GARDP
Global Antibiotic Research & Development Partnership

FROM INNOVATION TO ACCESS: DEVELOPING A NEW FIRST-IN-CLASS ANTIBIOTIC FOR GONORRHOEA

ZOLIFLODACIN: A CASE STUDY

1. The Need

When the US Food and Drug Administration (FDA) approved Nuzolvence® (zoliflodacin) in December 2025, it marked an important milestone in the fight against antimicrobial resistance (AMR). Not only was this a new first-in-class antibiotic, and the first new treatment developed solely for gonorrhoea in decades, but it also demonstrated how a novel not-for-profit partnership model can help to bring an innovative new drug to the world at a time when drug-resistant infections were beginning to outpace antibiotic development.

AMR is already one of the leading causes of death and illness worldwide, but a growing body of evidence now suggests that drug-resistant infections have reached a critical tipping point with the number of infections now rising sharply. Sexually transmitted infections (STIs) are at the forefront of this surge and therefore a priority for GARDP. This is partly because these kinds of infections can often initially be asymptomatic, leading to high rates of transmission and reinfection, but also because developing antibiotics for STIs poses an additional set of challenges.

One STI that stands out as a particularly urgent threat is gonorrhoea. Once easily treated with penicillin, the bacteria causing gonorrhoea has steadily developed resistance to every class of antibiotic used against it. Today, with 82 million new infections around the world each year, and only one recommended treatment remaining, ceftriaxone, there are now a growing number of cases that are resistant even to this. Because of this, gonorrhoea is in danger of becoming one of the first diseases to be no longer treatable (see box on gonorrhoea).

The World Health Organization (WHO) classifies *Neisseria gonorrhoeae* as a high "priority pathogen," signalling that new treatments are urgently needed. Yet with antibiotic research and development (R&D) in decline for decades, the pipeline for new antibiotics to treat gonorrhoea remains dangerously thin. Even when promising antibiotic compounds are identified, they often stall during development, long before they can reach patients. In recent years, such was the fate of two antibiotic candidates for gonorrhoea, both of which failed to make it through development.

GARDP's disease area strategy for STIs aims to address this crisis by developing a portfolio of effective new antibiotic treatments capable of reducing the burden of STIs while slowing the rate of drug resistance development. It aims to do this through the creation of a new antibiotic R&D ecosystem that prioritizes public health needs over commercial incentives.

GARDP's STI strategy focuses on first identifying suitable high-quality drug candidates that match their target product profile: ones that have the potential to meet an unmet public health need, where clinicians currently have vanishingly few treatment options left available; ones that are effective against multidrug-resistant priority pathogens; and ones that can be tailored to the needs of and made available in high-burden regions and populations, especially in resource-limited settings. With gonorrhoea, AZD0914 appeared to fit the bill.

GONORRHOEA

Neisseria gonorrhoeae affects both men and women in ways that can result in serious and permanent health consequences. It is most common among adolescents, young adults, men who have sex with men and vulnerable populations, such as sex workers and people living with HIV. If left untreated, gonorrhoea can cause chronic pain, infertility, increase the risk of HIV transmission, and in pregnant women, lead to severe complications for both mother and child. The burden falls disproportionately on low- and middle-income countries (LMICs), where access to diagnostics and treatment is often limited and disease surveillance is weak.

2. The Opportunity

Zoliflodacin was first identified as a new antibacterial chemical compound by AstraZeneca. Originally designated AZD0914, it belonged to a new chemical class, called spiropyrimidinetriones, which had a unique mechanism of action, capable of inhibiting a crucial bacterial enzyme that is essential for bacterial function and reproduction. This has been found to be active against several STI pathogens, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Mycoplasma genitalium*. With activity against all strains of *N. gonorrhoeae* tested, including those resistant to ceftriaxone, with no cross-resistance with other antibiotics and a low propensity to generate resistance, this provided a promising new candidate for clinical development.

However, despite a successful phase 1 trial in 2014, AstraZeneca took the decision not to pursue the project any further, as part of a broader strategy to shift its priorities away from small molecule anti-infectives. AstraZeneca implemented this shift by spinning out a new biotechnology company in 2015, called Entasis Therapeutics, Inc., that took over its antibacterial drug development portfolio with the aim of finding partners to help fund and support their ongoing development, including AZD0914.

Even before Entasis Therapeutics had formally been established, such a partnership was found, in the form of the US National Institute of Allergy and Infectious Diseases (NIAID), which sponsored a proof-of-concept phase 2 study and which was completed in 2015. The favourable outcome of the study supported the case for taking zoliflodacin into late-stage development.

The opportunity to make that happen came with the creation of GARDP in 2016. A not-for-profit global health organization, GARDP was precisely the kind of partner Entasis Therapeutics had been looking for to take late-stage development forwards. Publicly funded, GARDP offered a novel approach to antibiotic R&D, and one that was driven primarily by public health needs. At the same time, zoliflodacin was exactly what GARDP was looking for, meeting the requirements of its target product profile for a gonorrhoea antibiotic.

On the basis of this, in 2017 GARDP entered into an agreement with Entasis Therapeutics. This formed a new kind of public-private partnership that would see GARDP not just funding the ongoing development of zoliflodacin, but also leading on the clinical and manufacturing development.

3. The Approach

Under this agreement, GARDP took on responsibility for designing and leading on the next critical stage of zoliflodacin's development. The global phase 3 clinical trial needed to demonstrate safety and efficacy in support of Entasis' submission for approval by a stringent regulatory authority (US FDA) as well as a number of global authorities strategically important to the GARDP mission.

In parallel, GARDP took the lead on the pharmaceutical development of zoliflodacin. This included food effect, drug-drug interaction and other studies aimed supporting the phase 3 clinical trial, as well as ensuring that affordable formulation optimization progressed according to manufacturing standards, and that stability of the product was demonstrated for use in hot and humid climates. This was achieved through a manufacturing agreement with Aurigene Pharmaceutical Services Limited in India.

The phase 3 clinical trial design, country and site selection were undertaken with the primary aim of generating data that was representative of the populations and regions with the highest burden of disease. This was conducted from within public health STI services with local laboratory capability and subject to robust ethical review of clinical trials. Also important was the fact that the trial was conducted in partnership with national health institutions and clinical investigators, including in low- and middle-income countries (LMICs). This helped to make the trial incredibly cost-effective (see Cost-Effectiveness box).

Recruitment began in November 2019, with 930 patients eventually enrolled across 16 sites in five countries, including Belgium, the Netherlands, South Africa, Thailand and the US by March 2023. This made it the largest gonorrhoea trial ever undertaken and one of the most geographically, demographically and epidemiologically diverse. With participants including women, adolescents and people living with HIV, the scale and breadth of this trial was designed to help ensure the results would be robust across different populations and resistance patterns.

However, one of the big challenges of developing any new antibiotic is the way in which clinical trials need to be carried out. If effective treatments exist, it would be unethical to withhold treatment from patients, as this would increase their risk of serious complications and ongoing transmission. That rules out placebo-controlled trials. Similarly, drug-resistant infections must also be ruled out of clinical trials, because in order for a new drug to be tested against a benchmark drug, that benchmark drug must be effective, which by definition isn't the case with drug-resistant infections.

In fact, when it comes to treating susceptible infections, those that are not drug-resistant, the current standard of care – a combination of ceftriaxone and azithromycin – is incredibly effective, with a cure rate in excess of 99%. While this is good news for patients with non-resistant infections, it would be next to impossible for a new drug, like zoliflodacin, to show that it was in any way superior, especially if any advantages in terms of treating drug-resistant infections have to be excluded from the trial.

For this reason, non-inferiority trials tend to be preferred, where the new drug needs to demonstrate that it is at least comparable to the current standard of care. Even with these trials, however, promising drug candidates can fail because random factors can lead to small differences in the results that may ultimately threaten the new drug's ability to show comparable performance. Such statistical anomalies can be avoided by having a large sample size, which is another reason why GARDP chose to have such a large trial.

In addition, conducting clinical trials on gonorrhoea can be inherently challenging, due to, for example, the frequency with which infection can be asymptomatic, particularly in women. Similarly, other challenges include the need for parental consent for the recruitment of adolescents, the requirement to meet public health standards of same-day STI diagnosis and provision of treatment, the high potential for loss to follow up, and technical demands required to culture *N. gonorrhoeae* as the gold standard endpoint. Together with the comparator standard of care currently being highly effective, this necessitates a relatively large sample size to demonstrate non-inferiority of the new drug and dedicated site support to ensure quality of the data.

Despite all this, and the unprecedented challenges of the COVID-19 pandemic and subsequent Mpox outbreak that temporarily impacted operations at a number of public health sites, in March 2023, GARDP successfully completed this pivotal trial with zoliflodacin, demonstrating that it was as effective as the standard of care antibiotics at eliminating uncomplicated urogenital gonorrhoea. By this point, Entasis Therapeutics had been acquired and was now an affiliate company of Innoviva Specialty Therapeutics (IST).

The positive outcome of the pivotal trial, together with parallel evidence generation from several other clinical studies carried out by GARDP paved the way for Innoviva Specialty Therapeutics' submission of zoliflodacin to the US FDA and ultimately its approval in December 2025.

COST EFFECTIVENESS

GARDP's work on zoliflodacin represents good value for money. Its total costs for the development and initial registration of zoliflodacin will amount to approximately €80 million. This includes carrying out the full phase 3 trial involving nearly 1,000 patients across five countries; the pharmaceutical development of the final formulation of the drug; the preparation of the regulatory submission to the US FDA; registration in at least two priority countries, Thailand and South Africa; future access activities; chemistry, manufacturing and controls (CMC); campaign formulation improvement; cost of goods (COGS) reduction activities; and future expansion of the safety database in specific populations, such as breastfeeding women.

4. The Impact

With zoliflodacin approved in the US, and with its submission to European regulators due to follow, the race is now on to make this new antibiotic widely available to the people that need it, including those in high-burden countries. The challenge here is that often antibiotics are only registered in a few, predominantly wealthy nations, or are priced out of reach for the countries with most need. Between 1999 and 2014, fewer than half of the new antibiotics that entered the global market were registered in more than ten countries, most of which were high-income countries (HICs).

A central part of GARDP's STI strategy and its access programme is to address this through the innovative use of sub-licensing agreements. Unlike traditional pharmaceutical licensing, which focuses on commercial return, GARDP's priority is public health impact and specifically to maximize global, equitable and affordable access.

GARDP's agreement with IST, for example, includes the right to register and provide access to zoliflodacin in more than three-quarters of the world's countries, including all low-income countries, most middle-income countries, and several high-income countries. This will be made possible by sub-licensing agreements with two high-quality Indian pharmaceutical manufacturing companies. Aurigene Pharmaceutical Services Limited will manufacture zoliflodacin, while Dr. Reddy's Laboratories Ltd, will act as the market authorization holder initially in the first two of GARDP territories.

However, for that to occur, zoliflodacin will first need to be registered in countries. Because, while approval from a stringent regulatory authority like the FDA is an important milestone for any new drug, regulatory approval in other countries will still be required to make it more widely available. To this end, initially Dr. Reddy's is taking steps to obtain market authorization in the first two of GARDP's territory countries, Thailand and South Africa. These countries were selected not only because they have a high burden of disease, but also because of the close collaborations GARDP has within these countries and because of the key role they played in the phase 3 trial.

In November 2025, zoliflodacin was submitted for priority review in Thailand, with a submission in South Africa planned for early 2026. In Thailand, thanks to the commitment shown by the Thailand FDA in terms of priority review, it is possible that zoliflodacin —if approved—could become available in a GARDP territory only a few months after US registration.

However, to address inevitable delays to the availability of zoliflodacin, between completion of phase 3 clinical trials and regulatory approvals, GARDP will activate a managed Access Programme (MAP). This will consider requests from physicians on behalf of patients for whom there is limited, or no, treatment options. Supply will be dependent on meeting certain clinical criteria, availability of supplies and regulatory approval of each request in-country. At the same time, GARDP will conduct and support further research aimed at expanding future access to zoliflodacin.

Wherever it is made available, zoliflodacin will only be indicated to treat gonorrhoea. This was a key part of GARDP's STI strategy. Limiting its clinical use in this way should support good stewardship of the drug and help to delay the emergence of resistance, thereby prolonging the effectiveness of this new drug. Similarly, GARDP is continuing to work with countries to carry out surveillance and introduction studies that will help to identify the individual needs of countries and lay the groundwork for good stewardship once zoliflodacin is introduced.

All this shows that with vision, partnership and commitment to access, GARDP's not-for-profit model can provide a novel and highly effective way to develop next-generation antibiotics that are needed, and make them widely available. For gonorrhoea, zoliflodacin offers new hope for the treatment of drug-resistant infections and demonstrates a pathway forward for the sustainable development of future antibiotics.