EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU Regulatory Perspectives on Development of Antibacterial Medicines for Gonorrhoea

FDA Workshop on Development Considerations of Antimicrobial Drugs for the Treatment of Gonorrhoea
23 April 2021

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European Medicines Agency

Sexually transmitted infections worldwide and in the EU

- newly diagnosed STIs on the rise in Europe and worldwide in the last 20 years
- Incidences in the EU (2018)
  - *Chlamydia trachomatis* (146/100.000)
  - *Neisseria gonorrhoeae* (26.4/100.000)
  - *Treponema pallidum* (7/100.000)
- Gonorrhoea is on the rise in the EU/EEA over the last decade (240% more compared to 2008!)

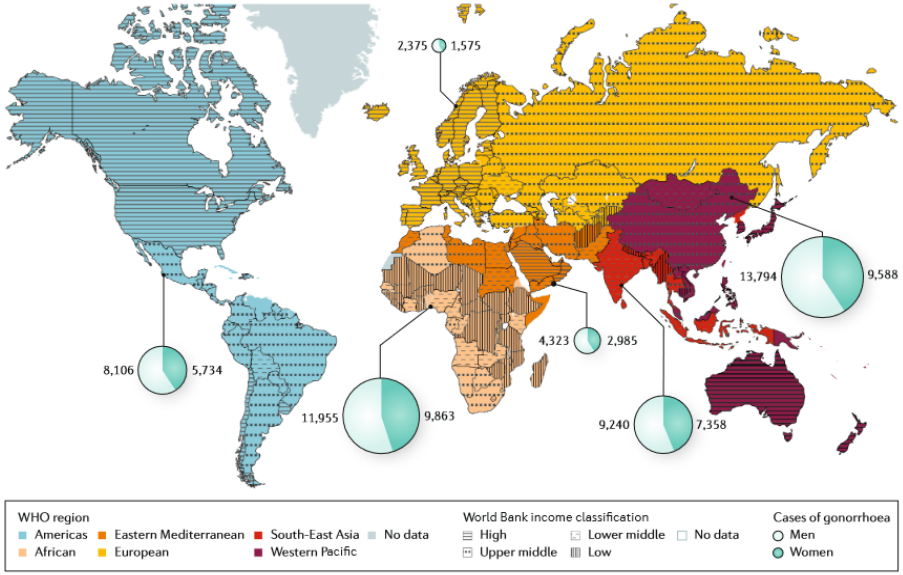
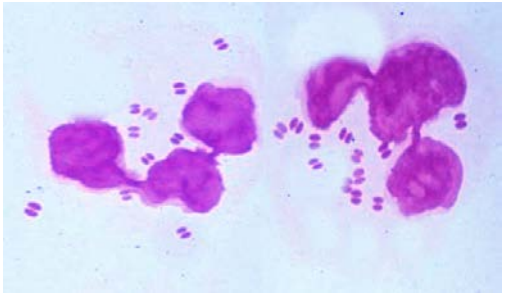


Fig. 2 | **Estimated new global cases of gonorrhoea in 2016.** Estimated numbers (in millions) of incident cases of gonorrhoea in adults (15–49 years of age) by WHO region[22]. These data correspond to 20 new gonococcal infections per 1,000 women and 26 per 1,000 men globally. The highest incidence was in the WHO African region, with 41 cases per 1,000 women and 50 per 1,000 men, followed by the WHO region of the Americas, with 23 cases per 1,000 women and 32 per 1,000 men; the lowest incidence was in the WHO European region, with 7 cases per 1,000 women and 11 per 1,000 men[22]. The World Bank Income Classification is also shown. Data from REF.[22].

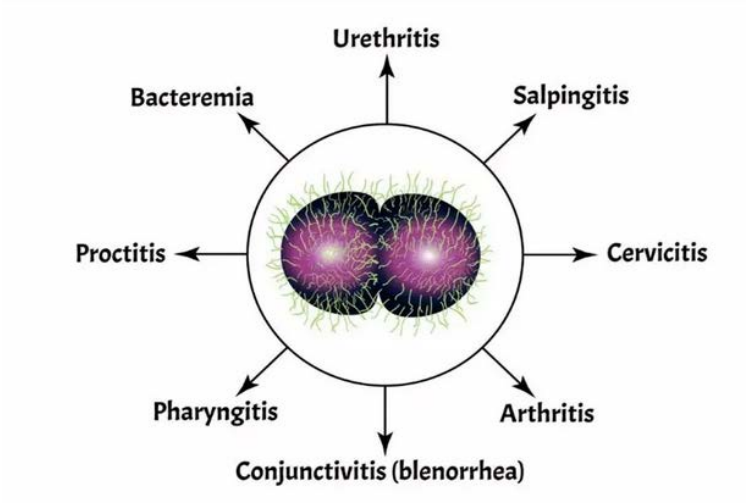
https://www.ecdc.europa.eu/sites/default/files/documents/gonorrhoea-annual-epidemiological-report-2018.pdf

Unemo, Magnus, et al. "Gonorrhoea." Nat. Rev. Dis. Primers, 2019 doi:10.1038/s41572-019-0128-6

Gonorrhoea

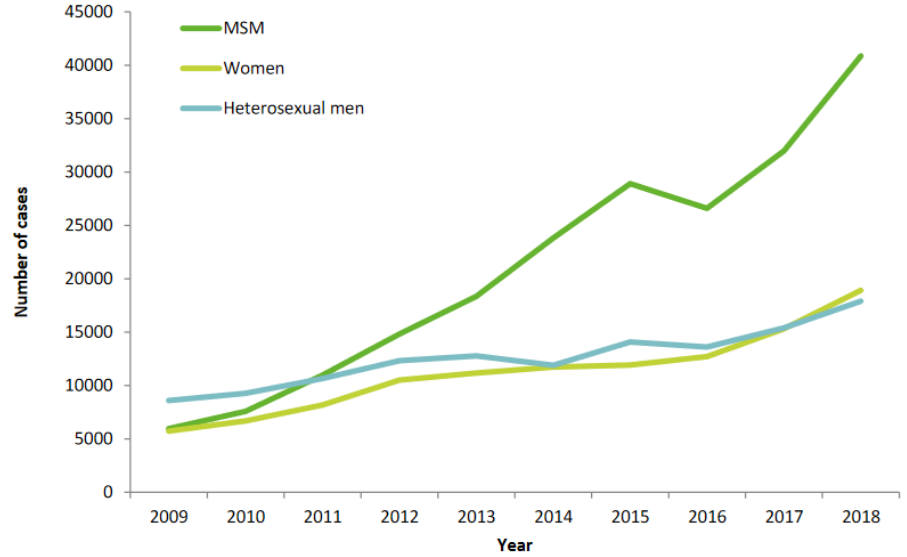


- sexually transmitted infection (STI) caused by obligate human Gram-negative diplococcus *Neisseria gonorrhoeae*
- infection of the columnar epithelium of the urethra, endocervix, rectum, pharynx and conjunctivae
- Signs and symptoms: reflect localised inflammation of the infected mucosal surfaces
- Cervicitis/urethritis/proctitis/ pharyngitis/disseminated



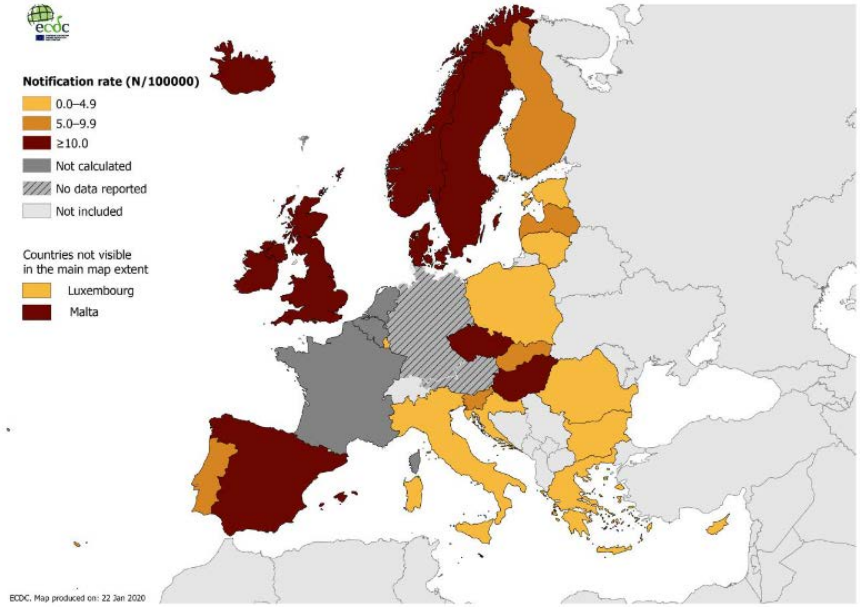
Number and geographical distribution of confirmed gonorrhoea cases in the EU

Figure 6. Number of confirmed gonorrhoea cases by gender, transmission category and year, EU/EEA countries reporting consistently, EU/EEA, 2009–2018



Source: Country reports from Czechia, Denmark, Greece, Latvia, Lithuania, the Netherlands, Norway, Romania, Slovenia, Sweden and the United Kingdom.

Figure 1. Distribution of confirmed gonorrhoea cases per 100 000 population by country, EU/EEA, 2018



https://www.ecdc.europa.eu/sites/default/files/documents/gonorrhoea-annual-epidemiological-report-2018.pdf

Antimicrobials used for treating gonorrhoea and occurrence of resistance

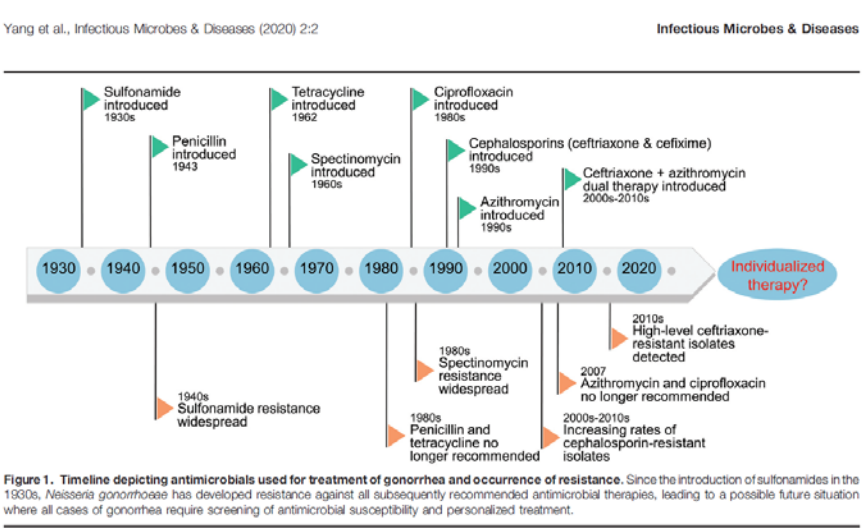


Figure 1. Timeline depicting antimicrobials used for treatment of gonorrhea and occurrence of resistance. Since the introduction of sulfonamides in the 1930s, *Neisseria gonorrhoeae* has developed resistance against all subsequently recommended antimicrobial therapies, leading to a possible future situation where all cases of gonorrhea require screening of antimicrobial susceptibility and personalized treatment.

doi:10.1097/IM9.0000000000000024

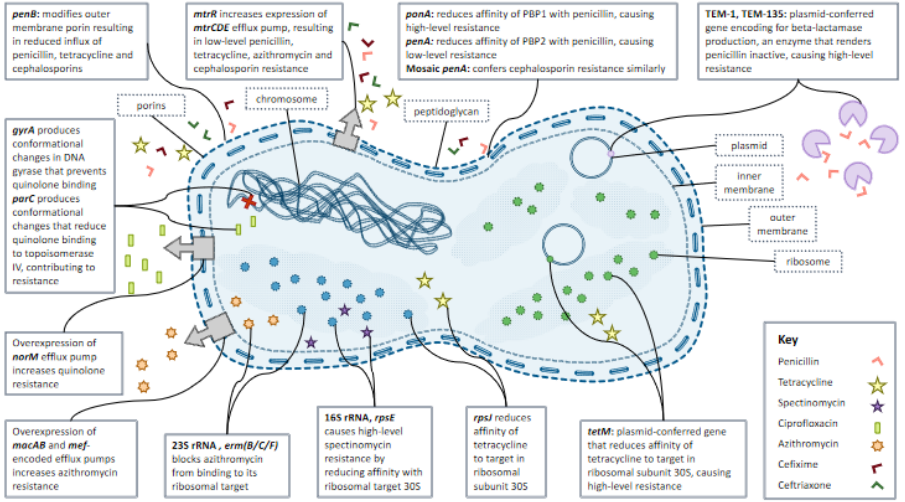


Figure 2. Known mechanisms of resistance in *N. gonorrhoeae* to clinically-relevant antibiotics.

Whittles, Lilith K., et al. "Epidemiological Trends of Antibiotic Resistant Gonorrhoea in the United Kingdom." Antibiotics, 2018, doi:10.3390/antibiotics7030060.

Resistance of *N.gonorrhoeae* to extended-spectrum cephalosporins and other antibiotics

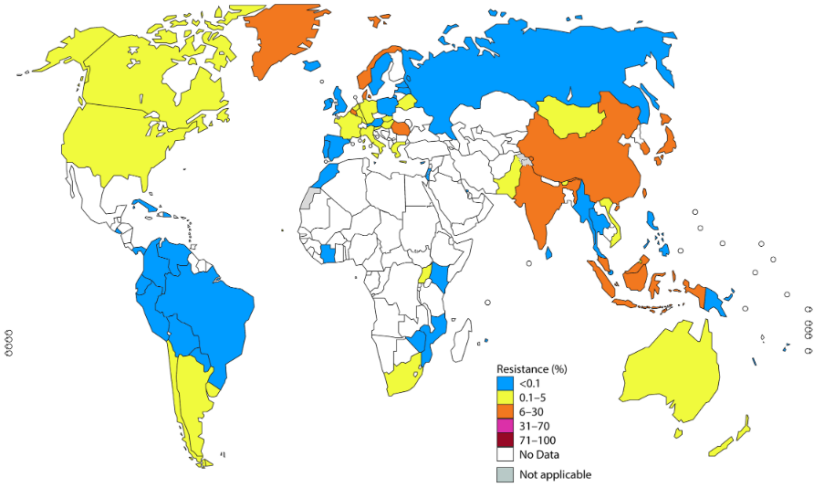
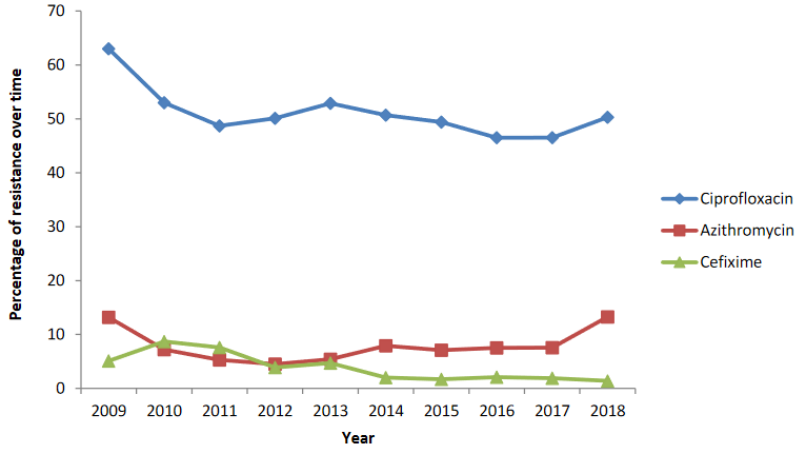


Fig 1. The percentage (%) of isolates with decreased susceptibility or resistance to extended-spectrum cephalosporin (ESC) (cefixime and/or ceftriaxone) according to the most recent World Health Organization (WHO) Gonococcal Antimicrobial Surveillance Programme (GASP) data (2014 for most countries, but for a few countries, only 2011–2013 data were available). Note: The areas in grey are disputed territories (e.g., Western Sahara, Jammu, and Kashmir), and no antimicrobial resistance (AMR) data are available from these regions.

https://doi.org/10.1371/journal.pmed.1002344.g001

Figure 1. Percentage of resistant *Neisseria gonorrhoeae* by antimicrobial and year, Euro-GASP, 2009–2018



Azithromycin data is presented using the historical EUCAST >0.5 mg/L resistance breakpoint in figure one and table three.

Gonococci on the WHO priority list and Euro-GASP

European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP)

Expanding Euro-GASP

In 2011, 21 out of 30 EU/EEA countries participated in Euro-GASP. The reasons for non-participation are primarily the lack of available cultures to refer to Euro-GASP (due to the use of nucleic acid amplification tests), the differences in diagnostic procedures in STI clinics, and the lack of resources for performing culture. Participation from central and eastern EU/EEA countries should be improved, as very limited information is available on the AMR profile in these countries.

In some countries, antimicrobial drugs seem to be easily available without prescription and the use of suboptimal medication as a second-line treatment seems to be common. These factors increase the risk of emergence of multidrug resistance *Neisseria gonorrhoeae* (MDR NG). Expanding Euro-GASP to more countries is therefore important to further control emergence and spread of MDR NG strains in Europe.

Actions

- Inclusion of two additional Member States in Euro-GASP 2012
- Ensuring that all Euro-GASP laboratories participate in the EQA programme
- Ensuring further dissemination of Euro-GASP results though the members of the European STI network

Indicators

- Number of countries participating in Euro-GASP
- Number of isolates reported through Euro-GASP
- Number of laboratories participating in the EQA programme

New EMA guideline on antibacterials and new EU diagnosis/treatment guideline

Revised guideline aims to strengthen global approach to development of new antibacterial medicines

Share

News 14/01/2019

EMA has published a revision of its guideline on the evaluation of human medicines indicated for the treatment of bacterial infections for a six-month public consultation. Stakeholders can send their comments by 31 July 2019 to idwpsecretariat@ema.europa.eu using the provided.

EMA plays an important role in the fight against antimicrobial resistance by supporting the development of new medicines and treatment approaches, especially for patients with infections caused by multi-drug resistant bacteria and limited therapeutic options.

Antimicrobial resistance is a global public health problem. Regulators in the European Union, the United States and Japan have had extensive discussions over the last few years to explore and agree how to align as much as possible their respective data requirements so that medicine developers can design clinical trials that meet the evidence needs of multiple regulatory agencies. The revised guidance reflects the outcome of these discussions.

In addition, it offers clarification on the clinical development of antibacterial agents that are expected to address an unmet medical need, in accordance with experience gained from previous regulatory decisions.

Specific advice has also been added with regards to the EU regulatory requirements to develop medicines for the treatment of uncomplicated urinary tract infections and gonorrhoea.

The draft revised guideline was adopted by EMA's human medicines committee (CHMP).

Guidelines

INTERNATIONAL JOURNAL OF STD & AIDS

2020 European guideline for the diagnosis and treatment of gonorrhoea in adults

International Journal of STD & AIDS
0(0) 1–17

DOI: 10.1177/0956462420949126
journals.sagepub.com/home/std
SAGE

M Unemo[1], JDC Ross[2], AB Serwin[3], M Gomberg[4], M Cusini[5] and JS Jensen[6]

Abstract

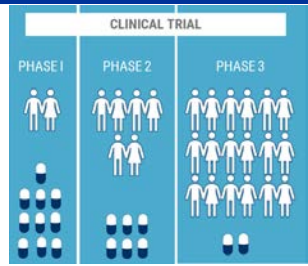
Gonorrhoea is a major public health concern globally. Increasing incidence and sporadic ceftriaxone-resistant cases, including treatment failures, are growing concerns. The 2020 European gonorrhoea guideline provides up-to-date evidence-based guidance regarding the diagnosis and treatment of gonorrhoea. The updates and recommendations emphasize significantly increasing gonorrhoea incidence; broad indications for increased testing with validated and quality-assured nucleic acid amplification tests and culture; dual antimicrobial therapy including high-dose ceftriaxone and azithromycin (ceftriaxone 1 g plus azithromycin 2 g) OR ceftriaxone 1 g monotherapy (ONLY in well-controlled settings, see guideline for details) for uncomplicated gonorrhoea when the antimicrobial susceptibility is unknown; recommendation of test of cure (TOC) in all gonorrhoea cases to ensure eradication of infection and identify resistance; and enhanced surveillance of treatment failures when recommended treatment regimens have been used. Improvements in access to appropriate testing, test performance, diagnostics, antimicrobial susceptibility surveillance and treatment, and follow-up of gonorrhoea patients are essential in controlling gonorrhoea and to mitigate the emergence and/or spread of ceftriaxone resistance and multidrug-resistant and extensively drug-resistant gonorrhoea. For detailed background, evidence base and discussions, see the background review for the present 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults (Unemo M, et al. Int J STD AIDS. 2020).

Keywords

Neisseria gonorrhoeae, gonorrhoea, sexually transmitted infection, Europe, management, diagnosis, antimicrobial resistance, treatment

Date received: 14 July 2020; accepted: 16 July 2020

Clinical trials for uncomplicated gonorrhoea in the EU

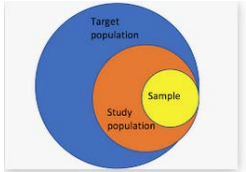


- trials that aim to demonstrate **non-inferiority** of the test regimen to an appropriate reference regimen **are acceptable**;
- if a **single trial** is proposed, consideration should be given to the *Points to consider on application with 1. Meta-analyses 2. One pivotal study* (CPMP/EWP/2330/99)
- Infection site-specific indications for use **may be supported by single pivotal studies with standard levels of alpha** (i.e. 2-sided 0.05) ***under certain circumstances***

Examples:

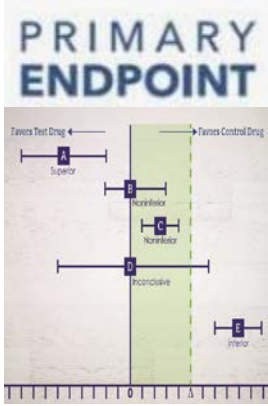
- Single trials in <u>either cUTI or uUTI</u> and a single trial in <u>uncomplicated gonorrhoea</u>
- When the test antibacterial agent addresses an unmet need.
    - In these cases, if the total evidence (nonclinical and clinical) is sufficient to support a pathogen-specific indication in patients with limited treatment options, ***additional infection-site specific indications may be granted based on a single pivotal trial per indication***

Patient selection



- evidence of **gonococcal cervicitis or urethritis at enrolment** based on finding characteristic Gram-negative diplococci in urethral or cervical pus or swabs at baseline
- If patients with evidence of rectal or pharyngeal gonorrhoea are enrolled, alone or in conjunction with urethral or cervical infection, it is recommended that there is stratification by infection site at randomisation.
- The **test-of-cure visit** may be conducted **within one week** (e.g. 3-4 days) **after treatment** to maximise the proportion with documented eradication.
- A late follow-up visit should be planned to capture late relapses, re-infections or new infections
- Patients eligible for the microbiological-MITT population should have a positive culture result for *N.* gonorrhoeae
- Enrolment of adolescents possible

Study design and primary endpoint/analysis (I)



- **Primary endpoint:** Culture-confirmed **microbiological eradication** of *N. gonorrhoeae* **in the microbiological-ITT population at TOC**
- **non-inferiority margin: -10%**.
- Comparative arm preferred (for safety and as internal control)
- Preferred comparator: one of the best available treatments based on clinical trials, medical opinion, infection type-specific treatment guidelines and the anticipated prevalence of resistance to the comparative agents at the trial sites.
- EU treatment GL 2020 recommends ceftriaxone 1g+azithromycin 2g* (also working on AZI-R strains) OR ceftriaxone 1g (not in ceftriaxone-resistant infections/oropharyngeal disease)

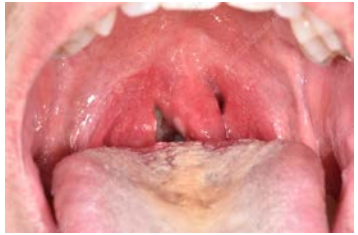
**Dose can be given as single dose or in 2x 1g doses for better tolerability*

Study design and primary endpoint/analysis (II)

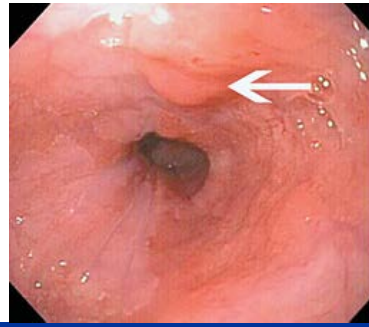
- ceftriaxone plus azithromycin (after meals!)
  - Attempt to avoid use of different doses by different sites
  - If it cannot be avoided, acceptable eradication rates should be shown

- ceftriaxone monotherapy may be acceptable in certain situations (not for pharyngeal gonorrhoea/caused by resistant strains)
- primary analysis should be confined to m-ITT subjects with N. gonorrhoeae that is susceptible to both of ceftriaxone and azithromycin
- Conduct sensitivity analysis in m-ITT subjects with culture-proven GC susceptible to only one of the two comparative agents and in m-ITT subjects with culture-proven GC regardless of susceptibility to either agent
- Open-label design may be acceptable, but proposals should be discussed with the EU regulator

Enrolment of extragenital gonorrhoea



- assessment of efficacy against pharyngeal /rectal gonorrhoea as a secondary objective is possible in a study that enrols genital gonorrhoea
- provide separate estimates for each infected site
- the lower bound of the CI should exceed 90% at least for the subset with urethritis and cervicitis
- Assess resistance at baseline and/or post-baseline in isolates obtained from treatment failures



Ongoing developments

Drug	Company	Clinical Phase	MoA	RoA
Debio-1453	Debiopharm	Preclinical	Enoyl-ACP reductase inhibitors	NA
Gepotidacin	GlaxoSmithKline	Phase III	DNA gyrase inhibitors; Type II DNA topoisomerase inhibitors	Oral
EVO100	Evofem Biosciences	Phase III	NA	Topical
Solithromycin	Melinta Therapeutics	Phase III	Protein 50S ribosomal subunit inhibitors	Oral
Zoliflodacin	Entasis Therapeutics	Phase III	DNA gyrase inhibitors	Oral

Evaluation of EVO100 for Prevention of Urogenital Chlamydia Trachomatis and Neisseria Gonorrhoeae Infection (EVOGUARD)

SAN DIEGO, Dec. 17, 2020 /PRNewswire/ -- Evofem Biosciences, Inc., (NASDAQ: EVFM) today announced that its pivotal Phase 3 trial, 'EVOGUARD,' of EVO100 for the prevention of chlamydia and gonorrhea remains firmly on schedule. EVOGUARD was initiated and the first patient was enrolled in October 2020, and study enrollment targets were met in both October and November 2020 despite the ongoing COVID-19 pandemic.

The first study (EAGLE-1) will compare gepotidacin to ceftriaxone plus azithromycin, a guideline recommended dual therapy approach, in approximately 600 patients with GC, one of the most common sexually transmitted infections.[2] The second study (EAGLE-2) will compare gepotidacin to nitrofurantoin, a licensed first-line antibiotic, in approximately 1200 patients with uUTI, an infection that is very common in women.[3] First results are expected by the end of 2021.

Entasis and GARDP have now announced the initiation of a global, Phase III trial to assess zoliflodacin in the treatment of uncomplicated gonorrhea. The trial, which is currently recruiting, will aim to enroll over 1,000 adults with urogenital gonorrhea from sites in the USA, Thailand, South Africa and the Netherlands [6]. Participants will be randomized to receive either zoliflodacin or a combination of ceftriaxone and azithromycin, and will be assessed after 1 week for persistence of the infection [6,7]. Data from the trial is expected in 2021.

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

Marcus Y Chen, Anna McNulty, Ann Avery, David Whiley, Sepehr N Tabrizi, Dwight Hardy, Anita F Das, Ashley Nenninger, Christopher K Fairley, Jane S Hocking, Catriona S Bradshaw, Basil Donovan, Benjamin P Howden, David Oldach, on behalf of the Solitaire-U Team

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.

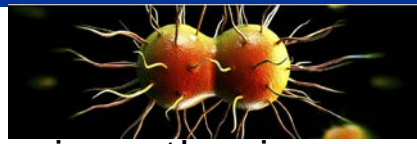
Methods We did an open-label, multicentre, non-inferiority trial of patients aged 15 years or older with uncomplicated untreated genital gonorrhoea at two sites in Australia and one site in the USA. Patients were randomly assigned (1:1) to receive single dose oral solithromycin 1000 mg or intramuscular 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.

Funding Cempra Pharmaceuticals.

Summary



- Gonorrhoea, the second most frequent sexually transmission infection is on the rise, worldwide and in the EU/EEA
- Concerns about development of resistance made WHO include Neisseria gonorrhoeae, (3rd generation cephalosporin-resistant, fluoroquinolone-resistant) on the WHO priority pathogens list for R&D of new antibiotics
- New antibiotics for this condition are currently considered an unmet medical need.
- Recent (2020) update of European clinical recommendations for diagnosis and treatment
- New draft EMA guideline on antibacterials adds recommendations for conducting studies in uncomplicated gonorrhoea
- For discussing any development it is recommended to apply for EU Scientific Advice

Any questions?

Further information

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