# Cover Sheet

**Study Title: MUCINEX for Treatment of Filamentary Keratitis**

**NCT No: NCT02859246**

**Date: Protocol Last updated 7/21/2016, Protocol approved by Human Research Protection Review Board 10/20/2016**

**Human Studies Committee**
Tel: 617-573-3732
Email: HSC@meei.harvard.edu

# HUMAN SUBJECTS RESEARCH PROTOCOL - RESEARCH SUMMARY (SUPP N)

**DATE: 7/21/2016**
**TITLE OF PROJECT:** MUCINEX ® for treatment of filamentary keratitis
**PRINCIPAL INVESTIGATOR: Reza Dana MD, MPH, MSc**
**FUNDING SOURCE: Pending**

## BACKGROUND

**1) Discuss the following in paragraph format**

- Discuss the importance of the topic (public health and/or clinical importance and impact on individuals/community; incidence, prevalence, mortality and morbidity)
- Critically appraise the relevant literature and discuss the state of current knowledge on the topic (including deficiencies in knowledge or gaps that make the study worth doing)
- Describe, in detail, your approach to address the research question
- Explain how your study will contribute to existing research and benefit other individuals or the wider community

**RESPONSE:** Mucolytics like n-acetylcystine have shown some success previously in the management of filamentary keratitis. There is no data evaluating whether Mucinex ® is also effective at decreasing severity. Anecdotally, patients have reported that filamentary keratitis symptoms improved with the use of mucinex ® for upper respiratory congestion. Filamentary keratitis is an uncommon (chronic) eye condition frequently associated with dry eye disease. Affected patients typically present with symptoms including foreign body sensation, grittiness, pain, photophobia, tearing and increased blink rate. On examination there are thread-like mucus filaments adherent to the corneal surface. Current management of filamentary keratitis addresses dry eye disease (lubrication, punctal plugs), inflammation (anti-inflammatory eye drops), mucous buildup (n-acetylcystine as a mucolytic) and filament removal with forceps.
Previous histologic evaluation has demonstrated that the filaments consist of a corneal epithelial core wrapped in mucus. Staining has established that there is significant overlap in the mucins produced in the eye and those from the respiratory tract, most notably MUC5AC and MUC16. There are several proposed mechanisms for filament formation. The general process begins with an insult to the epithelium, Bowman's membrane, or both, and is commonly associated with some degree of aqueous tear deficiency.
Primary treatment modalities include lubrication, filament removal, anti-inflammatories and mucolytics. Several past studies have shown limited success using n-acetylcysteine for its mucolytic properties. To date there are no trials studying Mucinex ®, which is well-tolerated, cost-effective and has been shown to hydrate respiratory mucus secretions, in the treatment of filamentary keratitis.

References:

Albietz, J., Sanfilippo, P., Troutbeck, R., & Lenton, L. M. (2003). Management of filamentary keratitis associated with aqueous-deficient dry eye. *Optometry and vision science : official publication of the American Academy of Optometry, 80*(6), 420-430. doi: 10.1097/00006324-200306000-00007

Ali, M. S., & Pearson, J. P. (2007). Upper Airway Mucin Gene Expression: A Review. *The Laryngoscope, 117*(5), 932-938. doi: 10.1097/MLG.0b013e3180383651

Diller, R., & Sant, S. (2005). A case report and review of filamentary keratitis. *Optometry - Journal of the American Optometric Association, 76*(1), 30-36. doi: 10.1016/S1529-1839(05)70252-9

Doughty, M. J. (2012). Goblet cells of the normal human bulbar conjunctiva and their assessment by impression cytology sampling. *The ocular surface, 10*(3), 149.

Goodman, L. S., Brunton, L. L., Blumenthal, D. K., Murri, N., & Hilal-Dandan, R. (2011). *Goodman & Gilman's The pharmacological basis of therapeutics*. New York: McGraw-Hill Medical.

Guzman-Aranguez, A., & Argüeso, P. (2010). Structure and Biological Roles of Mucin-type O-glycans at the Ocular Surface. *The ocular surface, 8*(1), 8-17. doi: 10.1016/S1542-0124(12)70213-6

Kim, K. C. (2012). Role of epithelial mucins during airway infection. *Pulmonary pharmacology & therapeutics, 25*(6), 415-419. doi: 10.1016/j.pupt.2011.12.003

Rose, M. C., & Voynow, J. A. (2006). Respiratory Tract Mucin Genes and Mucin Glycoproteins in Health and Disease. *Physiological Reviews, 86*(1), 245-278. doi: 10.1152/physrev.00010.2005

Seagrave, J. (2011). Effect of guaifenesin on mucin production, rheology, and mucociliary transport in differentiated human airway epithelial cells. *Experimental lung research, 37*(10), 606-614. doi: 10.3109/01902148.2011.623116

Seagrave, J., Albrecht, H. H., Hill, D. B., Rogers, D. F., & Solomon, G. (2012). Effects of guaifenesin, N-acetylcysteine, and ambroxol on MUC5AC and mucociliary transport in primary differentiated human tracheal-bronchial cells. *Respiratory research, 13*(1), 98-98. doi: 10.1186/1465-9921-13-98

Tanioka, H., Yokoi, N., Komuro, A., Shimamoto, T., Kawasaki, S., Matsuda, A., & Kinoshita, S. (2009). Investigation of the Corneal Filament in Filamentary Keratitis. *Investigative ophthalmology & visual science, 50*(8), 3696. doi: 10.1167/iovs.08-2938

Wang, G., Xu, Z., Wang, R., Al-Hijji, M., Salit, J., Strulovici-Barel, Y., . . . Crystal, R. G. (2012). Genes associated with MUC5AC expression in small airway epithelium of human smokers and non-smokers. *BMC medical genomics, 5*(1), 21-21. doi: 10.1186/1755-8794-5-21

## AIMS

**2)** Your aim(s) should arise from your literature review and state what the study hopes to accomplish.

**RESPONSE:** To determine the effectiveness of systemic mucinex ® in patients with filamentary keratitis.

## OBJECTIVES

**3)** Your focused research question needs to be further refined into one or more study objectives. The study objective(s) should be single and quantifiable statement(s) that will allow you to answer your research question.

**RESPONSE:** To determine if the mucolytic properties of Mucinex ® are effective in reducing the amount of corneal filaments and improving symptomatology in patients with filamentary keratitis.

## HYPOTHESES

**4a). Primary Hypothesis -** Hypotheses are more specific than objectives and amenable to statistical evaluation. Your primary hypothesis is your statement of the hypothesized effect on the primary outcome measure. A hypothesis is worded very simply and written as 'testable' statements. Your experimental results will prove or disprove your hypothesis. Hypotheses are generally stated in the null form ($H_o$) as they have their basis in inferential statistics. Rejecting the null hypothesis increases our confidence, with a given level of probability, that there is a relationship between the variables being studied. However, a classic scientific hypothesis includes both a null and alternative ($H_a$) hypothesis.

**e.g. $H_o$: Asthma prevalence rates are not different among children from low and high socioeconomic groups in Istanbul. $H_a$: Asthma prevalence rates are different among children from low and high socioeconomic groups in Istanbul.*

**RESPONSE:** H0: Oral Mucinex ® does not reduce corneal filaments or symptomatology in patients with filamentary keratitis. Ha: Oral Mucinex ® twice a day reduces corneal filaments and the symptomatology in patients with filamentary keratitis.

**4b). Secondary Hypotheses** - Although a study is usually based around a primary hypothesis, secondary hypotheses may also be pre-specified although based on outcomes of lesser importance or additional interest. As the primary hypothesis is usually the basis for statistical power calculations, secondary hypotheses with insufficient power will generally not lead to statistically robust conclusions.

**RESPONSE: N/A**

## STUDY DESIGN

**5)** State the design of the research (e.g. randomized controlled study, cross-sectional survey, prospective or retrospective cohort/case-control).

**Whatever the study design, you need to ensure that you provide the reader with a clear statement and description of your proposed design. You may also explain why the particular study design has been chosen in preference to other possible designs (i.e. justification for choice of study design)*

**RESPONSE:** Prospective, non-randomized, non-controlled study.

## ELIGIBILITY CRITERIA

**6a). Inclusion Criteria -** Inclusion criteria are the 'characteristics' that clearly describe the study population that are required for a subject to be included in the study. The criteria may be based on factors such as age, gender, the type and stage of a disease, previous treatment history, and co-morbid medical conditions. They may state appropriate criteria for admitting special 'at-risk' populations such as women of reproductive age, children or patients with disease states or organ impairment.

**RESPONSE:** 1)Patients 18 years or older who have filamentary keratitis in at least one eye. 2) Schirmers test ≥3mm in the eye diagnosed with filamentary keratitis (can be one eye or both the eyes).

**6b. Exclusion Criteria -** Provide details of participants that will be considered ineligible to participate and justification for their exclusion. These criteria are not always clinical in nature, aiming principally to accommodate participants in a safe and ethical manner. Criteria may include circumstances that interfere with the participant's ability to give informed consent (diminished understanding or comprehension, or a language other than English spoken and an interpreter unavailable), contraindications to the study treatment(s)/procedure(s), taking certain concomitant medication(s), or conditions that interfere with a patient's ability to comply with all treatment(s)/procedure(s).

**RESPONSE:** 1) Less than 18 years or older than 80 years of age; 2) Patients unable to provide informed consent; 3) Patients unable to attend a follow-up visit within 4 (±1) weeks; 4) Active ocular surface infection of any type; 5) Recent ocular surgery (< 30 days); 6) History of nephrolithiasis as Mucinex ® has been associated in rare cases to the development of kidney stones; 7) Schirmer test <3mm (in study eye; can be one eye or both the eyes); 8) History of hypersensitivity to Mucinex ®; 9) Concurrent eye disease requiring immediate initiation of a new treatment (e.g., topical steroids); 10) Restrictions for water intake can exacerbate the risk of nephrolithiasis and thus patients taking oral Mucinex ® are instructed to take each dose with a generous amount of water.

## STUDY OUTCOMES

**7a). Primary Outcome -** The primary outcome should be the most important and clinically relevant outcome (e.g. clinical, psychological, economic, or other) of the study. This is the measure used to answer your study aim. However, it is also the outcome used to calculate study sample size and power and test the primary research hypothesis. Generally, no more than 1-2 primary outcome measures are pre-specified. Primary outcome measures may be measured in various ways such as: binary (e.g. caesarean/no caesarean, blood loss ≥500mL/blood loss <500mL); continuous (e.g. weight - kg, blood loss - mL); ordinal (e.g. pain - mild, moderate, severe); time to event (e.g. survival), and counts (e.g. number of infections, number of events occurring).

**RESPONSE:** Reduction of symptoms according to the Ocular Surface Disease Index score after treatment with oral mucinex ® twice a day (total dose is 1.2 g/day) for 4 weeks

**7b). Secondary Outcome(s) -** Secondary outcome(s) are measures of additional or less important research interest. They may include additional clinical, psychological, economic, or safety outcomes (e.g. treatment related side effects/adverse events). However, as these endpoints are not used to calculate study power and sample size it is often not possible to draw robust conclusions from the results.

**RESPONSE:** Reduction in the number of corneal filaments after treatment with oral Mucinex ® twice a day (total dose is 1.2 g/day) for 4 weeks.

## STUDY PROCEDURES

**8)** In this section you need to clearly and comprehensively describe exactly what will happen to participants once they are enrolled in your study. Depending on the study it might include how potential participants will be approached, when they will be randomized, the frequency and duration of visits or whether they are expected to self-complete a daily diary at home, the duration of the study or follow-up, and any measurements taken at each visit (e.g. questionnaires, physical measurements, biological samples).

You should include precise details of the treatment(s)/intervention(s) intended for each group/participant. You should also provide details of any follow-up schedule (i.e. time between visits) and consider how you will monitor participants' adherence with the treatment schedule. You might also describe under which circumstances participants may be withdrawn and how this will occur. A schematic diagram or flow chart may be useful for this section.

RESPONSE: To test the hypothesis that Mucinex ®administration will reduce the signs and symptoms of filamentary keratitis, patients with the diagnosis of filamentary keratitis will be enrolled. At the initial visit (Day #1), visual acuity, number of filaments on the cornea, schirmers test, ocular surface symptoms, these are standard, non-invasive common clinic procedures that will be recorded. The patient will then be instructed to continue their current medication regimen, with no alterations. The patient will then be given 600mg tablets of extended-release Mucinex® to take home, and will be instructed to take them twice a day with abundant water until the next visit in 4 weeks. If patient misses a dose, they are not required to make up for missed dose and can continue to take the next dose. At the follow up visit the visual acuity, number of filaments on the cornea, and ocular surface symptoms will be assessed.

The investigators will screen the patients for a history of nephrolithiasis, a contraindication of this therapy prior to their enrollment. Patients will continue their usual eye treatment regimen while participating in this study.

**9) Randomization (if applicable)**
Include the method (including any software) used to generate the random allocation sequence. Describe type of randomization performed, ratio of assignment to groups, block size permutation and stratification if applicable. Explain the methods used to conceal group allocation until assignment. Also, include information on who will generate the allocation sequence and who will assign participants into their groups.

This section should also discuss if participants, the investigator, and those assessing/analyzing the outcome(s) will be blind (or masked) to group assignment or if the study will be an open-label study (investigators and subjects know their assigned group).

**RESPONSE: N/A**

**10) Study Specific Procedures:** List all procedures (interventions, tests, surveys, etc.) to be performed ONLY for research purposes.

**RESPONSE: None**

**11) Standard of Care Procedures:** Clearly list all standard of care (standard therapy) procedures (interventions, tests, etc.) to be performed regardless of the subject's enrollment in the study, but that will be included in the research assessment.

**RESPONSE:** 1) Dry eye symptoms assessment (Ocular Surface Disease Index questionnaire).

## MEASUREMENT TOOLS

**12)** It is essential to state how the data will be collected to assess the primary and secondary outcome(s) of the study (e.g. patient questionnaire, medical charts, routinely collected hospital/research database, biological specimens). Describe at what point(s) of the study data collection will occur. You should make statements that justify the validity of the study measure/instrument. If not, you will have to verify how you will ensure the validity and quality of data being collected. Also, mention here if you are going to have one or more assessors to collect data, their level of training/experience (or how they will be trained), and if you are planning to assess inter-rater reliability (if applicable).

**RESPONSE:** Data will be collected during the two clinical visits (baseline and follow-up), in which ocular surface symptoms score and number of corneal filaments will be will be recorded in a data collection sheet.

**13) Sample size and statistical power -** A sample size or power calculation should be performed. This calculation is used to estimate the number of subjects required to answer your primary study hypothesis with an accepted power. Conversely, it also allows you to estimate what power can be achieved with a limited number of participants. This number is calculated by specifying the magnitude of the effects that are expected (i.e. informed and clinically significant), variability of the measurements and the acceptable degree of type I and II errors. You need to specify the assumptions made for the calculation. It is recommended that you consult with a statistician for this section. Also keep in mind the estimated recruitment rate and whether you need to adjust for anticipated non-responders and losses to follow up.

**RESPONSE:**

This will be a first-of-its-kind study evaluating an FDA approved and over-the-counter available drug (guaifenesin; Mucinex®) to treat cough as part of the symptoms of common cold. Our study will be the first to evaluate the effect of Mucinex ® alleviating the symptoms of filamentary keratitis. No data are available to estimate the changes expected after initiation of Mucinex ®. This is a pilot study and represents minimal to no risk to participants, and involves no additional procedures other than the routinely performed clinical assessments. In this pilot study we aim to enroll 15 participants.

**14) Statistical methods -** The statistical methods used for the study objectives/hypotheses (e.g. t-test, chi-squared, multivariate modeling) must be sufficiently detailed. If conducting a randomized controlled study, you should state whether methods will include an "intention to treat" (ITT) analysis, per protocol analysis, or both. An ITT analysis is preferred as it compares all subjects in the groups to which they were originally randomly assigned (despite withdrawal, treatment failure or cross-over). Consultation with a statistician is strongly recommended. See Harvard Catalyst Statistical Consulting for more information.

**RESPONSE:** We will use a paired T test or a Wilcoxon signed-rank test, depending on the distribution of the data, to assess whether there is a significant difference between pre- and post-therapy symptoms of filamentary keratitis.

## DATA SAFETY MONITORING PLAN (DSMP)

Complete question 15 **OR** 16 depending on the risk of the study. If your study is submitted as minimal risk and determined by the HSC to be more than minimal risk you will be asked to complete question 16 during the review process.

**15)** If the research is **no more than minimal risk**, please describe any provisions in place to ensure the safety of participants and the validity and integrity of data. If safety monitoring will occur a safety monitoring plan may include elements such as: parameters for safety review, the frequency in which safety review will occur, the person(s) responsible for safety review, and the plan (including the person(s) responsible) for reporting adverse events, protocol deviations, or noncompliance to the HSC and others (where applicable). Data monitoring may include the specific elements that will be reviewed (e.g., informed consent documentation, verification of the accuracy of data), the frequency of data monitoring, and the person(s) responsible.

**RESPONSE:** The PI will assess for adverse events as per protocol. OCRO study staff will document any protocol deviation, patient's non-compliance and report them to HSC per policy.

**16)** If the research is **more than minimal risk**, a more detailed data and safety monitoring plan is required. Please detail the plan for this study below:

| QUESTION | RESPONSE |
|---|---|
| Please identify the types of monitoring (e.g., centralized[1] , on-site[2], a mix of both) that will be utilized for this study and the rationale for use (why these practices are appropriate given the nature (e.g., multisite) and risk of the study):<br>*If a multisite study* and centralized monitoring practices will be employed, describe how processes and expectations for site record keeping, data entry, and reporting will be communicated (e.g., through a Manual of Operations and/or SOP's): | N/A |
| Which individual(s) or group will be responsible for data and safety monitoring (e.g., PI, specific members of the study team, independent monitor(s), DSMB)? Please be specific and indicate who is responsible for what aspects of the study, including what responsibilities are shared: | N/A |
| Provide information related to the expertise and qualifications of the individual(s) and/or groups listed above relative to monitoring. Provide a description of any specific training/qualifications required for personnel carrying out monitoring activities including personnel conducting internal | N/A |

[1] Centralized monitoring means a remote evaluation carried out by study personnel or representatives at a location other than the site(s) at which the clinical investigation is being conducted.
[2] On-site monitoring means an in-person evaluation carried out by study personnel or representative(s) at the site at which the clinical investigation is being conducted.

| | |
|---|---|
| data monitoring, statistical monitoring, or other monitoring activities and the presence of scientific and/or clinical knowledge needed to adequately monitor the trial: | |
| For those who have monitoring responsibilities please describe the plan to provide mentoring, feedback, and additional training to investigators and study staff: | N/A |
| *If this is a multisite* study, explain the plans in place to facilitate timely communication of routine monitoring results and immediate reporting of significant monitoring issues to other sites and stakeholders (i.e., CRO, IRB(s)) as well as communication from sites to monitors: | N/A |
| Please explain how monitoring activities for this study will be documented (i.e., a monitoring log kept in the regulatory binder): | N/A |
| How are monitoring results communicated to stakeholders (investigator(s), IRB):<br>*Please note that the MEE HSC requires that monitoring reports be received within 5 business days of receipt by the MEE PI/study team.* | N/A |
| What processes are in place for addressing unresolved or significant issues (e.g., significant noncompliance with the protocol) identified by monitoring at MEE or across study sites (when applicable): | N/A |
| If applicable, describe the composition of the Data and Safety Monitoring Board (DSMB) including each member's relevant expertise, experience in clinical research and in serving on other DSMB's and the absence of serious conflicts of interest. Explain if any of the members have relationships with those sponsoring, organizing, conducting or regulating the trial and the nature of these relationships or if the members have no involvement in the design and conduct of the study:<br>Note whether or not a DSMB is required (e.g., by the funding agency):<br><br>Note whether or not a DSMB Charter exists for this study and include it as an appendices or indicate if it will be submitted separately to the HSC at a later date (if for example, the charter will be developed by the DSMB at the initial meeting): | N/A |

| | |
|---|---|
| Address the process for communication of Data and Safety Monitoring Board determinations to the investigator and to the HSC: | N/A |
| If applicable, please describe the electronic data capture systems you will be using and what training will be provided for those who will be using these systems: | N/A |
| Include specific data elements (e.g., review of informed consent documentation, confirmation of subject eligibility) that will be reviewed: | N/A |
| Specify the frequency of data monitoring (a specific number of times, at defined time points, after a certain number of subjects have been recruited or as needed): | N/A |
| Who will be responsible for data review (e.g., PI, study staff, DSMB)? If this is a shared responsibility indicate which specific elements each person or group is responsible for: | N/A |
| Specify the parameters (i.e., procedures, laboratory tests, or other measures) that will be used to evaluate the safety of the study treatment(s) or interventions; to include the methods and timing for assessing, recording, and analyzing these parameters: | N/A |
| Specify the frequency of safety observation (a number of times, at defined time points, after a certain number of subjects have been recruited or as needed): | N/A |
| Explain who will be responsible for safety review (e.g., PI, DSMB, monitor): | N/A |
| Address any “stopping rules” for individual research subjects including who will be responsible for making these determinations: | N/A |
| Address any “stopping rules” for parts of the study, or for the entire study including who will be responsible for making these determinations: | N/A |
| Address the frequency and process for eliciting adverse event information from research subjects: | N/A |
| Please acknowledge that adverse events and unanticipated problems will be reported to the HSC in accordance with the HSC policy on Reporting Adverse Events and Unanticipated Problems: | N/A |