1308

Microbiological Cure Rates and Antimicrobial Susceptibility of *Neisseria gonorrhoeae* to ETX0914 (AZD0914) in a Phase II Treatment Trial for Urogenital Gonorrhea

A.C. Seña[1], S.N. Taylor[2], J. Marrazzo[3,5], B.E. Batteiger[4], E.W. Hook[5], M. R. Wierzbicki[6], H. Kwak[6], S.M. Johnson[7], P. B. Dixon[5], K. Lawrence[8], J. Mueller[8]

[1]University of North Carolina, Chapel Hill, NC; [2]LSU Health Sciences Center, New Orleans, LA; [3]University of Washington, Seattle, WA; [4]Indiana University, Indianapolis, IN; [5]University of Alabama Birmingham, Birmingham, AL; [6]Emmes Corp., Rockville, MD; [7]FHI 360, Durham, NC; [8]Entasis Therapeutics, Waltham, MA

Background

- *Neisseria gonorrhoeae* has been identified as one of the most urgent antibiotic resistance threats in the United States (US). A total of 350,062 US cases of gonorrhea were reported in 2014, yet CDC estimates 820,000 new infections may occur each year (1),
- ETX0914 (AZD0914) is a novel spiropyrimidinetrione antibiotic that inhibits DNA synthesis through accumulation of double stranded cleavages that interfere with DNA gyrase. ETX0914 has demonstrated *in vitro* activity against *N. gonorrhoeae,* including isolates with decreased susceptibility or resistance to currently available agents (2).
- A multi-center, randomized, open-labeled Phase II trial comparing a single oral dose of 2 grams or 3 grams ETX0914 to 500 mg IM ceftriaxone for gonorrhea treatment demonstrated that ETX0914 was well tolerated and effective (Data presented at National STD Conference, Atlanta, GA, September 20-23, 2016).

Objectives

- We analyzed *N. gonorrhoeae* isolates collected from this Phase II trial to compare:
  - Microbiological cure rates and antimicrobial susceptibility to a single oral dose of 2g and 3g ETX0914 versus a single IM dose of 500 mg ceftriaxone.
  - Minimum inhibitory concentrations (MIC) of ETX0914 versus ceftriaxone, cefixime, ciprofloxacin, azithromycin, penicillin and spectinomycin.

Methods

- Participants were enrolled from five clinics located in New Orleans, Louisiana; Seattle, Washington; Indianapolis, Indiana; Birmingham, Alabama; and Durham, North Carolina.
- Eligibility criteria:
  - Men and non-pregnant women 18-55 years of age;
  - Signs and symptoms of urogenital gonorrhea, confirmed urogenital gonorrhea in past 14 days, or sexual contact with an individual diagnosed with gonorrhea in past 14 days.

Methods

- Participants were randomized approximately 70:70:40 using AdvantageEDC^{SM} software to receive a single dose of 2g or 3g ETX0914 orally or 500 mg IM ceftriaxone alone.
- Study visits included visit 1 (enrollment), visit 2 (test-of-cure, TOC) at 6±2 days after treatment, and visit 3 (safety monitoring) at 31±2 days.
- Urethral or cervical, pharyngeal, and rectal swabs were collected for *N. gonorrhoeae* cultures prior to study drug administration. At visit 2, culture specimens were obtained from all anatomic sites regardless of sexual exposure or negative cultures at enrollment.
- Agar dilution antimicrobial susceptibility testing was performed on all isolates to ETX0914, azithromycin, cefixime, ceftriaxone, ciprofloxacin, penicillin, and spectinomycin.
- Minimum inhibitory concentration (MIC) interpretation for all antibiotics was performed according to Clinical Laboratory Standards Institute (CLSI) criteria except for azithromycin and ETX0914 (CLSI Reference). The MIC breakpoints of ≥ 0.125 µg/mL for ceftriaxone and ≥ 2.0 µg/mL for azithromycin set by the CDC Gonococcal Isolate Surveillance Project (GISP) was used in our analysis (3). The MIC breakpoint of ≥ 0.5 was used for ETX0914.

Results

- From November 2014 through December 2015, 181 patients were screened and 179 (167 men and 12 women) were enrolled and randomized to treatment; 38 participants were excluded due to negative baseline urethral/cervical *N. gonorrhoeae* cultures.
- The per-protocol study population included 117 participants with positive urethral cultures, 19 with positive pharyngeal cultures, and 13 with positive rectal cultures.
- The microbiological cure rate was 98-100% among the per protocol population for either 2g or 3g ETX0914 based on urethral/cervical and rectal specimens.
- The cure rate for ETX0914 was lower at 67-78% from pharyngeal specimens (Table1).

Results

Table 1. Microbiological Cure Rates at TOC Visit in Per Protocol Population

Site	Therapy	Number of Confirmed Infections	Number of Cures	Microbiological Cure Rate %	Microbiological Cure % 95% CI
Urethral/Cervical	ETX0914 2g	49	48	98.0	89.2, 100.0
	ETX0914 3g	47	47	100.0	92.5, 100.0
	Ceftriaxone 500mg	21	21	100.0	83.9, 100.0
Rectal	ETX0914 2g	4	4	100.0	39.8, 100.0
	ETX0914 3g	6	6	100.0	54.1, 100.0
	Ceftriaxone 500mg	3	3	100.0	29.2, 100.0
Pharyngeal	ETX0914 2g	6	4	66.7	22.3, 95.7
	ETX0914 3g	9	7	77.8	40.0, 97.2
	Ceftriaxone 500mg	4	4	100.0	39.8, 100.0

Table 2. *N. gonorrhoeae* Antimicrobial Susceptibility of Baseline Isolates (n=148)* in Per Protocol Population

Antimicrobial	MIC Breakpoint (µg/mL)	MIC50 (µg/mL)	MIC90 (µg/mL)	Range (µg/mL)	Proportion at or above MIC Breakpoint n/N (%)
ETX0914	>=0.5	0.093	0.250	0.008, 0.250	0/148 (0)
Azithromycin	>=2	0.250	1	0.060, 4	4/148 (3)
Cefixime	>=0.25	0.015	0.030	0.002, 0.060	0/148 (0)
Ceftriaxone	>=0.125	0.008	0.015	0.001, 0.060	0/148 (0)
Ciprofloxacin	>=1	0.004	1	0.001, 8	15/148 (10)
Penicillin	>=2	0.500	2	0.030, 64	29/148 (20)
Spectinomycin	>=128	128	128	128, 128	0/148 (0)

Notes: *One rectal gonorrhea isolate did not undergo MIC testing. n=number of subjects at or above MIC breakpoint. N=number of subjects with antimicrobial results for anatomical site and population summarized..

- The $MIC_{50/90}$ determined from urethral/cervical specimens was 0.125/0.250 µg/mL for 2g ETX0914, and 0.125/0.125 µg/mL for 3g ETX0914.
- None of the baseline isolates (urethral/cervical, rectal, or pharyngeal) demonstrated resistance to ETX0914 or ceftriaxone.
- The proportion of isolates with ciprofloxacin resistance (Table 2) was 11% from both urethral/cervical and pharyngeal specimens. The proportion of isolates with reduced susceptibility to azithromycin were 3% of urethral/cervical specimens and 5% of pharyngeal specimens.

Conclusions

- ETX0914 was very effective in eradicating *N. gonorrhoeae* from urogenital and rectal sites as demonstrated by the high microbiological cure rates.
- ETX0914 did not perform as well compared to ceftriaxone for treatment of pharyngeal gonorrhea.
- ETX0914 had acceptable MICs among *N. gonorrhoeae* isolates including those resistant to penicillin, ciprofloxacin or azithromycin.

Limitations

- This phase II trial involved a small sample size of participants with *N. gonorrhoeae* from the US.
- The primary efficacy of the study was to assess ETX0914 for treatment of uncomplicated urogenital (urethral/cervical) gonorrhea, and not pharyngeal or rectal infections.

References

(1) Centers for Disease Control and Prevention. 2014 Sexually Transmitted Disease Surveillance: Gonorrhea. http://www.cdc.gov/std/stats14/gonorrhea.htmSupp

(2) Papp JR, Lawrence K, Sharpe S, Mueller J, Kirkcaldy RD. In vitro growth of multidrug-resistant *Neisseria gonorrhoeae* isolates is inhibited by ETX0914, a novel spiropyrimidinetrione. *Int J Antimicrob Agents.* 2016 Sep;48(3):328-30.

(3) Centers for Disease Control and Prevention. Gonococcal Isolate Surveillance Program (GISP). http://www.cdc.gov/std/gisp/gisp-protocol-may-2016.pdf

Acknowledgements

This study was supported by the NIAID Contract HHSN2722013000121 for the STI-CTG (Ned Hook, PI). We thank our patients; the clinical, laboratory and research teams at each site; Carolyn Deal, Peter Wolff, and Jill Long at NIH DMID; Linda McNeil at FHI360; EMMES Corp. and Entasis Therapeutics, Inc.