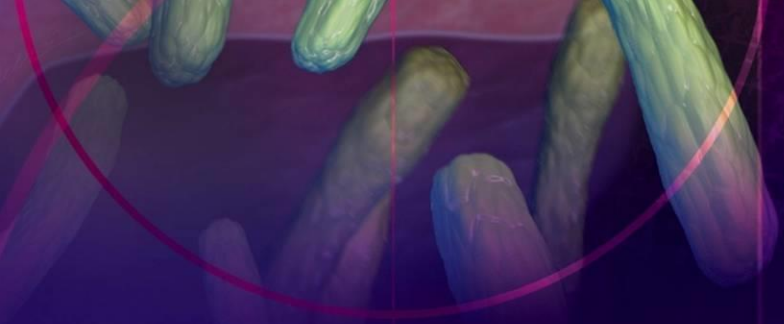

NTM Pipeline

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Disclosures

- Research support
  - FDA, PCORI, NTMir, COPD Foundation, Insmed
- Consulting honorarium
  - Insmed, Red hills, Paratek, Johnson and Johnson, Horizon

Currently Approved Therapies in NTM

- Azithromycin
  - Disseminated MAC in patients with HIV
  - “in combination with ethambutol”
- Clarithromycin
  - Disseminated MAC in patients with HIV
  - no mention of companion drugs needed

https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050662s044s050,50698s026s030,050775s015s019lbl.pdf

ANNALSATS SUPPLEMENT

Patient-Centered Research Priorities for Pulmonary Nontuberculous Mycobacteria (NTM) Infection

An NTM Research Consortium Workshop Report

Emily Henkle[1], Timothy Aksamit[2], Alan Barker[3], Charles L. Daley[4], David Griffith[5], Philip Leitman[6], Amy Leitman[6], Elisha Malanga[7], Theodore K. Marras[8], Kenneth N. Olivier[9], D. Rebecca Prevots[10], Delia Prieto[7], Alexandra L. Quittner[11], William Skach[12], John W. Walsh[7], Kevin L. Winthrop[13], and the NTMRC Patient Advisory Panel

Patient Advisory Panel Members
Cynthia Flora
Marge Gustafson
Bob Gustafson
Matthew Pozsgai
Mary Pozsgai
Margery Stalch
Sue Tsang

Treatment	**Reduce the burden of antibiotic treatment for NTM disease**	**Develop and evaluate alternative delivery systems for IV antibiotics** **Repurpose existing therapies** **Develop new, more effective drugs with a shorter therapy duration**
	Improve understanding of who needs or benefits from antibiotic therapy.	**Role of therapy in mild cases to prevent disease progression** **Predictors of treatment response**
Clinical outcomes	**Develop a composite measure of disease activity or severity.**	**Develop a composite index of disease activity or severity that include microbiological, chest imaging, and quality of life measures.**
	Identify and validate biomarkers associated with disease risk, prognosis, and treatment response	**Identify biomarkers associated with disease risk, prognosis, or treatment response**

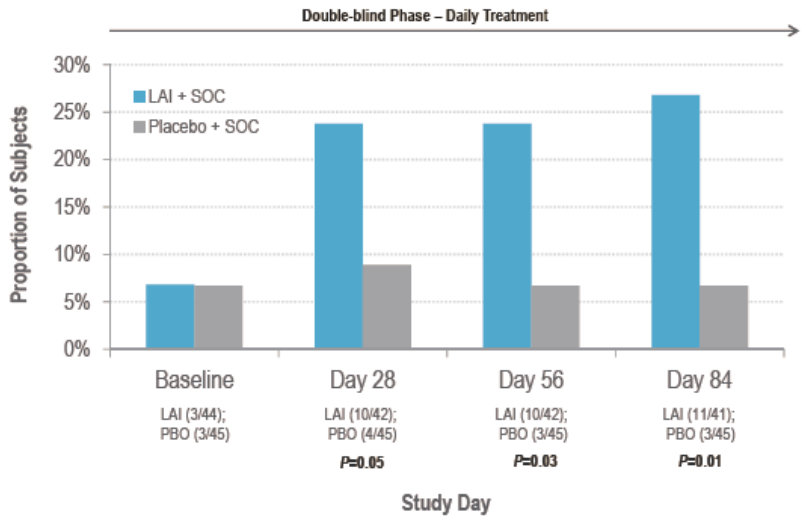
Current NTM RCTs

- *MAC*
  - Liposomal amikacin
  - Clofazimine
  - GM-CSF
  - NO
  - 2 v 3: AZI/EMB versus AZI/EMB/RIF
  - CLARI/RIF/EMB vs AZI/RIF/EMB
- *M xenopi*: CLARI/RIF/EMB vs MOXI/RIF/EMB
- *M. abscessus*
  - Liposomal amikacin
  - NO

https://www.clinicaltrials.gov/

Inhaled Liposomal Amikacin

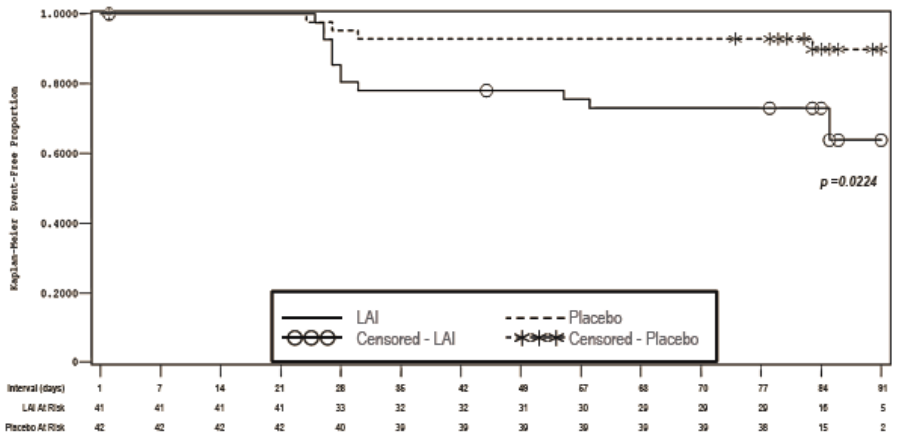
Proportion of Subjects with NTM Culture Conversion to Negative (mITT Population)



NOTE: Missing Values Excluded

P-value for stratified Cochran-Mantel-Haenszel test of treatment arm adjusting for the randomization strata

Kaplan-Meier Plot of Time from Study Baseline to NTM Culture Negative* (mITT Population)



* Censoring at Date of Last Contact or At Initiation of Open-Label LAI

Note: Subjects without event or censoring criteria are censored at study day 91.
Number at risk is the subjects remaining at risk after the corresponding interval day.

Olivier K et al. ATS 2014

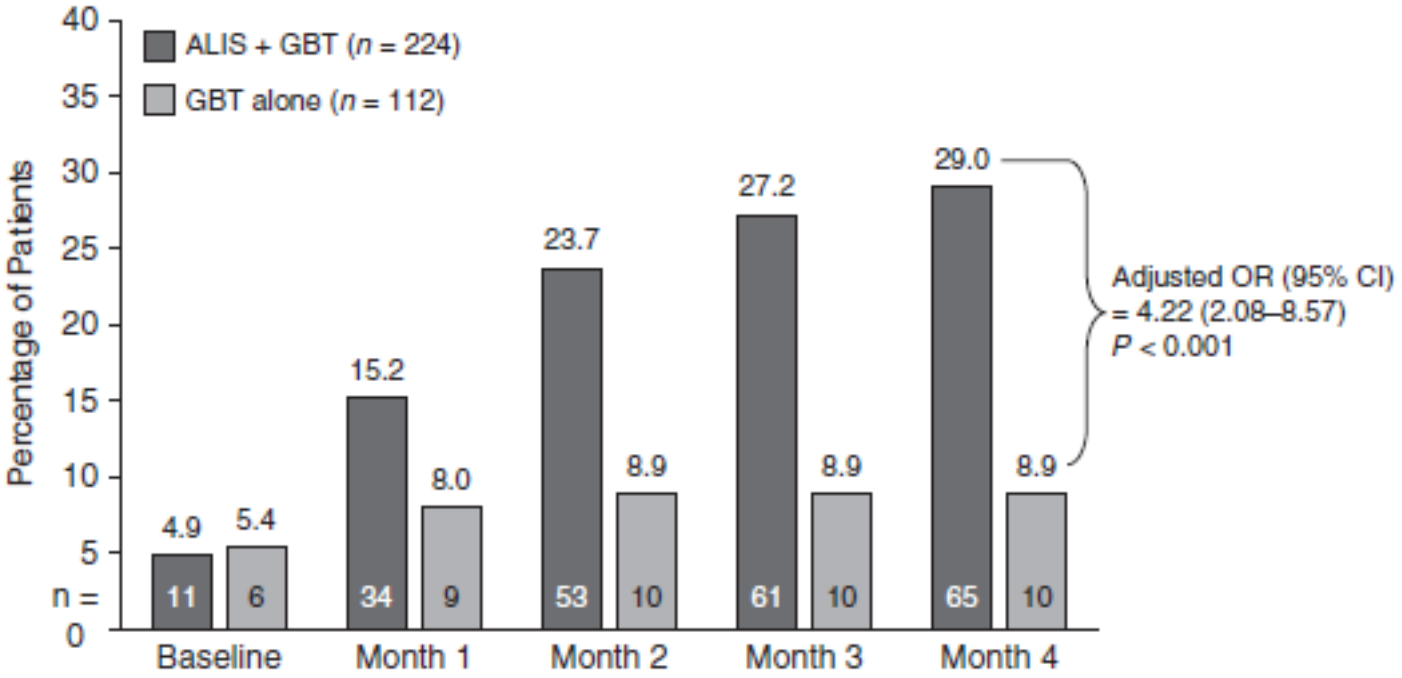
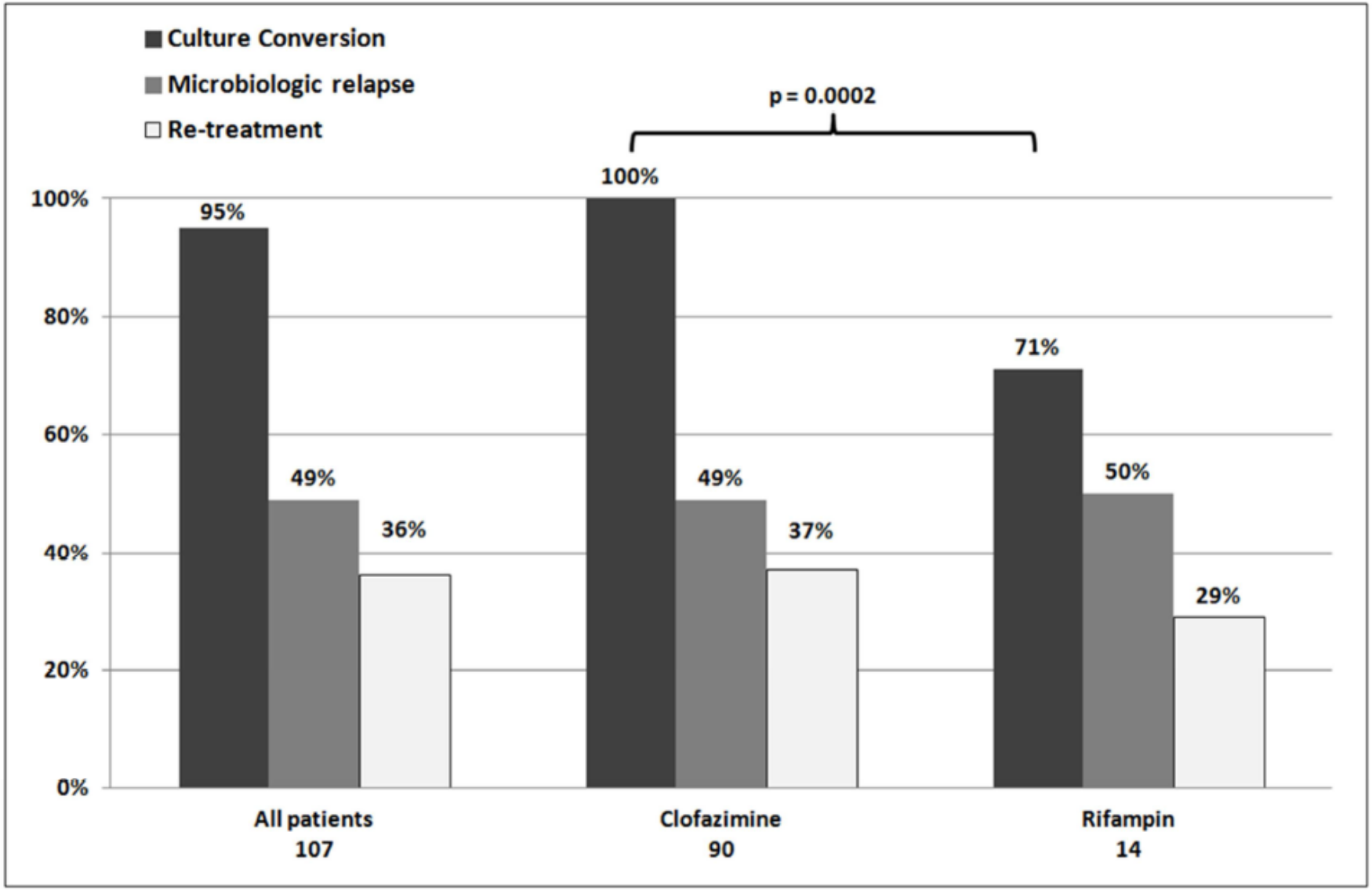


Figure 3. Proportion of patients achieving culture conversion, shown by the first month of conversion: intention-to-treat population. The cumulative proportion of patients achieving culture conversion is displayed by the first month at which sputum cultures were *Mycobacterium avium* complex negative. Month 4 was the latest time point at which a patient could achieve the first of three consecutive negative sputum cultures and be considered a converter in the primary endpoint analysis at Month 6. Patients with positive cultures during screening and negative cultures at baseline and Months 1 and 2 were considered converters at baseline. ALIS = amikacin liposome inhalation suspension; CI = confidence interval; GBT = guideline-based therapy; OR = odds ratio.

Griffith D, et al. Am J Respir Crit Care Med. 2018

Clofazimine



Jarand J et al. Chest 2015

FDA-sponsored Clofazimine Monotherapy Trial

- Trial Sites
  - OHSU, NJH, UT, NIH, (UC Chicago, Univ South Carolina)
- Randomized, placebo-controlled 24 weeks clofazimine monotherapy
  - 200 mg 16 weeks, 100 mg 8 weeks
  - N=102 patients
- Inclusion criteria
  - Stable pulmonary MAC patients
- Primary outcome
  - Culture conversion at 24 weeks
- Current enrollment
  - N= 21 randomized

MAC 2 Vs 3 Trial

- Large, multi-site pragmatic trial
  - NTM Consortium and Trials network (35 sites)
- RCT comparing 2- vs 3-drugs for pulmonary MAC
  - AZI/EMB vs AZI/EMB/RIF
  - Non-cavitary disease
- Co-primary outcomes at 12 months
  - Culture conversion and tolerability
  - Non-inferiority

https://www.clinicaltrials.gov/

Bedaquiline

TABLE 1] Semiquantitative Monthly Sputum Cultures of 10 Patients on a Bedaquiline-Containing Regimen

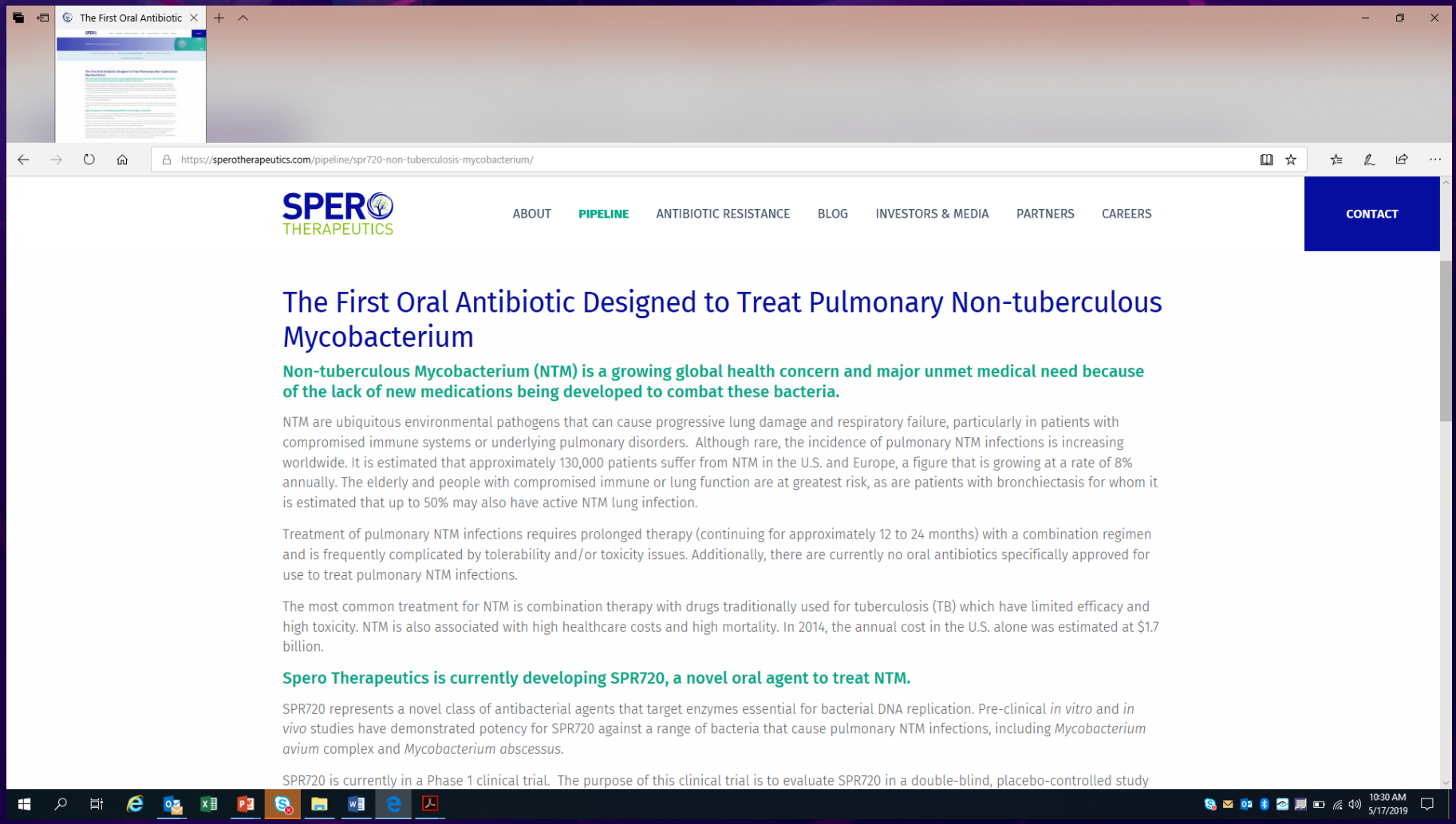
Patient No.	Baseline (at the Start of Therapy)	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo
1 Mab	4+	3+	1+	2+	3+	1+	2+
2 Mab	1+	3+	1+	35 colonies	37 colonies	16 colonies	3+
3 Mab	4+	28 colonies	Negative	8 colonies	Negative	Negative	32 colonies
4 Mab	4+	4+	4+	4+	4+	4+	4+
5 MAC	4+	3+	4+	4+	4+	4+	4+
6 MAC	4+	4+	Negative	Negative	2+	4+	3+
7 MAC	4+	4+	30 colonies	Negative	Negative	...[a]	...[a]
8 MAC	4+	1+	Negative	3+	4+	4+	4+
9 MAC	4+	2+	3+	1 colony	4 colonies	1+	4 colonies
10 MAC	30 colonies	8 colonies	Negative	1+	Negative	9 colonies	Negative

Solid media with countable colonies = 0-49 colonies; 1+ solid media growth = 50-99 colonies; 2+ solid media growth = 100-199 colonies; 3+ solid media growth = 200-299 colonies; 4+ solid media growth = ≥300 colonies. Negative indicates no bacterial growth. Mab = *Mycobacterium abscessus*; MAC = *Mycobacterium avium* complex. Negative = no bacterial growth.

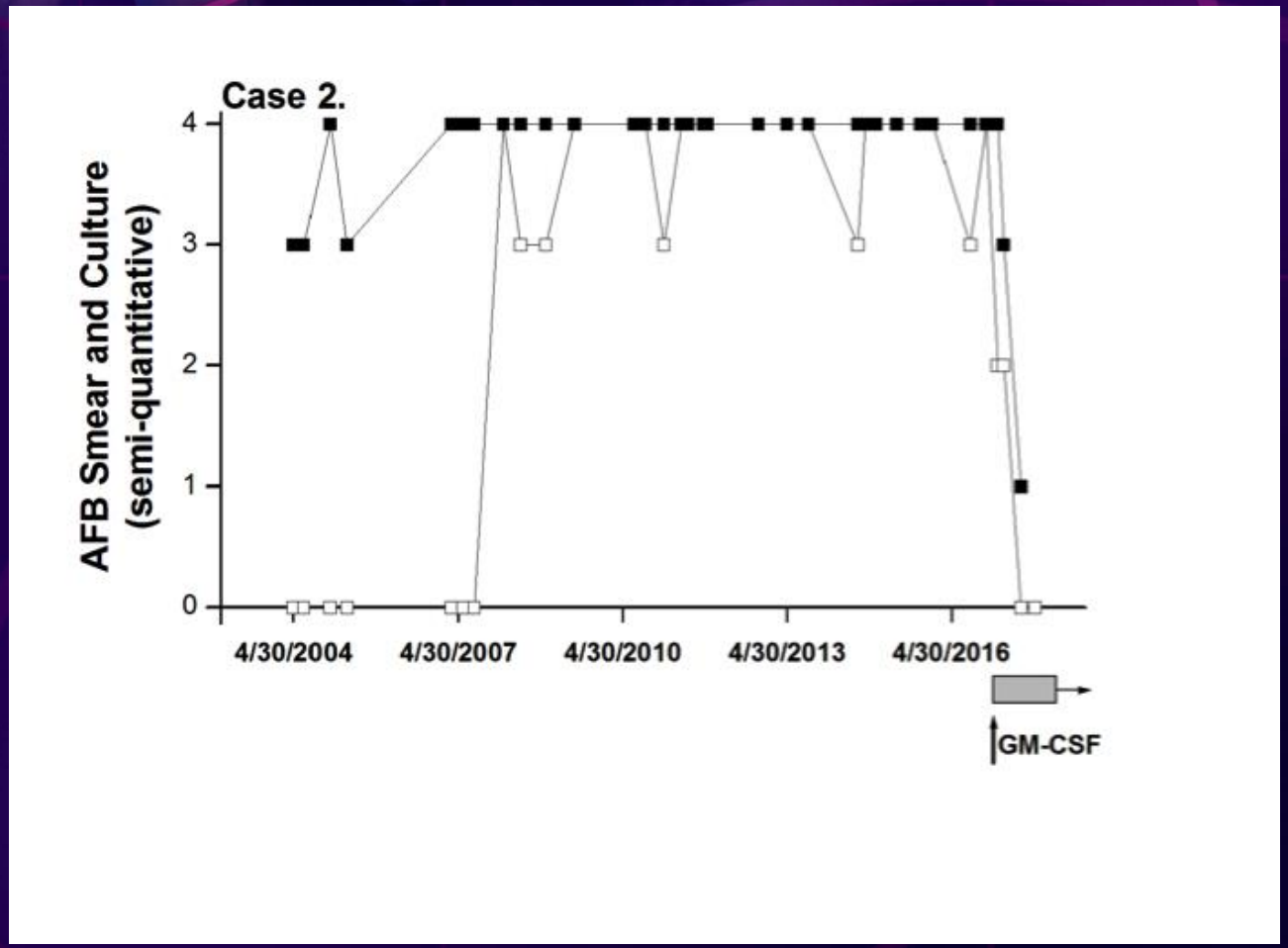
[a]Unable to produce sputum.

Philly J et al. Chest 2015

Other Abx

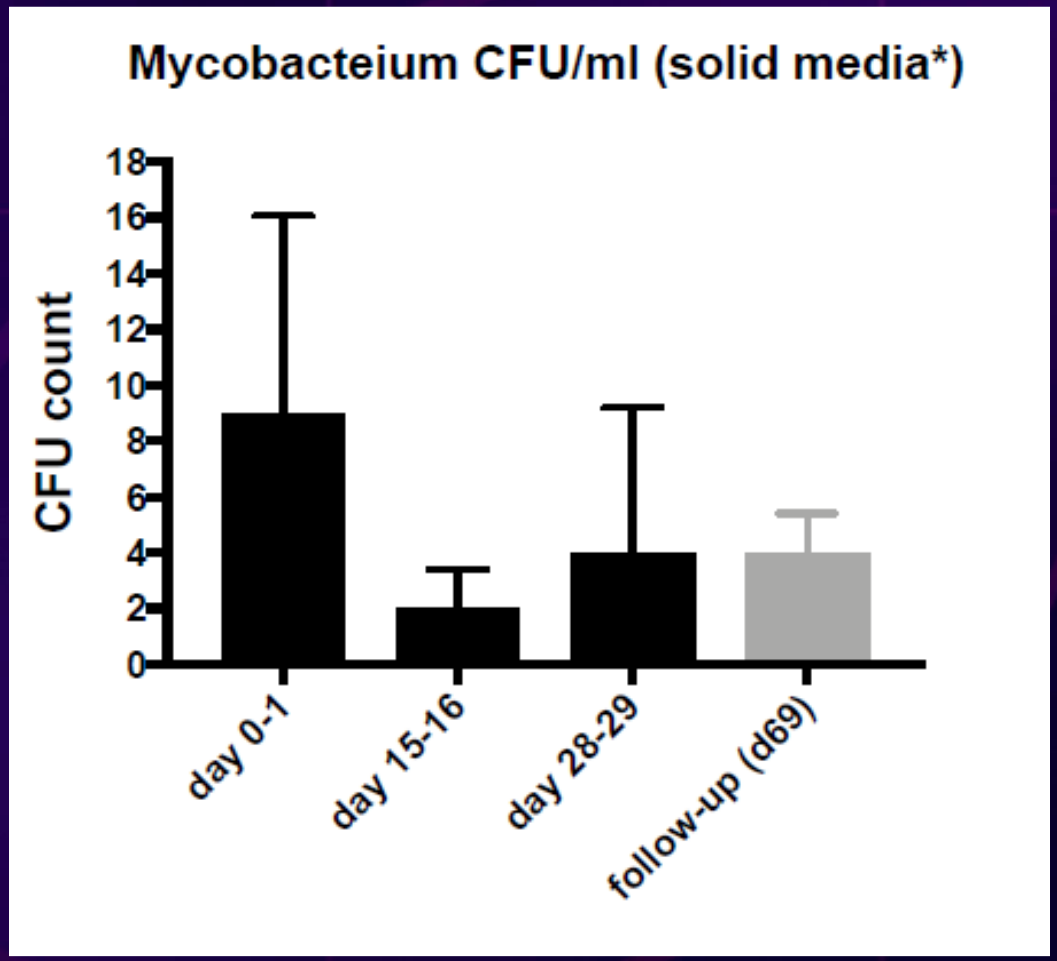

The First Oral Antibiotic
https://sperotherapeutics.com/pipeline/spr720-non-tuberculosis-mycobacterium/
SPERO THERAPEUTICS
ABOUT
PIPELINE
ANTIBIOTIC RESISTANCE
BLOG
INVESTORS & MEDIA
PARTNERS
CAREERS
CONTACT
The First Oral Antibiotic Designed to Treat Pulmonary Non-tuberculous Mycobacterium
Non-tuberculous Mycobacterium (NTM) is a growing global health concern and major unmet medical need because of the lack of new medications being developed to combat these bacteria.
NTM are ubiquitous environmental pathogens that can cause progressive lung damage and respiratory failure, particularly in patients with compromised immune systems or underlying pulmonary disorders. Although rare, the incidence of pulmonary NTM infections is increasing worldwide. It is estimated that approximately 130,000 patients suffer from NTM in the U.S. and Europe, a figure that is growing at a rate of 8% annually. The elderly and people with compromised immune or lung function are at greatest risk, as are patients with bronchiectasis for whom it is estimated that up to 50% may also have active NTM lung infection.
Treatment of pulmonary NTM infections requires prolonged therapy (continuing for approximately 12 to 24 months) with a combination regimen and is frequently complicated by tolerability and/or toxicity issues. Additionally, there are currently no oral antibiotics specifically approved for use to treat pulmonary NTM infections.
The most common treatment for NTM is combination therapy with drugs traditionally used for tuberculosis (TB) which have limited efficacy and high toxicity. NTM is also associated with high healthcare costs and high mortality. In 2014, the annual cost in the U.S. alone was estimated at $1.7 billion.
Spero Therapeutics is currently developing SPR720, a novel oral agent to treat NTM.
SPR720 represents a novel class of antibacterial agents that target enzymes essential for bacterial DNA replication. Pre-clinical in vitro and in vivo studies have demonstrated potency for SPR720 against a range of bacteria that cause pulmonary NTM infections, including Mycobacterium avium complex and Mycobacterium abscessus.
SPR720 is currently in a Phase 1 clinical trial. The purpose of this clinical trial is to evaluate SPR720 in a double-blind, placebo-controlled study
10:30 AM
5/17/2019

Inhaled GM-CSF



Scott JP et al ERS 2019

NO


Mycobacteium CFU/ml (solid media*)
CFU count
18
16
14
12
10
8
6
4
2
0
day 0-1
day 15-16
day 28-29
follow-up (d69)

Phage

Girl is first patient saved by GM virus treatment

Hannah Devlin
Science correspondent

A British teenager has made a remarkable recovery after being the first patient in the world to be given a genetically engineered virus to treat a drug-resistant infection.

The scientists behind the breakthrough say bacteria-killing viruses, known as phages, could become an alternative to antibiotics to treat bacterial infections resistant to the drugs.

Isabelle Holdaway, 17, nearly died after a lung transplant left her with an intractable infection that could not be cleared with antibiotics.

Following a nine-month stay at Great Ormond Street hospital in London, she returned to her home in Kent for palliative care, but recovered after her consultant teamed up with a US lab to develop the experimental therapy.

Isabelle's mother, Jo Holdaway, who made the initial suggestion of phage therapy to doctors at Great Ormond Street after reading about it online, said her daughter was "the luckiest child on Earth" to have got the treatment in time. "It's incredible medical science," she said. "It's been a miracle."

Isabelle has cystic fibrosis, a genetic disease that results in frequent infections clogging up the lungs with mucus. By summer 2017, her lungs had less than a third of their normal function and she had been plagued by two stubborn bacterial strains for eight years. She and her doctors decided that a double lung transplant was the best option – but this was fraught with risk that her

6 →

Acknowledgements

- Close colleagues and friends at variety of institutions including:
  - OHSU, NJMC, Mayo, UT Tyler, NIH, PCORI, Univ. Ontario, U Florida, CDC, ATS/IDSA, OHSU, OHA, ACR, EULAR, and ERS
  - FDA and industry partners