

MTN-016: EMBRACE

Regional Meeting 2013

29 October 2013

Cape Town, South Africa



Agenda

Time	Topic
1:30-2:00	MTN-016 Implementation Update
2:00-3:00	Protocol Amendment
3:00-3:30	BREAK
3:30-4:15	Clinical Skills Refresher: Woman
4:15-5:30	Clinical Skills Refresher: Infant

MTN-016 Implementation Update

- Studies contributing data to MTN-016:
 - MTN-002
 - MTN-003
 - MTN-008
 - MTN-020

MTN-002

- **Phase 1 Study of the Maternal Single-Dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas**
 - One site: Pitt CRS
 - Contributed 16 mother-infant pairs to MTN-016. All follow-up completed.



MTN-003: VOICE

- **Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women**
- 15 African sites (213 women, 185 infants)
- All but two sites have completed MTN-016 follow-up. Final infant visits expected in December 2013.

MTN-008

- **Expanded Safety of Tenofovir 1% Gel in Pregnancy and Lactation**
 - Two Sites:
 - Pitt CRS (58 women, 54 infants)
 - UAB CRS (30 women, 28 infants)
 - MTN-016 enrollment is complete. Last infant visits anticipated for September 2014.

MTN-020: ASPIRE

- **A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women**
- 15 activated sites for ASPIRE
 - Cape Town training to occur 31 Oct-1 Nov 2013
 - Blantyre and Lilongwe training to occur Q1 2014

MTN-016 Accrual from ASPIRE

Site	# Parent Study Pregnancies*	# eligible for 016†	Eligible, but Pending Enrollment	# women enrolled	# Eligible, but Not Enrolled§
South Africa: Durban MRC- Botha's Hill	1	0	0	0	0
South Africa: Durban MRC- Chatsworth	4	3	1	0	2
South Africa: Durban MRC- Isipingo	4	2	2	0	0
South Africa: Durban MRC- Tongaat	7	2	2	0	0
South Africa: Durban MRC- Umkomaas	3	2	0	2	0
South Africa: Durban MRC- Verulam	6	4	1	0	3
eThekwini (CAPRISA Durban)	5	1	0	1	0
South Africa: Johannesburg WRHI	2	1	1	0	0
South Africa: Cape Town					
Uganda: Kampala	1				
Zimbabwe: Harare - Spilhaus	2	2	1	1	0
TOTAL (MTN-020)	35	17	8	4	5

MTN-016 Version 2.0

Lisa M. Noguchi, MSN
Microbicide Trials Network
Washington, DC
USA



Objectives

- Review anticipated timelines for finalization of Version 2.0
- Review Summary of Changes including revised study objectives and modified visit procedures

Timeline

- Minimal site team comments on the draft amendment
- Currently responding to additional Medical Officer comments
- Early November 2013: DAIDS regulatory review submission
- December 2013: Version 2.0

Summary of Changes

- Updated Protocol Team Roster and Investigator Signature form
- Revised Protocol Summary
 - Increased sample size
 - Modified study objectives and endpoints (to prevent redundancy in data collection and analysis across protocols)



Old primary objectives

1. To evaluate the prevalence of **spontaneous pregnancy loss** in mothers exposed to an active study agent during pregnancy as compared to that in mothers not exposed to an active study agent during pregnancy.
2. To evaluate the prevalence of **major malformations** in infants of mothers exposed to an active study agent during pregnancy as compared to that in mothers not exposed to an active study agent during pregnancy.



New primary objectives

1. To compare **adverse pregnancy and delivery outcomes** between participant mothers assigned to an active agent with those of mothers assigned to placebo/control.
2. To compare the prevalence of **major malformations** identified in the first year of life between infants of mothers assigned to an active agent with those of infants of mothers assigned to placebo/control.



Old secondary objectives

1. To monitor for adverse pregnancy outcomes.
2. To evaluate growth parameters in the first year of life among infants born to mothers exposed to an active study agent during pregnancy, as compared to those of mothers not exposed to an active study agent during pregnancy.
3. To provide a cohort of infants not exposed to an active study agent representing the background incidence of major malformations among babies born to women participating in HIV prevention trials.



New secondary objectives

1. To compare **growth** parameters in the first year of life between infants of mothers assigned to an active agent with those of mothers assigned to placebo/control.
2. To evaluate the prevalence and persistence of **HIV drug resistance mutations** in plasma among HIV-infected infants.

One exploratory objective (developmental screening) have been omitted and one (resistance) has moved to secondary.

Summary of Changes (cont.)

- Section 2, INTRODUCTION
 - Updated background information
 - Omission of product-specific language – now flexible for ANY study product
- Section 3, STUDY OBJECTIVES
- Section 4, STUDY DESIGN (minor edits)
- Section 5, STUDY POPULATION
 - Eligibility criteria are clarified

Revised eligibility criteria

- During participation in a parent protocol, has/had a known confirmed pregnancy, meeting at least one of the following sets of criteria in A or B:
 - A: Two consecutive monthly study visits, **at least 14 days apart**, with positive pregnancy tests, **in the absence of signs/symptoms of miscarriage or participant report of pregnancy termination.**
 - B: One or more of the following assessments:
 - Auscultation of fetal heart tones
 - Positive pregnancy test confirmed by clinic staff in the presence of clinically confirmed enlarged uterus
 - Positive pregnancy test confirmed by clinic staff in the presence of missed menses (**no menses occurring at least 60 days from the first day of the last menses**) by participant report Clinical assessment of fetal movement
 - Demonstration of pregnancy by ultrasound



Summary of Changes (cont.)

- Section 7, STUDY PROCEDURES
 - Developmental screening assessment has been removed
- Section 8, ASSESSMENT OF SAFETY
 - Minor edits for clarity and consistency with current policy
- Section 9, CLINICAL MANAGEMENT
 - Minor edits for clarity and consistency with revised study procedures



Summary of Changes (cont.)

- Section 10, STATISTICAL CONSIDERATIONS
 - Revised study objectives and endpoints, power estimates, oversight of the Interim Study Review (ISR) Committee, and planned data analysis



Summary of Changes (cont.)

- Section 11, DATA HANDLING
 - Minor updates
- Section 12, SITE MONITORING
 - Revised to include all authorized representatives allowed to inspect study-related documentation
- Section 13, HUMAN SUBJECTS
 - Minor updates



Summary of Changes (cont.)

- Section 14, Publication Policy
 - Minor updates
- Sample informed consent documents
 - New language for off-site visits, VERY similar to ASPIRE
- Other minor updates, corrections, and clarifications are incorporated

Acknowledgements

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Protocol Amendment – Next Steps

- Once v2.0 is finalized, FHI 360 will contact sites with next steps
- All sites must prepare revised versions of the ICFs for approval by FHI 360
 - Use templates in protocol appendices
 - English, translations, and back translations must all be approved by FHI 360 before submission to IRBs



Protocol Amendment

- Once the updated ICFs have been finalized, submit the following to IRBs/ECs:
 - ICFs
 - Protocol Summary of Changes document
 - Protocol Version 2.0, in its entirety



Protocol Amendment

- While IRBs/ECs are reviewing this package, update:
 - SOPs
 - Visit Checklists
 - DoA*

The MTN-016 management team will provide updated template visit checklists, SSP Manual, and implementation tools posted on the website during this time.



Protocol Amendment

- Within 14 calendar days of final written IRB/EC approval for the amendment, submit the amendment registration package to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC).



Protocol Amendment

- Implementation of protocol version 2.0 may only begin after:
 - IRB/EC approval of the protocol amendment and all associated ICFs
 - Staff training
 - Final management team approval of site readiness



Protocol Amendment

Questions?