Considerations for the New Four-Month Rifapentine-Moxifloxacin Regimen for Drug-Susceptible TB in the U.S.

September 21, 2021

Jointly provided by the TB Centers of Excellence and the Centers for Disease Control and Prevention

CURRY INTERNATIONAL TUBERCULOSIS CENTER

HEARTLAND NATIONAL TB CENTER
THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT TYLER

Southeastern National Tuberculosis Center

RUTGERS Global Tuberculosis Institute
NEW JERSEY MEDICAL SCHOOL

Continuing Education

- **PHYSICIANS:** Rutgers Biomedical and Health Sciences designates this live activity for a maximum of **1.5** ***AMA PRA Category 1.5 Credits™***. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

- **NURSES:** This activity is awarded **1.5 contact hours (60-minute CH).** Nurses should only claim those contact hours actually spent participating in the activity.

- Completion of an evaluation is required to receive continuing education credits.

Questions?

Comments?

The Q&A will begin with pre-submitted questions. New questions will be addressed with the remaining time.

Please share your questions using the **Q&A** button.

Please share your comments using the **Chat** button.

Agenda

- **Welcome and Housekeeping**
- **Study Objectives and Methods** – Susan Dorman, MD
- **Study Results** – Payam Nahid, MD, MPH
- **Non-inferiority: What does it mean?** – Patrick Phillips, PhD
- **Subgroup Analyses** – Richard Chaisson, MD
- **Study Safety** – Ekaterina Kurbatova, MD, PhD, MPH
- **Q&A**
- **Wrap-up and closing remarks**

TB COE Principal Investigators

Lisa Chen, MD
Curry International TB Center

David Ashkin, MD
Southeastern National TB Center

Alfred Lardizabal, MD
Global TB Institute

Lisa Armitige, MD
Heartland National TB Center

S31 / A5349

Rifapentine-containing treatment shortening regimens for pulmonary TB: A randomized, open-label, controlled phase 3 clinical trial

Study Objectives & Methods

Susan E. Dorman, MD
Professor of Medicine
Medical University of South Carolina

TB Medical Consultant
South Carolina Dept of Health & Environmental Control

TBTC TB Trials Consortium CDC

ACTG AIDS CLINICAL TRIALS GROUP

Background

- Reducing the length of time for treating TB has been a longstanding public health goal
  - Shorter regimens cure patients faster, and have the potential to reduce treatment costs, improve patient quality of life, and increase completion of therapy

- **Key Study Question**
  - Does high dose daily rifapentine, with or without moxifloxacin, allow treatment shortening to 4 months for drug-susceptible TB?

Objectives

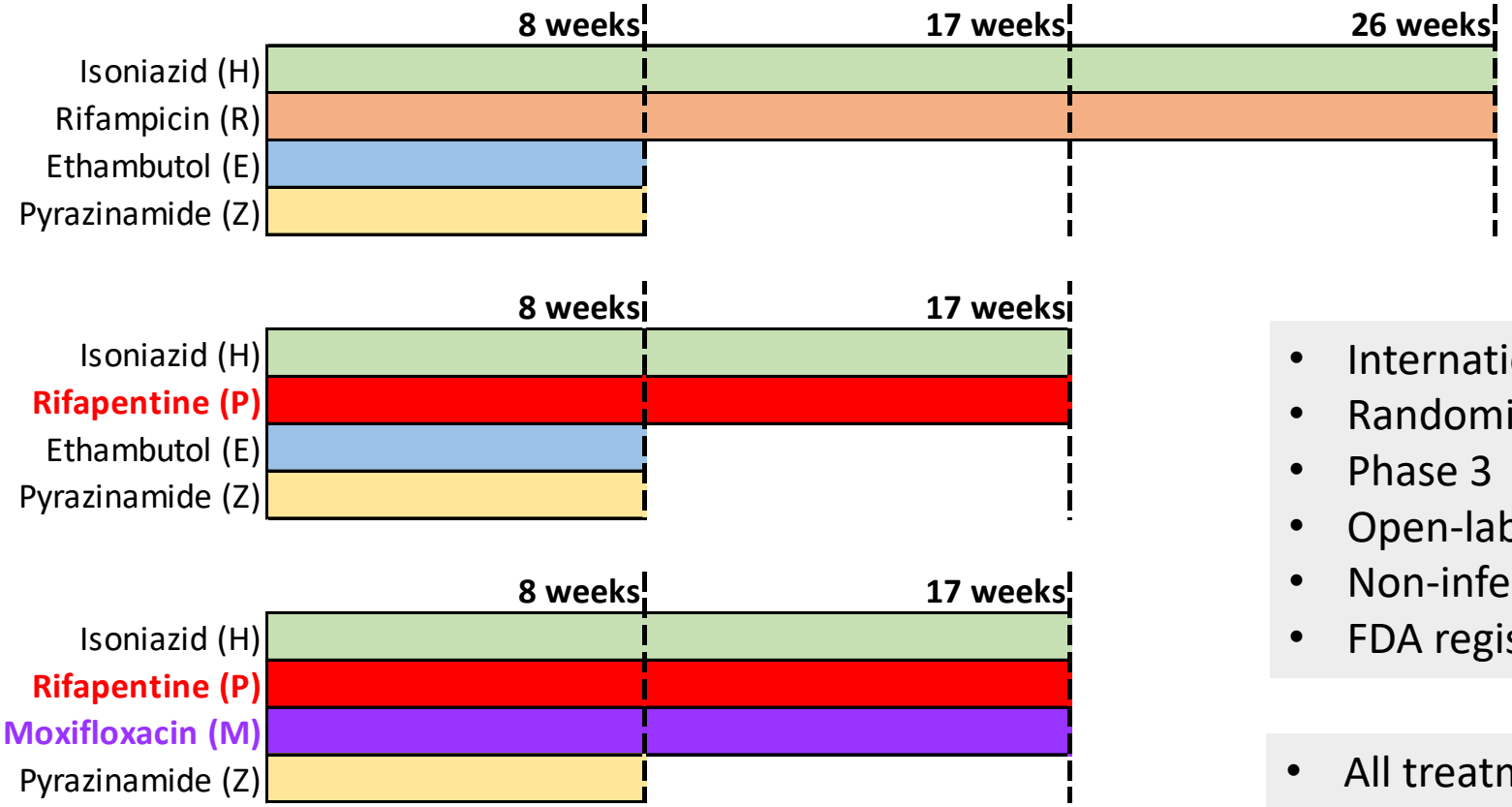
- Primary
  - To evaluate the efficacy [of 2HPZE/2HP] to determine whether the single substitution of rifapentine for rifampin makes it possible to reduce to 17 weeks the treatment of DS-pulmonary TB
  - To evaluate the efficacy [of 2HPZM/2HPM] to determine if substitution of rifapentine for rifampin, in addition to substitution of moxifloxacin for ethambutol with continuation of moxifloxacin during continuation phase, make it possible to reduce to 17 weeks the treatment of DS-pulmonary TB
- Secondary
  - To evaluate safety
  - To evaluate tolerability
  - To determine correlations of mycobacterial and clinical markers with time to culture conversion, treatment failure, relapse
  - To conduct a PK/PD study of the test drugs
  - To evaluate the PK of EFV-based ART among patients with HIV/TB

Study Design

3 arms
randomization 1:1:1

Primary efficacy endpoint: outcome at 12-months post-randomization

Follow-up: 18 months post-randomization



- International, multicenter
- Randomized, controlled
- Phase 3
- Open-label
- Non-inferiority design
- FDA registration quality

- All treatment: daily 7/7, **DOT 5/7**
- Flat P dose of 1200 mg
- M dose of 400 mg
- Food guidance: food with RPT, no food with RIF

Safety labs & adverse events check: Weeks 2, 4, 8, 12, 17, 22, 26
Sputum at above plus Months 9, 12, 15, 18

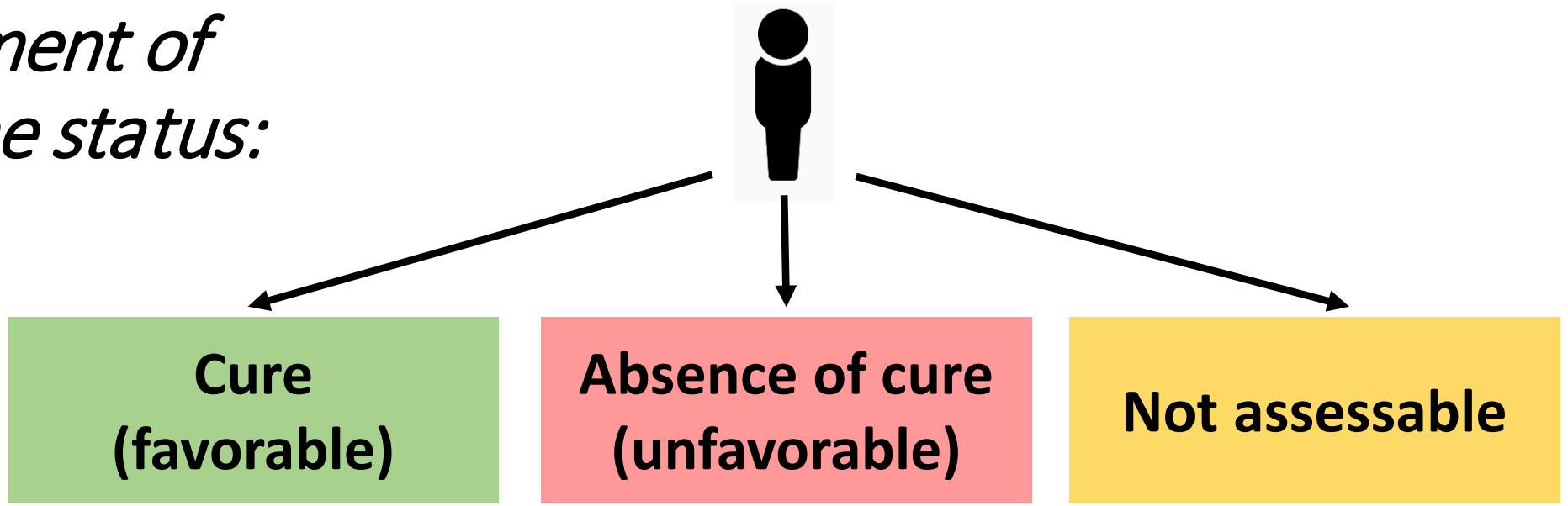
34 clinical research sites, 13 countries, 4 continents

Eligibility criteria

- Inclusion
  - Positive sputum smear for AFB or positive *Xpert MTB* with medium or high result
  - Age ≥12 y.o.
  - If HIV-positive, CD4 T cell count ≥100 cells/mm^3
  - Labs: ALT≤3xULN, bilirubin ≤2.5xULN, creatinine ≤2xULN, K+ ≥3.5 meq/L, Hgb ≥7 g/dL, platelets ≥100,000/mm^3
  - For women: not pregnant; willing to use contraception or abstain from heterosexual sex
  - Karnofsky score ≥ 60 (60=requires occasional assistance but able to care for most of own personal needs)
- Exclusion
  - >5 days systemic TB treatment within previous 6 months
  - >5 days treatment with anti-TB drugs within previous 30 days
  - TB of CNS, bones or joints, miliary, pericardial
  - Weight <40 kg
  - Unable to take oral medicines
  - Known h/o prolonged QT syndrome
  - Current or planned use within next 6 months of: HIV integrase inhibitors, HIV PIs, HIV NNRTIs except EFV, quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, terfenadine
  - At time of enrollment, Mtb isolate known to be resistant to one or more of INH, RIF, PZA, EMB, FQ
- Late Exclusion
  - Screening, baseline, and week 2 cultures all fail to grow Mtb
  - Mtb isolated around time of enrollment resistant to any one or more of INH, RIF, FQ

Primary outcome: TB disease-free survival at 12 months after study treatment assignment

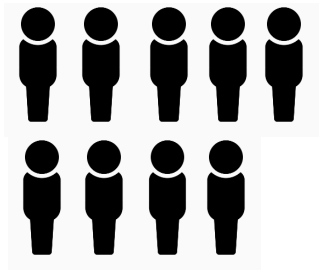
Assignment of outcome status:



Primary analysis populations:

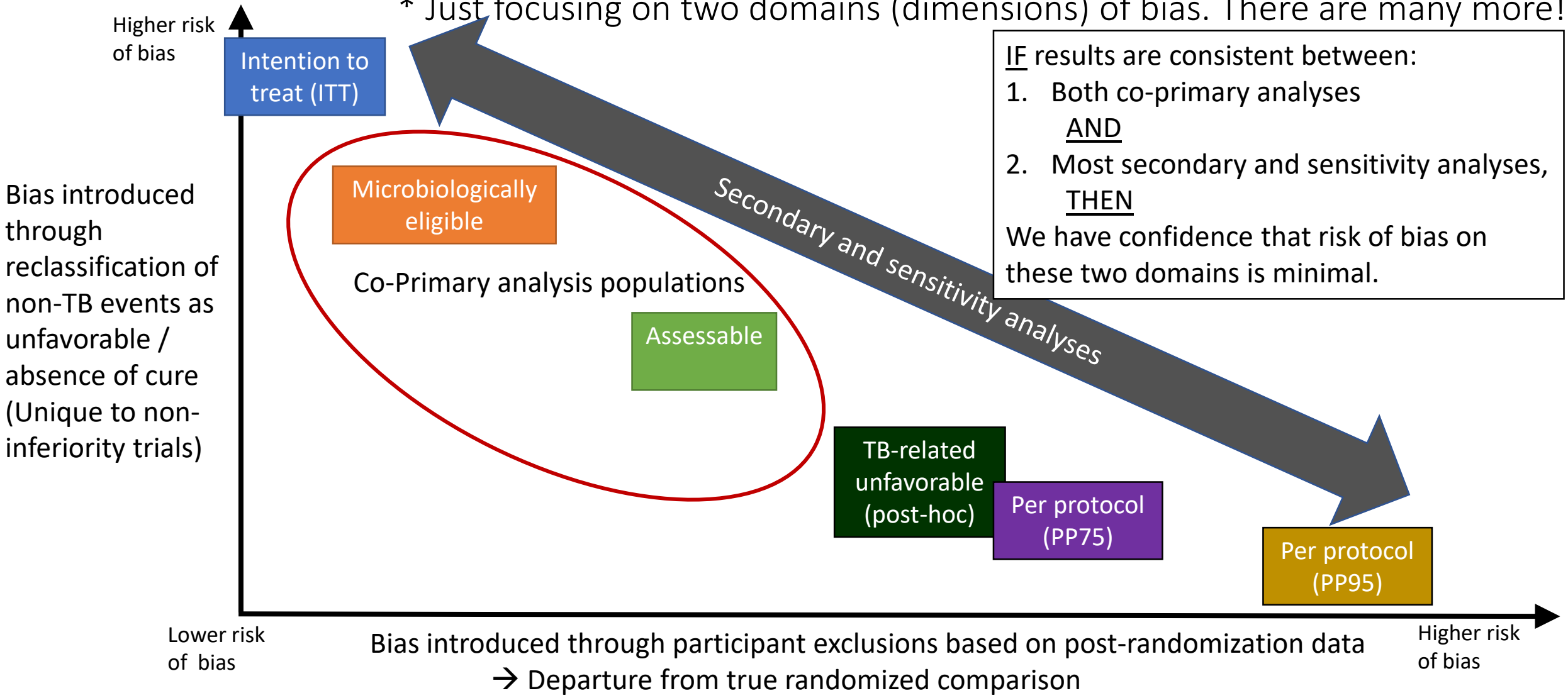
Microbiologically eligible analysis population

Assessable analysis population



Risk of bias with different analysis populations*

* Just focusing on two domains (dimensions) of bias. There are many more!



IF results are consistent between:

1. Both co-primary analyses
   AND
2. Most secondary and sensitivity analyses,
   THEN

We have confidence that risk of bias on these two domains is minimal.

Efficacy Analysis Populations in TBTC S31/ACTG A5349

Analysis populations	Exclusions	Total in analysis	Potential 'non-TB' outcomes reclassified as Unfavorable (Absence of cure)
Intention-to-treat (ITT)	None	2516 (100%)	• Culture negative at baseline • DR-TB at baseline • Late exclusions for ineligibility • Lost to follow-up • Non-TB death in follow-up • Withdrawals from treatment • Other not assessable
Microbiologically eligible	• Culture negative at baseline • DR-TB at baseline • Late exclusions for ineligibility	2343 (93%)	• Lost to follow-up • Non-TB death in follow-up • Withdrawals from treatment • Other not assessable
Assessable	As per microbiologically eligible, additionally: • Lost to follow-up • Non-TB death in follow-up • Withdrawals from treatment • Other not assessable	2234 (89%)	• Not received specific proportion of treatment doses
Adherent per-protocol 75% (PP75)	As per assessable, additionally: • Not received 75% of treatment	2094 (83%)	None
Adherent per-protocol 95% (PP95)	As per assessable, additionally: • Not received 95% of treatment	1854 (74%)	None
TB-related unfavorable (*post-hoc*)	As per assessable, additionally: • Any unfavorable outcome not considered related to TB	2113 (93%)	None

Co-primary: Microbiologically eligible, Assessable

Secondary: Per-protocol 95, Per-protocol 75, Intention-to-treat, TB-related unfavorable *(post-hoc)*

Study 31/A5349 Results

Rifapentine-containing treatment shortening regimens for pulmonary TB: A randomized, open-label, controlled phase 3 clinical trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

N Engl J Med. 2021 May 6;384(18):1705-1718.

Payam Nahid, MD, MPH
Professor of Pulmonary and Critical Care Medicine
University of California, San Francisco

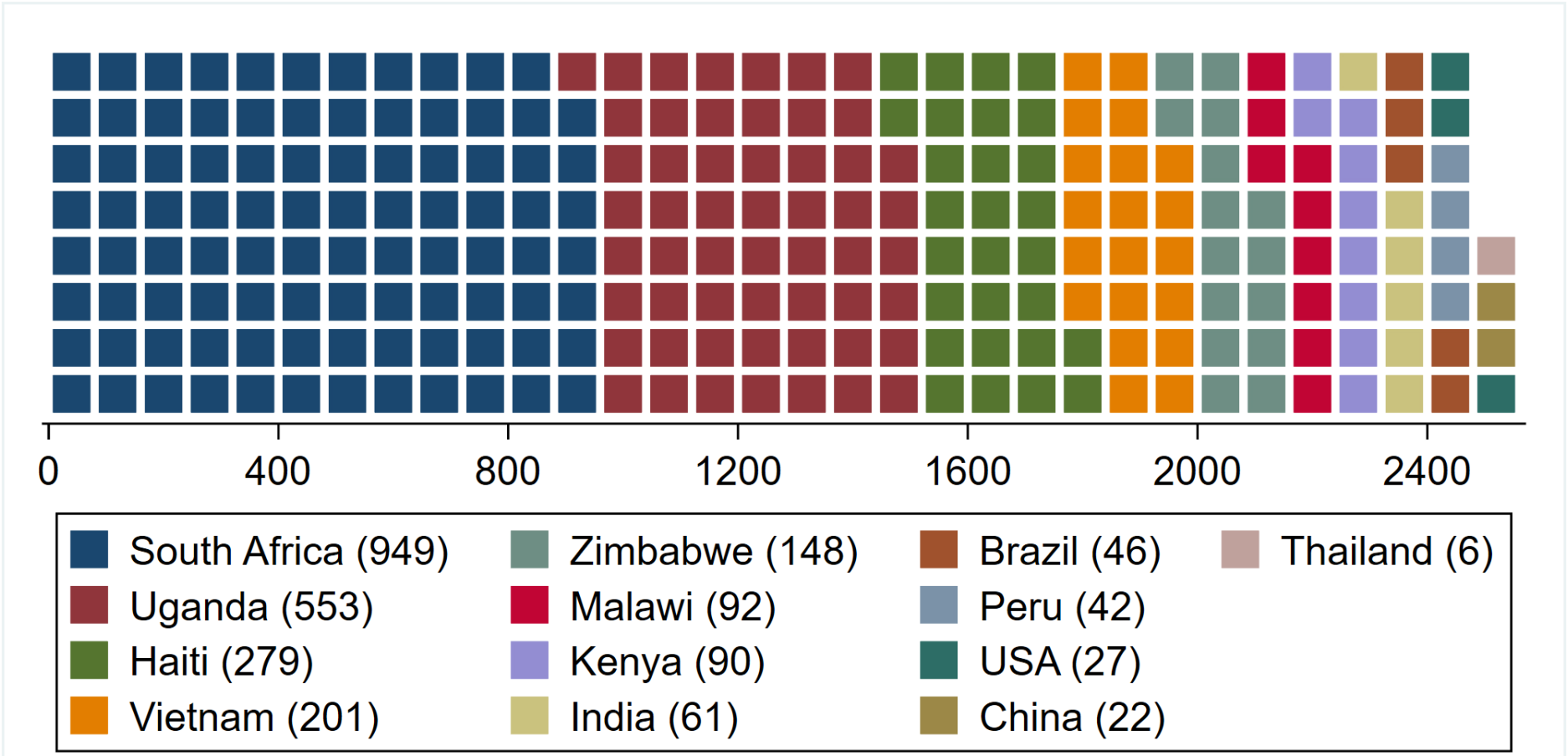
TBTC TB Trials Consortium

Center for Tuberculosis UCSF University of California San Francisco

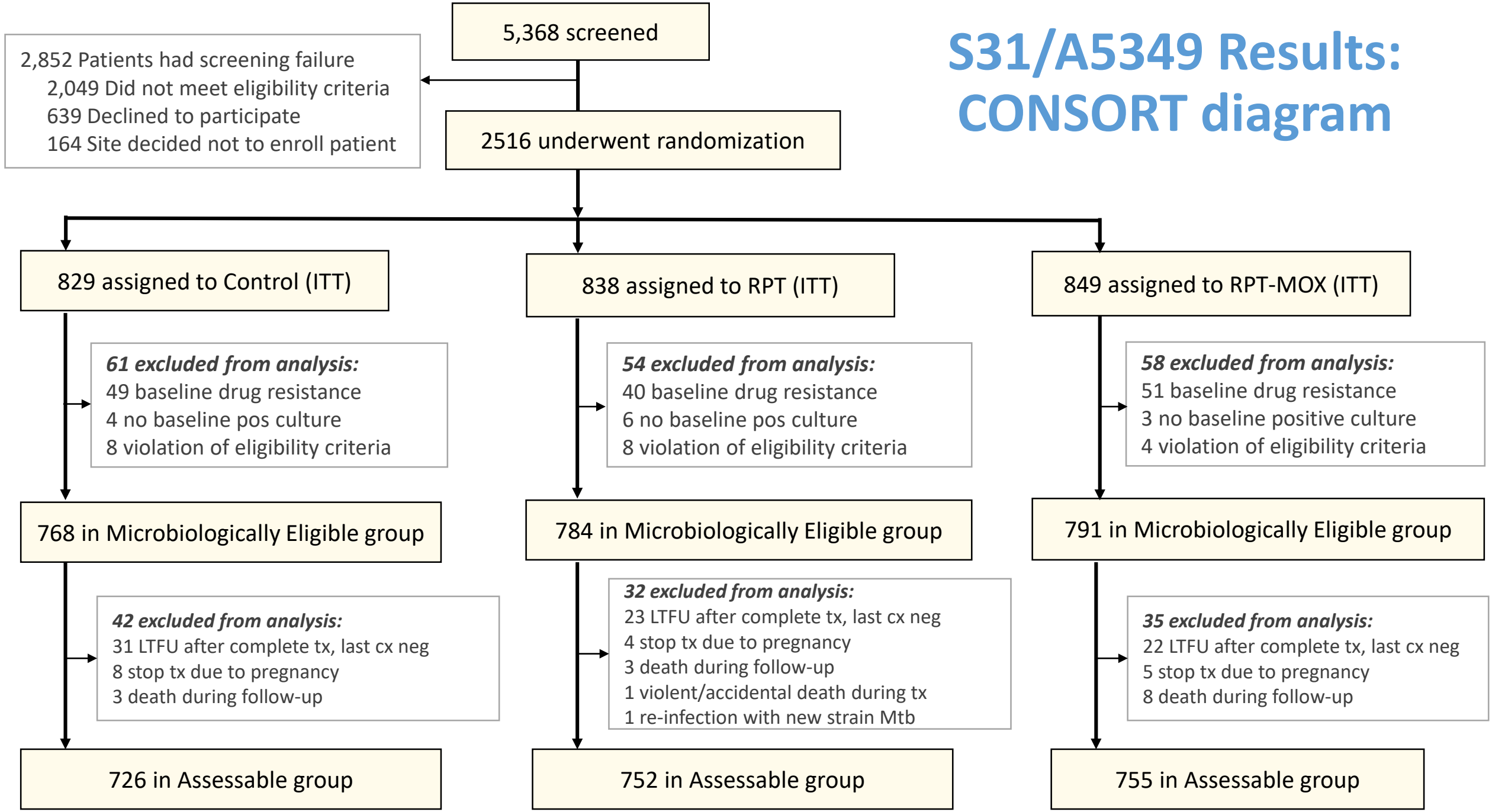
ACTG AIDS CLINICAL TRIALS GROUP

Recruitment by country

Total randomized = 2516



S31/A5349 Results: CONSORT diagram

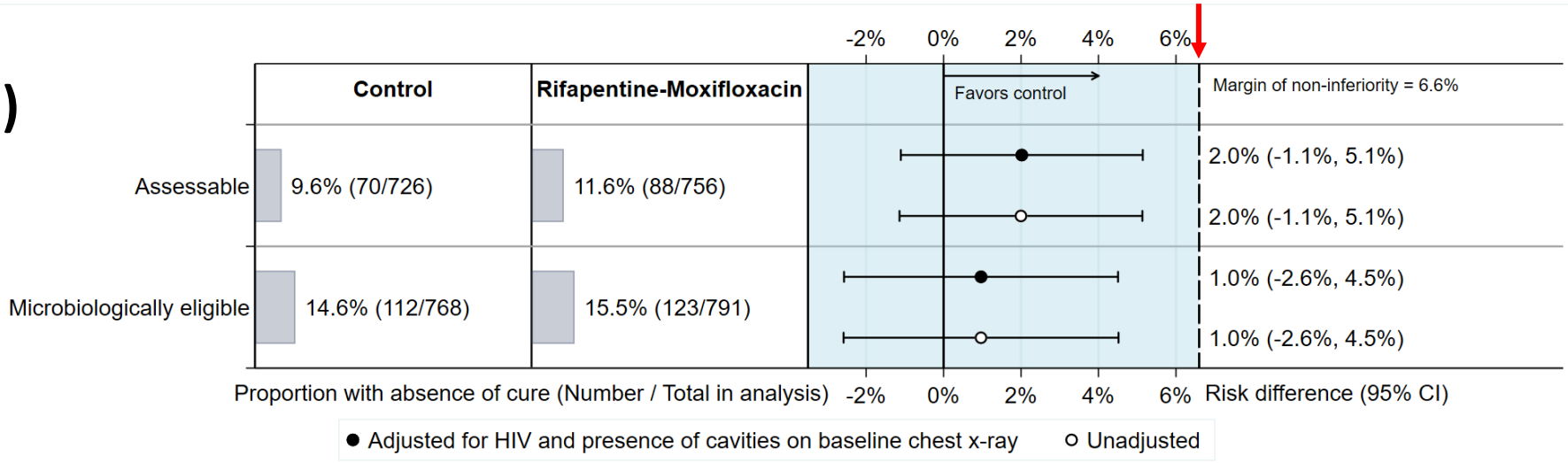


S31/A5349 Results: Baseline Characteristics of Microbiologically Eligible Population

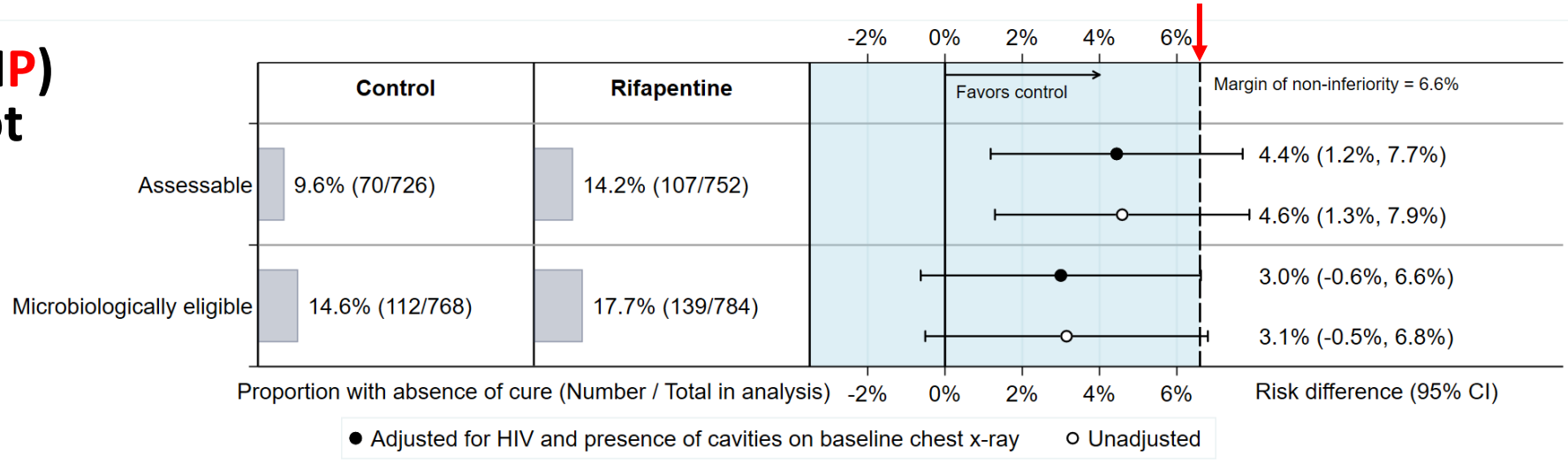
Characteristic	Control	RPT (2HPZE/2HP)	RPT-MOX (2HPZM/2HPM)	Total
Total in analysis population	768	784	791	**2343**
Male sex	544 (70.8%)	563 (71.8%)	563 (71.2%)	**1670 (71.3%)**
Age, median, range	30.9 (13.7- 77.5)	31.0 (14.1- 81.4)	31.0 (14.6- 72.5)	**31.0 (13.7- 81.4)**
Race of Participants				
Asian	86 (11.2%)	93 (11.9%)	89 (11.3%)	**268 (11.4%)**
Black or African American	553 (72%)	571 (72.8%)	552 (69.8%)	**1676 (71.5%)**
White	15 (2%)	8 (1%)	13 (1.6%)	**36 (1.5%)**
More than one race	111 (14.5%)	111 (14.2%)	136 (17.2%)	**358 (15.3%)**
Race not available	3 (0.4%)	1 (0.1%)	1 (0.1%)	**5 (0.2%)**
HIV positive	64 (8.3%)	67 (8.5%)	62 (7.8%)	**193 (8.2%)**
Cavitation on chest X-ray	557 (72.5%)	572 (73%)	572 (72.3%)	**1701 (72.6%)**
BMI, median, IQR	18.9 (17.4- 20.7)	18.9 (17.4- 20.8)	19.0 (17.4- 20.9)	**18.9 (17.4- 20.8)**
Weight, kg, median, IQR	52.9 (48.2- 59.0)	53.3 (47.9- 59.2)	53.0 (48.0- 59.3)	**53.1 (48.0- 59.1)**

Primary Efficacy Results

RPT-MOX (2HPZM/2HPM) regimen met non-inferiority criteria for efficacy in <u>both</u> analyses



RPT (2HPZE/2HP) regimen did not meet non-inferiority criteria for efficacy in either analysis



Outcome status: Favorable (Cure)
Primary efficacy analysis
Assessable analysis population

Outcome	Control (2HRZE/4HR)	RPT (2HPZE/2HP)	RPT-MOX (2HPZM/2HPM)	Total
Total in analysis population	**726**	**752**	**756**	**2234**
Total Favorable	**656 (90.4%)**	**645 (85.8%)**	**668 (88.4%)**	**1969 (88.1%)**
Culture negative at Month 12	643 (88.6%)	636 (84.6%)	656 (86.8%)	1935 (86.6%)
Seen at Month 12, but no sputum produced, or culture contaminated or unevaluable	13 (1.8%)	9 (1.2%)	12 (1.6%)	34 (1.5%)

Note. Percentages are column percent. Denominator is number of participants in each group in assessable population.

Outcome status: Unfavorable (Absence of cure)
Primary efficacy analysis

Assessable analysis population

Outcome	Control (2HRZE/4HR)	RPT (2HPZE/2HP)	RPT-MOX (2HPZM/2HPM)	Total
Total in analysis population	**726**	**752**	**756**	**2234**
Total Unfavorable	**70 (9.6%)**	**107 (14.2%)**	**88 (11.6%)**	**265 (11.9%)**
Total Unfavorable: TB-related	**24 (3.3%)**	**75 (10.0%)**	**45 (6.0%)**	**144 (6.4%)**
Two positive cultures at/after week 17 without intervening negative	11 (1.5%)	63 (8.4%)	34 (4.5%)	108 (4.8%)
Not seen at Month 12, last culture positive for *M. tuberculosis*	11 (1.5%)	4 (0.5%)	3 (0.4%)	18 (0.8%)
Treatment changed/restarted: Clinical recurrence, no positive cultures	1 (0.1%)	5 (0.7%)	4 (0.5%)	10 (0.4%)
Treatment changed/restarted: Extra-pulmonary TB	0	2 (0.3%)	2 (0.3%)	4 (0.2%)
Treatment changed/restarted: Clinical recurrence, 1 positive culture	1 (0.1%)	1 (0.1%)	2 (0.3%)	4 (0.2%)
Total Unfavorable: Not TB-related	**46 (6.3%)**	**32 (4.3%)**	**43 (5.7%)**	**121 (5.4%)**
Withdrawn during treatment: Consent withdrawn (no AE or PPTR)	14 (1.9%)	11 (1.5%)	15 (2.0%)	40 (1.8%)
Treatment changed/restarted: Adverse event	8 (1.1%)	9 (1.2%)	16 (2.1%)	33 (1.5%)
Death during treatment	7 (1.0%)	3 (0.4%)	3 (0.4%)	13 (0.6%)
Withdrawn during treatment: AE then withdrew consent	2 (0.3%)	3 (0.4%)	3 (0.4%)	8 (0.4%)
Withdrawn during treatment: Moved away	7 (1.0%)	0	1 (0.1%)	8 (0.4%)
Treatment changed/restarted: Restart after poor adherence	3 (0.4%)	1 (0.1%)	1 (0.1%)	5 (0.2%)
Withdrawn during treatment: Lost to follow-up	1 (0.1%)	2 (0.3%)	1 (0.1%)	4 (0.2%)
Treatment changed/restarted or withdrawn during treatment: Other	4 (0.6%)	3 (0.4%)	3 (0.4%)	10 (0.4%)

Note. Percentages are column percent. Denominator is number of participants in each group in assessable population.

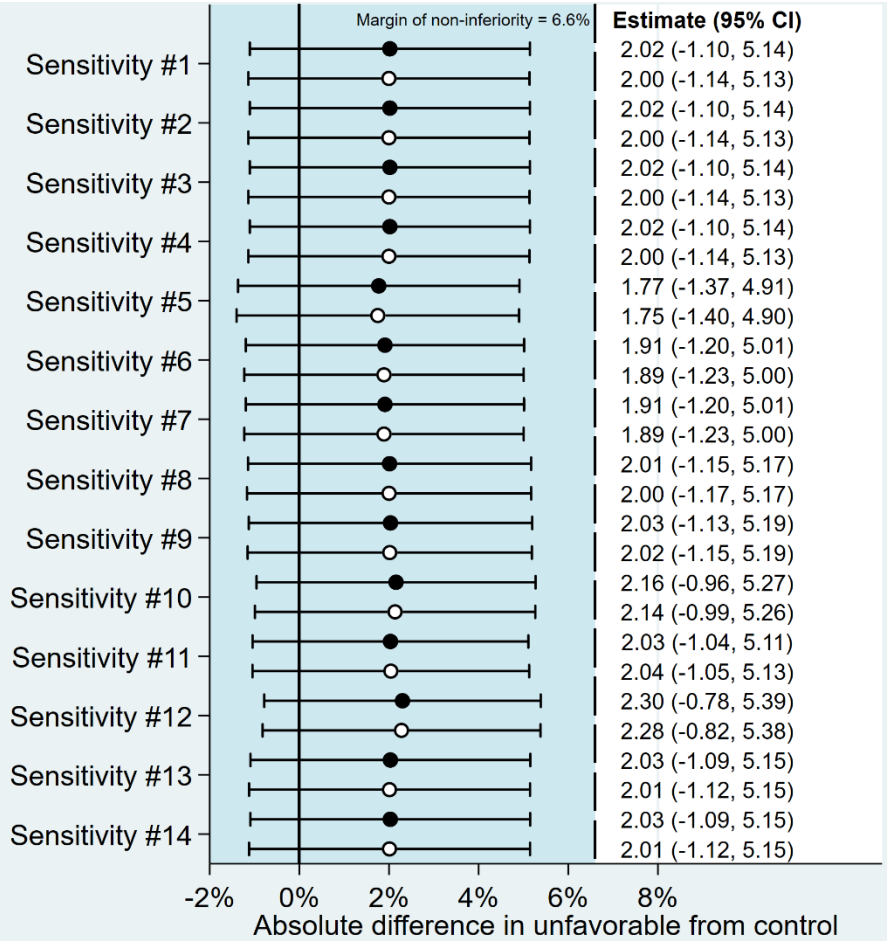
Outcome status: Not assessable
Primary efficacy analysis
Excluded from Assessable population

	Control (2HRZE/4HR)	RPT (2HPZE/2HP)	RPT-MOX (2HPZM/2HPM)	Total
Total Randomized	**829**	**838**	**849**	**2516**
Total Not Assessable	**42 (5.1%)**	**32 (3.8%)**	**35 (4.1%)**	**109 (4.3%)**
Not seen at Month 12, last culture negative for *M. tb*	31 (3.7%)	23 (2.7%)	22 (2.6%)	76 (3.0%)
Withdrawn from treatment due to pregnancy	8 (1.0%)	4 (0.5%)	5 (0.6%)	17 (0.7%)
Death in follow-up not related to TB	3 (0.4%)	3 (0.4%)	8 (0.9%)	14 (0.6%)
Violent or accidental death during treatment	0	1 (0.1%)	0	1 (0.0%)
Exogenous reinfection with *M. tb* and retreatment	0	1 (0.1%)	0	1 (0.0%)

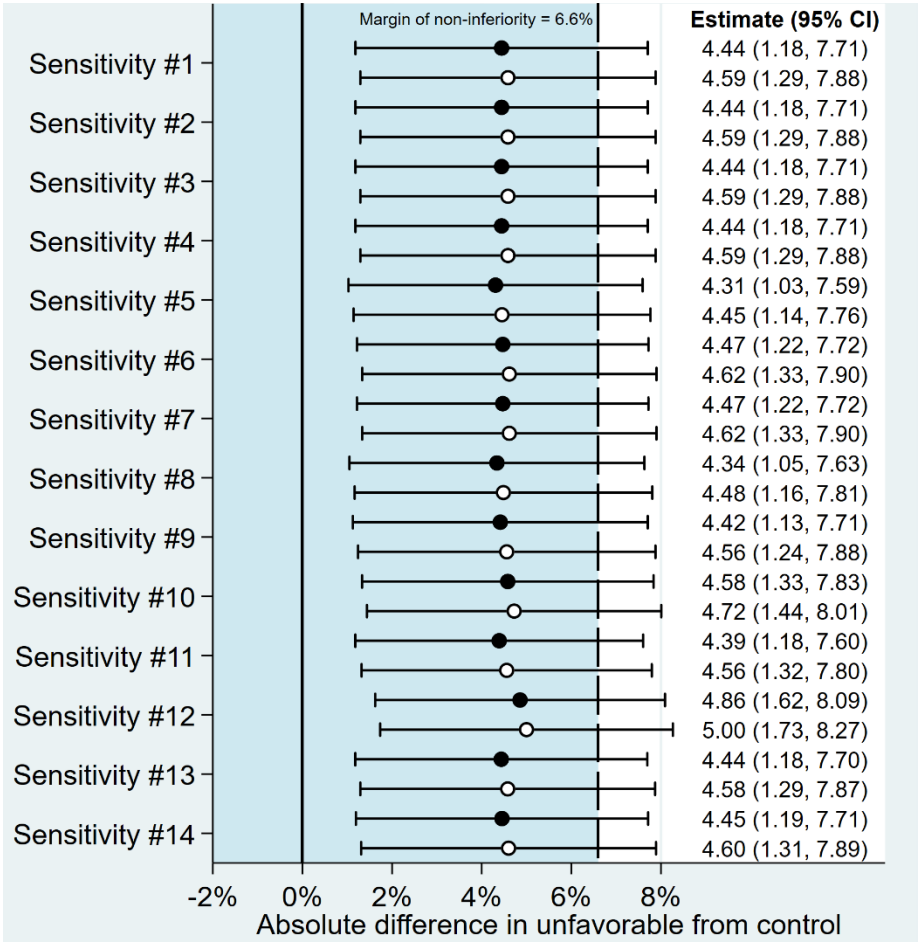
Note. Percentages are column percent. Denominator is total number of enrolled participants in each group.

Primary Efficacy Results: Sensitivity Analyses

RPT-MOX *meets* non-inferiority criteria for efficacy in all sensitivity analyses

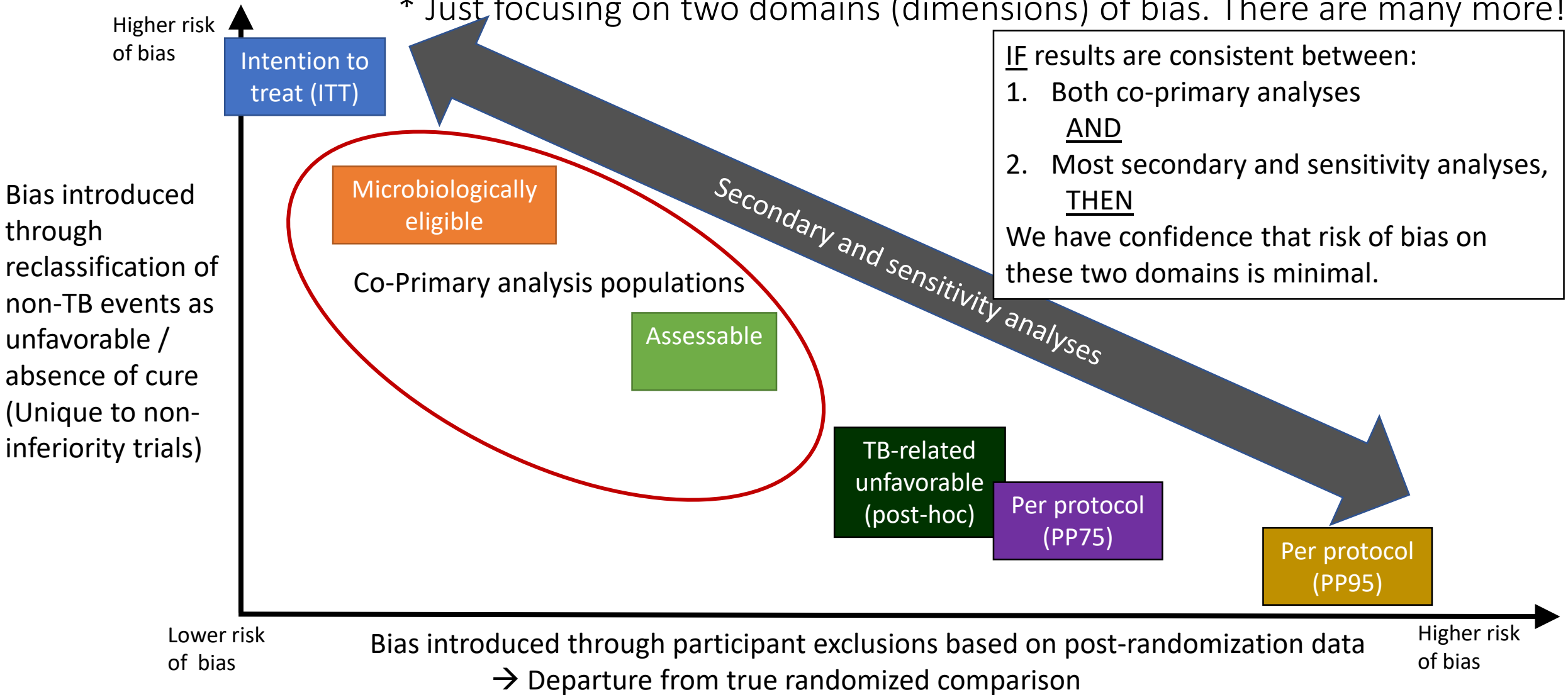


RPT *does not meet* non-inferiority criteria for efficacy in any sensitivity analysis



Risk of bias with different analysis populations*

* Just focusing on two domains (dimensions) of bias. There are many more!

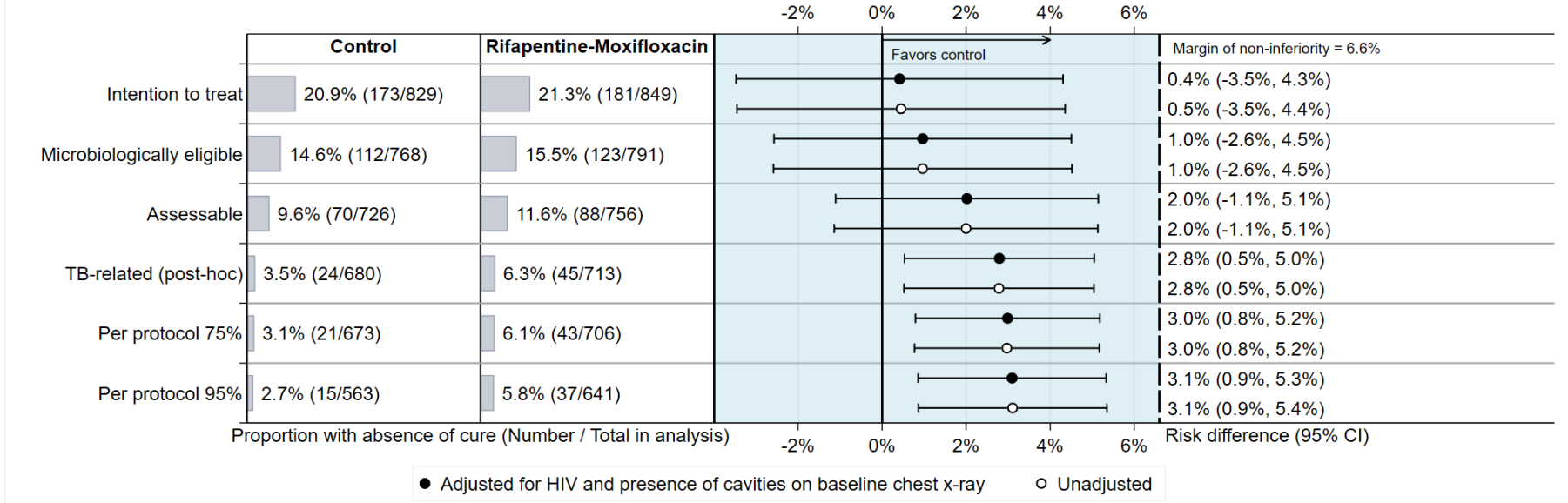


IF results are consistent between:

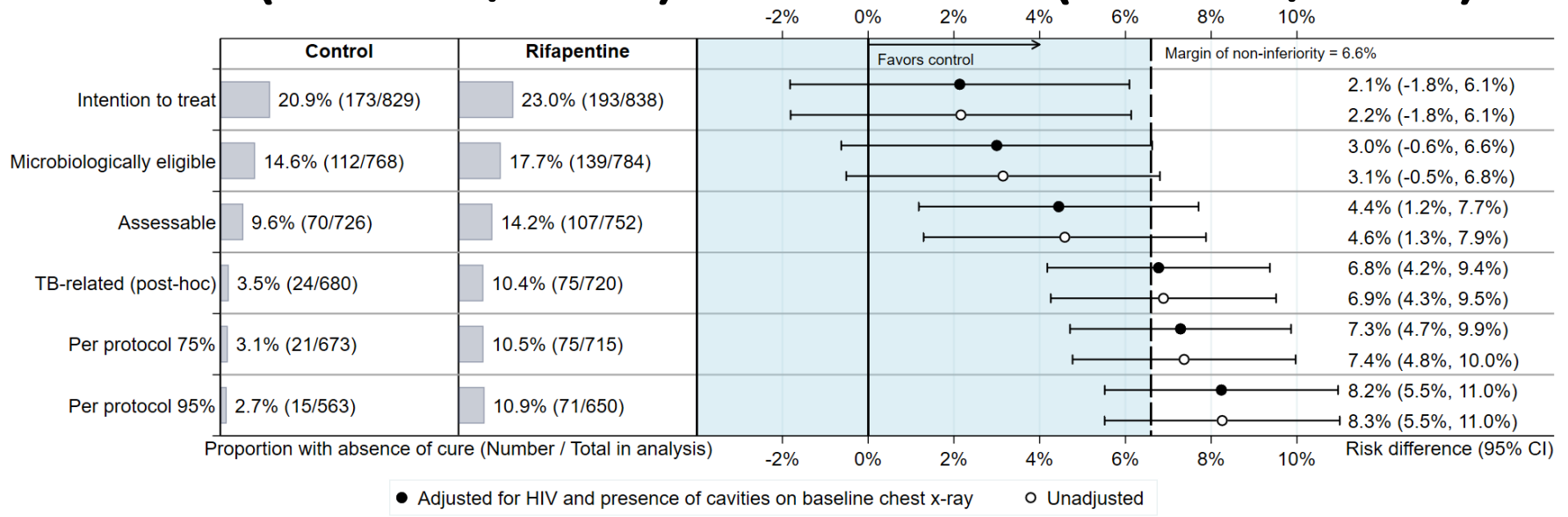
1. Both co-primary analyses
   AND
2. Most secondary and sensitivity analyses,
   THEN

We have confidence that risk of bias on these two domains is minimal.

RPT-MOX (2HPZM/2HPM) vs Control (2HRZE/4HR)

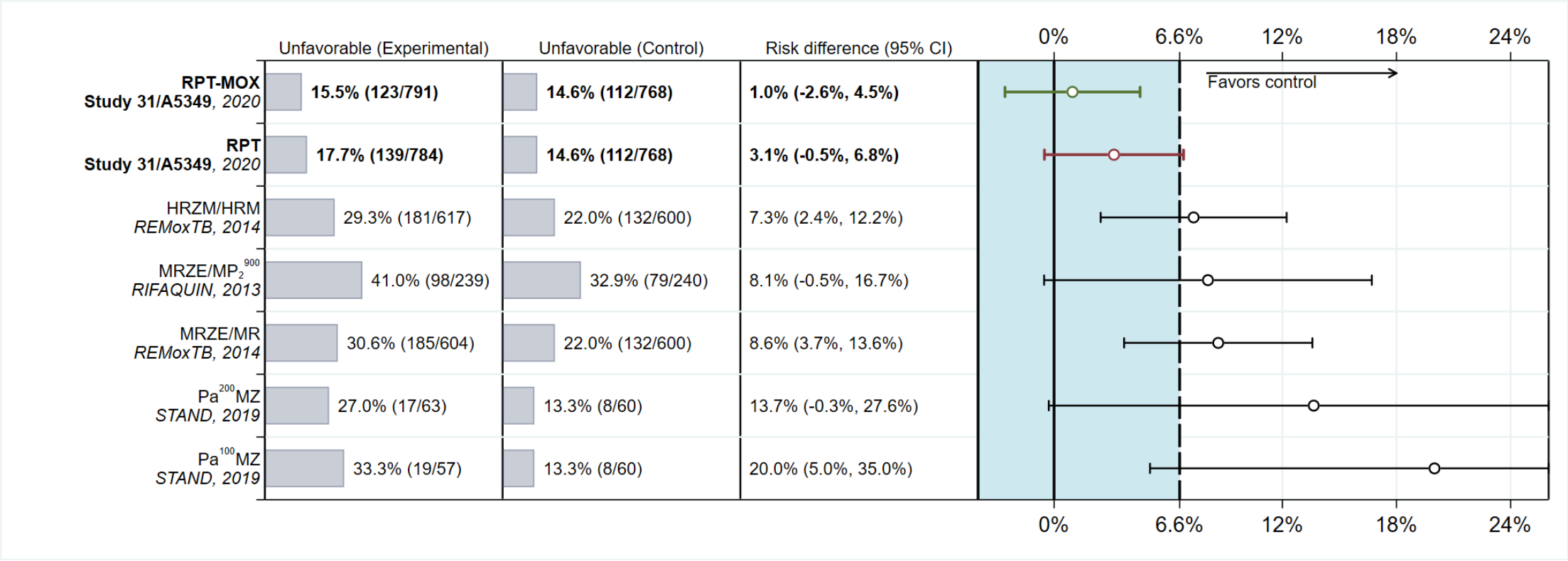


RPT (2HPZE/2HP) vs Control (2HRZE/4HR)



A history of 4-month DS-TB regimens in recent RCTs

Microbiologically Eligible analysis population (often labelled ‘strict MITT’)



E – Ethambutol, G – Gatifloxacin, H – Isoniazid, R – Rifampicin, M – Moxifloxacin, P – Rifapentine, Pa - Pretomanid

OFLOTUB results are secondary 18 months post-randomization.

Subscripts number of days of dosing each week (when not daily), superscripts indicated dosage (mg). Labels show the year of first public presentation of primary results.

Risk difference is unadjusted for comparability across trials.

Treatment of drug-susceptible tuberculosis: rapid communication

- “A review of evidence by WHO has shown similar performance of a shorter treatment regimen compared to the current standard regimen, both in terms of efficacy and safety.”
- “The 4-month regimen, which is shorter, effective and all-oral, would be a preference for many patients and also national TB programmes, allowing faster cure and easing the burden on both patients and the healthcare system.”
- “Shortened treatment has the potential to improve adherence and reduce patient and health system costs.”

June 2021

World Health Organization

Treatment of drug-susceptible tuberculosis: rapid communication

- Implementation and uptake of the new regimen in the short to medium term will be more feasible if the cost of rifapentine is reduced and availability improved.
- It will also require rigorous antibacterial stewardship to ensure the appropriate use of the first-line regimen given that it contains moxifloxacin, an antibiotic usually used for the treatment of drug-resistant TB.

June 2021

World Health Organization

S31/A5349 Summary

1. **2HPZM/2HPM meets non-inferiority criteria for efficacy**
   - Non-inferiority is consistently met in:
     - All primary and secondary analysis populations
     - All sensitivity analyses
     - Consistent in all sub-group analyses
2. **WHO GDG has endorsed the regimen.** Based on the outcomes of the GDG meeting in June, detailed recommendations will be presented in the 2021 update of the ***WHO consolidated guidelines on tuberculosis. Module 4: Treatment - Drug-Susceptible Tuberculosis Treatment.***

S31/A5349 Protocol Team

Payam Nahid* (TBTC Chair)
Susan Dorman* (TBTC Chair)
Susan Swindells^ (ACTG Chair)
Richard Chaisson*^ (ACTG co-Chair)
Ekaterina Kurbatova* (CDC Project Officer)
Patrick Phillips (Statistician)
Kwok-Chiu Chang*
Mark Cotton*^
Andrew Hockey (Sanofi)
Kelly Dooley*^
Melissa Engle*
Courtney Fletcher^
Phan Ha*
Richard Hafner^
Lara Hosey^
John L. Johnson*
Cynthia Lee (CRAG)
Cynthia Merrifield*
Michael Hughes^
Nguyen Viet Nhung*
April Pettit*
Anthony Podany^
Kathleen Robergeau (Westat)
Wadzanai Samaneka^ (ACTG co-Chair)
Erin Sizemore*
Andrew Vernon*
Mark Weiner*
Lisa Wolf*

**TBTC* *^ACTG*

Acknowledgments

- Funding and collaboration: CDC and NIH
- CDC Data and Coordinating Center and DTBE
- Drug supply and TB PK testing: Sanofi
- TBTC DSMB
- Staff of 34 clinical trial sites on 4 continents
- 2516 participants and their families and friends
- Community Representation Advisory Group
- Treatment Action Group

Questions and Discussion

University of California
San Francisco

Center for
Tuberculosis

University of California
San Francisco

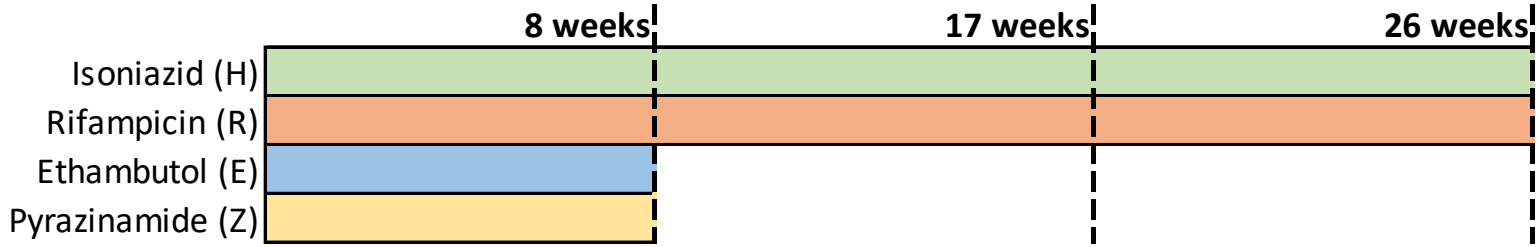
Non-inferiority: What does it mean?

Patrick Phillips
Patrick.Phillips@ucsf.edu

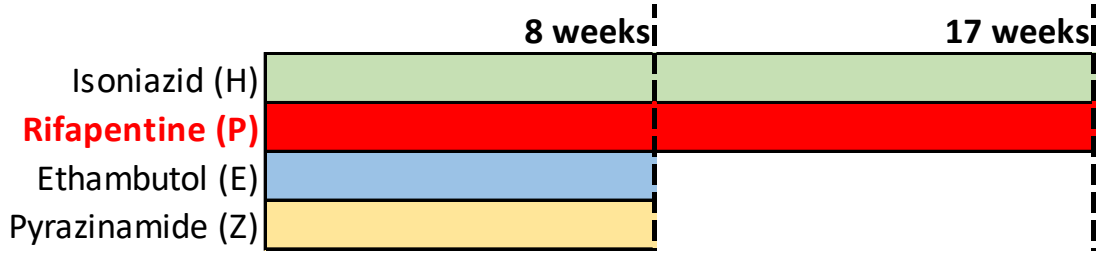
S31/A5349 Study Design

3 arms randomization 1:1:1

Control (2HRZE/4HR)

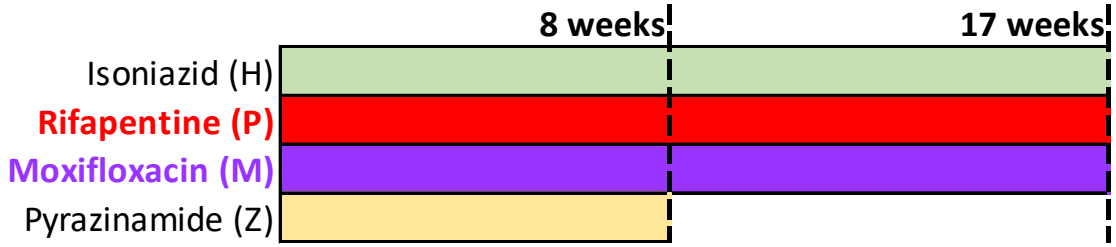


Rifapentine (2HPZE/2HP)



Was not non-inferior to control

Rifapentine-Moxifloxacin (2HPZM/2HPM)

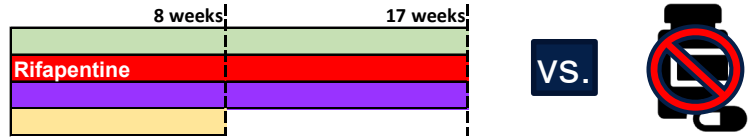


Was non-inferior to control

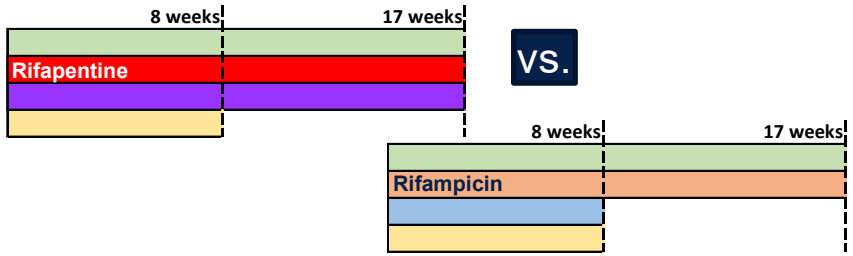
UCSF

S31/A5349 evaluated three efficacy comparisons

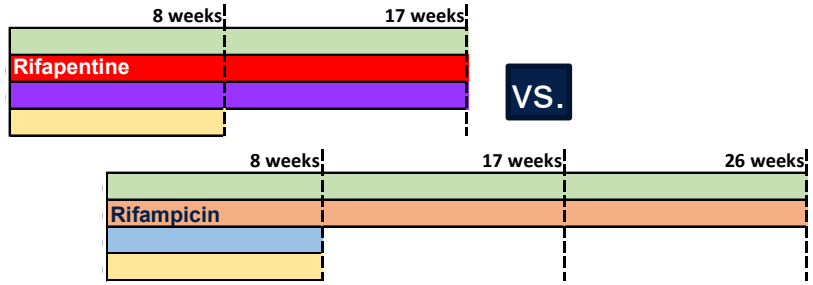
1. Is the novel 4-month regimen better than no treatment?
   - Indirect comparison → External data required for evaluation

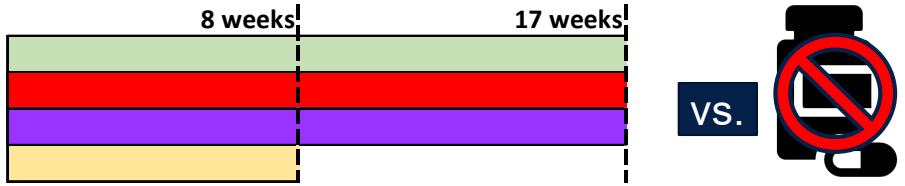


2. Is the novel 4-month regimen better than a 4-month rifampicin regimen?
   - Indirect comparison → External data required for evaluation



3. Is the novel 4-month regimen at least as good as the 6-month rifampicin regimen?
   - Direct comparison → No external data required





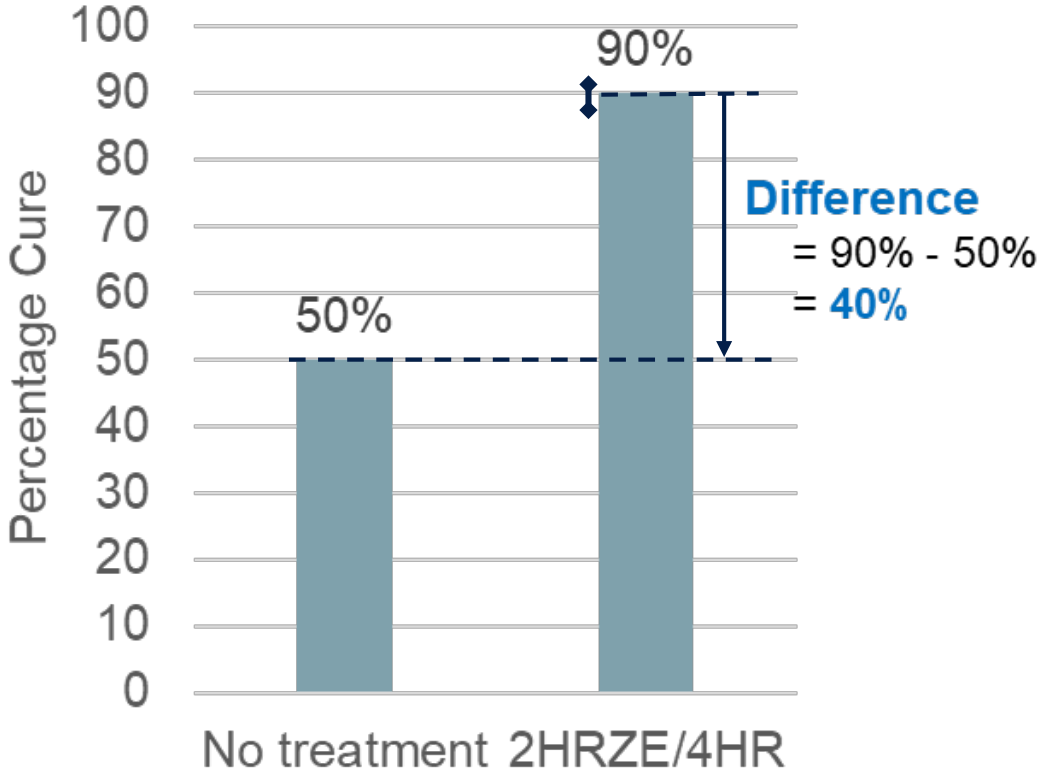
1. Is the novel 4-month regimen better than no treatment?

UCSF

1. Is the novel 4-month regimen better than no treatment?

Indirect comparison → External data required for evaluation

- External data (historical):
  - No treatment: ~50% cure*
  - 2HRZE/4HR: ~90% cure
- Is the **rifapentine-moxifloxacin** regimen better than no treatment?
  - Difference from 2HRZE/4HR:
    - 2.0%, 95% CI (-1.1% to **5.1%**)†
  - **Yes** 



†Assessable analysis population

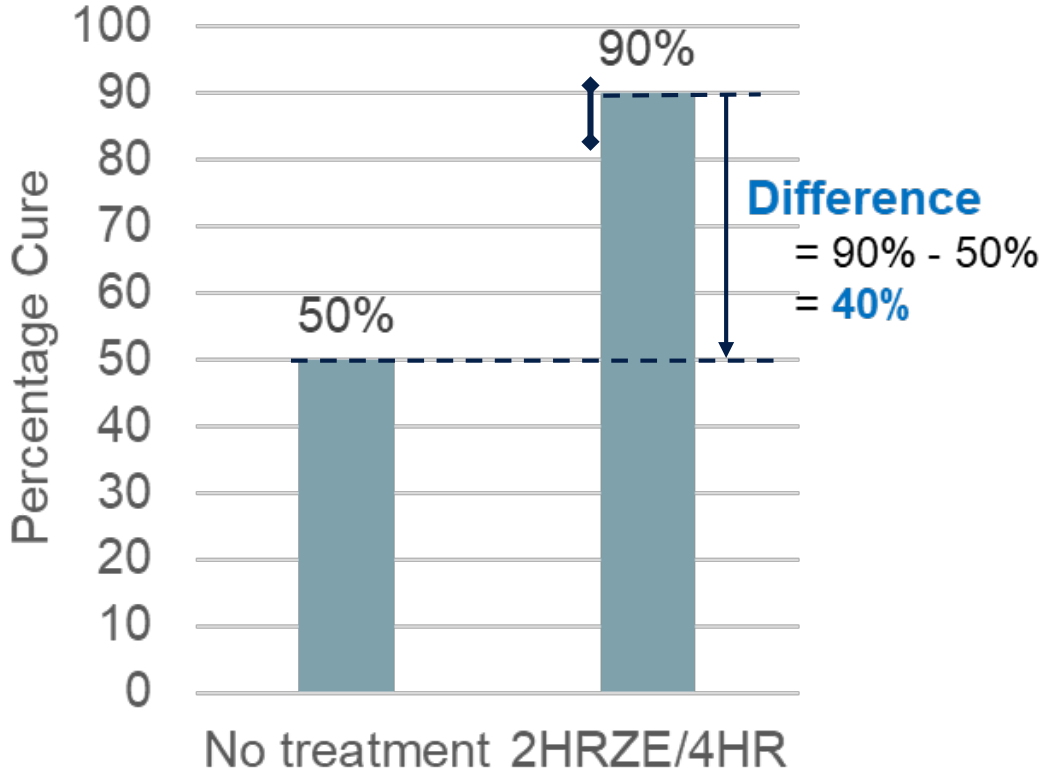
* Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.

UCSF

1. Is the novel 4-month regimen better than no treatment?

Indirect comparison → External data required for evaluation

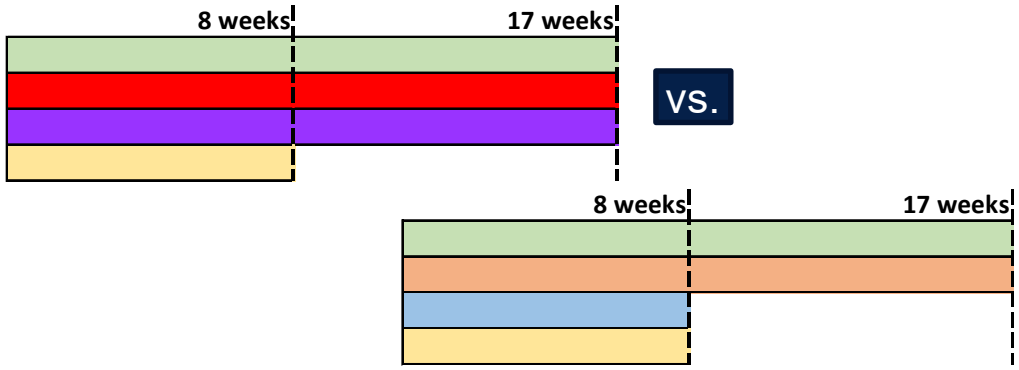
- External data (historical):
  - No treatment: ~50% cure*
  - 2HRZE/4HR: ~90% cure
- Is the **rifapentine** regimen better than no treatment?
  - Difference from 2HRZE/4HR:
    - 4.4%, 95% CI (-1.2% to **7.7%**) †
  - **Yes** 



†Assessable analysis population

* Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.

UCSF



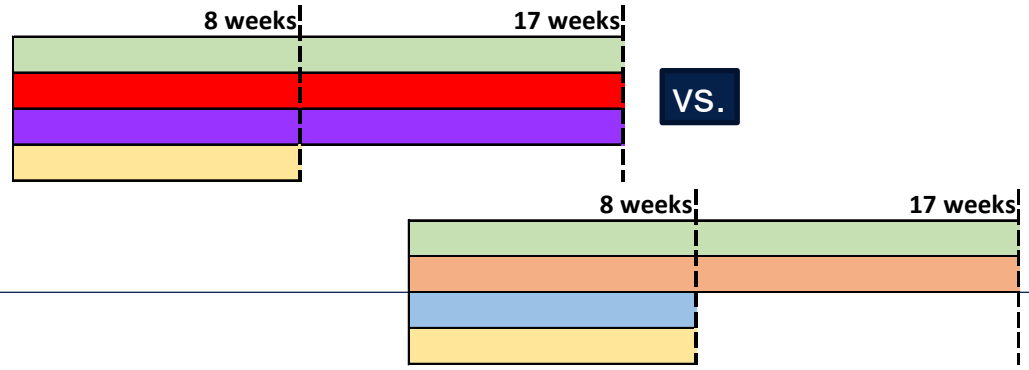
2. Is the novel 4-month regimen better than a 4-month rifampicin regimen?

UCSF

2. Is the novel 4-month regimen better than a 4-month rifampicin regimen?

Indirect comparison → External data required for evaluation

- Why is this comparison important?
  1. A 4-month rifampicin regimen is not used anywhere in the world.
  2. If a novel 4-month regimen is not better than a 4-month rifampicin regimen, it will not be used.
  3. Therefore, we require evidence that a novel 4-month regimen is better than a 4-month rifampicin regimen.



UCSF

2. Is the novel 4-month regimen better than a 4-month rifampicin regimen?

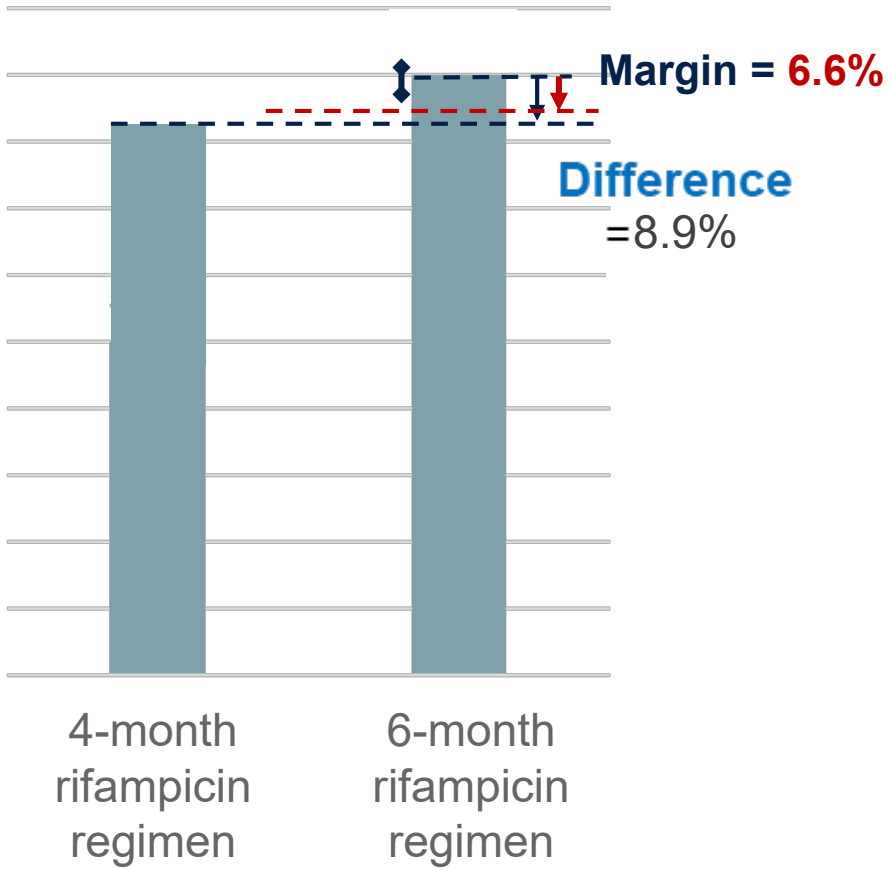
Indirect comparison → External data required for evaluation

- External data (historical – two randomized controlled trials)
  - What do we know about 4-month rifampicin regimens?
    - Pooled relapse in 4-month regimens: 11.8%, 95% CI (8.9% to 15.6%)
    - Pooled relapse in 6-month regimens: 2.9%, 95% CI (2.1% to 3.0%)
      - REMoxTB Statistical Analysis Plan, https://www.nejm.org/doi/suppl/10.1056/NEJMoa1407426/suppl_file/nejmoa1407426_protocol.pdf
      - Difference: 8.9%
    - Used to justify a 6.0% margin of non-inferiority in REMoxTB, RIFAQUIN, OFLOTUB
    - Used to justify 6.6% margin of non-inferiority in S31/A5349
      - Full justification for 6.6% margin in statistical analysis plan runs to 2.5 pages
      - S31/S5349 Statistical Analysis Plan, https://www.nejm.org/doi/suppl/10.1056/NEJMoa2033400/suppl_file/nejmoa2033400_protocol.pdf (p213)

2. Is the novel 4-month regimen better than a 4-month rifampicin regimen?

Indirect comparison → External data required for evaluation

- External data (historical):
  - Difference: 8.9%
- S31/A5349 margin of non-inferiority = 6.6%
- Is the **rifapentine-moxifloxacin** regimen better than a 4-month rifampicin regimen?
  - Difference from 2HRZE/4HR:
    - 2.0%, 95% CI (-1.1% to **5.1%**)†
  - **Yes** ✅



†Assessable analysis population

* Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.

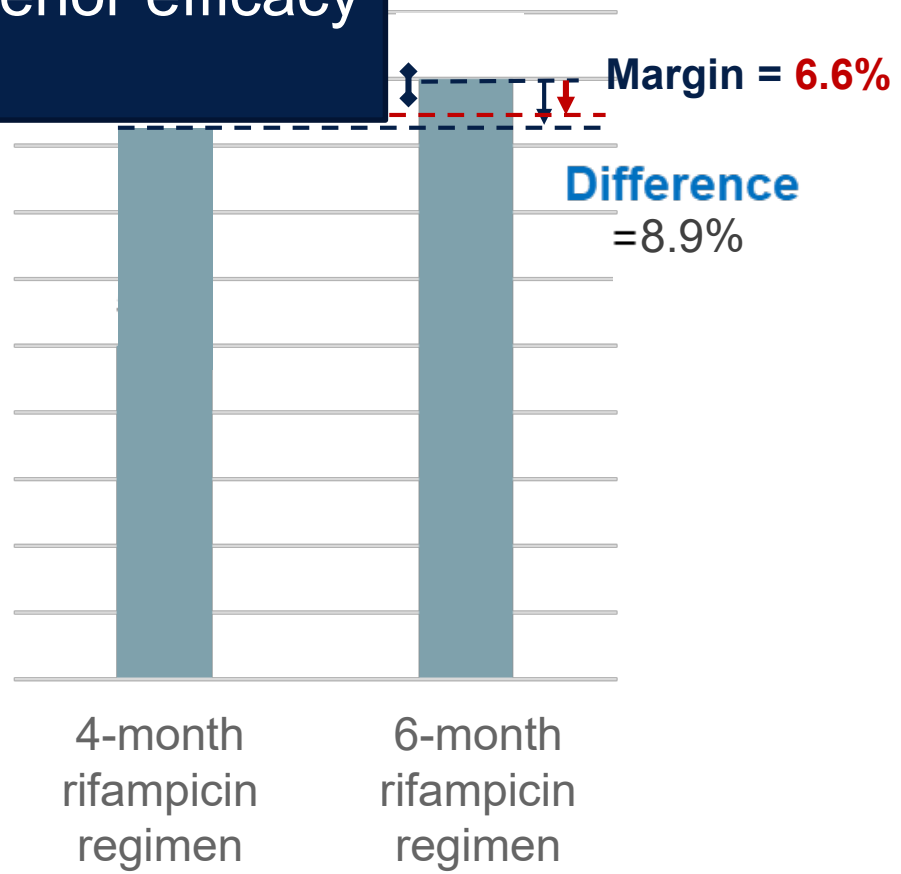
UCSF

- The upper bound of the 95% CI (5.1%) does not exceed the margin of non-inferiority (6.6%).
- Therefore S31/A5349 does provide evidence that the 4-month rifapentine-moxifloxacin regimen has superior efficacy to a 4-month rifampicin regimen.

picin regimen?

- Difference: 8.9%

- S31/A5349 margin of non-inferiority = 6.6%
- Is the **rifapentine-moxifloxacin** regimen better than a 4-month rifampicin regimen?
  - Difference from 2HRZE/4HR:
    - 2.0%, 95% CI (-1.1% to **5.1%**)†
  - **Yes** ✅



†Assessable analysis population

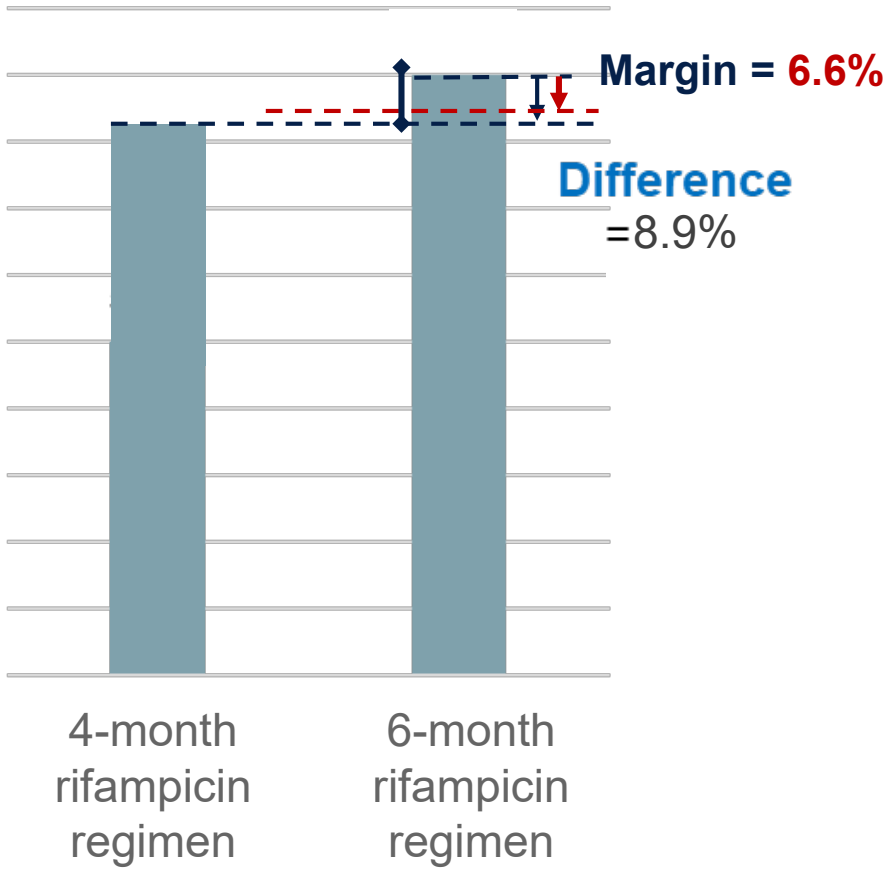
* Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.

UCSF

2. Is the novel 4-month regimen better than a 4-month rifampicin regimen?

Indirect comparison → External data required for evaluation

- External data (historical):
  - Difference: 8.9%
- S31/A5349 margin of non-inferiority = 6.6%
- Is the **rifapentine** regimen better than a 4-month rifampicin regimen?
  - Difference from 2HRZE/4HR:
    - 4.4%, 95% CI (-1.2% to **7.7%**) †
  - **Insufficient evidence**



†Assessable analysis population

* Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.

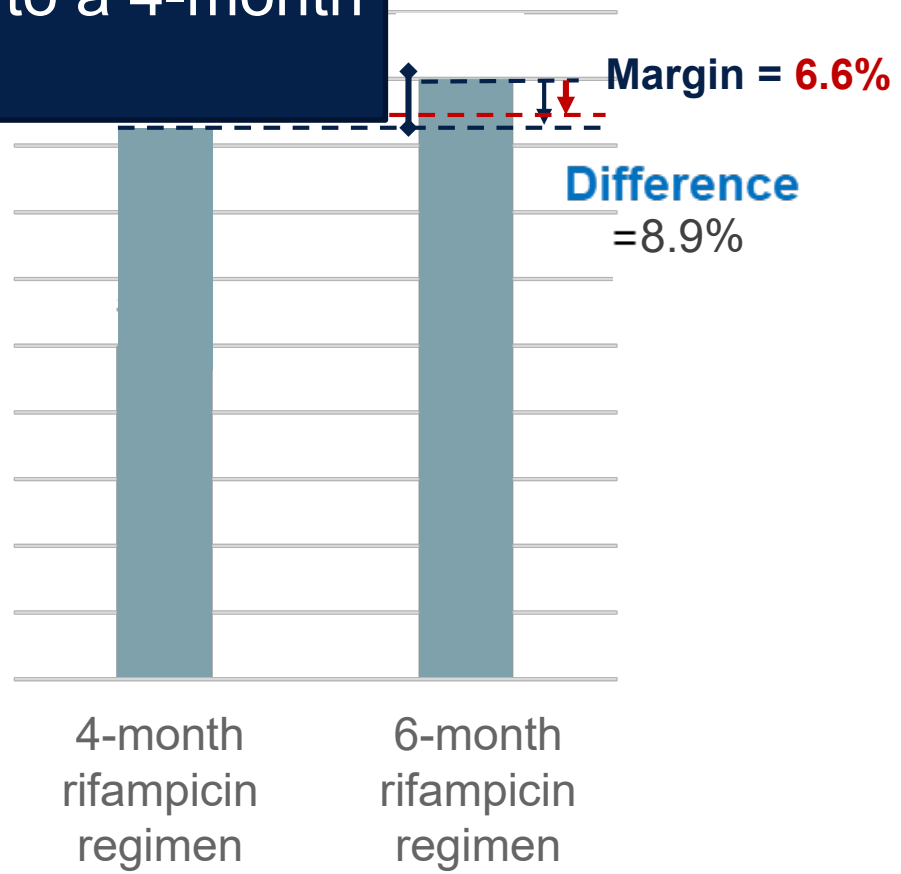
UCSF

- The upper bound of the 95% CI (7.7%) exceeds the margin of non-inferiority (6.6%).
- Therefore S31/A5349 does not provide evidence that the 4-month rifapentine regimen has superior efficacy to a 4-month rifampicin regimen.

picin regimen?

- Difference: 8.9%

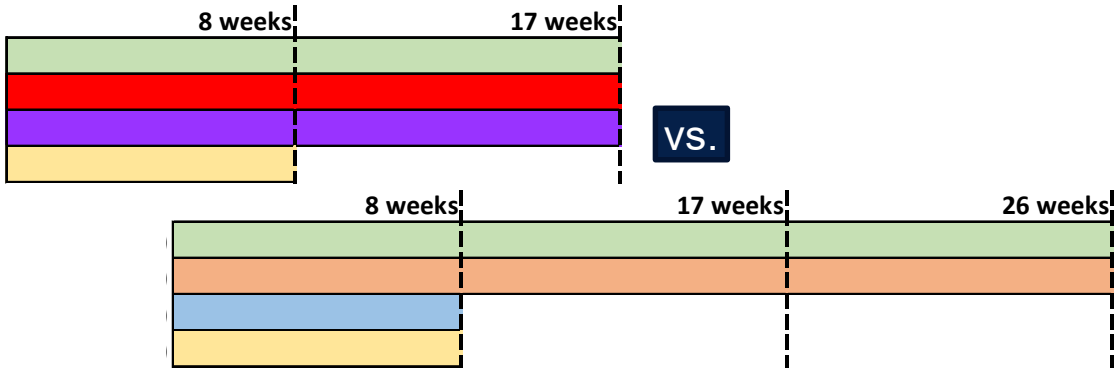
- S31/A5349 margin of non-inferiority = 6.6%
- Is the **rifapentine** regimen better than a 4-month rifampicin regimen?
  - Difference from 2HRZE/4HR:
    - 4.4%, 95% CI (-1.2% to **7.7%**) †
  - **Insufficient evidence**



†Assessable analysis population

* Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS One. 2011;6(4):e17601.

UCSF



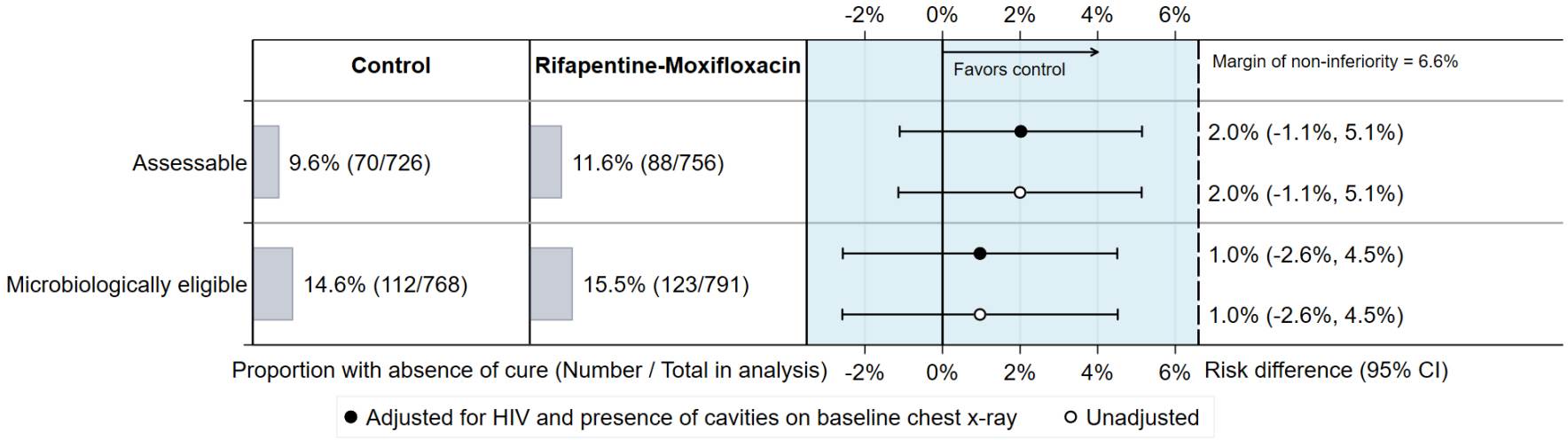
3. Is the novel 4-month regimen at least as good the 6-month rifampicin regimen?

How does the novel 4-month regimen compare to the 6-month rifampicin regimen?

UCSF

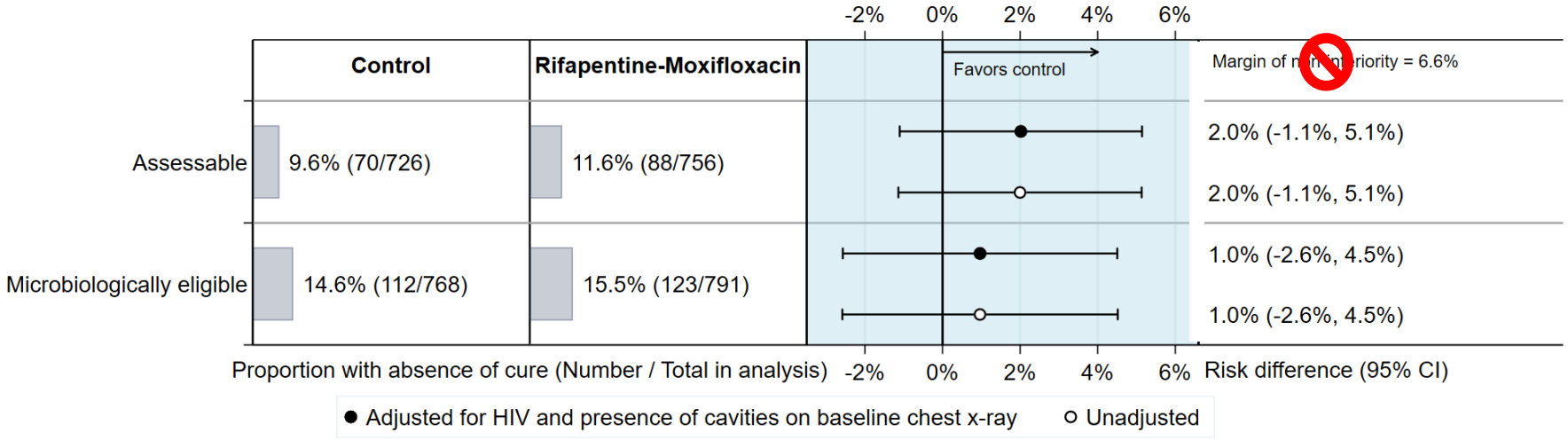
3. Is the novel 4-month regimen at least as good the 6-month rifampicin regimen?

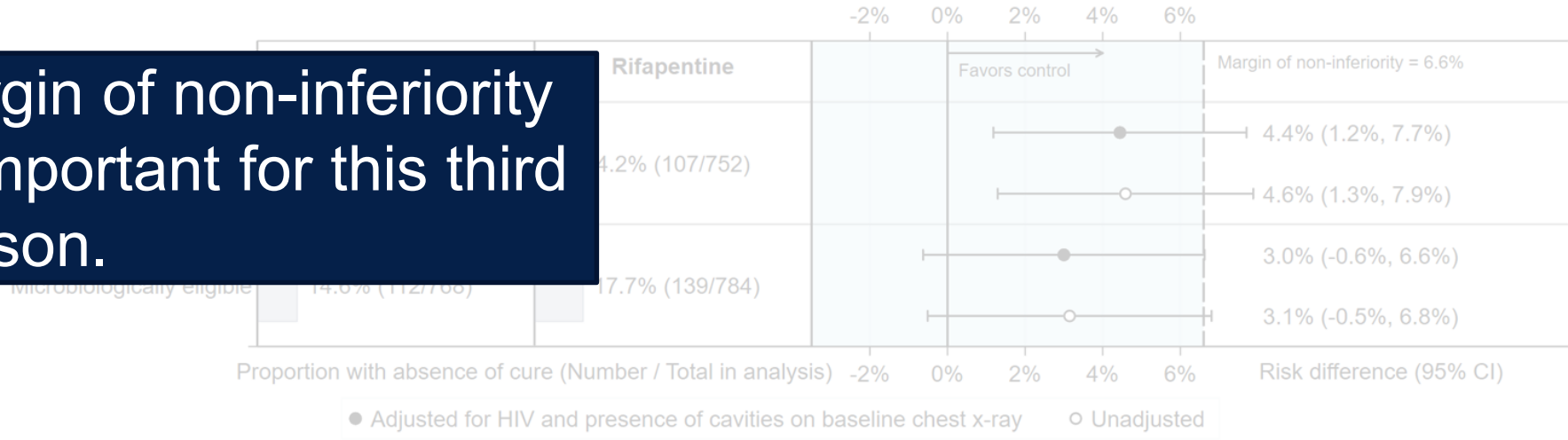
- Direct comparison → No external data required



3. Is the novel 4-month regimen at least as good the 6-month rifampicin regimen?

- Direct comparison → No external data required





The margin of non-inferiority is less important for this third comparison.

3. Is the novel 4-month regimen at least as good the 6-month rifampicin regimen?
A brief refresher on Number Needed to Treat (NNT)

- The Number Needed to Treat (NNT) is the average number of patients who need to be treated to prevent one additional bad outcome.

- A minimally effective treatment has a high NNT
  - More patients need to be treated to prevent one bad outcome

Minimally effective

- A highly effective treatment has a low NNT
  - Fewer patients need to be treated to prevent one bad outcome
  - A perfect treatment for a uniformly fatal disease, as compared to placebo, will have NNT = 1
    - One bad outcome (death) is prevented for every patient treated

Highly effective

Olliaro PL, Vaillant M. Designing noninferiority tuberculosis treatment trials: Identifying practical advantages for drug regimens with acceptable effectiveness. PLoS Med. 2019;16(7):e1002850.

https://en.wikipedia.org/wiki/Number_needed_to_treat

3. Is the novel 4-month regimen at least as good the 6-month rifampicin regimen?

NNT = Number Needed to Treat

- When considering NNT for a non-inferiority trial, the novel regimen is the comparator

- For a non-inferiority trial, we consider NNT as follows:
  - Suppose you are considering introducing the **rifapentine-moxifloxacin** regimen.
  - How high would the NNT of the 6-month rifampicin regimen need to be to prevent you from doing so?

3. Is the novel 4-month regimen at least as good the 6-month rifampicin regimen?

NNT = Number Needed to Treat

- For the **rifapentine-moxifloxacin** regimen, as compared to 2HRZE/4HR, the absolute difference was 2.0%† and the NNT is 50.

- Compared to the 4-month **rifapentine-moxifloxacin** regimen, you would need to treat 50 patients with the 6-month rifampicin regimen to prevent 1 additional relapse (NNT = 50).

- This corresponds to an extra 100 months of treatment to prevent 1 relapse. [(6 – 4) * 50 = 100]
  - What is the cost to the health system of 100 additional months of DOT?
  - What is the cost to the patient of an additional 2 months of treatment?
  - What is the cost to the patient, health system, and community of 1 additional relapse?

†Assessable analysis population

3. Is the novel 4-month regimen at least as good the 6-month rifampicin regimen?

NNT = Number Needed to Treat

- If we look at the extreme upper bound of the 95% CI:
  - Compared to the 4-month **rifapentine-moxifloxacin** regimen, it could be as few as 20 patients that would need to be treated with the 6-month rifampicin regimen to prevent 1 additional relapse.
  - Lower bound of 95% CI of NNT = 20

Conclusions

1. Both **rifapentine** and **rifapentine-moxifloxacin** regimens have superior efficacy to no treatment.

2. The **rifapentine-moxifloxacin** regimen has superior efficacy to a 4-month rifampicin regimen.
   There is insufficient evidence to say whether the **rifapentine** regimen has superior efficacy to a 4-month rifampicin regimen.

3. Compared to the 4-month **rifapentine-moxifloxacin** regimen, you would need to treat 50 patients with the 6-month rifampicin regimen to prevent 1 additional relapse (NNT = 50).

Center for
Tuberculosis

UCSF

University of California
San Francisco

Questions and Discussion

Outcome	Microbiologically Eligible Population				Assessable Population			
	Control (N=768)	Rifapentine–Moxifloxacin (N=791)	Rifapentine (N=784)	Total (N=2343)	Control (N=726)	Rifapentine–Moxifloxacin (N=756)	Rifapentine (N=752)	Total (N=2234)
Favorable								
Participants with outcome — no. (%)	656 (85.4)	668 (84.5)	645 (82.3)	1969 (84.0)	656 (90.4)	668 (88.4)	645 (85.8)	1969 (88.1)
Adjusted difference from control — percentage points (95% CI)	NA	1.0 (–2.6 to 4.5)	3.0 (–0.6 to 6.6)	NA	NA	2.0 (–1.1 to 5.1)	4.4 (1.2 to 7.7)	NA
Participant had negative culture at month 12 — no. (%)	643 (83.7)	656 (82.9)	636 (81.1)	1935 (82.6)	643 (88.6)	656 (86.8)	636 (84.6)	1935 (86.6)
Participant was seen at month 12 but no sputum was produced or cultures were contaminated but without evidence of *M. tuberculosis* — no. (%)	13 (1.7)	12 (1.5)	9 (1.1)	34 (1.5)	13 (1.8)	12 (1.6)	9 (1.2)	34 (1.5)
Unfavorable								
Participants with outcome — no. (%)	112 (14.6)	123 (15.5)	139 (17.7)	374 (16.0)	70 (9.6)	88 (11.6)	107 (14.2)	265 (11.9)
Outcome related to tuberculosis — no. (%)	24 (3.1)	45 (5.7)	75 (9.6)	144 (6.1)	24 (3.3)	45 (6.0)	75 (10.0)	144 (6.4)
Two consecutive positive cultures at or after week 17†	11 (1.4)	34 (4.3)	63 (8.0)	108 (4.6)	11 (1.5)	34 (4.5)	63 (8.4)	108 (4.8)
Participant not seen at month 12 but had positive culture when last seen	11 (1.4)	3 (0.4)	4 (0.5)	18 (0.8)	11 (1.5)	3 (0.4)	4 (0.5)	18 (0.8)
Clinical diagnosis of tuberculosis recurrence and treatment restarted	2 (0.3)	8 (1.0)	8 (1.0)	18 (0.8)	2 (0.3)	8 (1.1)	8 (1.1)	18 (0.8)
Outcome not related to tuberculosis — no. (%)	46 (6.0)	43 (5.4)	32 (4.1)	121 (5.2)	46 (6.3)	43 (5.7)	32 (4.3)	121 (5.4)
Consent withdrawn during treatment period with no adverse event reported	14 (1.8)	15 (1.9)	11 (1.4)	40 (1.7)	14 (1.9)	15 (2.0)	11 (1.5)	40 (1.8)
Change in treatment because of adverse event	8 (1.0)	16 (2.0)	9 (1.1)	33 (1.4)	8 (1.1)	16 (2.1)	9 (1.2)	33 (1.5)
Death during treatment period	7 (0.9)	3 (0.4)	3 (0.4)	13 (0.6)	7 (1.0)	3 (0.4)	3 (0.4)	13 (0.6)
Loss to follow-up during treatment period	8 (1.0)	2 (0.3)	2 (0.3)	12 (0.5)	8 (1.1)	2 (0.3)	2 (0.3)	12 (0.5)
Consent withdrawn during treatment period after occurrence of adverse event	2 (0.3)	3 (0.4)	3 (0.4)	8 (0.3)	2 (0.3)	3 (0.4)	3 (0.4)	8 (0.4)
Treatment changed or restarted for other reasons	7 (0.9)	4 (0.5)	4 (0.5)	15 (0.6)	7 (1.0)	4 (0.5)	4 (0.5)	15 (0.7)

Questions and Discussion

Study 31/A5349: Subgroup Analyses

Richard E. Chaisson, MD
Center for AIDS Research
Center for TB Research
Johns Hopkins University

Selected eligibility criteria

- Inclusion
  - Positive sputum smear for AFB or positive *Xpert MTB* with medium or high result
  - Age ≥12 y.o.
  - If HIV-positive, CD4 T cell count ≥100 cells/mm^3
    - EFV-1: On EFV with UD VL at enrollment
    - EFV-2: ART naïve, start EFV at 8 weeks
- Exclusion
  - >5 days systemic TB treatment within previous 6 months
  - >5 days treatment with anti-TB drugs within previous 30 days
  - TB of CNS, bones or joints, miliary, pericardial
  - Weight <40 kg

Efficacy analyses in key subgroups, including groups prespecified in Statistical Analysis Plan

- HIV-infected
- Adolescents
- People with diabetes
- Cavitation on baseline chest radiograph
- Other clinical, radiographic and microbiologic characteristics, including WHO scale smear quantification, MGIT days to detection, GeneXpert MTB/RIF Cycle Threshold
- Composite measures of disease burden

Baseline Characteristics of Microbiologically Eligible Population

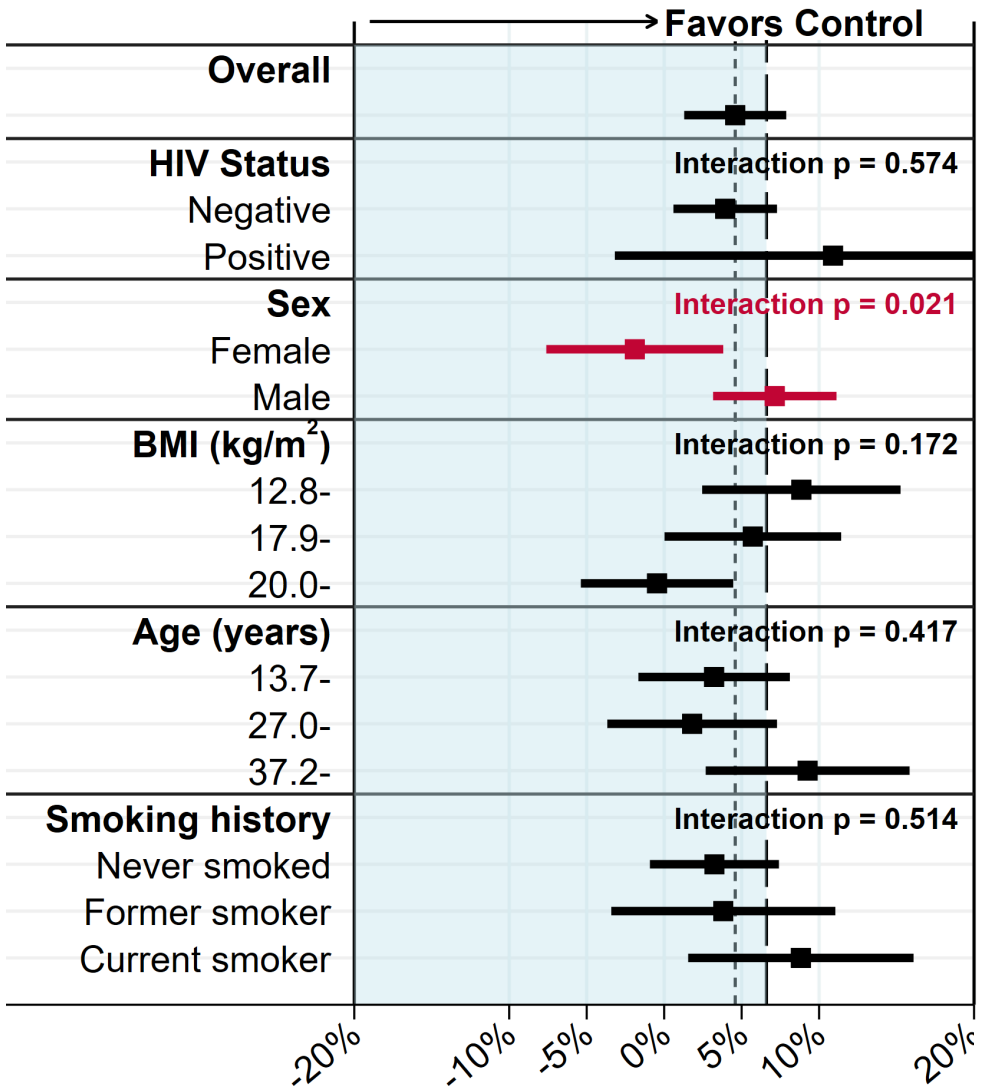
Characteristic	Category	Control (2HRZE/4HR)	RPT (2HPZE/2HP)	RPT-MOX (2HPZM/2HPM)	Total
Total in analysis population		**768**	**784**	**791**	**2343**
Male sex		544 (70.8%)	563 (71.8%)	563 (71.2%)	**1670 (71.3%)**
Age group	12-17 years	19 (2.5%)	19 (2.4%)	25 (3.2%)	**63 (2.7%)**
	18-35 years	479 (62.4%)	485 (61.9%)	486 (61.4%)	**1450 (61.9%)**
	>35 years	270 (35.2%)	280 (35.7%)	280 (35.4%)	**830 (35.4%)**
Race of Participants	Asian	86 (11.2%)	93 (11.9%)	89 (11.3%)	**268 (11.4%)**
	Black or African American	553 (72%)	571 (72.8%)	552 (69.8%)	**1676 (71.5%)**
	White	15 (2%)	8 (1%)	13 (1.6%)	**36 (1.5%)**
	More than one race	111 (14.5%)	111 (14.2%)	136 (17.2%)	**358 (15.3%)**
	Race not available	3 (0.4%)	1 (0.1%)	1 (0.1%)	**5 (0.2%)**
HIV positive		64 (8.3%)	67 (8.5%)	62 (7.8%)	**193 (8.2%)**
CD4 Count (among HIV pos)	Median (IQR)	334 (249 - 485)	351 (221 - 437)	346 (253 - 458)	**344 (223 – 455)**
Cavitation on chest X-ray		557 (72.5%)	572 (73%)	572 (72.3%)	**1701 (72.6%)**
Weight group (at enrollment)	<55kg	461 (60%)	468 (59.7%)	472 (59.7%)	**1401 (59.8%)**
	=55-75 kg	289 (37.6%)	294 (37.5%)	297 (37.5%)	**880 (37.6%)**
	>75 kg	18 (2.3%)	22 (2.8%)	22 (2.8%)	**62 (2.6%)**
Weight, kg	Median (IQR)	52.9 (48.2 - 59.0)	53.3 (47.9 - 59.2)	53.0 (48.0 - 59.3)	**53.1 (48.0 - 59.1)**
etes	Yes	30 (4%)	16 (2%)	35 (4%)	**81 (3.5%**

TBTC TB Trials Consortium

ACTG AIDS CLINICAL TRIALS GROUP

Sub-group analyses (Assessable analysis population)
RPT Regimen vs Control

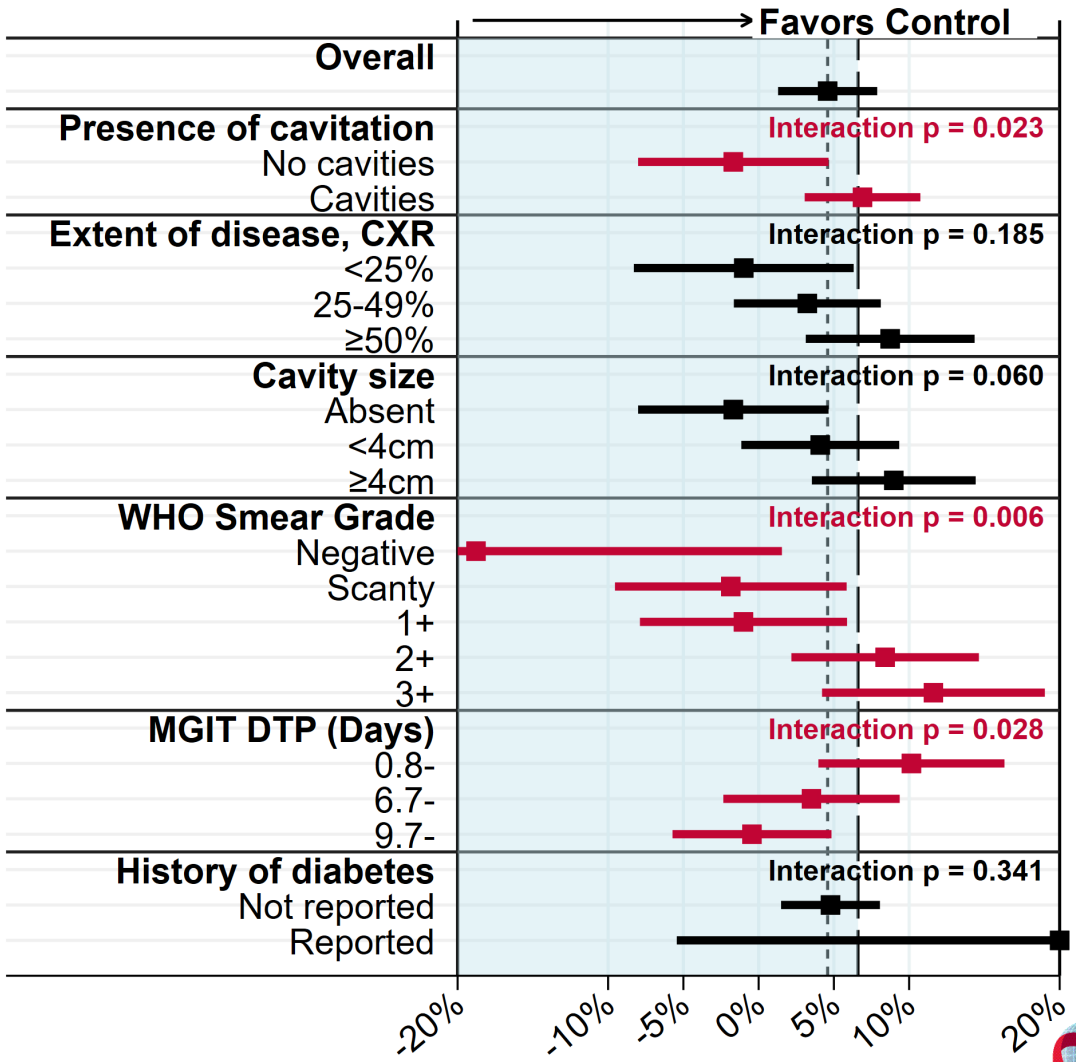
- There was evidence that the treatment effect for RPT Regimen differed among some sub-groups



Sub-group analyses (Assessable analysis population)
RPT Regimen vs Control

NI margin 6.6%

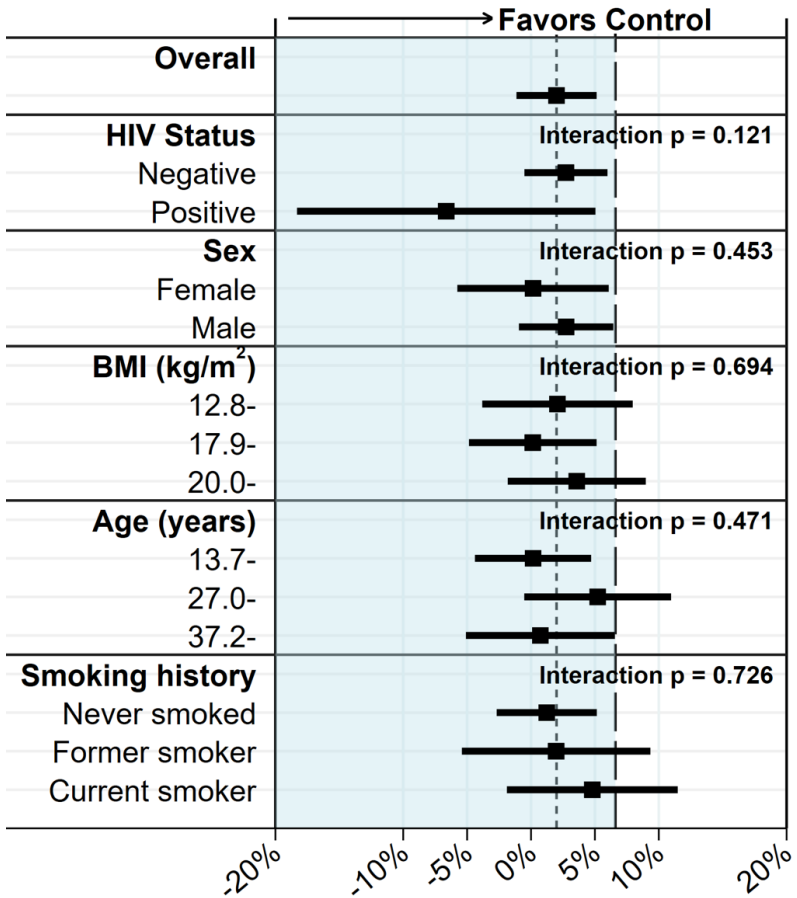
- The RPT regimen did not meet non-inferiority overall, but was non-inferior for participants:
  - Females
  - With no cavities on CXR
  - With low AFB smear grade
  - With high TTD on MGIT (i.e., lower burden)



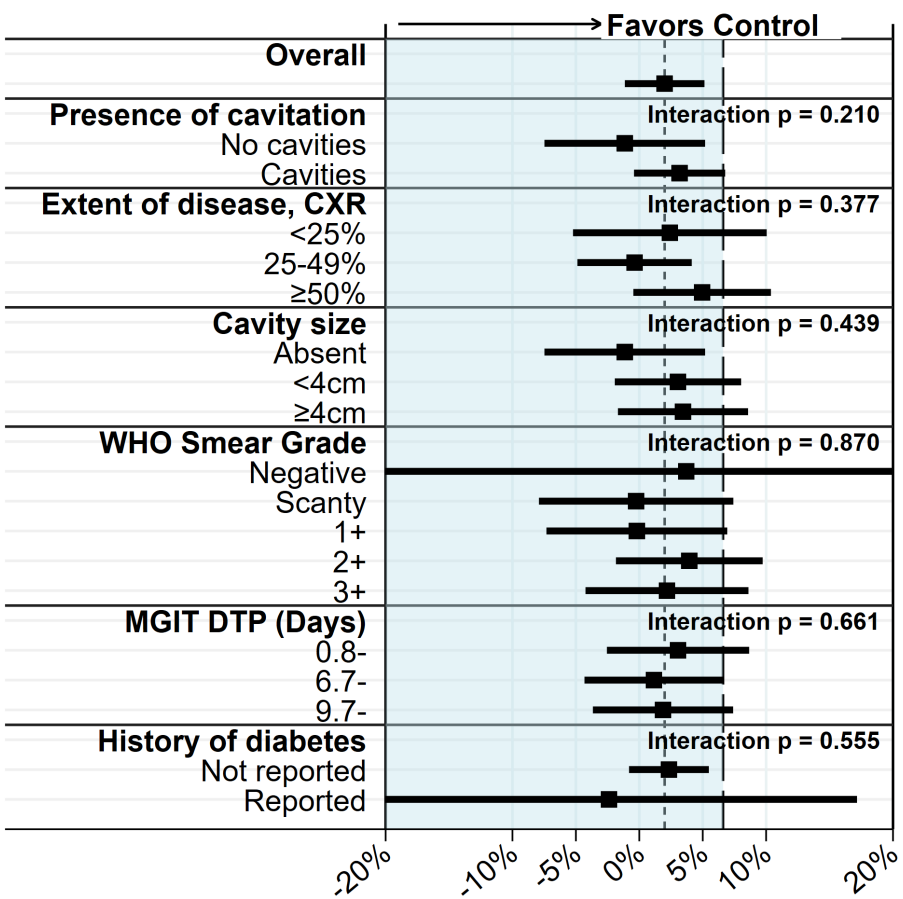
Sub-group analyses (Assessable analysis population)
MOX-RPT Regimen vs Control

- All interaction tests were non-significant for MOX-RPT Regimen
- **There was no evidence that the treatment effect differed by any sub-group for the MOX-RPT Regimen**

NI margin 6.6%



NI margin 6.6%



Results by HIV Status

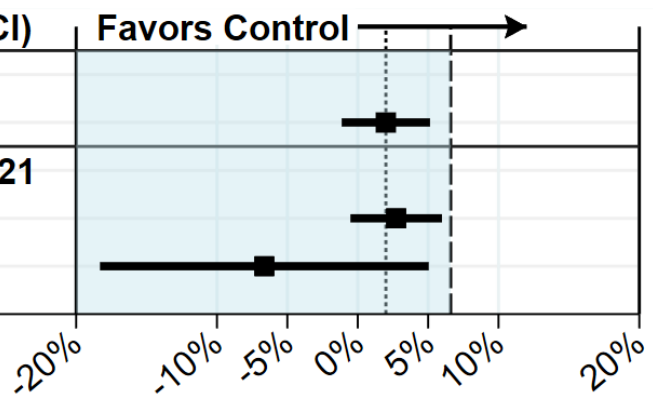
Microbiologically Eligible Population (N=2343)	HIV-seropositive N=194	HIV-negative* N=2148
Median (IQR) age, years	36 (30 - 43)	30 (24 - 41)
Male sex	120 (62%)	**1549 (72%)**
Race		
Asian	0 (0%)	268 (12%)
Black or African American	**180 (93%)**	1495 (70%)
White	2 (1%)	34 (2%)
More than one race	12 (6%)	346 (16%)
Missing	0 (0%)	5 (0.2%)
Median (IQR) baseline BMI, kg/m^2	19 (17 - 22)	19 (17 - 21)
Cavitary Disease	139 (72%)	1563 (73%)
Current smoking	41 (21%)	500 (23%)
Diabetes Mellitus	1 (0.5%)	**76 (3%)**

Pettit, et al., CROI 2021

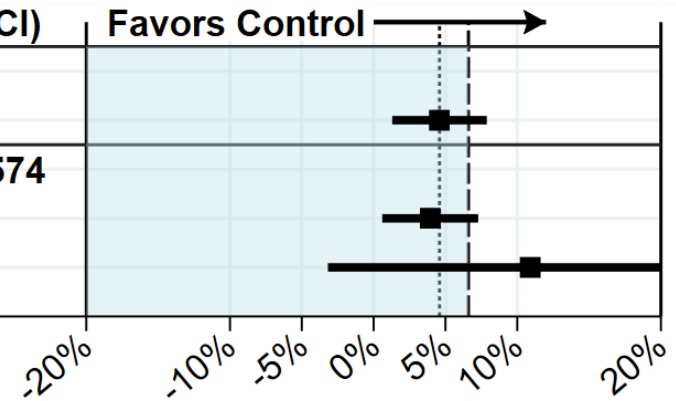
Results by HIV Status

Efficacy outcomes (% favorable)	Control	Rifapentine Moxifloxacin	Rifapentine	Total
Microbiologically eligible	50/64 (78%)	**53/62 (85%)**	48/68 (71%)	151/194 (78%)
Assessable	50/59 (85%)	**53/58 (91%)**	48/65 (74%)	151/182 (83%)

	Rifapentine-Moxifloxacin	Control	Unadj. diff. (95% CI)
Overall	88 (11.6%) / 756	70 (9.6%) / 726	2.0 (-1.1, 5.1)
HIV Status			**Interaction p = 0.121**
Negative	83 (11.9%) / 698	61 (9.2%) / 666	2.7 (-0.5, 6.0)
Positive	5 (8.6%) / 58	9 (15.3%) / 59	-6.6 (-18.3, 5.0)



	Rifapentine	Control	Unadj. diff. (95% CI)
Overall	107 (14.2%) / 752	70 (9.6%) / 726	4.6 (1.3, 7.9)
HIV Status			**Interaction p = 0.574**
Negative	90 (13.1%) / 687	61 (9.2%) / 666	3.9 (0.6, 7.3)
Positive	17 (26.2%) / 65	9 (15.3%) / 59	10.9 (-3.2, 25.0)



TB Trials Consortium

ACTG AIDS CLINICAL TRIALS GROUP

S31 HIV EFV-staging Safety Schema

Staged enrollment of participants with HIV infection:

- **EFV-1:** Stable on EFV ART ≥ 30 d
- Pause after n=31
- Confirm safety before continuing EFV-1 and starting EFV-2
- **EFV-2**: Starting ART after entry
- Pause after n=31
- Confirm safety before continuing EFV-2

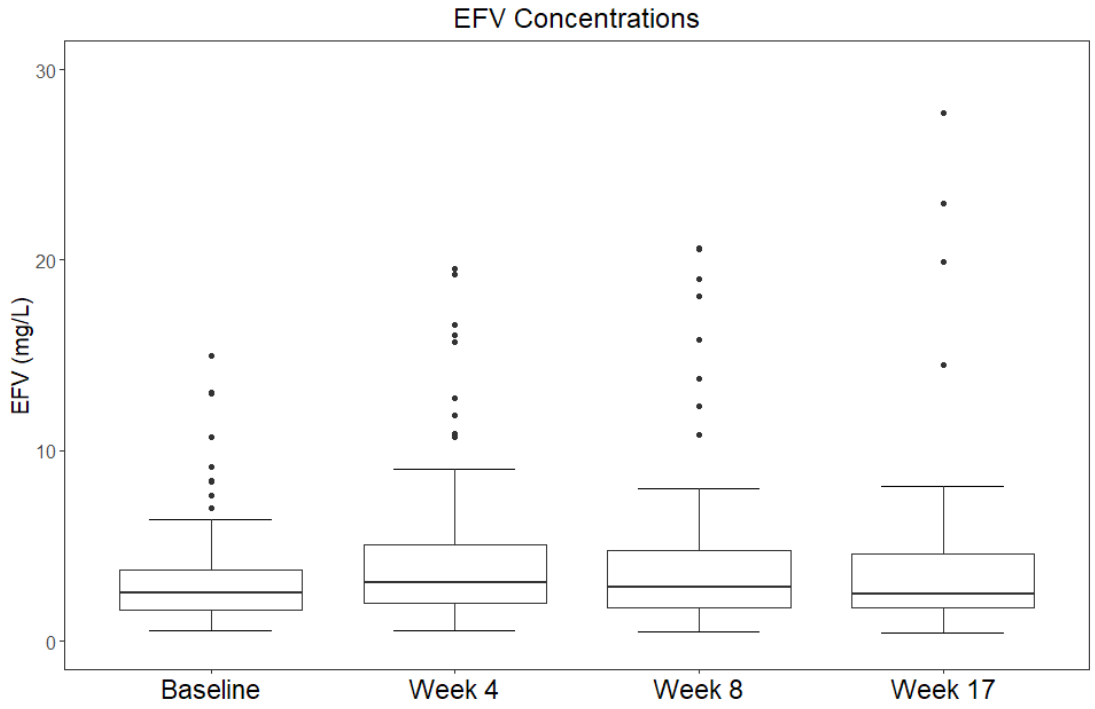
Safety defined for each group:

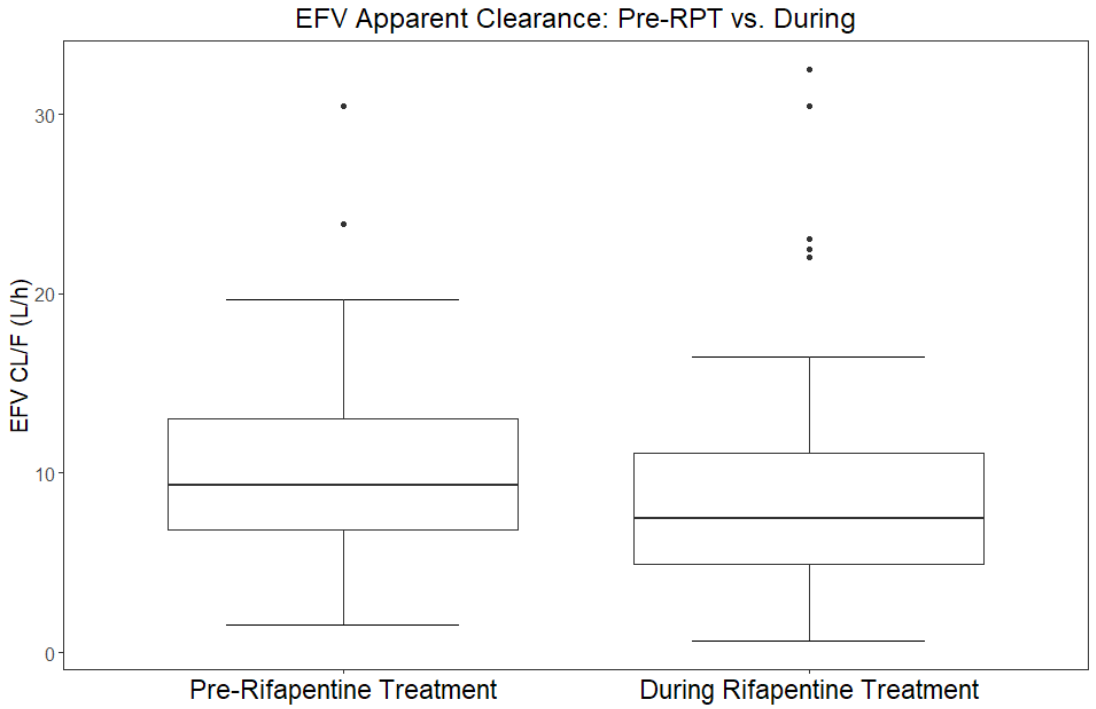
- 80% of 31 have acceptable EFV concentrations

Treatment arm:

- Eligibility and enrollment apply to all treatment arms
- EFV PK sampling and testing of participants in RPT treatment arms

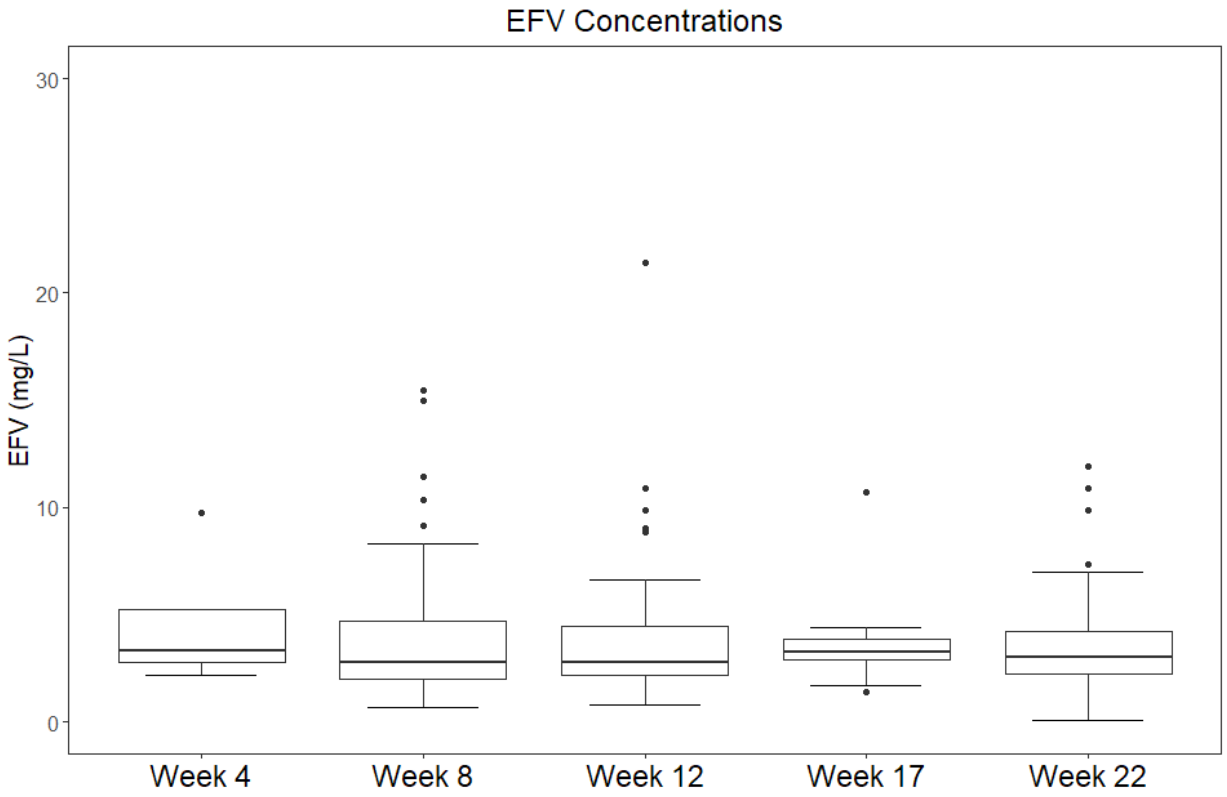
EFV-1 Results (n=67)
On EFV-based ART with undetectable VL at baseline

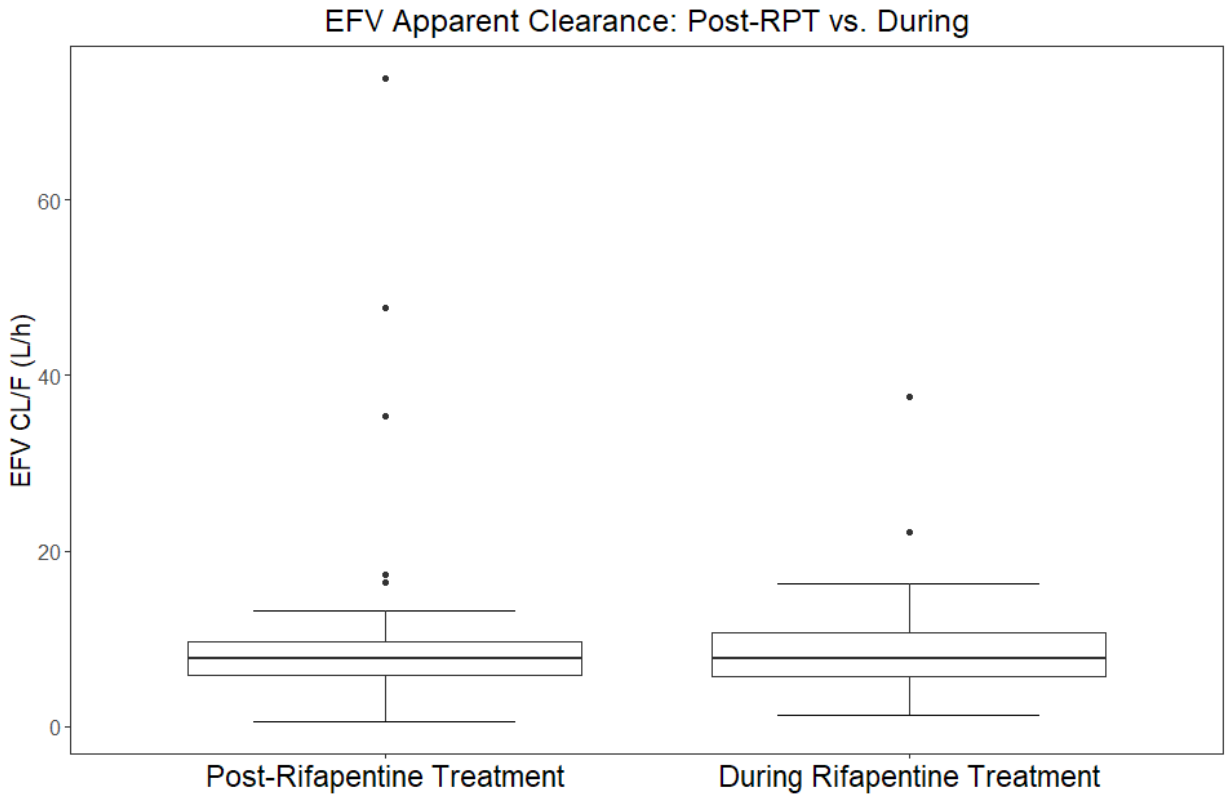




Podany et al CROI 2018, #455

EFV2 Results (n=34)
Began EFV-based ART after 8 weeks of TB Rx





Podany et al 2019 Int'l Workshop Clin Pharm HIV, Abstract #1

Adolescents (68 randomized)

Safety Outcomes	Control	RPT	RPT-MOX	Total
Total safety population	22	20	25	**67**
Primary Safety Outcome (Grade 3-5 AEs on treatment)	3 (13.6%)	2 (10.0%)	3 (12.0%)	**8 (11.9%)**
SAEs during treatment	0	0	0	**0**
Deaths	0	0	0	**0**

Efficacy outcomes	Control	RPT	RPT-MOX	Total
Primary: Assessable	1/19 (5.3%)	1/18 (5.6%)	2/25 (8.0%)	**4/62 (6.5%)**
Primary: Microbiologically eligible	1/19 (5.3%)	2/19 (10.5%)	2/25 (8.0%)	**5/63 (7.9%)**
Secondary: Per Protocol 95	0	0	1/18 (5.6%)	**1/43 (2.3%)**

TBTC TB Trials Consortium CDC

ACTG AIDS CLINICAL TRIALS GROUP

People living with diabetes (83 randomized)

Safety Outcomes	Control	RPT	RPT-MOX	Total
Total safety population	30	16	35	**81**
Primary Safety Outcome: Grade 3-5 AEs on treatment	17 (56.7%)	5 (31.3%)	12 (34.3%)	**34 (42.0%)**
SAEs during treatment	7 (23.3%)	4 (25.0%)	5 (14.3%)	**16 (19.8%)**
Deaths	0	0	0	**0**

Efficacy outcomes	Control	RPT	RPT-MOX	Total
Primary: Assessable	5/27 (18.5%)	6/14 (42.9%)	5/31 (16.1%)	**16/72 (22.2%)**
Primary: Microbiologically eligible	9/31 (29.0%)	6/14 (42.9%)	6/32 (18.8%)	**21/77 (27.3%)**
Secondary: Per Protocol 95	2/17 (11.8%)	4/10 (40.0%)	1/26 (3.8%)	**7/53 (13.2%)**

TBTC TB Trials Consortium CDC

ACTG AIDS CLINICAL TRIALS GROUP

S31/A5349 Subgroup Conclusions

1. The 4-month RPT-MOX regimen has non-inferior efficacy to the 6-month standard of care in both primary and secondary outcome analyses in all populations
   - Regimen effective in people with HIV, diabetes, more extensive disease and adolescents
2. No appreciable drug-drug interactions of RPT with EFV
   - ACTG A5406 will evaluate RPT-MOX with DTG
3. The 4-month RPT regimen is NOT non-inferior for efficacy but did perform adequately in some categories
   - Women
   - Non-cavitary disease
   - Lower disease burden (TTP in MGIT, low AFB smear grade)
4. No differences between investigational and control regimens in primary or secondary safety outcomes

S31/A5349 Protocol Team

Payam Nahid* (TBTC Chair)
Susan Dorman* (TBTC Chair)
Susan Swindells^ (ACTG Chair)
Richard Chaisson*^ (ACTG co-Chair)
Ekaterina Kurbatova* (CDC Project Officer)
Patrick Phillips (Statistician)
Kwok-Chiu Chang*
Mark Cotton*^
Andrew Hockey (Sanofi)
Kelly Dooley*^
Melissa Engle*
Courtney Fletcher^
Phan Ha*
Richard Hafner^
Lara Hosey^
John L. Johnson*
Cynthia Lee (CRAG)
Cynthia Merrifield*
Michael Hughes^
Nguyen Viet Nhung*
April Pettit*
Anthony Podany^
Kathleen Robergeau (Westat)
Wadzanai Samaneka^ (ACTG co-Chair)
Erin Sizemore*
Andrew Vernon*
Mark Weiner*
Lisa Wolf*

**TBTC* *^ACTG*

Acknowledgments

- CDC Data and Coordinating Center and DTBE
- Funding: CDC and NIH
- Drug supply and TB PK testing: Sanofi
- TBTC DSMB
- Staff of 34 clinical trial sites on 4 continents
- 2516 participants and their families and friends
- Community Representation Advisory Group
- Treatment Action Group

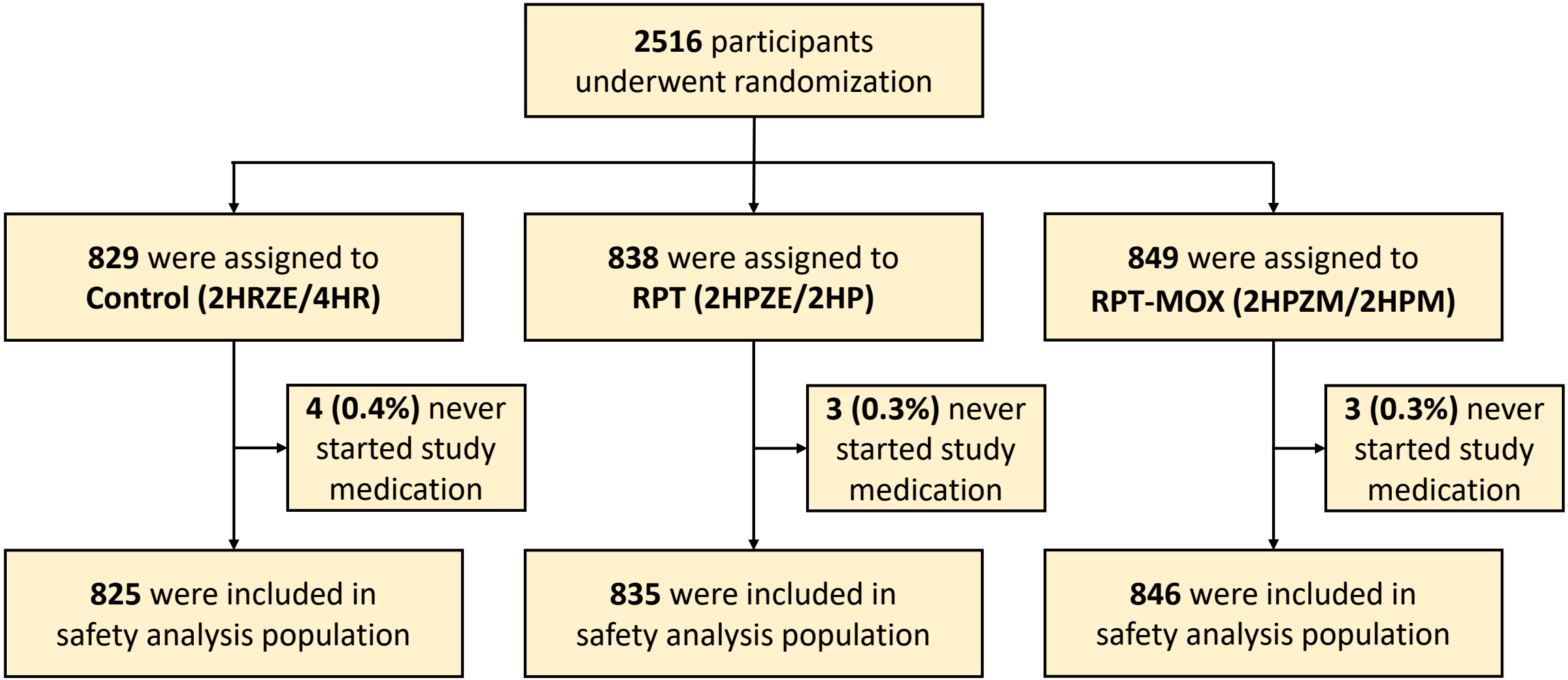
Questions and Discussion

Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial

Study 31/A5349
Safety

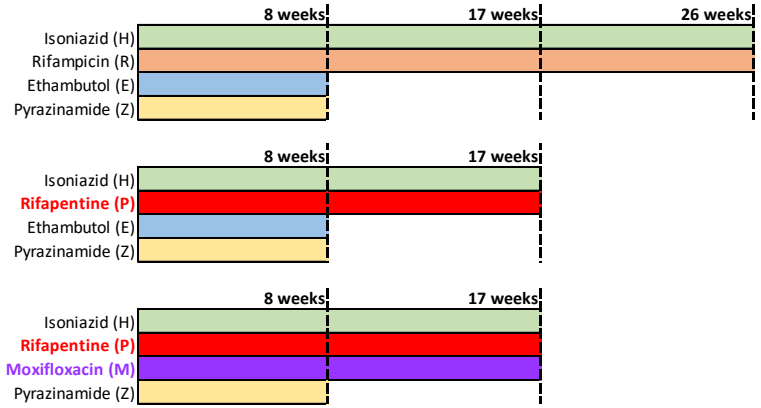
S31 Webinar
21 September 2021

Safety analysis population

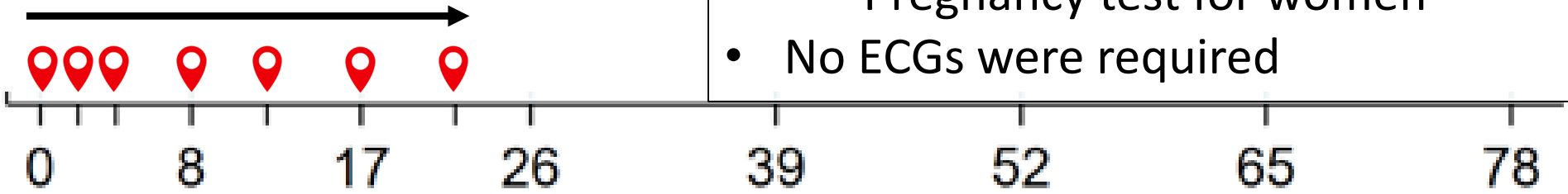


Safety monitoring

AE reports collected during full duration of the study follow-up



Safety laboratory tests on every study visit until week 22



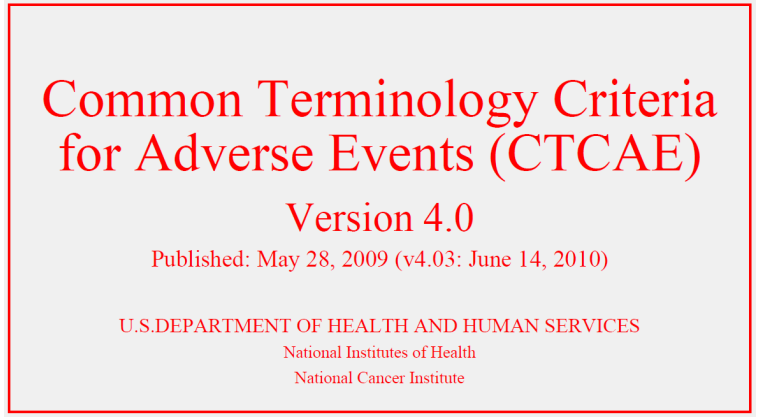
Weeks from randomization

Safety monitoring

- BL and weeks 2,4,8,12,17,22:
  - ALT, bilirubin, creatinine, hemoglobin, WBC with differential, platelets
- BL only:
  - Diabetes screen
  - Albumin, potassium
  - HIV test (CD4, VL if HIV+)
  - Pregnancy test for women
- No ECGs were required

Safety assessments

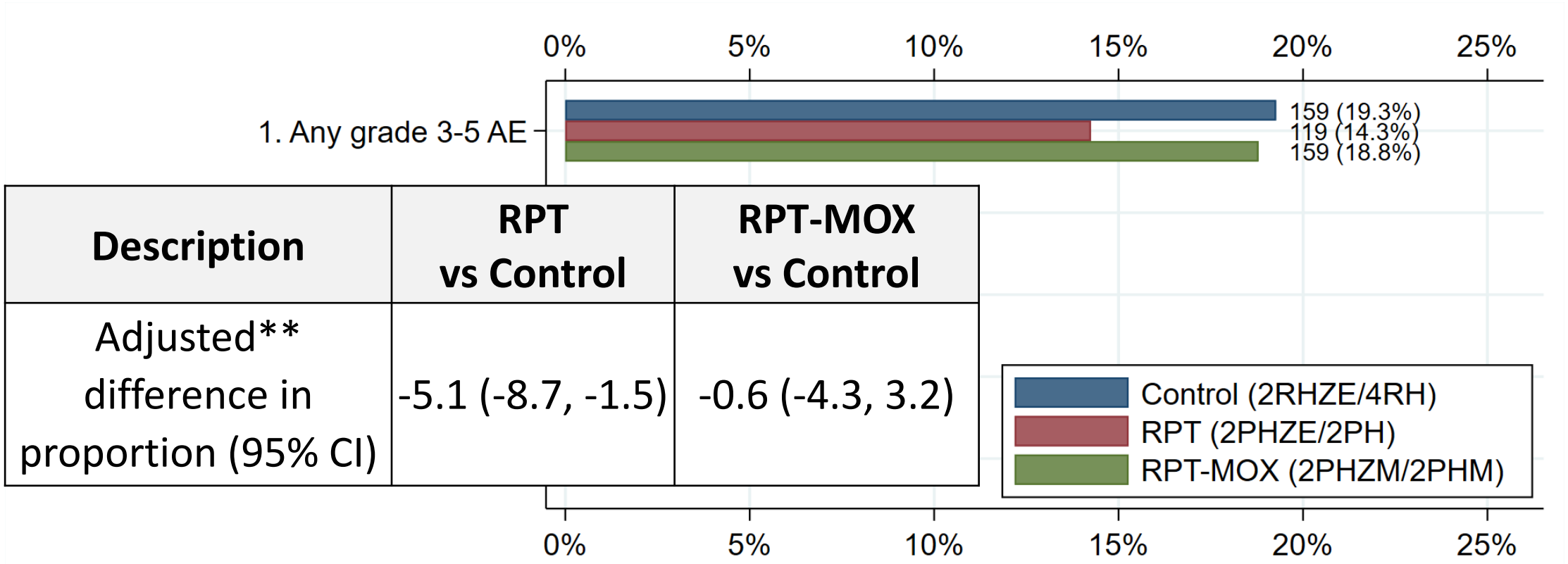
- **Reportable AEs**
  - Serious Adverse Events (SAEs)
  - Grade 3-5 (severe) AEs
  - New diagnoses (regardless severity grade)
- **Severity grading**: Common Terminology Criteria for Adverse Events (CTCAE) version 4.03
- Each AE report reviewed and coded in **MedDRA** v.20 by the CDC Safety Officer
- Open-label trial – but only DSMB reviewed data by arm



Primary Safety Outcome

Proportion of participants with all-cause grade 3 or higher (severe) AEs during study drug treatment (up to 14 days after the last study dose)

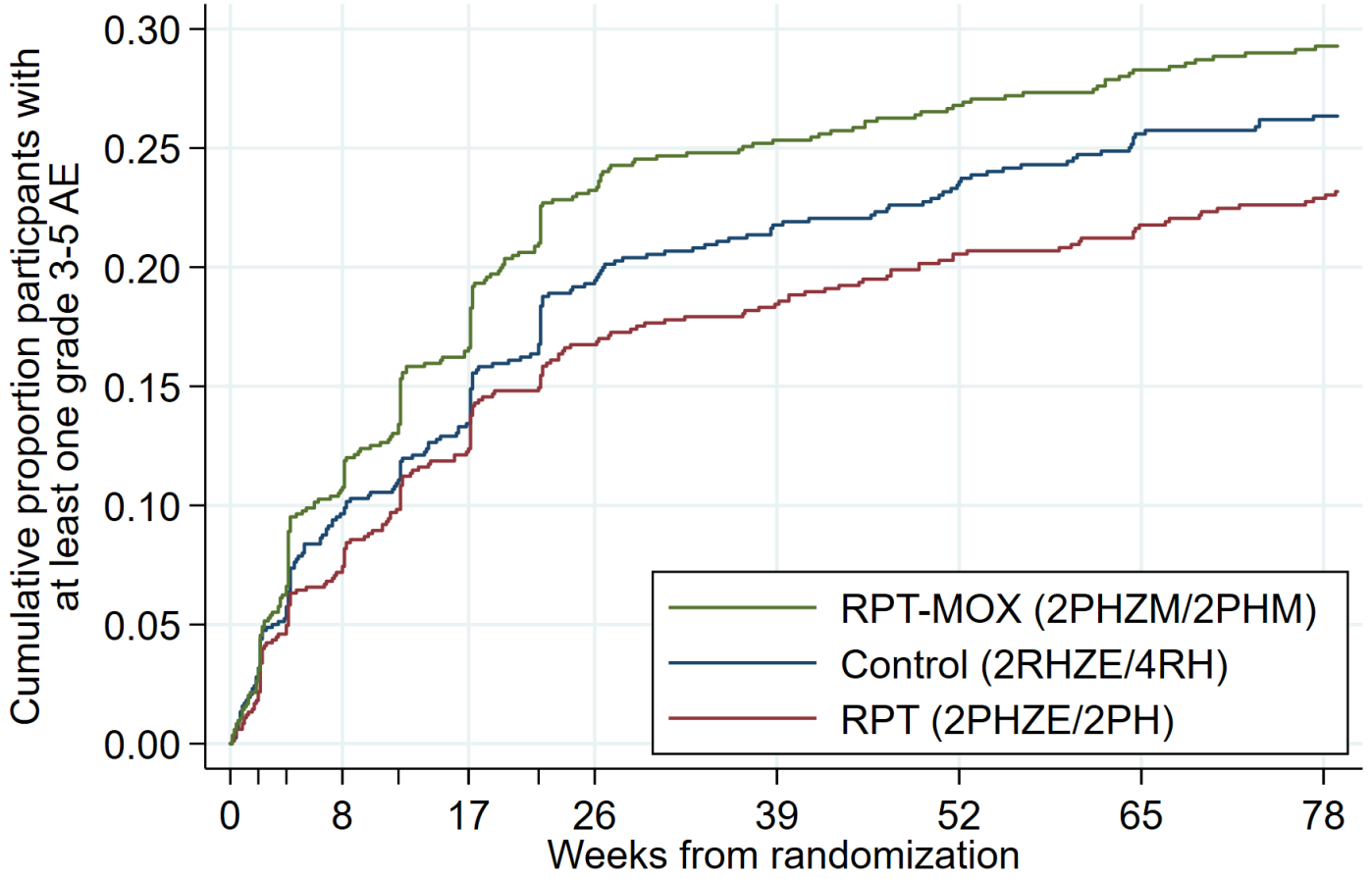
Description	RPT vs Control	RPT-MOX vs Control
Adjusted** difference in proportion (95% CI)	-5.1 (-8.7, -1.5)	-0.6 (-4.3, 3.2)



**The analysis was adjusted for the stratification factors of presence of cavitation on baseline chest radiography at baseline and HIV status.

Time to first all-cause grade 3 or higher AE

during treatment and follow-up



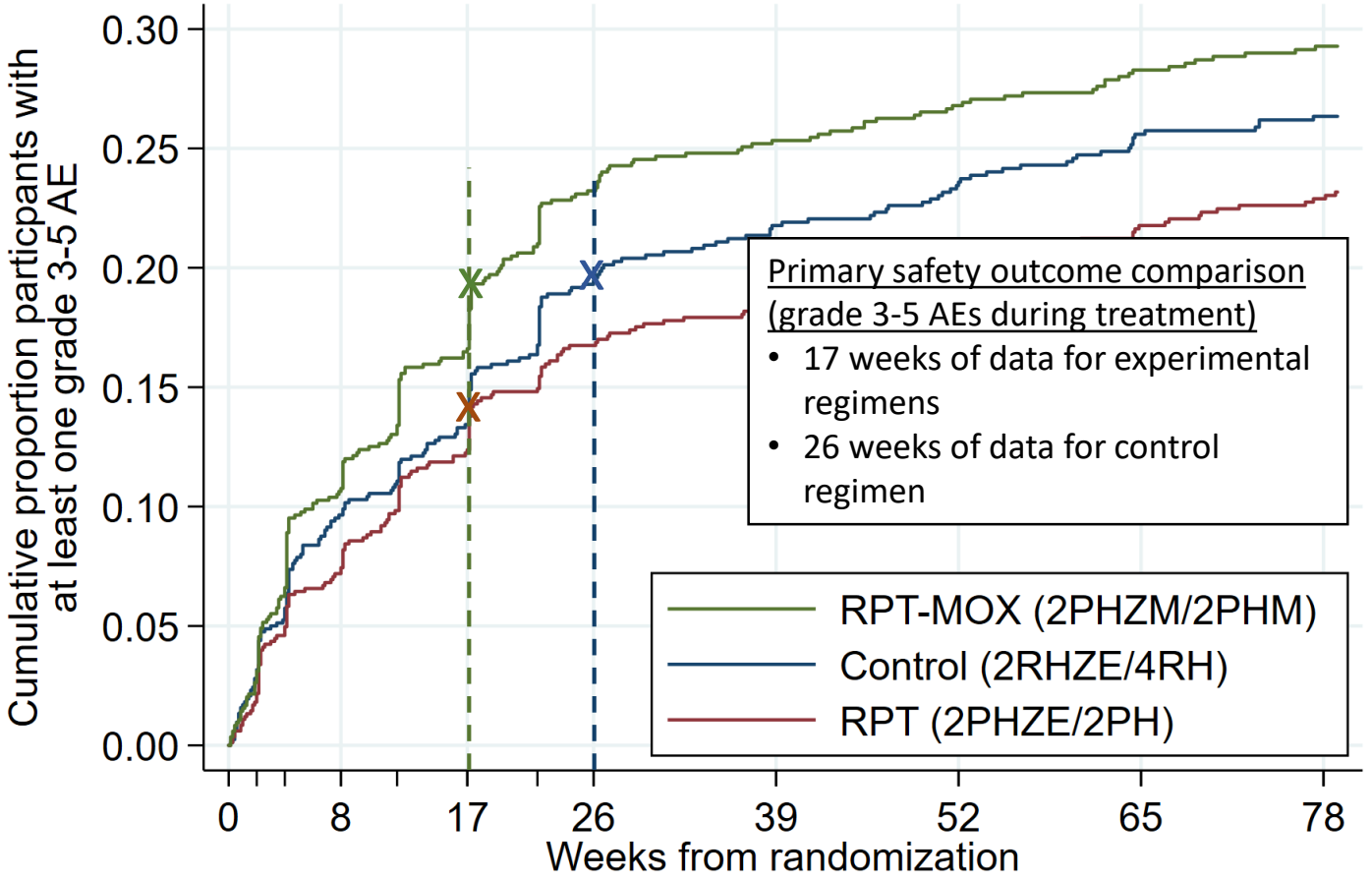
Number at risk

RPT-MOX	846	721	647	589	564	543	510	497
Control	825	712	654	599	568	538	504	492
RPT	835	746	686	645	621	596	561	550

Description	RPT vs Control	RPT-MOX vs Control
Log-rank test p-value	p=0.28	p=0.054

Time to first all-cause grade 3 or higher AE

during treatment and follow-up



Number at risk

RPT-MOX	846	721	647	589	564	543	510	497
Control	825	712	654	599	568	538	504	492
RPT	835	746	686	645	621	596	561	550

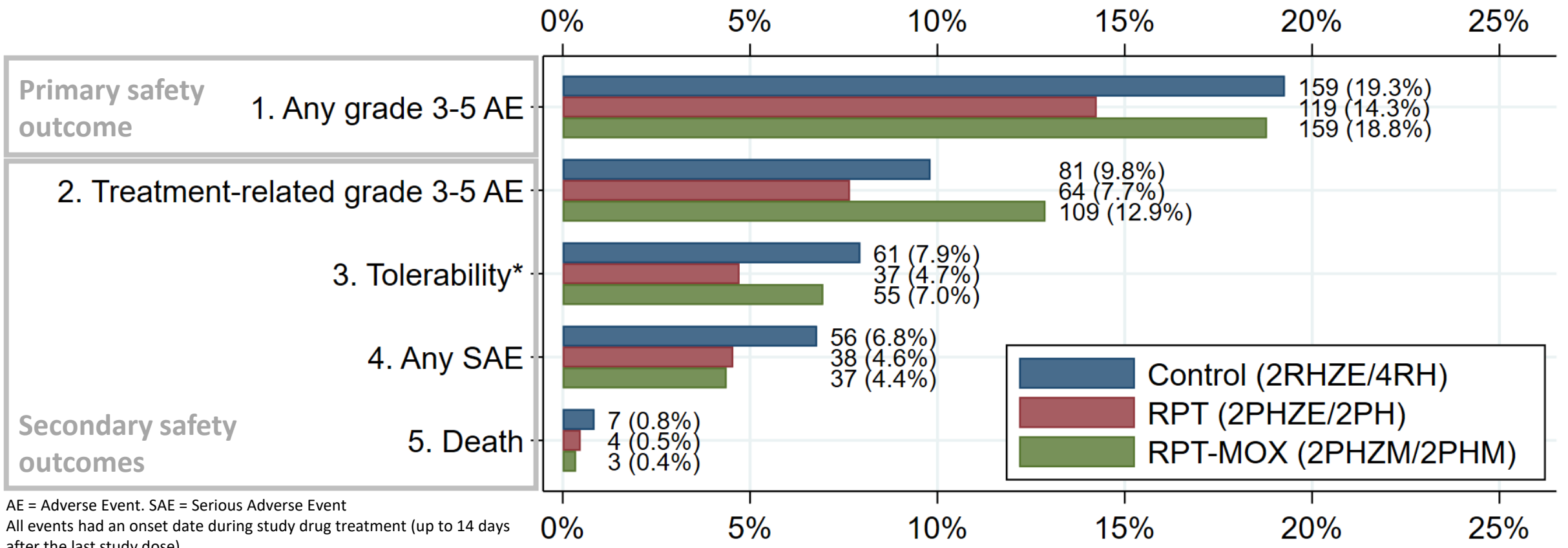
Description	RPT vs Control	RPT-MOX vs Control
Log-rank test p-value	p=0.28	p=0.054

Numbers of participants experiencing grade 3 or higher AE during treatment (up to 14 days after the last study dose), by MedDRA SOC

MedDRA System Organ Class (SOC)	Control	RPT	RPT-MOX	Total
Total in Safety Population	**825**	**835**	**846**	**2506**
Any grade 3-5 AE	**159 (19.3%)**	**119 (14.3%)**	**159 (18.8%)**	**437 (17.4%)**
Blood & Lymphatic System Disorders	51 (6.2%)	35 (4.2%)	61 (7.2%)	147 (5.9%)
Hepatobiliary Disorders	26 (3.2%)	26 (3.1%)	39 (4.6%)	91 (3.6%)
Vascular Disorders	17 (2.1%)	14 (1.7%)	12 (1.4%)	43 (1.7%)
Pregnancy, Puerperium & Perinatal Conditions	16 (1.9%)	9 (1.1%)	9 (1.1%)	34 (1.4%)
Infections & Infestations	16 (1.9%)	8 (1.0%)	10 (1.2%)	34 (1.4%)
Metabolism & Nutrition Disorders	11 (1.3%)	6 (0.7%)	9 (1.1%)	26 (1.0%)
Respiratory, Thoracic & Mediastinal Disorders	7 (0.8%)	5 (0.6%)	4 (0.5%)	16 (0.6%)
Injury, Poisoning & Procedural Complications	9 (1.1%)	6 (0.7%)	0	15 (0.6%)
Skin & Subcutaneous Tissue Disorders	1 (0.1%)	6 (0.7%)	6 (0.7%)	13 (0.5%)
Eye Disorders	4 (0.5%)	1 (0.1%)	4 (0.5%)	9 (0.4%)
Investigations	3 (0.4%)	3 (0.4%)	3 (0.4%)	9 (0.4%)
Nervous System Disorders	3 (0.4%)	1 (0.1%)	5 (0.6%)	9 (0.4%)
Gastrointestinal Disorders	3 (0.4%)	1 (0.1%)	2 (0.2%)	6 (0.2%)
Neoplasms Benign, Malignant & Unspecified (Incl Cysts & Polyps)	4 (0.5%)	1 (0.1%)	1 (0.1%)	6 (0.2%)
General Disorders & Administration Site Conditions	3 (0.4%)	1 (0.1%)	2 (0.2%)	6 (0.2%)
Musculoskeletal & Connective Tissue Disorders	3 (0.4%)	1 (0.1%)	1 (0.1%)	5 (0.2%)
Psychiatric Disorders	0	1 (0.1%)	2 (0.2%)	3 (0.1%)
Cardiac Disorders	0	0	3 (0.4%)	3 (0.1%)
Renal & Urinary Disorders	0	0	2 (0.2%)	2 (0.1%)
Immune System Disorders	0	0	1 (0.1%)	1 (0.0%)

≥3% in any arm

Primary and secondary safety outcomes



AE = Adverse Event. SAE = Serious Adverse Event
All events had an onset date during study drug treatment (up to 14 days after the last study dose)
*Denominator for tolerability is microbiologically eligible analysis population

All-cause deaths
during treatment and follow-up

Description	Control (2HRZE/4HR) n (%) N=825	RPT (2HPZE/2HP) n (%) N=835	RPT-MOX (2HPZM/2HPM) n (%) N=846	Total n (%) N=2506
Death during study treatment (up to 14 days after the last study dose)	7 (0.8%)	4 (0.5%)	3 (0.4%)	14 (0.6%)
TB-related	6 (0.7%)	1 (0.1%)	2 (0.2%)	9 (0.4%)
All deaths during treatment and follow-up	**12 (1.4)**	**11 (1.3)**	**13 (1.5)**	**36 (1.4)**
TB-related deaths	8 (1.0)	4 (0.5)	3 (0.4)	15 (0.6)

Deaths during study treatment, up to 14 days after last study dose

by MedDRA Preferred Term

Control (2HRZE/4HR) N=825	RPT (2HPZE/2HP) N=835	RPT-MOX (2HPZM/2HPM) N=846	Total N=2506
1 Death 1 Paracoccidioides Infection 1 Sepsis 1 Papillary Thyroid Cancer 1 Central Nervous System Lesion 1 Haemoptysis 1 Pulmonary Embolism	1 Death 1 Alcohol Poisoning 1 Road Traffic Accident 1 Pulmonary Embolism	1 Thrombotic Thrombocytopenic Purpura* 1 Cardiac Failure Congestive 1 Pulmonary Tuberculosis	
7 (0.8%)	**4 (0.5%)**	**3 (0.4%)**	**14 (0.6%)**

*Thrombotic Thrombocytopenic Purpura was a Suspected Unexpected Serious Adverse Reaction (SUSAR) event

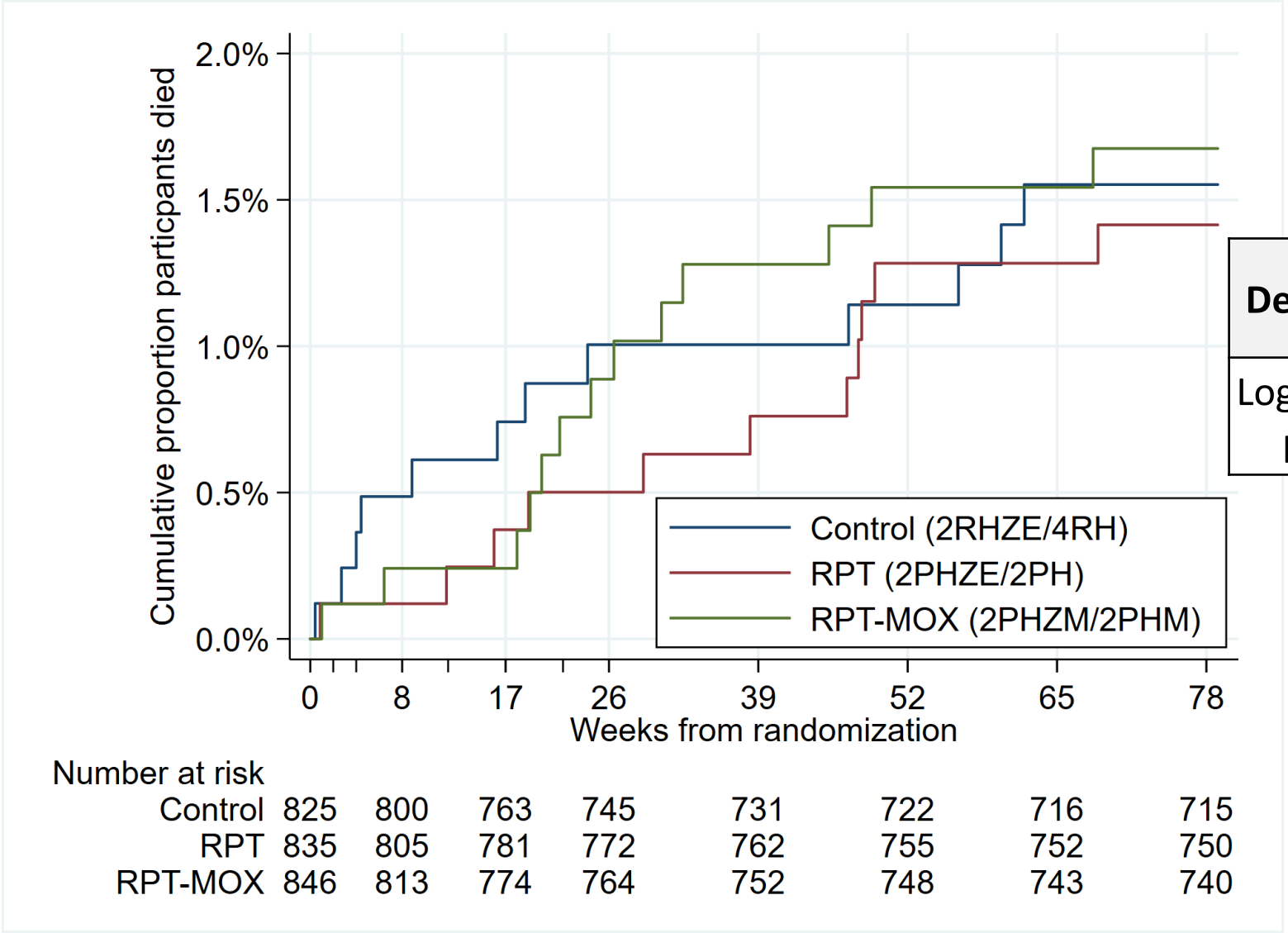
Deaths >14 days after the last study dose

by MedDRA Preferred Term

Control (2HRZE/4HR) N=825	RPT (2HPZE/2HP) N=835	RPT-MOX (2HPZM/2HPM) N=846	Total N=2506
1 Death	1 Death	1 Death	
1 Sudden Death	1 Alcoholic Liver Disease	1 Right Ventricular Failure	
1 Neoplasm Malignant	1 Lower Respiratory Tract Infection	1 Hepatitis	
1 Dyspnoea	1 Pulmonary Tuberculosis	1 Gun Shot Wound	
1 Pulmonary Mass	1 Gas Poisoning	2 Road Traffic Accident	
	1 Road Traffic Accident	1 Oesophageal Carcinoma	
	1 Bladder Transitional Cell Carcinoma	1 Squamous Cell Carcinoma	
		1 Pneumothorax	
		1 Pulmonary Embolism	
5 (0.6%)	**7 (0.8)**	**10 (1.2%)**	**22 (0.9%)**

All-cause deaths

during treatment and follow-up



Description	RPT vs Control	RPT-MOX vs Control
Log rank test p-value	p=0.66	p=0.55

Liver enzyme abnormalities

during study treatment (up to 14 days after the last study dose)

Highest value across visits	Control (2HRZE/4HR) n (%) N=825	RPT (2HPZE/2HP) n (%) N=835	RPT-MOX (2HPZM/2HPM) n (%) N=846	Total n (%) N=2506
ALT or AST ≥3X ULN	48 (5.8)	29 (3.5)	36 (4.3)	113 (4.5)
ALT or AST ≥5X ULN	24 (2.9)	13 (1.6)	16 (1.9)	53 (2.1)
ALT or AST ≥10X ULN	9 (1.1)	5 (0.6)	4 (0.5)	18 (0.7)
ALT or AST ≥20X ULN	4 (0.5)	2 (0.2)	1 (0.1)	7 (0.3)
ALT or AST ≥3X ULN with total bilirubin ≥2X ULN	7 (0.9)	8 (1.0)	10 (1.2)	25 (1.0)

FDA. Guidance for Industry: drug-induced liver injury: premarketing clinical evaluation. July 2009. https://www.fda.gov/media/116737/download.
ALT=Alanine Aminotransferase. AST=Aspartate Aminotransferase. ULN=Upper limit of normal.

Conclusions: Safety

High-dose rifapentine regimens were safe and well-tolerated

Acknowledgments

- CDC Data and Coordinating Center and DTBE
- Funding: CDC and NIH
- Drug supply and TB PK testing: Sanofi
- TBTC DSMB
- Staff of 34 clinical trial sites on 4 continents
- 2516 participants and their families and friends
- Community Representation Advisory Group
- Treatment Action Group

Questions and Discussion

Thank you for your participation!

Extended Q&A