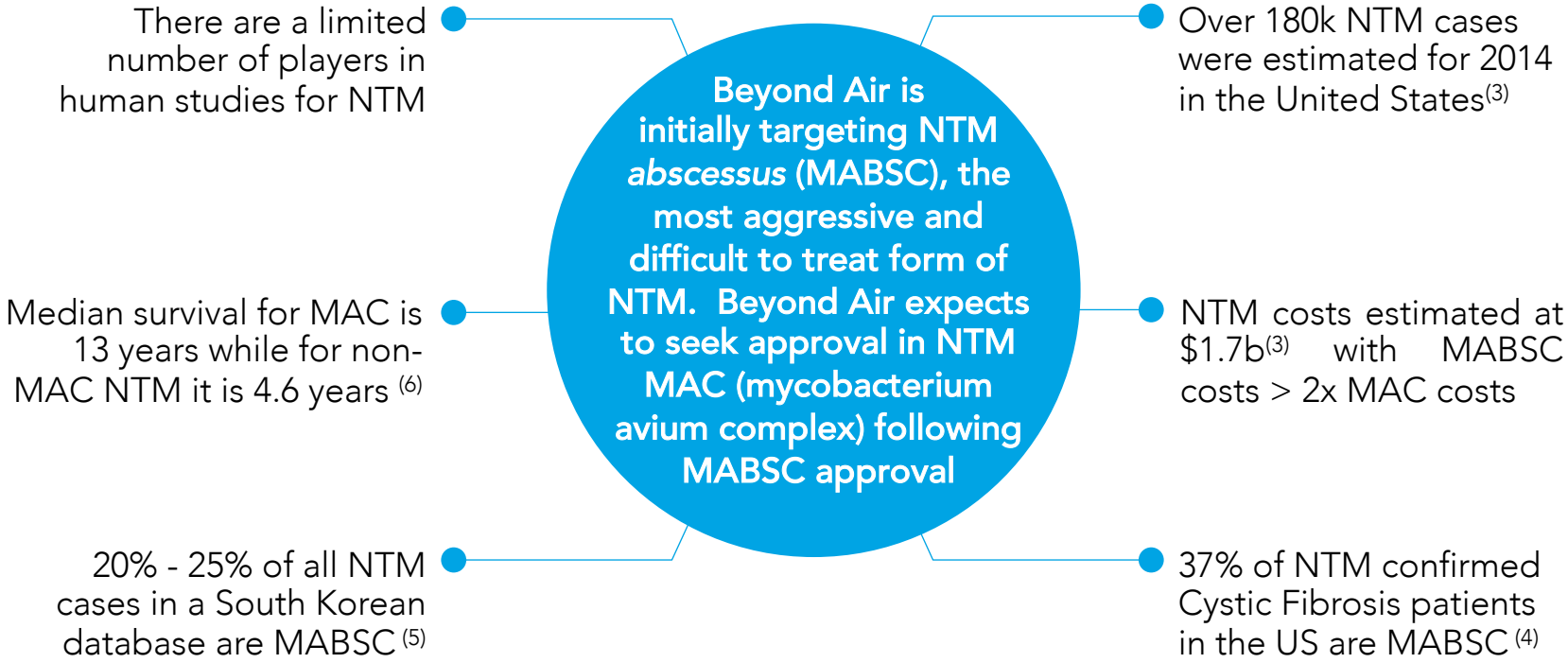
Third Indication: Nontuberculous Mycobacteria (NTM)

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

NTM Market Dynamics?



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

(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)

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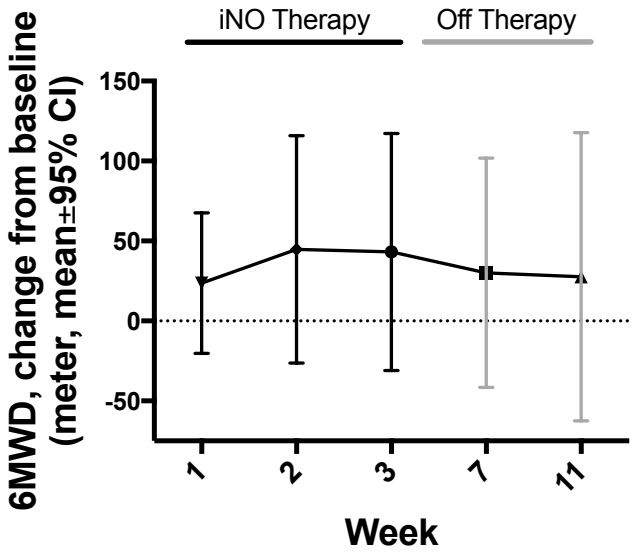
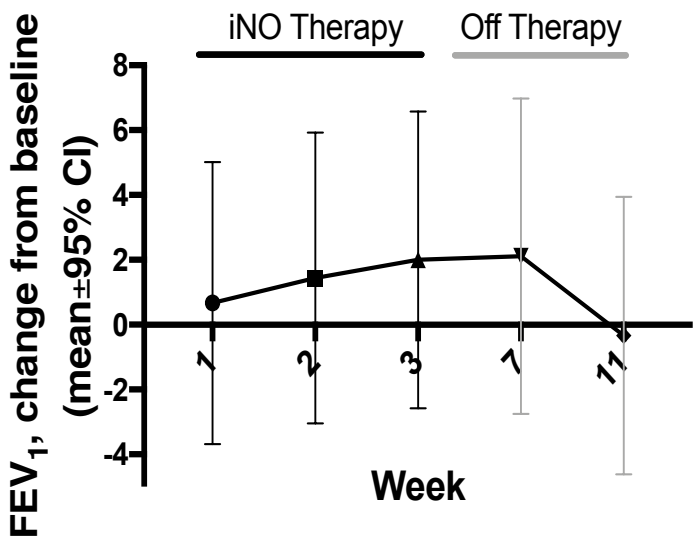
Pulmonary Infections: Nontuberculous Mycobacteria (NTM)

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

Mean change in 6MW Distance (meters) from Baseline



Mean change in FEV1 from Baseline



- 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 above
  - 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, two others had one negative culture
  - 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)

DATA PUBLISHED IN THE JOURNAL OF CYSTIC FIBROSIS

Source: Beyond Air management

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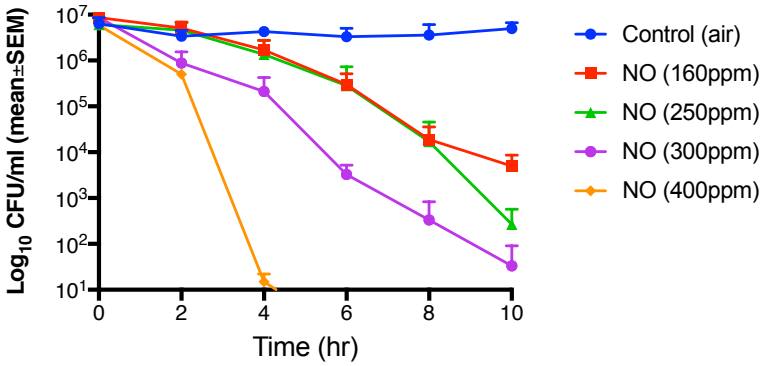
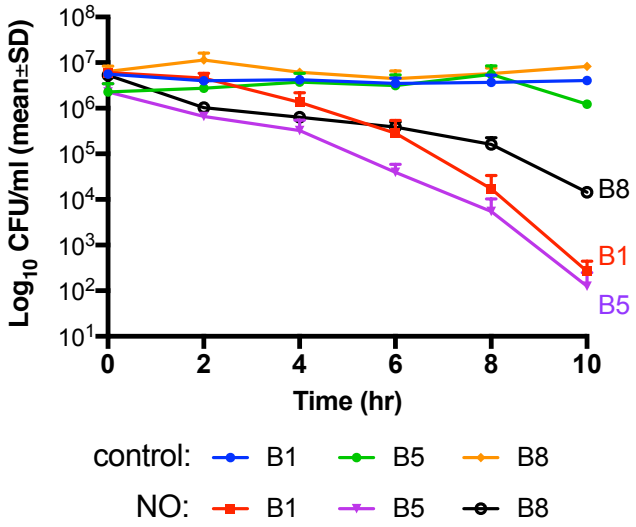
Pulmonary Infections: e.g. nontuberculous mycobacteria (NTM)

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

Dose Response (*M. abscessus* B1)

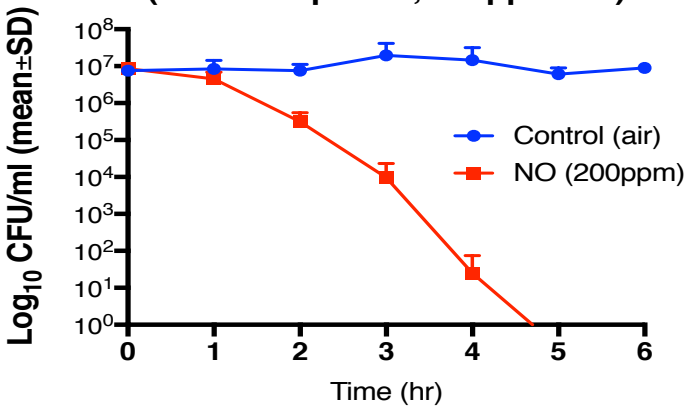


***M. abscessus* Clinical Isolates (250ppm NO)**



- Exogenous Nitric Oxide demonstrates a dose response effect against *M. abscessus* in vitro. Significant bacterial killing (>3-log reduction) is observed at 250ppm NO.
- 250ppm Nitric Oxide shows significant bactericidal activity after 10hr continuous exposure against various clinical isolates of *M. abscessus* in vitro.
- NO also demonstrates potent antibacterial activity against *P. aeruginosa*, the most common pulmonary pathogen in patients with cystic fibrosis. Continuous exposure to 200ppm NO led to 100% bacterial kill in 4-5hr.

***P. aeruginosa* (artificial sputum, 200ppm NO)**



DATA PRESENTED AT THE 3RD WORLD BRONCHIECTASIS CONFERENCE IN 2018

Source: Beyond Air management

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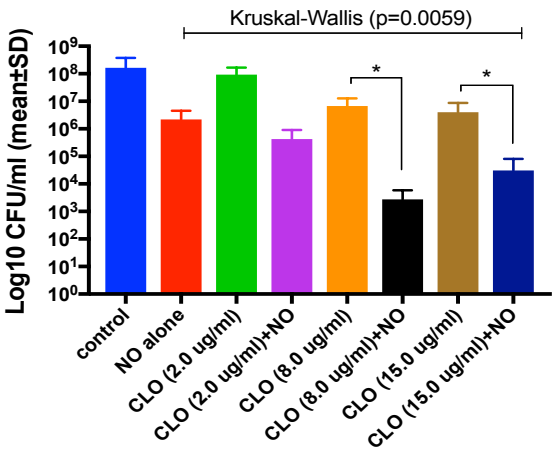
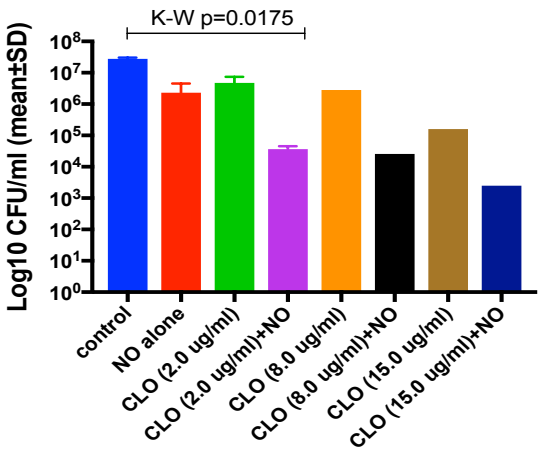
Pulmonary Infections: nontuberculous mycobacteria (NTM)

NO shows synergy with clofazimine and amikacin against drug-resistant M. abscessus in vitro

***M. abscessus* ATCC 19777**

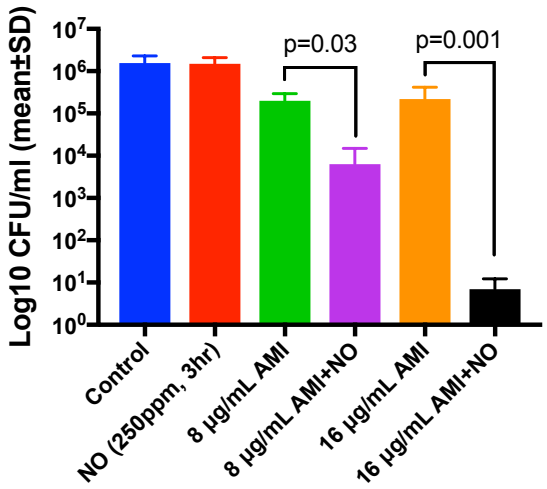


***M. abscessus* 110917_D11**

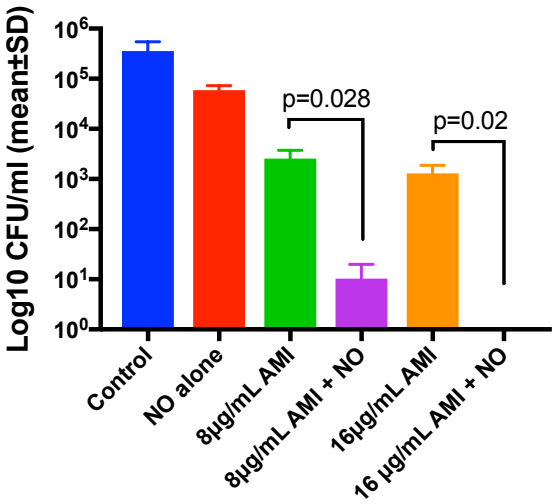


NO synergistic effect seen with clofazimine (CLO) and amikacin (AMI): Each drug in combination with 3hr continuous exposure of NO demonstrates significant bactericidal activity against clinical isolates of *M. abscessus*.

***NO + Amikacin (M. abscessus* B1)**

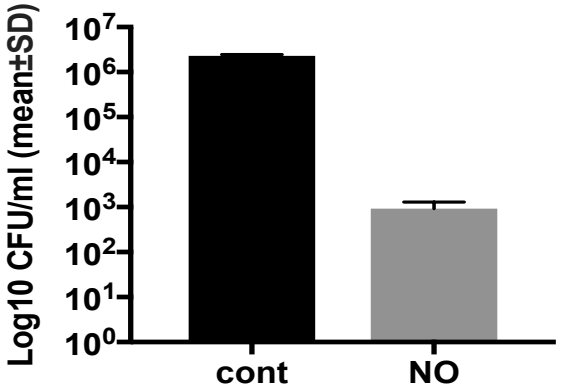


NO + Amikacin (M. abscessus D11)



Intermittent exposure to NO demonstrates anti-mycobacterium activity: 4x40min regimen mimics anticipated human treatment regimen

Intermittent 250 ppm NO (*M. abscessus* B1, 4x40min, 48hr)



DATA PRESENTED AT ATS 2019 NTM Mini Symposium and ERS 2019

Source: Beyond Air management

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Pulmonary Infections: Nontuberculous Mycobacteria (NTM)

Beyond Air's Goal is to initiate a pivotal trial in United States in late 2021

Beyond Air Plans for Approval

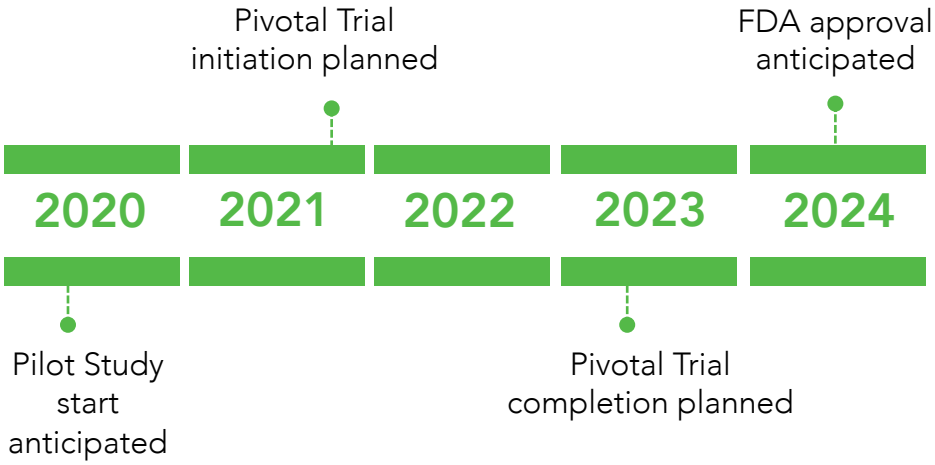
- FDA is asking for "evidence of efficacy for a clinically meaningful outcome evaluated in adequate and well controlled trials"
- Based on discussions with FDA, Beyond Air believes a placebo controlled trial with a PE based on a physical function endpoint, plus relevant SE endpoints (FEV1, bacterial 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 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 but not >250 ppm
- Extensive in-vitro data already exists to support the direct killing effect of NO on MABSC
- Beyond Air expects to make its NO therapy available to NTM patients in the US in 2024 and globally shortly thereafter
- Potentially other severe, chronic and refractory infections, such as p*seudomonas aeruginosa*, can be targeted

FDA Guidance(1)

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



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