

Phase 1 Human Trials of Rectal Microbicides

- **UC781: Completed**
- **Tenofovir: Planned to start**



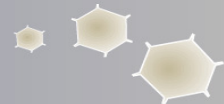
RM Trials under U19-IPCP grant

UC781 (topical) rectal trial – *completed*

A Phase I Randomized, Blinded, Placebo-Controlled Safety and Acceptability Study of the UC-781 Vaginal Microbicide Gel Formulation Applied Rectally in HIV-1 Seronegative Adults; Single site trial.

Tenofovir (topical & oral) rectal trial – *soon to start*

A 2-site, Phase 1, partially-blinded, placebo-controlled safety, acceptability and PK trial of topical, vaginally-formulated tenofovir 1% gel applied rectally, compared with oral 300 mg tenofovir disoproxil fumarate in HIV-1 seronegative adults



Phase 1 UC781 rectal microbicide trial

- First IND rectal safety trial of topical microbicide
- Animal toxicity studies in 2 species (rat/rabbit) conducted (no effect)
- IND submitted by CONRAD to FDA on 6/16/06 as amendment to vaginal formulation IND; responded to FDA's questions & suggestions.
- CONRAD oversaw delivery of labeled formulation and placebo in vaginal applicators

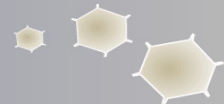
- Total time: 9/04 through 9/06 (overlapped with protocol develop)
- Trial effectively started: 1/07; ended 4/08



- **Primary Objective**: To evaluate the *safety and acceptability* of 0.1% and 0.25% UC781 vaginal gel vs placebo when applied rectally.

Indices:

- Frequency of \geq Grade 2 adverse events
- Acceptability assessments
- **Secondary Objectives**: Correlate use with rectal mucosal damage:
 - Epithelial sloughing
 - Histopathology
 - Mucosal mononuclear cell phenotype (flow)
 - Mucosal cytokine mRNA (tissue)
 - Mucosal immunoglobulins
 - Fecal calprotectin
 - Explants- susceptibility to HIV infection
- **Tertiary Objectives**: To determine the pharmacokinetics of UC781 vaginal gel administered rectally (subset).



Amended Toxicity Tables for AE (1° endpoint)

- DAIDS EAE Reporting Manual and DAIDS Toxicity Tables
- **Clarifications/Additions to avoid inaccurate AE reporting:**
 - “diarrhea”
 - “hematochezia” (from NCI, not in DAIDS)
 - “bloody diarrhea”
 - “Proctitis” (stricter definition than DAIDS; used by NIDDK)
 - “bruising” (to cover AE related to applicator injury)(NCI)
- Protocol team reviews; report issued every 2 weeks
- Trial suspended/SMC convened if 2 or more subjects have
≥ Grade 3 AE



PARAMETERS

Frequency of \geq Grade 2 Adverse Events

DAIDS Toxicity Table

Grade 1 – Mild

Grade 2 – Moderate

Grade 3 – Severe

Grade 4 – Potentially Life Threatening

Acceptability Assessments

Computer Assisted Self Interview (CASI)

In-Depth Phone Interview



UC781 HIV-seronegative Trial

- **Study Population:** HIV negative men and women with a history of RAI *

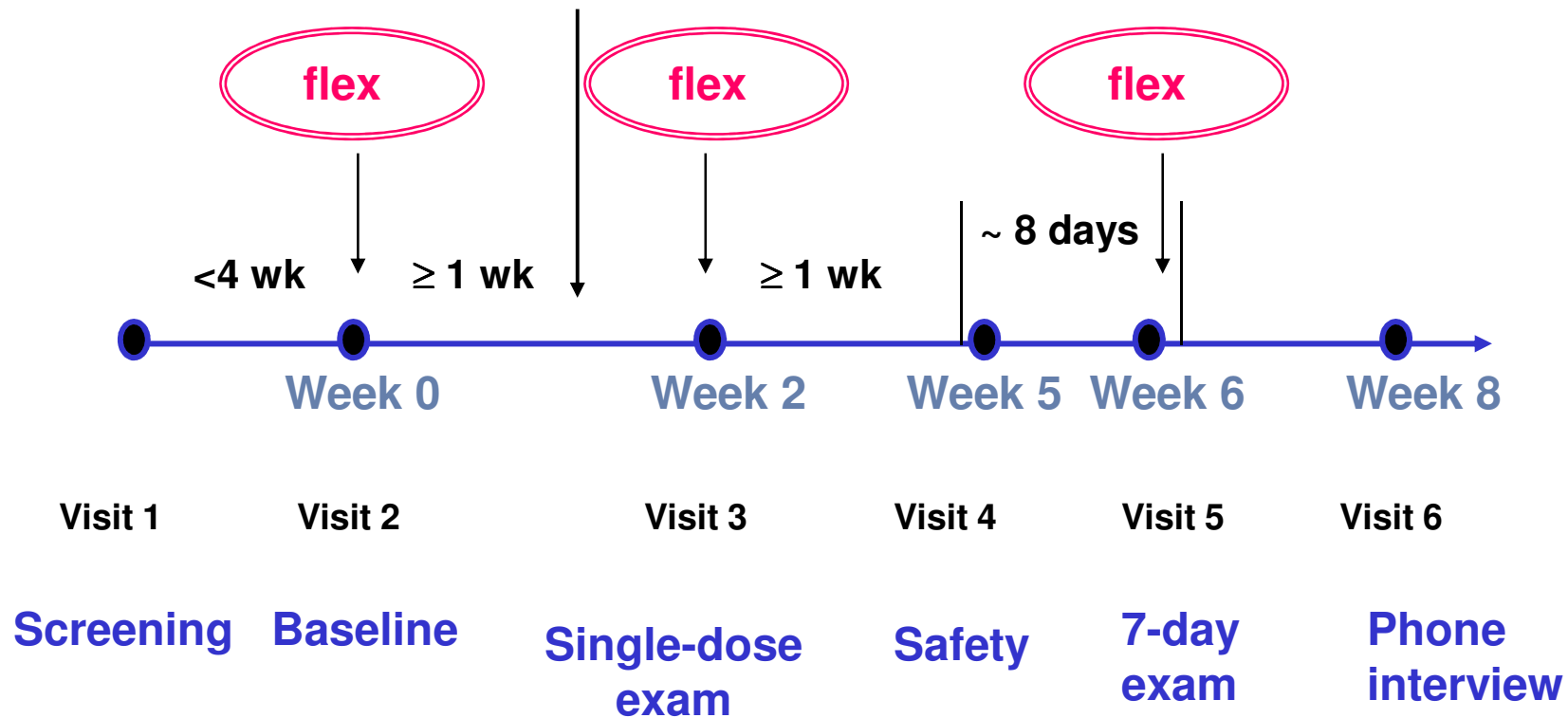
**in order to give context to acceptability assessments.*

- **Study Size:** 36 participants (men and women) in 3 arms
Subset of 9 participants assigned to pK study.
- **Accrual:** 9-12 months.
- **Duration:** 18 months.
- **Completed:** April, 2008



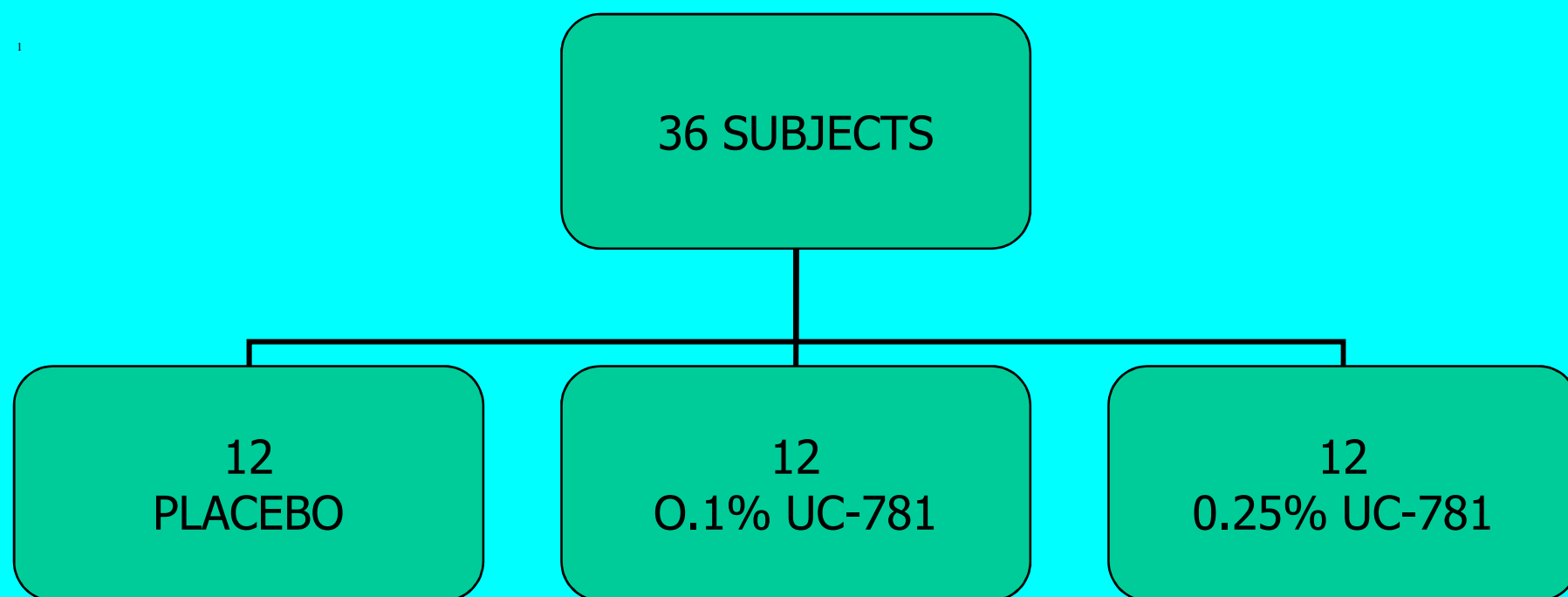
RM Phase 1 Trial Design

Randomization: 0.1% UC-781, 0.25% UC-781, or placebo



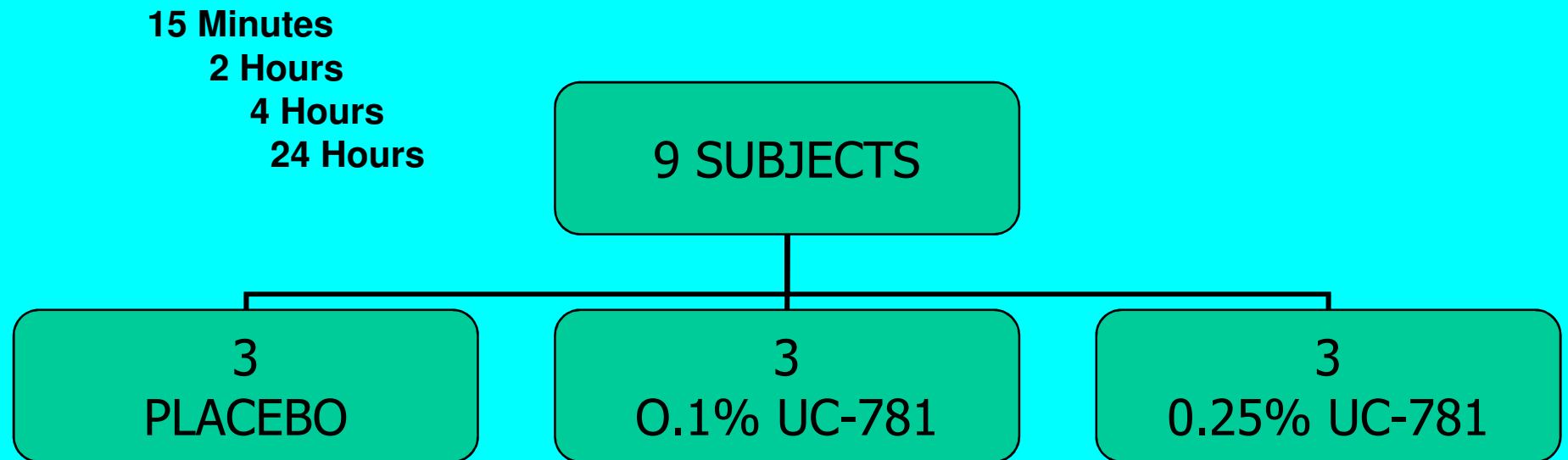
PRIMARY OBJECTIVE

- Evaluate the safety and acceptability of UC-781 Gel when applied to one of three Groups:

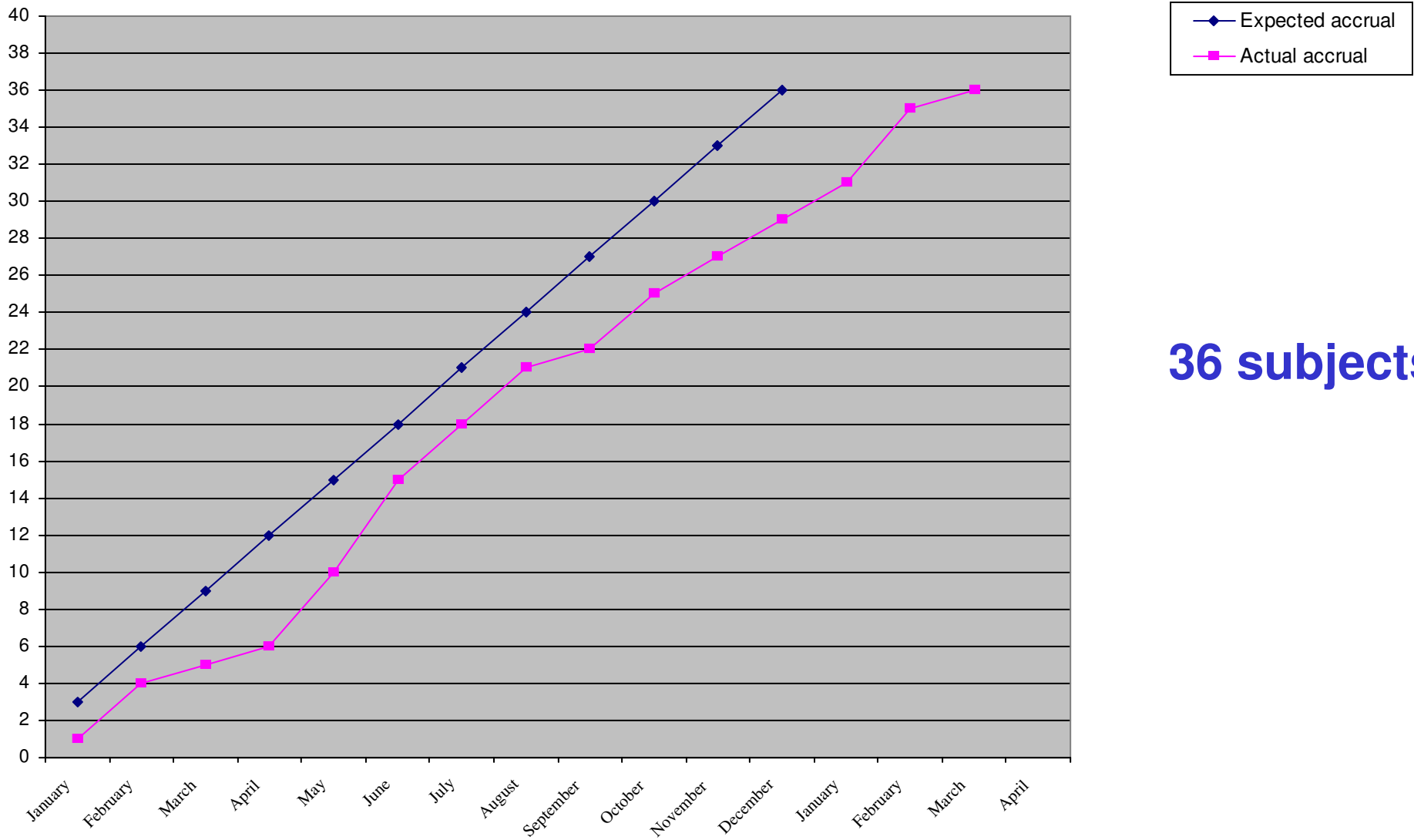


PHARMACOKINETICS Sub-Study

- Pharmacokinetics UC-781 vaginal microbicide gel administered rectally:



Accrual Data: 1/07-4/08

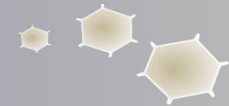


36 subjects

UCLA

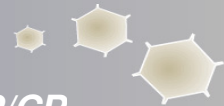


Microbicide Development Program



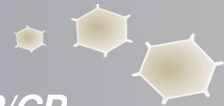
Results: Recruitment/Enrollment

- Recruit/Enroll: CFAR/IPCP Trial Registry *very* helpful.
 - 146 volunteers
 - 55 screened
 - 36 enrolled (entered V2)
 - 36 completed (66% of those screened)
 - 26 men (72%) and 10 women (28%)
 - no withdrawals (including due to procedures)
 - average of **80 phone calls/emails** to get each subject recruited and through trial
 - duration: 15½ months (First subject screened on 12/20/06 and the last subject completed study on 04/03/08)



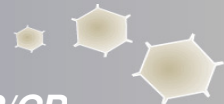
Results (1)

- Appears safe and well-tolerated
- **100% retention of all that passed screening**
- Procedures well tolerated (108 flexible sigmoidoscopies)
- **No Drop outs/withdrawals**
- **No Grade 3 or 4 AE**
- **No procedure related AE** (3,024 biopsies)
- 84 Grade 1 AEs reported
- 8 Grade 2 AEs reported in 5 of 36 individuals:
 - 4 from one individual at V3; not at V5) (possibly related)
 - 2 with limited diarrhea (possibly related)
 - 1 with isolated thrombocytopenia (not related)
 - 1 with spider bite (not related)
- New NIAID RM toxicity tables are useful in RM trials



Results (2)

- High acceptability (submitted for publication)
 - NO immunotox differences of significance seen c/w placebo, *in all categories*
 - Explants: marked *ex vivo* suppression of high viral dose infection by high UC781 microbicide *in vivo* (for more details, see CROI poster)
 - PK: NO plasma levels of UC781 detected in first 24 hrs. Tissue levels to correlate with explant data pending



Tenofovir (topical & oral) RM trial: MDP-02 / MTN-006:

A 2-site, Phase 1, partially-blinded,
placebo-controlled
safety, acceptability and PK trial of
topical, vaginally-formulated tenofovir 1% gel
applied rectally
compared with oral 300 mg tenofovir
disoproxil fumarate
in HIV-1 seronegative adults



MDP-02 / MTN-006

- **NOVEL:** Sponsored by CONRAD, MTN, Gilead, NIAID's U19 IP/CP
- 2 Sites: UCLA & McGee/U Pitt
- **Tenofovir (oral/topical) evaluated in 18 seronegatives (abstinent)**
- Oral: all get 300 mg tablet (single exposure only) with PK
- Topical: Randomized 2:1 (1% drug:placebo)(single; 7-day)
- pilot PK: plasma
- exploratory pK: *5 - 6 compartments* (includes intracellular)
- very intensive....to complement MTN-007



MDP-02 / MTN-006: Study design

INDs: Oral not required; topical to be submitted...will cover both RMP-02/MTN-006 and MTN-007

Protocol development: Completed. IRBs and FDA submission underway

Practical start/end dates: First enrolled 7/09; end enroll 11/09

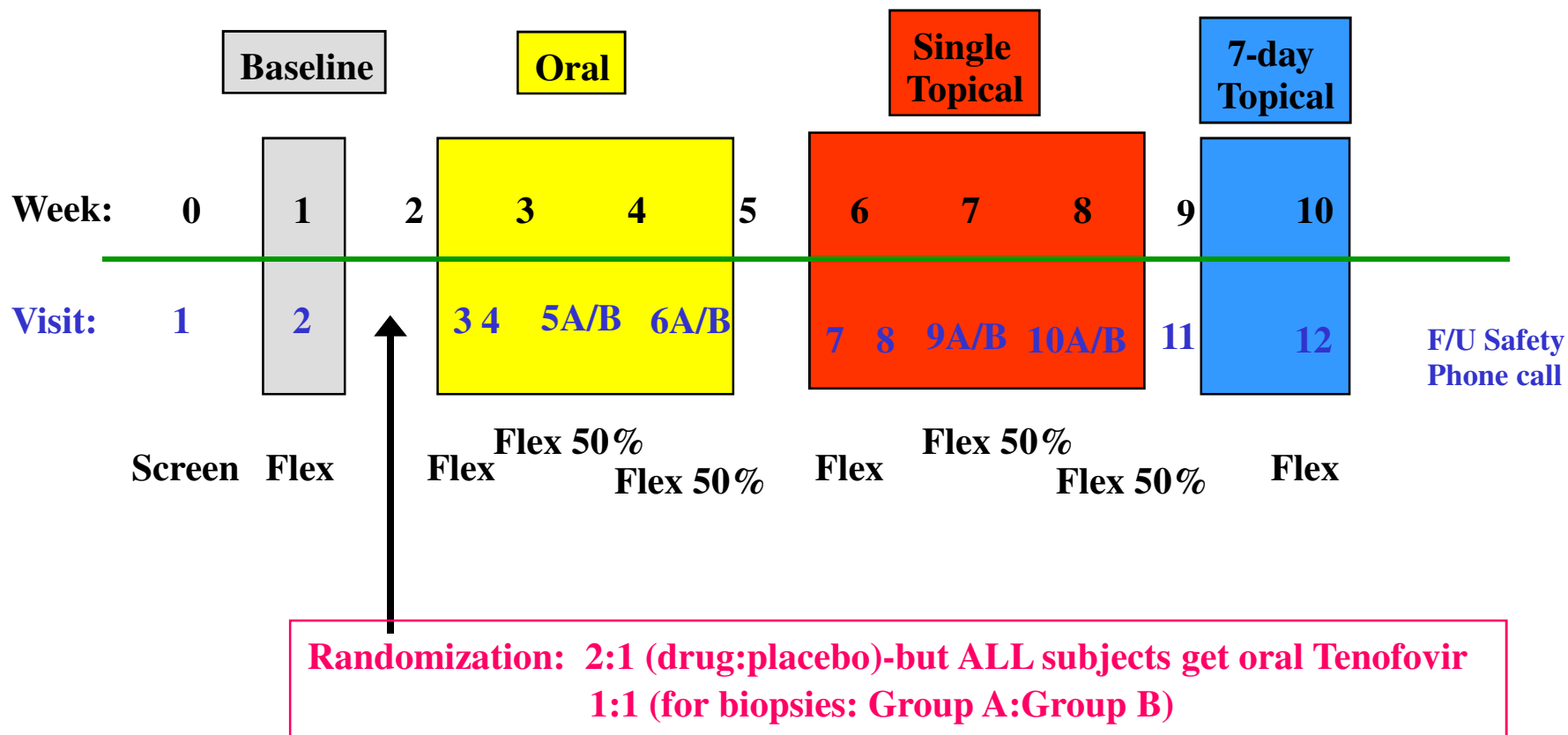
Endpoints:

- **Primary**: Safety & Acceptability & Immunotoxicity
- **Secondary**: Immunotoxicity and multi-compartment PK (including topical versus oral)
- **Tertiary**: Preliminary efficacy (explants)

Study: each subject with total of 8 flex sigs (10cm only); 5-6 compartments sampled for pK over 2 weeks; oral IC c/w topical IC of PBMC & MMC



MDP-02 / MTN-006: Study design



Group A flex sigs: Baseline, ORAL: 30', d 1-3, 7-9; TOPICAL (single): 30', d 1-3, 7-9; TOPICAL (7-day): 30'= 8 flex sigs

Group B flex sigs: Baseline, ORAL: 30', d 4-6, 10-12; TOPICAL (single): 30', d 1-3, 7-9; TOPICAL (7-day): 30'= 8 flex sigs

MDP-02 / MTN-006

Goals:

- 2nd rectal safety trial of vaginal microbicide in U19
- Human continuation of exciting macaque results
- Compare topical versus oral delivered pK
 - drug concentrations in blood and tissue
 - explant impact
- Biomarkers:
 - Assess repeat value of explant readout in clinical trials
 - Quantify single does exposure drug levels in tissue etc.
- Further clarify which mucosal indices are of value in trials



Human Rectal Microbicide Trials: *Discussion points*

- Essential: alone and complementary to vaginal trials (assays, PK, FDA..)
- Questions about rectal studies/design/safety?
- Single agent now...but soon to combination Rx
- Excessive list of rectal immunotox assays:
 - relevance?
 - how rationally reduce?
 - if abnormalities found, what are the implications?
- Importance of rectal-specific formulations
- Awareness of compartment distribution, target cell(s)
- Role of Acceptability early
- Need for rectal-specific applicator? Impact on dual-compartment use?
- Reproducibility and multi-site QA/QC? Use of 6 vs 10 vs 15 vs 30 cm sampling?
- Role and relevance of Explants in trials??

