Third Indication: Non Tuberculous Mycobacteria (NTM)

NTM is an FDA disease area of focus with limited options. Patients can die within a few years[1]

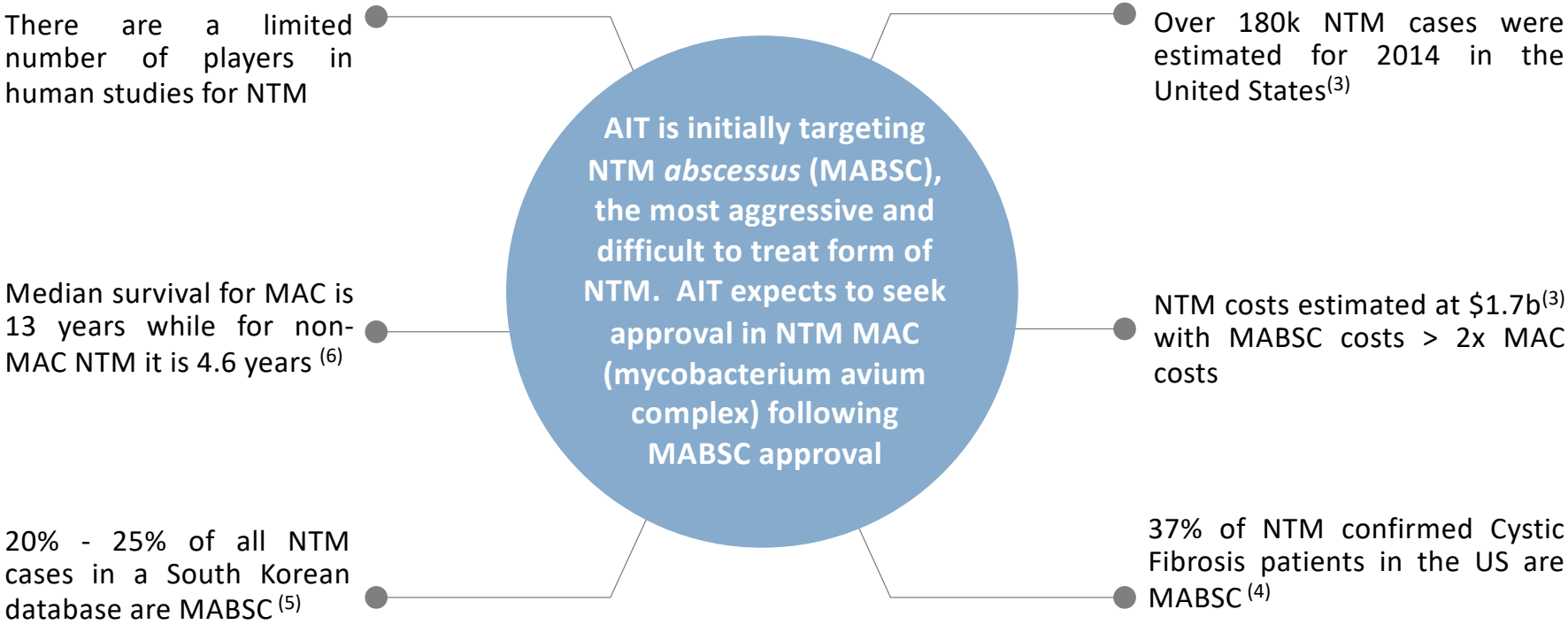
How is NTM Acquired? [2]

- Acquired by inhalation from the environment
- Water thought to be the main source
- Warmer climates have higher infection rates
- Patient to patient transmission possible

Who is at risk? [2]

- Underlying lung disease and/or genetic predisposition
- Cystic Fibrosis (CF) patients
- COPD (chronic obstructive pulmonary disease)
- Bronchiectasis patients
- Immunosuppressive therapy

NTM Market Dynamics?



(1) https://www.fda.gov/downloads/Drugs/NewsEvents/UCM471341.pdf
(2) Data: www.ntmfacts.com, FDA
(3) Strolloet al. The Burden of Pulmonary Nontuberculous Mycobacterial. Pub 27-July-2015
(4) Data presented at ATS 2017 (Derek Low et al, Medical University of South Carolina)
(5) Data presented at ATS 2017 (Keun Burn Chung et al, Seoul National University College of Medicine)
(6) Kotilainen, H. et al. "Clinical Findings in Relation to Mortality in Non-Tuberculous Mycobacterial Infections: Patients with Mycobacterium Avium Complex Have Better Survival than Patients with Other Mycobacteria." European Journal of Clinical Microbiology & Infectious Diseases 34.9 (2015)

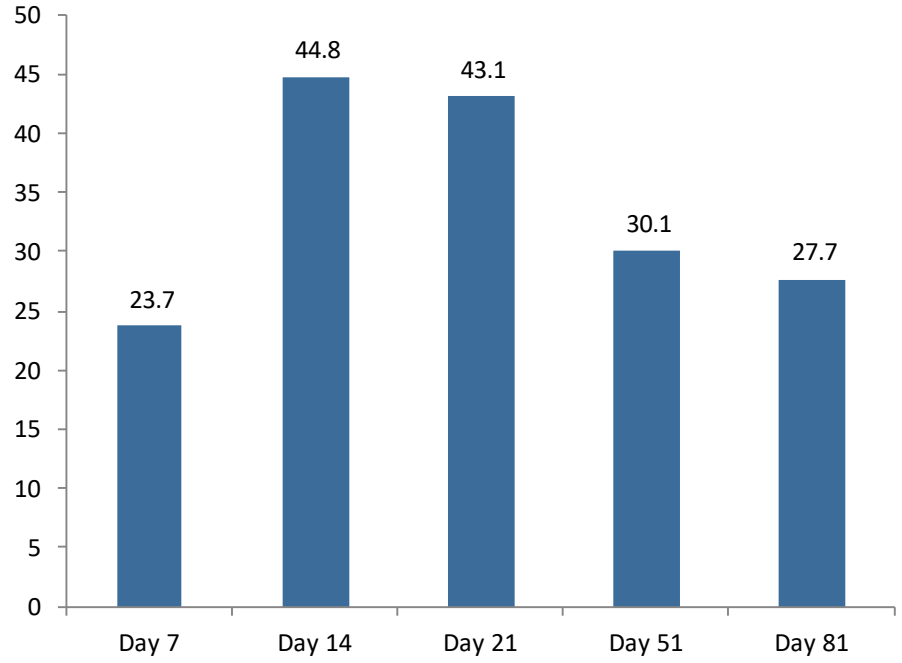
Pulmonary Infections: e.g. Non Tuberculous Mycobacteria (NTM)

Proprietary NO formulation yielded positive clinical results in humans in its single arm pilot NTM study

- 9 CF patients with refractory MABSC were treated at 3 centers in Israel with NO added to background antibiotic therapy
  - 160 ppm NO was given via mask for 30 min 5x/day for 14 days and 3x/day for 7 days
  - Primary endpoint of safety was met, with no NO-related serious adverse events (SAEs) observed
  - Key secondary endpoints of 6-minute walk (6MW) and FEV1 are shown in the charts below
  - Bacterial load, as measured by qPCR showed a 65% reduction at day 81 versus baseline
    - One patient was culture negative at Day 51 and Day 81
  - Quality-of-Life data showed positive trends on relevant questions (SF-36 used)
  - Tolerability not an issue as no patient requested that any treatment be stopped or not administered
- 4 patients treated under compassionate use experienced similar results (1 treated at NIH with generator, 1 culture conversion)

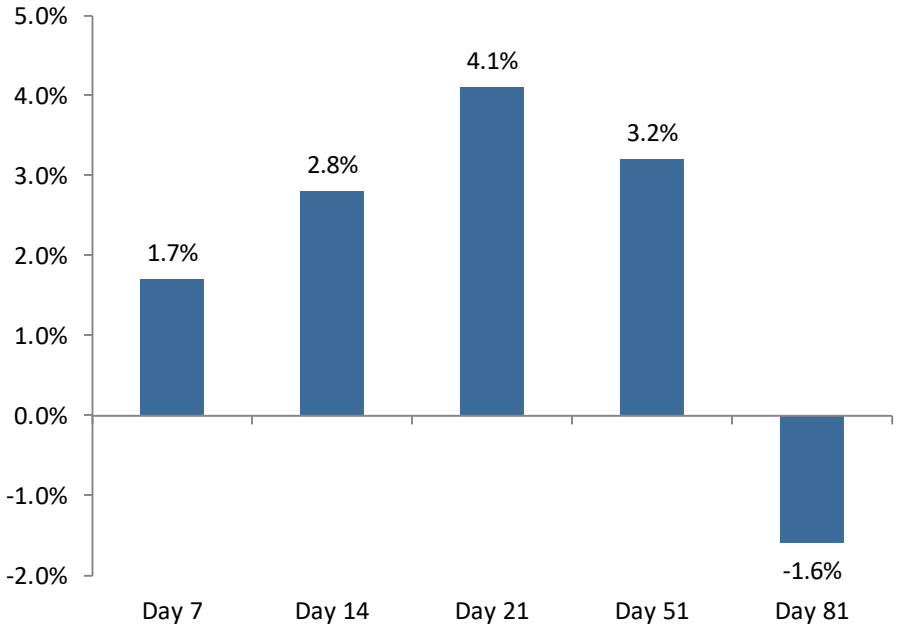
6MW Mean Inc. in Distance (meters) v. Baseline

On Therapy | Off Therapy



Mean % change in FEV1 from Baseline

On Therapy | Off Therapy



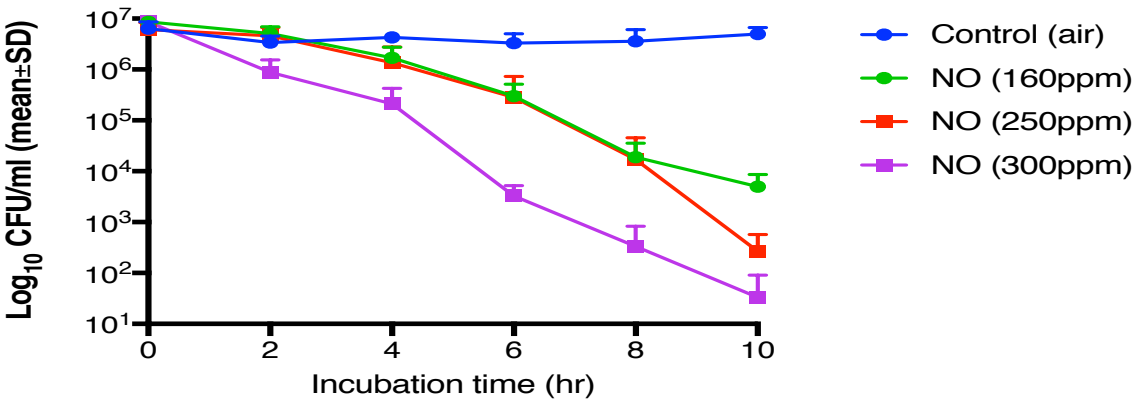
DATA PRESENTED IN AN ORAL SESSION AT AMERICAN THORACIC SOCIETY (ATS) 2018

Source: AIT management

Pulmonary Infections: e.g. Non Tuberculous Mycobacteria (NTM)

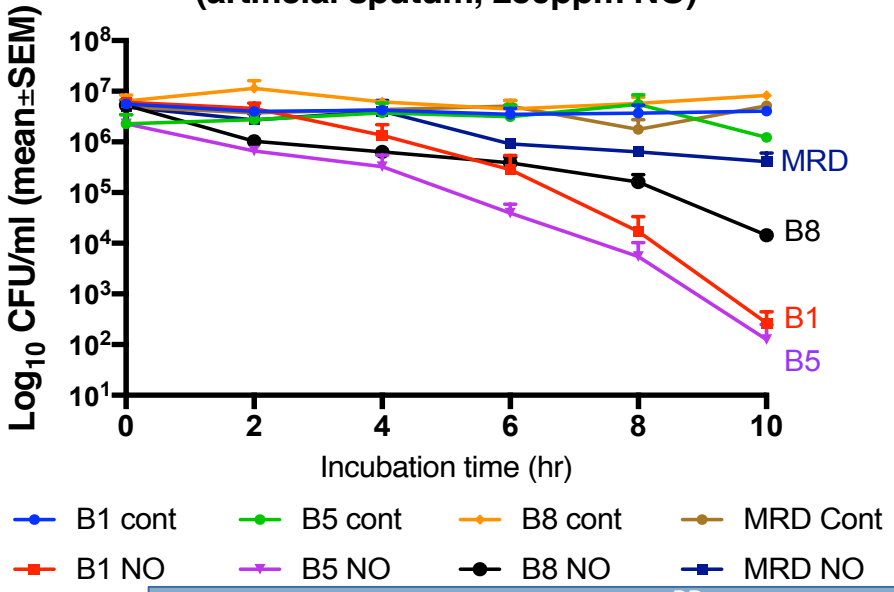
NO has direct killing effect on multi-drug resistant M. abscessus and P. aeruginosa *in vitro*

Dose Response
(M. abscessus B1, artificial sputum)

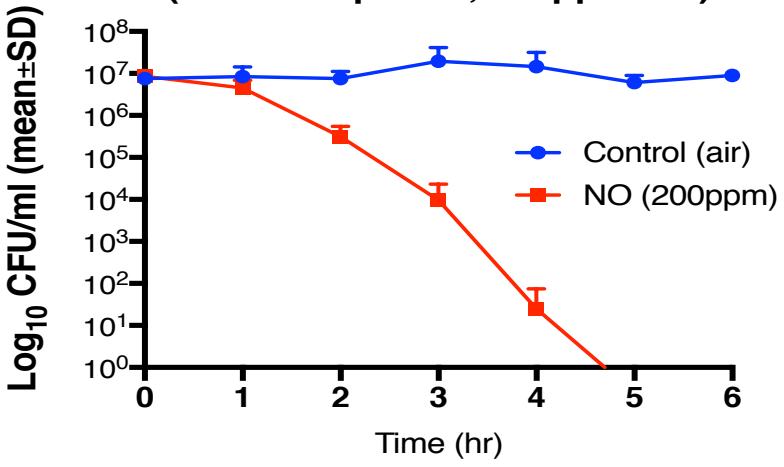


- *M. abscessus* B1 bacteria cultured in artificial sputum were treated with increasing doses of NO (160, 250, and 300ppm) for up to 10hrs .
- Time-kill curves show susceptibility of *M. abscessus* B1 (rough), B5 (smooth), B8 (rough), and MRD (rough) clinical isolates, cultured in artificial sputum, to continuous 250ppm NO treatment. All *M. abscessus* strains show susceptibility to NO treatment.
- *P. aeruginosa* were cultured at 10^6 CFU/ml in artificial sputum (2ml, planktonic), and treated continuously with 200ppm NO for up to 10hrs.

***M. abscessus* Clinical Isolates**
(artificial sputum, 250ppm NO)



P. aeruginosa
(artificial sputum, 200ppm NO)



DATA PRESENTED AT THE 3RD WORLD BRONCHIECTASIS CONFERENCE IN 2018

Source: AIT management

Pulmonary Infections: Non Tuberculous Mycobacteria (NTM)

AIT's Goal is to initiate a pivotal trial in United States in 2020

AIT Plans for Approval

- FDA is asking for "evidence of efficacy for a clinically meaningful outcome evaluated in adequate and well controlled trials"
- Based on discussions with FDA, AIT believes a placebo controlled trial with a PE of 6MWD (or other physical function endpoint), plus relevant SE endpoints (FEV1, bacterial load in sputum, culture conversion, QoL, safety) will be adequate for approval
- Prior to a pivotal study, a 12 week, single arm, multi-center pilot study in the US will begin in 1H20 with the endpoints listed above where patients, infected with either MABSC or MAC, will self-administer at home, potentially at NO concentrations >160 ppm
- Extensive in-vitro data already exists to support the direct killing effect of NO on MABSC
- AIT expects to make its NO therapy available to NTM patients in the US in 2024
- Potentially other severe, chronic and refractory infections, such as P*seudomonas Aeruginosa*, can be targeted

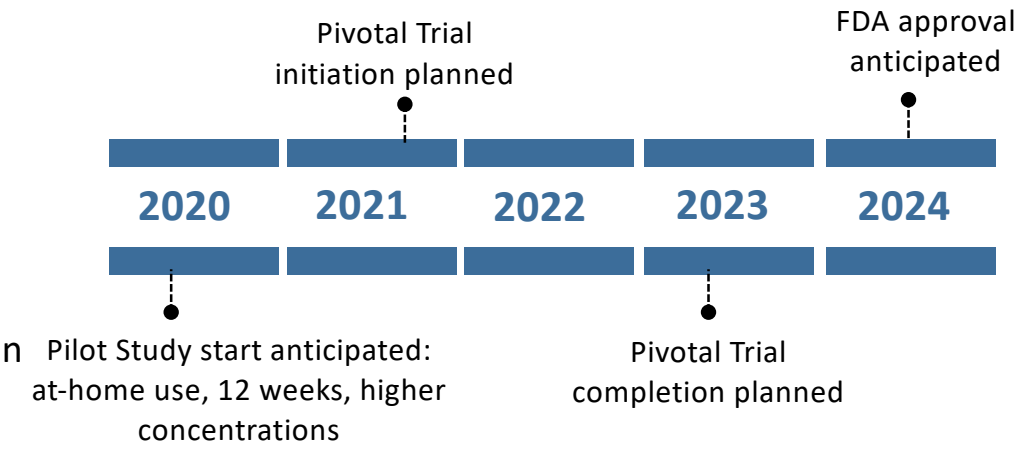
FDA Guidance(1)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Conclusions

- Drugs need to show evidence of *efficacy for a clinically meaningful outcome* evaluated in *adequate and well controlled trials*
- Surrogate markers can be used for approval if the surrogate has been shown to *predict/correlate with* a meaningful clinical outcome
- PROs, if validated, can be used for approval
- Co-development of a new test drug combination may be possible in certain situations

Timeline & Plan for Registration in the US



(1) https://www.fda.gov/downloads/Drugs/NewsEvents/UCM471341.pdf