Efficacy and Safety of Gepotidacin as Treatment of Uncomplicated Urogenital Gonorrhea (EAGLE-1): Design of a Randomized, Comparator-controlled, Phase 3 Study

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SUPPLEMENTARY MATERIAL

Inclusion Criteria

Age and Weight

- The participants were ≥ 12 years of age at the time of signing the informed consent/assent and had a body weight > 45 kg

Note: Although participants as young as 12 years may enroll in the study, study sites must follow their institutional ethics committee and local country/national regulatory guidelines and enrollment will be contingent upon such approvals regarding the allowed lower age limit for clinical study participants

Type of Participant and Disease Characteristics

- The participant has clinical suspicion of a urogenital gonococcal infection (including sexual contact within the past 14 days with a partner who has a confirmed gonococcal infection) with or without pharyngeal and/or rectal gonococcal infection and has 1 of the following:

  - male participants with purulent yellow, green, or white urethral discharge or female participants with abnormal cervical or vaginal mucopurulent discharge upon physical examination, or
  - a prior positive culture for NG from up to 5 days before Screening (as long as the participant has not received any treatment for this infection), or
  - a Gram or equivalent stain (urogenital specimens only) positive or presumptive for intracellular diplococci from up to 5 days before Screening (as long as the participant has not received any treatment for this infection), or
  - a prior positive NAAT assay for NG from up to 7 days before Screening (as long as the participant has not received any treatment for this infection)

- The participant must be willing to abstain from anal, oral, and vaginal sexual intercourse or use condoms for all forms of intercourse from the baseline visit through the test-of-cure visit

Note: A urogenital specimen will be taken from all participants (males and females) for NG culture at the baseline visit; however, these results will not be used to determine participant eligibility for enrollment in the study. The culture results will be used to identify the primary analysis population

Sex

- Male or female and must have his or her original urogenital anatomy at birth:
  - **Male participants:** A male participant must agree to use contraception (abstinence or the use of a male condom during intercourse) from the baseline visit through completion of the test-of-cure visit
  - **Female participants:** A female participant is eligible to participate if she is a woman of childbearing potential (WOCBP) who is not pregnant as confirmed by a high sensitivity urine pregnancy text at baseline (Day 1) regardless of current or prior contraception use or abstinence, is not breastfeeding, or is not a WOCBP

Informed Consent

The participant is capable of giving signed informed consent/assent, includes compliance with the requirements and restrictions listed in the informed consent form/assent form and in this protocol

Exclusion Criteria

Medical Conditions and History

- The following participants were excluded:

- Males with a current diagnosis of epididymitis and/or orchitis at the time of the baseline visit
- Has suspected or confirmed to have a *Chlamydia trachomatis* infection and per the investigator's judgment standard-of-care treatment for this infection cannot be safely postponed until the test-of-cure visit
- Has a body mass index ≥ 40 kg/m^2 or has a body mass index ≥ 35.0 kg/m^2 and is experiencing obesity-related health conditions such as uncontrolled high blood pressure or uncontrolled diabetes
- Has a history of sensitivity to the study treatments, or components thereof, or a history of a drug (including erythromycin and any macrolide or ketolide drug) or other allergy that, in the opinion of the investigator or medical monitor, contraindicates his or her participation
- Immunocompromised or has altered immune defenses that may predispose the participant to a higher risk of treatment failure and/or complications (e.g., participants with uncontrolled diabetes, renal transplant recipients, participants with clinically significant persistent granulocytopenia [absolute neutrophil count < 1000/µL], and participants receiving immunosuppressive therapy, including corticosteroid therapy [> 40 mg/day prednisolone or equivalent for > 1 week, ≥ 20 mg/day prednisolone or equivalent for > 2 weeks, or prednisolone or equivalent ≥ 10 mg/day for > 6 weeks]). Participants with a known CD4 count of < 200 cells/mm^3 should not be enrolled

Note: Participants taking pre-exposure prophylactics for human immunodeficiency virus (HIV) are allowed to enroll. HIV-infected participants are allowed to enroll, as long as their CD4 count is ≥ 200 cells/mm^3. Use of strong cytochrome P450 enzyme 3A4 (CYP3A4) inhibitors during the study is prohibited

- The participant has any of the following:

  - Medical condition that requires medication that may be impacted by inhibition of acetylcholinesterase, such as:
    - Poorly controlled asthma or chronic obstructive pulmonary disease at the baseline visit and, in the opinion of the investigator, not stable on current therapy
    - Acute severe pain, uncontrolled with conventional medical management
    - Active peptic ulcer disease
    - Parkinson's disease
    - Myasthenia gravis
    - A history of seizure disorder requiring medications for control (this does not include a history of childhood febrile seizures), or
  - Any surgical or medical condition (active or chronic) that may interfere with drug absorption, distribution, metabolism, or excretion of the study treatment (e.g., ileostomy or malabsorption syndrome)
- The participant has known anuria, oliguria, or severe impairment of renal function (creatinine clearance < 30 mL/min or clinically significant elevated serum creatinine as determined by the investigator)
- The participant, in the judgment of the investigator, would not be able or willing to comply with the protocol or complete study follow-up
- The participant has a serious underlying disease that could be imminently life threatening, or the participant is unlikely to survive for the duration of the study period

Cardiac Exclusions

- The participant has:
  - Congenital long QT syndrome or known prolongation of QTc
  - Uncompensated heart failure
  - Severe left ventricular hypertrophy

  - A family history of QT prolongation or sudden death
  - A recent history of vasovagal syncope or episodes of symptomatic bradycardia or bradyarrhythmia within the last 12 months
- The participant is taking QT-prolonging drugs or drugs known to increase the risk of torsades de pointes (TdP) per the www.crediblemeds.org "Known Risk of TdP" category at the time of his or her baseline visit, which cannot be safely discontinued from the baseline visit to the test-of-cure visit; or the participant is taking a strong CYP3A4 inhibitor

Cardiac Electrocardiogram (ECG) Exclusions

- For any participant ≥ 12 to < 18 years who has an abnormal ECG reading
- The participant has a QTc > 450 msec or a QTc > 480 msec for participants with bundle-branch block

Note: The QTc is the QT interval corrected for heart rate according to either Bazett's formula (QTcB), or Fridericia's (QTcF) formula, and/or another method. It is either machine read or manually overread. The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial

- The participant has a documented or recent history of uncorrected hypokalemia within the past 3 months

Hepatic Exclusions

- The participant has a known history of cholestatic jaundice or hepatic dysfunction associated with prior use of azithromycin

- The participant has a known alanine aminotransferase (ALT) value > 2 × upper limit of normal (ULN)
- The participant has a known bilirubin value > 1.5 × ULN (isolated bilirubin > 1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%)
- The participant has a current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), including symptomatic viral hepatitis or moderate-to-severe liver insufficiency (Child Pugh class B or C)

Note: Participants with asymptomatic viral hepatitis are eligible for study participation

Prior/Concurrent Clinical Study Experience Exclusions

- The participant has been previously enrolled in this study or has previously been treated with gepotidacin
- The participant has participated in a clinical trial and has received an investigational product within 30 days or 5 half-lives, whichever is longer

Gonococcal Infection Exclusions

- The participant has any of the following gonococcal infections that require a different dose or duration of treatment:
  - Suspected or confirmed pelvic inflammatory disease
  - Suspected or confirmed gonococcal arthritis
  - Suspected or confirmed gonococcal conjunctivitis
  - Suspected or confirmed gonococcal endocarditis
  - Other evidence of disseminated gonococcal infection

Prior Antibiotic/Antifungal Use and Concomitant Medication Exclusions

- The participant has received any antibacterial therapy for the treatment of a gonococcal infection within 14 days before the baseline visit
- The participant has received any systemic, topical, or intravaginal antibiotics or any systemic antifungals within 7 days before the baseline visit
- The participant must not use St John's wort or ergot derivatives from within 14 days before the baseline visit through the test-of-cure visit
- Due to gepotidacin's potential property of acetylcholinesterase inhibition, the concomitant use of succinylcholine or other nondepolarizing paralytic agents is also prohibited. Caution should be used in participants who have a condition requiring medication that may exacerbate the inhibition of acetylcholinesterase, or neuromuscular blocking agents.

Exploratory Endpoints

- Urogenital NG nucleic acid amplification test (NAAT) results at test-of-cure (Day 4 to 8) visit
- Pharyngeal NG NAAT results at test-of-cure (Day 4 to 8) visit and follow-up (Day 14 to 21) visit, where only participants who did not receive other systemic antimicrobials at or after the test-of-cure visit will be evaluated at the follow-up visit
- Rectal NG NAAT results at the test-of-cure (Day 4 to 8) visit
- Urogenital *Mycoplasma genitalium* NAAT results at the follow-up (Day 14 to 21) visit, where only participants who did not receive other systemic antimicrobials at or after the test-of-cure (Day 4 to 8) visit will be evaluated
- Gram stain (urogenital specimens only), bacterial culture and *in vitro* susceptibility test results from urogenital, pharyngeal, or rectal specimens at the baseline (Day 1), test-of-cure (Day 4 to 8) and follow-up (Day 14 to 21) visits, as data permit