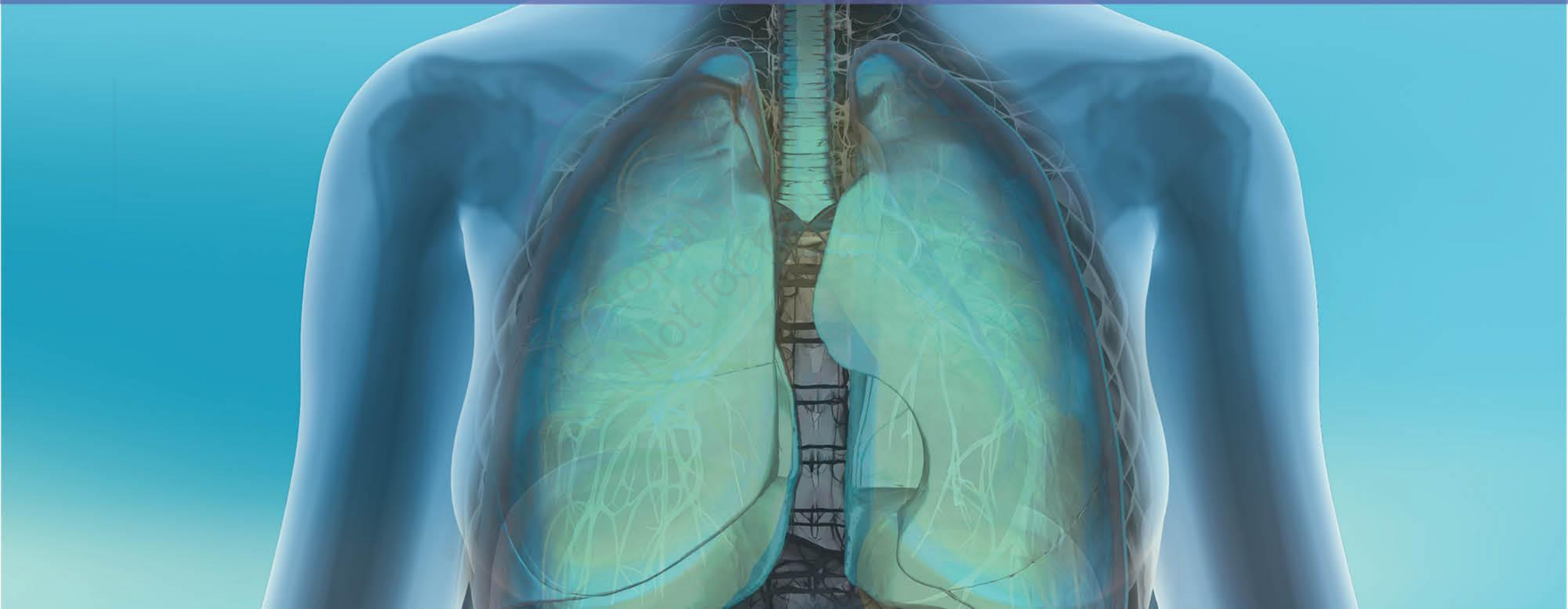
NTM Lecture Series for Providers

April 27-28, 2023
NATIONAL JEWISH HEALTH



Novel Therapy in NTM Infections

UNC SCHOOL OF MEDICINE

Kenneth N Olivier, MD, MPH
Pulmonary Diseases and Critical Care Medicine

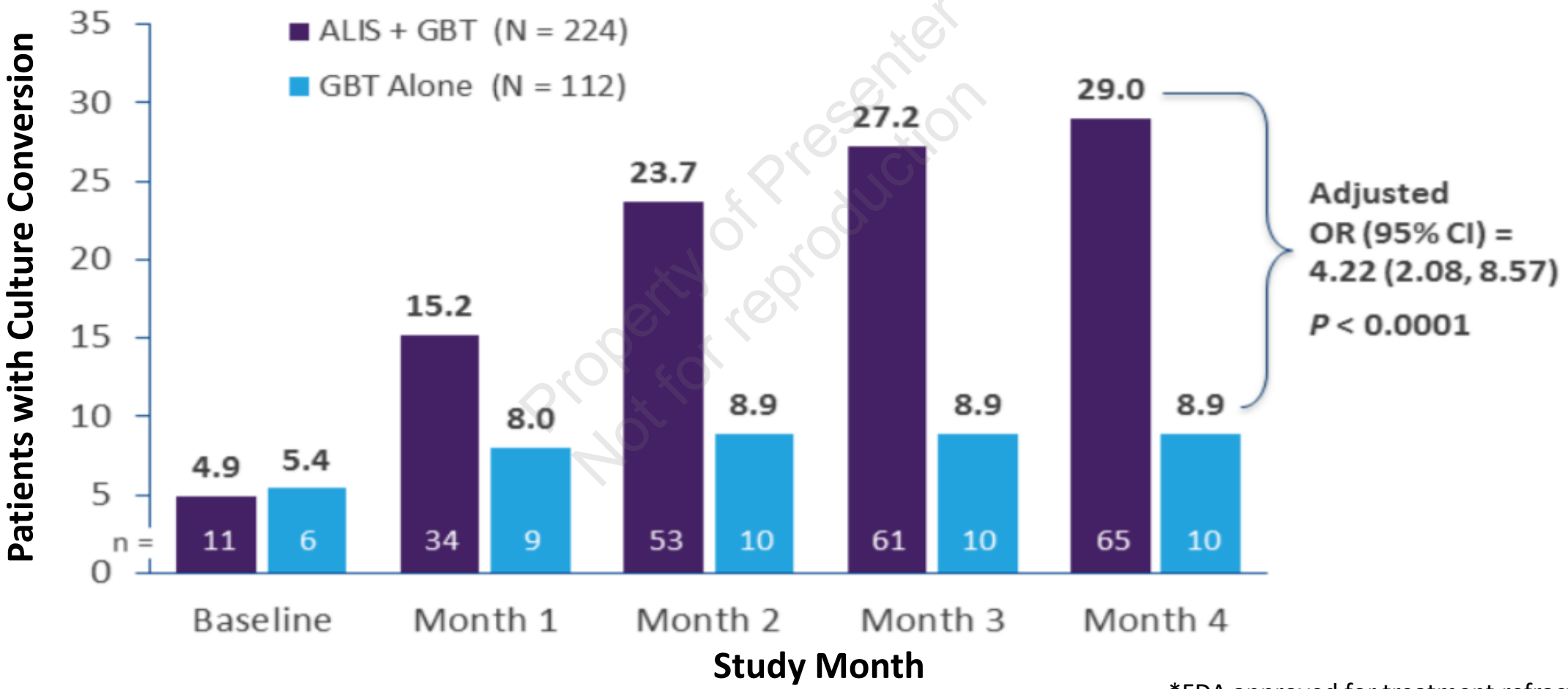
Disclosures

- Pfizer – AdBoard
- Mannkind Corporation – AdBoard
- Spero Therapeutics – AdBoard
- Paratek Pharma – AdBoard
- AN2 Therapeutics - AdBoard
- Beyond Air, Inc – Cooperative Research and Development Agreement

*Amikacin liposome inhalation suspension is the only FDA approved drug for treatment of pulmonary NTM disease
*All other drugs discussed are either off-label use or investigational

*Study results and design examples are all from published data or from listings on ClinicalTrials.gov

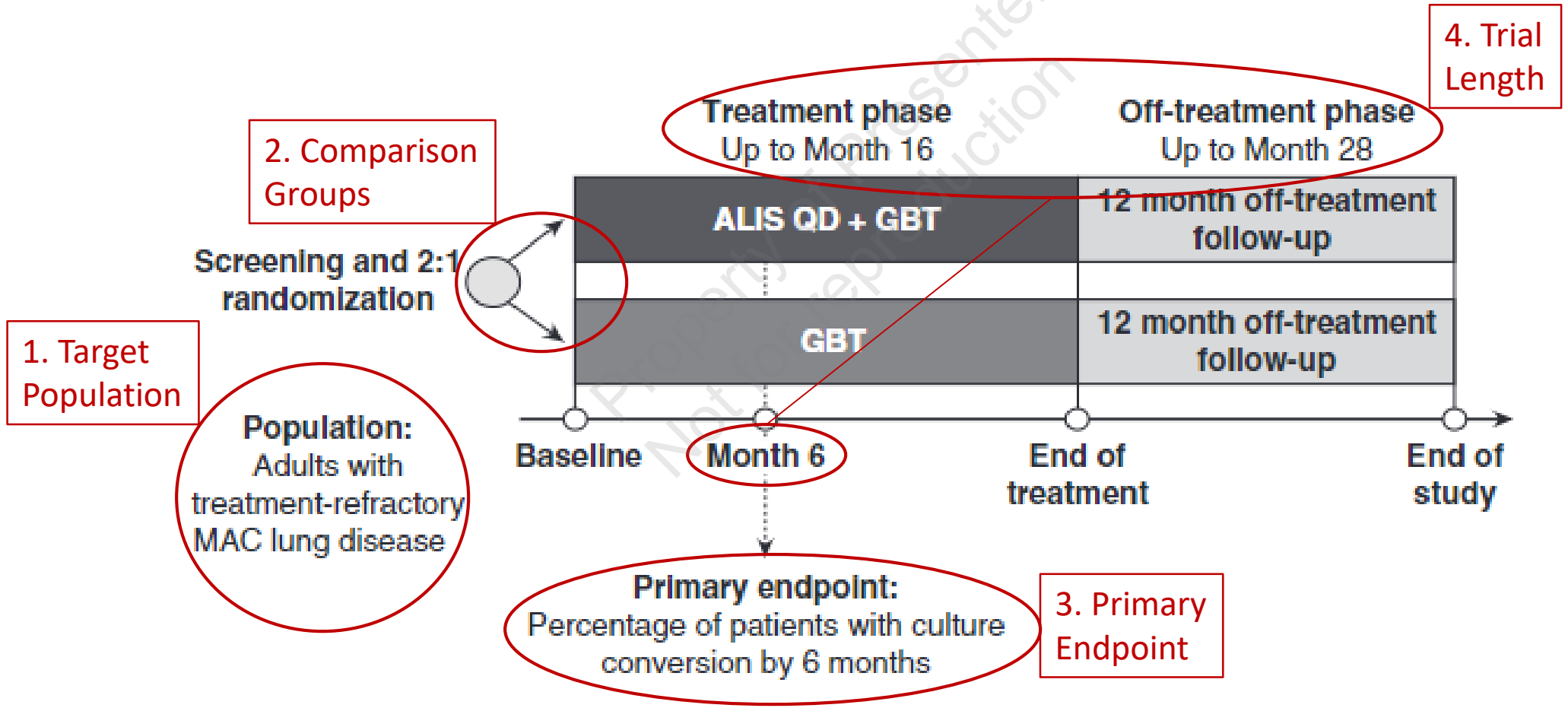
*Amikacin liposomal inhalation suspension: Phase 3



Griffith. Am J Respir Crit Care Med 2018

*FDA approved for treatment refractory *M. avium* complex lung disease

Anatomy of a NTM trial



FDA Workshop
Development of Antibacterial Drugs for the Treatment of Nontuberculous Mycobacterial Disease
April 8, 2019

GUIDANCE DOCUMENT

Nontuberculous Mycobacterial Pulmonary Disease Caused by Mycobacterium avium Complex: Developing Drugs for Treatment

Draft Guidance for Industry

SEPTEMBER 2021

https://www.fda.gov/media/152501/download

Development of Drugs for Nontuberculous Mycobacterial Disease

Clinicians' Interpretation of a US Food and Drug Administration Workshop

Patrick A. Flume, MD; David E. Griffith, MD; James D. Chalmers, MBChB, PhD; Charles L. Daley, MD; Kenneth Olivier, MD, MPH; Anne O'Donnell, MD; Timothy Aksamit, MD; Shannon Kasperbauer, MD; Amy Leitman, JD; and Kevin L. Winthrop, MD, MPH

CHEST 2021; 159(2):537-543

Target population heterogeneity

Disease Factors	Example	Example
Underlying disease, comorbidity	CF vs non-CF	COPD vs non-COPD
Radiographic features	Fibrocavitary vs nondular-bronchiectatic	Minimal (single lobe) vs extensive (multi-lobar)
NTM treatment status	Naïve vs refractory	Naïve vs previously treated
Pathogen and antimicrobial susceptibility	MAC vs *M. abscessus*	Macrolide, amikacin resistant vs susceptible
Clinical end points, disease stage	Too “well” to detect change	Too “sick” to detect change

Flume. Chest 2021

Treatment refractory

- Pro
  - Can power study with patients taking stable background multi-drug regimen
  - May be easier to attribute efficacy to study drug as placebo/GBT alone less likely to change
- Con
  - High bar for drug to reach
  - Patients may have more advanced disease with reduced capacity to improve
  - If background regimen continued, drugs may vary significantly

Treatment naïve

- Pro
  - Patients not as sick, easier to reverse
  - Can consider monotherapy trial – easier to attribute effect to study drug
  - Larger pool of patients for enrollment
- Con
  - Hard to sort those likely to progress from likely to remain stable
  - Higher likelihood of spontaneous conversion
  - For Mac, most patients respond to GBT – larger #'s to see effect in drug substitution trial

Comparison groups/trial design

- Phase 2
  - Delay of standard therapy may be appropriate
    - Select patients
    - Adequate monitoring
  - Short-term, randomized, placebo-controlled, proof-of-concept study evaluating a single agent

2021 FDA Draft Guidance

Comparison groups/trial design

- Phase 3
  - Conduct 2 randomized, double-blind phase 3 trials
    - Single trial showing robust evidence of efficacy with confirmatory evidence may also demonstrate substantial evidence of effectiveness
  - Trials should study test drug in combination with other antibacterial drugs
    - Superiority of [standard-of-care (SOC) regimen + *new drug*] vs. [SOC + *placebo*]
    - Superiority of [*new combination regimen*] vs. [*SOC*]
      - Justify contribution of each component to overall efficacy
    - Superiority of [*new combination regimen*] vs. [*placebo*] in treatment-naïve patients
      - Appropriate criteria for instituting rescue therapy
      - Justify contribution of each component to overall efficacy

2021 FDA Draft Guidance

Primary endpoint

- Drugs will provide benefit on a clinically meaningful endpoint
  - Most patients have microbiologic response to therapy, but data correlating with patient-reported outcomes or functional improvement are lacking
  - New drugs must improve how patient
    - Feels
    - Functions
    - Survives
- If considering a microbiologic outcome as a surrogate likely to predict clinical benefit, *should discuss with the Division*.

FDA Draft Guidance. https://www.fda.gov/media/152501/download

Study length

- May be different for Phase 2 and Phase 3
- What is predictive of ultimate success, “cure”?
- Is culture conversion predictive of sustained negative cultures during and after therapy? Predictive of clinically meaningful endpoint?
- Surrogates for culture conversion, e.g. EBA, TTP?
- How long to see improvement in symptoms?
- How long do patients need to be followed after completion of therapy?

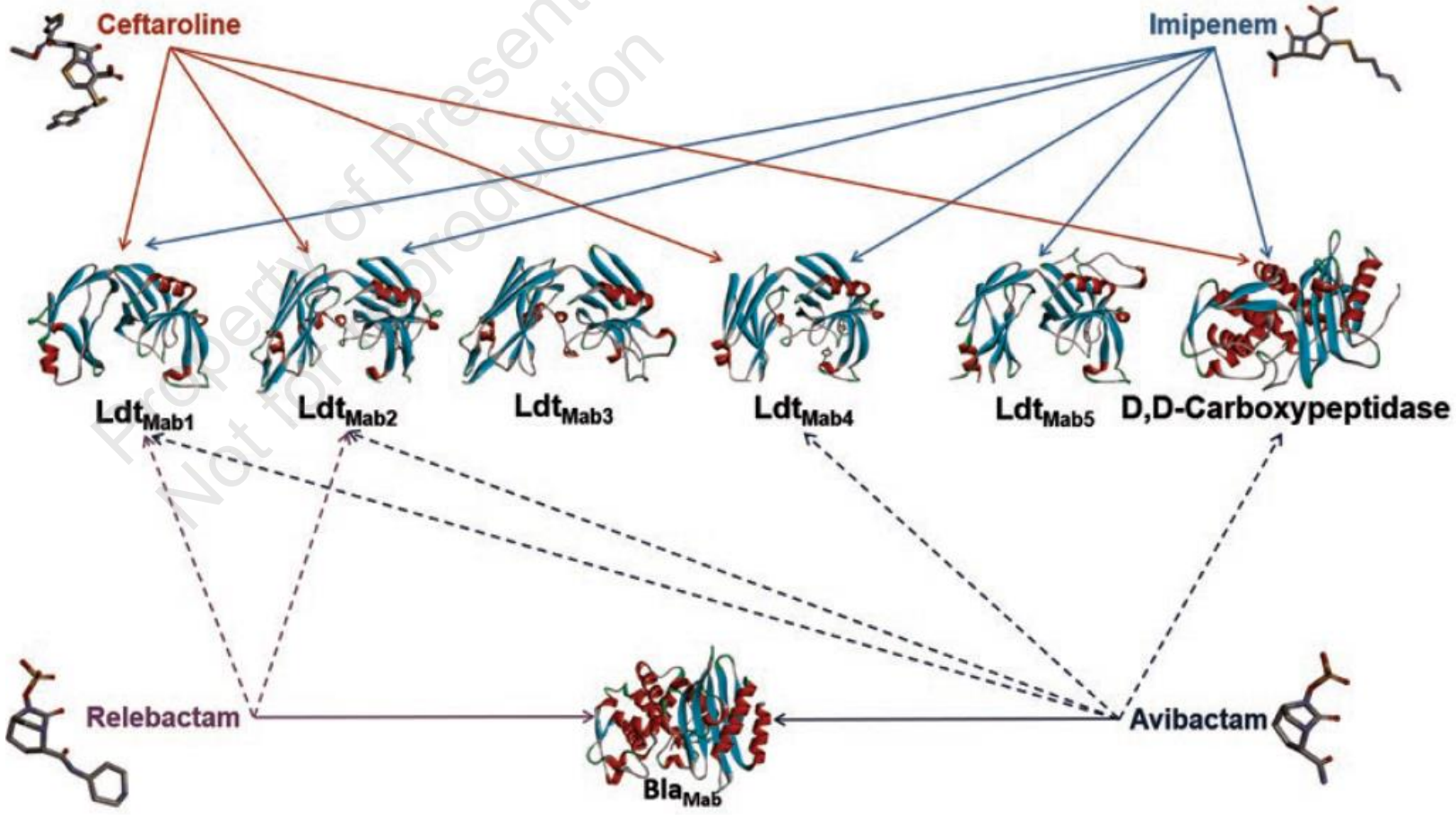
New regimens, available antibiotics

- Dual β-lactams
  - β-lactams have differing potencies vs specific Mabs transpeptidases
    - Ceftazidime plus either ceftaroline or imipenem
    - Imipenem-relebactam plus amoxicillin
- β-lactamase inhibitor combinations
  - "Non-β-lactam-based" β-lactamase inhibitors block Bla_{Mab}
    - Avibactam (available combined with ceftazidime)
    - Relebactam (available combined with imipenem-cilastatin)
    - Vaborbactam (available combined with meropenem)
- Omadacycline/Eravacycline

Pandey. mBio 2019; Lopeman. Sci Rep 2020; Lopeman. Sci Rep 2020;
Kaushik. Antimicrob Agents Chemother 2019; Hannelore. J Antimicrob Chemother

Dual beta lactams, newer Bla inhibitors

- Target redundancies
- L,D-transpeptidases used in peptidoglycan synthesis
  - Cephalosporins, carbapenems
- Chromosomally encoded, serine class A, Bla_{Mab}
  - Diazabicyclooctane inhibitors
  - Avibactam, relebactam, nacubactam, zidebactam

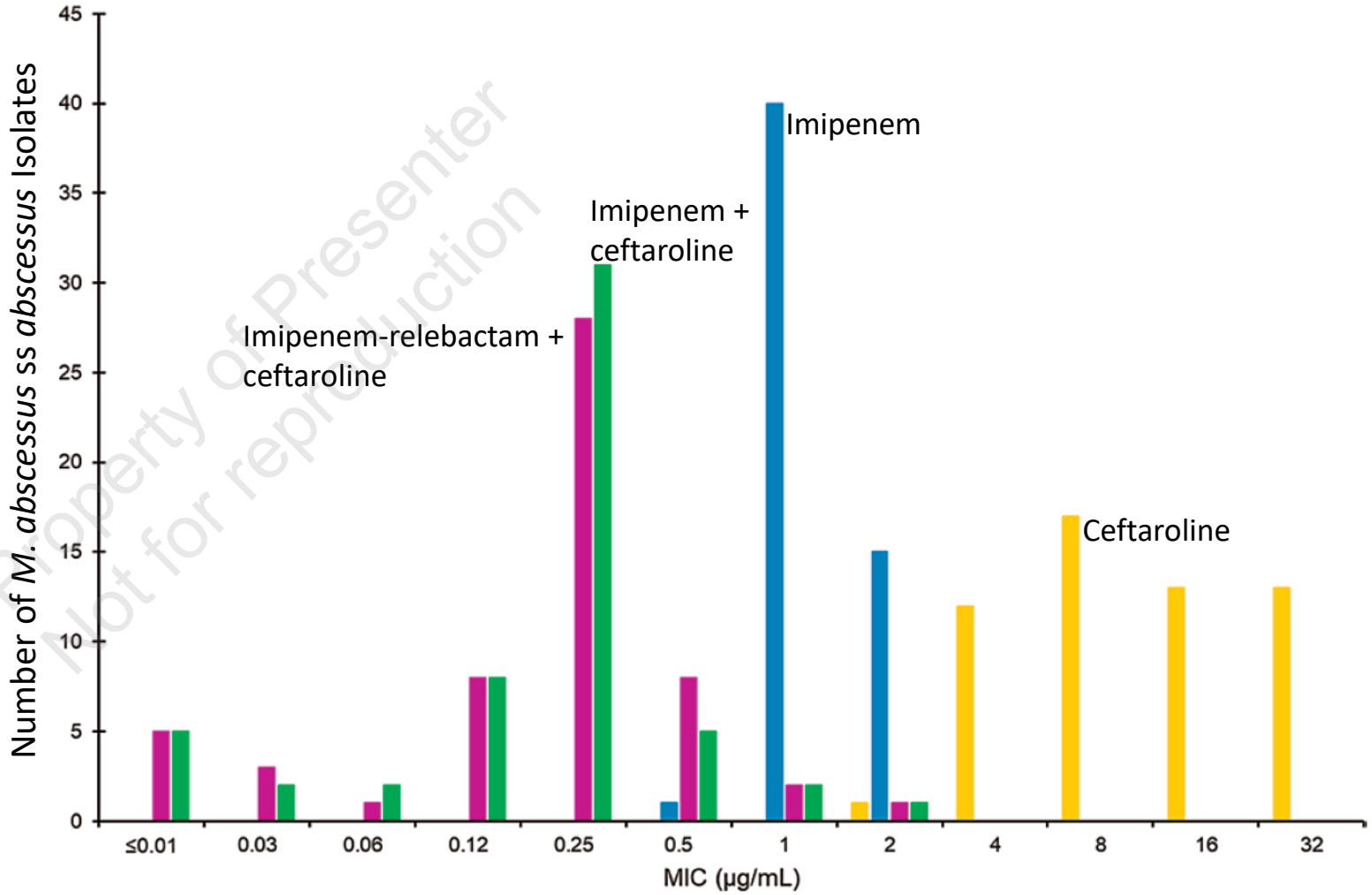


Nguyen. Clin Infect Dis 2021
Dousa. Antimicrob Agents Chemother 2020

Dual beta lactams, newer Bla inhibitors

- Fixed concentration of ceftaroline to imipenem markedly lowered MICs
- Avibactam > relebactam modestly increased ceftaroline activity

- Case/Cleveland VA Synergy Testing
  - Robert Bonomo MD
    - Robert.Bonomo@va.gov
  - Khalid Dousa MD
    - kxd231@case.edu



Nguyen. Clin Infect Dis 2021
Dousa. Antimicrob Agents Chemother 2020

Omadacycline, eravacycline

Isolate or MIC	*M. abscessus* subspecies	MIC (μg/ml) Tigecycline	Omadacycline	Eravacycline
MIC data	ATCC 19977 &			
MIC range	28 drug resistant	0.5–4	0.5–4	0.125–2
MIC_{50}	clinical isolates	1	1	0.5
MIC_{90}		2	2	1

- MIC_{50} & MIC_{90} equivalent for tigecycline & omadacycline & 2-fold lower for eravacycline
- From hollow fiber, omadacyline 8-10x & eravacycline 2x higher free drug AUC/MIC ratios relative to tigecycline

Kaushik. Antimicrob Agents Chemother 2019
Pearson. Open Forum Infect Dis 2020
Morrisette. Open Forum Infect Dis 2021

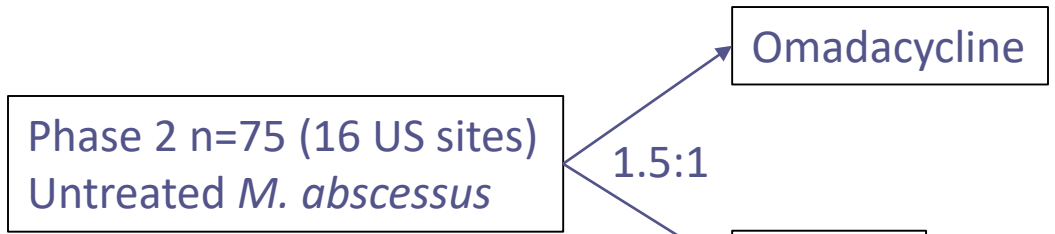
- Case series
  - Single site, 4 patients – 2 cutaneous, 1 pulmonary, 1 osteomyelitis & bacteremia
    - Omadacyline median 5.5 mos + other drugs
    - Clinical cure 3/4 (75%) cases, other improving
    - 1 patient d/c at 6 months due to nausea
  - Six sites, 12 patients – 7 pulmonary, 2 bone/joint, 3 other extrapulm sites
    - Omadacyline median 6.2 mos + other drugs
    - Clinical success in 9/12 (75%) cases
    - 1 GI symptoms, 1 ↑Cr, 1 AST/ALT >3x ULN

Oral Omadacycline vs. Placebo in Adults With NTM Pulmonary Disease Caused by *Mycobacterium abscessus*

ClinicalTrials.gov Identifier: NCT04922554

- Phase 2, randomized (1.5:1), double blind, parallel group, placebo controlled
- Inclusion
  - ≥18 years, symptoms, CT evidence
  - Positive sputum 6mos prior and at screening
  - GBT Rx will not be needed for 3 mos
- Exclusion
  - Rx for Mac or Mabs within 6 mos
  - Any antibiotic within 4 weeks
  - CF
  - Extrapulmonary NTM
  - Prior omadacycline, reaction to tetracyclines
- 300mg daily vs placebo for 3 months
- 75 participants
- Primary outcomes
  - Improved on NTM symptom assessment scale
  - Adverse events
    - Lab tests, vital signs, EKG
- Secondary outcomes - change from baseline
  - QoL-B, SGRQ, PROMIS 7a, etc.
  - Decrease in quantitative sputum
  - Time to positivity
  - Time to first negative culture

Oral Omadacycline vs. Placebo in Adults With NTM Pulmonary Disease Caused by *Mycobacterium abscessus*



- Minimal # (2) symptoms
- No antimycobacterials within 6 mos of screen
- Excludes CF
- Excludes cavities

Outcomes
3 months

- NTM Symptom Assessment Scale - Improvement in at least 50% of baseline symptoms
- Secondary:
  - 8 other PRO measures
  - Semi-quant culture scale
  - TTP
  - Time to 1st negative culture

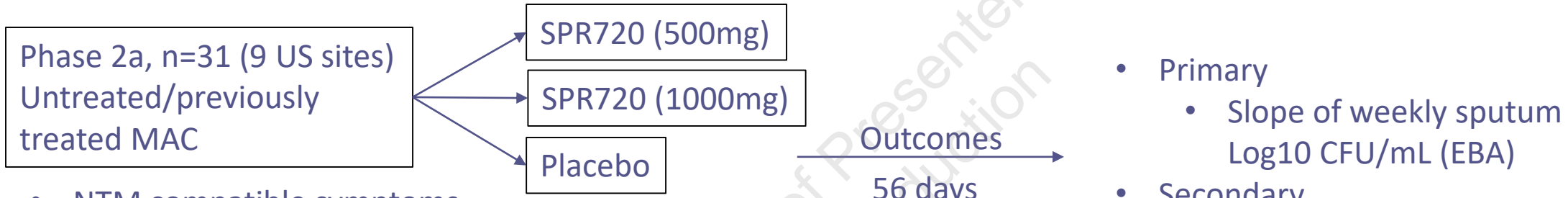
ClinicalTrials.gov Identifier: NCT04922554

New drugs, investigational antibiotics

- SPR720
  - Oral benzimidazole inhibitor bacterial DNA gyrase (GyrB)
  - Preclinical activity against M avium complex and M abscessus
- Epetraborole
  - Inhibitor of bacterial leucyl-tRNA synthetase
  - Preclinical activity against M avium complex and M abscessus
- Clofazimine inhalation suspension
  - Riminophenazine dye, exact mechanism unknown, binds mycobacterial DNA, inhibits energy metabolism

Sullivan. Plos Pathog 2021
Brown-Elliott. Antimicrob Agents Chemother 2018
Kunkel. Antimicrob Agents Chemother 2023

SPR720 Phase 2a, single agent for untreated MAC



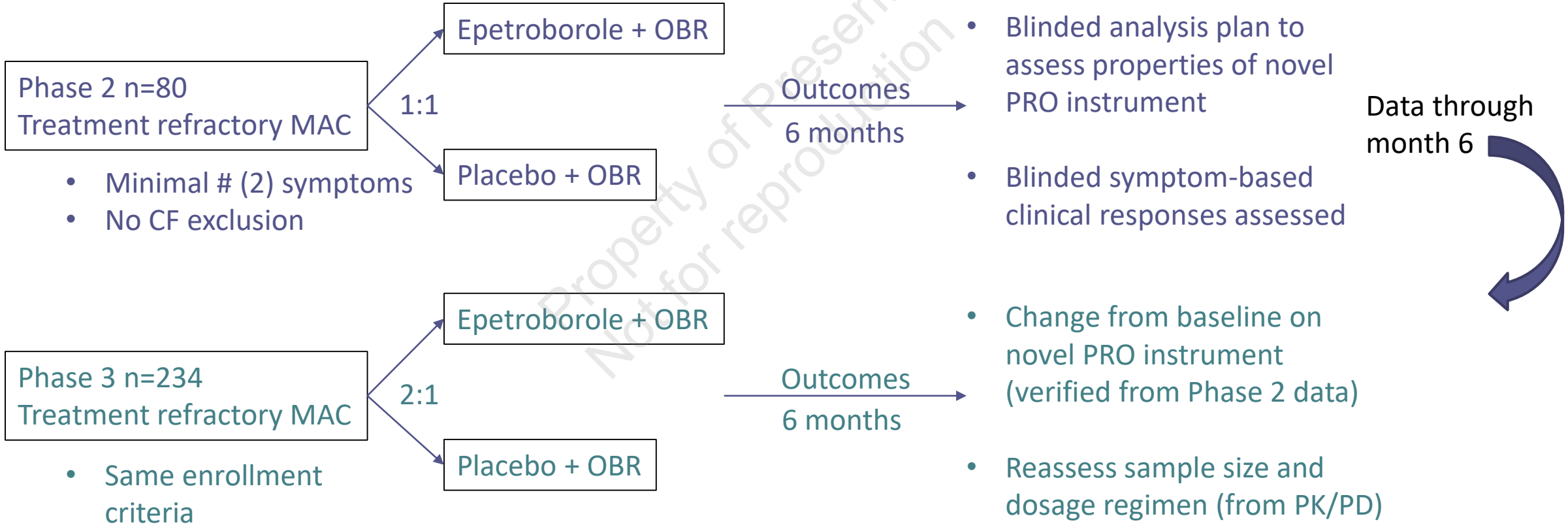
- NTM compatible symptoms
- Previous treatment
  - Successful treatment
  - Recent positive culture
  - Off Rx at least 3 mos

- Primary
  - Slope of weekly sputum Log10 CFU/mL (EBA)
- Secondary
  - 7 micro outcomes
  - 7 PRO outcomes
  - 5 PK measures
  - TEAE

ClinicalTrials.gov Identifier: NCT05496374

Epetraborole for Rx Refractory MAC

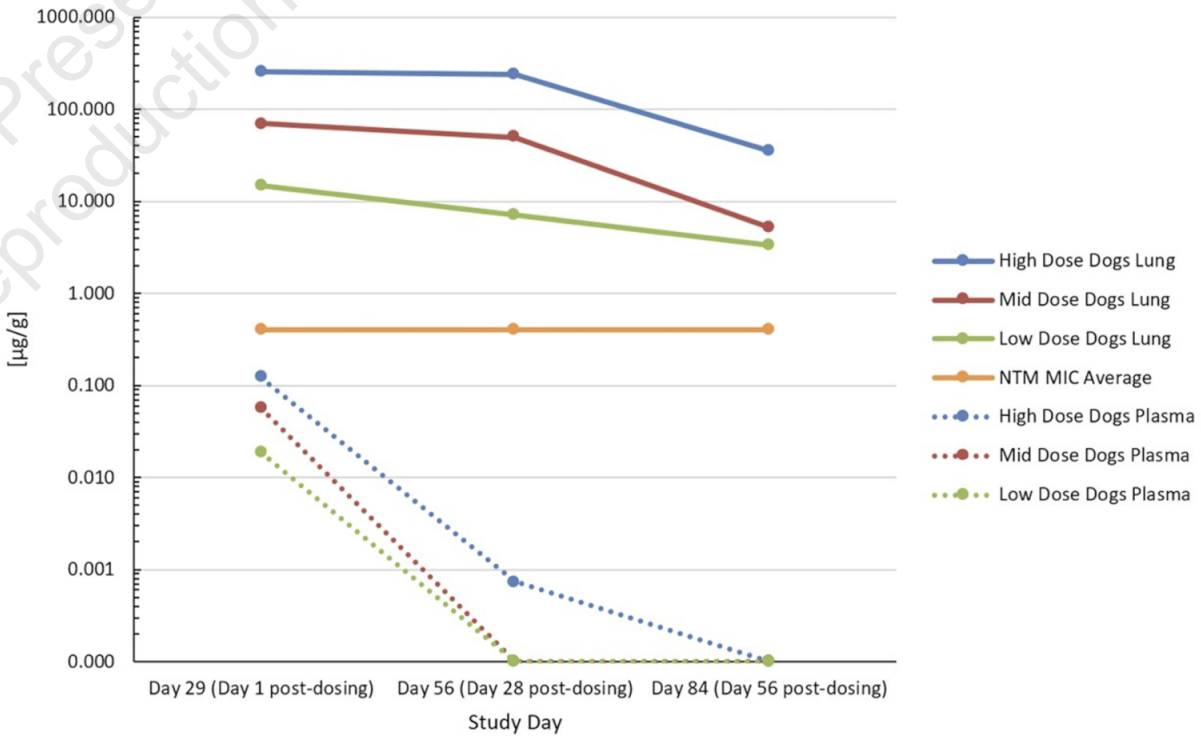
- Adaptive Phase 2/3 design, pilot PRO in Phase 2



ClinicalTrials.gov Identifier: NCT05327803

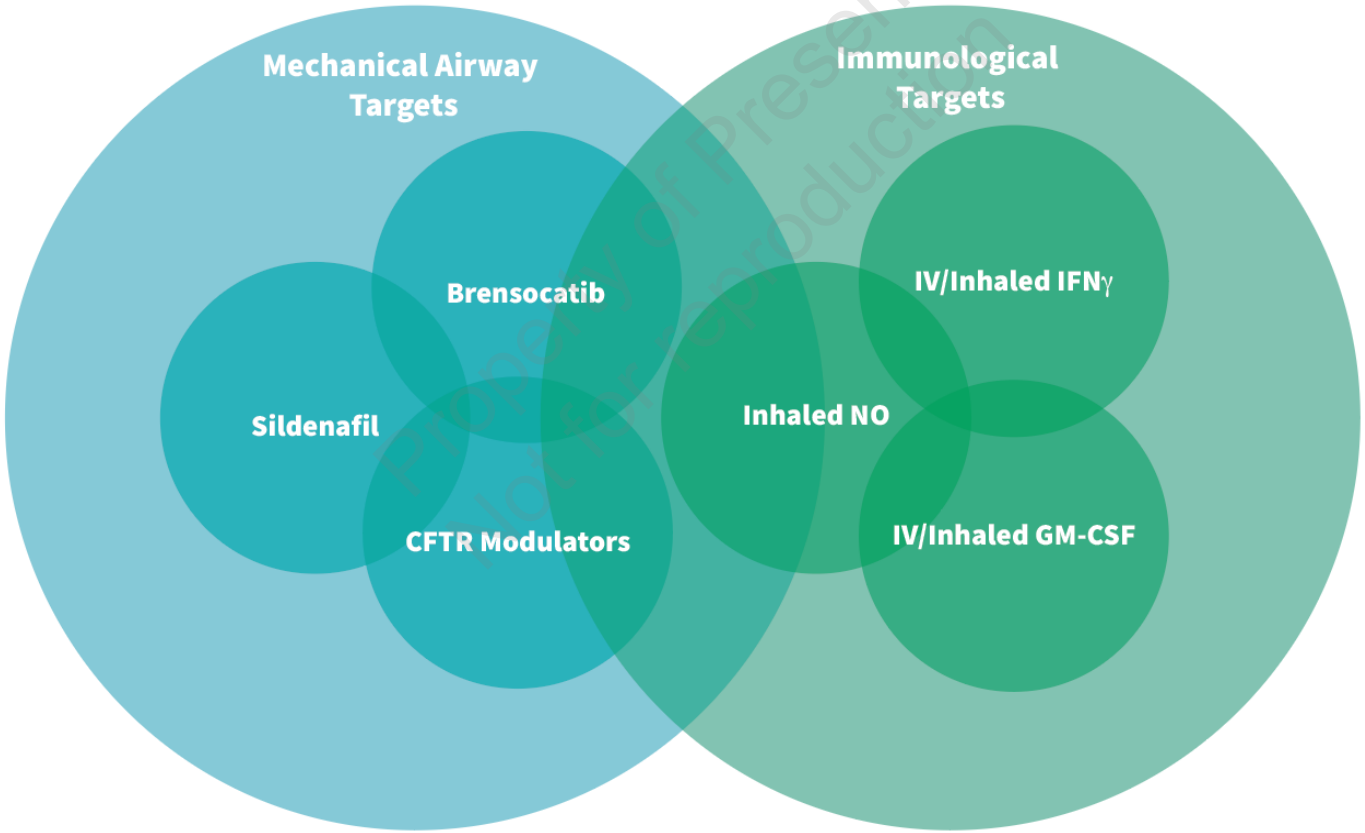
Clofazimine inhalation suspension, preclinical

- Novel inhaled liposomal formulation
- Administered to dogs once daily for 28 days
  - Levels > MIC through 56 days after dosing
  - No demonstrable toxicity
- Good activity against MAC and Mabs in mice
- Adaptive Phase 2/3 clinical trial planned with 28-day dosing followed by 56 day “holiday”



Kunkel. Antimicrob Agents Chemother 2023
Banaschewski. J Cyst Fibros 2019

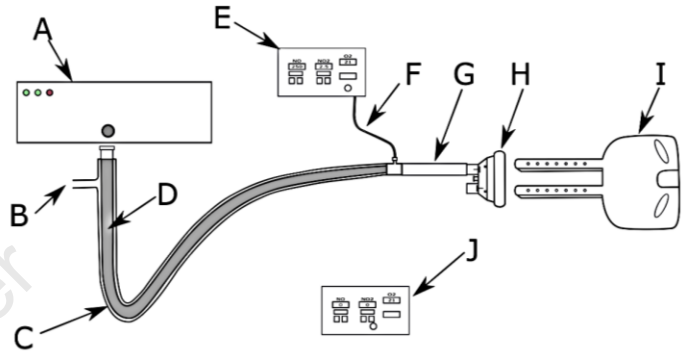
New therapies, host directed, non-drug approaches

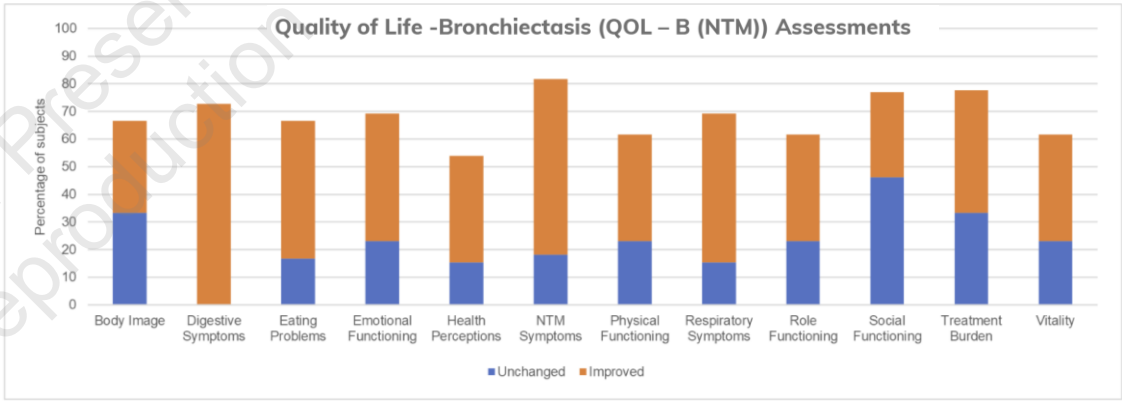


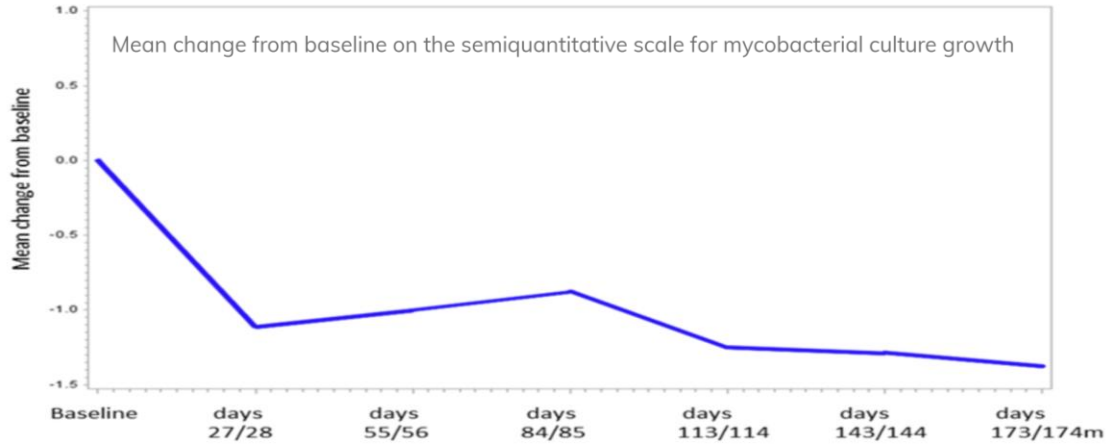
Anidi. Clin Chest Med 2023 (in review)

Inhaled Nitric Oxide

- Pilot study of at-home generator-based system
- Target Rx refractory MAC or Mabs, CF/nonCF
- Outcomes
  - Primary – TEAEs
  - Secondary
    - Culture conversion Day 174
    - Change in QoL
    - Change in FEV1, activity tracker, 6MWT
- Results (preliminary)
  - 15 enrolled (mean age 62, 22-82 years; F 75%)
  - Titrated to 250ppm in hospital, completed at home – compliance >90%/12weeks
  - No attributable SAEs



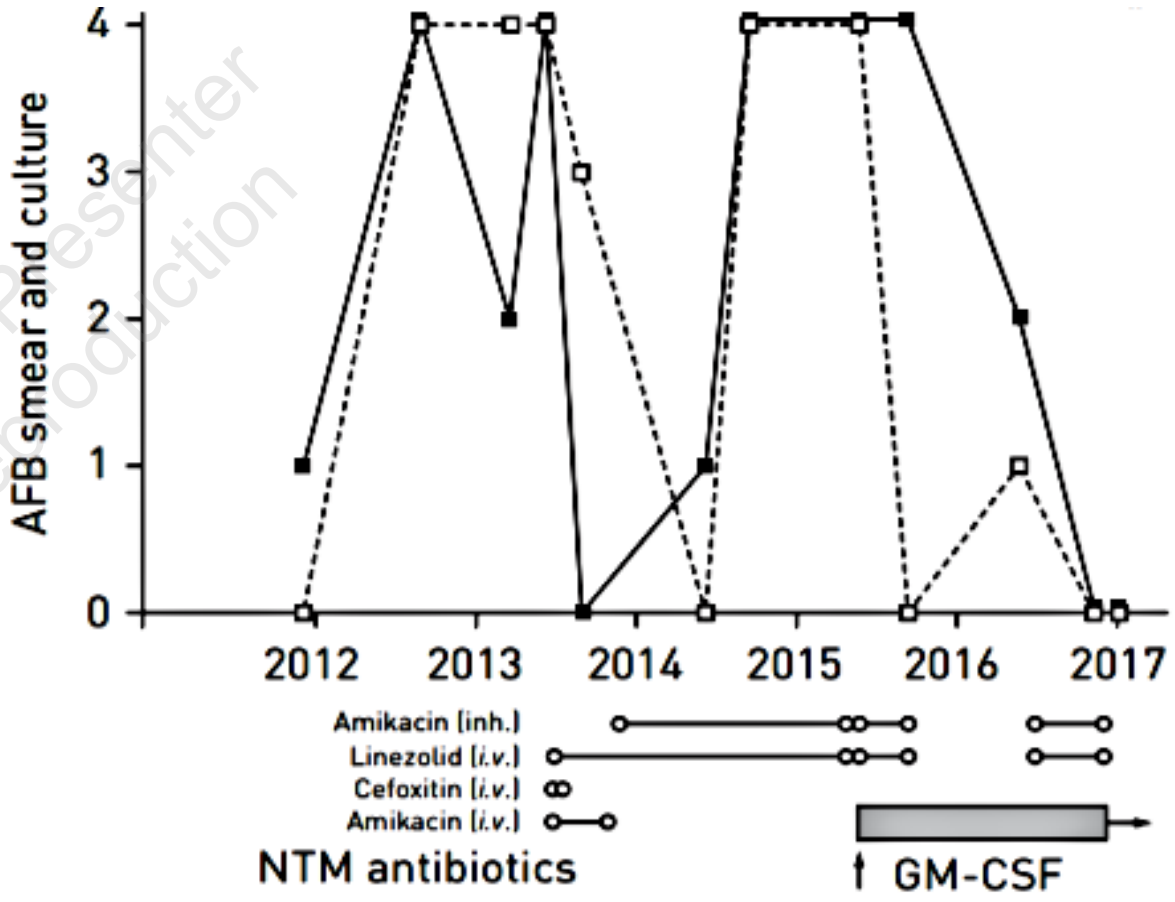




Thomson. Chest Annual Meeting 2022

Inhaled GMCSF

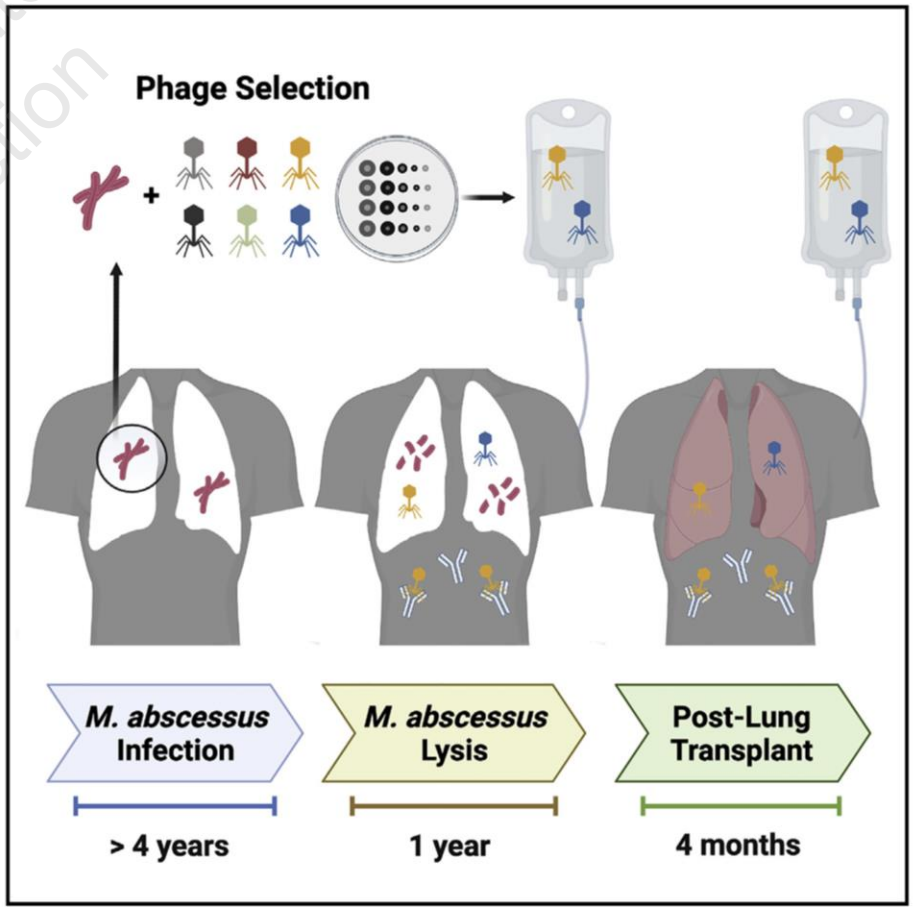
- Inhaled rhGM-CSF targeting macrophage activation, ↑ intracellular killing
  - 2 CF pts *M. abscessus* Rx inhaled GM-CSF
    - Improved smear/culture status
    - Improved lung function
  - OPTIMA: Ph2 open, non-CF, persistent MAC/Mab, 48wk/12wk f/u (Australia, UK)
    - ITT converted: MAC 5/24 (21%); Mab 0/8
    - 14 SAEs (1-TR); 3 deaths (0-TR)
  - ENCORE: Ph 2 open, CF, persistent MAC/Mab (US)
    - Enrollment closed due to COVID n=14/30



Scott. Eur Respir J 2018
https://savarapharma.com

Phage treatment of M abscessus

- Treatment-refractory M.abscessus pulmonary infection eradicated in person with CF
- Specific mycobacteriophages lysed bacteria over course of a year
- Mabs did not acquire resistance to phages
- Mabs eradication occurred despite partial antiphage antibody response
- Enabled successful lung transplant



Nick. Cell 2022

Summary

- Following approval of 1st drug for pulmonary NTM in 2018, there are now multiple novel therapies in the pipeline
- These therapeutic approaches include repurposing available drugs, investigational drugs, host directed therapies and other “non-drug”
- Obtaining better therapies for pulmonary NTM requires innovative, tailored clinical trial designs and, most importantly, patient participation

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Acknowledgements (Evolving…)

UNC Bronchiectasis/NTM Care & Research Center

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Priscilla Kitts, MSRC, RRT, RCP - Resp Clin Spec
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