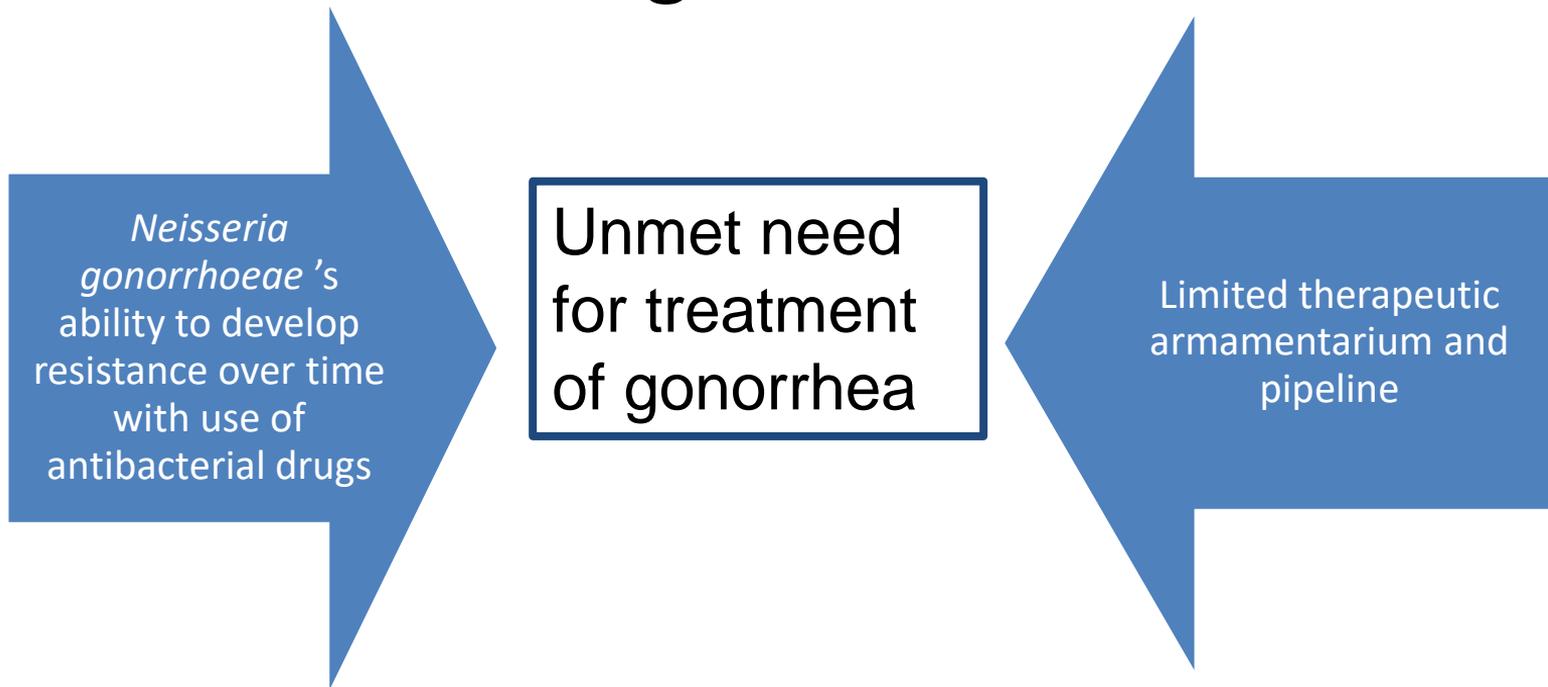


Development of Antibacterial Drugs for Uncomplicated Gonorrhea: A Regulatory Perspective

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FDA-CDC-NIAID Virtual Public Workshop
Development Considerations of Antimicrobial Drugs for the Treatment of Gonorrhea
April 23, 2021

Background



Overview

- Current approach to evaluation of antimicrobial drugs for gonorrhea
 - Statutory requirements
 - FDA's 2015 guidance document for developing drugs for treatment of uncomplicated gonorrhea (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/uncomplicated-gonorrhea-developing-drugs-treatment>)
- Recent development programs and challenges encountered
 - Delafloxacin and solithromycin
- Highlight challenges in design of clinical trials for the treatment of gonorrhea
 - Dose and dosing regimen selection
 - Trial population
 - Trial conduct
 - Trial design
 - Safety database considerations

Statutory Standards

- Substantial evidence: “evidence consisting of **adequate and well-controlled** investigations, including clinical investigations,…” (FD&C Act)
 - Section 115(a) of the Modernization Act clarified that the Agency may consider “data from one adequate and well-controlled clinical investigation and confirmatory evidence” to constitute substantial evidence

Adequate and Well-Controlled Trials

- Characteristics are outlined in 21 CFR 314.126(b) and are considered in determining whether an investigation is adequate and well-controlled
- Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is "substantial evidence" to support the claims of effectiveness for new drugs

Types of Controls

- **Active treatment concurrent control**
 - Randomized trial in which test drug is compared to known effective therapy (active control)
- **Placebo concurrent control**
 - Randomized trial in which test drug is compared to inactive drug that resembles the test drug
- **No treatment concurrent control**
 - Randomized trial in which test drug is compared to no treatment

Types of Controls (cont'd)

- Dose comparison concurrent control
 - Randomized trial in which two or more doses of the test drug are compared
- Historical control
 - Test drug is compared to historical experience – reserved for special circumstances (e.g., disease with high mortality, course of illness predictable, or where drug effect is self-evident such as in general anesthetics)

Types of Trials

- Superiority trials, where the test drug is better than comparator
 - Placebo, no treatment, dose-comparison, active control
- **Noninferiority trials**, where the test drug is no worse than an active comparator by a certain pre-specified amount (noninferiority margin)
 - Treatment effect of the active comparator compared to placebo needs to be estimated in the population being studied and for the outcome of interest

Considerations for Development of New Therapies for Gonorrhea

- Nonclinical
 - Proof of concept of activity against *N. gonorrhoeae* (*Ng*) (*in vitro*, hollow fiber and animal models)
 - Nonclinical pharmacokinetic (PK) and pharmacodynamic (PD) characteristics should be evaluated (in vitro PK/PD models, animal models of infection)
 - Nonclinical PK/PD along with Phase 1 PK assessments should inform appropriate dose and dosing regimens for evaluation in Phase 2 and Phase 3 clinical trials



Clinical Trial Design Considerations for Uncomplicated Gonorrhea

- Prospective, randomized and preferably double-blinded
- Noninferiority (NI) trial comparing new drug to Standard of Care (SoC)
- Pre-specified stratification (e.g., site of infection, sex)
- Geographical diversity is encouraged to strengthen generalizability of the trial results

Study Participant Considerations

- Entry criteria can be broad (e.g., any patient with evidence of uncomplicated gonorrhea without restriction to a site of infection) or focused (e.g., patients with urethritis or cervicitis)
- Exclusion criteria:
 - Patients that require different dose and/or duration of treatment (e.g., disseminated infection, pelvic inflammatory syndrome, epididymitis, conjunctivitis)
 - Patients who have received effective antibacterial therapy for the current gonococcal infection
- Consideration to include adolescents into Phase 3 trials
- Inclusion of pregnant patients only in cases where alternative treatment options are not available (e.g., pregnant women infected with isolate resistant to all available therapy)

Efficacy Considerations

- Efficacy considerations:
 - Primary endpoint: Microbiological cure defined as negative gonococcal culture at the site(s) of initial infection approximately 3-7 days following treatment
 - Nucleic acid amplification tests (NAATs) may be used for selection of patients for enrollment; however, they should not replace culture for initial diagnosis and establishment of test of cure (ToC)
 - Primary analysis population: Microbiological intention to treat (micro-ITT) population, all randomized patients who have *Ng* isolated on baseline culture
 - Secondary endpoints: NAAT results, symptom resolution in the subgroup of patients with baseline symptoms

Safety Database Considerations

- Safety population should include all patients who received the investigational drug during the trial
- In general, a pre-approval safety database of approximately 500 patients at the proposed dose and duration is recommended
 - Safety information from another indication can also be included in the database if the same or greater dose and duration of therapy were used in the clinical trial(s) for other indications

Experience from Recent Trials for *Gonorrhea*: Delafloxacin and Solithromycin



- Phase 3 NI trials (NI margin=10%), open-label, single dose test drug vs. active comparator (ceftriaxone for delafloxacin, and ceftriaxone plus azithromycin for solithromycin) for treatment of uncomplicated urogenital gonorrhea
- Primary endpoint: Proportion of patients with baseline positive urogenital culture for *Ng* who had eradication based on culture at ToC assessed on Day 7 \pm 3 days
- Majority of trial participants were males in both trials
- Both trials failed to meet the pre-specified non-inferiority margin

Topics for Discussion



- Dose and regimen selection
 - Role of nonclinical models in refining optimal dosing
 - Use of single vs. multi-dose regimens
- Trial population
 - How to improve recruitment of women and adolescents
 - Enrollment of urogenital vs. extragenital infection
- Trial conduct
 - Issues with multi-national studies and differing treatment guidelines/SoC
 - Harnessing technology to ensure follow-up and compliance
- Trial design
 - Optimal timing, diagnostics and role of culture for ToC
 - Handling of missing data in the primary analysis
- Safety database considerations

Thank you



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