Lefamulin for *Mycoplasma genitalium* treatment failures in the US

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Investigator Initiated Study Proposal to Nabriva Therapeutics
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STD Clinical Consultation Network (CCN), National Network of STD Clinical Prevention Training Centers (https://www.stdccn.org/render/Public)

Overview

We are requesting compassionate access to lefamulin for symptomatic patients with *Mycoplasma genitalium* who have failed (a) moxifloxacin and/or (b) other second or third line antimicrobials (e.g., minocycline, omadacycline, other), or when moxifloxacin is contraindicated.

We also request modest funding to cover the costs of prescribing and distributing lefamulin to patients across the US who meet criteria for compassionate access, document treatment outcomes to estimate the efficacy of lefamulin alone and of pre-treatment with doxycycline followed by lefamulin for MG treatment failures, and collect specimens for culture and assessment of minimum inhibitory concentrations (MICs).

Background

Declining efficacy of standard therapies and the emergence of antimicrobial resistance increasingly hinder the management of bacterial sexually transmitted infections (STIs). Although antibiotic resistant *Neisseria gonorrhoeae* (GC) has been classified as an urgent threat by the US Centers for Disease Control and Prevention (CDC) since 2013[1], the prevalence of antibiotic resistance in *Mycoplasma genitalium* (MG) is dramatically higher and multiple cases of untreatable MG have emerged[2,3]. In recognition of this, the CDC's *Antibiotic Resistance Threats in the United States, 2019* report includes MG as one of three organisms on a newly created Watch List.[4]

Moxifloxacin is currently recommended as second-line therapy for MG treatment failures, yet fluoroquinolone resistance in the US is already estimated at 12.8% (95% CI 0.4-34.2%)[5]. Although pristinamycin[6] and combination therapy with doxycycline and sitafloxacin[2] have shown efficacy in cases of MG treatment failures, neither pristinamycin nor sitafloxacin are available in the US. As a result, US providers' only recourse is to trial older antimicrobials (e.g., minocycline) in cases of moxifloxacin treatment failure or when moxifloxacin is contraindicated. This is not always successful.

Lefamulin is a highly potent novel antimicrobial of the pleuromutilin class that is approved by the FDA for the treatment of Community Acquired Bacterial Pneumonia (CABP)[7]. Lefamulin was well-tolerated in Phase II and Phase III studies,[8-10] and initial *in vitro* studies demonstrated high susceptibility of STI pathogens to lefamulin. Notably, susceptibility of CT ($MIC_{50/90}$, 0.02/0.04 mg/liter) and GC ($MIC_{50/90}$, 0.12/0.5 mg/liter) were good, and susceptibility of MG was excellent (MIC range, 0.002 to 0.063 mg/liter for multi-drug resistant strains).[11] Given this high degree of *in vitro* susceptibility and its favorable safety profile, lefamulin holds great promise for MG treatment failures and/or where moxifloxacin is contraindicated. Although the recommended oral dose for CABP is 600mg twice daily for 5 days, MG is a slow growing organism and may require longer durations of therapy.[12] Therefore, we propose to use **lefamulin 600mg orally twice daily for 7 days for *M. genitalium* treatment failures with or without pre-treatment with doxycycline 100mg twice daily for 7 days.**

Diagnostic testing for MG in the US is more limited than in Europe and Australia and only two nucleic acid amplification tests (NAAT) are currently approved by the FDA: the Hologic Aptima MG assay and the Roche TV/MG test. Several large commercial laboratories have also validated and offer their own in-house laboratory developed tests. Neither of the two FDA-approved assays includes the capability to detect macrolide resistance mutations (MRM). The SpeeDx ResistancePlus MG assay, which does have this capacity, is not yet FDA-approved and not available in the US. As such, the resistance-guided therapy approach developed by investigators at the Melbourne Sexual Health Centre[13,14] is rarely implemented in the US and macrolide resistance is infrequently documented. Instead, US providers infer its presence after treatment failure. Additionally, in recognition of increasing macrolide resistance in STI pathogens, doxycycline is replacing azithromycin as first line therapy for STI syndromes. Many STD clinics in the US now treat first with doxycycline, and then treat empirically with moxifloxacin when MG is detected. Not all MG treatment failures have previously received azithromycin. Therefore, eligibility for compassionate access to lefamulin will be determined on the basis of previous treatment failures.

Objective

To estimate the efficacy of lefamulin for the treatment of symptomatic MG treatment failures and/or where moxifloxacin is contraindicated.

Study Design

We propose to provide compassionate access to lefamulin and estimate the efficacy of lefamulin in treating antibiotic resistant MG through a coordinating center at the University of Washington (UW). We will enroll a total of 40 symptomatic patients with MG infections who have experienced treatment failure after moxifloxacin and/or other second or third line antimicrobials

or in whom moxifloxacin is contraindicated. Patients will be followed for 42 or 56 days, depending on the regimen they receive.

There is an increasing global trend to pre-treat MG infections with doxycycline to reduce organism load. There have also been several initial reports of treatment failure after a 7-day regimen of lefamulin alone, but successes after a regimen in which patients were pre-treated with doxycycline in the companion study in Melbourne, Australia. Therefore, we propose to also determine if pre-treatment with doxycycline is necessary. To simultaneously assess the efficacy of lefamulin alone (600mg orally twice daily for 7 days), and a regimen incorporating pre-treatment with doxycycline (doxycycline 100mg orally twice daily for 7 days followed by lefamulin 600mg orally twice daily for 7 days), we will randomize the first 20 patients to either Regimen A (lefamulin alone) or Regimen B (pretreatment with doxycycline followed by lefamulin) in a 1:1 ratio.

An interim analysis will be performed after the first 20 patients are enrolled to assess the efficacy of each of these two regimens for futility. Based on the results of this interim analysis, we will make one of three possible decisions:

- If neither of the regimens meet criteria for futility, we will continue randomizing patients to one of the two regimens until we have reached our target sample size of 40 patients (20 randomized per arm).
- If one of the regimens meets criteria for futility but the other regimen does not, we will drop the regimen that met futility criteria and continue to administer the other regimen to the remaining 20 patients for a total of 30 randomized patients in the retained regimen.
- If both regimens meet criteria for futility, we will halt the study and reassess the possibility of using alternative dosing regimens.

Criteria for futility are outlined in the section on sample size on p. 6.

<u>Study population:</u>

Symptomatic patients with MG treatment failure will be eligible. Treatment failure will be defined as persistent symptoms and a positive NAAT test after (a) moxifloxacin and/or (b) other second or third line antimicrobials (e.g., minocycline, omadacycline, other), or (c) when moxifloxacin is contraindicated. Additional inclusion and exclusion criteria are:

Inclusion Criteria:

- Physician referral
- Persistent symptomatic urogenital MG infection documented by any NAAT 14-90 days after completion of the prior antimicrobial regimen for MG
- Low risk of reinfection defined as no unprotected sex with an untreated sex partner since completion of the prior antimicrobial regimen
- Male or female sex at birth
- ≥18 years of age
- English-speaking
- Able to provide written informed consent
- Able to undergo a test to confirm MG infection at baseline and tests of cure 21-28 days and 42-47 days after completing lefamulin

- Referring physician willing and able to provide needed patient information
- Living in the US

Exclusion Criteria:

- Females with PID, pregnancy, or currently breastfeeding
- Females of reproductive age not on a highly effective method of contraception (i.e., IUD, Nexplanon, progesterone only depot injection with last injection <3 months, or oral contraceptive pill and last menstrual period <28 days prior)
- Known QT prolongation, ventricular arrhythmias including torsades de pointes
- Receiving concurrent drugs known to prolong QT interval (e.g., Class IA or Class III antiarrhythmics, antipsychotics, erythromycin, pimozide, moxifloxacin, tricyclic antidepressants).
- Receiving strong or moderate CYP3A or P-gp inducers, strong CYP3A or P-gp inhibitors, moderate CYP3A or P-gp inhibitors or sensitive CYP3A4 substrates that prolong QT interval
- Moderate or severe liver impairment
- Renal failure requiring dialysis
- Known allergy to doxycycline, other tetracyclines, and/or lefamulin
- Known liver disease
- Not willing or unable to undergo a test to confirm MG infection at baseline and tests of cure 21-28 days and 42-47 days after completion of lefamulin
- Not fluent in English and/or not able to provide written informed consent
- Referring physician unwilling or unable to provide needed patient information
- At the study physician's discretion
- Rectal MG infection only

Recruitment

STI care in the US is decentralized and there is no single clinic where MG treatment failures receive care. Instead, cases come to the attention of our team when individual providers and patients throughout the country contact us, and through clinical consultation requests submitted to the STD Clinical Consultation Network (CCN), National Network of STD Clinical Prevention Training Centers (https://www.stdccn.org/render/Public). The study physician, Dr. Barbee, is a consulting physician in the CCN and handles requests for consultation. In addition to leveraging the CCN to link providers with the study team, we will also post the protocol on clinicaltrials.gov.

The referring provider for patients with documented symptomatic MG treatment failure will be the official point of contact. Patients who contact team members directly will be provided contact information for the study team and asked to have their health care provider contact the team.

Enrollment and consent

After the referring provider obtains verbal consent from their patient to contact the study team, the study physician will conduct an initial telephone or zoom consultation with the referring provider to discuss the patient's case and to determine initial eligibility. The study physician will complete the case report form (CRF) as a UW ITHS REDCap form, the referring provider will

indicate that verbal consent was obtained in a UW ITHS REDCap form, and sign and date the form. The CDC has developed an MG Treatment Failure Case Report Form (CRF) to document and track treatment failures that was approved by the OMB in March 2021. We propose to use this CRF to document cases of treatment failure, allowing us to link with the eventual CDC process for tracking MG treatment failures. The study physician will abstract information on concomitant medications, and other relevant medical history, to confirm eligibility and enter this information into a UW ITHS REDCap form. Where available, the study physician will also abstract Gram stain results and chemistry panel with liver function test results.

Upon receipt of the CRF, a research coordinator will arrange a zoom discussion between the study physician and the patient to explain the study procedures, answer questions, and obtain written informed consent, using the UW ITHS REDCap electronic signature process for consent. The UW-ITHS-supported version of REDCap meets the FDA's Part 11 electronic system requirements. The additional clinical information and the CRF will be completed by the study physician during the discussion with the patient to confirm eligibility and prior to prescribing lefamulin (and doxycycline for patients randomized to sequential therapy).

Dispensing lefamulin (and doxycycline, as warranted)

Dr. Barbee will be the prescribing physician of record and partner with the UW Harborview Medical Center Investigational Drug Services (HMC IDS) to check for drug interactions and/or contraindications to lefamulin (and doxycycline for patients randomized to sequential therapy). Lefamulin and doxycycline will be stored in and dispensed from the UW HMC IDS Pharmacy, which will serve as the pharmacy of record. This is a locked, temperature-controlled facility adjacent to the PHSKC Sexual Health Clinic that manages and dispenses all medications for research studies conducted at the Harborview campus. HMC IDS will be responsible for tracking, documentation, and return/disposal of any unused drug provided by Nabriva.

Upon receipt of a prescription from Dr. Barbee, HMC IDS will prepare the medication packet(s). The research coordinator will ship the medication packet(s) to the patient. Mailing antibiotics across state lines is permissible with an IND exemption in place, which is the case here. Per our consultation with a clinical trials pharmacist, "*when a clinical study is found to be IND exempt [21 CFR 312.2(b)], the FDA has granted that study the same permissions as a study with an IND (such as placing investigational drug into interstate commerce). … with a documented IND exemption, … the drug can be shipped across state lines when a subject has been enrolled in the study [21 CFR 312.40].*" (full text of letter noting on file in the regulatory binder). The FDA has granted this study an IND exemption, cross-referencing Nabriva Therapeutics' existing IND. In addition to the lefamulin tablets, the medication package will include a drug information sheet for lefamulin; contact information for any patient questions about the antibiotic, side effects, or both; a letter, which provides an overview of the study; a specimen collection instruction sheet for each specimen; a return shipment instruction sheet; and materials for patients to collect and return two specimens (one specimen for culture and assessment of MICs; the other specimen to confirm MG infection at baseline). For patients randomized to sequential therapy, the medication package will also contain doxycycline tablets and a drug information sheet for doxycycline.

Culture Specimens

Each medication package will include one Copan flocked swab, one vial of Copan Universal Transport Medium [UTM]), and materials and instructions for returning culture specimens to the UW Global Health STI Laboratory. Male patients will be instructed to collect a self-obtained meatal swab and place it into the tube containing UTM before the first dose of lefamulin (or doxycycline if randomized to sequential therapy) is taken. Female patients will be instructed to take a self-obtained vaginal swab as described above. Both types of self-obtained swabs have demonstrated comparable sensitivity and specificity for diagnostic testing relative to clinician obtained swabs, and are acceptable to patients.[15,16] Additional culture specimen collection materials and instructions will be included along with the Aptima test kits mailed out for tests of cure (see below).

Upon receipt in the Global Health STI Laboratory at the UW, culture specimens will be stored immediately at -70ºC or colder. They will subsequently be shipped in batches to Dr. Jørgen Jensen's laboratory at Statens Serum Institute. Dr. Jensen's laboratory is one of only a few worldwide with the demonstrated capacity to consistently cultivate *M. genitalium* and perform antimicrobial resistance testing. His laboratory will perform the culture and susceptibility testing for lefamulin, as well as for azithromycin and moxifloxacin, under a separate contract. Performing culture and MICs will enable us to assess whether there is any pre-existing resistance to lefamulin, whether any resistance to lefamulin is selected for during treatment, and whether the efficacy of lefamulin differs for azithromycin-resistant and moxifloxacin-resistant strains.

Tests of cure

Tests of cure will be performed in the UW Global Health STI Laboratory (laboratory director Olusegun Soge). The Hologic Aptima MG assay, which we propose to use for tests of cure, has higher sensitivity and specificity than most other assays. Thus, test-of-cure windows when using this assay are generally longer (21-28 days) than when other assays are used. Furthermore, instances of MG recrudescing after an initial negative test subsequent to treatment have been reported,[17,18] suggesting that additional follow-up after an initial test of cure is warranted in studies of novel antimicrobials. Therefore, we will perform two tests of cure (one at 21-28 days and one at 42-47 days after completion of lefamulin).

The research coordinator will ship Aptima test kits to enrolled patients, one 21-48 days, and one 42-47 days after completion of Lefamulin. In addition to the Aptima collection kit and instructions and shipping materials to return the Aptima tubes to the UW Global Health STI Laboratory, that package will also include materials and instructions for culture specimen collection as described above. Culture specimens will be shipped at the same time as the test of cure specimens.

Clinical, symptom, adherence, and side effects data

In addition to the CDC MG Treatment Failure CRF, the study physician will ask about other aspects of the patient medical history and enter this information into a separate UW ITHS REDCap form (concomitant medications, other relevant medical history, etc.). Where available, the study physician will also obtain Gram stain results and chemistry panel with liver function test results.

We will also program electronic surveys, using the UW ITHS REDCap platform, that will be completed by the patient on the start date of the first antibiotic course, upon completion of the antibiotic regimen (lefamulin alone or lefamulin and doxycycline), and at the 21-28-day and the 42-47-day test-of-cure timepoints. The REDCap surveys will collect information on dates of

antibiotic use, symptoms, antibiotic adherence, sexual behavior, and side effects. We will also program electronic reminders to remind the patient to complete the REDCap surveys and to mail in the test of cure and culture specimens.

Outcomes

We will assess one primary outcome and five secondary outcomes.

- Primary Outcome
    - Microbiologic cure defined as a negative Aptima MG test 21-28 days after completing lefamulin
- Secondary Outcomes
    - Microbiologic cure, as defined above, after lefamulin alone compared to microbiologic cure after sequential treatment with doxycycline followed by lefamulin
    - Clinical cure defined as absence of symptoms, absence of visible discharge, and absence of other clinical signs (<5PMNs/hpf on Gram stained smear where available) 21-28 days after completion of the lefamulin
    - Reported adherence to lefamulin (defined by self-reported number of tablets taken)
    - Reported adverse events (defined by self-reported adverse events)
    - Sustained microbiologic cure defined as a negative Aptima MG test 42-47 days after completing lefamulin

Criteria for futility

Given the absence of alternative therapies for *M. genitalium* treatment failures, even modest efficacy of 60% would be useful for some patients. Therefore, futility will be defined as <5% probability that true efficacy is 60% (or higher), given the number of treatment failures that occur in the first 10 patients. The probability of observing three or fewer cures (e.g., at least 7 treatment failures) in the first 10 patients if the true efficacy is 60% is 5%. Therefore, if three or fewer of the first ten patients in either arm experience microbiologic cure, we would declare futility for that regimen.

Sample size

We initially estimated the sample size needed based on the precision around efficacy estimates for lefamulin in a single arm study and estimated that a total of 30 patients with complete data on tests of cure, adherence, and adverse events would provide precision to estimate efficacy ≥90% with binomial exact 95% CI's ranging from 73.5% - 99.9%. Assuming loss to follow-up of up to 30%, **a total of 40 patients will need to be enrolled**.

Because there are fewer people in each arm of a two-arm randomized pilot trial, the statistical power and precision will be somewhat than that estimated for a single arm study. Table 2 compares precision for an arm with 20 randomized persons to one with 30 randomized persons. Even in the case where an arm has only 20 randomized persons, the lower bound of the confidence intervals is >60%, which would still demonstrate benefit.

Table 2: Precision around estimated cure rates assuming 40 patients are enrolled and outcome data are available on either 20 participants randomized per arm (if neither regimen meets criteria for futility), or 30 participants randomized to an arm (if one of the regimens meets criteria for futility)

Lefamulin failures (n)	N=20		N=30	
	Estimated cure	95% confidence intervals	Estimated cure	95% confidence intervals
3	85%	62.11 – 96.79	90%	73.5 – 97.9
2	90%	68.30 – 98.77	93%	77.9 – 99.2
1	95%	75.13 – 99.87	96%	82.8 – 99.9

Data analysis

We will calculate and present simple proportions and 95% CIs for each of our outcomes. We will not require complete data on all outcomes to be included in analyses. Instead, the denominator will be the total number of patients for whom we have complete outcome data for the outcome of interest. For example, patients with test of cure data but without clinical cure data will be included in the calculation of microbiologic cure but excluded from the calculation of clinical cure.

Side effects

We will collect data on the following potential side effects of lefamulin and of doxycycline through our electronic REDCap surveys upon completion of the regimen and at 21-28 days and at 42-47 days after completion of the regimen.

- Gastrointestinal complaints: diarrhea, nausea, vomiting
- Other systemic complaints: photosensitivity, excess vaginal yeast with itching
- Other (open text field for patients to record other events)

Ethics Approvals

The University of Washington Institutional Review Board (IRB) will serve as the IRB of record for this study. We will secure IRB approval prior to initiating any study activities.

Timeline and publication

We estimate it will take one calendar year to enroll and follow 40 patients. Data analysis and preparation of a final report for Nabriva and a peer-reviewed publication will be completed within 12 weeks of the completion of the last follow-up visit of the final participant.

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