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

Current and future challenges

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• 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

N=201 evaluable
Ceftriaxone (single dose, 500mg, im)
Azithromycin (single dose, 1g oral)

N=402 evaluable
Zolifodacin (single dose, oral 3g)
Granules for oral suspension formulation

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 zolifodacin 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

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

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?


Thank you