Full Title of Study/Programme	A multi-center, randomized, open-label, noninferiority Trial to evaluate the efficacy and safety of a Single, oral dose of zoliflodacin compared to a Combination of a single intramuscular dose of Ceftriaxone and a single oral dose of azithromycin in the Treatment of patients with uncomplicated gonorrhoea
Technical Focus Area/Key Words	Sexually transmitted infections, Gonorrhoea, Zoliflodacin, Phase 3.
Rationale	There is growing concerns over progressive antimicrobial resistance and the development pipeline for uncomplicated gonorrhoea remains relatively empty with only two new chemical entities (NCE) currently in development: zoliflodacin and gepotidacin. Zoliflodacin (AZD0914) has shown extremely good activity against a large collection of isolates (standard and clinical), from different geographical origins, including multi-drug resistant (MDR) and extremely drug resistant (XDR) strains. Zoliflodacin has proven to be an excellent clinical candidate both in terms of efficacy and safety. The drug is well tolerated, can be administered orally and has shown high rates of cure for urethral, cervical and rectal gonococcal infection in phase II. In summary, zoliflodacin is a new promising option to address the risk posed by the threat of drug-resistant gonorrhoea. The purpose of this phase III multi-center, randomized, open-label, non-inferiority trial is to confirm the efficacy and safety outcomes observed in the phase II trial and to generate the necessary evidence to support a marketing authorization application in the USA, the European Union (EU), South Africa and Thailand.
Primary Objectives	To assess the efficacy of a single, oral, 3g dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin for the treatment of uncomplicated urogenital gonorrhoea
Secondary Objectives	1. To assess the safety and tolerability of a single, oral, 3 g dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin in participants with uncomplicated gonorrhea 2. To determine microbiological cure rate of pharyngeal gonorrhoea after administration of a single, oral, 3 g dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin 3. To determine microbiological cure rate of rectal gonorrhoea after administration of a single, oral, 3 g dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin 4. To determine the clinical cure rate of symptomatic gonorrhoea in male participants after administration of a single, oral, 3 g dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin

	5. To determine the microbiological cure rate of urogenital gonorrhoea among women and men respectively, after administration of a single, oral, 3g dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1g oral dose of azithromycin 6. determine the microbiological cure rate of NG at urethral or cervical sites in the subset of participants with pre-existing resistance to antibiotics commonly used for NG treatment (including to ceftriaxone alone, to azithromycin alone and to both) 7. To determine the antimicrobial susceptibility profile of gonococcal strains isolated from participants with uncomplicated gonorrhoea at baseline and the TOC visit 8. To determine the eradication rate of NG nucleic acid from urethral, cervical, rectal, pharyngeal specimens after administration of a single, oral, 3 g dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin.
Primary Endpoint/Outcome	Microbiological cure as determined by culture at urethral or cervical sites at TOC (day 6 ±2)
Secondary Endpoint/Outcome	1. Incidence, severity, causality, and seriousness of treatment-emergent adverse events and the evaluation of changes from baseline in safety laboratory test results and physical examinations 2. Proportion of participants with microbiological cure as determined by culture at pharyngeal sites at TOC (day 6±2) 3. Proportion of male participants with clinical cure at TOC (day 6 ±2) 4. Proportion of female and male participants respectively with microbiological cure as determined by culture at cervical or urethral site at TOC (day 6 ±2) 5. Proportion of participants with microbiological cure as determined by culture at urethral or cervical sites at the TOC visit and for whom the baseline antimicrobial susceptibility profile indicated pre-existing resistance to antibiotics commonly used for NG treatment (including to ceftriaxone alone, to azithromycin alone and to both) 6. pre-existing resistance to antibiotics commonly used for NG treatment (including to ceftriaxone alone, to azithromycin alone and to both) 7. Proportion of participants with a negative NG NAAT from urethral or cervical sites at TOC (day 6 ±2) Proportion of participants with a negative NG NAAT from oropharyngeal sites at TOC (day 6 ±2) Proportion of participants with a negative NG NAAT from rectal sites at TOC (day 6 ±2)
Study Design	This trial will be a multi-center, open label, randomized controlled, non-inferiority phase III trial evaluating the safety and efficacy of a 3 g oral dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a

	single 1 g oral dose of azithromycin for the treatment of uncomplicated gonorrhoea.
Study arms	Two arms (randomization 1:2). 3 g oral dose of zoliflodacin compared to a combination of a single IM 500 mg dose of ceftriaxone and a single 1 g oral dose of azithromycin.
Study population	Sexually-active, HIV-uninfected adolescents (<18 years old at time of enrollment)
Study sample size	The target sample size is 603 evaluable participants: 402 in the zoliflodacin group and 201 in the comparator group, with a maximum randomisation sample size of 928. The Johannesburg site will be enrolling 221 participants.
Follow up/duration	The total duration for individual participants will be 30 days (± 3 days) in total, unless the participant drops off or withdraws consent. The total duration for enrollment is anticipated to be 18 months.
Study/Programme sites	Ward 21 CRS, Johannesburg, South Africa
Study/Programme duration	Participant recruitment will take approximately 18-24 months.
Intervention	Single oral 3 g dose of zoliflodacin granules as oral suspension Comparator: Combination of a single intramuscular 500 mg dose of ceftriaxone and a single oral 1 g dose of azithromycin
Investigators	IOR: Prof Sinead Delany-Moretlwe Sub Investigators: Dr Danielle Travill, Dr Jeanne Omony
Other Partners & Collaborators	MRC
Sponsors/Donors	GARDP, Chemin Louis Dunant, 15, 1202 Geneva, Switzerland; Phone: +41 22 555 19 90
Linked Sub-studies	PK substudy: To evaluate the plasma PK of a single, oral, 3 g dose of zoliflodacin: • in human immunodeficiency virus (HIV) negative adult participants (≥ 18 years old) and HIV positive adult participants whose anti-retroviral therapy does not include inhibitors of cytochrome P450 3A (CYP3A) with uncomplicated gonorrhoea • in HIV positive adult participants (≥ 18 years old) whose anti-retroviral therapy (ART) includes inhibitors of CYP3A with uncomplicated gonorrhoea • in HIV negative adolescent participants (≥ 15 and < 18 years old) with uncomplicated gonorrhoea
Publications/key presentations to date	None
Progress Update:	This study is complete and results are due for dissemination in April 2024.

Frequency of donor narrative report	Annual
Overall Study/Project Contact	Prof Sinead Delany-Moretlwe