range was provided in the published article.

Reviewer comment: In the trials summarized above, there is a male predominance, as would be expected for PSP. Also as expected, the median age is young (20's) for the trials evaluating patients with Primary SP and is older for the studies where the

population includes patients with Secondary SP, who, by definition, have underlying pulmonary disease. For Almind, no median age was provided in the paper, but the age range of participants was 18-88 and 59% of patients in the trial were in the age range of 18-40.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The following applicant table summarizes the Dosage, Treatment and Success of the 7 comparative studies utilizing talc for pneumothorax.

Table 16: Talc Dose in Literature Comparative Studies for Pneumothorax (Applicant Table)

Investigator, Publication	Dosage	Treatment	Success
Agarwal R et al., <i>Respir</i> 2011; 16: 1064-1069	5 g cosmetic talc	Drainage output < 150 mL/day, cosmetic talc	Pnx: 14/14 -100%
Almind M et al., <i>Thorax</i> 1989;44:627-630	5 g in 250 mL NS	Talc pleurodesis	22/24 (91.66%)
Kim SJ et al., <i>Korean J Thorac Cardiovasc Surg</i> 2011;44:225-228	Not given	Conventional treatment (chest tube insertion and chemical (talc) pleurodesis)	27/39 (69%) (Recurrence: 12/39 (31%))
	2 g talc	Video-assisted thoroscopic Surgery (VATS) with Talc	21/22 (95.5%) (Recurrence: 1/22 (4.5%))
Moreno-Merino, <i>Interactive CardioVascular and Thoracic Surgery</i> 0 (2012) 1-5	2-3 g STERITALC®	Talc poudrage, via insufflating	395/399 (98.99%) (Re-intervention in 4 cases, 4 cases of recurrence (1.01%))
Ng CK et al., 2010 <i>Int J Tuberc Lung Dis</i> 14(10): 1342-1346	2.5 – 5.0 g in 100 mL NS	Talc Pleurodesis: Talc slurry via the intercostal tube	Immediate Success: 46 (71.9%)

Investigator, Publication	Dosage	Treatment	Success
Noppen M et al., <i>Eur Respir J</i> 1997; 10: 412-416	2 g talc (insufflated)	Thoracoscopic talcage in patients with PSP	29/31 (93.5%) (Recurrence: 2/31 (6.5%))
	2 g talc (insufflated)	Thoracoscopic talcage in patients with SSP	21/23 (91.3%) (Recurrence: 2/23 (8.7%))
Tschopp, <i>Eur Respir J</i> 2002; 20: 1003-1009	2 g talc + 1 % lignocaine	Simple thoracoscopic talcage (TT) w/ local anesthesia	60/61 (98.4%) (Immediate recurrence: 1/61 (1.6%))
			56/59 (95%) Recurrence after 5 years: 3/59 (5%)

In these comparative trials, the dose of talc administered varied between 2 and 5 g. In the non-comparative trials (Table 13), the dose varied between 2 and 5 g, when a dose was provided, except Pletinckx (2005) utilized a dose of 8 g (+/- bullectomy) in treatment of 15 patients with PSP and 5 patients with SSP. The large retrospective trials of Weissberg (2000) and Cardillo (2006) utilized a dose of 2 g with high incidence of success. The sponsor proposes a dose of (b) (4) 2 g for the pneumothorax indication. There does not appear to be literature support for a dose less than 2 g.

Reviewer Comment: *All the references from the published literature submitted by the sponsor and the results of literature search by FDA specify a talc dose 2g for the pneumothorax indication. There is not enough information to consider if the dose for talc administered as poudrage should be different from the dose administered as slurry.*

Also, see sections 6.1.8 and 9.2 of this review.

7 Review of Safety

Safety Summary

This 505(b)(2) submission references the NDAs for two FDA-approved Bryan intrapleural talc products, Sclerosol (NDA 20,857) and Sterile Talc Powder (NDA 21,388). No clinical trials were conducted for these referenced NDAs. No clinical trials have been conducted for the Novatech NDA. The Bryan products are approved for the MPE indication, but not the PNx indication. Novatech references Sclerosol and Sterile Talc Powder for both indications, because all 3 products contain talc in powder form to be used as a sclerosant to cause pleural symphysis. All three products have the same chemical formula ($\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$). Bryan's Sclerosol differs from the other products in that it contains an aerosol propellant (1,1,1,2-Tetrafluoroethane (HFA-134a)). At the time of initial approval, Sclerosol contained (b) (4)

The previous [505(b)(2)] FDA Clinical Reviews of NDA 20,857 and NDA 21,388 contain detailed safety data for talc administered as poudrage and slurry, respectively, for the MPE diagnosis. Randomized controlled trials and single arm trials from the published literature were referenced for safety data to support both NDAs, and efficacy and safety of Sclerosol were additionally referenced for the Sterile Talc Powder NDA. Randomized controlled trials, single arm trials, and systematic reviews from the published literature also support the safety of Steritalc for both proposed indications. Of particular interest are the large prospective trials with Steritalc, conducted by Janssen (2007) and Bridevaux (2011) in Europe, designed to evaluate the safety of talc pleurodesis in patients with MPE and PNx, respectively.

The most common adverse events (AEs) associated with talc pleurodesis are short-term pain and post-procedure fever. Empyema and local infection are infrequent, the latter more likely associated with indwelling tube thoracostomy required for administration of slurry. Some references suggest that empyema was related to variable practices for sterilizing talc, especially when unregulated, compounded talc was in common use.

Over the years, there have been reports of Adult Respiratory Distress Syndrome (ARDS) in the literature in patients treated with talc for MPE. There have also been such reports to the FDA Adverse Event Reporting System (FAERS) for the approved Bryan products. Sahn (2002) estimated the incidence of ARDS with talc pleurodesis to be

approximately 1%. From the absence of reports of ARDS in many large trials, the current incidence appears to be lower than 1%. Multiple authors state (Ferrer 2001, Janssen 2007, Aelony 2007, Bridevaux 2011, Tschopp [ERS Guidelines] 2015, etc.) that ARDS is associated with talc products with a larger proportion of smaller particles, due to the greater potential for systemic absorption. These authors suggest improved safety for “graded talc” such as the Novatech product, from which smaller particles are removed, and emphasize that reports of ARDS predominate from US and UK, where “mixed” talc is used. The data are inconclusive, but there is thought to be an association between the development of ARDS and use of higher doses of talc ≥ 10 g. Trauma to pleural surfaces prior to talc pleurodesis could also facilitate systemic absorption of talc.

If asbestos-free talc is used for pleurodesis, carcinogenicity is not a serious concern. Several long-term follow-up studies have shown good preservation of pulmonary function many years after talc pleurodesis for PNx. In the study by Lange (1988) of patients 22-35 years after treatment with talc for PSP, no patients had developed mesothelioma.

7.1 Methods

Novatech has submitted a single Summary of Clinical Safety that supports the use of talc in (b) (4) both malignant pleural effusion (MPE) and pneumothorax (PNx). The applicant conducted a literature search in PubMed for the published studies cited in the FDA Clinical Reviews for NDA 20,587 and NDA 21,388 that were deemed adequate and well-controlled. In addition, the applicant searched PubMed by “malignant pleural effusion” and “talc pleurodesis.” Novatech obtained 154 references and determined that 37 literature studies with 4950 patients were pertinent to the safety of talc for the indications. They have provided some analysis of the safety data contained in these studies.

To assess the completeness of the applicant’s submitted database, the clinical reviewer conducted an independent literature search, with focus on references published subsequent to approval of the RLDs. The search terms were “Malignant Pleural Effusion” and “Talc” and “Pneumothorax” and “Talc.” The databases searched were PubMed, EMBASE and Cochrane from 1990 through July 2016. There was extensive overlap of the applicant and FDA databases for safety. However, the Novatech database did not reference the published guidelines (2015) of the European Respiratory Society (ERS) on treatment of Primary Spontaneous Pneumothorax (PSP).

The previous [505(b)(2)] FDA reviews of NDA 20,857 and NDA 21,388 contain detailed safety data for talc administered as poudrage and slurry, respectively, for MPE, based on review of the published literature. This safety review will focus on data from published trials that identify Steritalc as the talc product utilized for both the MPE and PNx indications, systematic literature reviews that evaluate the safety of talc pleurodesis, some larger non-comparative studies, and published comparative trials in

the pneumothorax setting, The published literature includes data on more than 900 patients treated with Steritalc in Europe and elsewhere for the PNx indication and more than 700 patients treated for MPE. (b) (4) talc (similar to Novatech Steritalc) has been available in Europe in 1989. (b) (4)

Since 1999, Steritalc has been packaged as a powder in a vial for poudrage or administration as slurry and is now marketed in more than 50 countries.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This review will focus on safety data from published trials that identify Steritalc as the talc product administered for both the MPE (Table 18) and PNx (Table 17) indications, systematic literature reviews that evaluate safety of talc pleurodesis, some larger non-comparative studies, and published comparative trials in the pneumothorax setting. Bridevaux (2011) conducted a European, multicenter, prospective safety trial, designed specifically to evaluate short-term safety of thoracoscopic talc pleurodesis for recurrent PSP using “large particle talc” (Steritalc). The large, retrospective, historically controlled trial of talc poudrage vs. pleural abrasion for pneumothorax by Moreno-Merino (2012) utilized Steritalc 2-3g by poudrage (399 patients). Casas (2011) and Pletinckx (2005) were retrospective, non-comparative studies that utilized Steritalc 3 g and 8 g, respectively for pneumothorax (see Table 14 and 17). Janssen (2007) conducted a large, multi-center prospective single arm trial (n=558) in patients with MPE, which was designed to demonstrate safety of talc poudrage and utilized “large particle talc” (Steritalc). Two additional comparative, published MPE trials also reference Steritalc by brand name (Stefani 2006, Mohsen 2011) and several additional studies reference French talc or large particle talc. Maskell (2004) conducted a randomized trial in patients with symptomatic MPE to compare the pulmonary toxicity of mixed talc (similar to US product) with that of graded talc (“Novatech talc”) for pleurodesis.

Additional published studies and review articles will be discussed that address issues related to the safety of talc and concerns about pulmonary toxicity.

7.2 Adequacy of Safety Assessments

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

In the studies referenced from the clinical literature, almost all subjects received only a single intrapleural administration of talc as poudrage or slurry via chest tube, at doses ranging from 2 g to 10 g. Of the 37 reports evaluated by the applicant for safety data for the MPE and PNx indications, the most frequent talc doses were 5 g (10 articles), 4 g (6 articles), and 2 g (5 articles). The demographics of the patients referenced from the published literature were representative of patients with the diagnoses of MPE and PNx, respectively.

Talc dose administered for MPE in the published trials is summarized in Tables 10 and 11, and available demographic information in Table 9. For the PNX studies, Tables 12, 14, and 16 reference the talc dose administered, and Table 15 contains available demographic information.

7.2.3 Special Animal and/or In Vitro Testing

The published literature for talc makes frequent references to the size of talc particles as an important risk factor for pulmonary toxicity (How 2013, Bridevaux 2011, Kennedy 1994). The literature distinguishes between the safety of graded talc such as Steritalc, marketed in Europe for many years, compared with the low frequency but serious pulmonary reactions such as pneumonitis and ARDs reported with the US-approved products, Sclerosol and Sterile Talc Powder, which contain more particles of smaller size.

Ferrer *et al* (2001) compared the physical characteristics of 8 talc preparations used for pleurodesis, 4 from the US, and one each from Brazil, France, Spain, and Taiwan. The US products were obtained from Sigma, Malinckrodt, Baker, and Integra Chemical. The Spanish talc was identified as Luzenac talc, as was the French talc (Luzenac, Toulouse). There were differences in the impurities between products, and there was marked variation in particle size distribution. The mean particle size ranged from 10.8 for one of the US products (Sigma) to >30 for French talc. There was marked variation in the 10th percentile for the different talcs, 10.5 µm for French talc and 2.4-3.1 µm for US talcs tested. The authors note that small particles would be more likely to be absorbed through pleural lymphatics, which measure approximately 6.2 µm in diameter. None of the US talc products evaluated in this study is an approved product. However, in another published reference (Gonzalez 2010), the particle size distribution of Sclerosol was reported as: median diameter 18.2 µm and 10th and 90th percentiles were 5.3 µm and 34.4 µm, respectively, by scanning microscope. Smaller particles (b) (4) are supposed to be largely removed from Steritalc “graded” talc.

In view of the reported differences in physical characteristics and more favorable safety profile that has been described in the European literature for Steritalc, FDA Center for Drug Evaluation and Research (CDER)/Office of Testing and Research (OTR)/Office of Product Quality and Research (OPQ) conducted comparative *in vitro* testing of Novatech Steritalc and the US-approved talc products, Sclerosol and Sterile Talc Powder. Dr. Akhtar Siddiqui (CDER/OPQ/OTR/Division of Product Quality and Research (DPQR)) conducted laboratory evaluation of the physicochemical and permeability properties of the 3 talc products. Particle size evaluation was conducted by several techniques: (b) (4)

The studies confirmed that there were differences in particle size for the Novatech and Bryan talc products. The d10 and d25 values were smaller for Bryan talc compared with Novatech talc. (For details, see Dr. Siddiqui's study report, appended to the CMC review.)

7.3 Major Safety Results

7.3.1 Deaths

Procedure-related deaths were uncommon in the literature reports (see section 7.3.5, below), and deaths occurring within 30 days were usually attributed to rapidly progressive malignancy in patients with MPE or risks of operative procedures in patients with significant comorbidities. The 2 large prospective, European, safety trials of pleurodesis with graded talc (Steritalc) described below reported no cases of Adult Respiratory Distress Syndrome (ARDS). There were no deaths in the Bridevaux (2001) trial in 418 patients with Primary Spontaneous Pneumothorax (PSP). In the Janssen (2007) trial in 558 patients with MPE who underwent talc poudrage, 11 patients (2%) died within 30 days, due to progressive malignancy or complications related to advanced malignancy.

A US Intergroup phase 3 randomized trial conducted by Dresler and colleagues (2006) in patients with MPE, described below (section 7.3.5), reported a higher incidence of deaths than most literature reports. Of 240 evaluable patients treated with talc insufflation (TTI) and 240 evaluable patients treated with talc slurry (TS), the 30-day mortality was 14% and 20% respectively. Seven treatment-related deaths were reported for TS (5 respiratory, 2 cardiac) and 9 for TTI (6 respiratory, 1 cardiac, and 2 infection).

Kennedy and Rusch, et al. (1994) conducted a retrospective review of patients treated with talc slurry at Memorial Sloan-Kettering from 1991-1992. USP asbestos-free talc 10 g was used. Fifty-six patients underwent 73 procedures. Although 5 patients had short-term respiratory failure, including one patient who had bilateral procedures, there were no deaths.

7.3.5 Submission Specific Primary Safety Concerns

In a review of chemical pleurodesis for pneumothorax, How (2013) summarized that there have been at least 32 cases of Adult Respiratory Distress Syndrome (ARDS) following intrapleural talc administration in the literature, 17 following talc slurry, and 15 following talc insufflation. Most of the fatal cases were treated for MPE. A retrospective single institution review by Kennedy (1994) using USP asbestos-free talc slurry (10 g) reported a 4% (3/73) incidence of hypoxemic respiratory failure. Almost all of these procedures reported by Kennedy were for MPE, with 14 patients having more than a single administration of talc. A literature review by Sahn (2000) of 12 case series from 1958 to 2001 totaling 659 patients treated with talc poudrage for pneumothorax reported only one patient (0.15%) with respiratory failure. Systemic distribution of talc was demonstrated after intrapleural administration in rats in a study with ungraded talc, but not in a study with larger particle talc (Tschopp, ESR 2015). This provides support that talc particle size may be a significant risk factor in the etiology of serious respiratory toxicity observed in some series.

The two prospective trials described below were designed to evaluate the short-term safety of talc pleurodesis, utilizing graded talc, which excludes particles of smaller size.

Bridevaux (2011) and colleagues conducted a prospective, multicenter safety trial in 418 patients with recurrent primary spontaneous pneumothorax (PSP), enrolled between 2002 and 2008 in 9 centers in Europe. The trial was designed to evaluate the short-term safety of large-particle talc for thoracoscopic pleurodesis. There had been concern following US reports of ARDS after talc pleurodesis, especially in patients with MPE (Kennedy and Sahn 1995, Campos 1997, Rehse 1999, and Gonzalez 2010.) Patients with recurrent PSP, for which the physician considered talc pleurodesis appropriate, were prospectively enrolled. Talc 2g (STERITALC, Novatech, La Ciotat, France) was insufflated under visual control over the entire pleural surface. At the end of the procedure a chest tube was inserted for drainage of air and fluid. Drains were removed within 4 days in 80% of patients. For 5 days, vital signs, use of supplemental oxygen and any medical or surgical complications were recorded. Serious adverse events (including ARDS, death) were recorded for 30-days post procedure. Oxygen saturation, supplemental oxygen use and temperature were recorded daily at baseline and after pleurodesis. The primary endpoint was ARDs during the first 30 days. After an interim analysis, accrual was stopped after 418 cases because no patient experienced ARDS or required Intensive Care Unit admission. The mean age of patients was 30.5 years and 72.7% were male. By day 5, only 6 (.01%) patients were still on supplemental oxygen, with mean flow decreased from 1.9 L/min at baseline to 0.5 on day 5. Temperature elevation from baseline was significant until day 4, with return to baseline on day 5. The mean maximal rise was 0.41° C on day 1 and 0.37° C on day 2. On day 1, temperature exceeded 37.9° C in 83 (21.2% of) patients. There were 7 adverse events, including 3 pulmonary infections requiring antibiotics, 1 urinary retention on opiates, 1 contralateral pneumothorax, 1 persisting pneumothorax, and 1 sub-cutaneous emphysema. Four patients had persistent leaks for >2 days and required a surgical procedure. Bridevaux concluded that the trial demonstrated safety of graded talc for pleurodesis in recurrent PSP, as had been previously shown in several large retrospective studies.

Reviewer comment: *The Bridevaux trial was designed as a prospective, multicenter safety study. Steritalc 2 g administered by poudrage in 418 patients with recurrent PSP was not associated with any cases of ARDS during the 30 day observation period. Temperature elevation was noted from baseline until day 4.*

Previously, Janssen and colleagues (2007) had conducted a large, prospective single arm trial in 558 patients with MPE, which was designed to evaluate the safety of pleurodesis by talc poudrage. Janssen observed that the reports of respiratory failure and ARDS in some studies and the absence in others, was independent of disease (MPE or PNx), the dose of talc (2-10 g) or the technique of instillation (slurry or poudrage). Janssen referenced studies by Kennedy (1994) and others that had suggested that the occurrence of ARDS after talc pleurodesis is related to particle size

of the talc product used. The Janssen study used STERITALC (Novatech, la Ciotat, France), with mean particle size of 24.5 µm. The concentration of small particles (<5 µm) in Steritalc is reported to be 11% compared with 54% in US talc, and up to 82% in some Brazilian talcs. Thoracoscopy was done by standard technique. Pleural biopsy was permitted. Novatech talc 4 g (sterile graded talc) was administered by a pneumatic atomizer. A chest tube was inserted thereafter. Chest X-rays were done daily. Temperatures were recorded twice daily the day before the procedure and on subsequent days 1-5. The amount of supplemental oxygen and oxygen saturation were recorded. Patient ages ranged from 30-96 years (mean 64.4). No patients developed ARDS. One patient developed respiratory failure not related to the procedure, but due to contralateral pneumothorax, which was treated and the patient recovered. No other patients had serious pulmonary complications with 48 hours of the procedure. Other serious AEs included deaths within 30 days, most due to tumor progression, 1 pulmonary embolism, 1 pulmonary infiltrate with high fever responsive to antibiotics, 1 pericardial effusion, and 1 non-pulmonary sepsis. Janssen concluded, "Side effects from thoracoscopic pleurodesis were mild in our study."

Reviewer comment: *The patient population in the Janssen study was older and sicker, with multiple comorbidities compared to patients in the PSP study above. Although there were SAEs, including deaths within 30 days, most deaths were due to cancer, and the main AE attributable to talc pleurodesis appears to be a significant increase in temperature for days 1-4. Some increase in supplemental oxygen use was recorded on days 1-2 but no difference in oxygen saturation. In both prospectively designed safety studies, the investigators determined that "large particle talc is safe" for pleurodesis in the respective populations.*

In contrast to the trials of Bridevaux and Janssen, described above, which were prospectively designed safety studies, the experience of Gonzalez and colleagues, described below, was a retrospective evaluation of pulmonary toxicity observed in a single North American Center utilizing the only commercially available sterile talc for thoracoscopic talc insufflation (TTI). The investigator states the review was prompted by the Janssen trial showing no cases of ARDS after TTI for MPE and recent articles suggesting that differences in talc preparation could account for variable incidences of respiratory failure.

Gonzalez (2010) conducted a retrospective review of all patients treated over a 13-year period with TTI for pleural effusions or pneumothorax at the Lahey Clinic. The objective was to assess the rate of treatment-associated Lung Injury. Patients were treated between Jan. 1994 and July 2007. During the 13 year period, the only talc used for pleurodesis was SCLEROSOL (Bryan), the only US FDA-approved product for TTI. There were 142 procedures for 138 patients, 3 of which were for PNx; the others were to treat pleural effusion, of which 75% were MPE. The median Sclerosol dose was 6 g. The mean age was 67 and 47% were women. The median and mean survival times for patients with MPE were 5.5 months and 9.5 months. Twelve patients developed dyspnea and increased oxygen requirements within 72 hours of talc insufflation (8.5%).

However, talc-related lung injury was believed to have occurred in only 4 of the 142 procedures (2.8%), but may have contributed to respiratory deterioration in 4 additional patients. However, there were no cases of ARDS. The authors review published data about variation in talc particle size and potential for systemic dissemination. They suggest that variation in the incidence of respiratory failure across centers could be due to differences in available talc preparations. They conclude that the results of the study “reinforce previous concerns regarding the talc used for pleurodesis in North America.”

Reviewer comment: *A retrospective study has limitations in determining the incidence of talc-associated pulmonary toxicity. However, the consensus in the literature seems to be that graded talc is a superior product. Aelony (2011), in a Letter to the Editor regarding the Gonzalez paper states, “I second Gonzalez’ call for the FDA to approve the European-graded (large-particle) talc because it has been shown prospectively not to cause ARDS in 558 cases, and it has a long-term effectiveness of about 90% in thousands of cases.”*

Maskell (2004) conducted two randomized clinical trials in UK to evaluate lung inflammation after pleurodesis with talc of varying particle size. In one trial, 20 patients with symptomatic MPE received tetracycline or mixed talc (Thornton and Ross, UK) and assessments were made of lung clearance scans, oxygen saturation, and C-reactive protein from baseline to 48 hours. The second trial was conducted in 48 patients with symptomatic MPE who received either mixed or graded talc, and assessments were made of alveolar-arterial oxygen gradient. The goals of the second trial, informed by the results of the first, were to “compare the severity of arterial hypoxemia, fever, and systemic inflammation after pleurodesis” with mixed (standard UK and US) talc vs. graded talc that has had the majority of particles < 10 µm removed (standard European talc, mean particle size > 25 µm). Novatech talc is the graded talc used in this study, “sorted during manufacture so it contains less than 50% of particles smaller than 20 µm.” The dose of talc in both trials was 4 g. The dose of tetracycline in the first trial was 20 mg/kg. The authors state that there was no difference in treatment efficacy between the two preparations of talc. However, they conclude,

“We have shown that pleurodesis with mixed talc causes a greater systemic inflammatory response than graded talc and tetracycline. This is associated with greater hypoxemia and a fall in the clearance half time of inhaled DTPA from the contralateral lung, demonstrating significant lung inflammation. These results suggest that the severe hypoxemia and adult respiratory distress syndrome described after talc pleurodesis are probably the severe ends of a widely detectable spectrum of toxicity and are likely to be minimized by using graded talc (with its smallest particles removed). We conclude that talc from which most particles of less than 15 µm have been removed is probably a safer agent for pleurodesis than standard mixed talc.”

Reviewer comment: *In a small randomized controlled trial conducted in patients with MPE comparing pulmonary effects of pleurodesis with mixed talc vs. graded talc (“Novatech talc”), the data suggest that graded talc is the safer product.*

The following trial conducted in the US, demonstrated a very high rate of pulmonary toxicity. Although not specified, presumably FDA-approved (mixed) talc was administered.

Dresler (2006) and colleagues conducted a randomized Phase 3 US Intergroup trial designed to compare the efficacy and safety of talc pleurodesis for MPE by talc insufflation (TTI) vs. talc slurry (TS) via chest tube. TTI was conducted during thoracoscopy in the operating room, and TS was administered at the bedside, following drainage of pleural fluid. Patients received either 4 or 5 g of talc. Eligibility requirements for the trial had included performance status of 0-2 and expected survival of at least 2 months. Of 501 patients randomized, there were 242 evaluable subjects who received TTI and 240 who received talc slurry. Demographics and types of malignancy were similar in both arms, with the majority of patients having lung or breast cancer. The efficacy was similar for both treatment arms for the endpoint of initial lung re-expansion > 90% and successful pleurodesis at day 30 (TTI= 73%, TS=68%). The 30-day mortality was 20% among TS patients and 14% among TTI patients. Respiratory failure occurred in 4% of TS cases and 8% of TTI cases, with 5 toxic deaths and 6 toxic deaths, respectively. Seven treatment-related deaths were reported for TS (5 respiratory, 2 cardiac) and 9 for TTI (6 respiratory, 1 cardiac, and 2 infection). Additional common AEs were post-procedure fever, dyspnea, and pain, similar in both treatment groups.

Reviewer comment: *In this trial, the rate of successful pleurodesis was similar for both methods. The higher incidence of Serious AEs in both arms of this trial is concerning, especially compared to the experience of Janssen (Steritalc) and other trials of talc pleurodesis in MPE reported in the literature. The authors state, “The etiology of acute respiratory complications is unclear.” Although the authors have not explicitly stated which talc products they administered, the specified dose of talc “4 or 5 g” corresponds to the available presentations of US-approved talc, 4 g for poudrage and 5g for TS. The reported higher incidence of respiratory complications for mixed talc vs. graded talc is a possible explanation for the safety findings in this trial.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The next two tables summarize the trials for PNx and MPE, respectively, in which Steritalc was the brand of talc specified.

Table 17 : Literature Trials with Steritalc Poudrage for Pneumothorax (Reviewer Table)

Reference	Therapy	Dose	Patient #	Adverse Events (AEs)	Comments
Bridevaux 2011	Poudrage Steritalc	2 g	418 Recurrent PSP ^a	Day 1 temperature >37.9° C (21%) No ARDs ^d	Prospective safety study, No SAEs ^b
Moreno-Merino 2012	Poudrage Steritalc	2-3 g	399 talc PSP	1 hemothorax 1 atelectasis No ARDS	Retrospective comparison w/ pleural abrasion
Casaz 2011	VATS+ Poudrage Steritalc	3 g	130	No ARDS, no specific complications ^c	Retrospective PSP
Pletinckx 2005	Poudrage Steritalc +/- bullectomy	8 g	15 PSP 5 SSP ^c	"No respiratory complications"	Retrospective

^a Primary Spontaneous Pneumothorax

^b Serious Adverse Events

^c Secondary Spontaneous Pneumothorax

^d Adult Respiratory Distress Syndrome

The design and safety results of the Bridevaux trial are discussed in detail in section 7.3.5, above. Since this trial was designed as a safety study, monitoring of vital signs and oxygen utilization were pre-specified. The main adverse event (AE) attributable to talc (Steritalc) pleurodesis was temperature elevation from baseline until day 4, with return to baseline on day 5. See table 12 for additional information about design and efficacy for the Moreno-Merino (2012) trial, and the trial is described more fully in Section 2.2 (Efficacy of Talc for PNx). In this retrospective controlled trial of Steritalc poudrage vs. pleural abrasion for PSP, talc was determined to be more effective (99%) with less morbidity. See table 14 for additional information about the design and efficacy for the Casaz (2011) and Pletinckx (2005) trials. Casaz was a retrospective study of VATS and poudrage with Steritalc 3 g for PSP, which reported "no specific complication such as empyema, pachypleuritis, or ARDS." Pletinckx was a retrospective review of 15 sequential patients with PSP and 5 patients with SSP treated from 1999-2004 with VATS pleurodesis with 8 g of Steritalc. (The publication also reports 21 patients treated for MPE.) No patients developed pulmonary insufficiency; 1 patient had pain at a trocar insertion site.

Reviewer comment: These 4 studies included 967 patients treated for PNx by poudrage using Steritalc (2-8 g). No respiratory insufficiency was observed related to talc. The only prospective trial (Bridevaux) that was specifically designed to assess safety, identified low-grade temperature elevation in post-procedure days as the only AE attributable to Steritalc treatment.

Other PNx trials were described as using “French” talc, but Steritalc was not identified by brand name. These references (from Table 14, non-comparative talc poudrage trials) include the Gyorek (2007) and Ramos-Izquierdo (2010) studies. No cases of ARDs were reported in these trials, which included 112 patients with PSP and 124 patients with PSP, respectively.

Reviewer comment: *There are 967 patients with PNx treated with talc clearly identified as Steritalc and another 236 with talc that appears to be Steritalc (“French Talc”), for a total of 1203 patients, none experiencing ARDS.*

The next table summarizes information for the 3 published literature trials for MPE which identified Steritalc as the source of talc. The Janssen trial is a prospective, single arm trial, specifically designed as a safety trial. There were 558 patients administered poudrage with Steritalc 4 g. See section 7.3.5, above, for an extensive discussion of this trial. There was no ARDS. The main AE attributable to talc pleurodesis appears to be a low-grade increase in temperature for days 1-4. Some increase in supplemental oxygen use was recorded on days 1-2, but no difference in oxygen saturation.

Table 18: Literature Trials with Steritalc for MPE (Reviewer Table)

Reference	Therapy	Dose	Patient #	Adverse Events	Comments
Janssen 2007	Poudrage	4 g	558	No ARDS; fever, ↑ O ₂ supplement	Prospective safety
Stefani 2006	Poudrage vs. Slurry	6 g 6 g	TP ^a = 72 TS ^b = 37	No ARDS; fever, chest pain	Prospective comparative
Mohsen 2011	Poudrage vs. local ^c Iodine 10%	4 g 20 mL	TP = 22 °P-Iodine = 20	No ARDS; fever, chest pain	Prospective randomized controlled

^a Talc Poudrage

^b Talc Slurry

^c Povidone-Iodine 10% by chest tube

Stefani (2006) was a prospective, comparative study comparing poudrage vs. slurry (see Table 4, Table 9, Table 18) in 787 patients with MPE treated from 1992 to 2010 at a single institution in Spain. Forty-nine patients had lung cancer, 28 breast cancer, 10 mesothelioma, and 22 “other” malignancies. Patients were treated with Steritalc 6 g, either as poudrage or slurry. There was no mortality deemed procedure-related. Eight deaths (7 TS and 1 TP) occurred in the first 30 days in these patients with advanced cancer. No patients developed talc-induced acute respiratory failure. Chest pain was slightly more common in the TS group. Fever was the other common symptom. The following table is taken from that trial, and summarizes the adverse events in both treatment arms.

TP versus TS: comparison of morbidity

Type of complication	TP (n = 72)	TS (n = 37)	p-value
Chest pain	26 (36.1)	18 (48.6)	0.237
Fever (>37.5°)	28 (38.8)	13 (35.1)	0.544
Empyema	1 (1.4)	0	—
Pneumonia	0	2 (5.4)	—
Prolonged air leak (>2days)	2 (2.7)	0	—
Wound infection	1 (1.4)	0	—
Re-expansion pulmonary oedema	3 (4.1)	0	—

Data are presented as number (%) of patients.

Mohsen (2011) was a randomized controlled trial comparing thoracoscopic talc poudrage (TTP) with povidone-iodine pleurodesis (PIP) through a thoracostomy tube for MPE due to metastatic breast cancer. The trial was conducted at Cairo University Hospitals from 2002-2005. Twenty-two patients were treated with TTP and 20 with PIP. Steritalc 4 g was used. All patients had moderate to severe dyspnea at baseline. Both groups underwent VATS evaluation and multiple biopsies before the procedures. (Success rates were similar for the 2 groups, 91% for TTP/85% for PIP.) There was no treatment-related mortality and no ARDS. Chest pain and fever were the most common adverse events. Pain occurred in 4/22 (18%) of the TTP patients, and fever occurred in 4/22 (18%) of the TTP patients. The author states their observations are consistent with published reports (Kennedy 1994) that fever (usually 38° C) occurs in 16-69% of cases, typically at 4-12 hours after instillation and lasts no longer than 72 hours.

Reviewer comment: Pain and fever were the common post-procedure adverse events. *Acute respiratory failure/ARDS did not occur in the approximately 719 patients treated with Steritalc for MPE in the 3 published trials listed in Table 18 above. ARDS was not reported in the approximately 129 patients with MPE in the 5 published, controlled trials of talc slurry, variously sourced, (see Table 6 of this review for the references and the Clinical Review for NDA 21,388 for more details).*

7.5.1 Dose Dependency for Adverse Events

Several studies have suggested a possible dose effect regarding the development of respiratory insufficiency following talc pleurodesis. Rinaldo (1983) reported ARDS in 3 patients treated with 10 g talc slurry by chest tube. Two patients recovered. Kennedy, Strange, *et al* (1994) reported on 58 patients who received talc slurry (USP 10 g) by tube thoracostomy at Memorial Sloan-Kettering Cancer Center, of whom 3 experienced respiratory failure attributed to talc, but survived with mechanical ventilation.

Reviewer comment: *Although there are concerns that there might be a dose effect, the role of dose is inconclusive. Many patients have been treated with high dose without developing pulmonary insufficiency. ARDS has also been reported with lower doses of talc. Bouchama (1984) reported a patient who developed symptoms of ARDS*

starting 3 hours after administration of talc 2 g. Bronchopulmonary lavage demonstrated the presence of talc fibers. The patient had undergone pleural biopsy immediately before talc pleurodesis; possible local pleural vascular injury was postulated as a mechanism for systemic dissemination of talc.

7.5.2 Time Dependency for Adverse Events

Pulmonary Function

Several published studies provide information on long term effects of talc pleurodesis on pulmonary function. In the study by Ramos-Izquierdo (2010), there was no decline in lung function in 124 patients followed up to 36 months after VATS talc pleurodesis therapy for PSP. Cardillo (2006) reported no respiratory impairment in 26 patients with a follow-up longer than 60 months after VATS talc poudrage for PSP. Lange (1988) assessed lung function in 114 consecutive patients from 2 chest clinics in Copenhagen at 22-35 years after treatment for their first episode of idiopathic spontaneous pneumothorax with talc poudrage (n=60) or simple drainage (n=54). Twenty patients from the drainage group relapsed and subsequently received talc poudrage. No subjects developed mesothelioma. Seventy-five subjects were available for evaluation of pulmonary function. In the talc group (n=46), the mean total lung capacity (TLC) was 89% of predicted, compared with 96% in the drainage only group (n=29). There were no significant differences in Vital Capacity and FEV1 for the 2 treatment groups.

Gyorik (2007) conducted long-term follow-up in 63 of 112 patients who underwent pleurodesis with French graded talc (50% particles > 10µm) for PSP. The median duration of follow-up after pleurodesis was 118 months. Patients who were non-smokers had normal lung function assessed at a median follow-up of 10 years.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In response to two Citizen Petitions regarding a possible association of cosmetic talc and ovarian cancer, the Center for Food Safety and Applied Nutrition (CFSAN) determined in April 2014 that there is no conclusive link of perineal talc exposure with ovarian cancer outcomes, based on existing epidemiology studies and post-market reports from the CFSAN Adverse Event Reporting System (CAERS).

The clinical reviewer conducted an independent literature search in PubMed, Embase and Web of Science using search terms “Talc” and “Ovarian Cancer.” Pertinent articles were identified and reviewed. A number of observational studies since the 1980’s have suggested an association with the perineal use of cosmetic talc in women and increased risk of ovarian cancer. The authors of a meta-analysis (Huncharek 2003) pooled data from 15 case-control and one cohort analysis, obtaining a summary relative risk of 1.33 (1.16-1.45). However, they concluded that there is not enough credible

evidence to support the role of talc in the etiology of ovarian cancer because of the lack of a clear dose-response relationship, selection bias, and uncontrolled confounding factors. In a more recent review by Huncharek and Muscat (2011), the authors again conclude that a weak statistical association in epidemiological studies does not support a causal association. They further note that “multiple long-term clinical studies have not shown a single case of cancer secondary to direct talc application to the human pleura.” A review funded by Cancer Registry of Norway by Langseth *et al* (2007) had similarly concluded, “The body of evidence was insufficient to establish a causal association between perineal use of talc and ovarian cancer risk.”

One of the clinical studies with long-term follow up that does not support an association between intrapleural application of talc and malignancy is the study by Lange *et al* (1988). Patients were followed for 22-35 years after treatment of pneumothorax with talc poudrage or simple drainage. Of the 80 patients treated with talc poudrage, no cases of mesothelioma were reported.

7.6.3 Pediatrics and Assessment of Effects on Growth

McGahren (1990) conducted a controlled nonclinical study to evaluate the effects of talc pleurodesis on the lung and pleura in a rapidly growing porcine model. The purpose was to evaluate the long-term effect on pulmonary compliance to support the use of talc pleurodesis in children with cystic fibrosis suffering from spontaneous pneumothorax. Six animals were anesthetized and intubated, and 3 pigs underwent unilateral thoracoscopy and pleurodesis with 6 g of USP purified sterile talc. Dynamic and static respiratory mechanics were studied 5 and 10 weeks later. The authors stated “the data indicate that talc pleurodesis has minimal long-term effects on pulmonary compliance in growing pigs, and are consistent with clinical findings of the safety of talc pleurodesis in humans.” Although young adults were included in several spontaneous pneumothorax clinical trials from the published literature, no children were treated in these clinical trials.

Based on acceptable limits for lead exposure in children, the applicant’s proposed specification for lead per gram of Novatech talc may exceed that recommended in the International Council on Harmonization (ICH) Q3D Guidance on Elemental Impurities. If the recommended specifications are exceeded, the FDA toxicology review team recommends excluding the pediatric population from treatment with Steritalc for the benign indication.

8 Postmarket Experience

Steritalc is not marketed in the US. Section 2.6 of this review contains a list of the approximately 54 countries in which Steritalc is marketed. It has been marketed since 1999 in many countries of the European Union. Steritalc is marketed as a device, rather

than a drug, in all countries except S. Korea. The applicant states there have been no safety reports.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

- Pneumothorax Indication
 - ⊖ The pneumothorax indication should specify, “Steritalc is indicated in adults to decrease the recurrence of (b) (4) pneumothorax (b) (4) (b) (4)”. This is based on (b) (4)
 - (b) (4)
 - (b) (4) Also, based on the concerns of the Toxicology Reviewers that the content of lead as an excipient may exceed ICH Guidelines for permissible levels for children, Steritalc should be restricted to adults for the benign indication.
- Dose of Steritalc by Indication
 - MPE – The applicant proposes a Steritalc dose of 2-5 g, which agrees with their European label. The RLDs are labelled for doses of: Sclerosol 4-8 g and Sterile Talc Powder 5 g. A dose of 2-5 g is acceptable, based on reports from the published literature. However 4-5 g is the dose most frequently used in randomized controlled trials from the literature for MPE.
 - Pneumothorax – The applicant proposes a Steritalc dose of (b) (4) 2 g, which agrees with their European label. The labeled dose should be 2 g. All the references from the published literature submitted by the sponsor and the result of literature search by FDA specify a talc dose 2g for the pneumothorax indication. The FDA Pulmonary Consultant, Dr. Lydia Gilbert-McClain, concurs with a labelled dose of 2 g but also suggested including a statement in the Dosage and Administration Section of the label, (b) (4)

9.3 Advisory Committee Meeting

There was no Advisory Committee meeting to discuss the approval of Steritalc.

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/s/

NANCY S SCHER
03/04/2017

LALEH AMIRI KORDESTANI
03/06/2017

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS
MEDICAL OFFICER CONSULTATION

Date: September 6, 2016
To: Nancy Scher, MD, Medical Officer, OHOP/DOP1
From: Lydia Gilbert-McClain, MD, FCCP, Deputy Division Director
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Through: Badrul Chowdhury, MD PhD, Director, Division of Pulmonary Allergy,
and Rheumatology Products
Subject: NDA 205-555 STERITALC (sterile talc powder) for pneumothorax

Introduction

Novatech S.A. submitted an NDA under the 505(b) (2) pathway for sterile talc powder (STERITALC) for (b) (4) malignant pleural effusions and for (b) (4) pneumothorax. The applicant is relying on literature references to support the efficacy and safety of their product and the 2 previously approved talc products SCLEROSOL® (NDA 20-587) and Sterile Talc Powder (NDA 21-388). These two approved talc products are only approved for the (b) (4) of malignant pleural effusions. Approval for these two NDAs was based entirely on literature references. There are no FDA approved products for pleurodesis in the setting of pneumothorax. The Division of Oncology requests DPARP input on a number of questions regarding the use of talc for the (b) (4) of pneumothorax.

Background

Talc

Talc has been used in the management of complicated or recurrent pneumothorax since the 1940's. The use of talc for pleural symphysis was first described in 1935 based on animal studies in cats and dogs. Pneumothoraces were created in these animals followed by the insufflation of iodinated talc (Kennedy & Sahn, 1994). While talc is not approved for pneumothorax, the same principle that governs the use of talc in malignant pleural effusions is applicable to the condition of recurrent (b) (4) pneumothorax in that the goal is to achieve symphysis of the parietal and visceral pleura (pleurodesis) to prevent recurrence.

Talc is a tri-layered magnesium sheet silicate. The empirical chemical compound $\text{Mg}_3\text{Si}_4\text{O}_{10}(\text{OH})_2$ is rarely found as a pure entity in nature because of frequent cation substitutions wherein the magnesium is replaced by iron, nickel, chromium, or manganese. The source of talc (i.e. where the talc is mined) has bearing on the quality of the talc. Geologic processes reacting on diverse preexisting rock types commonly result in the formation of impurities such as temolite, chrysotile, and anthophyllite. The composition of talc ore varies widely depending on the source (Weiss & Boettner, 1967).

The literature describes “mixed talc” and “graded talc” noting that the talc used in the United Kingdom and here in the United States is “mixed talc” (i.e. containing small [$< 10\mu\text{m}$] talc particles) whereas in Europe “graded talc” (sorted during manufacturing to exclude the vast majority of particles of less than $10\mu\text{m}$) is used (Maskell et.al, 2004). This difference in particle size is important because particle size (and dose) have been linked to cases of respiratory failure and ARDS. Most of the reports of hypoxemia, respiratory failure and ARDS following talc pleurodesis for malignant pleural effusions came from the United Kingdom and the United States (Gonzalez et.al., 2010; Campos et.al., 1997; Nandi et.al., 1980) and only rarely reported from Europe (Rodriguez-Panadero F & Antony VB., 1997). Maskell et. Al (2004) reported on 2 trials describing whether talc pleurodesis with a mean particle size of $< 15\mu\text{m}$ (“mixed talc”) produces more systemic inflammation than tetracycline or “grade talc” (i.e. most particles $< 10\mu\text{m}$ were removed). The 2 trials were prospective, randomized, parallel group trials conducted at a single center in the United Kingdom (Oxford, UK). In the first trial, a total of 20 patients (with underlying malignant effusions) were randomized to receive tetracycline or “mixed talc.” In the second trial, a total of 48 patients were randomized to “mixed talc” vs. “graded talc”. The patients were blinded to which talc preparation they received. Measures of gas exchange (A-a gradient) and measures of systemic inflammation (C-reactive protein) were worse in the patients who received “mixed talc.”

The particle size reported in the literature for STERITALC is a median particle size of $31.5\mu\text{m}$ and is reported in the literature to be larger than the particle size of the talc products manufactured in the U.S. (Bridevaux, 2010).

Pneumothorax

A pneumothorax is defined as the presence of air in the pleural space with secondary lung collapse. When there is no preceding event it is classified as spontaneous, otherwise a pneumothorax can be as a result of direct or indirect trauma or iatrogenic (e.g. as a complication of a central line placement). Spontaneous pneumothorax (i.e. without any preceding event) is further classified into primary spontaneous pneumothorax and secondary spontaneous pneumothorax. Primary spontaneous pneumothorax (PSP) occurs most often in healthy young people (particularly males) without any clinically apparent lung disorder. Smoking has been identified as a significant risk factor (particularly in males) for PSP. In actuality most individuals with primary spontaneous pneumothorax (PSP) may have unrecognized lung disease (e.g. pleural blebs) with the pneumothorax resulting from rupture of a subpleural bleb. Secondary pneumothorax occurs as a complication of underlying lung disease (most commonly COPD with bullous disease).

The estimated incidence of PSP is 7.4 cases per 100,000 (men) and 1.2 cases/100,000 (women) in the United States. PSP has a recurrence range from 25 percent to more than 50 percent with most recurrences seen within the first year (UptoDate).

With PSP, recurrences progressively increase after a second or third episode (How CH, 2013). One of the most important issues of managing spontaneous pneumothorax is to prevent

pneumothorax recurrence. There are published clinical guidelines that discuss the management of PSP (Baumann MH et.al, 2001; Tschopp JM et.al., 2015). Management of PSP includes consideration for pleurodesis following drainage. Both surgical and chemical methods have been used for pleurodesis and there is a large body of literature that covers decades of the use of sclerosing agents and/or surgical methods.

There has been a wide variation in practice in the management of spontaneous pneumothoraces. To address this variation in care, in 2001, the American College of Chest Physicians (ACCP) commissioned the development of a practice guideline for the management of spontaneous pneumothorax (Baumann, MH et.al., 2001). These guidelines provide recommendations based on a literature review from 1967 to 1999. The literature search retrieved nine articles which included 8 randomized trials and one practice guideline. For pneumothorax recurrence prevention, the ACCP guidelines recommend that except for patients with persistent air leaks (patients with air leaks persisting beyond 4 days); procedures to prevent the recurrence of a PSP should be reserved for the second occurrence (85% of panel members). Although 15% of panel members voted to offer patients an intervention to prevent a recurrence after the first pneumothorax, considerations that should be factored into the decision for an intervention to prevent a recurrence after a first event include patient's preference, and interests in continuing activities that would place them at high risk if a pneumothorax occurred (e.g. scuba diving or flying). In terms of choice of procedure, the guidelines note that the instillation of sclerosing agents through a chest tube (slurry) is an acceptable approach for pneumothorax prevention in patients who wish to avoid surgery, and for patients who present with increased surgical risk. The Guidelines note that success rates with chemical pleurodesis are 78 to 91% compared to success rates of 95 to 100% with surgical intervention. It is important to keep in mind that this success rate is a general one including all sclerosing agents. More recent articles cite a success rate for talc pleurodesis of > 95% that is comparable to that of surgical abrasion (Tschopp JM et.al., 2015).

For pneumothorax recurrence prevention in patients with secondary spontaneous pneumothorax most panel members (81%) recommend an intervention to prevent a recurrence after the first pneumothorax because of the potential lethality of secondary pneumothoraces in this population with underlying lung disease. For these patients, the ACCP guidelines recommend surgery as the preferred method but for patients who are unable to undergo surgery or prefer to avoid surgery the instillation of a sclerosing agent through the chest tube may be used (Baumann MH, et.al., 2001).

The ACCP guidelines suggest a preference for talc slurry over poudrage. However, the European guidelines cite a clear preference for poudrage. The ETS guidelines note that the technique of talc poudrage is very old and a simple procedure performed under visual control by medical thoracoscopy and local anesthesia. Current methods now commonly used are VATS (video-assisted thoracic surgery) (Tschopp et. al., 2015). Regardless of the method, both talc slurry, and poudrage appear to be equally efficacious and method of choice used may be more dependent on institutional experience and resources and patient preference.

Since the publication of the ACCP guidelines, the British Thoracic Society guidelines (2010) and ERS task force statement on diagnosis and treatment of PSP (2015) have been published. While there are differences in recommendations regarding the most appropriate method for drainage of a pneumothorax for the first occurrence (i.e. needle aspiration and/or chest tube evacuation vs. initial observation), there is general agreement that talc is an effective sclerosant for patients in whom pleurodesis is recommended to prevent recurrence.

Consult Questions

Question: Is there sufficient information from the literature and experience with the RLDs to evaluate benefit vs. risk for talc for the pneumothorax indication?

DPARP Response:

We concur that there is sufficient information from the literature to evaluate benefit vs. risk for talc for the pneumothorax indication. Talc pleurodesis has been shown to be efficacious and safe with a success rate of ~ 95% in multiple large observational case series and has been used for decades. The use of talc for pleural symphysis was first described in 1935 (Kennedy & Sahn 1994).

The pleurodesis options to reduce recurrence of pneumothorax are either surgical (i.e. via mechanical abrasion of the pleura) or chemical (via the use of sclerosing agents). The decision to utilize a surgical approach vs. chemical abrasion is multifactorial and includes patient considerations, as well as patient preference, and the underlying condition. For instance, the ACCP guidelines recommend that patients with a first occurrence of a secondary spontaneous PTX should generally have a surgical procedure (unless there are reasons that preclude surgery). Although several literature sources note that chemical abrasion with talc is as effective as surgery, the ACCP guidelines comment that surgery is the most effective procedure (~ 100% success) and provides the opportunity for performing other procedures that may be necessary (e.g. bullectomy).

Most of the literature references do not mention the actual talc product used except to say that the talc is sterile, and asbestos-free. In some references the particle size of the fibers is given and some references may state that the talc used is “graded” talc. The proposed use of the two reference products SCLEROSAL (NDA 20,587) and Sterile Talc powder (NDA 21,388); albeit for a different patient population [malignant pleural effusion] is relevant to the proposed indication from the standpoint of efficacy (i.e. the ability of talc to achieve symphysis of the pleural space via chemical abrasion).

There are 2 case series reported in the literature where the applicant's proposed product (STERITALC) is used for pneumothorax (n = 806) so there appears to be adequate information to evaluate the efficacy and safety of the applicant's talc product on its own without having to rely on efficacy (or safety information) from the reference products.

Efficacy

There are several case series reported in the literature (most are retrospective uncontrolled series) that span decades of use of talc for chemical pleurodesis. Five of the larger case series are summarized briefly below. The total number of patients exposed to talc from these 5 literature sources = 1902 of which 806 were exposed to the applicant's product STERITALC.

Moreno-Merino et. al., (2012) described a retrospective controlled study in 787 patients with primary spontaneous pneumothorax. Patients treated at the University Hospital in Seville Spain between July 1992 and December 2010 were retrospectively identified. Of the 787 patients, 399 were managed with surgical abrasion while 388 had talc pleurodesis. Sterile, asbestos-free talc (STERITALC) 2 to 3 grams was used. Talc pleurodesis was performed by talc poudrage.

The mean age of the surgical abrasion group was 25.2 years, while the mean age of the talc group was 29.4. The majority of the patients were male (only 12 women in the study) and had been smokers (53.6% in the surgical abrasion group and 60% in the talc group). The demographic characteristics of these patients are consistent with the condition of PSP.

The recurrence rate and need for re-intervention was reported to be 2.76% in the surgical abrasion group and 1.03% in the talc group. The authors concluded that both pleural abrasion and talc poudrage are effective methods of pleurodesis.

Cardillo et. al., (2006) described their experience with 861 cases undergoing videothorascopic (VATS) talc poudrage for primary spontaneous pneumothorax. From September 1995 to January 2004, a total of 861 patients had talc poudrage for primary spontaneous pneumothorax (578 men, 283 women, mean age 28.6 years and 59% smokers). For the majority of patients (n = 792) the reason for the procedure was a recurrent ipsilateral pneumothorax.

The specific talc product used is not stated. The article notes that talc was selected according to the Italian pharmacopeia standards: (length of fibers < 50 μ M) and states that asbestos free-sterilized talc was used. The dose in this study was 2 g. a total of 805 patients were followed at every 1, 3 and 12 months post-operatively up to November 30 2004, and 26 patients had

follow up beyond 5 years. A total of 14 patients (1.73%) had a recurrence. Most of the recurrence (n =12) occurred within 48 months of follow up.

Ramos-Izquierdo (2010) in another study retrospective uncontrolled study, looked at 124 patients with a history of PSP (19 women) following VATS talc pleurodesis between 2000 to 2008 at one institution. The mean age was 26.6 and 52% were smokers. Ipsilateral recurrence of pneumothorax was the most common (87/124 [65%]) reason for the procedure. Patients had chemical pleurodesis with sterile, asbestos-free graded talc 2 grams with 50% particles > 10µM. There was 100% outpatient follow up for 36 months and no findings of respiratory failure or respiratory compromise. Four patients (2 of whom had pleural blebs) had a recurrence.

Weissburg et. al., (2000) looked at the outcome of pneumothorax in 1119 patients in a retrospective review covering the period from 1980 – 1997. There were 723 cases of spontaneous pneumothorax (218 primary and 505 secondary), 403 cases of pneumothorax due to trauma, and 73 cases of pneumothorax due to iatrogenic causes. A total of 166 cases had a pleuroscopy procedure and 111 had talc insufflation. The talc used was sterile asbestos-free talc, and the dose used was 2 g. The reason for pleuroscopy was recurrent pneumothorax, or persistent pneumothorax.

Bridevaux et. al (2010) conducted a prospective uncontrolled study in 418 patients with recurrent spontaneous pneumothorax in which 2g STERITALC® (Novatech La Crotat, France) was used for pleurodesis. Patients were enrolled between 2002 and 2008 and were recruited because of recurrent spontaneous pneumothorax for which the physician felt that talc pleurodesis was indicated. The study was primarily to access safety and was stopped after 418 patients because an interim analysis showed that there were no cases of ARDS or respiratory distress.

Safety

ARDS

There were no cases of ARDS or respiratory insufficiency or pneumonitis reported in any patient in any of these studies discussed above. There were no deaths and no long term respiratory discomfort in any of these case series discussed above. There are several other literature reports of retrospective studies looking at the use of talc for pleurodesis for pneumothorax as this procedure has been in use for decades. The study by Bridevaux et. al., (2010) was a dedicated prospective uncontrolled study with a primary objective of evaluating the safety of talc pleurodesis in recurrent primary spontaneous pneumothorax. This prospective European multicenter study was conducted following anecdotal reports of ARDS following talc pleurodesis for malignant pleural effusions. The study was stopped after an interim looked showed that there were no cases of ARDS or respiratory insufficiency, deaths, or ICU admissions in the 418 patients enrolled.

Lung Function

Patients have been followed long term for lung function impairment. In the study by Ramon-Izquierdo, patients were followed out to 36 months and no cases of lung function decline was reported. In the report by Cardillo et. al (2006) there was no respiratory impairment after 36 months of follow up and 26 patients had followed up for more than 5 years. The longest follow up for lung function is reported by Lange et. al., (1988) in another case series where patients were evaluated 22 to 35 years following treatment of idiopathic spontaneous pneumothorax with talc pleurodesis or simple drainage. The long term effects were assessed in 114 patients studied for 22 - 35-years after their first primary pneumothorax with measurement of static and dynamic lung volumes. A total of 80 patients treated with talc and 34 patients treated with simple drainage were followed. At follow up 17 patients had died of unrelated causes and 2 patients had emigrated. Of the remaining patients, 75 participated in the assessment. In the talc group there was mild restrictive impairment of lung function with a mean TLC of 89% predicted. One subject had extensive calcifications and a substantial decline in lung function (TLC 58%) with some evidence of lung fibrosis. No subjects developed mesothelioma.

Post-procedural pain

The most common complaint following talc pleurodesis was pain (chest pain at the operative site) which resolved over time and there was no complaints of persistent intercostal pain in patients that were followed up beyond a year or longer.

Long-term sequela

For younger people, considerations regarding the efficiency of talc to produce pleural symphysis should be weighed against the concern for thoracotomy in the future and some physicians suggest that this thought process should be included in deciding on the use of talc for pleurodesis in young people (Harrison, 1995).

Malignancy

No cases of mesothelioma or other malignancies were reported in any of the literature references and in the report by Lang et.al (1988) in the longest follow up (22 to 35 years) of patients who had talc pleurodesis.

Question: Compared with existing treatments, especially considering the risk of ARDS and recent concerns about carcinogenicity of talc products, should talc be considered only for refractory patients with recurrent pneumothorax? Or not considered for patients without malignant disease?

DPARP Response:

Treatment options for pleurodesis for pneumothorax include surgical abrasion, or chemical pleurodesis. Talc is the most common agent used for chemical pleurodesis and has the best

success rate compared to other agents used. There are no approved sclerosing agents for pleurodesis for pneumothorax but according to the reports in the literature talc is the most effective and is best tolerated (less pain) compared to other sclerosing agents.

In a randomized prospective study by Almind et. al (1989) 96 patients with spontaneous pneumothorax between 1978 to 1985 were randomized to simple drainage (n = 34), talc pleurodesis (n = 29) or pleurodesis with tetracycline (n =33). There was no difference in the mean hospital stay, length of time of tube drainage, or persistence of pneumothorax. The talc (Pharmacopeia Danica) dose was 5 g in 250 ml isotonic saline. At a follow up in 1987, 89 patients could be accounted for. The incidence of recurrence was 36% in the simple drainage group, 13% in the tetracycline group, and 8% in the talc group.

In a recent study by Chen et. al (2013) 214 patients with a first episode of pneumothorax were randomized to drainage alone (control), or drainage followed by pleurodesis with 300 mg of minocycline. There were no specific complications to either procedure. After a 1-year follow up period, recurrent pneumothorax occurred in 49.1% of patients in the control group compared with 29.2% in the minocycline group.

Although there are no well controlled trials evaluating the management of persistent or recurrent primary spontaneous pneumothorax, there is general agreement among experts in the field that definitive treatment (i.e. pleurodesis) should be offered to patients with recurrent or persistent pneumothorax.

This reviewer did not find any reports of ARDS or respiratory failure in large case series with talc pleurodesis for pneumothorax. The risk of ARDS appears to be related to the size of the particles in the kind of talc used and also the dose. There are 32 cases of ARDS/respiratory failure reported in the literature following talc pleurodesis but none of these cases occurred in the setting of pleurodesis for pneumothorax. As discussed above most of the cases occurred in the United States and the United Kingdom where talc containing smaller fibers (“mixed talc”) was used.

The Applicant’s proposed indication statement

(b) (4)

(b) (4)

(b) (4)

Question: Is there sufficient information to label a dose for pneumothorax, particularly since toxicity (ARDS risk) appears related to dose (and particle size)?

DPARP Response:

We believe that there is sufficient information available to label a dose for pneumothorax. There is a large body of literature describing the use of talc in the management of pneumothorax recurrence prevention. In the majority of cases a dose of 2 grams has been used and the dose of the sponsor's product STERILAC used in the literature sources cited is 2 grams.

The Applicant is proposing a dose of (b) (4) 2 g. However, all of the large case series described above used 2 grams of talc (and higher in some cases) for pleurodesis which was effective and without any serious adverse effects. (b) (4)

(b) (4) this may be the reason for the Applicant's proposal (b) (4) (u) (4) (b) (4) Although, we can find no cases in the literature where a dose of (b) (4) gram was used for pleurodesis, there is discussion in the literature that would suggest that (b) (4) (b) (4) should be used for (b) (4) pneumothorax.

In the State of the Art paper by Rodriguez-Panadero and Antony (1997), they caution against the use of large doses of talc for pleurodesis in otherwise healthy young patients. The article points out that the normal mesothelial surface of the pleura in these otherwise healthy patients renders the pleura more responsive to sclerosing agents (making it necessary to use higher doses of analgesics) and a lower dose of the sclerosing agent should be used. Furthermore, the article cautions against using too high of dose of talc that would render the symphysis induced impossible or extremely risky for the patient to undergo a thoracotomy in the future. This issue of the "double-edged sword" efficiency of talc is further alluded to in the commentary by Harrison (1995) on the article by Kennedy & Shan (1994). Harrison (1995) recommends the exercise of caution in the use of talc poudrage in pneumothorax management in young people (particularly smokers) who may someday require a thoracotomy.

(b) (4)

(b) (4) Since all the cases of pleurodesis with STERITALC used a dose of 2 grams we recommend that the labeled dose be 2 grams but that a general statement in the Dosage and Administration section can be included such as (b) (4)

(b) (4) "We note that the sponsor recommends (b) (4)

(b) (4)

(b) (4)

Question: How commonly is talc used off label for pleurodesis following pneumothorax and under what clinical circumstances?

DPARP Response:

Talc is the most commonly used sclerosing agent for chemical pleurodesis (followed by tetracycline and derivatives). Although other agents have been used (see background) talc is by far the most commonly used agent and has the most clinical experience that goes back to several decades (see previous responses).

Question: Are there any products approved by the FDA for pleurodesis in patients with pneumothorax? What products are commonly used off-label for the indication?

DPARP Response:

No, there are no FDA approved products for this indication. Intravenous tetracycline used to be the most commonly used sclerosing agent, however since it is no longer available in the U.S.; talc has become the most commonly used agent over the last 20 years. Tetracycline derivatives (minocycline) are still being used according to literature reports. Other products used off label (reported in the literature) include silver nitrate, bleomycin, autologous blood patch, iodopovidone, and picibanil.

Although bleomycin has been used in malignant effusions it is not recommended to be used as a pleural sclerosants in patients with non-neoplastic disease such as pneumothorax. Autologous blood patch has been described but possible complications have included empyema, pleural effusions, and tension pneumothorax (from the risk of an obstructing clot in the chest tube). Autologous blood patch pleurodesis does not cause severe pain or systemic inflammatory reactions. Picibanil (OK-432) is a lyophilized mixture of a low virulence strain (su) of streptococcus pyogenes incubated with benzypenicillin. It is described in literature reports as sclerotherapy for neck lymphangioma, malignant pleural effusion, and intractable pneumothorax. Iodopovidone is a topical antiseptic that has been described in several studies as a sclerosing agent (20 ml 10% iodopovidone and 80 mL normal saline). The most common side effect reported was chest pain but fever and empyema were also mentioned in these studies (How, Cheng-Hung, et.al, 2013).

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

/s/

LYDIA I GILBERT MCCLAIN
09/06/2016

BADRUL A CHOWDHURY
09/06/2016

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205,555

Applicant: Novatech S.A.

Stamp Date: April 14, 2016

Drug Name: STERITALC®

**NDA Type: Type 5,
Resubmission after RTF**

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 common technical document (eCTD).				eCTD
2.	Is the clinical section legible and 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			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm)	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Section 2.7.3 (separate for indications)
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Section 2.7.4 (combined for indications)
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 2.5.6 (brief)
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?				SCLEROSOL® & Sterile Talc Powder; literature for new indication (pneumothorax)
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			
14.	Describe the scientific bridge (e.g., BA/BE studies)				Waiver requested for BA studies
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number:				Doses differ from RLD, based on literature

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Study Title: Sample Size: Treatment Arms: Location in submission:				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication: Pivotal Study #2 Indication:			X	Reference to RLD and literature
17.	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	
18.	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	
19.	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					
20.	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	
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary ² used for			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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
26.	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			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	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					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested (Orphan Designation for Indications)
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm)?	X			Section 8 of draft label
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	US and foreign literature submitted
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			X	
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
37.	Are all datasets to support the critical safety analyses available and complete?			X	
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					

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).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			X	
40.	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					
41.	Has the applicant submitted the required Financial Disclosure information?			X	No clinical trials were conducted
GOOD CLINICAL PRACTICE					
42.	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	No clinical trials were conducted

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

None

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Form 356h, item 22 should be corrected to read that the application is a resubmission after RTF (not initial).

Nancy S. Scher, MD	May 27, 2016
Reviewing Medical Officer	Date

Laleh Amiri-Kordestani, MD	May 27, 2016
Clinical Team Leader	Date

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

/s/

NANCY S SCHER
06/10/2016

LALEH AMIRI KORDESTANI
06/10/2016