Vaginal Microbicide Guidance: Trial Design Considerations

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January 7, 2013

This presentation outlines sections from the draft FDA guidance "*Human Immunodeficiency Virus: Developing Vaginal Microbicides for HIV Prevention*"

FDA Microbicide Guidance

- **The draft guidance was released on November 21, 2012**
- **The public comment period ends on February 21, 2013**
  - **Feedback can be submitted as written comments or electronically at** www.regulations.gov
- **When finalized, the guidance will represent FDA's current thinking for developing vaginal microbicides**

Microbicide Guidance

- Nonclinical development
- Clinical development
  - Early phase clinical considerations
  - Safety and efficacy considerations for phase 3
  - Safety data in specific populations (pregnancy, adolescents)
  - Developing combination microbicide products
- Risk-benefit considerations

Focus of today's presentation

- **Trial design issues in the guidance which are applicable to biomedical prevention trials i.e., oral PrEP or microbicides**
  - **Role of oral FTC/TDF as a comparator in phase 3 trials or as part of the background prevention package**

Current Phase 3 Trials

- **Double-blind with a placebo control**
- **Endpoint-driven, measuring incident HIV infections**
  - **No evidence supporting surrogate marker predictive of HIV acquisition**
- **Standard background prevention package consisting risk-reduction counseling and promoting use of condoms**

Longer duration trials

- **Preferred as expected to mimic real-world effects of the prevention product***
- **Expected to capture effects of adherence, fluctuations in high-risk behavior, concurrent use of other prevention methods over time**
- **Provide long-term safety data**
  - **Microbicide trials require minimum 12 month follow-up for all subjects**

*Lagakos SW, Gale AR, *Editors*, 2008, Methodological Challenges in Biomedical HIV Prevention Trials

Sample Size

- **Trial size is determined by**
  - **Anticipated effect of the investigational agent**
  - **Local HIV incidence**
  - **Contribution of other available prevention methods**
  - **Participant discontinuation rate, losses to follow-up, pregnancy**

- **Effectiveness trials are typically quite large**
  - **Enrolling several thousand subjects per treatment arm in order to show benefit over placebo**

Challenges with including FTC/TDF PrEP in Phase 3 trials

- **Challenges with designing active control trials (investigational PrEP agent vs. FTC/TDF)**
- **Challenges with including FTC/TDF in the background prevention package (example, in a microbicide vs. placebo trial)**

Comparator Arm Challenges

- **With an approved product, demonstrating superiority to placebo may not be considered appropriate**

- **Comparing efficacy to the approved product is appropriate: demonstrating either superiority or non-inferiority to the approved agent**
  - **Are superiority trials feasible?**
    - **Will require an even larger sample size than present-day trials**
  - **Challenges with designing noninferiority (NI) trials**

NI Trial

- **An NI trial "seeks to show that the difference in response between active control and the test drug is less than some pre-specified NI margin"**
- **Relies heavily on previously demonstrated effect of the active control**
- **NI margin calculation based on demonstrated effect of the control drug including confidence intervals around this effect**

Oral PrEP NI trials

- **Issues with calculating NI margin for FTC/TDF comparator**
  - **Wide range of effect observed in iPrEx, Partners PrEP, and Fem-PrEP trials**
  - **Effects were highly dependent on adherence**

- **NI margin influenced by expected level of adherence**
  - **Assumptions based on overall effectiveness observed vs. efficacy in highly adherent groups**

Microbicide NI trials

- **Similar challenge may arise for future microbicide trials**
  - **Tenofovir gel example: if approved, then determining effect size may be challenging based on 6-60% confidence interval observed in one trial CAPRISA 004**

- **Justifying the NI margin essential and discussions with the FDA necessary prior to initiating trials**

Offering FTC/TDF as part of background package

- **Add-on placebo design (microbicide + TDF/FTC vs. placebo + TDF/FTC, in addition to condoms/risk-reduction counseling for all)**

- **Considerations**
  - **Alignment with local standard-of-care for HIV prevention**
    - **FTC/TDF implemented as part of national prevention policy for the trial population (MSM, women)**
    - **Local access/availability: access to FTC/TDF PrEP after trial completion**

Offering FTC/TDF as part of background package

- **Considerations**
  - **Sample size requirements to compensate/offset protective effects of background interventions**
  - **PrEP acceptability**
  - **Alternative: trial enrolls only those participants who refuse FTC/TDF as a result of intolerance, side-effects, or personal preference**

Summary

- **FDA draft guidance for microbicides identifies trial design challenges relevant to oral PrEP**

- **Major challenges**
  - **Whether NI trials can definitively provide answers**
  - **How to position FTC/TDF in superiority designs**
  - **Ethical issues with not providing FTC/TDF as background**
  - **Feasibility with providing FTC/TDF as background**

- **We recognize these are unresolved issues and expect public comments**

Acknowledgements

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