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

Study 31/A5349 Results Update

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on behalf of S31/A5349 team

UNION NAR CONFERENCE
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Background

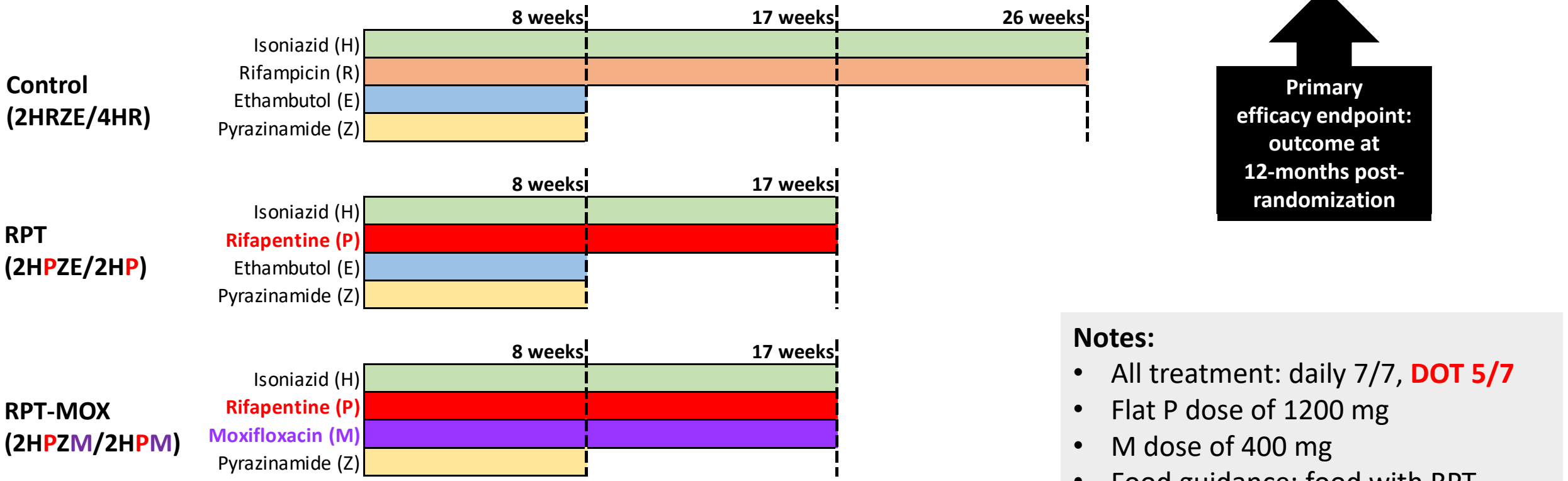
- Reducing the length of time for treating TB has been a longstanding public health goal
  - Shorter regimens cure patients faster, and have the potential to reduce treatment costs, improve patient quality of life, and increase completion of therapy

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

Study Design

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

3 arms, randomization 1:1:1



Notes:

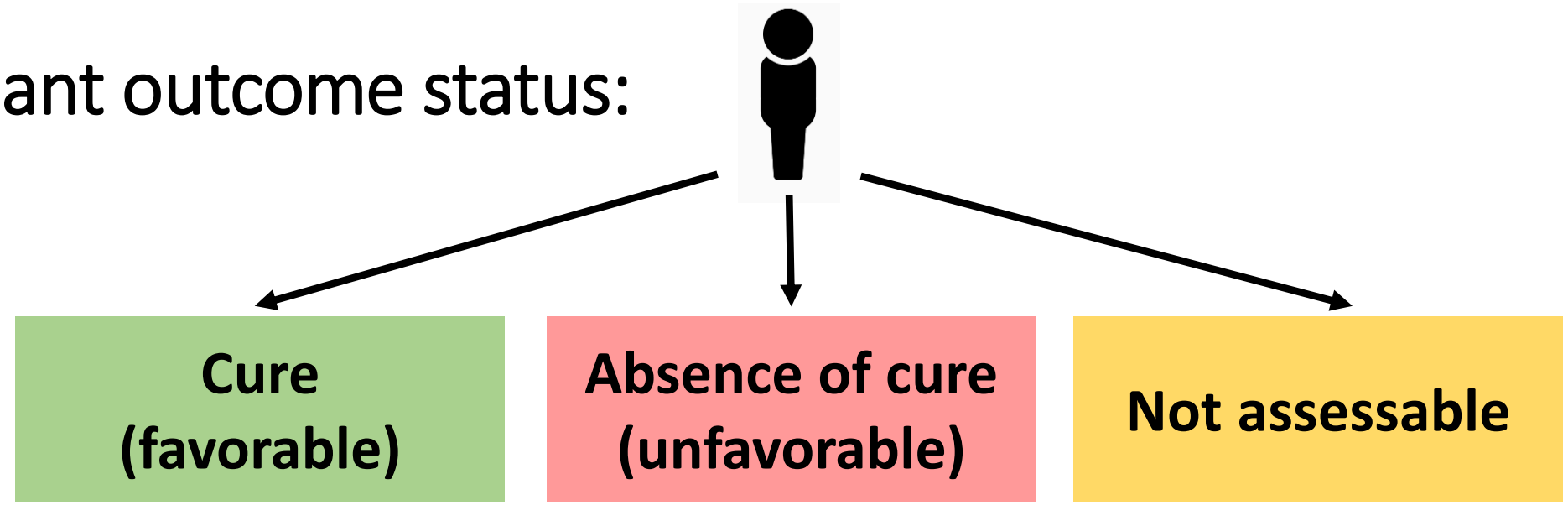
- All treatment: daily 7/7, **DOT 5/7**
- Flat P dose of 1200 mg
- M dose of 400 mg
- Food guidance: food with RPT, no food with RIF

Selected eligibility criteria

- Inclusion
  - Positive AFB sputum smear or positive *Xpert MTB* (medium/high, no RIF-R)
  - Age ≥12 y.o.
  - If HIV-positive, CD4 T cell count ≥100 cells/mm^3, on (or planned) EFV-based ART
- Exclusion
  - Pregnant and breastfeeding women
  - Recent receiving TB drugs
    - >5 days systemic TB treatment within previous 6 months
    - >5 days treatment with anti-TB drugs within previous 30 days
  - Known history of prolonged QT syndrome
  - Extrapulmonary TB (CNS, bones or joints, miliary, pericardial)
  - Weight <40 kg
  - Known drug resistance

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

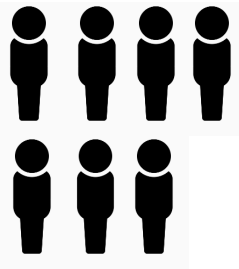
Participant outcome status:



Primary analysis populations:

Microbiologically eligible analysis population

Assessable analysis population



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)**

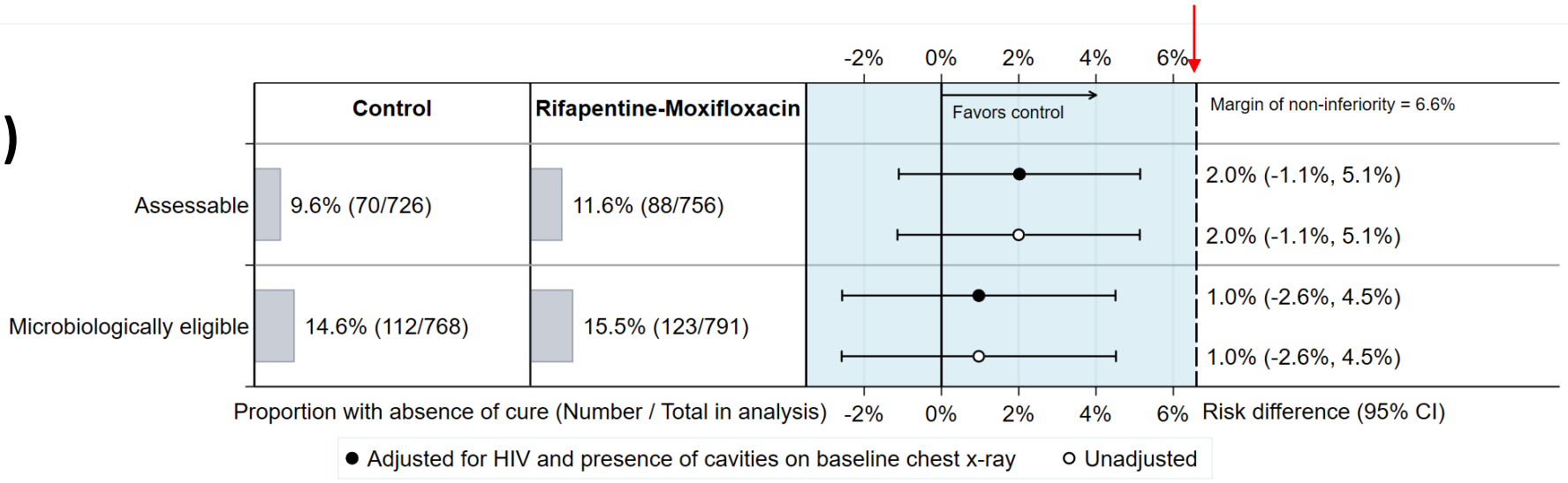
TBTC TB Trials Consortium

ACTG AIDS CLINICAL TRIALS GROUP

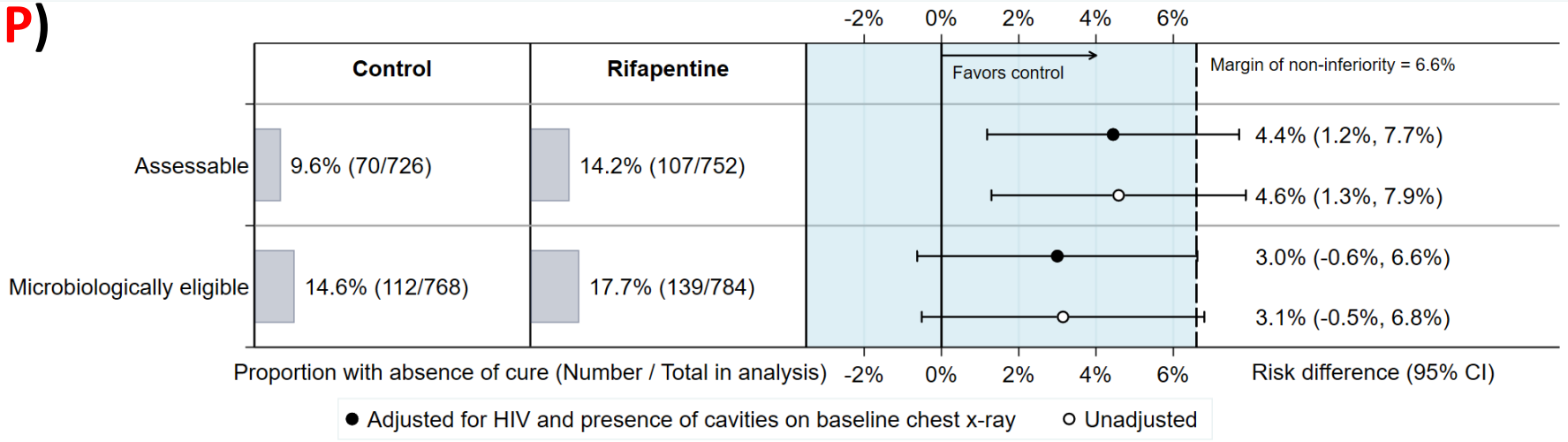
12 month results

Primary Efficacy Results

RPT-MOX (2HPZM/2HPM) regimen meets non-inferiority criteria for efficacy in all analyses



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



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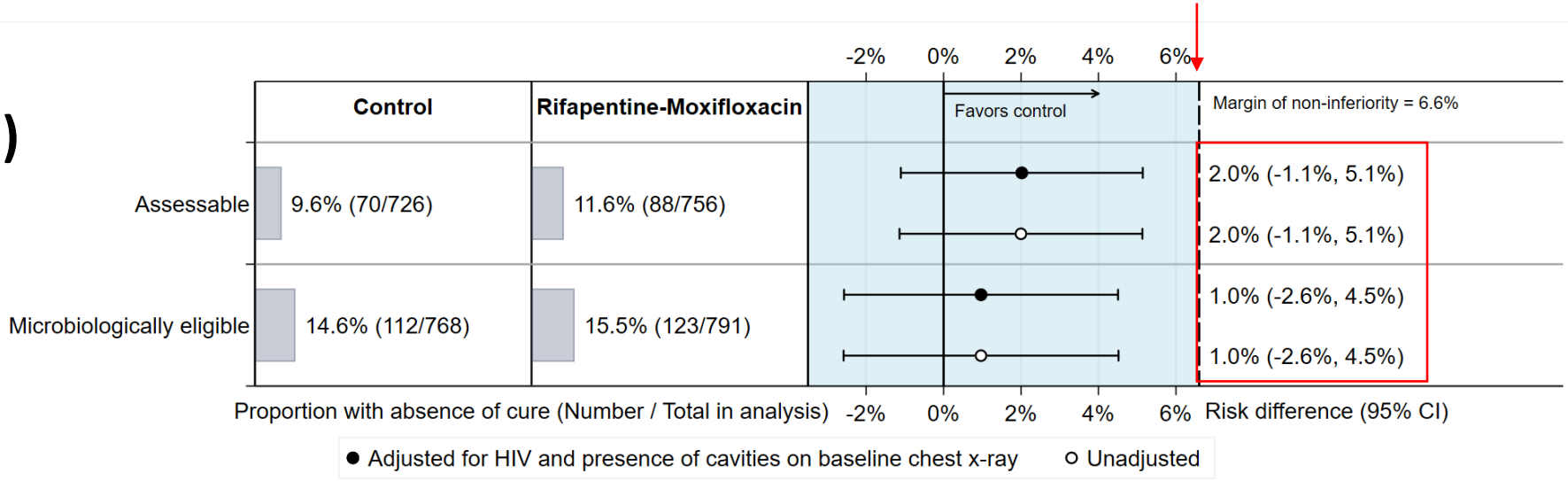
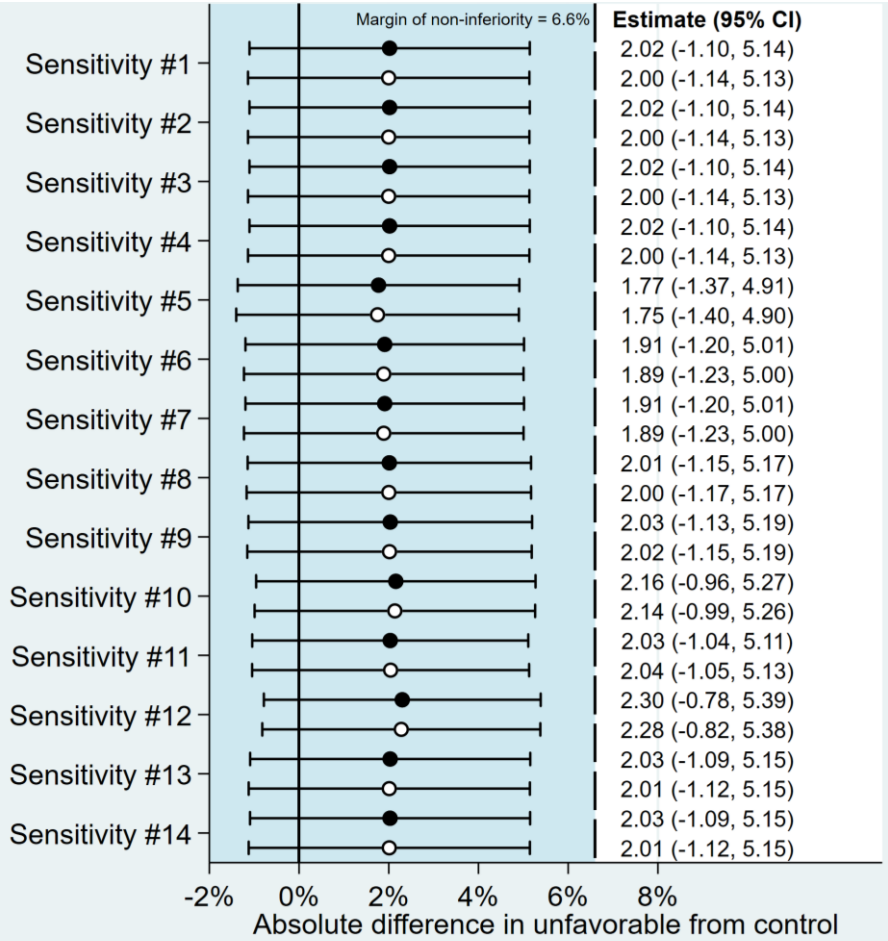


Risk differences (95% CI) *in favor of streptomycin (control)* for trials in which streptomycin was replaced by ethambutol:

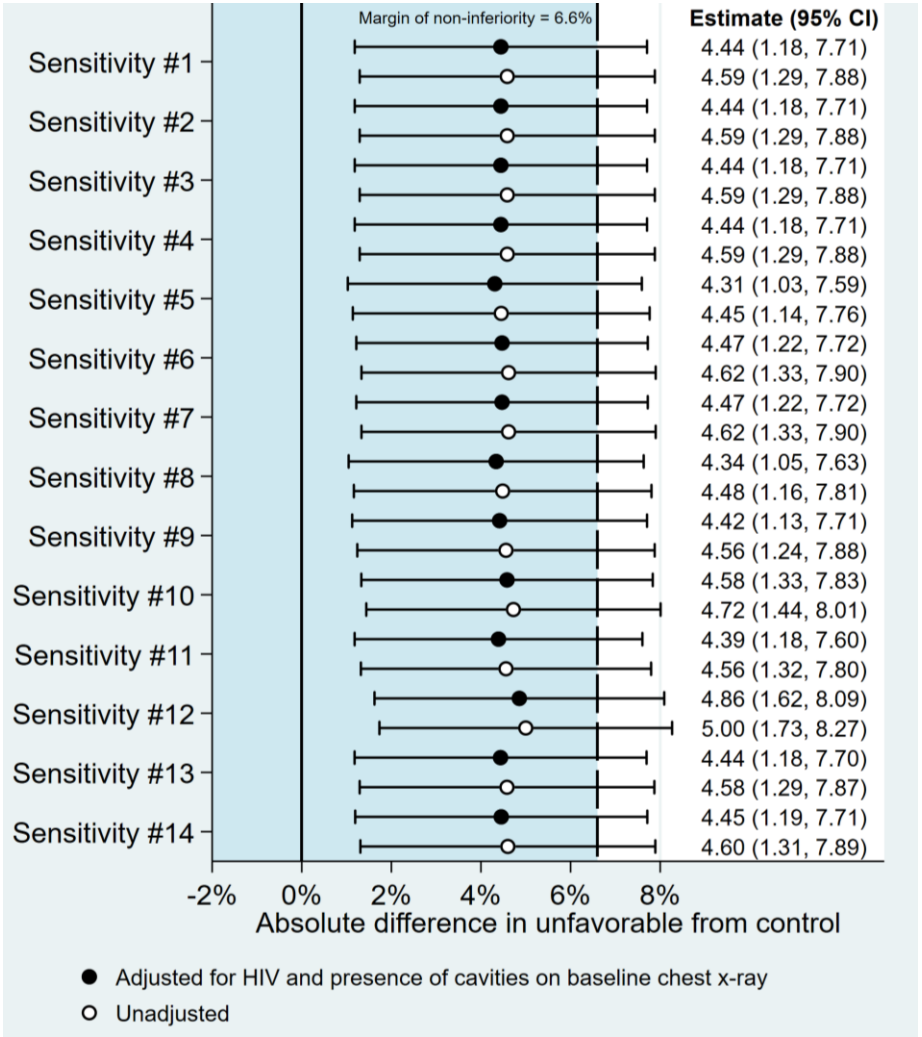
- 2.1% (-1.2%, 5.5%) British Thoracic Society, Br J Dis Chest 1984;78:330-6
- 3.1% (-0.6%, 6.7%) Hong Kong Chest Service, Am Rev Respir Dis 1987;136:1339-42

Primary Efficacy Results: Sensitivity Analyses

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

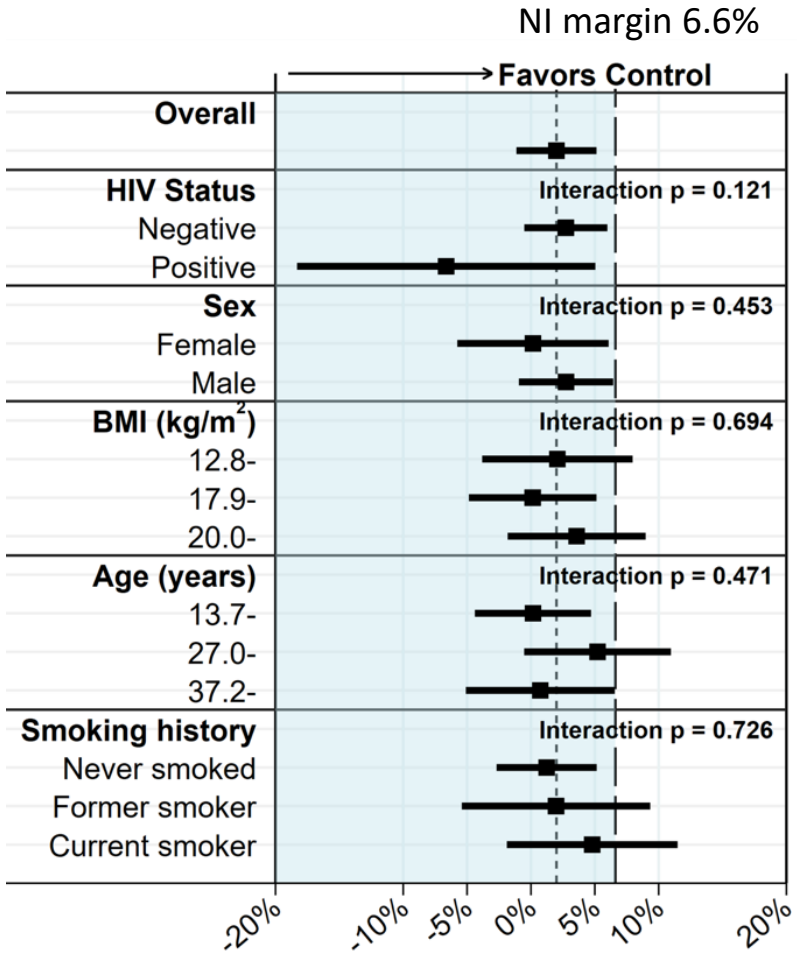


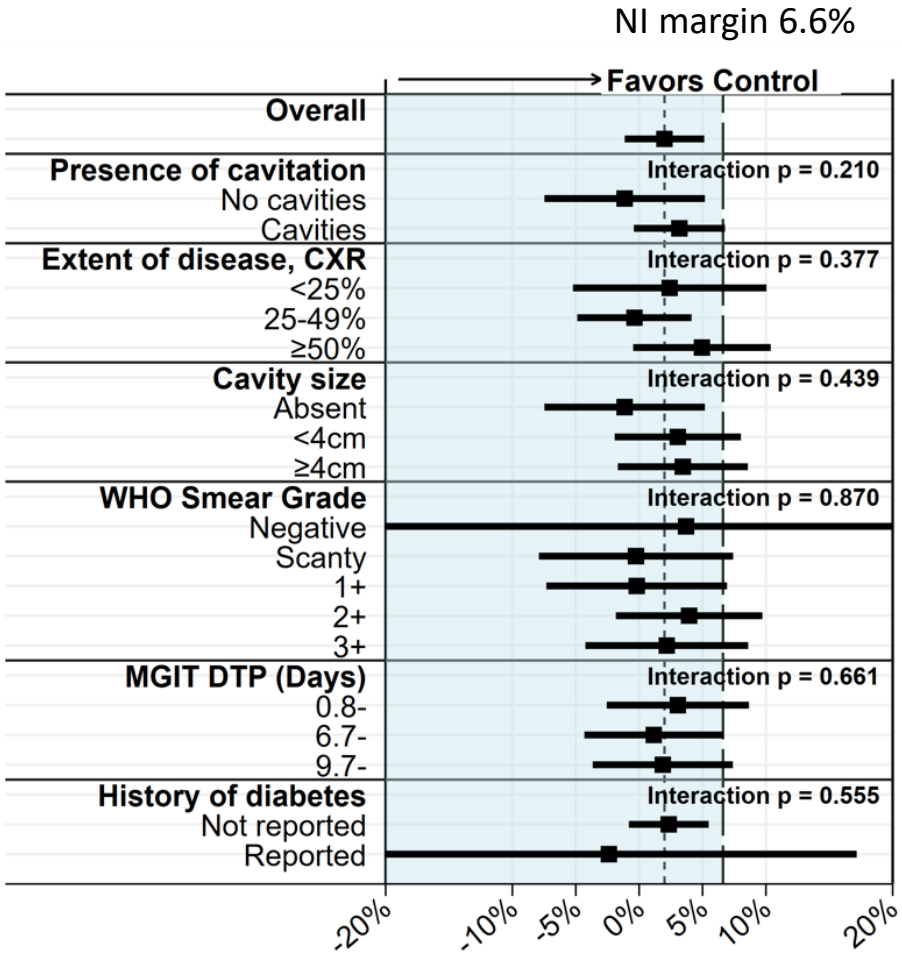
RPT *does not meet* non-inferiority criteria for efficacy in any sensitivity analysis



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

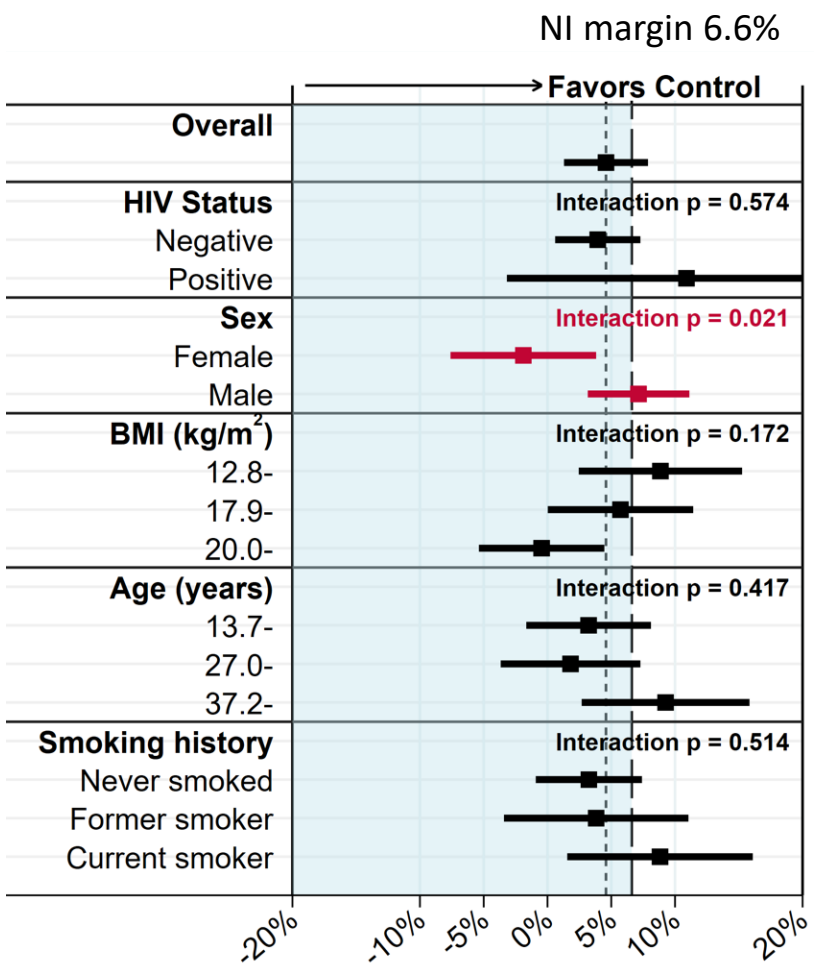
- All interaction tests were non-significant for MOX-RPT Regimen
- There was no evidence that the treatment effect differed by any sub-group for the MOX-RPT Regimen

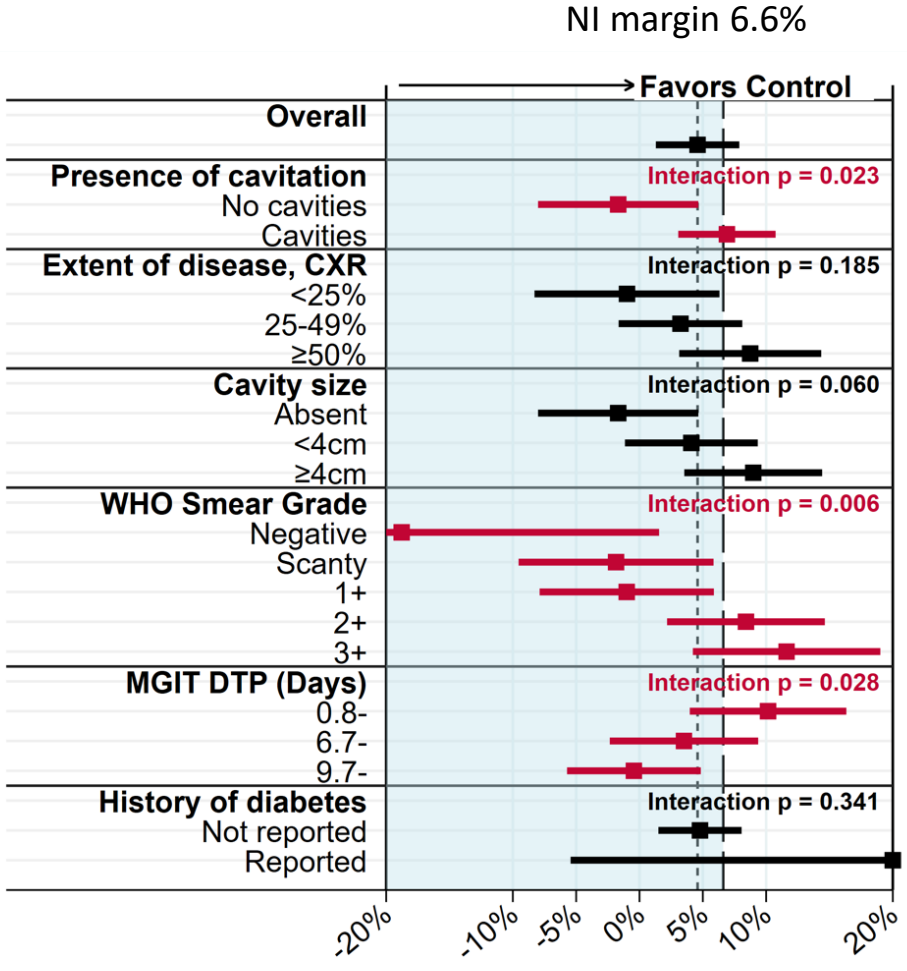




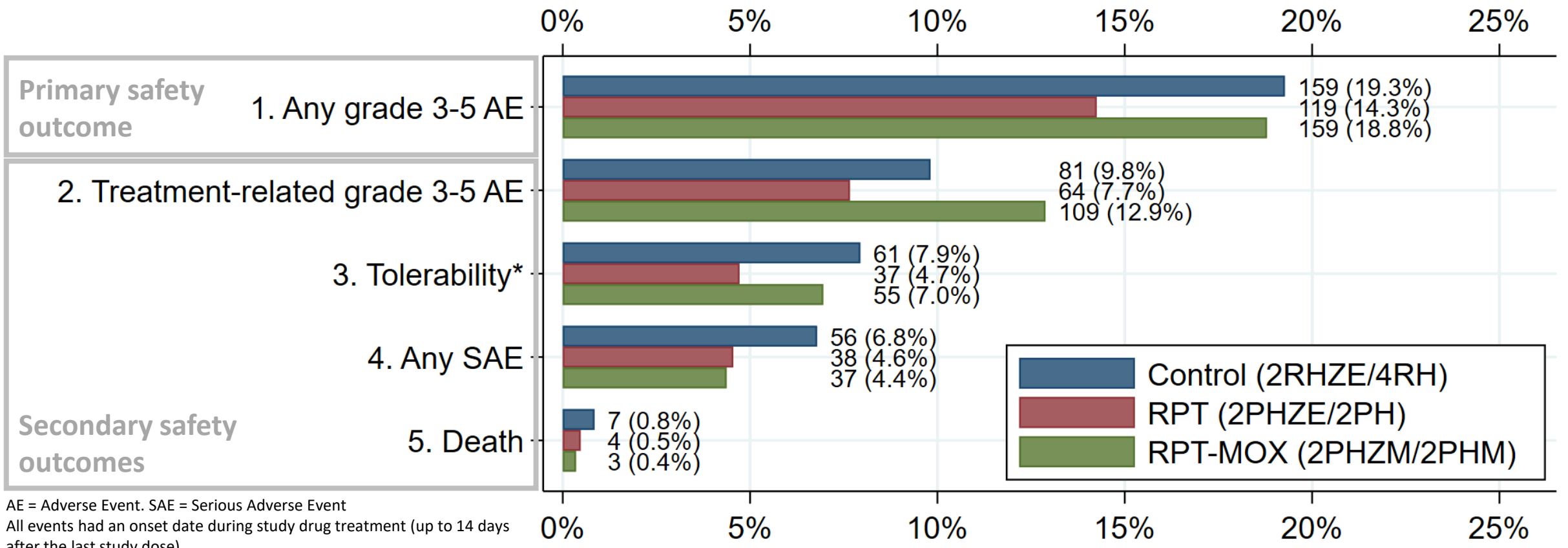
Sub-group analyses (Assessable analysis population) RPT Regimen vs Control

- There <u>was</u> evidence that the treatment effect for RPT Regimen differed among sub-groups
- The RPT regimen <u>did not meet non-inferiority overall</u>, but was non-inferior for select participant subgroups:
  - Females
  - With no cavities on CXR
  - With low AFB smear grade
  - With high TTD on MGIT (i.e., lower burden)





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

Conclusions (12 month results)

Efficacy

- **RPT-MOX (2HPZM/2HPM) regimen consistently met non-inferiority criteria for efficacy**
  - All primary and secondary analysis populations
  - All 14 sensitivity analyses
  - All sub-group analyses
- **RPT (2HPZE/2HP) regimen did not meet non-inferiority criteria for efficacy**
  - Non-inferiority was not met in any analysis, except certain participant sub-groups

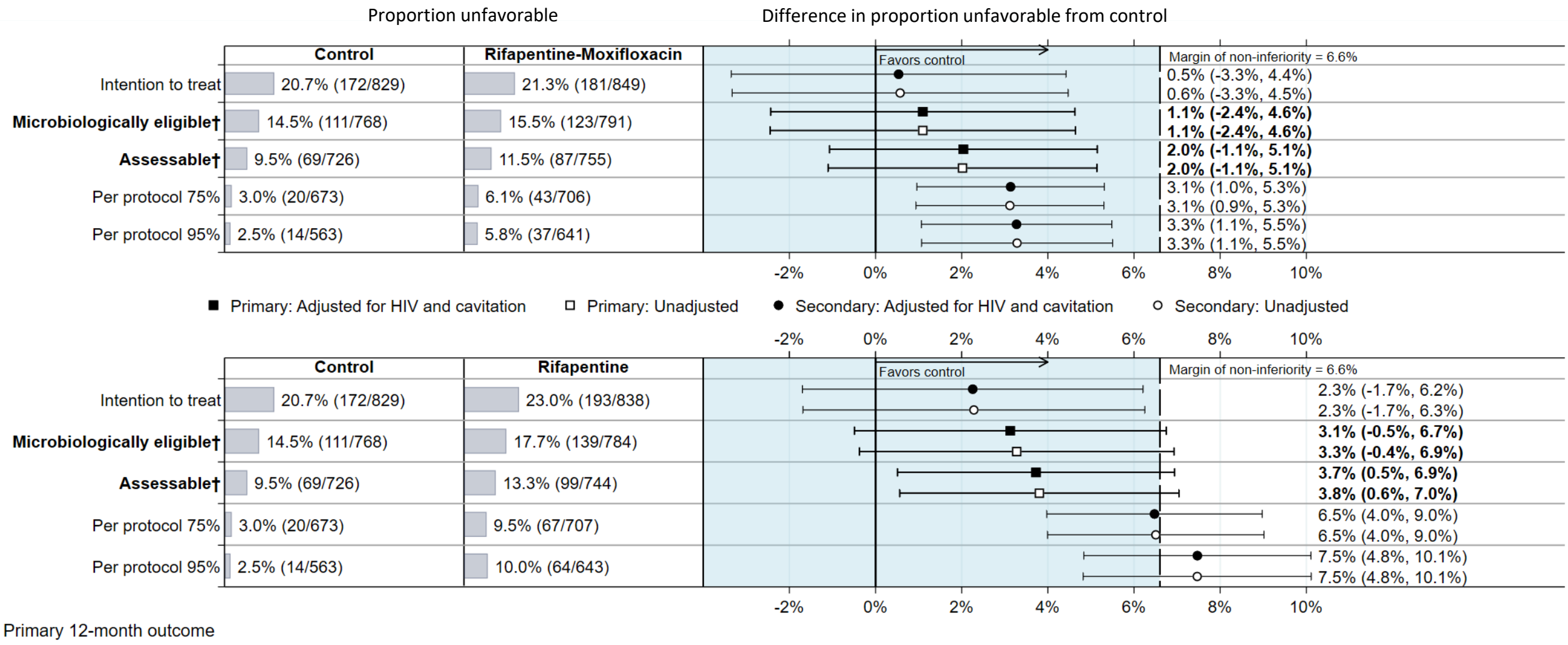
Safety

- **Both high-dose rifapentine regimens safe**

18 month results

Primary 12-month outcome

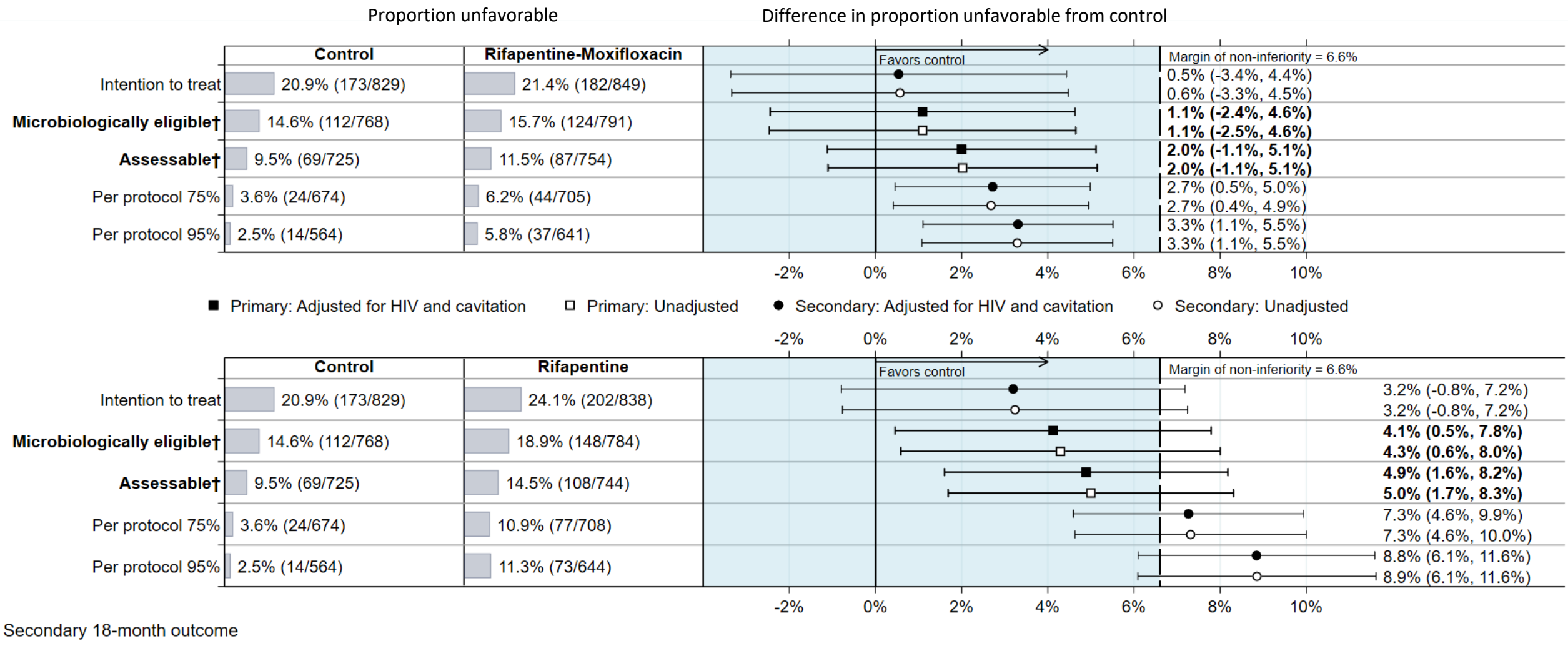
Rifapentine-moxifloxacin non-inferior to control
Rifapentine <u>not non-inferior</u> to control



Primary 12-month outcome

Secondary 18-month outcome

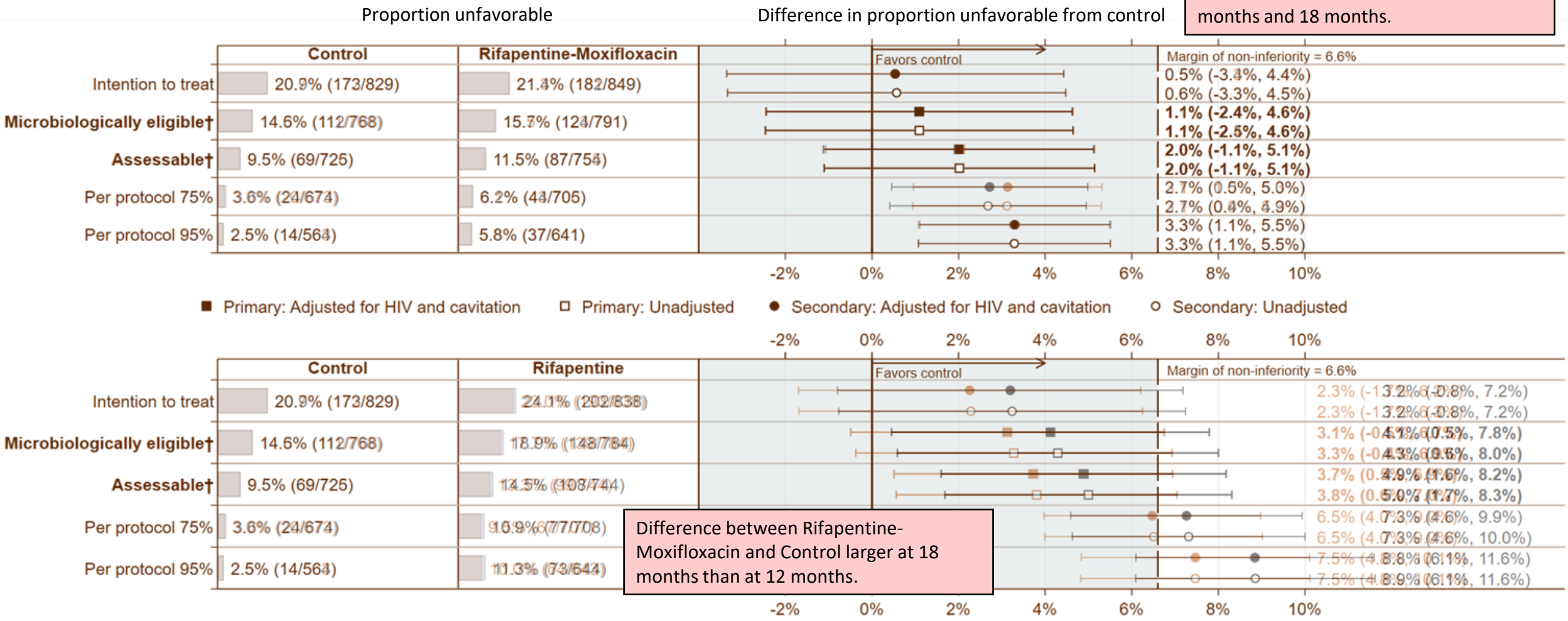
Rifapentine-moxifloxacin non-inferior to control
Rifapentine <u>not non-inferior</u> to control



Secondary 18-month outcome

12-month outcome (orange) overlayed on 18-month outcome (black)

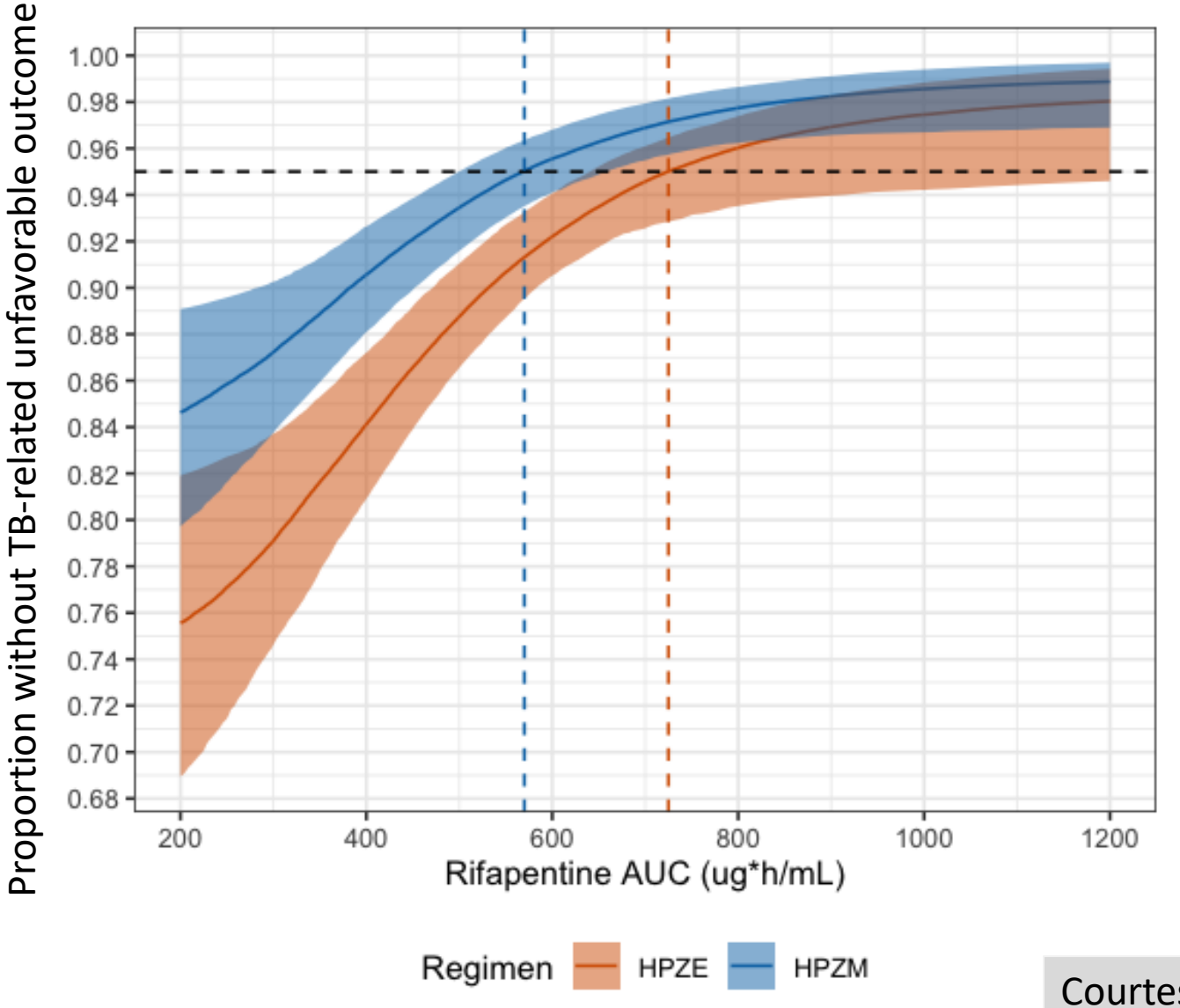
Rifapentine-Moxifloxacin comparison with Control almost identical at 12 months and 18 months.



Difference between Rifapentine-Moxifloxacin and Control larger at 18 months than at 12 months.

PK/PD Analyses

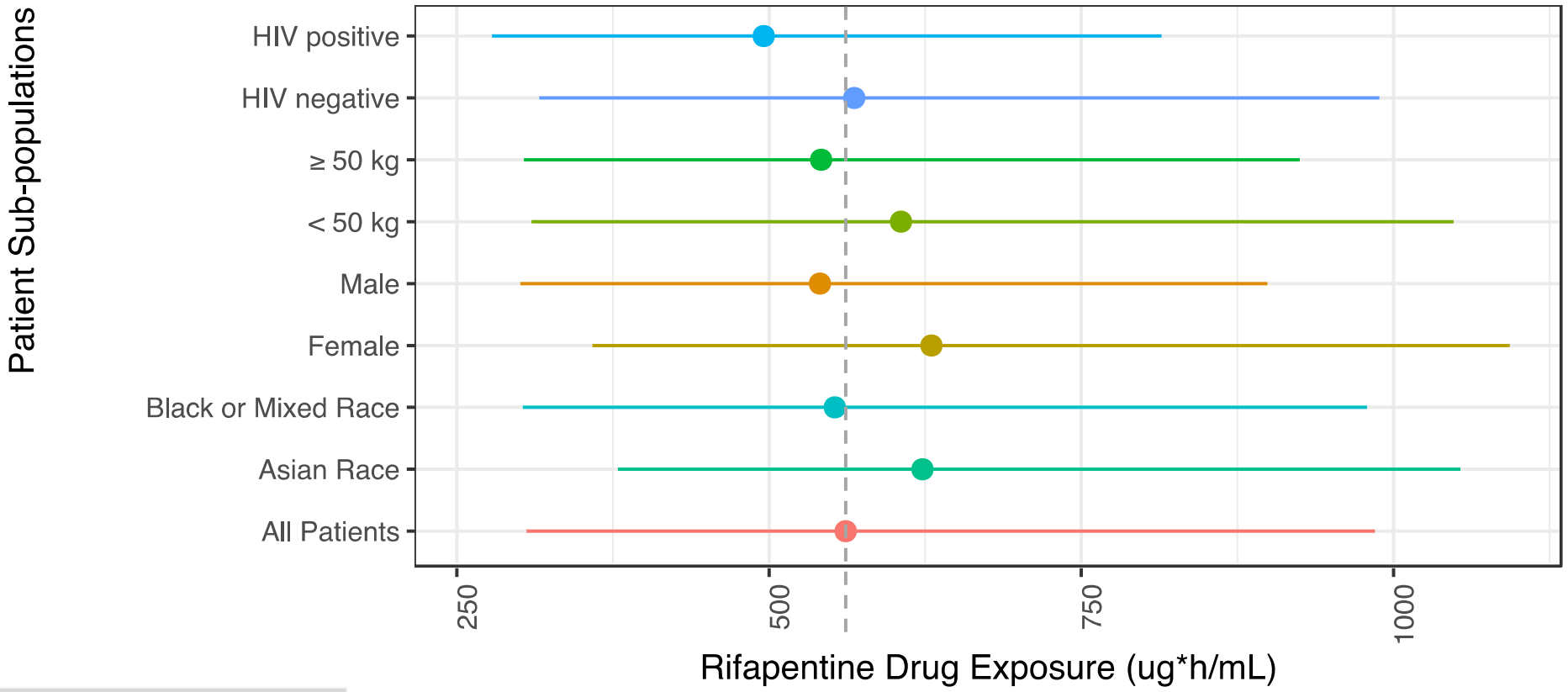
RIFAPENTINE – SIGMOIDAL EMAX RELATIONSHIP



- Rifapentine exposure is the single largest and most significant predictor for TB-related unfavorable outcomes (P = 0.00001)
- After accounting for rifapentine, on or off moxifloxacin was the only other significant drug effect (P = 0.00116)
- To achieve a target of 95% of people without a TB-related unfavorable outcome, the target rifapentine exposure (as HPZM regimen) is 570 ug*h/mL.

Courtesy of R. Savic and V. Chang

S31/A5349: Rifapentine AUC overall and for subpopulations



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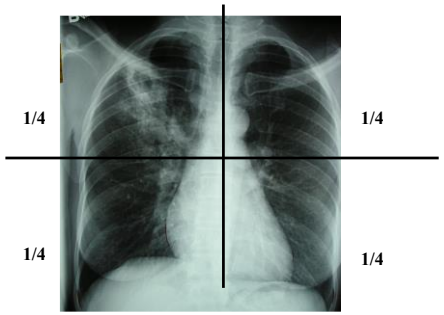
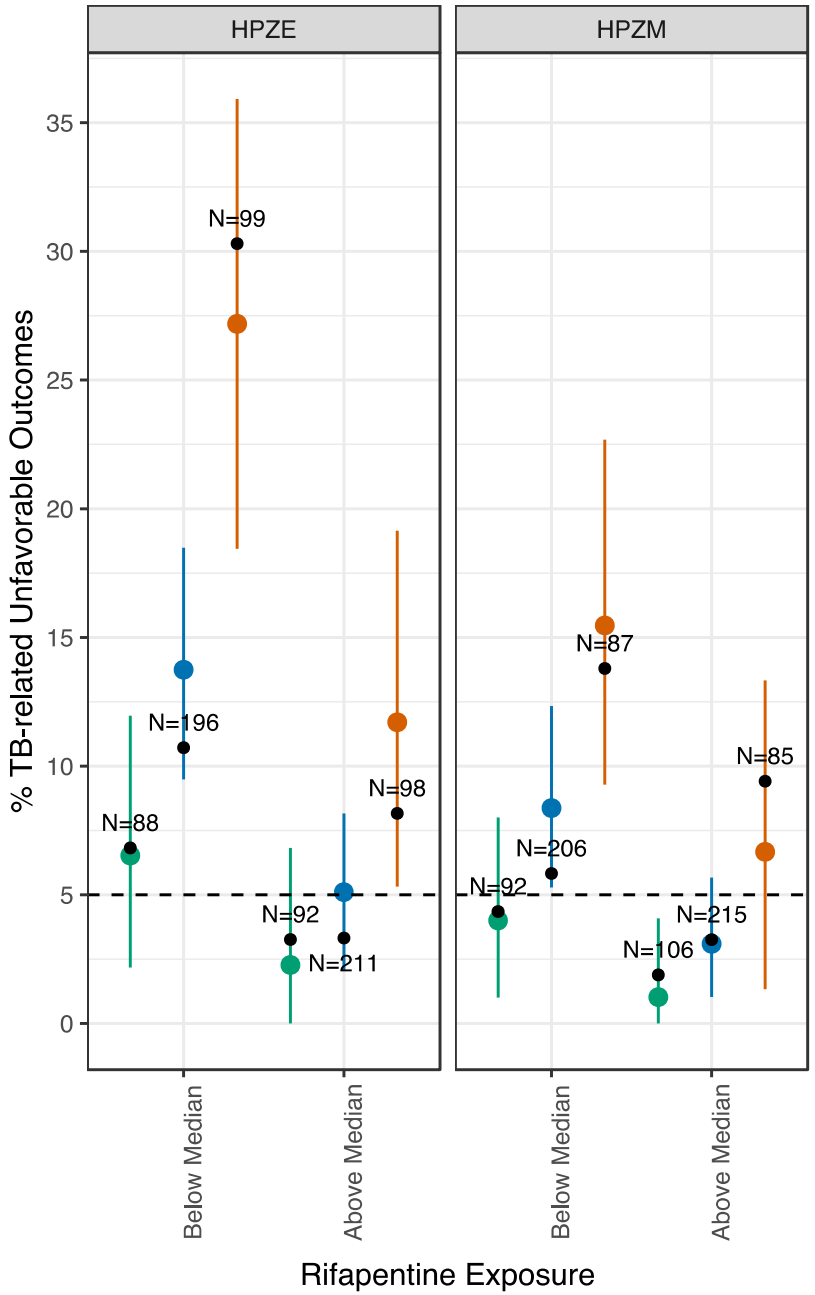


Xpert and CXR extent of disease can stratify patients into risk groups

	Gene Xpert < 18 CT	Gene Xpert ≥ 18 CT
Disease Extent < 50%	Medium Risk	Low Risk
Disease Extent ≥ 50%	High Risk	Medium Risk

- **For patients with low RPT exposure, moxifloxacin improves outcomes**
- **For medium & high risk groups, rifapentine exposure is critical factor**
- **Rifapentine exposure is more crucial in HPZE than HPZM**

Courtesy of R. Savic and V. Chang



*black dots are observed data and number of patients in strata, colored points and ranges are medians and 95% prediction interval of PKPD model.

TBTC Study 22: High risk of relapse among patients with DS-PTB who have BOTH cavitation on CXR at baseline & month 2 sputum culture positive

TABLE 5. RISK FACTORS FOR TUBERCULOSIS RELAPSE, ADJUSTING FOR SEX, AGE, AND INTERACTION OF SEX AND AGE

	Stratified Group			
	Underweight		Not Underweight	
Variable	OR (*95% CI*)	p Value	OR (*95% CI*)	p Value
⩽ 5% weight gain*	2.4 (1.1–5.5)	0.03	1.0 (0.4–2.6)	0.96
Cavity and sputum culture + after 2 mo of treatment†	7.9 (2.2–28.4)	0.02	17.8 (4.7–68.0)	< 0.0001
Cavity or sputum culture + after 2 mo of treatment†	3.5 (1.0–12.1)	0.05	3.1 (0.8–12.1)	0.10
Rifapentine treatment arm	2.0 (0.9–4.4)	0.10	1.3 (0.5–3.2)	0.59
White race	2.9 (1.3–6.7)	0.01	1.5 (0.5–4.7)	0.48

Definition of abbreviations: CI = confidence interval; OR = odds ratio.

Multivariate logistic regression analysis. Results are stratified according to whether or not patients were ⩾ 10% below ideal body weight (underweight) at diagnosis.

* Between diagnosis and completion of 2-mo intensive phase therapy.

† Compared with persons with no cavity on chest radiograph and negative sputum culture after 2 mo of treatment.

Khan A, Sterling TR, Vernon A et al. AJRCCM 2006;174:344-348

Summary

- **RPT-MOX (2HPZM/2HPM) regimen consistently met non-inferiority criteria for efficacy**
    - All primary and secondary analysis populations
    - All 14 sensitivity analyses
    - All sub-group analyses
    - 12 month f/u and 18 month f/u results almost identical

- **RPT (2HPZE/2HP) regimen did not meet non-inferiority criteria for efficacy**
    - Non-inferiority was not met in any analysis, except certain participant sub-groups
    - Difference between RPT and control regimen was larger at 18 months than at 12 months

- **Both regimens safe, well-tolerated**

- **Rifapentine exposure was the largest & most significant predictor of TB-related unfavorable outcome**

- **Baseline Xpert MTB/RIF and CXR extent of disease can stratify patients into risk groups**
    - For medium & high risk groups, rifapentine exposure is critical factor

Acknowledgments

- S31/A5349 Protocol Team
- 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