Development of treatments for gonorrhoea : Addressing the global public health need

Current and future challenges

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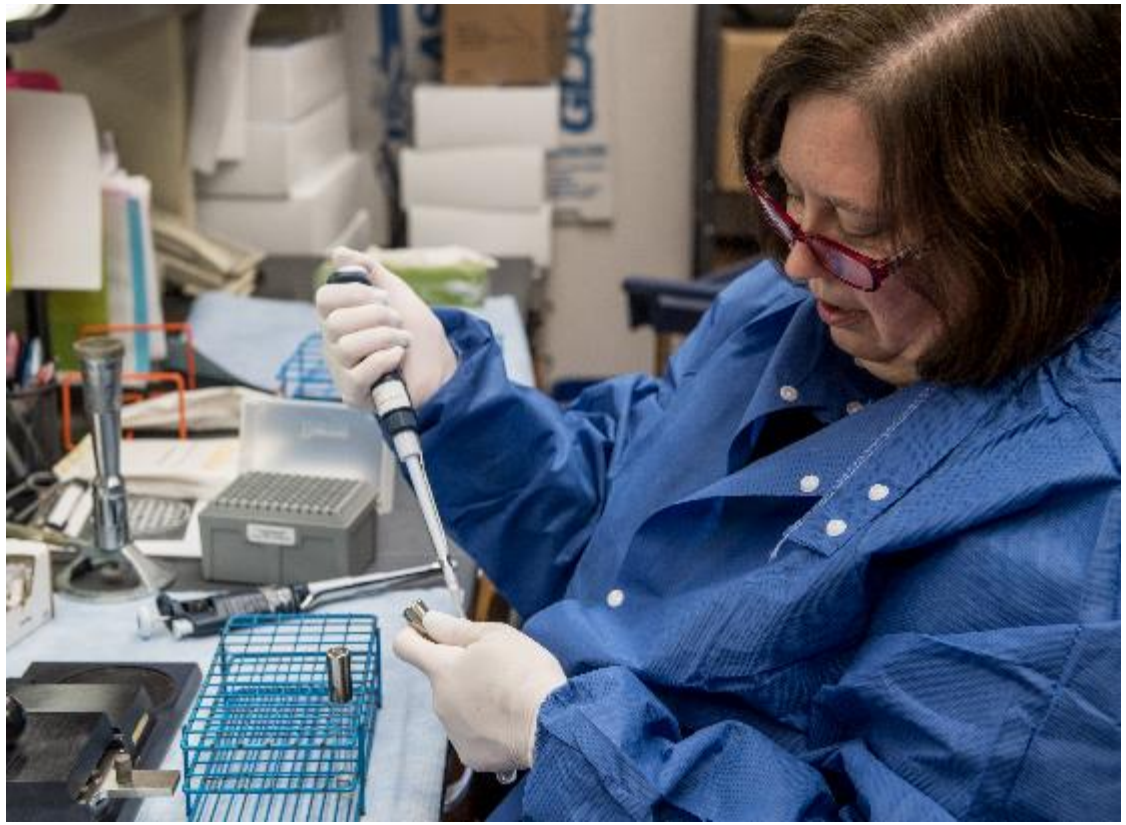
GARDP Sexually Transmitted Infections (STI) Portfolio approach

- Goal is to focus on public health treatments rather than just new drug development
- Identify those antibiotics that have the best potential to address unmet need and avoid emergence of resistance
- Development plan defined by regulatory pathways (e.g. uncomplicated gonorrhea)
- Syndromic treatment in place until rapid bacterial identification and susceptibility testing is widely available
- Combination therapy is expected to be required to provide adequate bacterial coverage
- Significant development post primary indication (if you get there) – to confirm public health regimens for key populations and GC, Chlamydia and M.g causative infections

Partnership with Entasis Therapeutics



GARDP is partnering on a novel, first-in-class antibiotic - zoliflodacin - developed specifically to treat resistant strains of gonorrhoea.

GARDP sponsoring clinical development post phase 2 proof of concept including P3 trial

Leading formulation and manufacturing development plan

Developing a public health focused access strategy with implementation in priority countries

GARDP will have commercial rights for zoliflodacin in up to **168 low- and middle-income countries.**

Phase 3 efficacy and safety of zolifodacin vs ceftriaxone + azithromycin for treatment of uncomplicated gonorrhoea

603 culture positive patients with uncomplicated gonorrhoea from max of 928 randomised in countries with high incidence of disease

USA, Netherlands, South Africa, Thailand

R

2:1

N= 402 evaluable

Zoilfodacin (single dose, oral 3g)

Granules for oral suspension formulation

N=201 evaluable

Ceftriaxone (single dose, 500mg, im)

Azithromycin (single dose, 1g oral)

Inclusion criteria :
Signs and symptoms of urethral or cervical uncomplicated gonorrhoea
or
Positive culture, Gram stain or NAAT 14days prior to screening
or
Unprotected sexual contact with partner 14 days prior

Non-inferiority (10%), parallel, open label

Primary endpoint:

- Microbiological cure by culture at urethral or cervical sites at TOC (day 6 ±2) in micro mITT popn

Secondary endpoints (selected):

- Safety and tolerability profile of zoliflodacin compared to cef-atm , 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 and rectal sites at TOC (day 6 ±2)
- Limited pharmacological endpoints

Phase 3 development – What does success look like?

Regulatory success for a **new oral treatment** currently based on demonstration of non-inferiority based on difference of 10% in the primary endpoint using a micro-ITT population.

Is this a significant barrier to reach first base for success?

Comparator (im ceftriaxone +/- azithromycin) – that rarely fails

- Large sample size needed to just demonstrate active is not worse than 10% and cure rate is greater than 95% threshold at lower bound for 95% CI for CDC guidelines
- Analysis of recent P2 and P3 trials indicates for oral monotherapy a delta of at least -4% between active and comparator should be considered

Analysis population (micro-ITT)

- Patients with positive culture at baseline but lost to follow up or exceed the window of the ToC visit will be considered treatment failures – exacerbated by Covid.
- Missing ToC may not be equally addressed across treatment arms with impact greater for a new oral agent vs a strong comparator with a 99% microbiological cure rate
- With a 10% NI Margin, with a -4% delta, 10 to 15% missed ToC could lead to a failed study

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Addressing public health needs
What is the definition of success?

- Personal health - treatment efficacy and safety at the level of the patient in the clinic
- Effectiveness and suitability for key impacted populations (eg, women, partners, adolescents)
- Successful option for co-treatment of HIV patients and at risk populations
- Reduced transmission of disease
- Treatment of difficult to treat resistant infections
- Suppression of spread of existing antibiotic resistance and emergence of new
- Diverse treatment options are needed before resistant infections are widespread
    - Current reliance on a single class with parenteral ceftriaxone as “last option”
- Oral agents, with novel MOA, that can address drug resistant infections provide a strong public health option for patients and partners
    - but may fail based on current guidance as first step on the pathway

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Addressing public health needs – Improving the likelihood of success – Questions (1)

Pivotal phase 3

- What could be considered as successful outcome from a public health perspective (% success rate)?
- Is a larger NI margin now justified from a public health/unmet need perspective?
  - Examples from other infection syndromes and priority pathogens (Carbapenem-resistant: Enterobacterales, *Acinetobacter baumannii & Pseudomonas aeruginosa*)
- Is the primary analysis to include only those patients that are evaluable?
  - With efficacy analysis in m-ITT as key secondary endpoints
- Consider other endpoints (e.g., DOOR/RADAR) in combination with a non-inferiority outcome to provide a broader value assessment of a new treatment
- Is one adequate, well controlled study, based on an aggregate of individual outcomes the way forward for all candidates and to address the public health value?
- What can be implemented to ensure we have options in advance of the reduced utility of ceftriaxone

H.H Handsfield & J.M Zenilman. Standards for Treatment and Control Regimens in Therapeutic Trials for Gonorrhea: Lessons From a "Failed" Trial. Sex Transm Dis. 2019 May;46(5):287-289
E.Hook III et al. Development of New Antimicrobials for Urogenital Gonorrhea Therapy: Clinical Trial Design Considerations. Clinical Infectious Diseases. 2019 Sept; (70) 7.

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Addressing public health needs – Improving the likelihood of success – Questions (2)

Broader development programme

- Is a urogenital gonorrhoea development pathway, with a phase 3 study at its core, sufficient?
- Can future development pathways be supported by regulatory framework to address key public access questions for new treatments?
  - Specific populations, resistant infections, salvage treatment, transmission impact, mode of administration
- Can adaptive and master protocols, via networks, support such studies in addition to more pragmatic core Ph3 studies?
- Without true POCT should syndromic infection pathways (urethritis, cervicitis) be considered?

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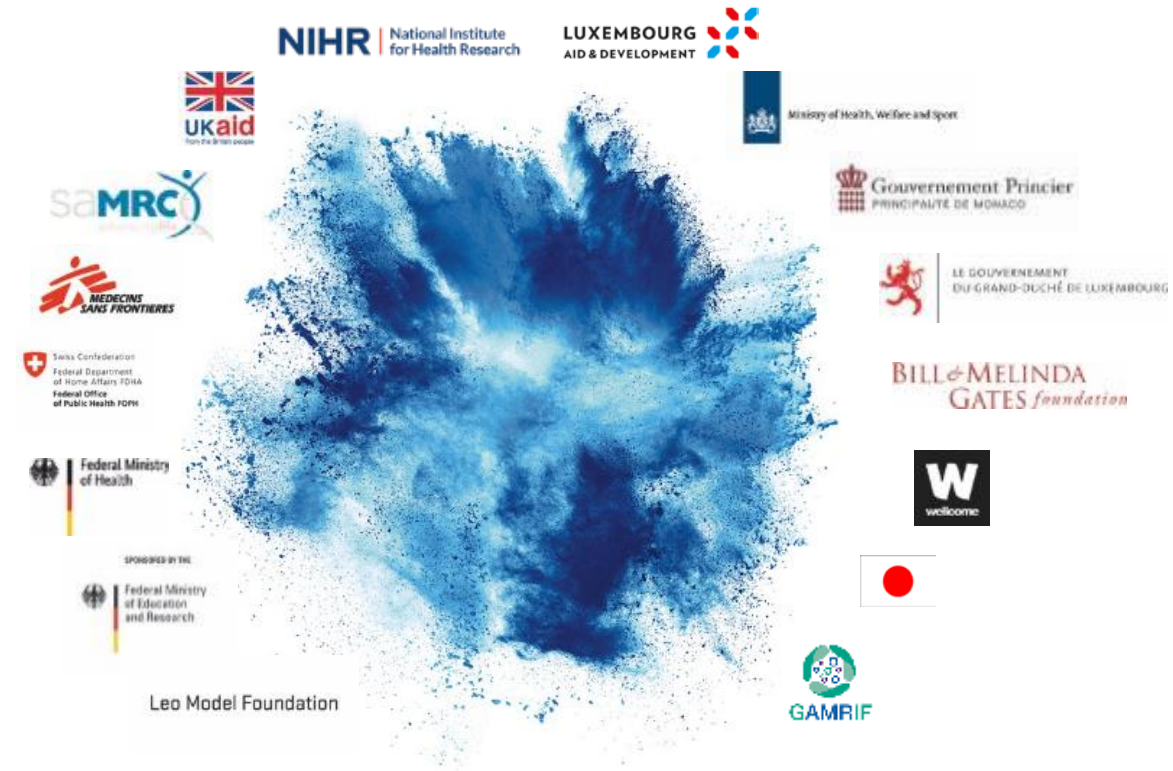

Thank you

World Health Organization

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DNDi Drugs for Neglected Diseases initiative

www.gardp.org