Pulmonary Infections: Nontuberculous Mycobacteria (NTM)*

Where does it comes from?

- More than 150 species recognized
- 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?

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



* Data: www.ntmfacts.com, FDA

Market Dynamics: NTM

There is no competition in MABSC and limited competition in MAC

Median survival for MAC is 13 years while for non-MAC NTM it is 4.6 years ****

20% - 25% of all NTM cases in a South Korean database are MABSC***

Over 180k NTM cases were estimated for 2014 in the United States*

NTM costs estimated at $1.7b* with MABSC costs > 2x MAC costs

37% of NTM confirmed Cystic Fibrosis patients in the US are MABSC**

AIT is initially targeting NTM abscessus (MABSC), the most aggressive and difficult to treat form of NTM. AIT expects to seek approval in NTM MAC (mycobacterium avium complex) following MABSC approval

* Strolloet al. The Burden of Pulmonary Nontuberculous Mycobacterial. Pub 27-July-2015 ** Data presented at ATS 2017 (Derek Low et al, Medical University of South Carolina) *** Data presented at ATS 2017 (Keun Burn Chung et al, Seoul National University College of Medicine) **** 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)

What is FDA Guidance for NTM Lung Infection Trials?*

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

*FDA guidance given in October 2015

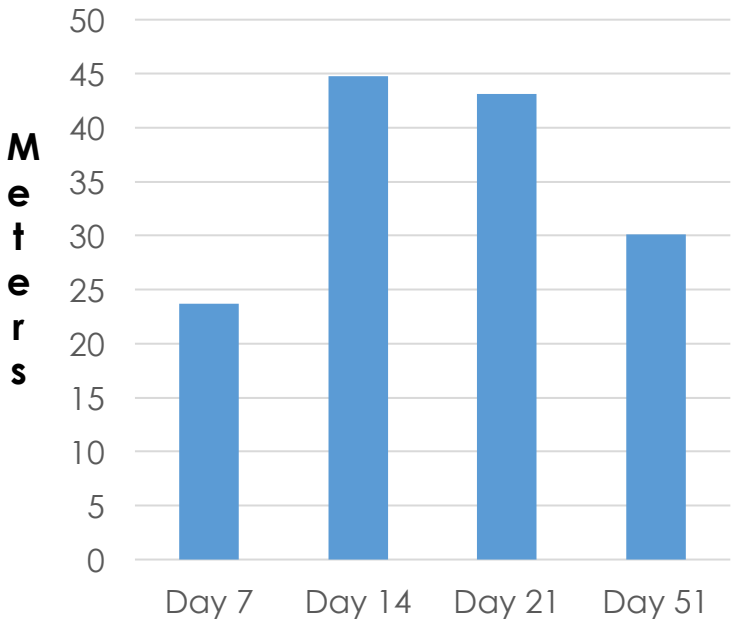
NO-NTM *Abscessus* Phase 2 Trial Design and Results

Single-Arm, Open-Label Trial in Israel

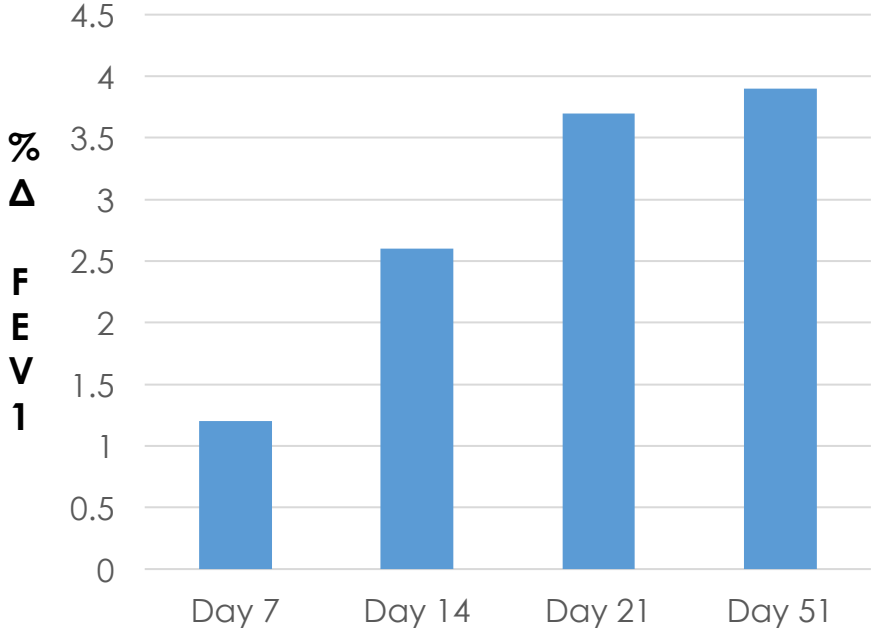
- 9 patients with MABSC, who were refractory to standard-of-care, were enrolled
- In addition to standard-of-care at the physician's discretion, Patients received:
  - 5 treatments per day of 160 ppm inhaled NO for 30-minutes for 14 days in the hospital setting
  - 3 treatments per day of 160 ppm inhaled NO for 30-minutes for 7 days in the ambulatory setting
- **Primary Endpoint of safety was met**
  - There were no SAEs related to NO treatment over the 21 day treatment period
  - Methemoglobin and Nitrogen dioxide (NO2) levels were below acceptable levels at all times
- Quality-of-Life data showed positive trends on relevant questions (SF-36 used)
- One patient achieved culture conversion at the end of treatment on day 21
  - Given the short duration of therapy, conversion was not anticipated
- Tolerability not an issue as no patient requested that any treatment be stopped or not administered
- **6-Minute Walk (6MW) and FEV1 improvements over baseline were significant (see tables on next slide)**

6MW and FEV1 Results

Mean Change in 6MW from Baseline



Mean Percent Change in FEV1 from Baseline



NO treatment was administered 5x per day through day 14, then 3x per day through day 21. NO was not administered after day 21.

NO Used to Treat MABSC in CF Patients – Compassion Setting

Three Patients Have Been Treated Under Compassionate Use, Two in Israel at Rambam Medical Center and One in the United States at the National Heart, Lung and Blood Institute (NHLBI)

- **Patient at the NHLBI was treated with AIT's generator based system**
- All refractory to standard of care (cocktail of antibiotics recommended by the American Thoracic Society)
- All had significant adverse events associated with standard of care
- NO was added to standard of care
- NO Treatment Regimen: 160 ppm NO 5x/day for 14 days, then 3x/day for the next 7 days
  - One patient received 160 ppm NO 5x/day for 5 days, then 2 or 3x/day for the next 21 days
- ***M. abscessus* bacteria were eradicated in one of three patients at the end of the 21 day treatment period**
- **There were no serious adverse events related to NO therapy**
- **6-minute walk improved in 2 patients (6-minute walk not recorded for one patient) at day 21 vs baseline**
- **FEV1 improved for 2 patients and declined for one patient at day 21 vs baseline**
  - **Each % improvement > % decline**
- **Quality-of-Life improvements were seen at day 21 vs baseline for all patients**

AIT Plans for NTM in the United States

Our Goal is to Begin a Trial, Potentially a Pivotal Trial, in the Second Half of 2018

- FDA is asking for "evidence of efficacy for a clinically meaningful outcome evaluated in adequate and well controlled trials"
  - AIT believes that a placebo controlled trial with a primary endpoint of 6MW, plus relevant secondary endpoints, will be adequate for approval
  - Secondary endpoints would include FEV1, bacterial load in sputum, QoL and safety
- Length of therapy would potentially extend beyond 21 days
  - The use of our proprietary generator as the source for NO provides the potential flexibility to have patients self-administer at home
- Make our NO therapy available to NTM patients in the US by the end of 2020
  - AIT must execute and work closely with FDA to make this happen
  - NTM *abscessus* patients will be targeted first, followed by NTM MAC and others asap