A multi-center, randomized, open-labe, 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.

Published: 11-10-2019
Last updated: 25-03-2025

To assess the efficacy of a single, oral, 3 grams (g) dose of zoliflodacin compared to a combination of a singleintramuscular (IM) 500 milligram (mg) dose of ceftriaxone and a single 1 g oral dose of azithromycin for the treatment ofuncomplicated…

Ethical review	Approved WMO
Status	Completed
Health condition type	Bacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON54942

Source
ToetsingOnline

Brief title
STI_ZOLI001

Condition

- Bacterial infectious disorders

Synonym
Gonorrhoea, Neisseria gonorrhoeae

Research involving
Human

Sponsors and support

Primary sponsor: Institution Global Antibiotics Research and Development Partnership (GARDP)
Source(s) of monetary or material Support: WHO en GARDP

Intervention

Keyword: Antibiotic, Gonorrhoea, open label, Phase III

Outcome measures

Primary outcome

Microbiological cure as determined by culture at urethral or cervical sites at

TOC (day 6 ±2)

Secondary outcome

Secondary endpoints

* 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

* Proportion of participants with microbiological cure as determined by culture

at pharyngeal sites at TOC (day 6 ±2)

* Proportion of participants with microbiological cure as determined by culture

at rectal sites at TOC (day 6 ±2)

* Proportion of male participants with clinical cure at TOC (day 6 ±2)

* Proportion of female and male participants respectively with microbiological

cure as determined by culture at cervical or urethral site at TOC (day 6 ±2)

* Proportion of participants with microbiological cure as determined by culture at urethral or cervical sites at TOC 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)

* Antimicrobial susceptibility profile of gonococcal strains isolated at baseline and at TOC (day 6 ±2)

* Proportion of participants with a negative NG nucleic acid amplification test (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 description

Background summary

Bacterial sexually transmitted infections (STI) are a major public health concern globally, affecting over 357 million people every year. Neisseria gonorrhoeae (NG), the etiological agent of gonorrhoea, is estimated to have caused 78 million infections in 2012. The Western Pacific and African regions have the highest incidence of gonococcal infections worldwide, with 89 and 50 cases per 100*000 population respectively. Rates of male urethral discharge (UD), which is primarily due to NG or Chlamydia trachomatis (CT), are also highest for these two regions, amounting to 567 per 100*000 in Africa and 141 per 100*000 in the Western Pacific. In high income countries (HIC), gonorrhoea is also raising significant concerns. In the
United States of America (USA) it is the second most frequently reported notifiable infectious diseases, with about 400*000 infections reported per

year. NG has been included as one of three organisms presenting an urgent threat due to progressive antimicrobial resistance by the US Centers for Disease Control and Prevention (US CDC). Gonorrhoea affects both men and women. In men, infections commonly manifest as
urethritis. Symptoms develop in 75% of the men within four to eight days of genital infection and in 80 to 90% within two weeks. UD is the most frequent presenting symptom and is often undistinguishable from non-gonococcal urethritis (e.g. CT infections). Acute unilateral epididymitis can be a complication of gonococcal infection, although it is more common with CT infections. In women, gonococcal infections are often (>=50% of the cases) asymptomatic. Genital infections, in particular cervical infections, are the most common infections. When symptomatic, cervical infection typically manifests as mucopurulent discharge. If left untreated, NG infections can ascend to involve the uterus and fallopian tubes.
Gonorrhoea is associated with significant morbidity and if not treated appropriately, can have serious consequences on reproductive health. Pelvic inflammatory disease (PID), ectopic pregnancies, abortions, neonatal conjunctivitis and blindness are among the possible complications. Studies have also shown that gonorrhoea enhances the transmission of human immunodeficiency virus (HIV) by three to five fold.
Most individuals with gonorrhoea are managed in the community, and clinical management is often empiric and syndromic: treatment is based on the presence of easily recognized signs (e.g. urethral or vaginal discharge), and the provision of antibiotics that deal with the majority
of, or the most serious, organisms responsible for the syndrome. Extended spectrum cephalosporins (ESC) constitute the mainstay of gonorrhoea treatment. However, with increasing resistance to ESC emerging globally, and in particular to cefixime, several countries have now switched from ESC monotherapy to a dual therapy that includes an injectable ESC - ceftriaxone- and azithromycin (10,11), the underlying, unproven, assumption being that a dual therapy would slow down resistance emergence.
Over the past few years, the World Health Organization (WHO) and others have raised concerns over the spread of gonococcal antimicrobial resistance (AMR), warning that infections due to NG may soon become untreatable. Reports of treatment failures with ESC and azithromycin monotherapy have multiplied over the past few years, and clinical failures to dual therapy have been reported. Despite this, the drug development
pipeline for NG remains insufficient. In 2012, the WHO launched a global action plan to control the spread and impact of antimicrobial resistance in NG. Identifying new treatment options for multi-drug resistant (MDR) gonorrhoea is a key element of the WHO global action plan, and has long been called for by clinicians and microbiologists.

Zoliflodacin (ETX0914) belongs to a new class of antibiotics that inhibit bacterial deoxyribonucleic acid (DNA) replication. It shows in vitro antibacterial activity against several Gram-positive pathogens such as Staphylococcus spp. and Streptococcus spp. as well as fastidious Gram-negative

pathogens such as Haemophilus influenzae, Moraxella catarrhalis and NG. Minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC90) values for NG range from 0.125 to 0.25 microgram (µg)/millilitre (mL). A complete program of both oral and intravenous (IV) toxicity studies was performed in the rat and dog. Data collected included clinical observations, body weight changes, food
consumption, clinical pathology and histopathology. Also completed was a battery of genetic toxicology studies and single dose safety pharmacology studies to assess cardiovascular, central nervous system, renal, respiratory and gastrointestinal endpoints. Detailed results of
these pre-clinical evaluations are summarized in the investigator brochure (IB). Studies performed in the Staphylococcus aureus (S. aureus) neutropenic thigh model indicated that the ratio between the area under the concentration-time curve (AUC) and the MIC was the driver of log kill. Those studies also supported a predicted efficacious mean AUC in humans of 49 µg*hour(h)/mL. Overall the preclinical data supported progression to phase I trials.

Zoliflodacin is being developed as an oral, single dose treatment. Final data is available from five clinical trials : a phase I single-ascending dose (SAD) trial, a phase I absorption, distribution, metabolism, excretion (ADME) trial, a phase II trial involving participants with confirmed urogenital gonococcal infection (clinicaltrials.gov NCT02257918), a phase I relative bioavailability (rBA) trial (clinicaltrials.gov NCT03404167) and a phase I food effect trial with healthy volunteers to assess the effect of food on the PK characteristics of a newly developed formulation (clinicaltrials.gov NCT03718806). The SAD and ADME trials showed that zoliflodacin was well tolerated at all doses tested (200 mg- 4*000 mg). In phase 1
clinical trials, the most common adverse events (AEs) were dysgeusia, corrected QT interval (QTc) change from baseline and headache.
In the phase II, 96% (95%CI: 88-100%) cure rates were observed with both the 2 g and the 3 g doses in the microbiological intent-to-treat (micro ITT) population at the urogenital site (55 out of 57 and 54 out of 56 participants respectively) compared to 100% (95% CI:88-100) in the
comparator arm of ceftriaxone 500 mg IM. All participants with concomitant rectal infections were cured with either dose of zoliflodacin, while for those with concurrent oropharyngeal infections, cure rates were lower (2 g 50% [95%CI: 16-84]; 3 g 82% [95%CI: 48- 98]) compared to 100% (95%CI: 40-100) for ceftriaxone. The small number of participants with concurrent oropharyngeal infections included in the phase II (8 participants in the 2 g arm, 11 participants in the 3 g arm and 4 in the ceftriaxone arm) however precludes any firm conclusion about efficacy at this site. In the phase II, the safety profile of zoliflodacin was generally similar to ceftriaxone; the most common adverse events (excluding infection-related
AEs) were diarrhoea, headache, and nausea. The drug was overall generally well tolerated.

Study objective

To assess the efficacy of a single, oral, 3 grams (g) dose of zoliflodacin compared to a combination of a single intramuscular (IM) 500 milligram (mg) dose of ceftriaxone and a single 1 g oral dose of azithromycin for the treatment of uncomplicated urogenital gonorrhoea

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 with uncomplicated gonorrhoea
• in HIV negative adolescent participants (>= 12 and < 18 years old) with uncomplicated gonorrhoea

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. Participants will present to the clinic for assessment of eligibility after informed consent is signed on Day 1. Should eligibility be confirmed, they will be randomised to either the zoliflodacin group or the ceftriaxone/azithromycin combination group, undergo baseline assessments and dosed with the trial treatment on the same day.

The randomization sequence will be obtained by computer-generated random numbers and provided to each trial site through a web-based randomization system. Trial participants will be assigned to receive either zoliflodacin or a ceftriaxone/azithromycin combination in a 2:1 allocation ratio. Unequal randomization has been chosen to increase the number of individuals from which safety data is gathered. Randomisation will be performed using random permutated blocks of 3, 6, and 9 by site with stratification by sex at birth.

Those participants who are assigned to the zoliflodacin group and who will also have consented to be enrolled in the PK sub-study will undergo blood sampling on Day 1 and return to the clinic on Day 2 for further blood sampling. Sites staff will call participants on Day 3 for safety monitoring purposes and to enquire about sex behaviour since the previous clinic visit. Participants will return to the clinic on Day 6 for the TOC visit, involving safety and efficacy assessments (primary endpoint for the trial will be assessed at the TOC visit). Those participants that will a posteriori have been diagnosed with a CT infection via NAAT at baseline and who were randomised to the zoliflodacin arm will then be treated for the CT infection as per standard of care. Participants will be asked to return to the clinic for the end of trial visit on Day 30 for

final safety and efficacy assessments.Participants will be asked to return to the clinic for a follow up visit on Day 30 for final safety and efficacy assessments.

Intervention

Reference treatment: Combination of a single dose ceftriaxone 500 mg IM, dissolved in lidocaine 1% and a single oral 1 g dose of azithromycin
Studiemedication: Single oral 3 g dose of zoliflodacin granules as oral suspension

Study burden and risks

The study medication may be less effective than the current standard treatment: treatment failure. In that case, the study participants will receive the standard treatment (7-14 days after the study of medication).
In the phase II, the safety profile of zoliflodacin was generally similar to ceftriaxone; the most common adverse events (excluding infection-related AEs) were diarrhoea, headache, and nausea. The drug was overall generally well tolerated.
The effect of zoliflodacin administration has not been studied in pregnant women. Therefore, all eligible women of reproductive age must not be pregnant and have a negative pregnancy test before they can be included in the trial.

GARDP have received preliminary results from recent Physiologically Based Pharmacokinetic (PBPK) modelling which provides estimation of exposure in subjects in various conditions, including when taking strong CYP3A4 inhibitors. GARDP have evaluated these data with respect to the potential for risk of QTc prolongation in certain situations. Pending full assessment of the data, GARDP are taking a conservative step with this protocol amendment by excluding from the trial participants taking strong or moderate CYP3A4 inhibitors. As a consequence, it is expected only a minority of HIV positive participants will be eligible.

Contacts

Public
Institution Global Antibiotics Research and Development Partnership (GARDP)

Chemin Camille Vidart 15
Geneva 1202
CH
Scientific
Institution Global Antibiotics Research and Development Partnership (GARDP)

Chemin Camille Vidart 15
Geneva 1202
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)

Inclusion criteria

1. >= 12 years old (if enrolment of minors is in agreement with local regulations and ethics guidance, for Dutch site 16 years and older will be maintained)
2. >= 35 kilogram (kg)
3. Signs and symptoms consistent with urethral or cervical gonorrhoea
OR
Urethral or cervical uncomplicated gonorrhoea as determined by either a positive culture or NAAT or Gram stain or methylene blue/gentian violet stain in the past 14 days prior to screening
OR
Unprotected sexual contact with an individual confirmed to be infected with NG in the past 14 days prior to screening (positive NAAT, Gram stain, methylene blue/gentian violet stain or culture)
4. For females of child-bearing potential, a negative urine pregnancy test at screening
5.For females of child bearing potential, use of highly effective method of contraception at the time of IMP administration on Day 1 (see Appendix 1: contraception methods considered as highly effective and required duration) and until at least 28 days after treatment. Females on oral contraceptives must also use a barrier contraception method during participatien in the study.
6. For males with a female partner of child-bearing age, willingness to delay conception during the trial and for 28 days after treatment
7. Willingness to comply with trial protocol
8. For participants in the PK sub-study: Willingness to undergo HIV testing

9. Willingness to abstain from sexual intercourse or use condoms for vaginal, anal and oral sex from enrollment until end of trial (EOT) visit
10. Willingness and ability to give written informed consent or be consented by a legal representative, or provide assent and parental consent (for minors, as appropriate)

Exclusion criteria

1. Confirmed or suspected complicated or disseminated gonorrhoea
2. Pregnant or breastfeeding females
3. Known concomitant infection which would require immediate additional systemic antibiotics with activity against NG
4. Use of any systemic or intravaginal antibiotics with activity against NG within 30 days prior to screening
5. Use of systemic corticoid drugs or other immunosuppressive therapy within 30 days prior to screening
6. Use of moderate or strong CYP3A4 inducers (e.g. efavirenz, rifampicin, carbamazepine, phenobarbital) within 30 days or five halflives of the drug, whichever is greater, prior to screening
7. Cytotoxic or radiation therapy within 30 days prior to screening
8. Known chronic renal, hepatic, hematologic impairment or other condition interfering with the absorption, distribution or elimination of the drug, based on medical history and physical examination
9. History of urogenital sex-reassignment surgery
10. Immunosuppression as evidence by medical history, clinical examination or a recent (<=1 month) CD4 count below 200 cells/microliter (µL)
11. Known clinically relevant cardiac pro-arrhythmic conditions such ascardiac arrhythmia, congenital or documented QT prolongation
12. Known history of severe allergy to cephalosporin, penicillin, monobactams, carbapenems or macrolide antibiotics
13. Known or suspected allergies or hypersensitivities to lidocaine, methylparaben, lactose or any of the components of the study drugs (refer to the zoliflodacin investigator brochure (IB) and ummaries of product characteristics (SmPC) for the comparator treatments)
14. Receipt or planned receipt of an investigational product in a clinical trial within 30 days or five half-lives of the drug, whichever is greater prior to screening until end of participation to this clinical trial
15. History of alcohol or drug abuse in the 12 months prior to screening which would compromise trial participation in the judgement of the investigator
16. Severe medical or psychiatric condition that, in the opinion of the investigator, may increase the risk associated with trial participation or may interfere with the interpretation of trial results or affect the individual's ability to provide informed consent
17. Individuals whom, in the judgement of the investigator, are unlikely or

unable to comply with this trial protocol
18. Previous randomisation in this clinical trial
19. Use of moderate or strong CYP3A4 inhibitors within 30 days or five half-lives of the drug, whichever is greater, prior to screening

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	25-06-2020
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rocephin
Generic name:	Ceftriaxone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zithromax
Generic name:	Azithromycine
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Zoliflodacin
Generic name:	Zoliflodacin

Ethics review

Approved WMO Date:	11-10-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-11-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-01-2022
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-000990-22-NL
CCMO	NL70051.018.19

Study results

Date completed:	16-03-2023
Results posted:	12-03-2024
Actual enrolment:	21

First publication
15-02-2024

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents
File