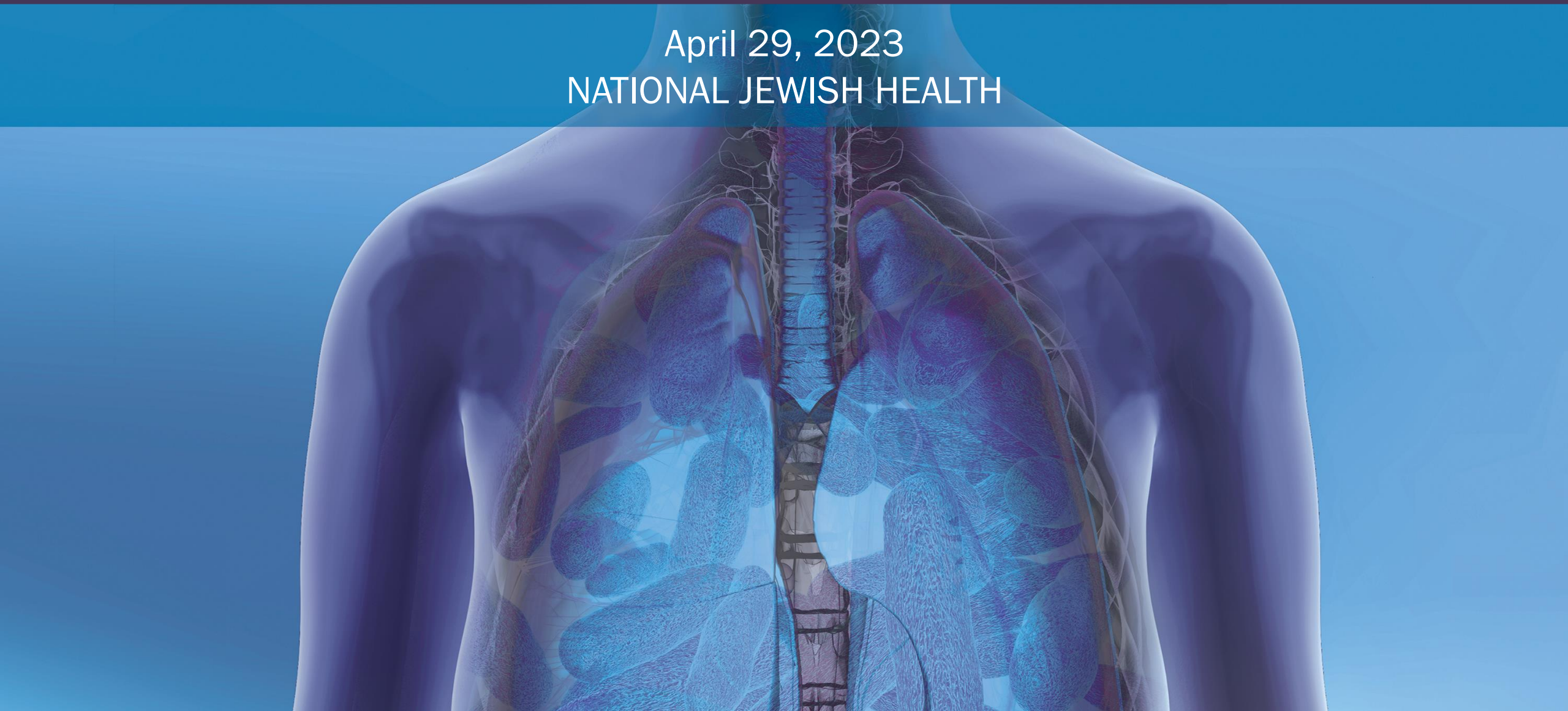
NTM Lecture Series for Patients

April 29, 2023
NATIONAL JEWISH HEALTH



Novel Therapeutics

UNC SCHOOL OF MEDICINE

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

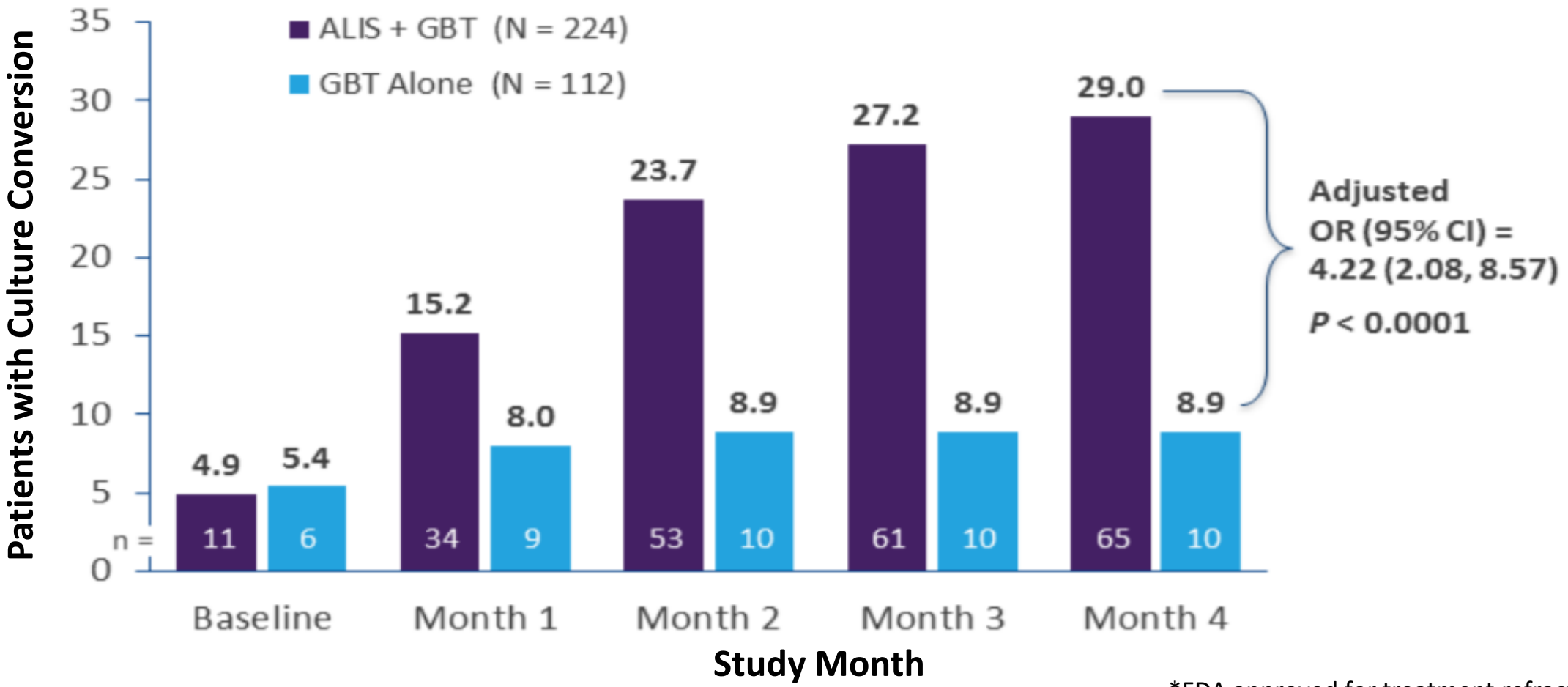
Disclosures

- 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

Drug approval for NTM

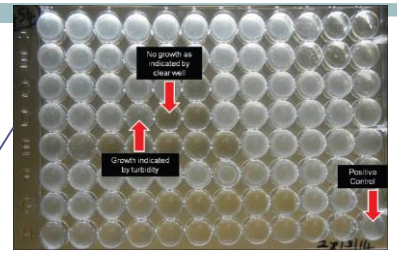
Clinical | Preclinical

Phase 3 Clinical Trial
- Target population (large)
- Registration
- Efficacy/safety

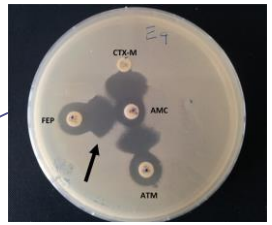
Phase 2b Clinical Trial
- Target population (small)
- Dose ranging
- Efficacy/safety

Phase 2a Clinical Trial
- Target population (small)
- Dose ranging/PK
- Safety +/- efficacy

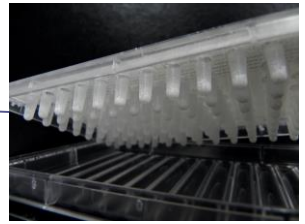
Phase 1 Clinical Trial
- Healthy volunteers
- Drug tolerance/pharmacokinetics



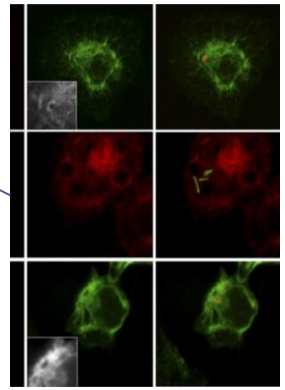
Determine “MIC” (minimum inhibitory concentration) of drug against NTM (this should be a small number)



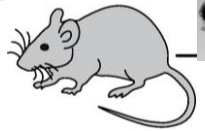
Check for interaction with other drugs

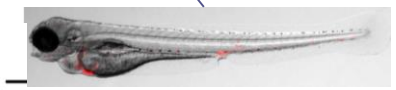


Activity in biofilm and other airway conditions



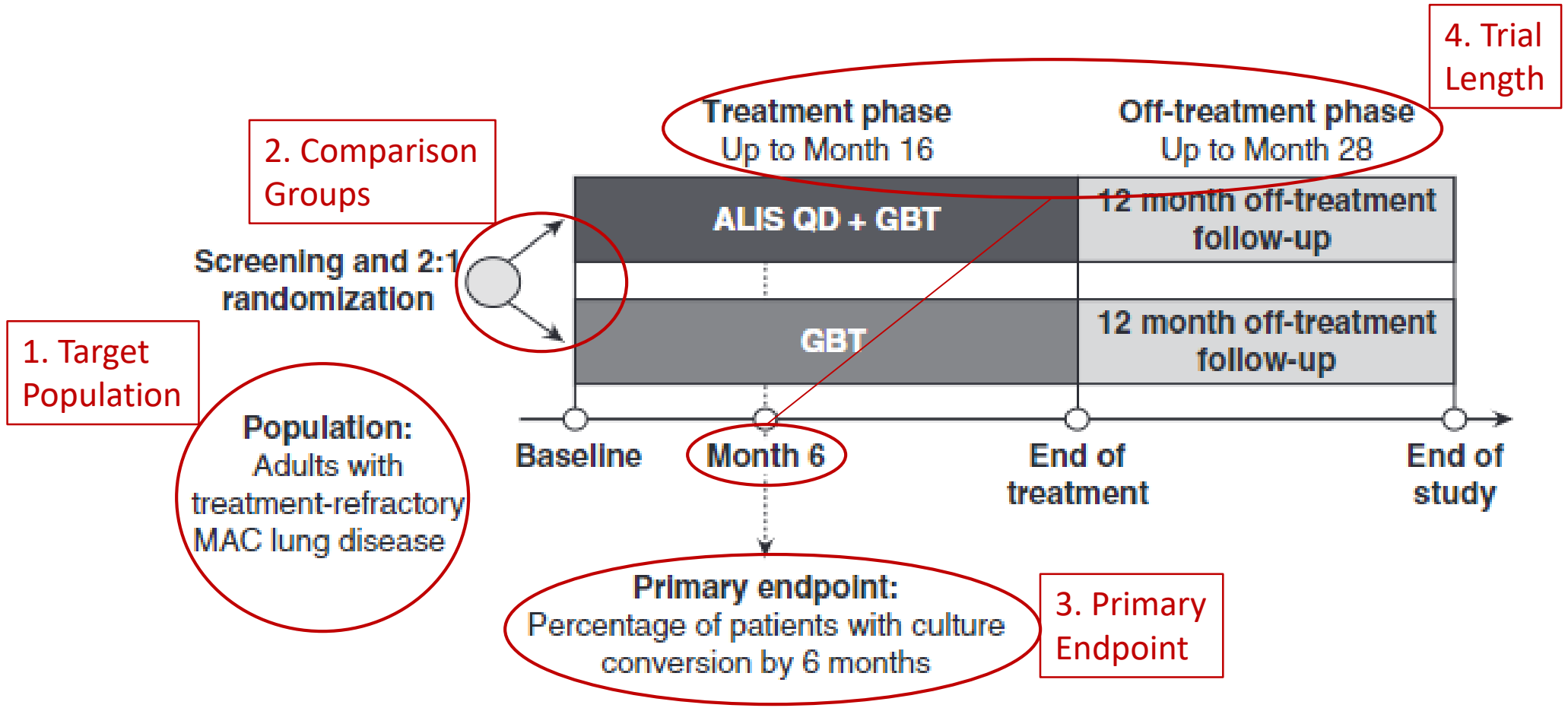
Intracellular killing assay





Animal models

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

Never treated or previously treated

- 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

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

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?
- How long to see improvement in symptoms?
- How long do patients need to be followed after completion of therapy?

Drug trial, existing drug (omadacyline)

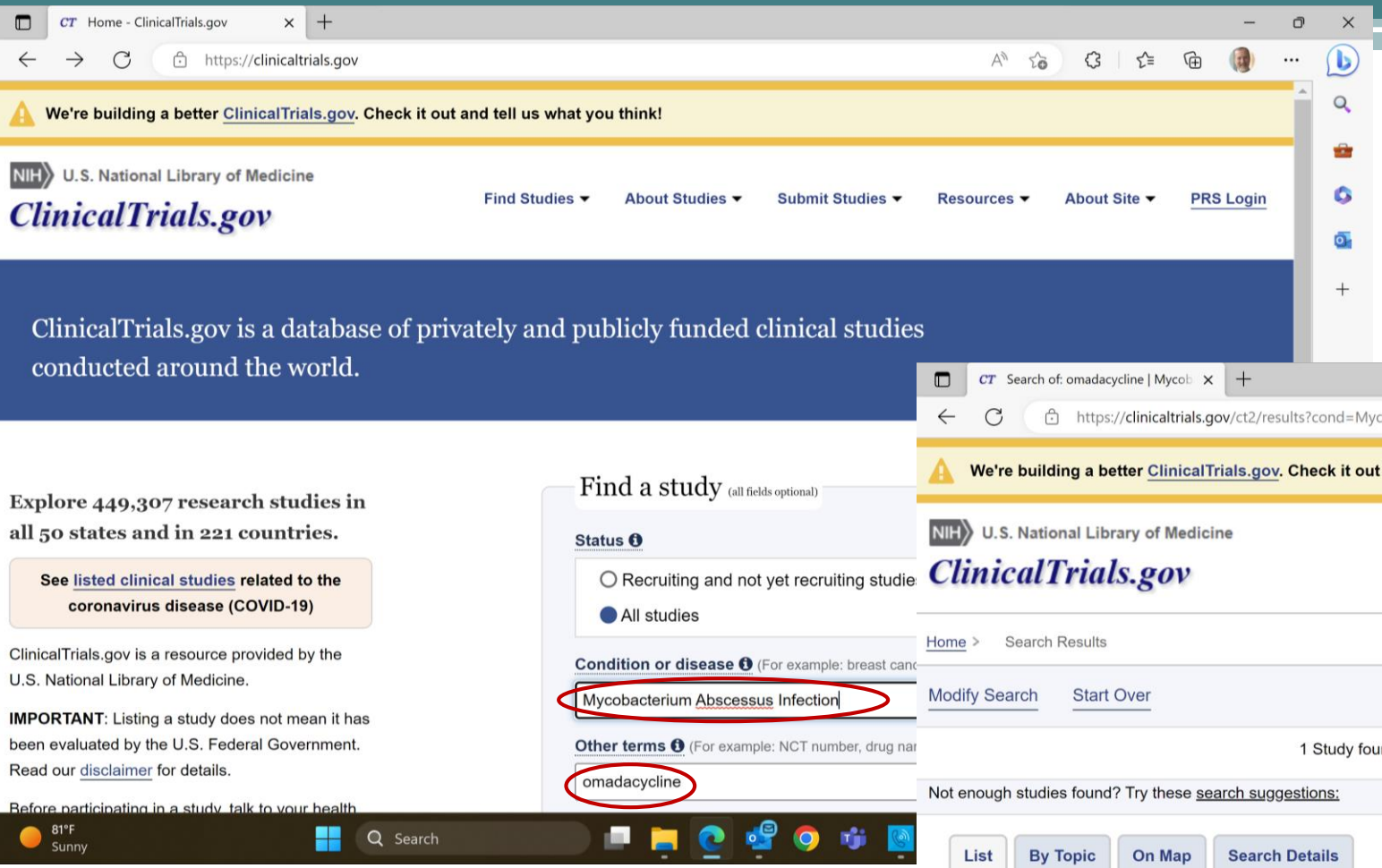
Isolate or MIC	*M. abscessus* subspecies	MIC (μg/ml) Tigecycline	Omadacycline	Eravacycline
MIC data	ATCC 19977 &			
MIC range	28 drug resistant	0.5–4	0.5–4	0.125–2
MIC_{50}	clinical isolates	1	1	0.5
MIC_{90}		2	2	1

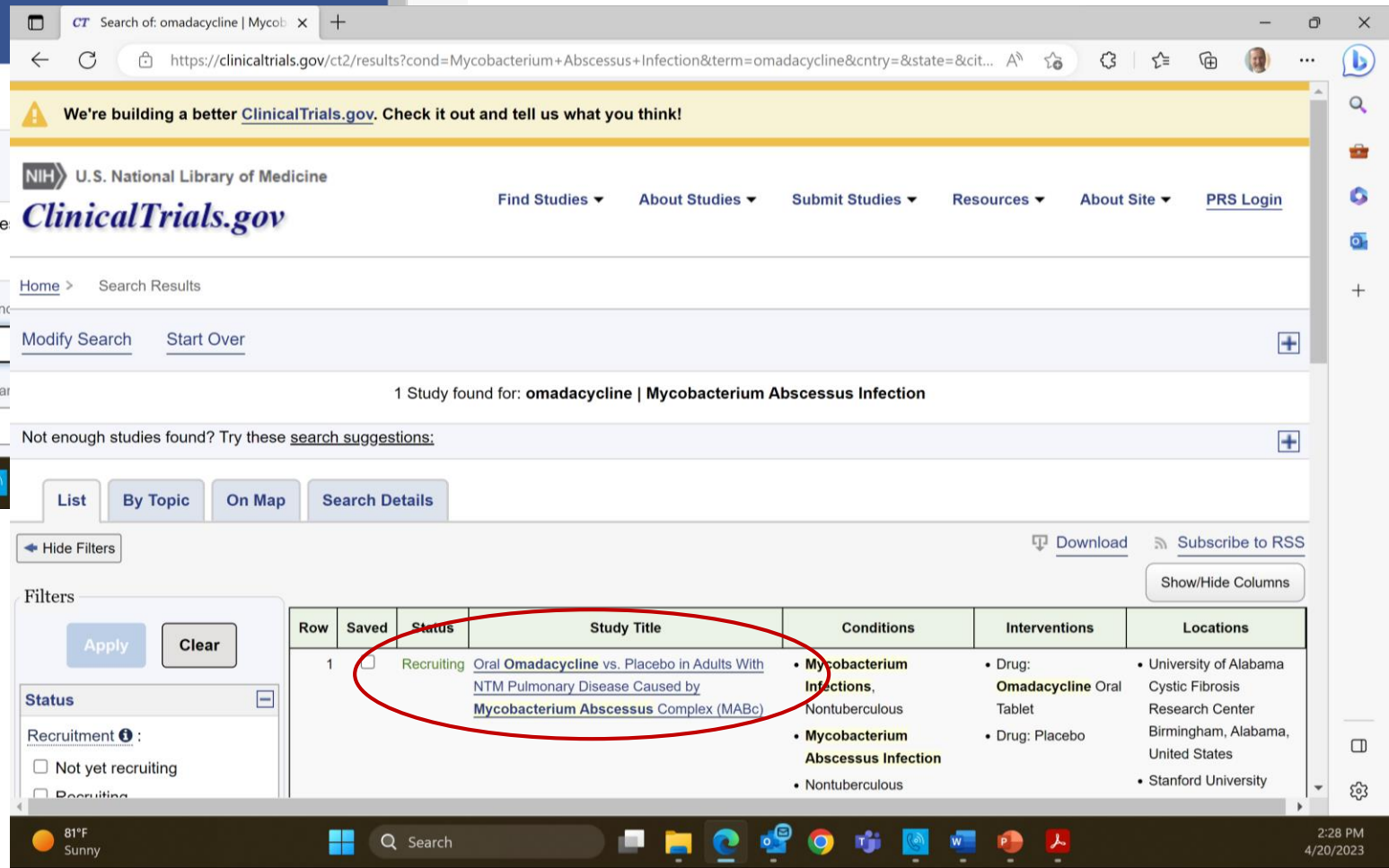
- Has very low MICs (takes small amount of drug to kill bug) against M abscessus
- Has good intracellular killing at drug levels that can be achieved with standard dosing

- 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

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

ClinicalTrials.gov





ClinicalTrials.gov

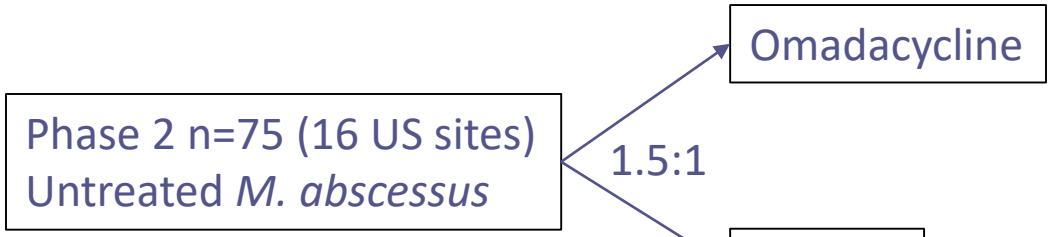
Oral Omadacycline vs. Placebo in Adults With NTM Pulmonary Disease Caused by *Mycobacterium abscessus*

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
  - Guidelines Based Treatment 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

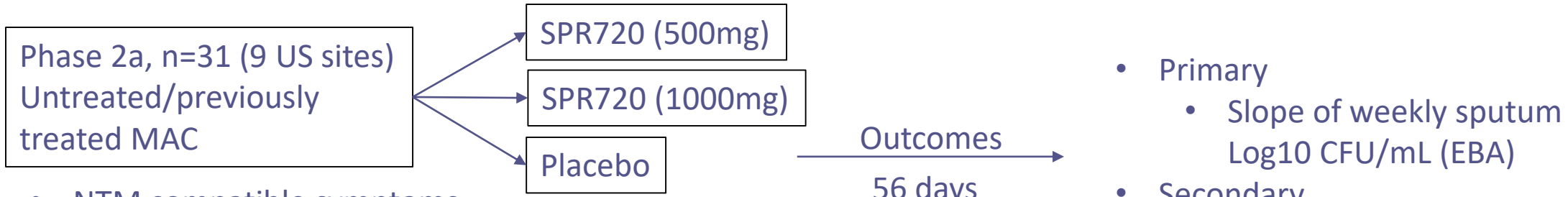
ClinicalTrials.gov Identifier: NCT04922554

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
  - Preclinical activity against M avium complex and M abscessus

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

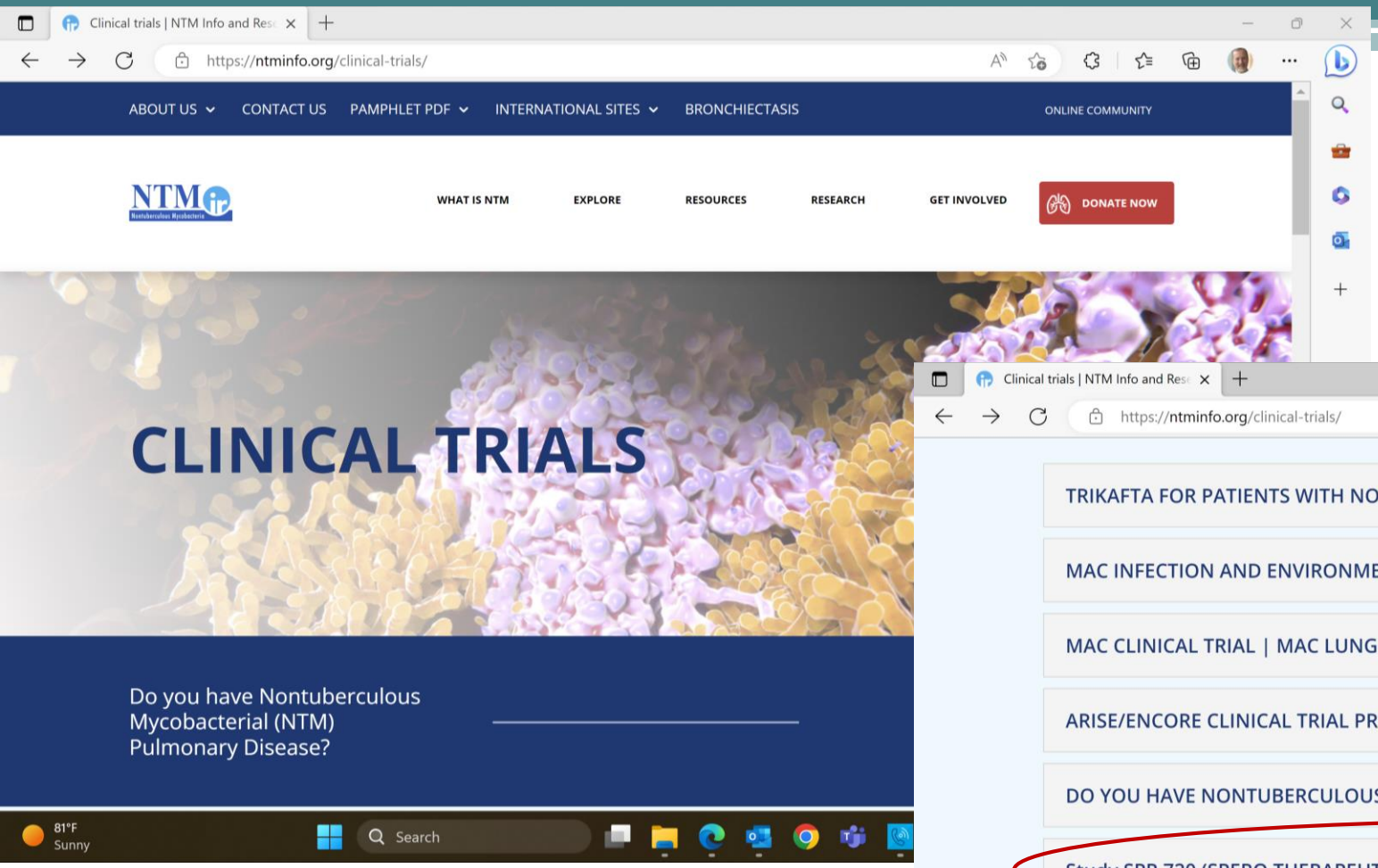
SPR720 Phase 2a, single agent for untreated MAC



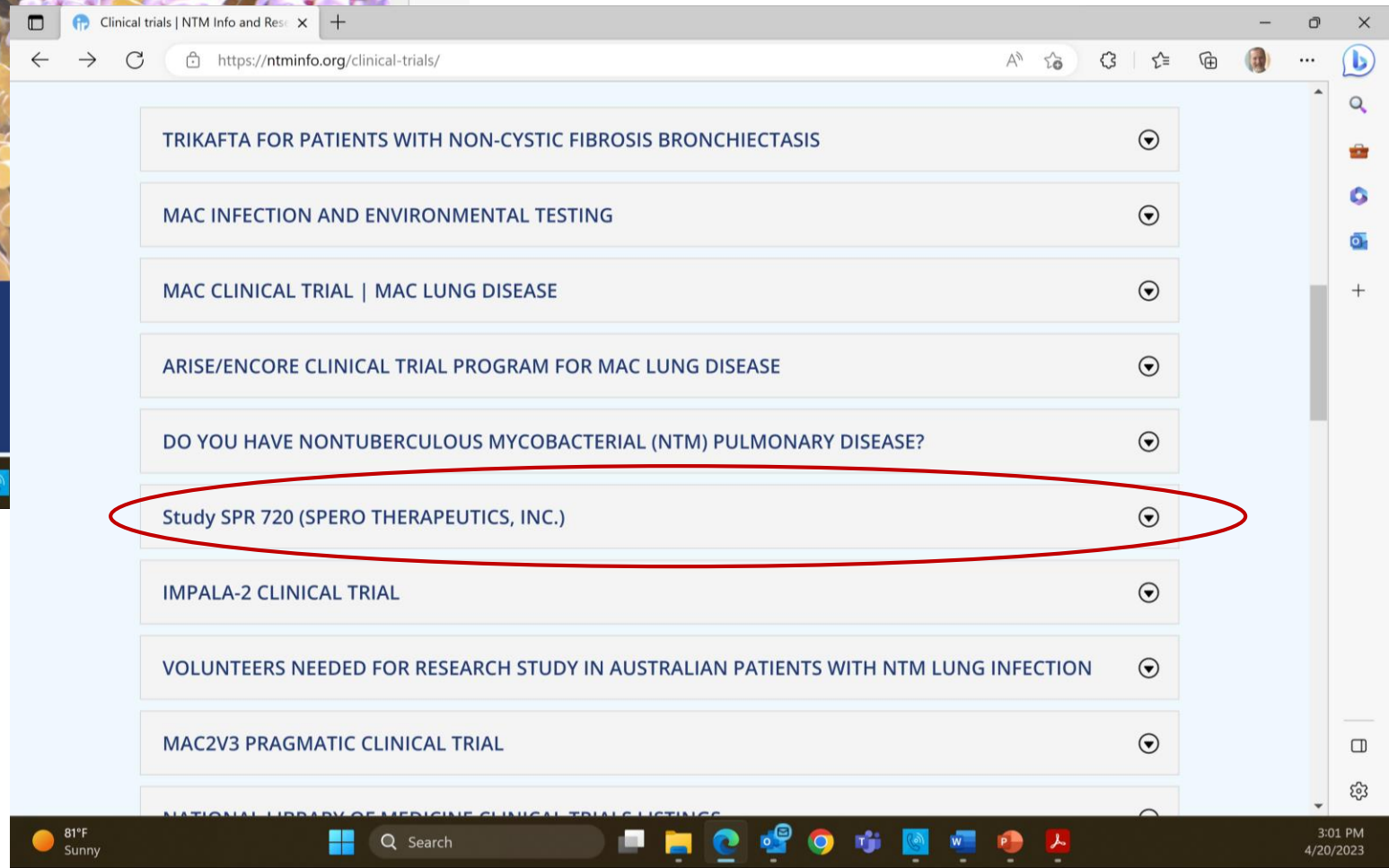
- NTM compatible symptoms
- Previous treatment
  - Successful treatment
  - Recent positive culture
  - Off Rx at least 3 mos

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

ClinicalTrials.gov Identifier: NCT05496374



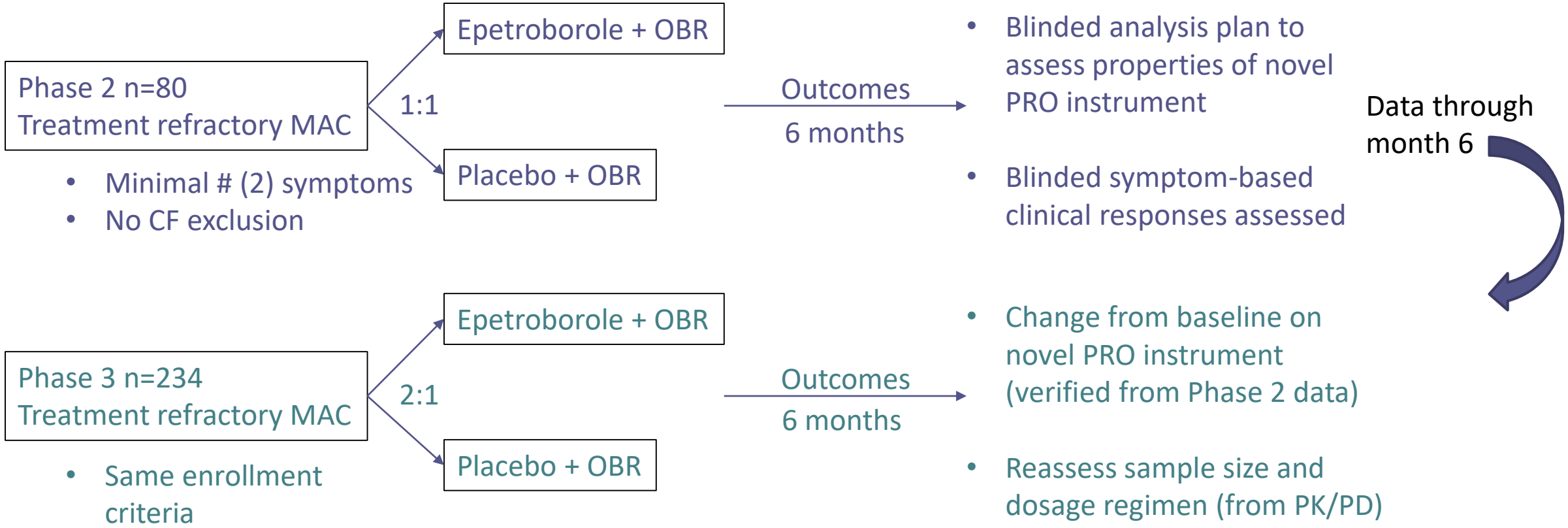
NTMinfo.org/clinical-trials/



NTMinfo.org/clinical-trials/

Epetraborole for Rx Refractory MAC

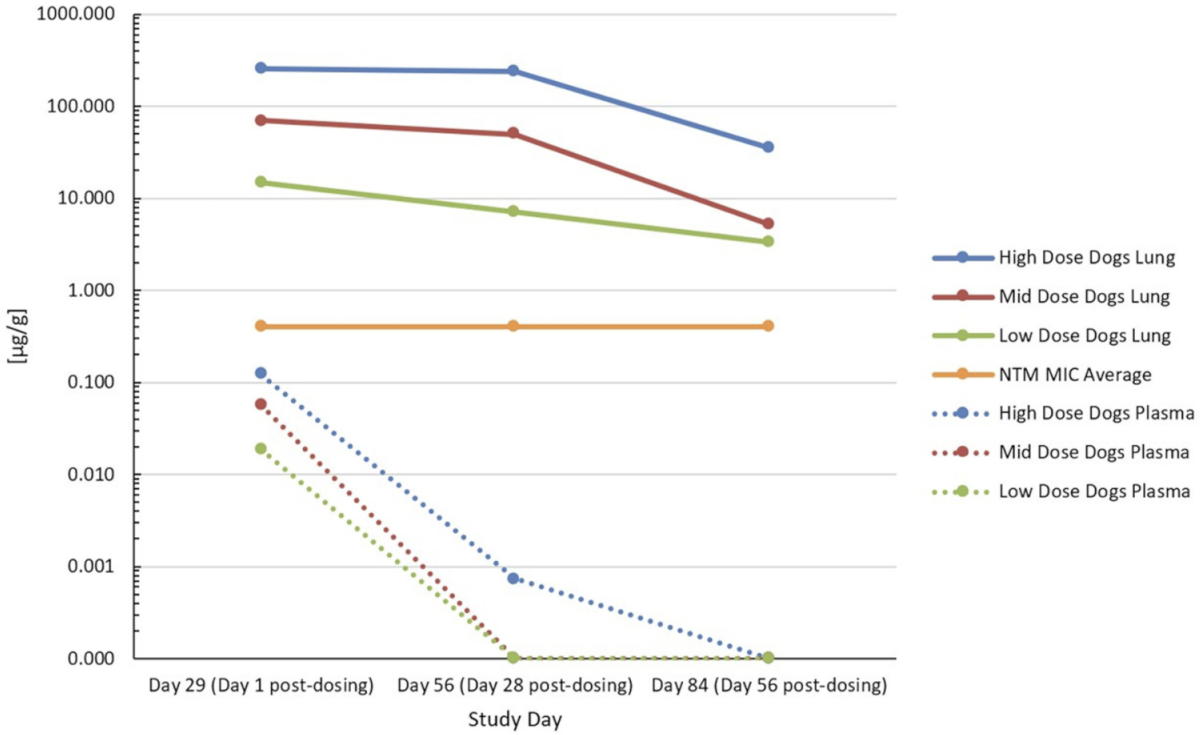
- Adaptive Phase 2/3 design, pilot PRO in Phase 2



ClinicalTrials.gov Identifier: NCT05327803

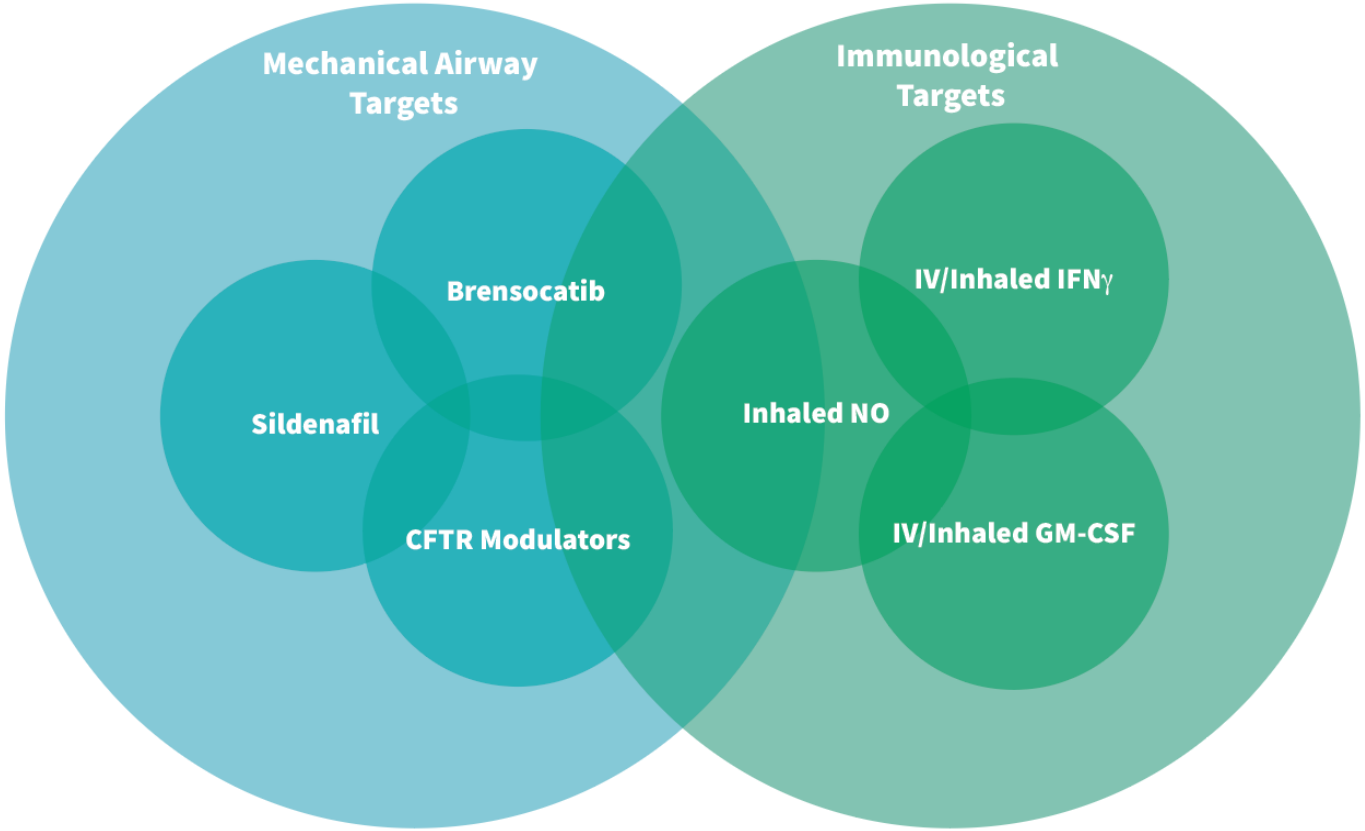
Clofazimine inhalation suspension, preclinical

- 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

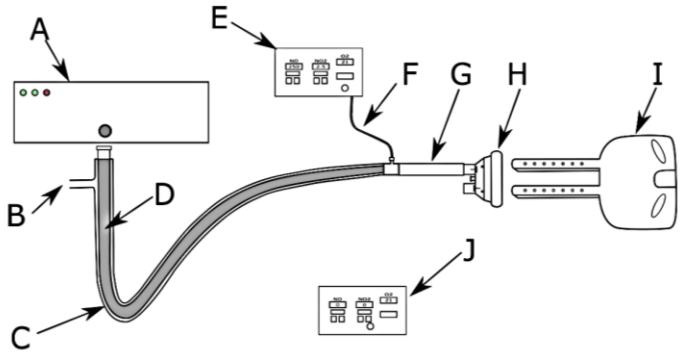
New therapies, host directed, non-drug approaches

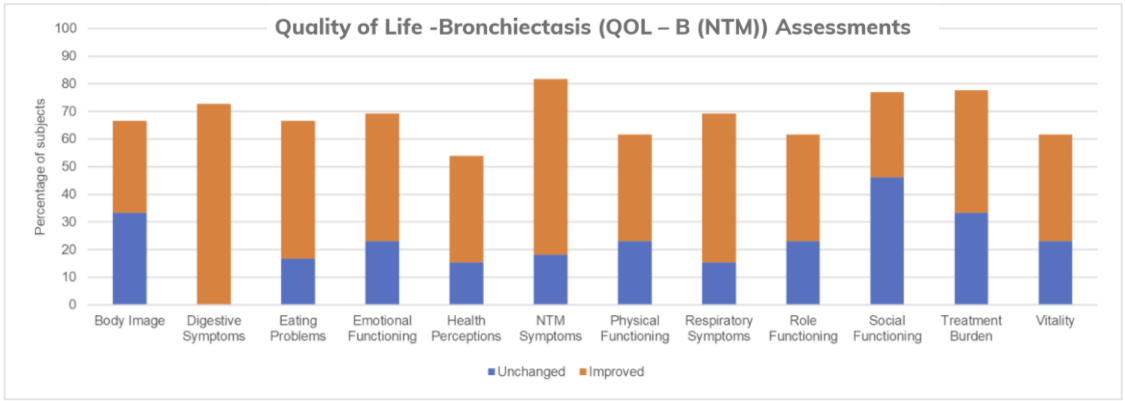


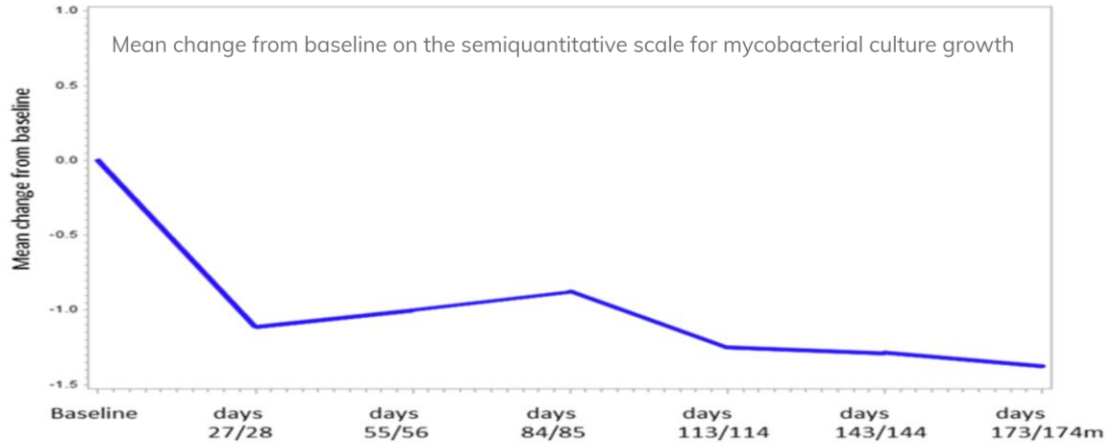
Anidi. Clin Chest Med 2023 (in review)

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



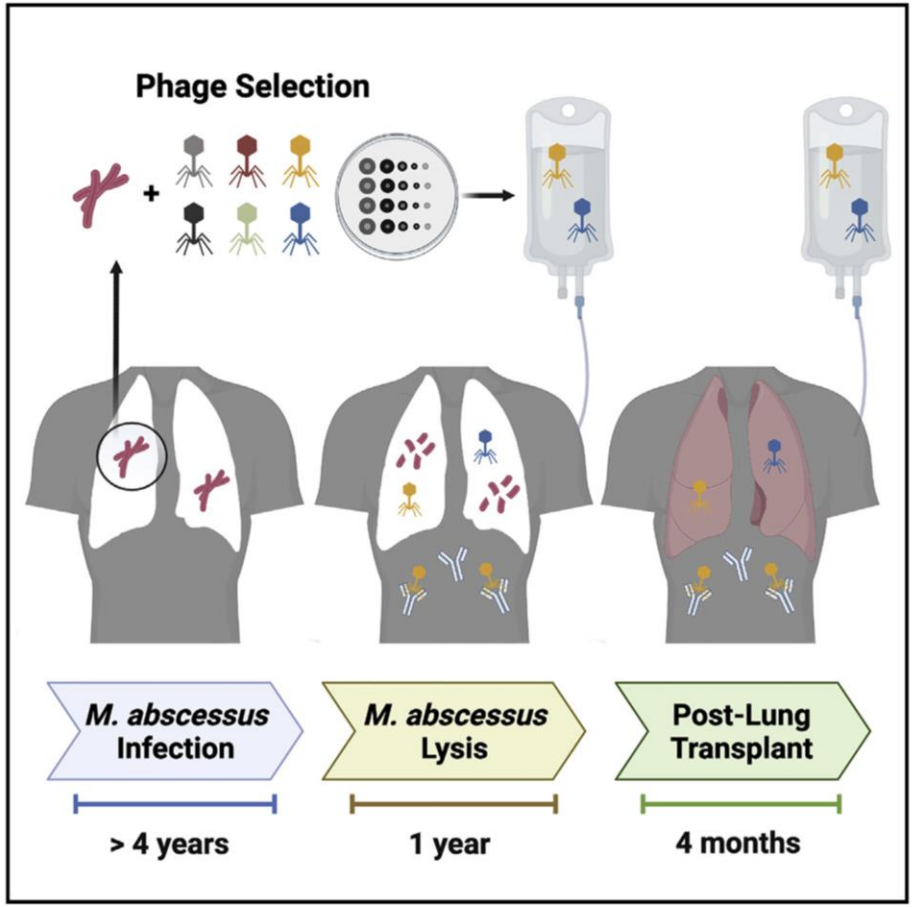




Thomson. Chest Annual Meeting 2022

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

Clinical Team

Leigh Anne Daniels, MD, MPH – Clinic Director
Kunal Patel, MD, PhD
Kunal Jakharia, MD
Karen Ellis, RN – Nurse Coordinator
Priscilla Kitts, MSRC, RRT, RCP - Resp Clin Spec
Morgan Jones, PharmD, BCACP, CPP - Clin Pharm Practitioner
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Kelsey Haywood, BS – Div PD/CCM Research Program Director