# Solithromycin versus ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea (SOLITAIRE-U): a randomised phase 3 non-inferiority trial

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## Summary

**Background** Antibiotic-resistant gonorrhoea represents a global public health threat, and new therapies are needed. We aimed to compare the efficacy and safety of solithromycin, a fourth generation macrolide, with ceftriaxone plus azithromycin for the treatment of gonorrhoea.

**Methods** We did an open-label, multicentre, non-inferiority trial of patients aged 15 years or older with uncomplicated untreated genital gonorrhoea at two sites in Australia and one site in the USA. Patients were randomly assigned (1:1) to receive single dose oral solithromycin 1000 mg or intramuscular ceftriaxone 500 mg plus oral azithromycin 1000 mg. *Neisseria gonorrhoeae* cultures were obtained at baseline and test of cure (day 7 ± 2). The primary outcome was the proportion of patients with eradication of genital *N gonorrhoeae* based on culture at test of cure, assessed in the microbiological intention-to-treat (mITT) population, which included all randomly assigned patients who received any dose of study drug and had a positive genital culture for *N gonorrhoeae* at baseline. Non-inferiority of solithromycin was to be concluded if the lower limit of the 95% CI for the between-group differences was greater than –10%. Safety was analysed in all patients who received any dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT02210325.

**Findings** Between Sept 3, 2014, and Aug 27, 2015, 262 patients were randomly assigned and 261 received treatment (130 in the solithromycin group and 131 in the ceftriaxone plus azithromycin group). In the mITT population, 99 (80%) of 123 patients in the solithromycin group and 109 (84%) of 129 patients in the ceftriaxone plus azithromycin group had *N gonorrhoeae* eradication at test of cure (difference –4·0%, 95% CI –13·6 to 5·5), thus solithromycin did not meet the criterion for non-inferiority at the prespecified –10% margin. The frequency of adverse events was higher in the solithromycin group than the ceftriaxone plus azithromycin group (69 [53%] of 130 patients *vs* 45 [34%] of 131 patients), the most common of which were diarrhoea (31 [24%] of 130 patients *vs* 20 [15%] of 131 patients), and nausea (27 [21%] of 130 patients *vs* 15 [11%] of 131 patients).

**Interpretation** Solithromycin as a single 1000 mg dose is not a suitable alternative to ceftriaxone plus azithromycin as first-line treatment for gonorrhoea. If insufficient duration of solithromycin exposure at the infection site in a subset of individuals was the reason for treatment failures, this might be adequately addressed with dose adjustment. However, any further trials with longer dosing need to consider the potential risk of gastrointestinal effects and liver enzyme elevations.

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## Introduction

Gonorrhoea is one of the most prevalent bacterial sexually transmitted infections worldwide with an estimated 78 million new cases of gonorrhoea occurring globally in 2012.[1] Genital infection with *Neisseria gonorrhoeae* causes urethral discharge in men and vaginal discharge in women. In women, gonococcal infections can cause pelvic inflammatory disease and resultant sequelae, and can be transmitted from mother to child resulting in neonatal infection. Extragenital *N gonorrhoeae* infections of the pharynx and rectum are usually asymptomatic, act as reservoirs for further transmission, and are prevalent among men who have sex with men.[2,3] Gonorrhoea is believed to increase the risk for HIV transmission.[4]

*N gonorrhoeae* has a propensity to acquire mutations conferring antimicrobial resistance, and has acquired resistance to all antibiotics used to treat gonorrhoea.[5] Several national and regional guidelines[6–9] recommend combination therapy with single dose ceftriaxone (250 or 500 mg) plus azithromycin (1 or 2 g) as first-line therapy. However, evidence of high-level azithromycin resistance in *N gonorrhoeae* isolates is increasing worldwide,[10,11] and reports of high-level resistance to ceftriaxone and sporadic ceftriaxone treatment failures are of concern.[12–14] Cases of *N gonorrhoeae* resistant to

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## Research in context

### Evidence before this study

Antimicrobial resistance in *Neisseria gonorrhoeae* is increasing worldwide and poses a global threat to public health. This has been highlighted by gonorrhoea cases resistant to both ceftriaxone and azithromycin. There have not been any new antibiotics approved to treat gonorrhoea for many years. We searched PubMed between Jan 1, 2000, and Aug 8, 2018, using the terms "uncomplicated gonorrhoea" or "uncomplicated gonorrhea" and "clinical trial", and ClinicalTrials.gov using the term "gonorrhea" for randomised clinical trials (phase 2–4). Our search identified seven trials of drugs other than solithromycin for the treatment of uncomplicated gonorrhoea. Of these, only gemifloxacin and gentamicin are options in WHO and US Centers for Disease and Control Prevention treatment guidelines for uncomplicated gonorrhea, and these drugs are only recommended in combination with azithromycin, either as an alternative therapy for patients with cephalosporin allergies or as a retreatment option after treatment failure using a first-line option. In a phase 2 trial of uncomplicated gonorrhoeae, 100% of patients treated with solithrymoycin had *N gonorrhoeae* eradication based on culture.

### Added value of this study

In this randomised, multicentre trial, we compared the efficacy of single dose solithromycin with ceftriaxone plus azithromycin for the treatment of genital gonorrhoea. We found that solithromycin did not demonstrate non-inferiority to ceftriaxone plus azithromycin, with a higher rate of persistently positive genital *N gonorrhoeae* culture at test of cure. To our knowledge, this is the first randomised trial of gonorrhoea treatment that includes a rigorous algorithm for assessing repeat infection as a potential cause of persistent infection using whole genome sequencing.

### Implications of all the available evidence

Solithromycin as a single 1000 mg dose is not a suitable first-line treatment for gonorrhoea. We found no in-vitro evidence that solithromycin treatment failure was due to solithromycin resistance. Insufficient duration of drug exposure at the infection site might account for treatment failure. Efficacy could potentially be improved through adjustment of solithromycin dose; however, any future trials aimed at determining the efficacy of longer dosing must consider the potential for adverse events.

both ceftriaxone and azithromycin have been reported in the UK and Australia.[15] These reports indicate that untreatable gonorrhoea is a global public health threat; however, a limited number of new drugs are in development for the treatment of gonorrhoea.[16]

Solithromycin, a fourth generation macrolide, has potent in-vitro activity against *N gonorrhoeae* and against other genital pathogens including *Chlamydia trachomatis*.[17,18] Solithromycin has additional binding sites to the 23S RNA of the 50S ribosomal subunit relative to older macrolides, resulting in the in-vitro activity observed against macrolide-resistant strains.[19] In a phase 2 study[20] of gonorrhoea in men and women, solithromycin eradicated all *N gonorrhoeae* infections (genital, pharyngeal, and rectal) as determined by culture at both 1200 mg and 1000 mg doses. Although the efficacy of solithromycin was comparable across both doses, 1000 mg was better tolerated than 1200 mg with fewer gastrointestinal adverse events (eg, diarrhoea, vomiting), supporting further evaluation of the 1000 mg dose in a phase 3 study.

See Online for appendix

We therefore did this phase 3 study to compare the efficacy of solithromycin with combination ceftriaxone plus azithromycin for the treatment of uncomplicated genital gonorrhoea.

## Methods

### Study design and patients

This open-label, randomised, controlled, phase 3, non-inferiority trial was done at two sites in Australia (Melbourne Sexual Health Centre [Melbourne, VIC] and Sydney Sexual Health Centre [Sydney, NSW]) and one recruitment site in the USA (Thomas F McCafferty Health Center [Cleveland, OH] and J Glen Smith Health Center [Cleveland, OH]).

Eligible patients were aged 15 years or older with untreated uncomplicated genital gonorrhoea who had tested positive for *N gonorrhoeae* by genital culture or nucleic acid amplification test (NAAT) within the previous 2 weeks, or who had a urethral or cervical Gram stain demonstrating Gram-negative intracellular diplococci and leucocytes. Patients with complicated or systemic gonococcal infection, and individuals who had received systemic or intravaginal antibacterial treatment during the previous 7 days were excluded. Full inclusion and exclusion criteria are available in the study protocol (appendix p 10). The study protocol was approved by the institutional board or ethics committee of all participating centres and all patients provided written informed consent.

### Randomisation and masking

Patients were randomly assigned (1:1) to receive either solithromycin or ceftriaxone plus azithromycin. Randomisation was done by an interactive web response system with a randomisation block size of four, stratified by sex, age (<18 years or ≥18 years), and country (Australia or USA). The randomisation schedule was generated by the clinical research organisation. Patients and all investigators were unmasked to treatment assignment.

### Procedures

At the enrolment visit (day 1), patients received a single dose of oral solithromycin 1000 mg (Cempra Pharmaceuticals,

Chapel Hill, NC, USA) or combination intramuscular ceftriaxone 500 mg plus oral azithromycin 1000 mg. Solithromycin dose was selected on the basis of results from a previous multidose phase 2 clinical trial.[20] Ceftriaxone and azithromycin dose selection was based on the recommended treatment regimen in Australia, the UK, and Europe.[6,8,9] The ceftriaxone dose we used was higher than the dose recommended by the US Centers for Disease Control and Prevention (250 mg).[7]

At enrolment (day 1), demographic, medical history, and baseline clinical assessments were recorded, and baseline microbiological and safety laboratory specimens were collected. The study drug was administered after baseline assessments were done, under direct observation by clinical site staff. Baseline microbiological testing included: *N gonorrhoeae* culture from genital sites (urethral culture for men, cervical culture for women), pharyngeal, and rectal sites, and NAATs for *N gonorrhoeae* and *C trachomatis* from genital sites (urine sample for men, vaginal swab for women), pharyngeal, and rectal sites. At the test of cure visit on day 7 (±2 days), patients completed a questionnaire about sexual activity between day 1 and 7, clinical assessments were recorded and anatomical sites that were positive for *N gonorrhoeae* by culture or NAAT on day 1 were resampled and tested. Test of cure for gonorrhoea using culture at day 7 (±2 days) was adopted in line with the US Food and Drug Administration guidance on gonorrhoea treatment trial design,[21] balancing the time needed for treatment effect against the risk of reinfections as a cause of persistent culture positivity. Patients with a positive baseline NAAT result for *C trachomatis* were asked to return for a follow-up visit on day 21 (±2 days) for repeat *C trachomatis* NAAT testing from the anatomical site that was positive for chlamydia at baseline.

*N gonorrhoeae* was cultured and identified using selective agar media (modified Thayer Martin media or equivalent, incubated overnight at 35–37°C in 5% $CO_2$), colony morphology, Gram stains, oxidase tests, and carbohydrate utilisation assays. The cobas 4800 CT/NG test (Roche, Basel, Switzerland; Australian sites) or Aptima Combo 2 Assay (Hologic, Marlborough, MA, USA; US site) were used for the detection of *N gonorrhoeae* and *C trachomatis* nucleic acid in genital, pharyngeal, and rectal specimens. For specimens in which *N gonorrhoeae* was detected by the cobas assay, specimens were considered positive if confirmatory testing with quantitative PCR targeting the *opa* gene was also positive.[22] For extragenital samples in which *N gonorrhoeae* was detected by the cobas assay, specimens were considered positive if quantitative PCR targeting the *opa* gene and quantitative PCR targeting the *porA* pseudogene were both positive.[23]

All *N gonorrhoeae* isolates were subjected to susceptibility testing by agar dilution for solithromycin, azithromycin, ceftriaxone, cefixime, ciprofloxacin, penicillin, spectinomycin, and tetracycline.[24] The quality control strain *N gonorrhoeae* ATCC 49226 was included in each test run.[25] Multilocus sequence typing (MLST) and antimicrobial resistance genotyping were done on all *N gonorrhoeae* isolates using the MassArray iPLEX platform (Sequenom, San Diego, CA, USA). Antimicrobial resistance determinants investigated included: five related to macrolide resistance (2059 and 2611 mutations of 23S rRNA, three *mtrR* mutations that affect the MtrCDE multidrug efflux pump); four related to penicillin-binding proteins (*ponA1* mutation, penicillin-binding protein 2 [PBP2] mosaic allele, PBP2 345A insertion, PBP2 501 mutation); and two mutations in *gyrA* associated with fluoroquinolone resistance.[26] For patients with suspected treatment failure, *N gonorrhoeae* isolates cultured from the same site at baseline and test of cure were subjected to whole genome sequencing. Libraries were prepared using the Nextera XT DNA Library prep kit (Illumina, San Diego, CA, USA), and sequenced using the NextSeq 500 Sequencing System v2 (150 base pair paired-end reads; Illumina). The raw FASTQ sequence files were analysed using the Nullarbor data analysis tool (version 2.5).[27]

Safety assessments of vital signs, physical examinations, and serum chemistries were done at baseline and day 7 (±2 days). Adverse events and concomitant medications or treatments were recorded throughout the study. Adverse events were coded with the Medical Dictionary for Regulatory Authorities (version 17.1). All adverse events recorded in this study were considered treatment emergent adverse events (defined as adverse events that began or worsened on or after the first dose of study drug through study completion). Serum chemistry values were graded according to the Division of Microbiology and Infectious Diseases Adult Toxicity Scale (November 2007).[28] Laboratory abnormalities were considered treatment emergent if the post-baseline grade was greater than the baseline grade.

### Outcomes

Microbiological outcomes based on *N gonorrhoeae* culture at day 7 (±2 days) were classified as follows: eradication (negative culture), persistence (positive culture), or indeterminate (culture result not available). Microbiological outcomes based on *N gonorrhoeae* or *C trachomatis* NAAT were classified as: clearance (negative NAAT at day 7 [±2 days] for *N gonorrhoeae*, or at day 21 [±2 days] for *C trachomatis*) or persistence (positive NAAT at day 7 [±2 days] for *N gonorrhoeae*, or at day 21 [±2 days] for *C trachomatis*).

The primary outcome was the proportion of patients with eradication of genital *N gonorrhoeae* based on culture at day 7. Secondary outcomes were the proportion of patients with eradication of *N gonorrhoeae* based on culture at day 7 at each anatomical site; eradication of *N gonorrhoeae* based on culture at day 7 at all anatomical sites by patient, whereby all baseline culture positive sites were culture negative at day 7; the proportion of patients

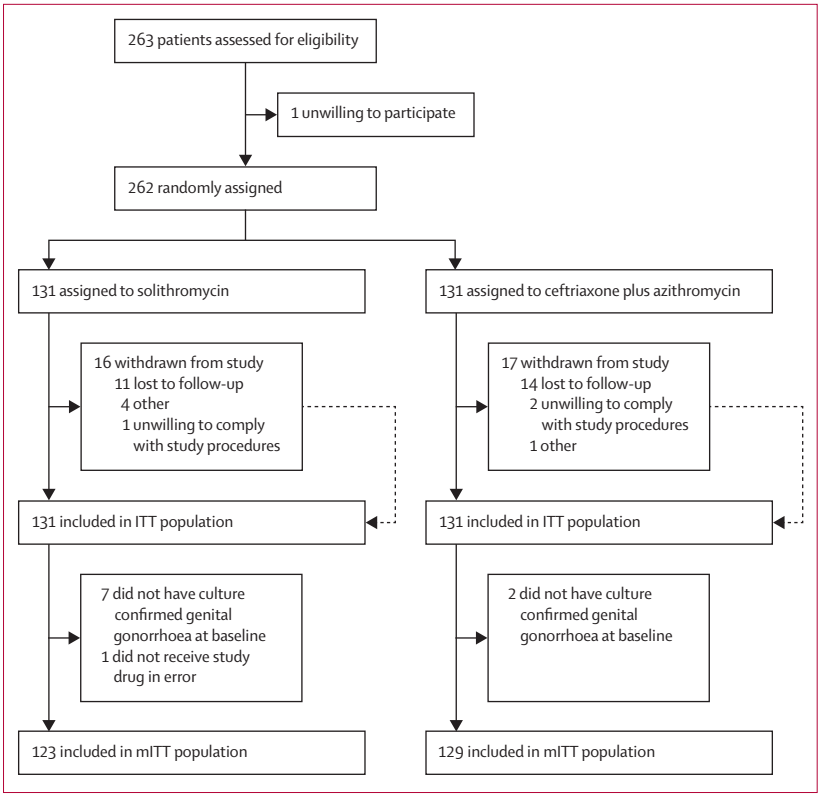


***Figure:*** **Trial profile**
ITT=intention-to-treat. mITT=microbiological intention-to-treat.

with clearance of *N gonorrhoeae* based on NAAT at day 7; and the proportion of patients with clearance of *C trachomatis* based on NAAT at day 21.

Exploratory outcomes were the proportion of patients with clearance or persistence for *Mycoplasma genitalium* based on NAAT of genital specimens at day 21. These exploratory outcomes have not been presented due to the small number of *M genitalium* infections detected.

### Statistical analysis

The primary outcome was analysed in the microbiological intention-to-treat (mITT) population, which included all randomly assigned patients who received any dose of study drug and had a positive genital culture for *N gonorrhoeae* at baseline. All secondary outcomes associated with *N gonorrhoeae* culture were analysed in the microbiologically evaluable population, which included all patients who had a positive baseline culture for *N gonorrhoeae* at any anatomical site, and repeat culture at day 7. Secondary outcomes associated with NAATs were analysed in microbiologically evaluable NAAT populations, which included all patients with baseline NAAT for *N gonorrhoeae* or *C trachomatis* at any anatomical site, with repeat NAAT results at day 7 or day 21 for *N gonorrhoeae* or *C trachomatis*, respectively. Safety was analysed in all patients who received any dose of study drug.

On the basis of the Farrington and Manning method,[29] we calculated that a sample size of 244 patients (122 per treatment group) would be needed for the trial to have 80% power with a one-sided α of 0·025 to determine non-inferiority at a margin of 10%, assuming that 93% of patients would have achieved eradication in each treatment group at day 7. We used the method of Miettinen and Nurminen[30] to calculate an unadjusted two-sided 95% CI and p values for the observed difference in the genital gonorrhoea eradication rate between the solithromycin and ceftriaxone plus azithromycin groups at day 7. Non-inferiority of solithromycin was to be concluded if the lower limit of the 95% CI for the between-group differences was greater than –10%. In this analysis, individuals with indeterminate outcomes (ie, no test of cure) were deemed to have treatment failure. This non-inferiority margin was based on the US Food and Drug Administration guidance on clinical trial design for drugs being developed to treat gonorrhoea which, based on published literature, estimated the treatment effect of antibiotics to be sufficiently large to justify a 10% non-inferiority margin.[21]

Secondary outcomes were analysed by determining unadjusted two-sided 95% CIs for the observed differences in eradication or clearance rates.

An independent data monitoring committee monitored safety data after patient enrolment was completed. This trial is registered with ClinicalTrials.gov, number NCT02210325.

### Role of the funding source

The funder of the study was responsible for study design, data collection, data monitoring, and data analyses, and contributed to writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Sept 3, 2014, and Aug 27, 2015, 263 patients were assessed for eligibility. 262 patients were randomly allocated to receive solithromycin (n=131) or ceftriaxone plus azithromycin (n=131; figure), of whom 261 received treatment (130 in the solithromycin group and 131 in the ceftriaxone plus azithromycin group). The most common reason for study discontinuation was loss to follow-up (ie, patients did not return for an indicated visit [day 7 or day 21]). Five men and four women who had a negative genital culture for *N gonorrhoeae* at baseline, and one man randomly assigned to receive solithromycin who did not receive the study drug in error, were excluded from the mITT population; thus 123 patients in the solithroymycin group and 129 patients in the ceftriaxone plus azithromycin were analysed for the primary outcome. 261 patients (130 patients in the solithromycin group and 131 patients in the ceftriaxone plus azithromycin group) were included in the safety analysis.

Baseline characteristics of patients in the intention-to-treat population are shown in table 1. Most patients were men (94%), in particular men who have sex with men (72%). 253 patients had genital gonorrhoea infections detected by culture (241 urethral and 12 cervical). Positivity for genital gonorrhoea by NAAT assay was similar to culture, with *N gonorrhoeae* identified in 237 urine specimens and 13 vaginal swabs. 83 (32%) of 262 patients had pharyngeal gonorrhoeae and 42 (16%) of 262 patients had rectal gonorrhoeae detected by NAAT assay. In men, fewer positive *N gonorrhoeae* cases were identified with culture than NAAT at pharyngeal (15% *vs* 28%) and rectal sites (8% *vs* 15%). At baseline, 31 (12%) of 262 patients had genital chlamydia infection, eight (3%) of 262 patients had pharyngeal chlamydia infection, and 24 (9%) of 262 patients had rectal chlamydia infection.

313 baseline *N gonorrhoeae* isolates (248 genital, 43 pharyngeal, and 22 rectal) were viable for susceptibility testing (appendix p 2). 24·9% of isolates were resistant to ciprofloxacin, 18·5% to penicillin, and 28·1% to tetracycline. All isolates were susceptible to ceftriaxone and 99·4% were susceptible to cefixime using Clinical and Laboratory Standards Institute breakpoints.[25] A single urethral isolate had an azithromycin minimum inhibitory concentration (MIC) of 2 µg/mL, which is considered to indicate reduced susceptibility according to US Centers for Disease Control and Prevention criteria (MIC ≥2·0 µg/mL). An additional ten isolates (eight urethral, two pharyngeal) had an azithromycin MIC of 1 µg/mL, giving 11 isolates in total considered resistant according to European Committee on Antimicrobial Susceptibility Testing breakpoint criteria (MIC >0·5 µg/mL). All other isolates had an azithromycin MIC of less than 1 µg/mL. All isolates were susceptible to solithromycin using tentative MIC interpretive criteria (MIC range 0·004–0·25 µg/mL, and an $MIC_{50/90}$ [the lowest concentration of the solithromycin at which 50% and 90% of the isolates were inhibited, respectively] of 0·12/0·25 µg/mL). MIC distributions were similar across anatomical sites for all antibiotics tested (data not shown).

Microbiological response rates for *N gonorrhoeae* infection at day 7 in are shown in table 2. At test of cure, 99 (80%) of 123 patients in the solithromycin group and 109 (84%) of 129 patients in the ceftriaxone plus azithromycin group had genital *N gonorrhoeae* eradication (difference –4·0%, 95% CI –13·6 to 5·5); thus solithromycin did not meet the criterion for non-inferiority. The proportion of patients with *N gonorrhoeae* eradication at test of cure was lower than expected in both treatment groups, due to the number of patients with indeterminate cure status (ie, patients who did not return for test of cure assessment at day 7). Genital gonorrhoea infection persisted in eight (7%) of 123 patients in the solithromycin group at test of cure. No patients in the ceftriaxone plus azithromycin group had genital gonorrhoea at test of cure.

| | Solithromycin (n=131) | Ceftriaxone plus azithromycin (n=131) |
|---|---|---|
| Country | | |
| Australia | 98 (75%) | 98 (75%) |
| USA | 33 (25%) | 33 (25%) |
| Age, years | 30·1 (9·2) | 29·4 (10·3) |
| Sex | | |
| Women | 9 (7%) | 7 (5%) |
| Men | 122 (93%) | 124 (95%) |
| Sexual orientation | | |
| Heterosexual men | 27/122 (22%) | 29/124 (23%) |
| Men who have sex with men | 95/122 (78%) | 95/124 (77%) |
| HIV positive | 11 (8%) | 4 (3%) |
| Dysuria (women) | 1/9 (11%) | 0 |
| Cervical or vaginal discharge (women) | 4/9 (44%) | 5/7 (71%) |
| Dysuria (men) | 103/122 (84%) | 102/124 (82%) |
| Urethral discharge (men) | 119/122 (98%) | 120/124 (97%) |
| *N gonorrhoeae* culture positive at any anatomical site | 126 (96%) | 129 (98%) |
| *N gonorrhoeae* positive genital culture* | | |
| Women | 6/9 (67%) | 6/7 (86%) |
| Men | 118/122 (97%) | 123/124 (99%) |
| *N gonorrhoeae* positive pharyngeal culture | | |
| Women | 5/9 (56%) | 1/7 (14%) |
| Men | 20/122 (16%) | 20/124 (16%) |
| *N gonorrhoeae* positive rectal culture | | |
| Women | 1/9 (11%) | 1/7 (14%) |
| Men | 8/122 (7%) | 12/124 (10%) |
| *N gonorrhoeae* NAAT positive at any anatomical site | 127 (97%) | 127 (97%) |
| *N gonorrhoeae* positive genital NAAT† | | |
| Women | 6/9 (67%) | 7/7 (100%) |
| Men | 118/122 (97%) | 119/124 (96%) |
| *N gonorrhoeae* positive pharyngeal NAAT | | |
| Women | 6/9 (67%) | 4/7 (57%) |
| Men | 35/122 (29%) | 38/124 (31%) |
| *N gonorrhoeae* positive rectal NAAT | | |
| Women | 1/9 (11%) | 2/7 (29%) |
| Men | 16/122 (13%) | 23/124 (19%) |
| *C trachomatis* NAAT positive at any anatomical site | 30 (23%) | 23 (18%) |
| *C trachomatis* positive genital NAAT† | | |
| Women | 3/9 (33%) | 1/7 (14%) |
| Men | 14/122 (11%) | 13/124 (10%) |
| *C trachomatis* positive pharyngeal NAAT | | |
| Women | 1/9 (11%) | 0 |
| Men | 3/122 (2%) | 4/124 (3%) |
| *C trachomatis* positive rectal NAAT | | |
| Women | 0 | 2/7 (2%) |
| Men | 12/122 (10%) | 10/124 (8%) |

Data are n (%), mean (SD), or n/N (%). *N gonorrhoeae=Neisseria gonorrhoeae*. NAAT=nucleic acid amplification test. *C trachomatis=Chlamydia trachomatis*. *Cervical specimens were obtained from women, and urethral specimens from men. †Vaginal swabs were obtained from women and urine samples from men.

***Table 1:*** **Baseline characteristics in the intention-to-treat population (n=262)**

Among the 213 patients in the microbiologically evaluable population (106 in the solithromycin group and 107 patients in the ceftriaxone plus azithromycin group),

| | Solithromycin (n=123) | Ceftriaxone plus azithromycin (n=129) | Difference (95% CI) |
|---|---|---|---|
| **Primary outcome** | | | |
| Eradication | 99 (80%) | 109 (84%) | −4·0% (−13·6 to 5·5)* |
| Persistence | 8 (7%) | 0 | .. |
| Indeterminate | 16 (13%) | 20 (16%) | .. |
| **Secondary outcomes†** | | | |
| Eradication of genital gonorrhea | | | |
| Overall | 97/105 (92%) | 107/107 (100%) | −7·6 (−14·3 to −3·9) |
| Women | 5/5 (100%) | 5/5 (100%) | .. |
| Men | 92/100 (92%) | 102/102 (100%) | .. |
| Eradication of pharyngeal gonorrhea | | | |
| Overall | 15/16 (94%) | 19/19 (100%) | −6·3 (−28·8 to 11·6) |
| Women | 2/2 (100%) | 1/1 (100%) | .. |
| Men | 13/14 (93%) | 18/18 (100%) | .. |
| Eradication of rectal gonorrhea | | | |
| Overall | 5/6 (83%) | 12/12 (100%) | −16·7 (−57·4 to 11·6) |
| Women | 1/1 (100%) | 1/1 (100%) | .. |
| Men | 4/5 (80%) | 11/11 (100%) | .. |
| Eradication of gonorrhea at all anatomical sites (by-patient analysis)‡ | | | |
| Overall | 95/104§ (91%) | 107/107 (100%) | −8·7 (−15·7 to −4·6) |
| Women | 5/5 (100%) | 5/5 (100%) | .. |
| Men | 90/99 (91%) | 102/102 (100%) | −9·1 (−16·4 to −4·8) |
| Heterosexual men | 20/21 (95%) | 24/24 (100%) | −4·8 (−23·0 to 9·7) |
| Men who have sex with men | 70/78 (90%) | 78/78 (100%) | −10·3 (−19·0 to −5·3) |

Data are n (%) or n/N (%). *$p_{non\text{-}inferiority}$=0·1082. †Microbiological responses assessed in the microbiologically evaluable population, which included all patients who had a positive baseline culture for *N gonorrhoeae* at any anatomical site (n=106 for the solithromycin group; n=107 for the ceftriaxone plus azithromycin group), were eradication (negative culture at day 7 [± 2 days]), and persistence (positive culture at day 7 [± 2 days]). For simplicity, only eradication rates are shown for secondary analyses. ‡Assessed at the patient level, whereby eradication required that any sites that were *N gonorrhoeae* positive by culture at baseline were negative by culture at day 7—ie, all anatomical site infections were cured. §Two patients did not have available culture results at day 7 for all infection sites that were positive at baseline and were excluded from this analysis.

***Table 2:*** **Microbiological response rates for *Neisseria gonorrhoeae* infection at test of cure by culture in the microbiological intention-to-treat (n=252) and microbiologically evaluable (n=213) populations**

by culture at day 7, 97 (92%) of 105 patients in the solithromycin group were negative for genital gonorrhoea, 15 (94%) of 16 patients were negative for pharyngeal gonorrhoea, and five (83%) of six patients were negative for rectal gonorrhoea (table 2). All patients in the ceftriaxone plus azithromycin group were negative for gonorrhoea across all infection sites at day 7 (table 2). In a by-patient analysis, 95 (91%) of 104 patients in the solithromycin group versus 107 (100%) of 107 patients in the ceftriaxone plus azithromycin group who were positive for gonorrhoea at baseline (at any anatomical site) had negative cultures at all anatomical sites at day 7. At day 7, gonorrhoea had persisted in nine patients in the solithromycin group, of whom seven had baseline urethral infection and persistence at test of cure, one patient with both urethral and rectal infection at baseline and persistence at both sites at test of cure, and one patient with urethral and pharyngeal infection at baseline and only pharyngeal persistence at test of cure. All nine patients were men, and eight were men who have sex with men. At day 7, among patients in the solithromycin group included in the microbiologically evaluable population, all women (five [100%] of five women), 20 (95%) of 21 heterosexual men, and 70 (90%) of 78 men who have sex with men were negative for genital gonorrhoeae by culture.

No differences in MIC values for solithromycin were identified between patients with treatment failure and those without (data not shown). All isolates with the highest solithromycin MICs for each infection site were eradicated after treatment with solithromycin: ten genital isolates with an MIC of 0·25 µg/mL, two pharyngeal isolates with an MIC of 0·25 µg/mL, and three rectal isolates with an MIC of 0·12 µg/mL (appendix p 3). All patients who had treatment failure had isolates with solithromycin MICs of 0·06 or 0·12 µg/mL (azithromycin MIC range for these isolates 0·06–0·50 µg/mL). Furthermore, decreasing susceptibility to solithromycin, defined as an increase in *N gonorrhoeae* MIC of four times or more between baseline and day 7, was not observed. All pretreatment and post-treatment isolate pairs had the same MIC, or were within one two-fold dilution of each other.

Among the nine men with persistence of *N gonorrhoeae* by culture at day 7, only one man reported any sexual contact between treatment and test of cure. The patient had persistent urethral gonorrhoea and reported condomless receptive and insertive oral sex with a regular male sexual partner between treatment and test of cure. The other eight men reported that they did not participate in any sexual contact during this period. Genotyping and whole genome sequencing results of pretreatment and post-treatment pairs of isolates available for six of the nine patients in whom treatment failed showed that pairs had the same MLST and NG-multiantigen sequence typing genotypes (appendix p 4), and few single nucleotide polymorphisms (data not shown), indicating that the isolate pairs were closely related. Collectively, these data do not suggest reinfection with a different strain between treatment and test of cure; however, this does not exclude the possibility of reinfection with the same strain.

MLST and antimicrobial resistance genotyping of all *N gonorrhoeae* isolates identified 39 different MLST types, indicating a wide range of different gonococcal strains in this study (appendix p 4). Similarly, a wide range of key resistance mechanisms were observed. Nine isolates (six baseline urethral, one baseline pharyngeal, and one baseline-test of cure urethral isolate pair from the same patient) had a mosaic PBP2 of the MLST 1901, a clone that is typically resistant to cefixime with susceptibility to ceftriaxone.[12] However, all nine isolates were susceptible to ceftriaxone and seven of nine were susceptible to cefixime. All nine isolates were obtained from patients enrolled in Sydney. No isolates contained the 2059 or 2611 23S rRNA macrolide resistant mutations.

Clearance of *N gonorrhoeae* from any site was assessed in 212 male and female patients with a positive baseline *N gonorrhoeae* NAAT result who had repeat NAAT at the day 7 test of cure (107 male and female patients in the

solithromycin group and 105 male and female patients in the ceftriaxone plus azithromycin group; appendix p 8). At day 7, among the solithromycin group, 95 (90%) of 105 patients had clearance of *N gonorrhoeae* at genital sites, 22 (76%) of 29 patients had clearance of *N gonorrhoeae* at pharyngeal sites, and 13 (87%) of 15 patients had clearance at rectal sites. Among ceftriaxone plus azithromycin group, 102 (97%) of 105 patients had clearance of *N gonorrhoeae* at genital sites, 33 (94%) of 35 patients had clearance at pharyngeal sites, and 19 (95%) of 20 patients had clearance at rectal sites.

Clearance of *C trachomatis* from any site was assessed in 38 patients (22 patients in the solithromycin group and 16 patients in the ceftriaxone plus azithromycin group) with a positive baseline *C trachomatis* NAAT result who had repeat NAAT at day 21. At day 21, among the solithromycin group, eight (80%) of ten patients had chlamydia clearance at genital sites, and seven (70%) of ten patients had clearance at rectal sites. Among patients in the ceftriaxone plus azithromycin group, eight (100%) of eight patients had clearance of *C trachomatis* at genital sites, and four (80%) of five patients had clearance at rectal sites (appendix p 8).

The most common adverse events were similar across treatment groups, but the proportion of patients with adverse events was higher in the solithromycin group than the ceftriaxone plus azithromycin group (69 [53%] of 130 patients *vs* 45 [34%] of 131 patients). Gastrointestinal adverse events were the most common, and were more frequent in the solithromycin group than the ceftriaxone plus azithromycin group (table 3). The most common adverse events were diarrhoea (31 [24%] of 130 patients in the solithromycin group *vs* 20 [15%] of 131 patients in the ceftriaxone plus azithromycin group), and nausea (27 [21%] of 130 patients *vs* 15 [11%] of 131 patients). All adverse events in the solithromycin group were mild to moderate in severity. One patient in the ceftriaxone plus azithromycin group had severe diarrhoea, which was considered related to study drug. Treatment emergent liver enzyme abnormalities are shown in the appendix (p 9). Of the patients who had blood tests at day 1 and 7, eight grade 1 (1·1 to <2 times the upper limit of normal) alanine aminotransferase elevations were observed (five [4%] of 118 patients in the solithromycin group *vs* three [3%] of 116 patients in the ceftriaxone plus azithromycin group) and three grade 2 (2 to <3 times the upper limit of normal) elevations were observed (two [2%] of 118 patients in the solithromycin group *vs* one [1%] of 116 in the ceftriaxone plus azithromycin group). No treatment emergent elevations in alanine aminotransferase or aspartate aminotransferase three times higher than the upper limit of normal or more were observed.

| | Solithromycin (n=130) | Ceftriaxone plus azithromycin (n=131) |
|---|---|---|
| One or more adverse events | 69 (53%) | 45 (34%) |
| Adverse events related to study drug | 56 (43%) | 33 (25%) |
| Gastrointestinal disorders | 57 (44%) | 31 (24%) |
| Adverse events in >2% of patients* | | |
| Diarrhoea | 31 (24%) | 20 (15%) |
| Nausea | 27 (21%) | 15 (11%) |
| Abdominal pain | 4 (3%) | 4 (3%) |
| Abdominal discomfort | 3 (2%) | 0 |
| Abdominal distension | 3 (2%) | 0 |
| Abdominal pain upper | 3 (2%) | 0 |
| Vomiting | 3 (2%) | 0 |
| Headache | 8 (6%) | 7 (5%) |
| Dizziness | 1 (1%) | 3 (2%) |
| Lethargy | 0 | 3 (2%) |
| Trichomoniasis | 3 (2%) | 0 |

Data are n (%). Adverse events were coded with the Medical Dictionary for Regulatory Authorities (version 17.1). *Any adverse event that occurred in more than 2% of patients in either treatment group.

***Table 3:*** **Adverse events in the safety population**

## Discussion

In this randomised trial of uncomplicated genital gonorrhoea, solithromycin was not shown to be non-inferior to ceftriaxone plus azithromycin. Among the mITT population, 80% of patients in the solithromycin group versus 84% of patients in the ceftriaxone plus azithromycin group had eradication of genital gonorrhoeae at day 7. Persistence of genital *N gonorrhoeae* by culture at day 7 was higher in the solithromycin group than ceftriaxone plus azithromycin group, in which no patients had persistence of gonorrhoea. All patients treated with solithromycin who had genital treatment failure were men with persistent urethral *N gonorrhoeae* by culture.

The number of patients with gastrointestinal adverse events was higher in the solithromycin group than the ceftriaxone plus azithromycin group, with the most common being diarrhoea and nausea. In clinical trials of oral or intravenous-to-oral solithromycin administered for 5–7 days for the treatment of community-acquired pneumonia, elevations in alanine aminotransferase of three times the upper limit of normal or higher were observed in 5% and 9% of recipients, respectively.[31,32] In this study of a single dose of 1000 mg solithromycin, treatment emergent elevations in alanine aminotransferase of 1·1 to less than two or two to less than three times the upper limit of normal were observed in 4% and 2% of recipients, respectively. No treatment emergent elevations in alanine aminotransferase more than three times the upper limit of normal were observed in this trial.

To the best of our knowledge, this is the first randomised trial of gonorrhoea treatment that incorporates whole genome sequencing of *N gonorrhoeae* isolates associated with suspected treatment failure combined with specific questioning about sexual activity and therefore potential re-exposure to gonorrhoea before test of cure. Whole genome sequencing provides the highest

resolution analysis of relationships between bacterial isolates. Repeat positive *N gonorrhoeae* cultures at test-of-cure that have the same or a closely related genomic sequence as those at baseline could reflect treatment failure or reinfection with the same strain, whereas test-of-cure isolates with different sequences indicate reinfection with a different strain. Examination of susceptibility profiles, genotypes, and genomic evidence did not suggest reinfection with a different strain in the treatment failures in this trial.

Considering that susceptibility testing did not indicate in-vitro resistance to solithromycin and the absence of evidence for reinfection in most patients, it is possible the treatment failures were due to insufficient duration of drug exposure at the infection site in some individuals. A previous study[33] showed that solithromycin achieves high maximum plasma concentrations (1·3 µg/mL and 2·0 µg/mL after single doses of 800 mg and 1200 mg, respectively). However, after single doses, based on area under the plasma concentration-time curve, variable exposure was observed among individuals. After multiple doses, solithromycin exposure was higher and plasma half-life was extended.[33] In our trial, we did not measure solithromycin plasma concentrations. It is possible that treatment failure was associated with insufficient drug exposure and that an alternate dose (eg, a two-dose regimen) might reduce the number of patients with treatment failure.

Previous studies indicate that azithromycin resistance is becoming more prevalent internationally. Solithromycin has been shown to maintain activity against most azithromycin-resistant strains. In a study[18] of 246 *N gonorrhoeae* clinical isolates and reference strains, 37·8% of isolates had a MIC higher than 0·5 µg/mL for azithromycin and 2·4% of isolates had a MIC higher than 0·5 µg/mL for solithromycin. The $MIC_{50/90}$ of baseline isolates demonstrates that solithromycin had potent in-vitro activity against clinical isolates of *N gonorrhoeae* in this study. This trial could not, however, assess solithromycin efficacy against azithromycin-resistant strains since we identified only one isolate with reduced susceptibility to azithromycin, which was treated with ceftriaxone plus azithromycin. Further clinical trials that include isolates resistant to azithromycin would be required to determine the efficacy of solithromycin against azithromycin-resistant gonorrhoea.

This study had a number of limitations. First, the primary outcome—eradication of genital gonorrhoea—was based on an analysis in which patients lost to followup (ie, individuals who did not have a test of cure; 13% of patients in the solithromycin group and 16% of patients in the ceftriaxone plus azithromycin group) were considered to have treatment failure. In the analysis in the microbiologically evaluable population, which excluded patients lost to follow-up and patients who received other potentially effective antibiotic therapy, the difference in eradication of genital gonorrhoea between the groups was –7·6% (95% CI –14·3 to –3·9) in favour of ceftriaxone plus azithromycin. Although we did not prespecify a superiority test controlling for the overall α level, considering that the upper bound of the CI is below zero, ceftriaxone plus azithromycin seems to be superior to solithromycin in this analysis. Second, solithromycin was used as monotherapy in this trial because if combined with another antibiotic, the efficacy of solithromycin alone could not be determined. Third, culture for *N gonorrhoeae* was used for microbiological confirmation of baseline infection because NAATs for gonorrhoea can produce false positive results. Although NAATs would be expected to be more sensitive than culture, the higher number of culture positive genital infections compared with NAAT positive genital infections might reflect NAAT inhibition or suboptimal sampling. Culture was also used to confirm cure as persistently positive NAAT might occur with non-viable *N gonorrhoeae*. Fourth, the number of extragenital gonorrhoea and chlamydia infections among patients recruited into the study were relatively small; assessing the efficacy of solithromycin against these infections would require a study with sufficient numbers of these infections. Fifth, the number of women included in the trial was small because of the predominance of men who have sex with men among patients with gonorrhoea at the study sites. Sixth, pharmacokinetic data on solithryomycin was not collected from patients in this trial; however, a separate phase 1 trial investigating the genitourinary and pharyngeal pharmacokinetics of solithromycin has been completed (NCT02348424).

Combination ceftriaxone plus azithromycin is the recommended standard of care in the treatment of gonorrhoea in several regions. However, in view of increasing azithromycin resistance and the threat of more widespread ceftriaxone resistance, new drugs and combinations effective against gonorrhoea are required. The results of the present trial indicate that oral solithromycin as a single 1000 mg dose is not suitable as a first-line alternative to combination ceftriaxone plus azithromycin. Additional studies would be required to assess the efficacy of multiple-dose solithromycin in the treatment of genital and extragenital gonorrhoea, including azithromycin-resistant *N gonorrhoeae*. However, any further trials with increased dosing need to consider the potential for increased adverse events, since gastrointestinal events were common at the 1000 mg dose.

#### Contributors

MYC, AM, and AA were the study investigators and enrolled patients into the trial, collected primary data for outcomes and pathogens, participated in the analysis, and reviewed and wrote the manuscript. DO contributed to the design and writing of the protocol, served as the medical monitor, analysed data, and contributed to the first draft of the manuscript. DW, SNT, DH, BPH collected microbiological data and contributed to the writing and review of the manuscript. AFD was the study statistician and contributed to the design of the protocol and all study analyses. AN analysed data and contributed to the first draft of the manuscript. CKF, JSH, CSB, and BD contributed to the design of the study and review of the manuscript.

**Declaration of interests**
MYC reports grants from Cempra Pharmaceuticals during the conduct of this study, and grants from Merck outside the submitted work. AA reports grants from Cempra Pharmaceuticals during the conduct of this study. DW reports grants from Cempra Pharmaceuticals during the conduct of this study, and grants from SpeeDx outside the submitted work. DH reports grants from Cempra Pharmaceuticals during the conduct of the study; and grants from Lab Specialists, Jones Group, and International Management Health Associates outside the submitted work. AFD reports personal fees from Cempra Pharmaceuticals, during the conduct of the study; and personal fees from Contrafect, Tetraphase, Nabriva, Paratek, Achaogen, Zavante, UTILITY, Iterum, Union Therapeutics, and Wockhardt, outside the submitted work. AN was an employee of, and owned stock or stock options in, Cempra Pharmaceuticals and Melinta Therapeutics. CFK reports grants from Cempra Pharmaceuticals during the conduct of this study. CBS reports grants from Cempra Pharmaceuticals during the conduct of this study, and grants from SpeeDx outside the submitted work. DO was an employee of, and owned stock or stock options in, Cempra Pharmaceuticals. AM, SNT, JSH, BD, and BPH declare no competing interests.

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**References**

1 Newman L, Rowley J, Vander Hoorn S, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. *PLoS One* 2015; **10:** e0143304.

2 Patton ME, Kidd S, Llata E, et al. Extragenital gonorrhea and chlamydia testing and infection among men who have sex with men—STD Surveillance Network, United States, 2010–2012. *Clin Infect Dis* 2014; **58:** 1564–70.

3 Fairley CK, Hocking JS, Zhang L, Chow EP. Frequent transmission of gonorrhea in men who have sex with men. *Emerg Infect Dis* 2017; **23:** 102–04.

4 Barbee LA, Khosropour CM, Dombrowksi JC, Golden MR. New human immunodeficiency virus diagnosis independently associated with rectal gonorrhea and chlamydia in men who have sex with men. *Sex Transm Dis* 2017; **44:** 385–89.

5 Goire N, Lahra MM, Chen MY, et al. Molecular approaches to enhance surveillance of gonococcal antimicrobial resistance. *Nat Rev Microbiol* 2014; **12:** 223–29.

6 Bignell C, Fitzgerald M, Guideline Development Group, British Association for Sexual Health and HIV UK. UK national guideline for the management of gonorrhoea in adults, 2011. *Int J STD AIDS* 2011; **22:** 541–47.

7 Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep* 2015; **64:** 1–137.

8 WHO. WHO guidelines for the treatment of *Neisseria gonorrhoeae*. Geneva: World Health Organization, 2016.http://www.who.int/reproductivehealth/publications/rtis/gonorrhoea-treatment-guidelines/en/ (accessed Nov 26, 2018).

9 Australasian Society for HIV Medicine. Australian STI management guidelines for use in primary care. Gonorrhoea. 2018. http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea/ (accessed Nov 29, 2018).

10 Stevens K, Zaia A, Tawil S, et al. *Neisseria gonorrhoeae* isolates with high-level resistance to azithromycin in Australia. *J Antimicrob Chemother* 2015; **70:** 1267–68.

11 Chisholm SA, Wilson J, Alexander S, et al. An outbreak of high-level azithromycin resistant *Neisseria gonorrhoeae* in England. *Sex Transm Infect* 2016; **92:** 365–67.

12 Unemo M, Golparian D, Nicholas R, Ohnishi M, Gallay A, Sednaoui P. High-level cefixime- and ceftriaxone-resistant *Neisseria gonorrhoeae* in France: novel penA mosaic allele in a successful international clone causes treatment failure. *Antimicrob Agents Chemother* 2012; **56:** 1273–80.

13 Lahra MM, Ryder N, Whiley DM. A new multidrug-resistant strain of *Neisseria gonorrhoeae* in Australia. *N Engl J Med* 2014; **371:** 1850–51.

14 Fifer H, Natarajan U, Jones L, et al. Failure of dual antimicrobial therapy in treatment of gonorrhea. *N Engl J Med* 2016; **374:** 2504–06.

15 Public Health England. Update on investigation of UK case of *Neisseria gonorrhoeae* with high-level resistance to azithromycin and resistance to ceftriaxone acquired abroad. 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/701185/hpr1418_MDRGC.pdf (accessed Nov 26, 2018).

16 Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. *N Engl J Med* 2012; **366:** 485–87.

17 Roblin PM, Kohlhoff SA, Parker C, Hammerschlag MR. In vitro activity of CEM-101, a new fluoroketolide antibiotic, against *Chlamydia trachomatis* and *Chlamydia (Chlamydophila) pneumoniae*. *Antimicrob Agents Chemother* 2010; **54:** 1358–59.

18 Golparian D, Fernandes P, Ohnishi M, Jensen JS, Unemo M. In vitro activity of the new fluoroketolide solithromycin (CEM-101) against a large collection of clinical *Neisseria gonorrhoeae* isolates and international reference strains, including those with high-level antimicrobial resistance: potential treatment option for gonorrhea? *Antimicrob Agents Chemother* 2012; **56:** 2739–42.

19 Llano-Sotelo B, Dunkle J, Klepacki D, et al. Binding and action of CEM-101, a new fluoroketolide antibiotic that inhibits protein synthesis. *Antimicrob Agents Chemother* 2010; **54:** 4961–70.

20 Hook EW 3rd, Golden M, Jamieson BD, et al. A phase 2 trial of oral solithromycin 1200 mg or 1000 mg as single-dose oral therapy for uncomplicated gonorrhea. *Clin Infect Dis* 2015; **61:** 1043–48.

21 US Food and Drug Administration. Uncomplicated gonorrhoea: developing drugs for treatment. 2015. Center for Drug Evaluation and Research. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401620.pdf (accessed Dec 20, 2018).

22 Tabrizi SN, Chen S, Tapsall J, Garland SM. Evaluation of opa-based real-time PCR for detection of *Neisseria gonorrhoeae*. *Sex Transm Dis* 2005; **32:** 199–202.

23 Whiley DM, Anderson TP, Barratt K, et al. Evidence that the gonococcal porA pseudogene is present in a broad range of *Neisseria gonorrhoeae* strains; suitability as a diagnostic target. *Pathology* 2006; **38:** 445–48.

24 Clinical and Laboratory Standards Institute. M07–A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard–tenth edition. Wayne, PA: Clinical and Laboratory Standards Institute, 2015.

25 Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing: 26th informational supplement M100–S26. Wayne, PA: Clinical and Laboratory Standards Institute, 2016.

26 Trembizki E, Wand H, Donovan B, et al. The molecular epidemiology and antimicrobial resistance of *Neisseria gonorrhoeae* in Australia: a nationwide cross-sectional study, 2012. *Clin Infect Dis* 2016; **63:** 1591–98.

27 Kwong JC, McCallum N, Sintchenko V, Howden BP. Whole genome sequencing in clinical and public health microbiology. *Pathology* 2015; **47:** 199–210.

28 Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases. Division of Microbiology and Infectious Diseases adult toxicity table. 2007. https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf (accessed May 23, 2019).

29 Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Stat Med* 1990; **9:** 1447–54.

30 Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985; **4:** 213–26.

31 Barrera CM, Mykietiuk A, Metev H, et al. Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (SOLITAIRE-ORAL). *Lancet Infect Dis* 2016; **16:** 421–30.

32 File TM Jr, Rewerska B, Vucinic-Mihailovic V, et al. SOLITAIRE-IV: a randomized, double-blind, multicenter study comparing the efficacy and safety of intravenous-to-oral solithromycin to intravenous-to-oral moxifloxacin for treatment of community-acquired bacterial pneumonia. *Clin Infect Dis* 2016; **63:** 1007–16.

33 Still JG, Schranz J, Degenhardt TP, et al. Pharmacokinetics of solithromycin (CEM-101) after single or multiple oral doses and effects of food on single-dose bioavailability in healthy adult subjects. *Antimicrob Agents Chemother* 2011; **55:** 1997–2003.