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Developers Perspective on Lessons Learned and Recent Challenges

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Gepotidacin Study BTZ116577 [EAGLE 1]

Phase 3 Background Information

- Gepotidacin, a novel antibacterial agent in P3 development by GSK, in partnership with BARDA (Agreement HHSO100201300011C), for GC and uUTI.
- A Study Evaluating Efficacy and Safety of Gepotidacin Compared With Ceftriaxone Plus Azithromycin in the Treatment of Uncomplicated Urogenital Gonorrhea - Full Text View - ClinicalTrials.gov. NCT04010539
- Study start October 2019
- Original study completion April 2021 (estimated 600 participants enrolled in 18 months), revised estimated completion date September 8th, 2023.
- Individuals aged 12 years and older are eligible, body weight of >45 kilogram (kg)
- Study follows FDA guidance for Industry
- Study has sites open in 6 countries (US, AUS, UK, GER, Spain, Mexico) with the last country opening sites beginning April 21
- COVID -19 pandemic driven operational challenges

Operational Challenge- Selection of Comparator:

Current Standard of Care (SoC) by Country

- Phase 3 protocol BTZ116577 comparator 500mg IM ceftriaxone (CRO) plus 1gm oral azithromycin (AZM)

Country	Recommended SoC for urogenital NG
USA	500mg CRO: Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020 | MMWR *Previous : 250mg CRO plus 1g AZM*: https://www.cdc.gov/std/tg2015/gonorrhea.htm
Australia	500mg CRO plus 1g AZM: http://www.sti.guidelines.org.au/sexually-transmissible-infections/gonorrhoea#management
UK	1g CRO: https://www.bashhguidelines.org/current-guidelines/all-guidelines/
Spain	500mg CRO plus 1g AZM:
Germany	1g CRO plus 1.5g AZM: BMC Infect Dis. 2018; 18: 44.
Mexico	250mg CRO plus 1g AZM: WHO 2016 guidelines: https://www.who.int/selection_medicines/committees/expert/21/applications/s6_gonorrhoea.pdf

- With the exception of US and UK, all other countries use dual therapy with AZM at varying doses.
- Global agreement on SoC or comparator for Clinical trial purposes urgently needed

Operational Challenge

Culture vs NAAT testing as primary endpoint

- Primary endpoint is culture confirmed eradication of infection and defines the primary microITT population
- NAAT testing used to enrich for enrollment of evaluable participants & secondary endpoint

HOWEVER

- Principle Investigator Capability and Capacity to participate in clinical trials is a challenge:
  - Very little training in obtaining cultures & bedside plating or local lab availability to maintain viability
  - Limited global network of experts & competition from sponsors
- For all sponsors, access to the local/regional WHO/GISP testing laboratories who have reliable culture and isolate transport conditions established would reduce variability and out of window shipments and help improve pathogen recovery and isolate transport
- Consideration for NAAT as primary endpoint and culture as a secondary endpoint
  - More countries and PIs utilize NAAT
  - Culture and susceptibility testing still required to determine Breakpoints from a subset of sites

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Operational Challenge

Body site sampling/ Enriching participant populations/ Multidose regimen

- Sampling at all three-body sites- urogenital, pharyngeal & rectal for both culture and NAAT is a huge burden for both the participant and the site staff
  - Including testing for CT, M.gen
- Enriching for female and adolescent participants is very challenging:
  - 50% of women are asymptomatic, difficult to obtain cultures and present at OB/GYN clinics
  - Incidence of STIs highest in adolescents – difficult to recruit and obtain consent
- Multidose regimen requires operational considerations to ensure second dose is taken
  - Gepotidacin is a two-dose regimen

Pandemic Related Operational Challenges

COVID-19 has had a significant impact on the trial from both a startup and enrollment

- Sexual Health deprioritized by:
  - Regulators, Ethics/IRBs (delays to review & CTA approvals)
  - Academic Institutions (Re deployment of Infectious Disease Specialists to focus on COVID)
  - Health Authorities (non-essential clinical trials put on hold in UK & AUS, re application required)
- Study Visits
  - Pandemic restrictions and lockdowns impact clinic visits, with time on site becoming a huge burden
  - Participants are reluctant to spent time in clinic
- Can Visits be Remote
  - E- consent – not acceptable in all countries
  - Telemedicine to collect Med and Sexual Hx and remote F/U visit

Non-inferiority (NI) Margin

NI margin and study N vs highly effective gold standard comparator

- Uncomplicated Gonorrhea FDA guidance released in August 2015 proposed a NI margin of 10%.
- This NI margin was based on trials in which effective therapy was compared to ineffective or less effective therapy (3 trials identified, 2 from 1986 and 1 from 2001)
- More recent trials allow a NI margin to be recalculated using SOC (ceftriaxone) and proxy for placebo.
- Given the obstacles to developing a new drug in GC, a larger clinically acceptable difference (NI margin) could be considered based on an updated meta-analysis of more recent studies

Pragmatic Trial Considerations

New drugs for GC therapy are urgently needed.

- All current sponsors are utilizing public, private partnerships
  - Can public funding be utilized more effectively
  - Platform Trial design or a master protocol could drive efficiency
    - For example: sponsored by NIAID, a single comparator arm with multiple sponsors joining the trial
  - A global network of GC professionals supporting the platform study
  - Sites specializing in recruiting women
  - Sites with ethical pre- approved to recruit adolescents
- Harmonized regulatory CTA approval and Ethics review
- NAAT testing for primary population definition and primary endpoint
- Shared access to local/regional WHO/GISP testing laboratories for all cultures