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

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Background

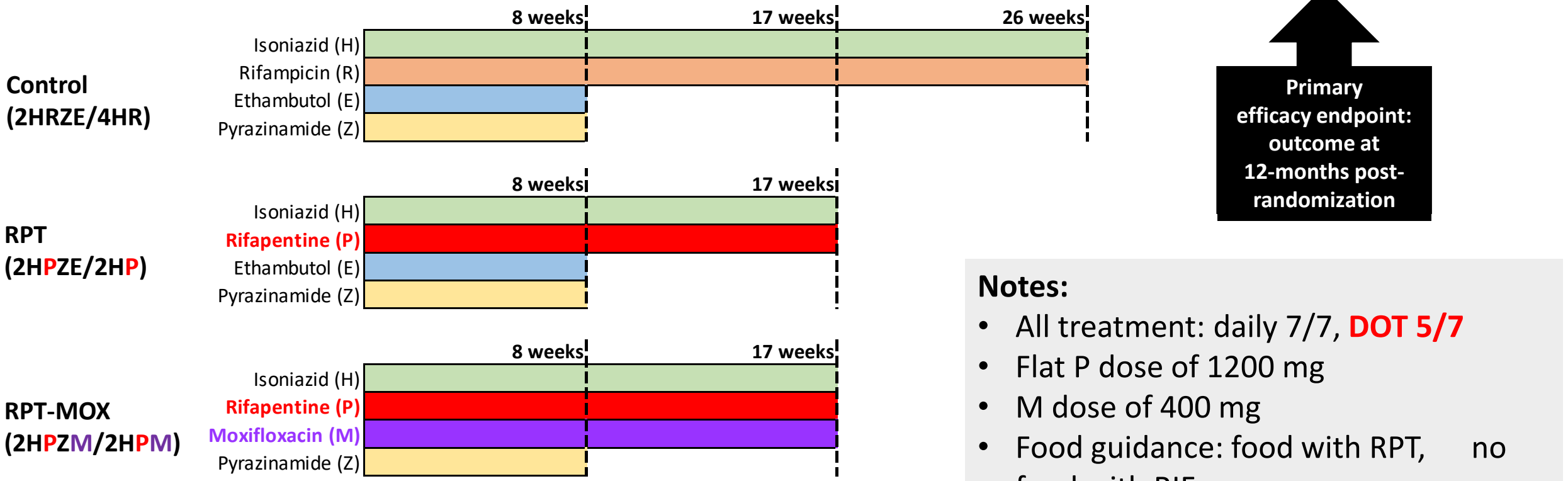
- Reducing the duration of treatment required for TB cure is a longstanding public health goal
  - Shorter regimens cure patients faster, and have the potential to reduce treatment costs, improve patient quality of life, and increase completion of therapy

- **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:

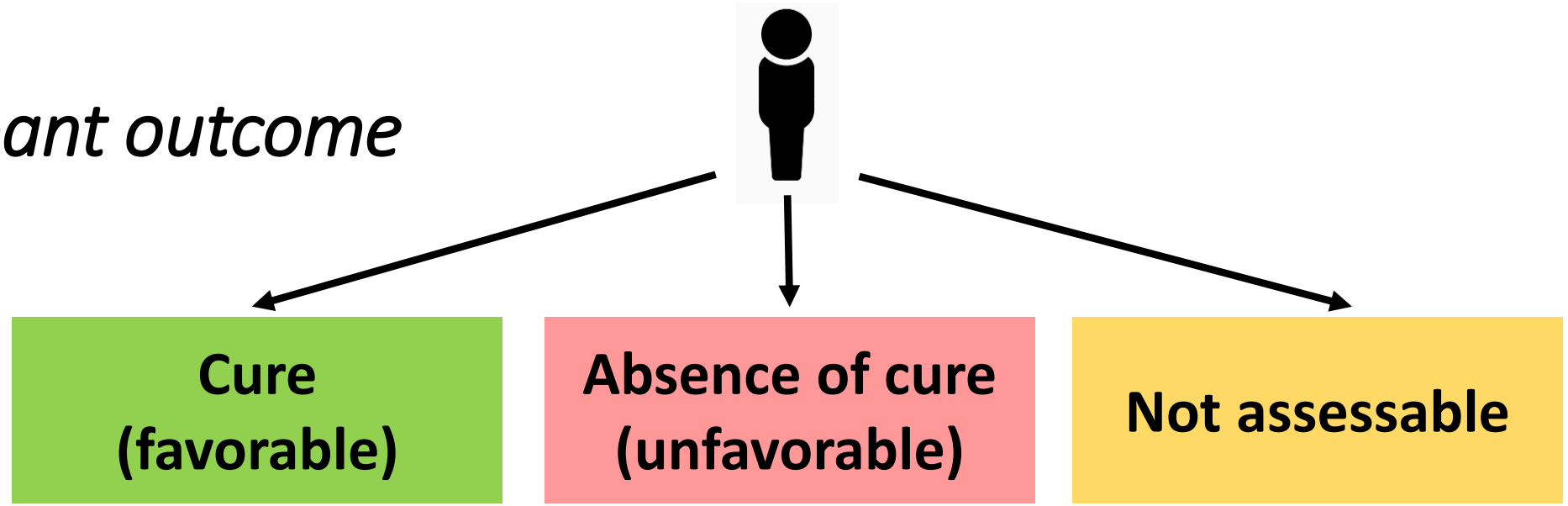
- All treatment: daily 7/7, **DOT 5/7**
- Flat P dose of 1200 mg
- M dose of 400 mg
- Food guidance: food with RPT, no food with RIF

Key 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:

2516 participants enrolled at
34 clinical research sites in 13 countries on 4 continents

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 for efficacy and safety

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

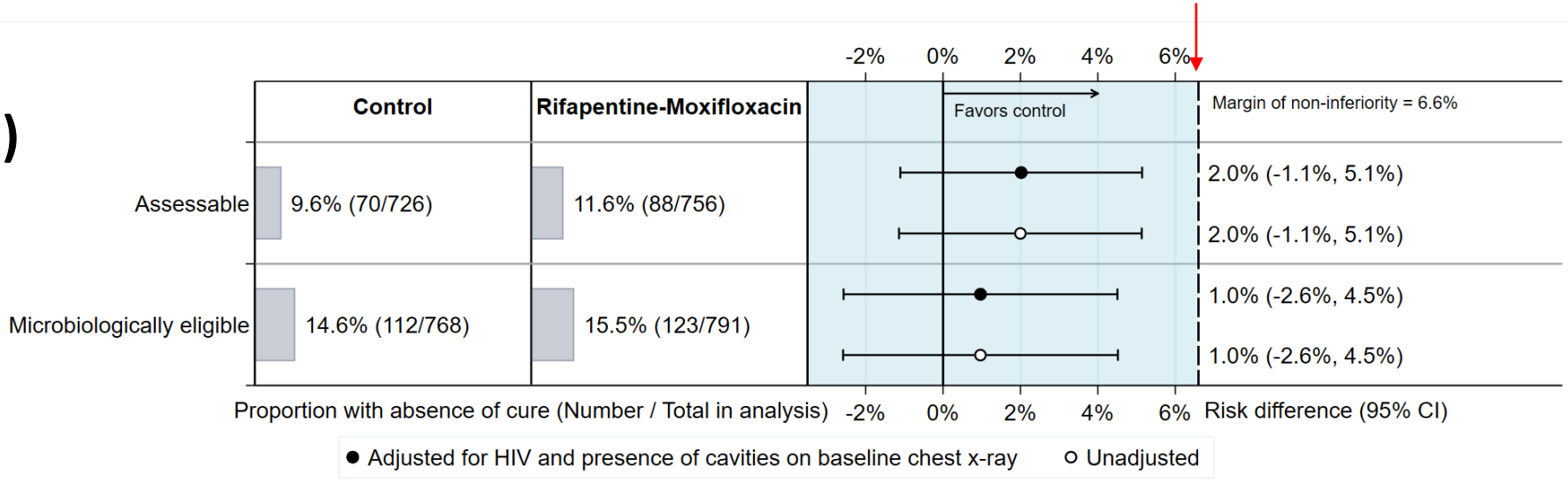
Assessable analysis population

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%)

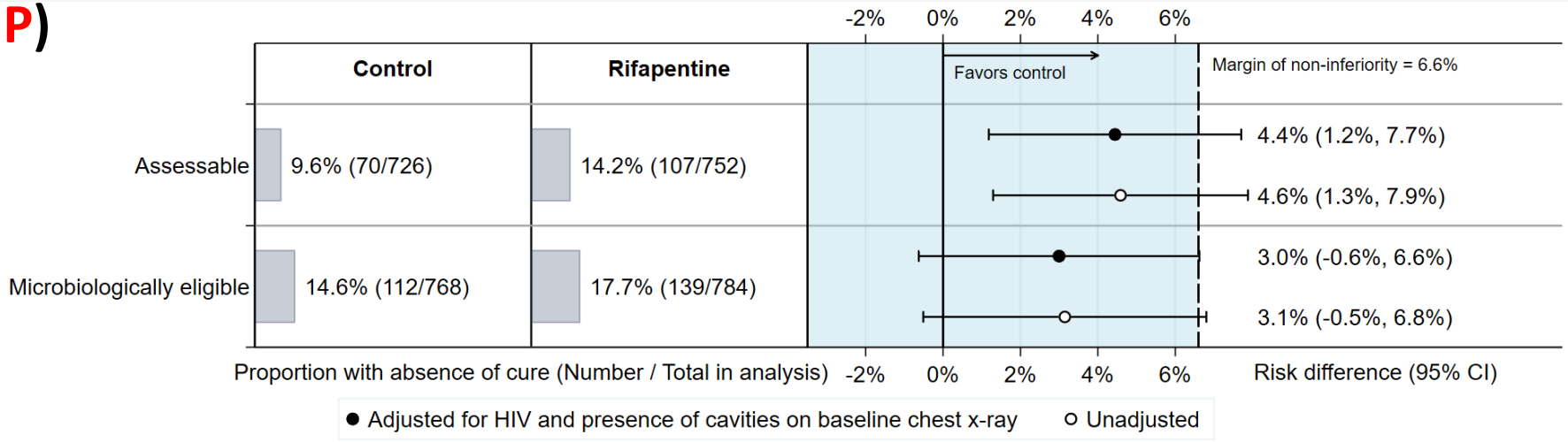
Note. Percentages are column percent. Denominator is number of participants in each group in assessable population.

Primary Efficacy Results

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



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



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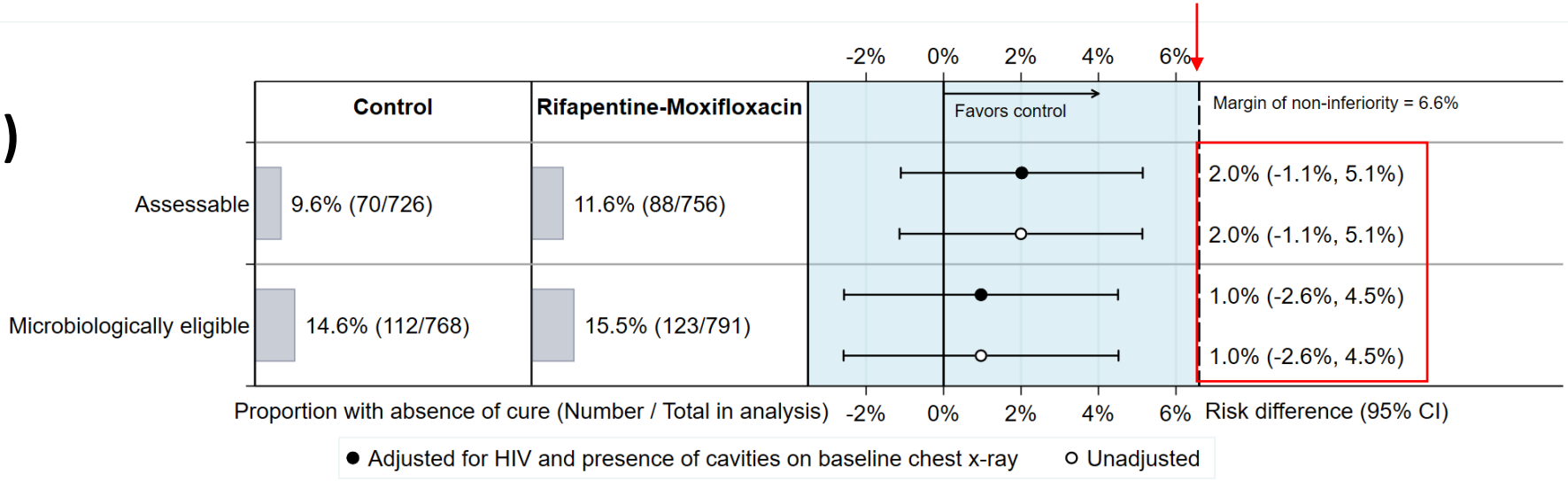
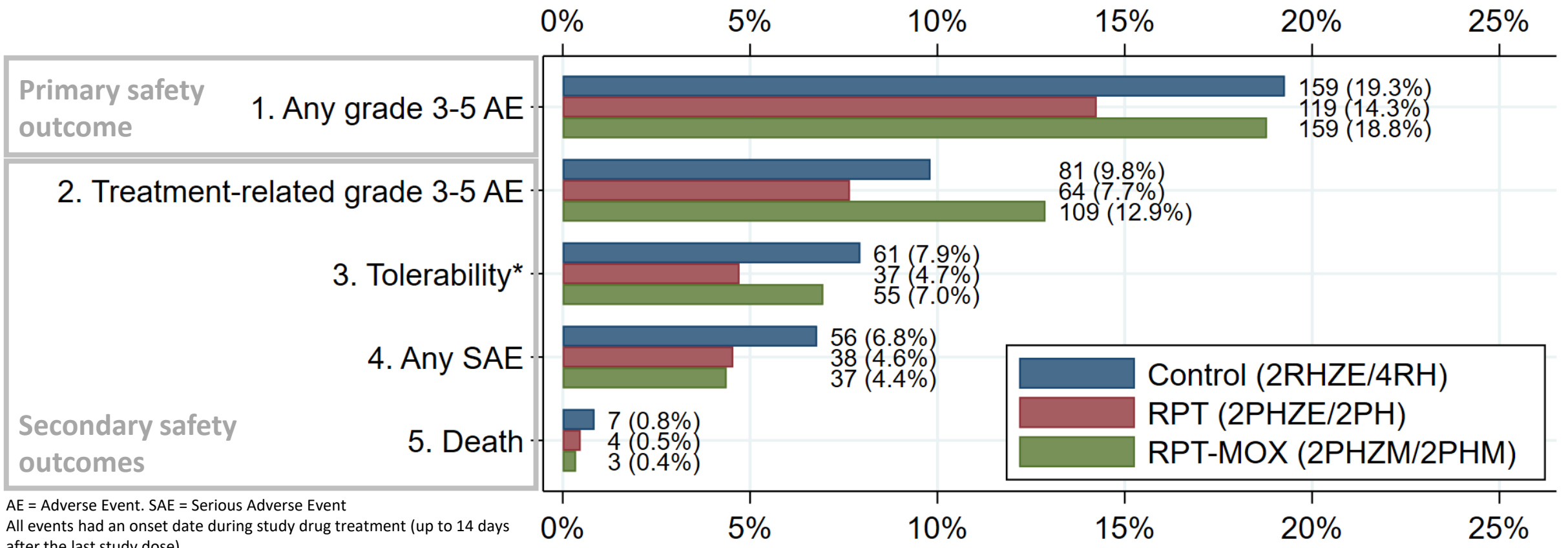


Risk differences (95% CI) *in favor of streptomycin (control)* for trials in which streptomycin was replaced by ethambutol:

- 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 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

Liver chemistries in S31/A5349

- FDA perspective: 3 major indicators of a potential for severe drug induced liver injury (DILI):
  - An excess of aminotransferase elevations to >3X ULN compared to a control group;
  - Marked elevations of aminotransferases to 5X, 10X, or 20X ULN in modest numbers of subjects in a test drug group and not seen (or seen much less frequently) in the control group;
  - Newly elevated total serum bilirubin to >2X ULN in a setting of pure hepatocellular injury, with no other explanation, accompanied by an overall increased incidence of aminotransferase elevations >3X ULN in the test drug group compared to placebo.

FDA. Guidance for Industry: drug-induced liver injury: premarketing clinical evaluation. July 2009. https://www.fda.gov/media/116737/download.

1. **An excess of aminotransferase elevations to >3X ULN compared to the control group.**
This was not observed in S31/A5349 (Table 1).

Table 1	Control (n=825)	RPT (n=835)	RPT-MOX (n=846)
ALT or AST ≥3X ULN	49 (5.9%)	36 (4.3%)	45 (5.3%)

2. **Marked elevations of aminotransferases to 5X, 10X, or 20X ULN in modest numbers of subjects in a test drug group and not seen (or seen much less frequently) in the control group.**
This was not observed in S31/A5349 (Table 2).

Table 2	Control (n=825)	RPT (n=835)	RPT-MOX (n=846)
ALT or AST ≥5X ULN	25 (3.0%)	15 (1.8%)	20 (2.4%)
ALT or AST ≥10X ULN	10 (1.2%)	5 (0.6%)	4 (0.5%)
ALT or AST ≥20X ULN	4 (0.5%)	2 (0.2%)	1 (0.1%)

3. Newly elevated total serum bilirubin to >2X ULN in a setting of pure hepatocellular injury, with no other explanation, accompanied by an overall increased incidence of aminotransferase elevations >3X ULN in the test drug group compared to placebo.

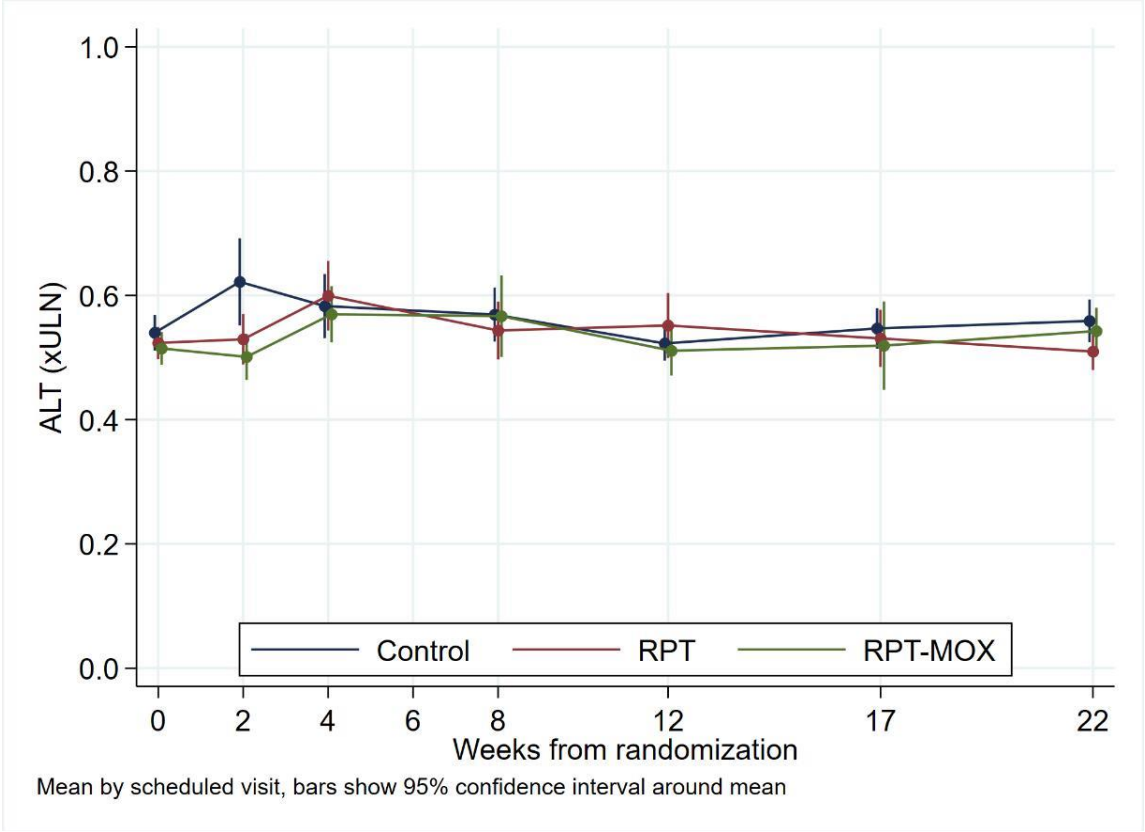
The following table (Table 3) includes all participants who had a serum total bilirubin ≥ 2X ULN at any time during study participation and a serum ALT or AST ≥ 3X ULN at any time during study participation.

Table 3	Control (n=825)	RPT (n=835)	RPT-MOX (n=846)
Total bilirubin ≥2X ULN **AND ALT or AST ≥3X ULN**	8 (1.0%)	12 (1.4%)	16 (1.9%)

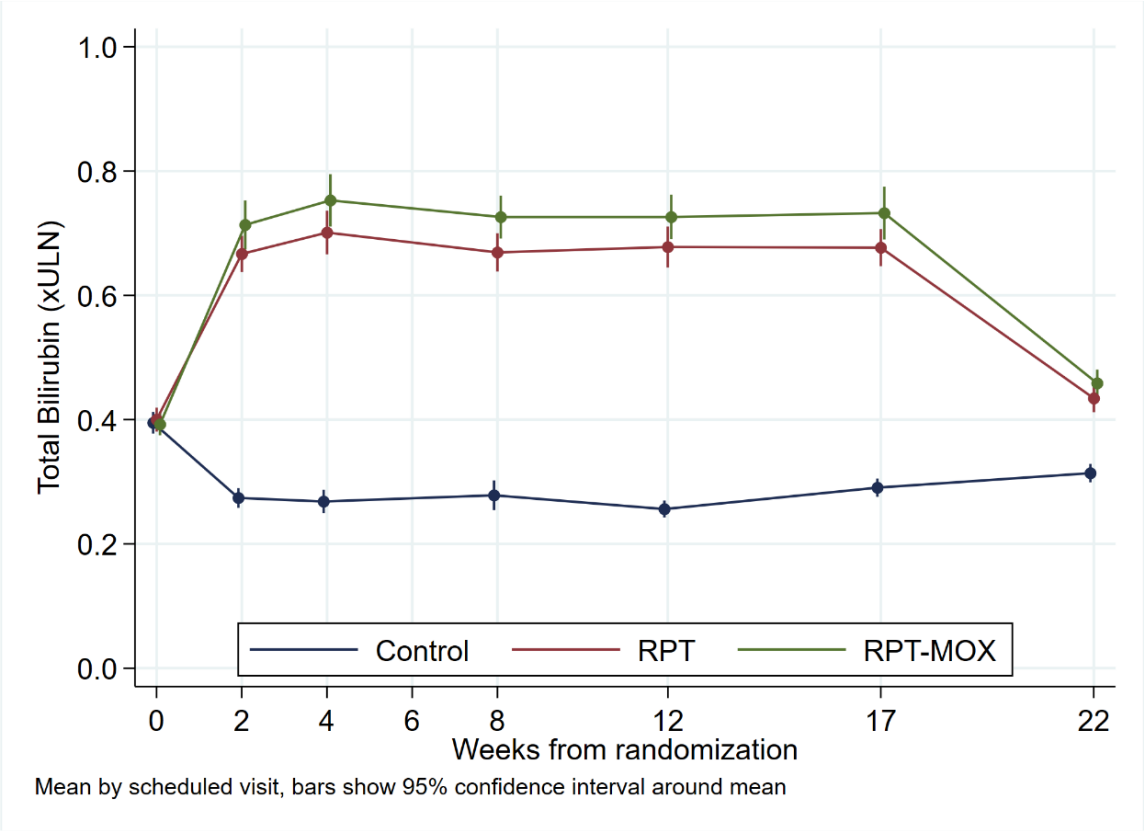
Table 4	Control (n=825)	RPT (n=835)	RPT-MOX (n=846)
Total bilirubin ≥2X ULN **AND ALT or AST ≥3X ULN**	8 (1.0%)	12 (1.4%)	16 (1.9%)
Total bilirubin ≥2X ULN **AND ALT or AST ≥5X ULN**	6 (0.7%)	8 (1.0%)	9 (1.0%)
Total bilirubin ≥2X ULN **AND ALT or AST ≥10X ULN**	3 (0.4%)	4 (0.5%)	2 (0.2%)

S31/A5349

Mean values over time for blood ALT and blood total bilirubin among participants in the safety analysis population



Alanine aminotransferase



Blood total bilirubin

Mechanisms of rifamycin-associated bilirubin increases

- Hepatocellular injury
- Dose-dependent interference with bilirubin uptake
- Inhibition of bile salt exporter pumps
- Competition with bilirubin for clearance at the sinusoidal membrane
- Impedance of bilirubin secretion at the canalicular level

1. Chitturi S and Farrell G. Drug-induced liver disease. In: Shiff ER, Sorrell MF, Maddrey WC, eds. Schiff's diseases of the liver, 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2002. Pp 1059-1128.
2. Saukkonen JJ et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006;174:935-952.
3. Grosset J, Leventis S. Adverse effects of rifampin. Rev Infect Dis 1983;5:S440-450.
4. Capelle P et al. Effect of rifampicin on liver function in man. Gut 1972;13:366-371.
5. Byrne JA et al. The human bile salt export pump: characterization of substrate specificity and identification of inhibitors. Gastroenterology 2002;123:1649-1658.

Liver chemistries in S31/A5349

CONCLUSION

In S31/A5349, elevations in serum bilirubin without marked elevations in aminotransferases appear to be more consistent with rifamycin’s known effects on bilirubin handling than with severe hepatocellular injury.

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

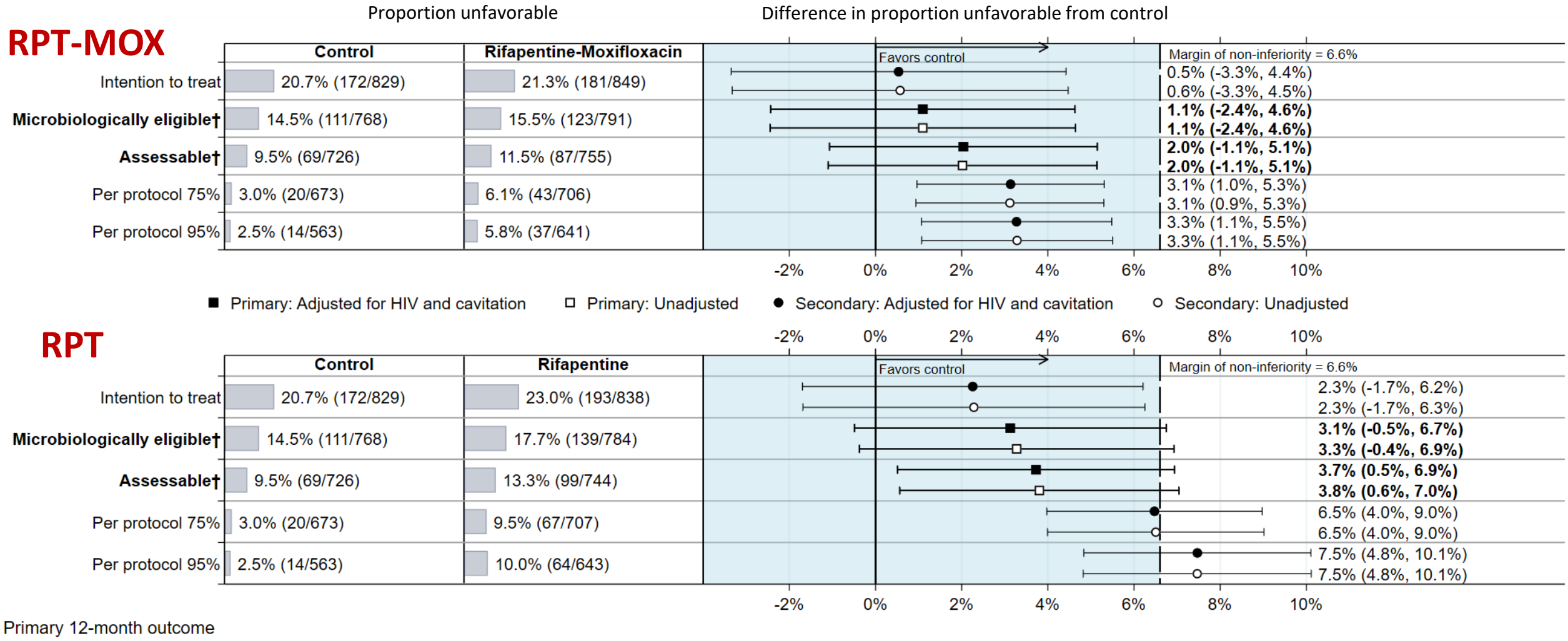
Safety

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

18 month results

Primary 12-month outcome

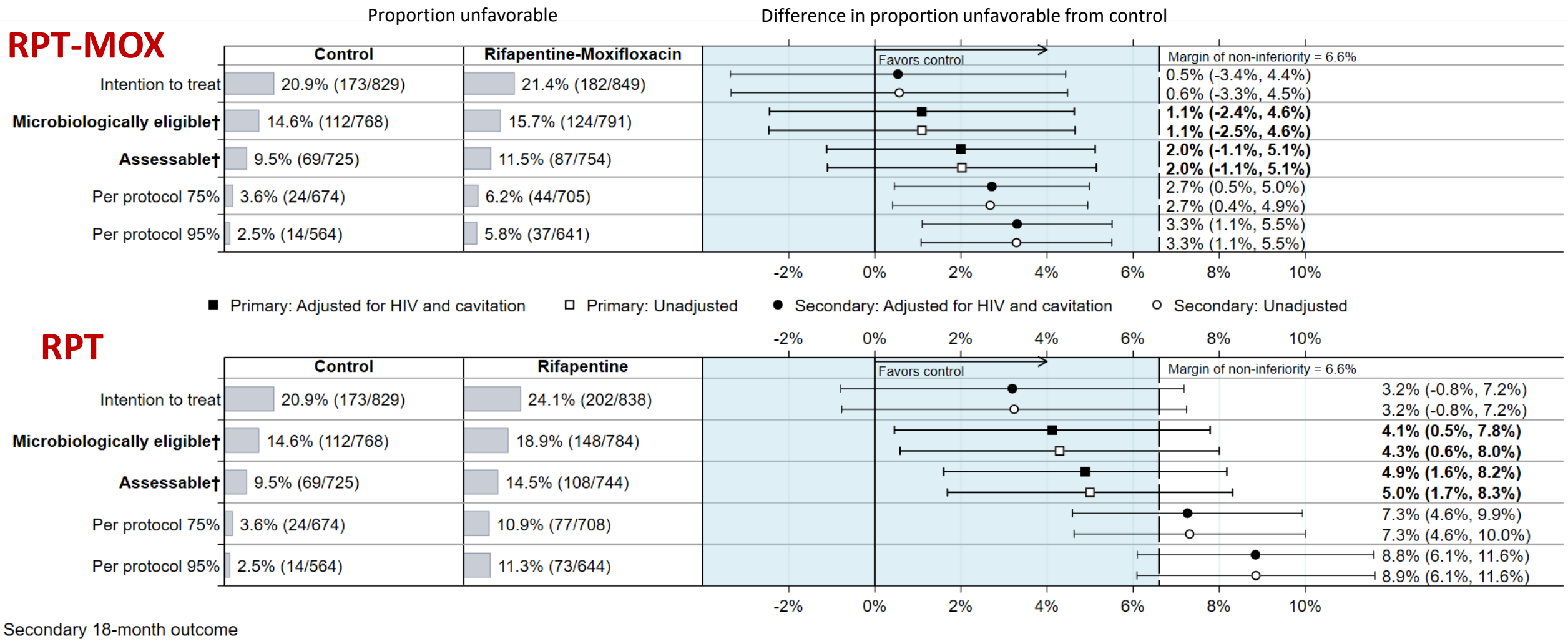
Rifapentine-moxifloxacin non-inferior to control
Rifapentine not non-inferior to control



Primary 12-month outcome

Secondary 18-month outcome

Rifapentine-moxifloxacin non-inferior to control
Rifapentine not non-inferior to control

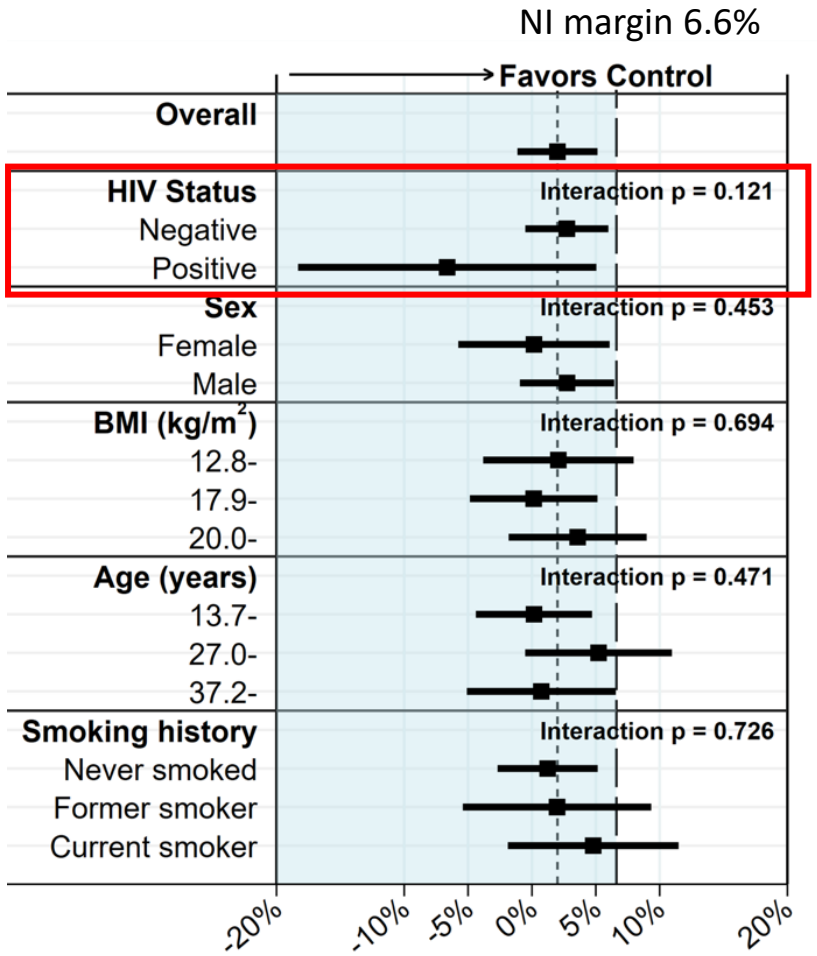


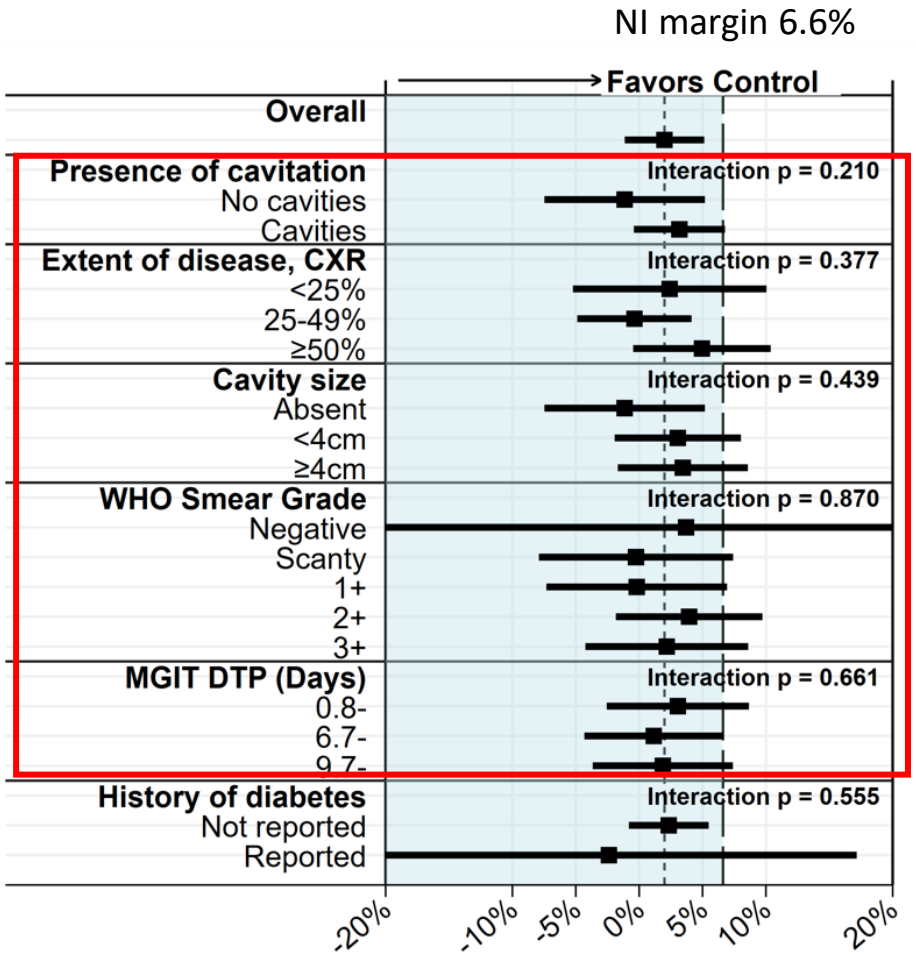
Secondary 18-month outcome

Subgroup Analyses

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





HIV-infected Population (214 randomized)

Safety Outcomes	Control	RPT	RPT-MOX	Total
Total safety population	**70**	**71**	**72**	213
Primary Safety Outcome (Grade 3-5 AEs on treatment)	16 (22.9%)	14 (19.7%)	12 (16.7%)	42 (19.7%)
SAEs during treatment	8 (11.4%)	6 (8.5%)	2 (2.8%)	16 (7.5%)
Deaths	2 (2.9%)	3 (4.2%)	0 (0.0%)	5 (2.3%)

Efficacy outcomes (% unfavorable)	Control	RPT	RPT-MOX	Total
Primary: Assessable	9/59 (15.3%)	17/65 (26.2%)	5/58 (8.6%)	31/182 (17.0%)
Primary: Microbiologically eligible	14/64 (21.9%)	20/68 (29.4%)	9/62 (14.5%)	43/194 (22.2%)

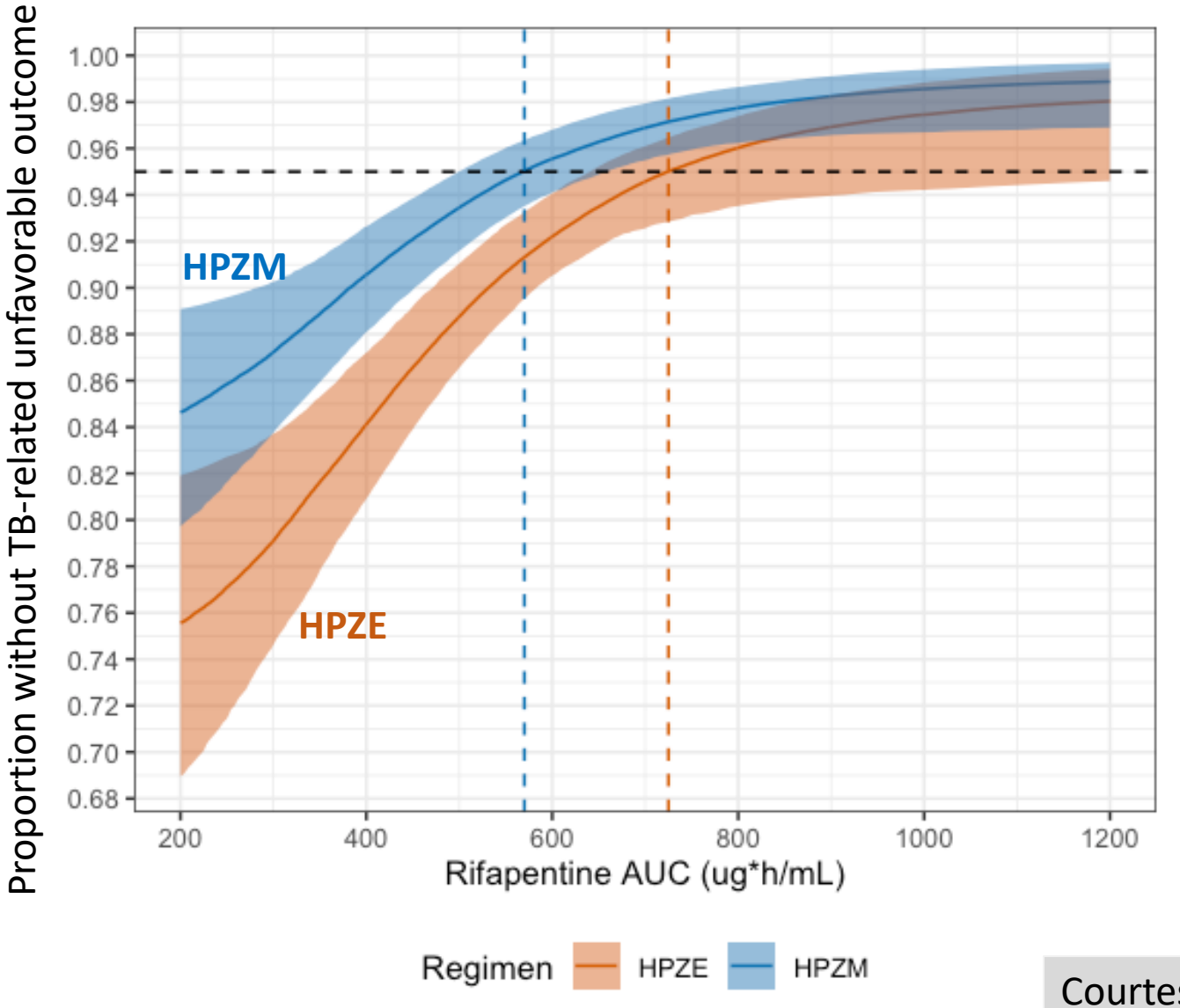
Adolescents (68 randomized)

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 (% unfavorable)	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%)

Pharmacokinetic / Pharmacodynamic Analyses

RIFAPENTINE – SIGMOIDAL EMAX RELATIONSHIP

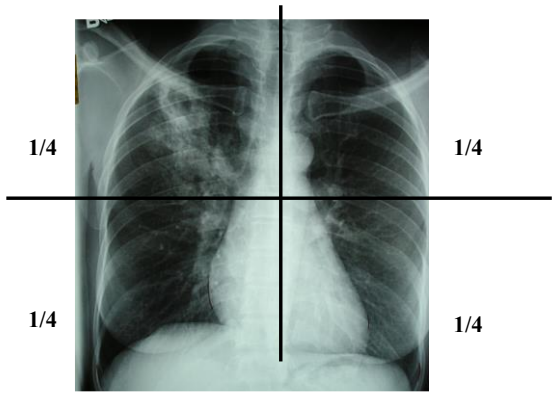


- Rifapentine exposure is the single largest and most significant predictor for TB-related unfavorable outcomes (P = 0.00001)
- After accounting for rifapentine, on or off moxifloxacin was the only other significant drug effect (P = 0.00116)
- To achieve a target of 95% of people without a TB-related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

Courtesy of R. Savic and V. Chang

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

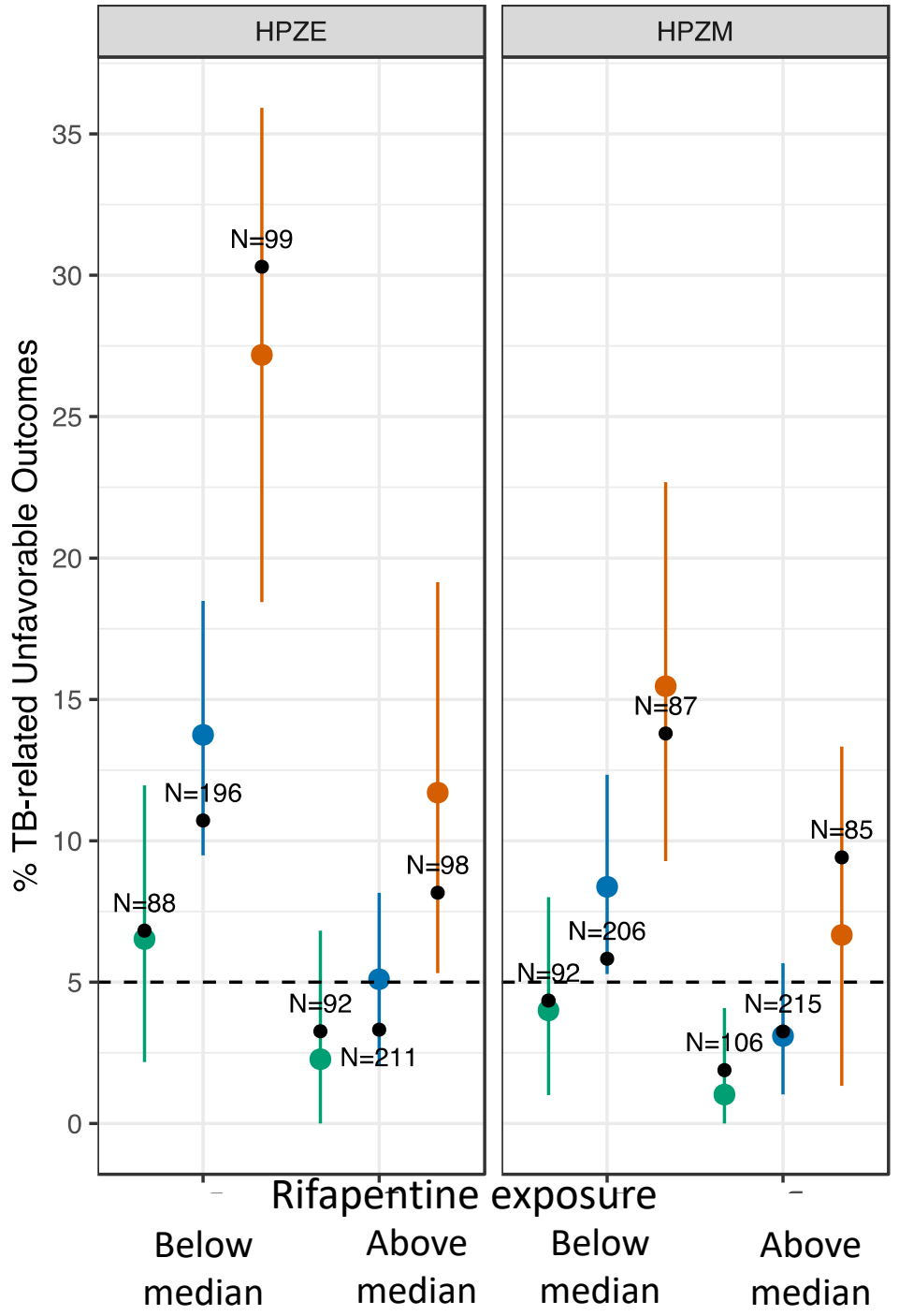
Courtesy of R. Savic and V. Chang



	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 (esp in high risk group)**
- **For medium & high risk groups, rifapentine exposure is critical factor**
- **Rifapentine exposure is more crucial in HPZE than HPZM**

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



Patient classification based on baseline Xpert and CXR extent of dz:

- HIGH RISK
- MEDIUM RISK
- LOW RISK

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**

Some concluding thoughts…

- There was no cure for TB when our grandparents were kids
- Past 75 years: cure in 24 months…to 18…to 9…to 6…**to 4**…to 2?
- Envision a TB-free future!
  - Socioeconomic progress – the rising tide that lifts all boats
  - Your hard (TB program) work & care for people with TB and across the spectrum of TB infection and risk
  - Research and its application

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

Supplemental Slides

Margin of non-inferiority of 6.6%

Important differences between:

1. Trials of completely novel regimens
2. Substitution treatment-shortening trials

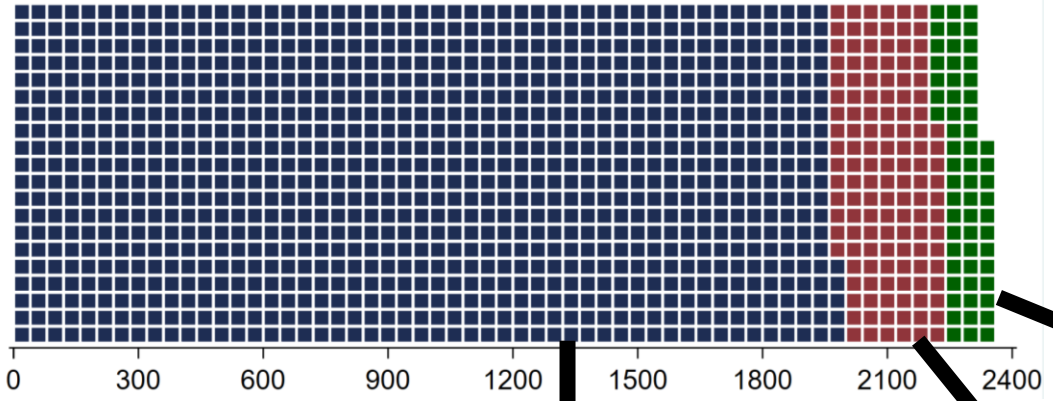
- **New regimens**: e.g. STAND (**12%**), SimpliciTB (**12%**), STREAM (**10%**), endTB (**12%**), TRUNCATE (**12%**)
- **1- or 2-drug substitution**: e.g. REMoxTB (**6%**), RIFAQUIN (**6%**), OFLOTUB (**6%**), NIRT CTRI/2012/10/003060 (**5%**), S31/A5349 (**6.6%**)

Two-pronged justification for S31/A5349

- Statistical:
  - 6.6% is sufficiently small to provide evidence that 4-month regimens are superior to no treatment AND superior to 4-month HRZE (standard therapy).
- Clinical: Two large publicly-funded international consortia of TB stakeholders (TBTC and ACTG) consider:
  - The benefits of a 4-month rifapentine- based regimen justify the margin of 6.6%.
  - 600 patients per arm sufficiently large to provide adequate precision on the difference in efficacy between the regimens to determine whether an intervention regimen might be considered not inferior to the control regimen.

12-month outcomes

Microbiologically eligible analysis population



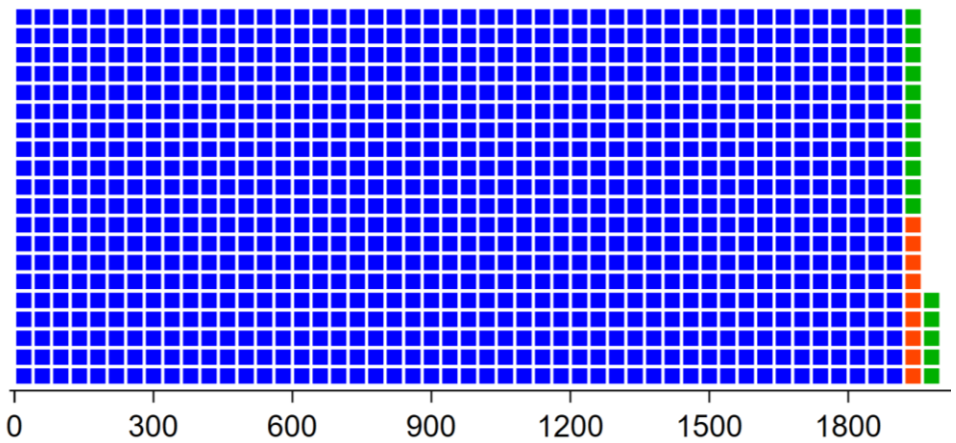
Favorable: 1970 (84.1%)

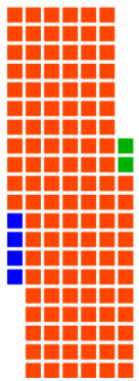
Unfavorable: 255 (10.9%)

Not Assessable: 118 (5.0%)

What changed from 12 to 18 months?

18-month outcomes





Favorable: 7 (2.8%)

Unfavorable: 245 (96.1%)

Not assessable: 3 (1.2%)

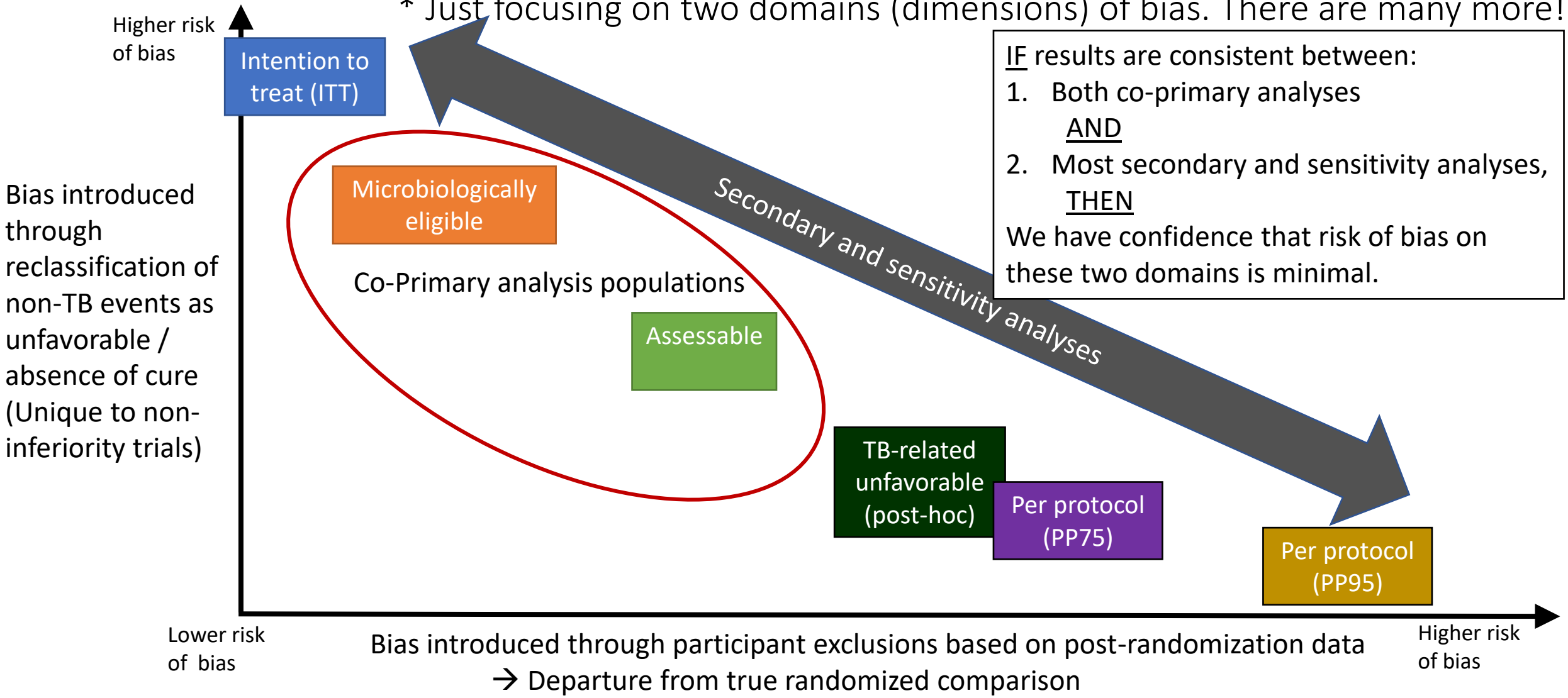
Favorable: 33 (27.8%)

Unfavorable: 1 (0.9%)

Not assessable: 84 (71.2%)

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.