

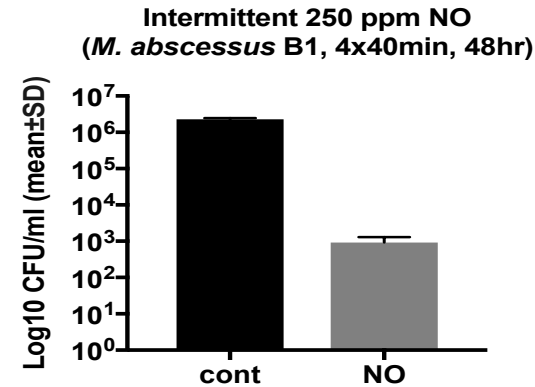
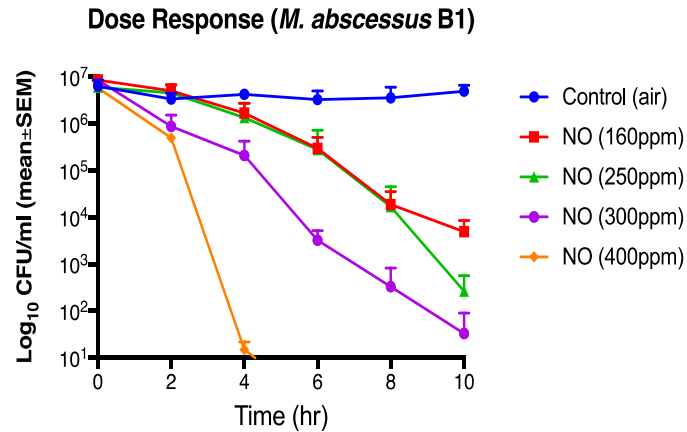


# ***Nontuberculous Mycobacteria***

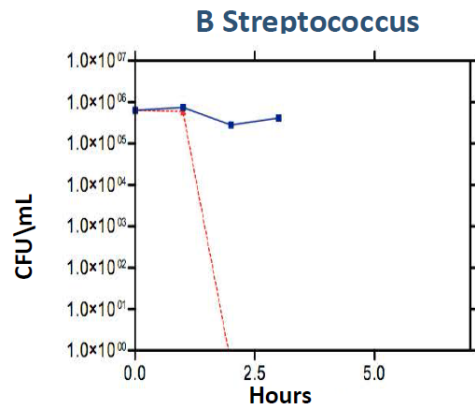
*Expanding NO into the home market for lung infections*

# 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

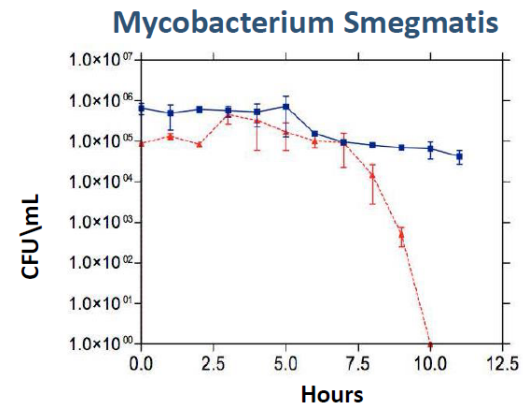


NO has BROAD-SPECTRUM activity against multiple bacteria and fungi at 200 ppm2



**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)

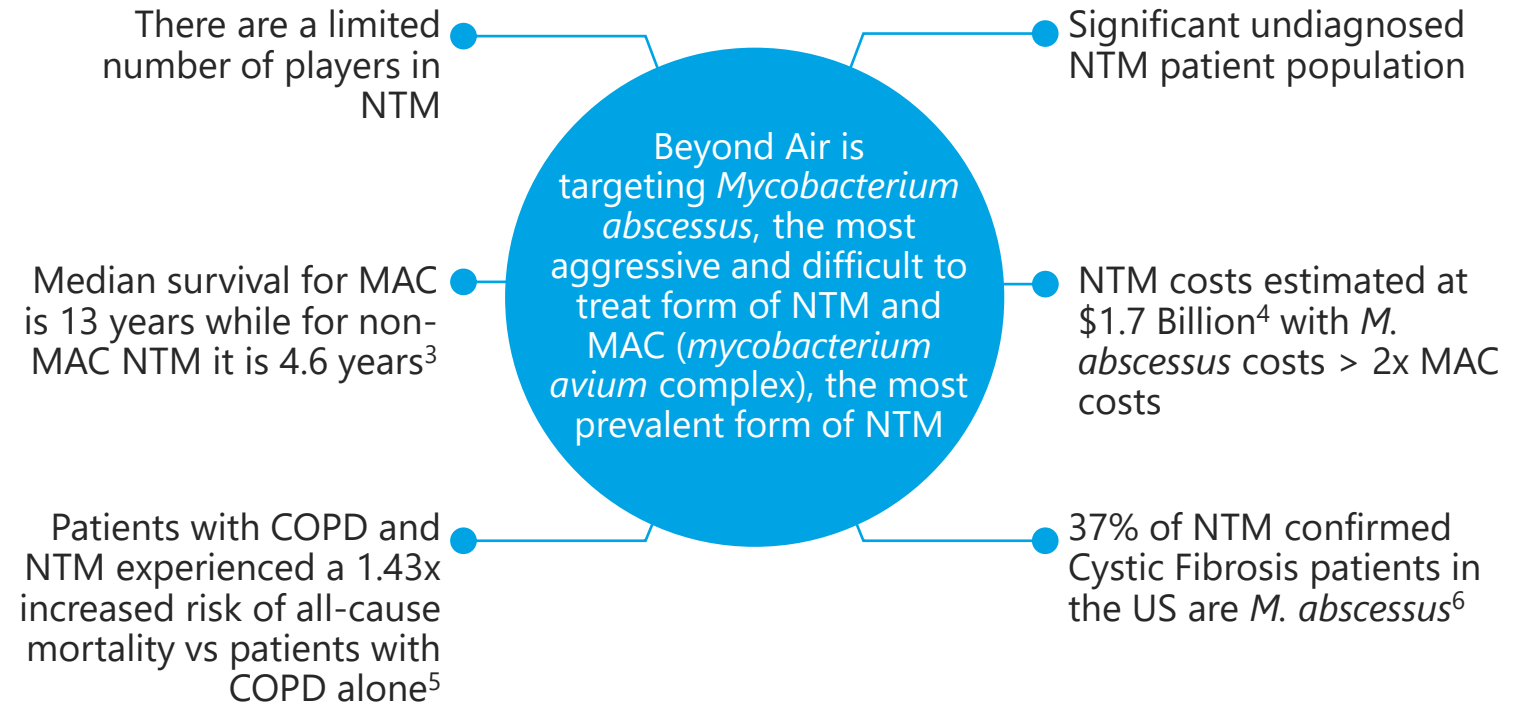
## How is NTM acquired?

- 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 samples<sup>1</sup>
- Warmer climates have higher infection rates
  - Gulf States account for 70% of annual NTM cases in the United States<sup>2</sup>
- 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 US<sup>1</sup>

~4K

Refractory NTM patients in the EU<sup>2</sup>

~15K

Refractory NTM patients in Japan<sup>3</sup>

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 US<sup>1</sup>

~75%

of NTM cases are caused by MAC<sup>5</sup>

~25%

of NTM cases are caused by *M. abscesses*<sup>5</sup>

1) Winthrop et al. Incidence and prevalence of nontuberculous mycobacterial lung disease in a large U.S. managed care health plan, 2008-2015. *Ann Am Thorac Soc*, 17 (2020), pp. 178-185

2) Ringshausen et al. Prevalence of Nontuberculous Mycobacterial Pulmonary Disease, Germany, 2009-2014. *Emerg Infect Dis*. 2016;22(6):1102-1105.

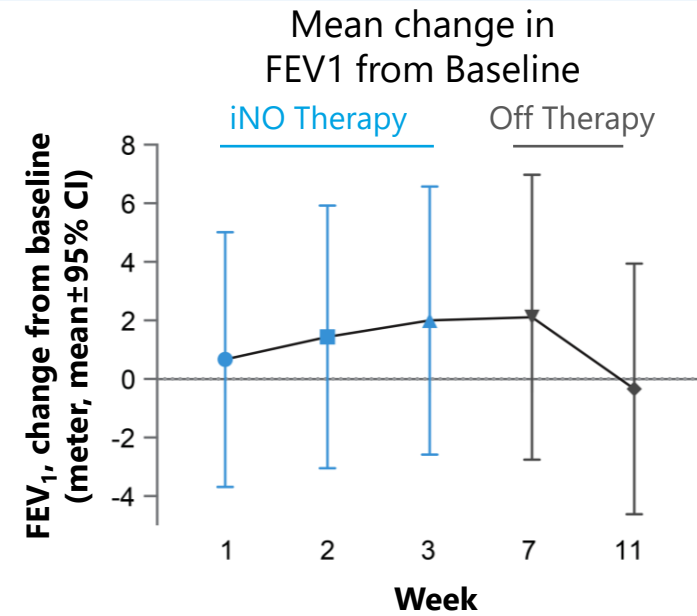
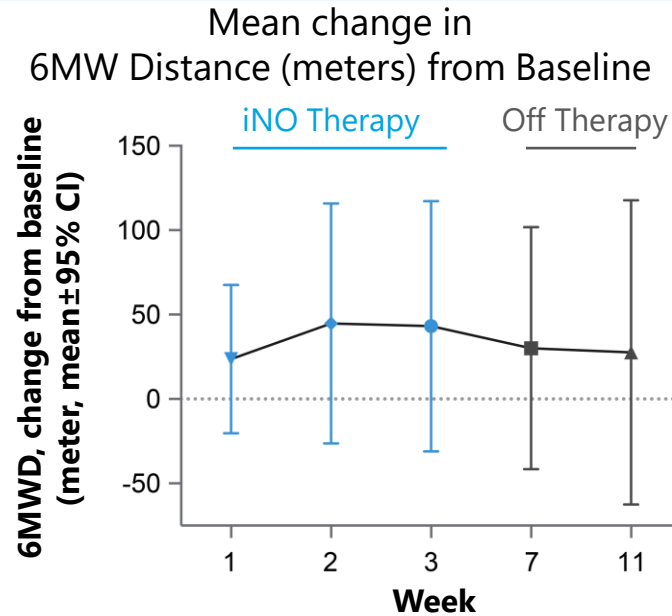
3) Izumi et al. Epidemiology of Adults and Children Treated for Nontuberculous Mycobacterial Pulmonary Disease in Japan. *Ann Am Thorac Soc*. 2019 Mar;16(3):341-347.

4) Diel R et al. High mortality in patients with MAC lung disease: a systematic review. *BMC Infect Dis*. 2018;18(1):206. Published 2018 May 3

5) According to the Cystic Fibrosis Foundation

# Pilot Study in NTM infected CF Patients 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

- Open label pilot study with 12 weeks of treatment and 12 weeks of observation
- Approximately 20 subjects >18 years of age with NTM lung infection refractory to antibiotic therapy
  - Both MAC (Mycobacterium avium complex) and *Mycobacterium abscessus* will be included in CF and non-CF patients
- Study start fourth quarter 2020 with interim results expected late 2Q21 and final results in 2H21
- Four doses of NO per day for 14 days followed by two doses of NO per day for 70 days (all patients will remain on background antibiotic therapy)
  - Each dose lasts 40 minutes and are 4-5 hours/at least 9 hours apart
  - Subjects will be titrated from 150 ppm up to 250 ppm in hospital with all subsequent administrations at home
- Primary endpoint is safety
- Key Secondary endpoints
  - Culture conversion/bacterial load
  - Quality of Life
  - Respiratory function
  - Physical function (activity tracker, 6MWT, etc.)

# How Big is the Home Market for Severe Lung Infections?

## COPD...

- ...is the largest at-risk population for opportunistic lung infections
- There are an estimated 30m people in the US suffering from COPD<sup>(1)</sup> with 10% considered severe<sup>(2)</sup>

## Data from 2010 Show<sup>3</sup>

- 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 yrs<sup>(4)</sup>.

## ECLIPSE

- In the ECLIPSE<sup>(5)</sup> 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  $\geq 2$  exacerbations in at least one of the three study years
  - 30% of patients had  $\geq 1$  exacerbation in each of the three study years
  - 12% of patients had  $\geq 2$  exacerbations in each of the three study years