The Key to Success for Developing a New Regimen to Advance TB Treatment: Lessons from TBTC Study 31 (S31/A5349)

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On behalf of the S31/A5349 community

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.

TBTC TB Trials Consortium CDC

Center for Tuberculosis

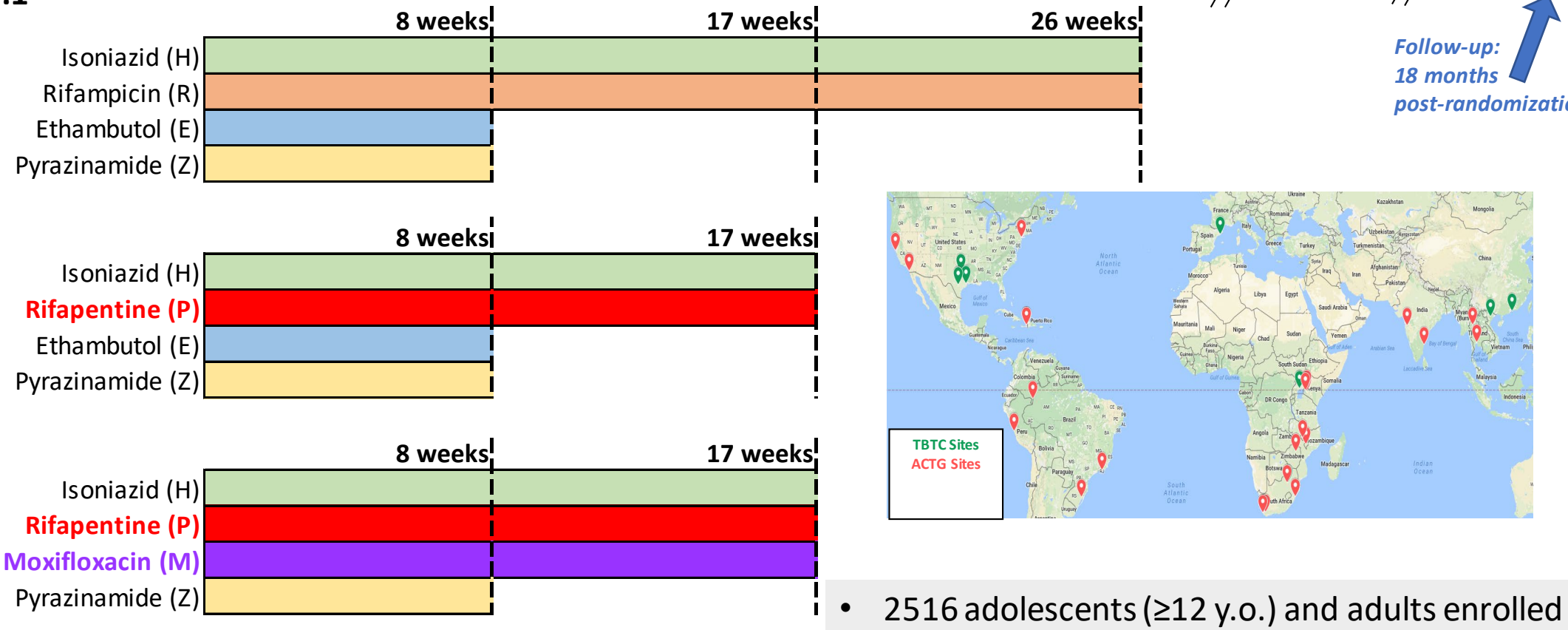
UCSF University of California San Francisco

ACTG AIDS CLINICAL TRIALS GROUP

Phase 3 Non-Inferiority Trial

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

3 arms randomization 1:1:1

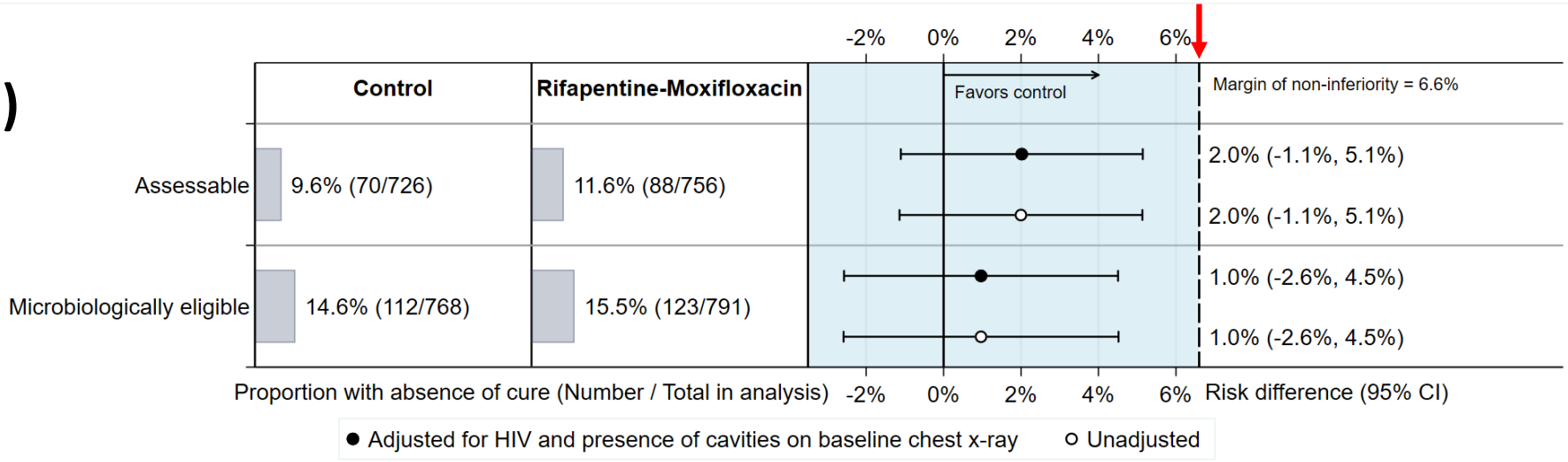


- 2516 adolescents (≥12 y.o.) and adults enrolled
- HIV-infected (CD4≥100) and HIV-uninfected
- All treatment: daily 7/7, **DOT 5/7**
- Flat RPT dose of 1200 mg; MOX dose of 400 mg
- Open label: food with RPT, no food with RIF

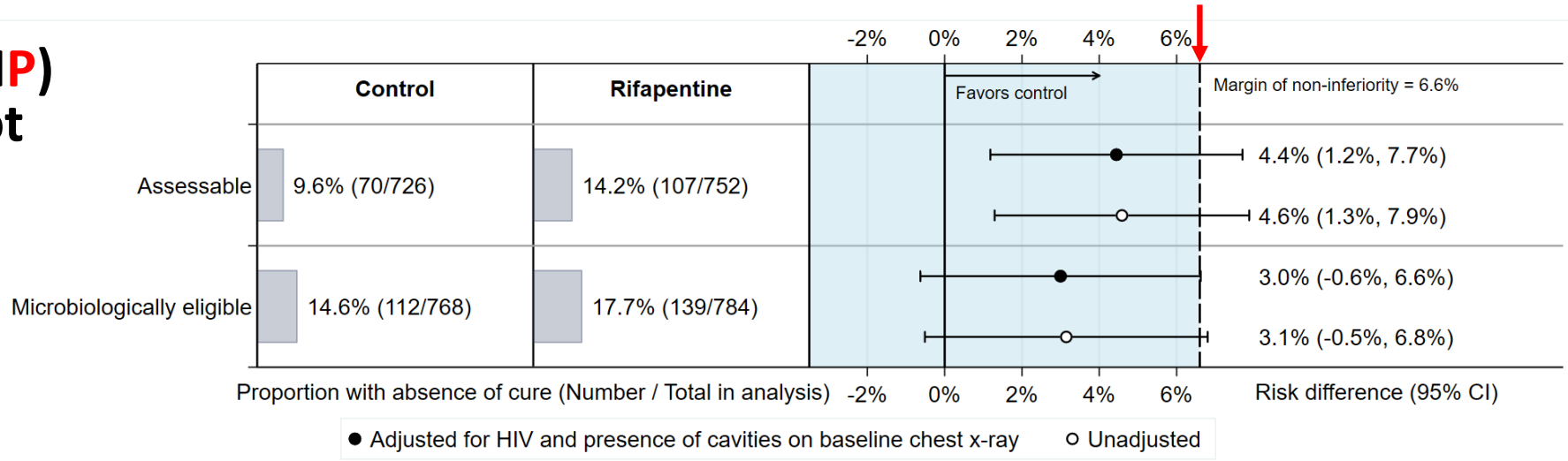
Sputum, safety labs & AE checks: Weeks 2, 4, 8, 12, 17, 22, 26
Post-tx completion f/u visits Months 9, 12, 15, 18

Primary Efficacy Results

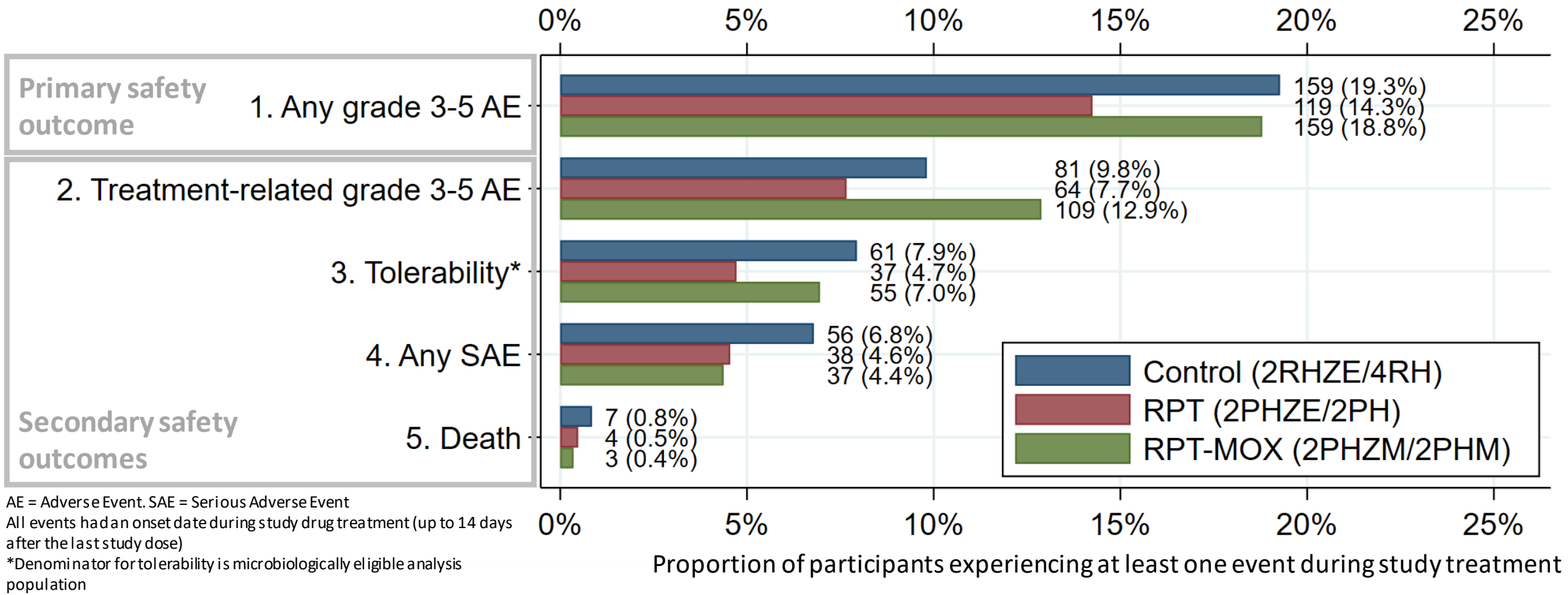
RPT-MOX (2HPZM/2HPM) regimen met non-inferiority criteria for efficacy in <u>both</u> analyses



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



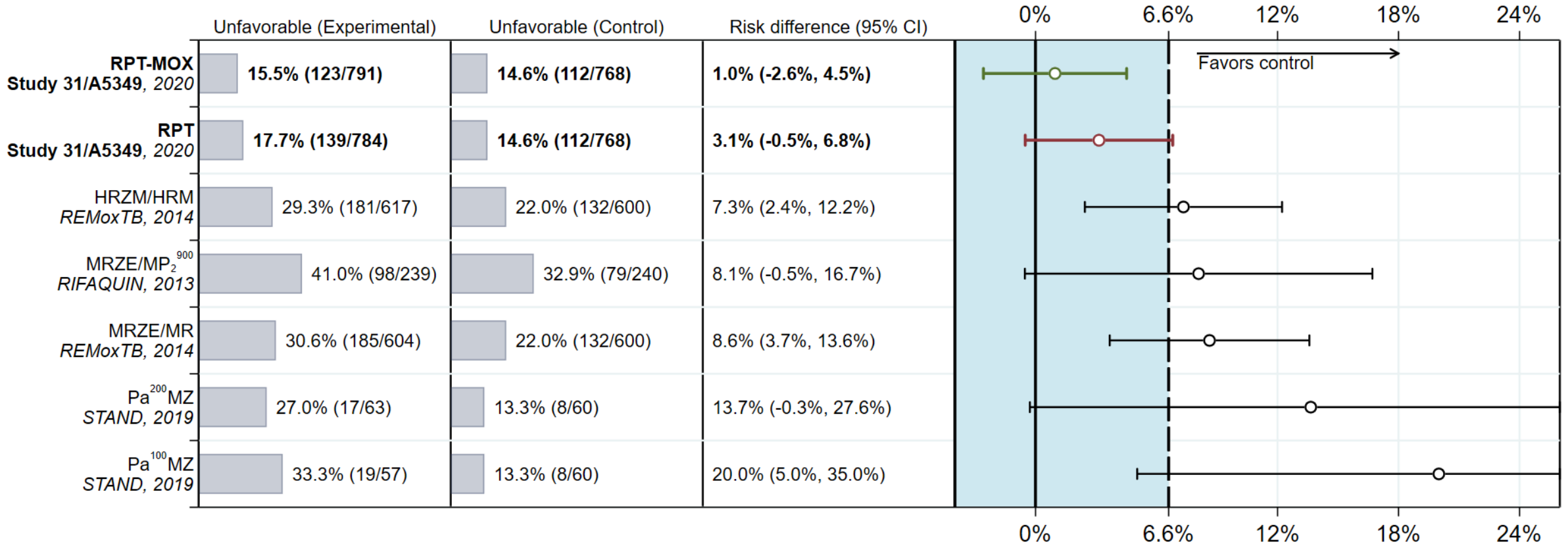
Primary and secondary safety outcomes



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

Context in 4-month DS-TB regimens from 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.

Courtesy Patrick Phillips, UCSF

How did S31/A5349 get here? It's been a long road.

BMRC and Chinese RPT PK studies – weekly dosing emphasized

Chinese RPT weekly trial

TBTC Study 22

FDA approval of weekly RPT/H in continuation phase

Phase 2 MOX trials

-Conde (Brazil)

-Rustomjee (SA)

-TBTC Study 27

-TBTC Study 28

Phase 3 MOX trials
-ReMOX
-OfloTUB

RPT-MOX trials
-RioMAR
-JHU/UCT
-Rifaquin

High-dose RPT trials
-TBTC Study 29
-TBTC Study 29x

TBTC Study 31/ACTG A5349

Murine Studies (Mitchison, Grosset, Nuermberger)

1980s 1990s 2000s 2010s 2020

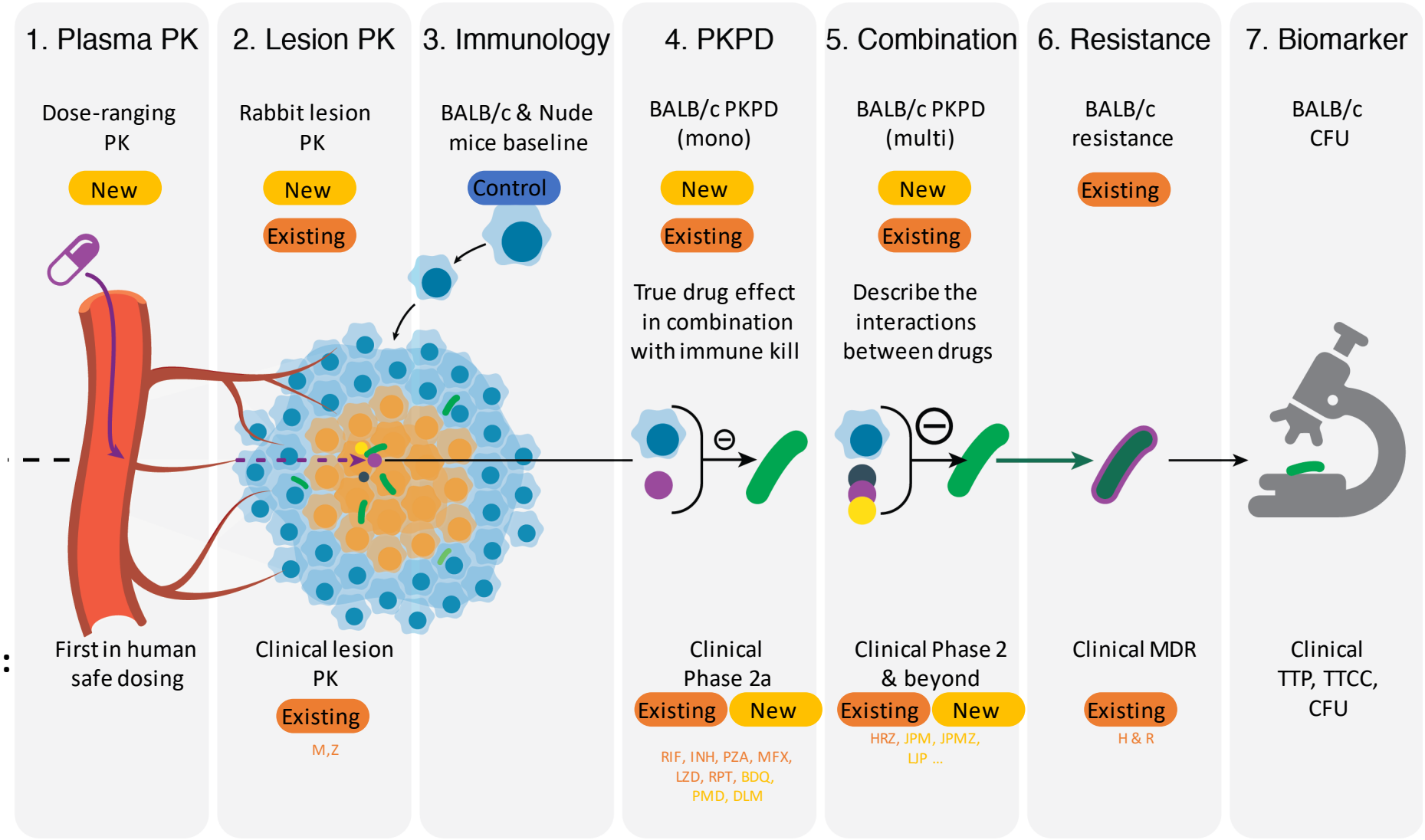
PK Studies (Weiner, McIlleron, Dooley, Savic, Podany)

Courtesy Dick Chaisson, JHU

De-risking S31/A5349 through learnings

1. Prioritized experimental murine models
2. Conducted iterative phase 2 trials w/ moxifloxacin and rifapentine
3. Embedded Intensive and sparse PK substudies to support *exposure-response* analyses
   - Modelling of PK, efficacy data, tolerability data, biomarker data, defining the impact of key variables and food on finding **the optimal dose**
   - Not the lowest effective dose, rather targeting the maximal tolerated exposure

Quantitative Translation Toolbox for TB Regimen Development



Courtesy Rada Savic, UCSF / Ernest JP et al, Annu Rev Pharmacol Toxicol. 2021

Mitigating risk through S31/A5349 design and conduct

- Sample size of 2500 participants allowed for assessment in subgroups
- Sparse PK was implemented across all arms, all TB drugs, all patients
- HIV enrollment staged with EFV PK and viral load assessments for safety
- Measuring adherence and maximizing retention to give regimens their best chance ("high assay sensitivity for non-inferiority").
- Standardization of laboratory practices across sites, earnestly adopted
- Real-time data management and reports facilitating QA at sites, monitoring and DSMB reviews
- Placing priority on minimizing bias when measuring endpoints (extensive trainings, *"Possible Poor Treatment Response"* procedure)
- Embedding substudies of innovative biomarkers, PK, other investigations (intensive PK, 31A, 31B, adolescents) enrich learnings.

Summary of Lessons learned

1. It's a long road – learn from who went before and build. Beware of short cuts!
2. Experimental models including murine studies, biomarkers and novel tools are non-negotiable. Pre-clinical work using new tools that provide orthogonal information should be prioritized. Test the exact regimens and interpret results cautiously.
3. Get the Phase 2 designs set up right from the outset. If designed well, Phase 2,in combo with PK and PD studies will pave the way and de-risk decisions.
4. Don't put all your eggs in one basket / build-in protections (RPT/MOX arm) / add substudies to enrich learning.
5. Recruit broadly and representatively. Try to conduct programme-based studies. In combination, these will maximize learnings and aid adoption in global policy.
6. Collaboration is key / be a good collaborator / share the credit.

S31/A5349 Protocol Team

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S31/A5349 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

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Patrick Phillips, UCSF

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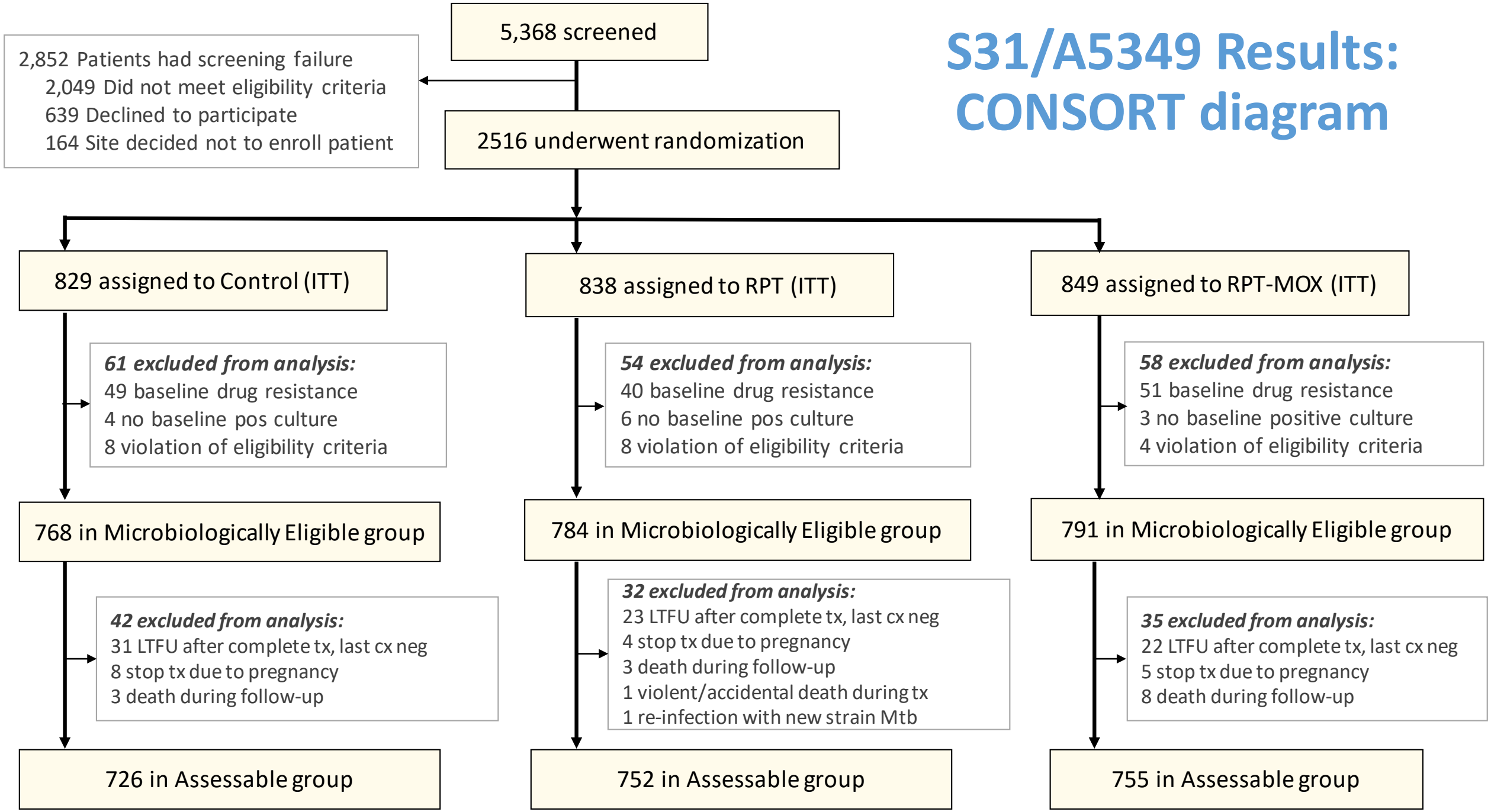
Back-Up Slides

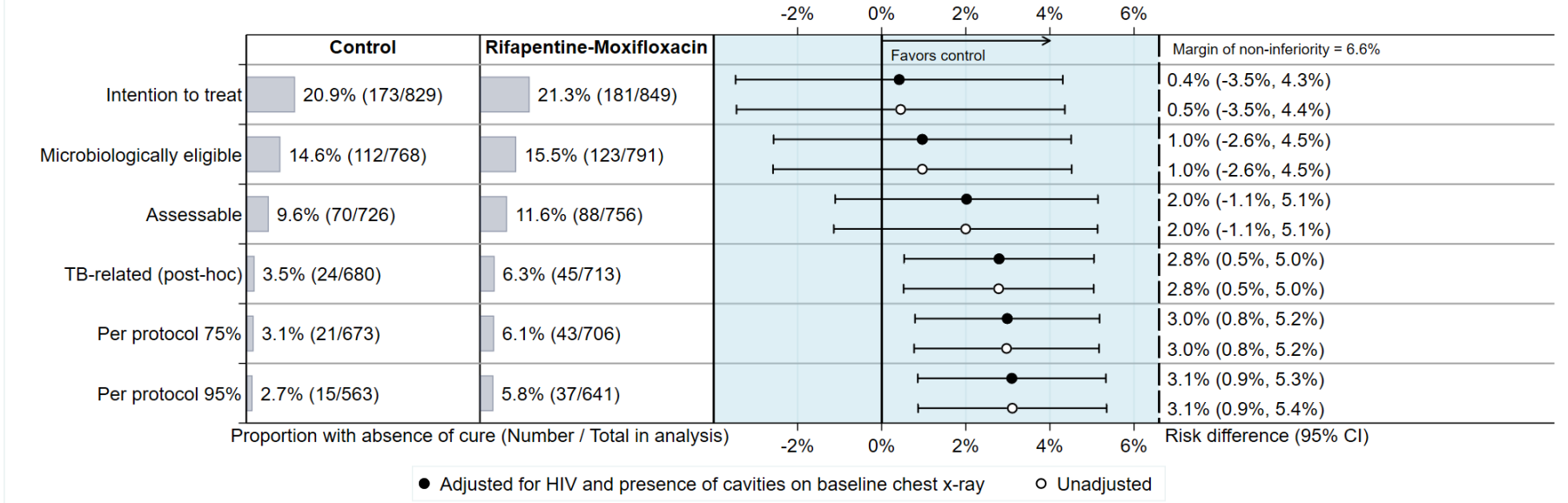
S31/A5349 Results: CONSORT diagram



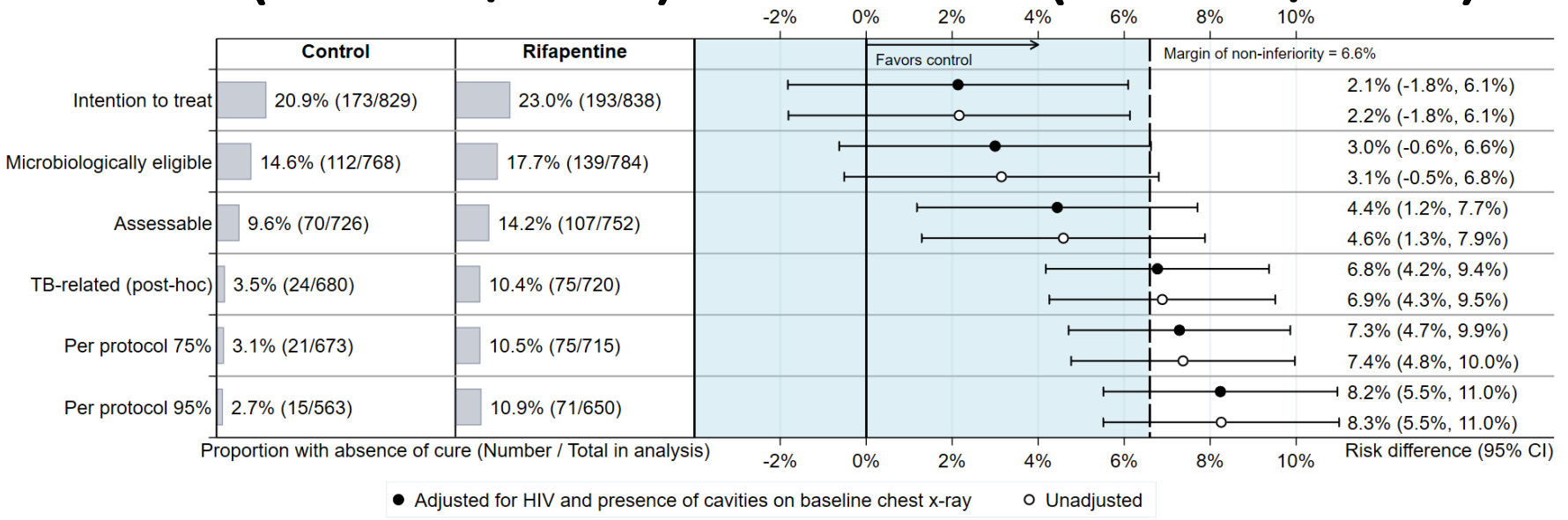
S31/A5349 Results: Baseline Characteristics of Microbiologically Eligible Population

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)**

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

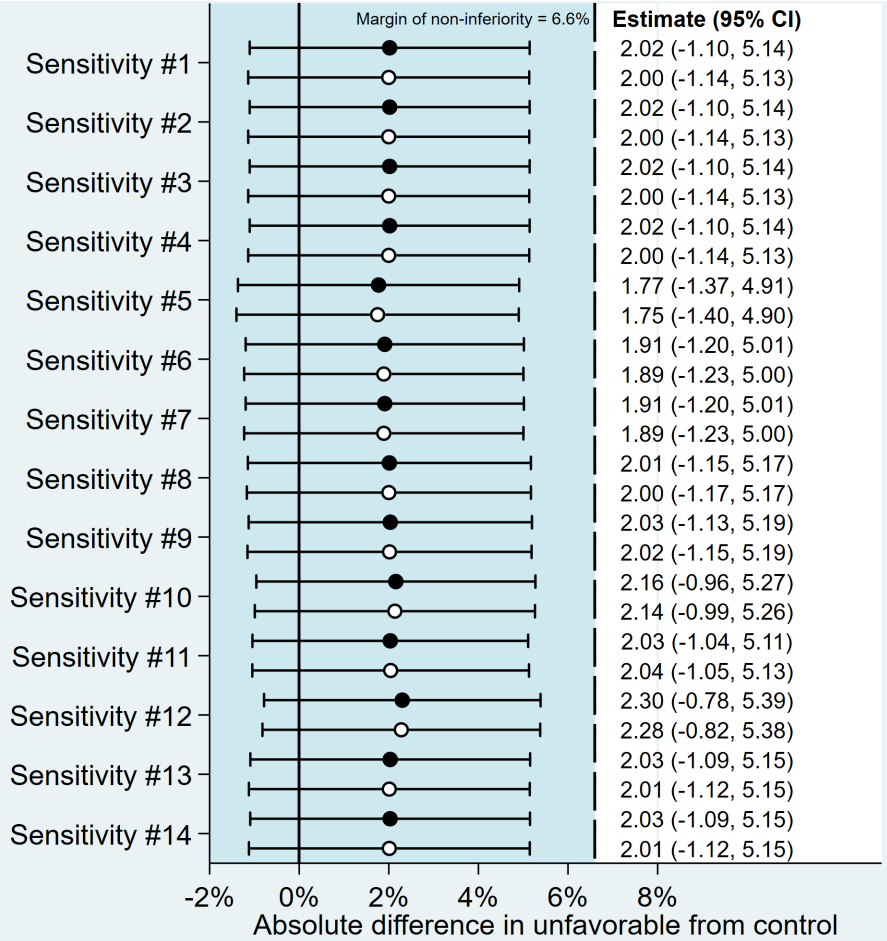


RPT (2HPZE/2HP) vs Control (2HRZE/4HR)

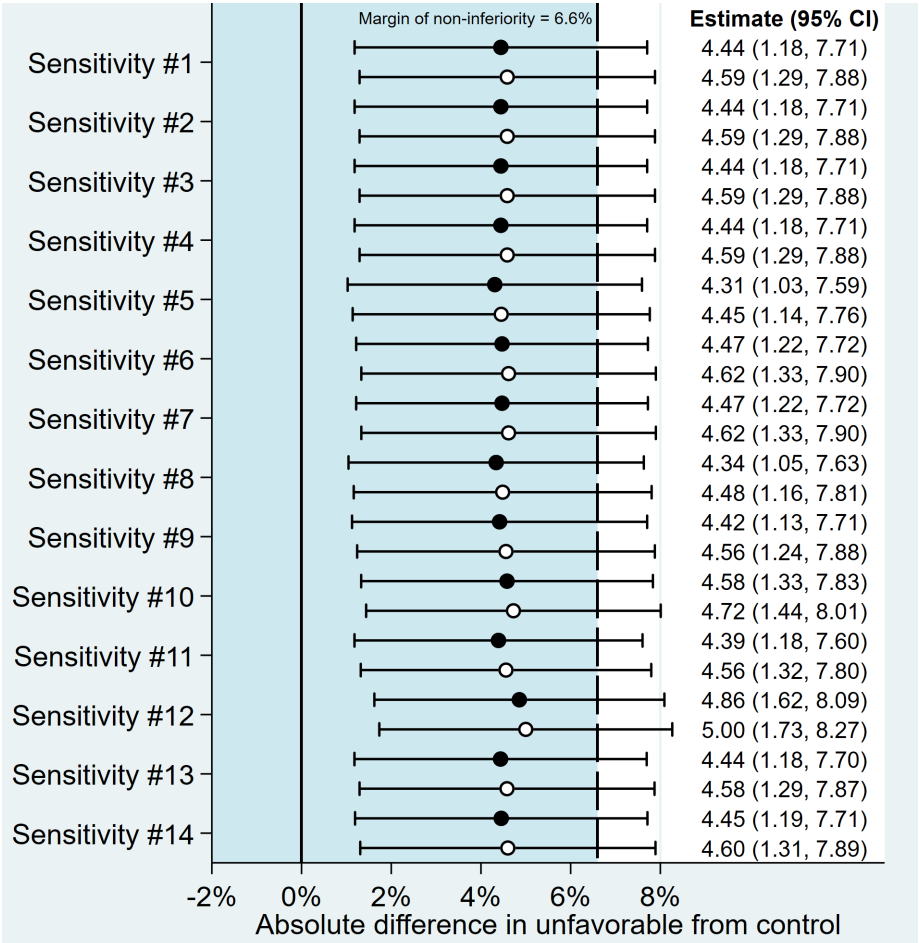


Primary Efficacy Results: Sensitivity Analyses

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



OPEN ACCESS Freely available online PLoS MEDICINE

Daily Dosing of Rifapentine Cures Tuberculosis in Three Months or Less in the Murine Model

Ian M. Rosenthal[1,2], Ming Zhang[1], Kathy N. Williams[1], Charles A. Peloquin[3], Sandeep Tyagi[1], Andrew A. Vernon[4], William R. Bishai[1,2], Richard E. Chaisson[1,2], Jacques H. Grosset[1], Eric L. Nuermberger[1,2*]

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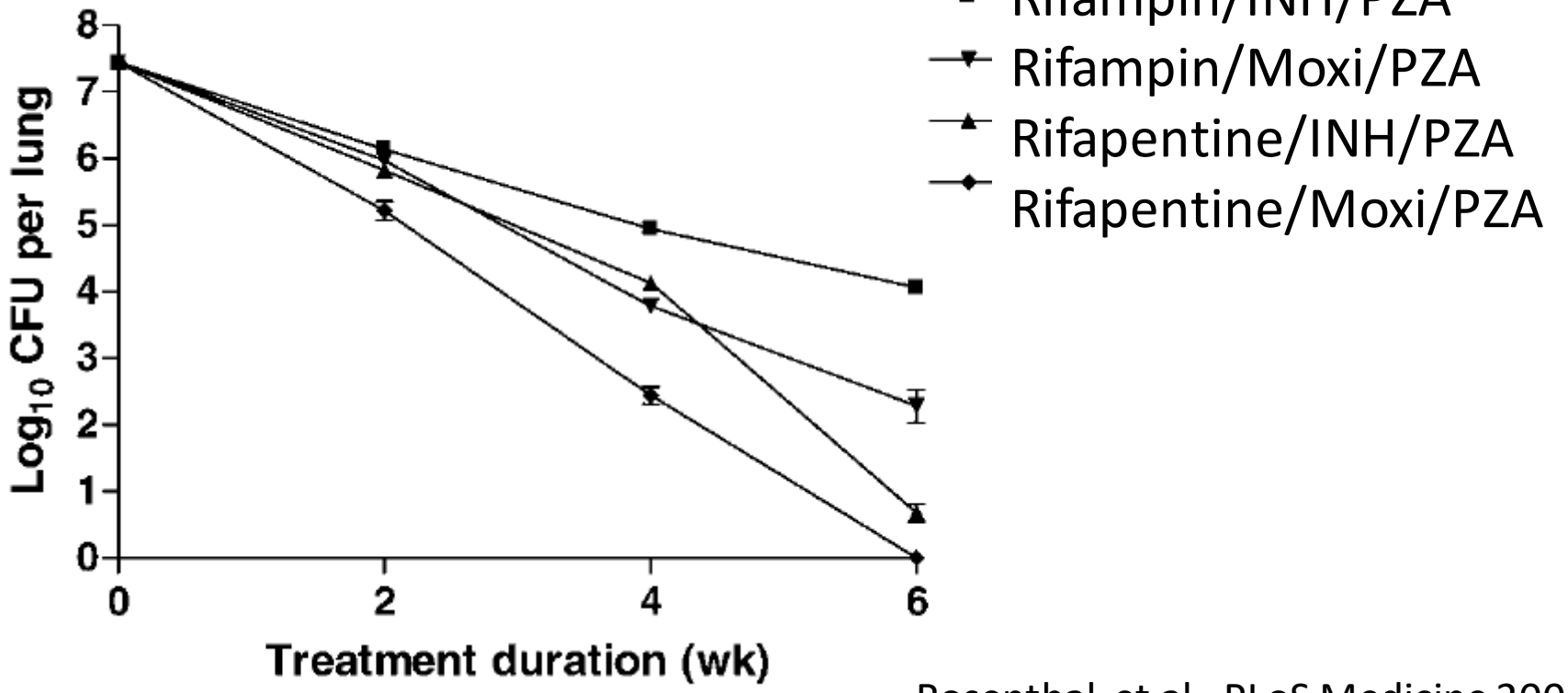
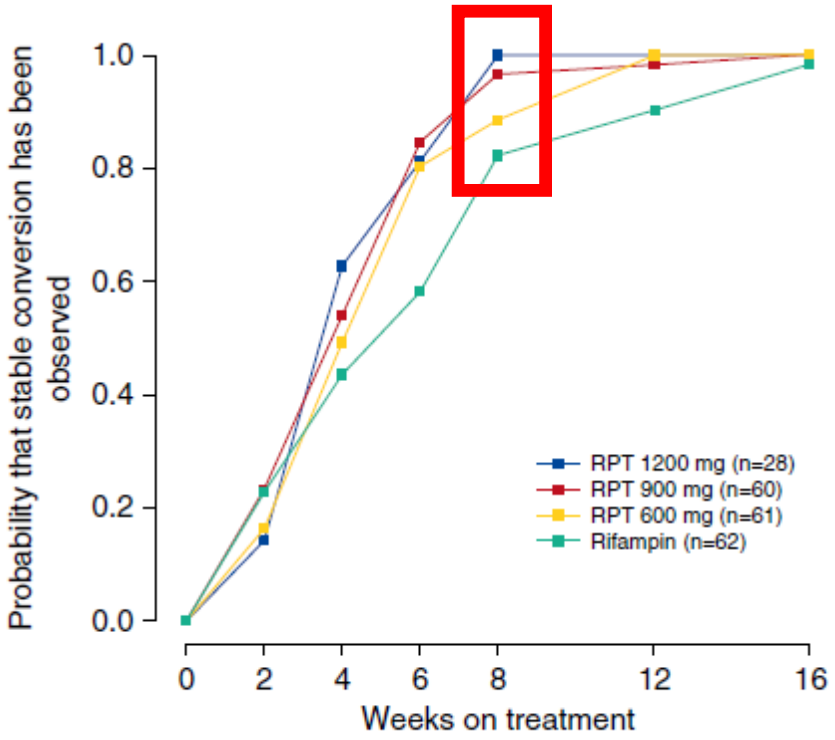


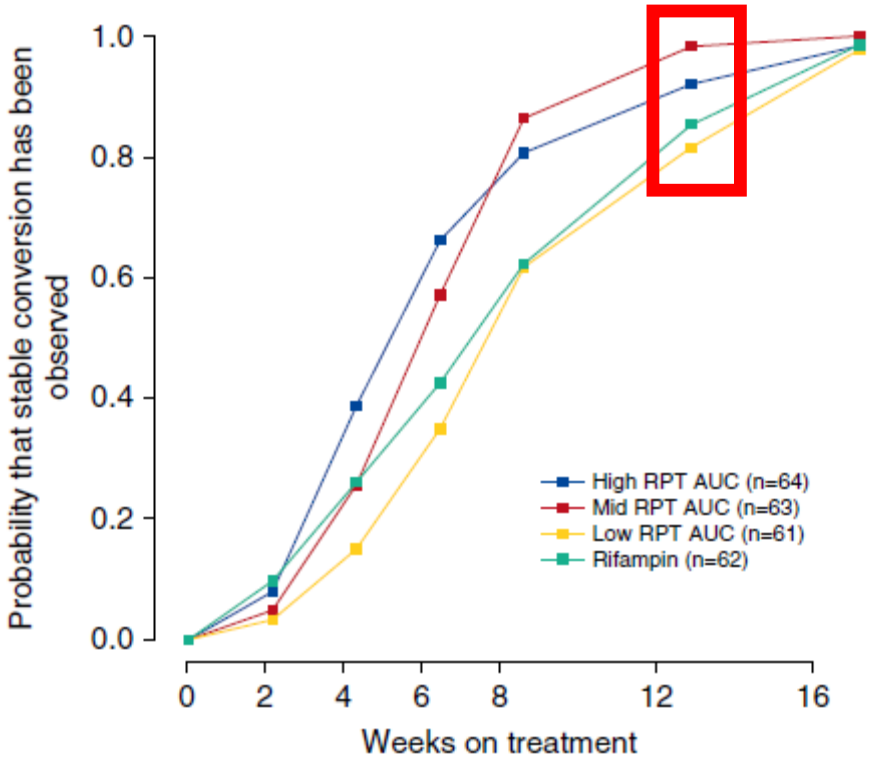
Rosenthal, et al., PLoS Medicine 2007;4(12):e344

TBTC Study 29X: Rifapentine in intensive phase of TB treatment
Culture conversion by dose and exposure (AUC)

By dosage of rifamycin

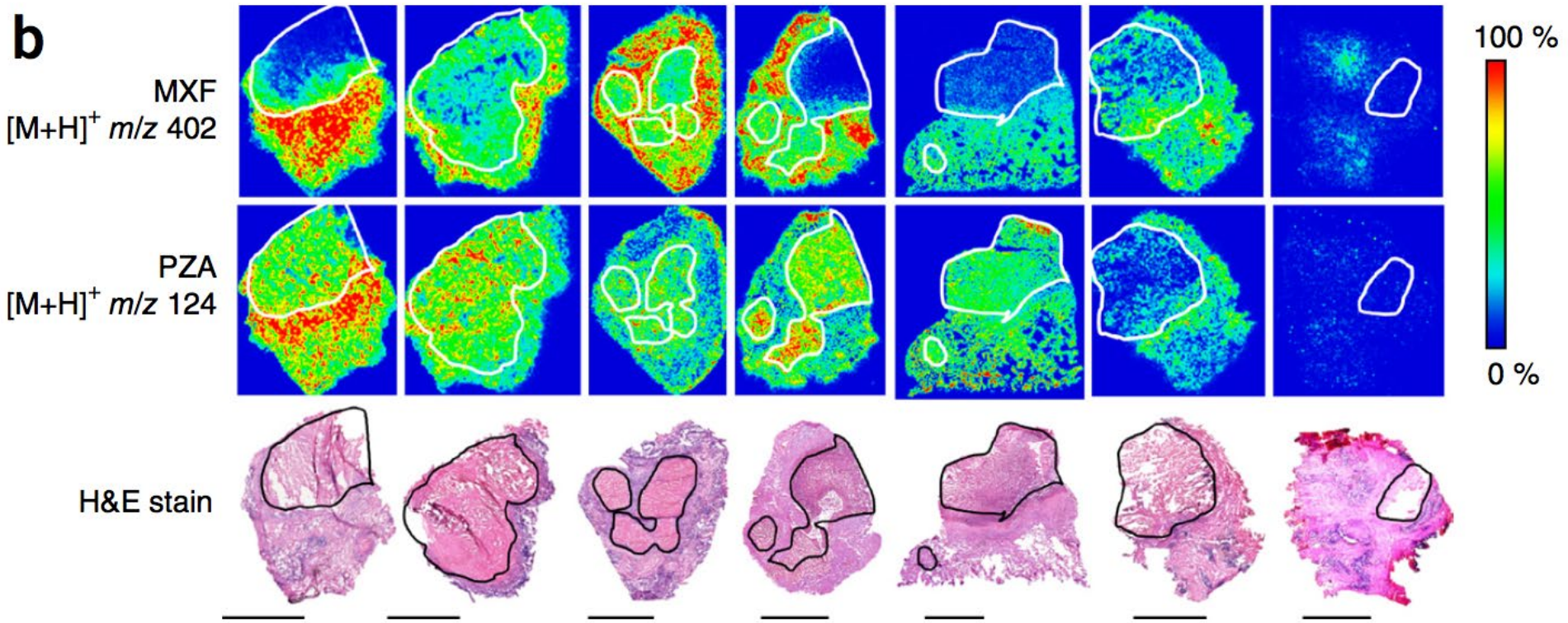


By exposure to rifamycin



Dorman, Savic, et al., Am J Respir Crit Care Med. 2015,191:333–343,

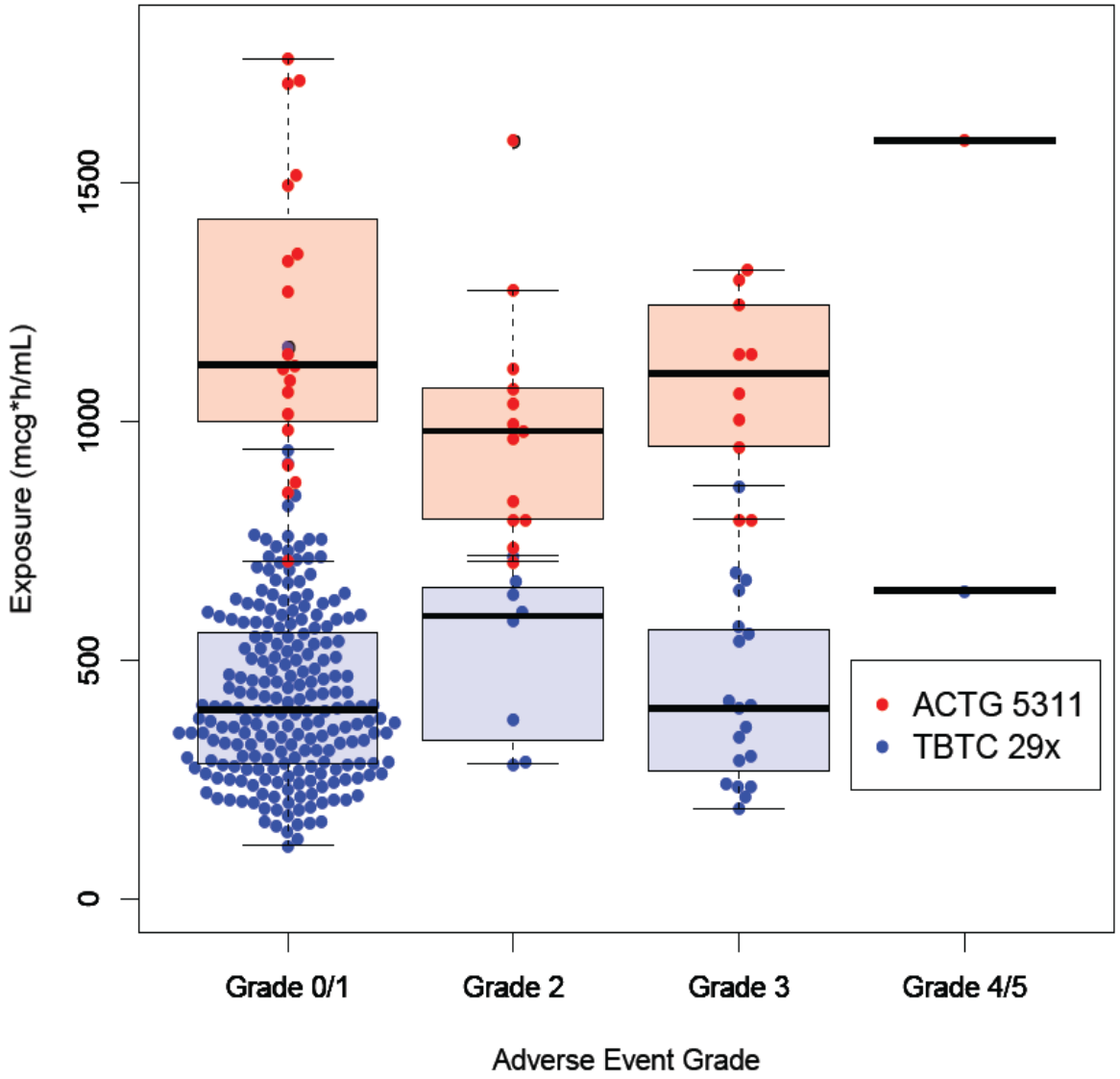
Spatial distribution of TB drugs in intact lesions



PZA diffused favorably and rapidly into the necrotic cores
MXF accumulated in cellular regions, it did not diffuse well into acellular caseum

Prideaux, Nature Med 2015

Tolerability of Rifapentine 1200 mg



RELATIONSHIP BETWEEN EXPOSURE (AUC_{0-24}) AND ADVERSE EVENTS AMONG PARTICIPANTS IN

- **ACTG A5311 (RED – healthy volunteers)**
- **TBTC 29X (BLUE – TB patients)**