



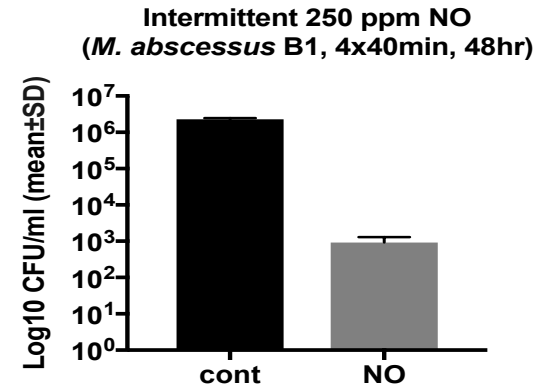
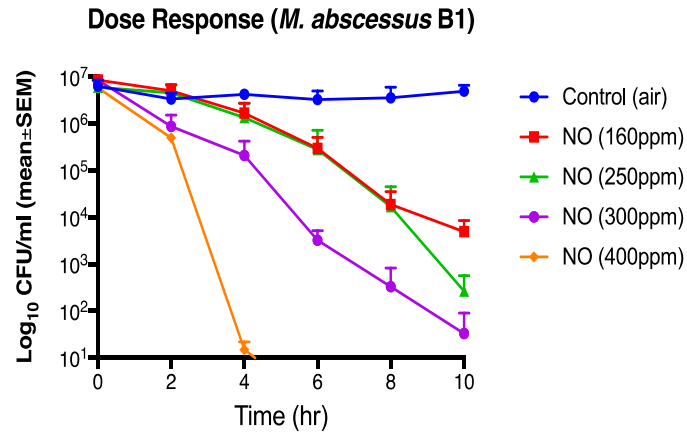
Nontuberculous Mycobacteria

Expanding NO into the home market for lung infections

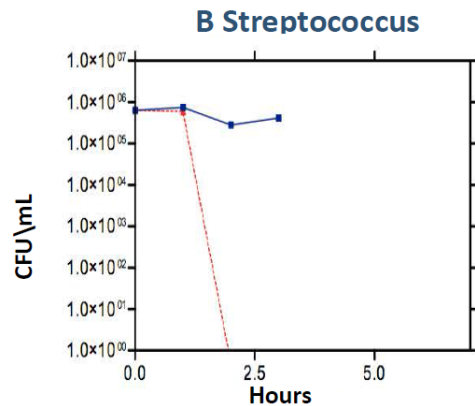


NO has a significant bactericidal effect on nontuberculous Mycobacterium abscessus and other bacteria in vitro

NO activity against multi-drug resistant *M. abscessus*1 with continuous or intermittent exposure

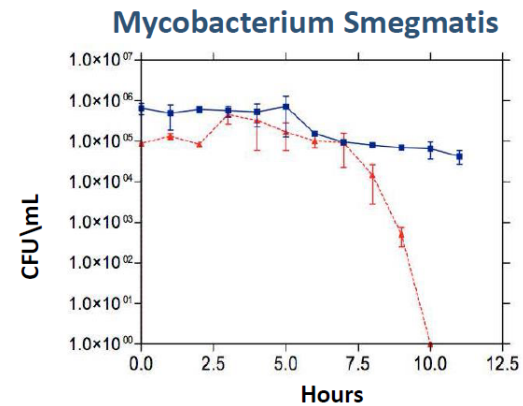


NO has BROAD-SPECTRUM activity against multiple bacteria and fungi at 200 ppm²



Additional Bacteria

1. *S. aureus*
2. *P. aeruginosa*
3. *S. marcescens*
4. *Klebsiella*
5. *S. maltophilia*
6. *E. aerogenes*
7. *A. baumannii*
8. MRSA
9. *C. albicans*
10. *E. coli*



NO exposure time to eliminate bacteria ranged from 2 – 10 h with exposure kill times for additional microbes (table on right) inside this exposure range

Home Market: Nontuberculous Mycobacteria (NTM)

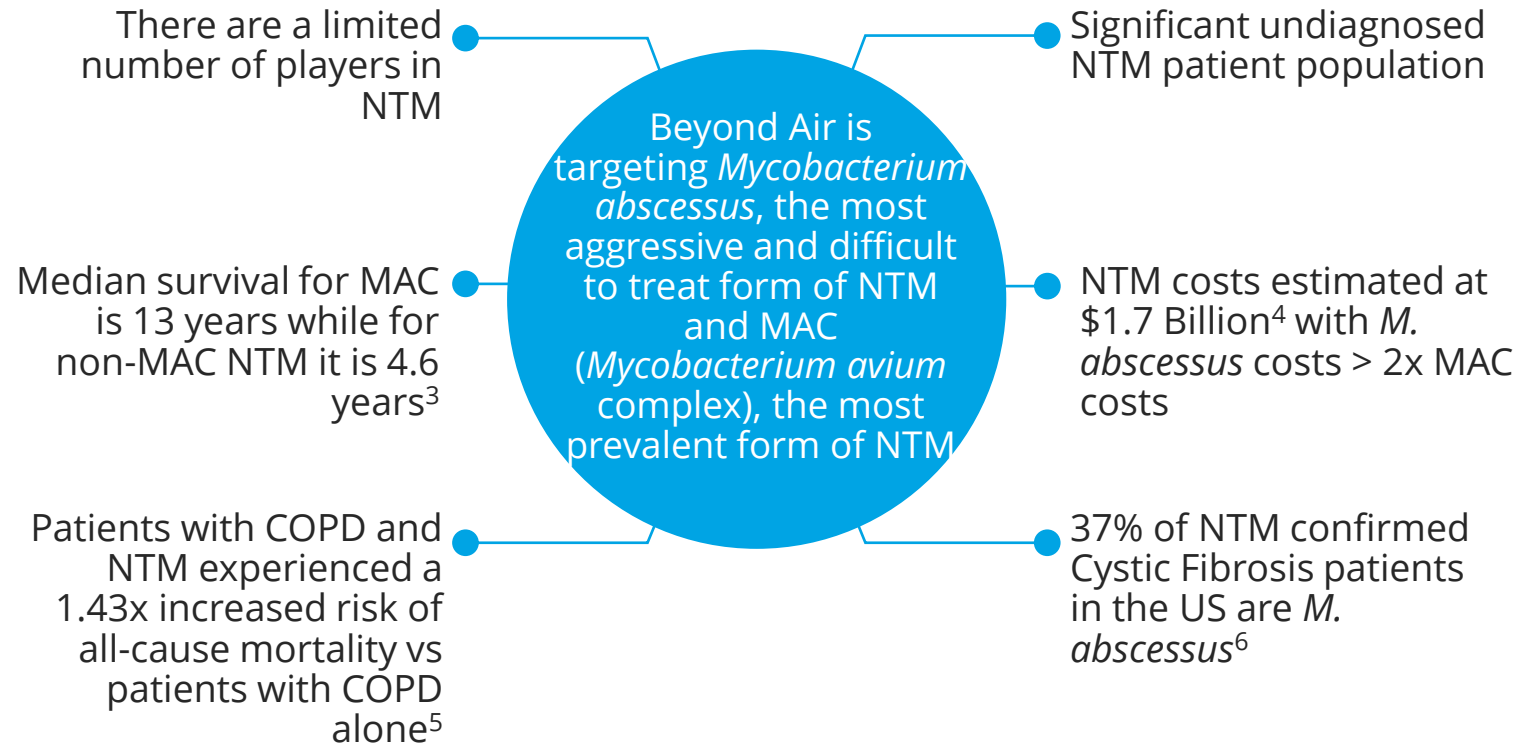
How is NTM acquired?

- Acquired by inhalation from the environment
- Water thought to be the main source
 - US study across 25 states showed that NTM bacteria were found in nearly 8 out of 10 water samples¹
- Warmer climates have higher infection rates
 - Gulf States account for 70% of annual NTM cases in the United States²
- Patient to patient transmission possible

Who is at risk?

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

NTM Market Dynamics



Nitric Oxide Market Dynamics for NTM

Targeting Refractory *Mycobacterium avium* complex (MAC) & *M. abscesses* NTM Patients

~15K

Refractory NTM patients in US¹

~4K

Refractory NTM patients in the EU²

~15K

Refractory NTM patients in Japan³

NTM is an FDA disease area of focus with limited treatment options resulting in high unmet medical need

7.5%

annual prevalence growth in the US¹

~75%

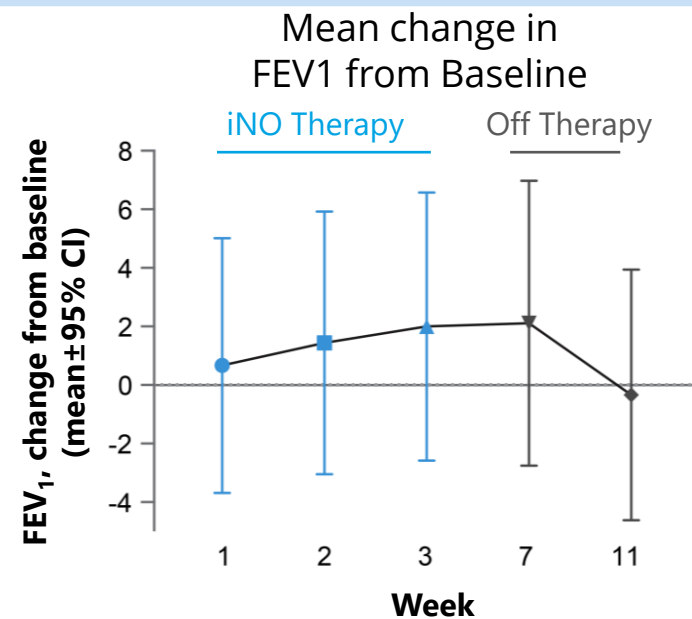
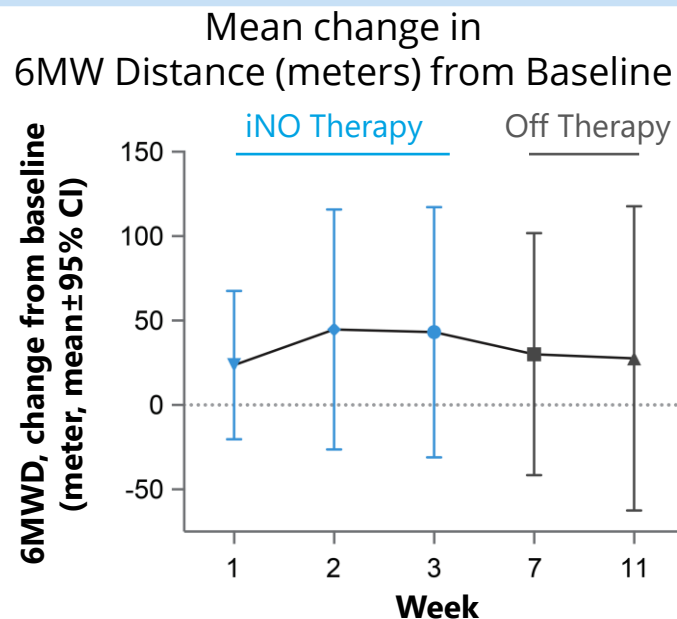
of NTM cases are caused by MAC⁵

~25%

of NTM cases are caused by *M. abscesses*⁵

Pilot Study in CF Patients with NTM Lung Infections Demonstrates Safety and Efficacy

Single arm study with 160 ppm NO showed a reduction in bacterial load and improvements in quality of life
Data Published in the Journal of Cystic Fibrosis (Bentur et al., 2019)

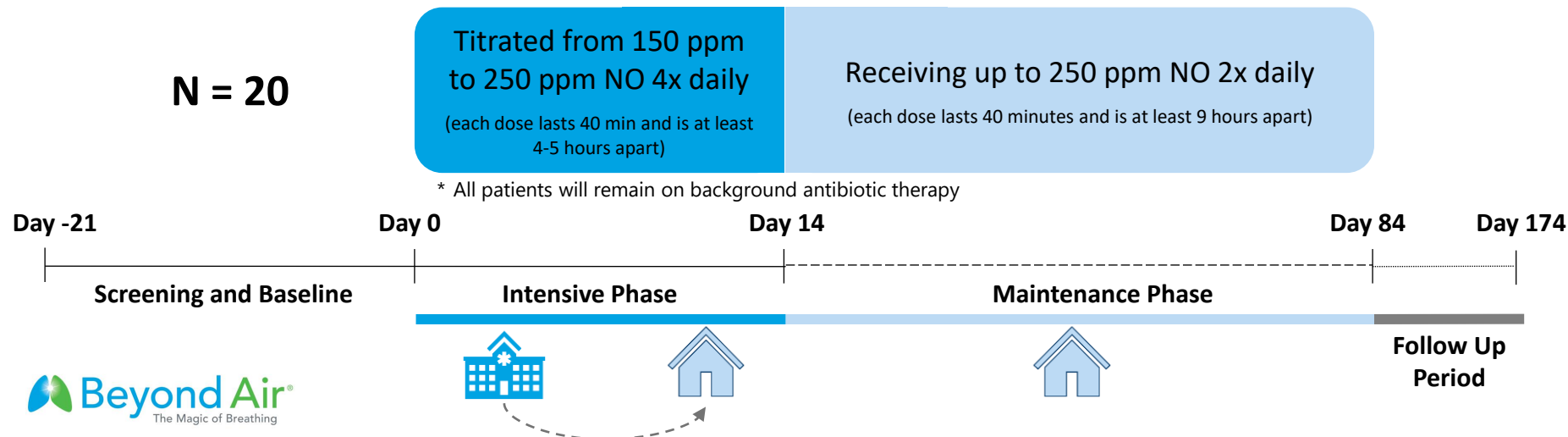


- 9 CF patients with refractory MABSC were treated at 3 centers in Israel with NO added to background antibiotic therapy
 - 160 ppm NO was given via mask for 30 min 5x/day for 14 days and 3x/day for 7 days
 - Primary endpoint of safety was met, with no NO-related serious adverse events (SAEs) observed
 - 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
- 4 patients treated under compassionate use experienced similar results
 - 1 treated at NIH with LungFit®, 1 treated safely with 250 ppm NO, 1 culture conversion

Pilot LungFit® NTM Study Protocol Summary

Pilot Clinical Trial in Australia

- ✓ Began Screening in December 2020
- ✓ First Patient Dosed in January 2021
- ✓ Received grant for up to \$2.17 million from the Cystic Fibrosis Foundation to help fund pilot study
- ✓ Interim results announced Fall-2021:
 - ✓ 250 ppm NO was well-tolerated with no study discontinuations or treatment-related serious adverse events observed
 - ✓ At the time of data cutoff, on September 6th 2021, 8 subjects were successfully titrated up to 250 ppm NO and none titrated down while in the study
 - ✓ Methemoglobin and NO₂ concentrations remained below safety thresholds of 10% and 5 PPM, respectively, during NO treatment in all subjects
- 12-week, single-arm, multicenter study enrolling ~20 adult Cystic Fibrosis (CF) or non-CF bronchiectasis patients with refractory *Mycobacterium avium* complex (MAC) or *Mycobacterium abscessus* complex (MABSC) lung infections
- Complete safety and efficacy results to be reported in 2022
- Objective: establish safety at up to 250 ppm NO when patients self-administer treatment in the home setting



Outcome Measures

Primary endpoint:
establishing safety at 250 ppm

Secondary endpoints include:

- 1) Culture conversion/bacterial load
- 2) Quality of Life
- 3) Respiratory function
- 4) Physical function (activity tracker, 6MWT, etc.)

How Big is the Home Market for Severe Lung Infections?

COPD...

- ...is the largest at-risk population for recurrent and opportunistic lung infections
- There are an estimated 30m people in the US suffering from COPD¹ with 10% considered severe²

Data from 2010 Show³

- 1,075,575 estimated acute COPD exacerbation-related hospitalizations in 2010
- Average COPD exacerbation hospital LOS was 6 days in 2010
- \$38,455 cost per hospitalization in 2010 translates to >\$41b in cost

Mortality rate

- After hospitalization varies between 16% and 19% in the 3 months following hospitalization, between 23% and 43% at 1 yr and is 55–60% at 5 yrs⁴.

ECLIPSE

- In the ECLIPSE⁵ study (Hurst et al. NEJM 2010), a 3 year observation of 1,679 moderate to severe COPD patients (GOLD 2,3 & 4)
 - 77% of patients had at least one exacerbation during the observation period
 - 47% of patients had ≥ 2 exacerbations in at least one of the three study years
 - 30% of patients had ≥ 1 exacerbation in each of the three study years
 - 12% of patients had ≥ 2 exacerbations in each of the three study years