AIT Therapeutics (AITB)

Initiation Report

LifeSci Investment Abstract

AIT Therapeutics (OTCBB: AITB) is a medical device Company developing a drug-device combination that is designed to safely deliver intermittent high-doses of nitric oxide (NO) therapy to treat lower respiratory tract infections (LRTI). The Company is currently pursuing bronchiolitis in hospitalized patients and non-tuberculosis mycobacteria (NTM) infections caused by M. abscessus, two respiratory indications with pressing unmet medical needs. AIT expects to report Phase II data from the NTM trial in Q4 2017, which could pave the way for a Phase III trial by mid-2018 if positive. The Company also expects to report topline bronchiolitis results from a Phase III trial in H1 2018. Both of these readouts represent major milestones for AIT that will help clarify the clinical risk and market potential of their programs.

Key Points of Discussion

- **Nitric Oxide Can Be Used to Treat Serious Respiratory Infections.** NO is known to have broad spectrum activity against a wide variety of bacteria, parasites, and viruses at high doses. Since NO is already an approved treatment for neonates, the drug has a long-standing track record of safety with more than 100,000 premature babies treated to date. The only device that is currently marketed in the US—Mallinckrodt Pharmaceuticals’ (NYSE: MNK) INOMax—delivers NO at 20 ppm, which is insufficient to treat severe respiratory infections. AIT expects that intermittent high-dose NO therapy can treat a wide range of LRTIs and is well-positioned to become the first device capable of delivering high-dose therapy, if approved. NO therapy may even work synergistically with inhaled antibiotics and thus could be used as adjunctive therapy on top of standard-of-care.

- **Strong Phase II Data Lowers Risk for AIT’s Clinical Program.** To date, AIT has completed a Phase I safety study in healthy volunteers as well as a Phase II study in bronchiolitis patients. In the Phase II study, AIT demonstrated that NO therapy resulted in a 44% reduction in time to reach normal oxygenation (p=0.0275), and a 34% reduction in hospital length of stay (p=0.0587). Following these results, AIT launched a Phase III trial in Israel that is evaluating AIT’s drug-device combo in 120 infants hospitalized for acute bronchiolitis. The primary endpoint for this Phase III trial is length of hospitalization, which is a validated FDA endpoint that the Company has already shown to improve with NO therapy. The Company expects to report topline results in the first half of 2018 and file an IND in 2018 to support a Phase III trial in the US.

Expected Upcoming Milestones

- Q4 2017 – Readout from Phase II trial in NTM infections.
- H1 2018 – Topline results expected from 1st Phase III trial in bronchiolitis.
- Mid-2018 – Potential launch for a Phase III trial in NTM infections.

Analysts

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Market Data

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For analyst certification and disclosures please see page 27
Large Market Opportunity in Bronchiolitis. Roughly 66% of infants are infected with RSV by 1 year of age, and by the age of 2, RSV will have infected nearly all children at least once. Typically, infected individuals recover within 7 days of infection only presenting symptoms of fever and coughing; however, 0.5-2% will be hospitalized and diagnosed with bronchiolitis (50-90%) or pneumonia (5-40%). RSV infection remains a leading cause of hospitalization for infants less than 1 year. Worldwide, there are an estimated 34 million new pediatric cases, leading to more than 3.4 million hospitalizations and 200,000 pediatric deaths annually. Annually in the US, there are 1.5 million outpatient visits for children less than 5 years and an estimated 146,000 hospitalizations for RSV infection. Elderly patients, who are also susceptible to bronchiolitis, represent an additional 164,000 hospitalizations each year. With an average hospital stay of 3.5 days per patient, there is a pressing need for novel therapies that can reduce hospital length of stay and thus overall treatment costs. The current Phase III trial in Israel is testing hospital length of stay as the primary endpoint. If AIT is able to show that high-dose NO therapy can meaningfully reduce hospitalization time, then this could provide a strong pharmacoeconomic rationale for the broad adoption of their device.

NO Therapy to Treat NTM Infections in Patients with Severe Pulmonary Disease. People with severe pulmonary diseases, such as cystic fibrosis (CF), chronic obstructive pulmonary diseases (COPD), or α-1 antitrypsin deficiency, are particularly vulnerable to persistent infections by non-tuberculosis mycobacteria (NTM), which are found everywhere but normally don’t pose much threat to healthy individuals. AIT has demonstrated proof-of-concept in a small, open-label Phase II study and plans to launch a second Phase II trial in the near-term. This new trial will test the safety and efficacy of 21 days of NO therapy to account for the difficulty in treating M. abscessus infections. The Company expects to report data from the trial in the fourth quarter of 2017, which could permit a subsequent Phase III trial launch by the middle of 2018. The clinical program currently focuses on M. abscessus, the most difficult-to-treat subtype of infection, due to the lack of expected competition and thus greater commercial prospects.

No Available Therapies to Address M. Abscessus Infection. There are more than 150 species of NTM that are found prevalently throughout the environment. Those with underlying lung disease and/or genetic dispositions are the most likely to develop an NTM infection. While M. avium complex (MAC) is the most common pathogen underlying NTM infection, M. abscessus infections are the most difficult to detect and treat due its rapid growth and multidrug resistance. In the US, there are thought to be roughly 181,000 cases each year. Consistent with most infections, elderly patients are also more susceptible, as approximately 69% of NTM infections occur in those 65 years of age or older. NTM infections in the US account for a healthcare expenditure of $1.7 billion, corresponding to approximately $9,400 per patient.

References:
AIT Expects to Launch Phase II Study for *M. Abscessus* in Near-Term. AIT plans to launch an open-label Phase II study evaluating the safety and efficacy of NO therapy in patients infected with *M. abscessus*. The trial will enroll 10 patients over 6 years old with a confirmed pulmonary NTM infection caused by *M. abscessus*. Enrolled patients will receive 91 30-minute sessions of 160 ppm NO therapy with at least 3 hours between each session. The primary endpoint is safety, as measured by NO-related serious adverse events (SAE). Secondary endpoints include the six-minute walk test, *M. abscessus* bacterial load, NO-related AEs including Met-hemoglobin and NO2 levels, and type and frequency of NO-related AEs. AIT expects to report results from the trial in the fourth quarter of 2017, which could position the Company for a pivotal Phase III trial launch as early as the middle of 2018.

Financial Discussion

**Reverse Merger.** In January 2017, AIT closed a reverse merger with KokiCare to go public. Concurrent with the closing of this merger, AIT raised roughly $10.2 million in gross proceeds through the sale of 1.701 million shares of common shares and warrants to purchase 3.403 million common shares. The Company raised an additional $663,000 in gross proceeds through a second private placement.

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7 https://clinicaltrials.gov/ct2/show/NCT03208764
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Company Description

AIT is a medical device Company focused on the development of a drug-device combination that can safely deliver intermittent high-doses of nitric oxide (NO) therapy to individuals with serious lung diseases in order to prevent and treat lower respiratory tract infections (LRTI). NO is known to have broad spectrum activity against a wide variety of bacteria, parasites, and viruses at high doses (>100ppm). The Company’s lead indication, as shown in Figure 1, is the treatment of bronchiolitis exacerbations in infants that require hospitalization. Bronchiolitis is an acute respiratory infection characterized by obstruction, inflammation, and potentially damage to the distal airways, and is most commonly caused by respiratory syntactical virus (RSV) infection. While RSV infection is typically mild for most individuals, infants, elderly, and immunocompromised patients are more severely affected and roughly 0.5–2% require hospitalization. While Synagis (palivizumab) is used prophylactically to protect high-risk infants from infection, there are no forms of protection for elderly or immunocompromised patients and no approved therapies to treat bronchiolitis. AIT is developing their drug-device combo to address the unmet need for all patients that are hospitalized for bronchiolitis, which is a market opportunity that could exceed $2 billion annually. The Company is currently conducting a Phase III trial in Israel evaluating NO therapy in infants hospitalized due to bronchiolitis exacerbation and expects to report topline results in the first half of 2018. Following this readout, AIT plans to file and IND with the FDA in 2018 to support a pivotal Phase III study in the US.

Figure 1. AIT’s Development Pipeline

![Figure 1. AIT’s Development Pipeline](image)

The Company is also developing high-dose NO therapy to treat respiratory infections caused by nontuberculous mycobacteria (NTM), a group of naturally occurring bacteria that can cause severe pulmonary disease in susceptible individuals with lung diseases like cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD). The most prevalent strain of NTM is *Mycobacterium avium complex* (MAC), although *M. abscessus* is more difficult to treat because of its antimicrobial multidrug resistance. There are no approved therapies for NTM, and no treatments that can address infections caused by *M. abscessus*. In the US, there are thought to be roughly 181,000 cases of NTM infection annually.

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each year with 25% caused by *M. abscessus*.\(^{10}\) Elderly patients are the most susceptible, with approximately 69% of NTM cases occurring in those 65 years of age or older. AIT’s high-dose therapy provides a means of reducing bacterial load for these patients in the hospital setting. AIT has evaluated the use of high-dose NO therapy in a Phase IIa study in CF patients as well as a compassionate use study in 2 CF patients infected with *M. abscessus*. Although the trial was small, the compassionate use study achieved a 99% reduction in bacterial load by utilizing a 21-day treatment regimen. AIT plans to launch a Phase II study in individuals infected with NTM infections with a specific focus on *M. abscessus*. The Company expects to report data from the trial in the fourth quarter of 2017, which could permit a subsequent Phase III trial launch by the middle of 2018.

AIT also plans to explore use of NO therapy in a variety of additional indications, although these programs will depend on securing additional financing. Some of the other areas of interest include COPD, diabetic foot ulcers (DFU), stroke, and CF exacerbations. If the Company chooses to pursue one or more of these indications, they would likely move directly into a Phase II trial.

**Nitric Oxide Delivery to Treat Respiratory Infections**

AIT has developed a novel drug-device combination allowing for the precise administration of high-doses of nitric oxide (NO) to patients with serious lung diseases in order to prevent and treat lower respiratory tract infections (LRTI). According to the World Health Organization (WHO), there are over 1.5 million hospitalizations caused by this type of infection, leading to 3 million deaths annually. The device is designed to deliver NO at therapeutic doses as high as 160 parts per million (PPM), which is an important differentiator relative to competitors in the space, and can be used in non-intubated patients in either the hospital or home setting. NO is an important signaling molecule that is endogenously found in the human body. It is a potent vasodilator that is released from the endothelium to regulate smooth muscles. NO is also involved in neurotransmission and is naturally produced in the body as a component of the innate immune system. In the US, NO is primarily used in neonates to promote pulmonary and capillary dilation in hypoxemic respiratory failure and persistent pulmonary hypertension.\(^{11,12}\) Since NO is already an approved treatment for neonates, the drug has a long-standing track record of safety with more than 100,000 premature babies treated to date.

NO is known to have broad spectrum activity against a wide variety of bacteria, parasites, and viruses at high doses.\(^{13}\) The only device that is currently approved and marketed in the US—Mallinckrodt Pharmaceuticals’ (NYSE: MNK) INOmax—delivers NO at 20 ppm, which is insufficient to treat severe respiratory infections. While continuous delivery at 160 ppm would pose safety risks, in vivo and in vitro studies have shown that intermittent therapy can provide for antimicrobial therapy while significantly reducing the risk of adverse events. AIT expects that intermittent high-dose NO therapy can treat a wide range of LRTIs and is well-positioned to become the first device capable of delivering high-dose therapy, if approved. NO therapy may even work synergistically with inhaled antibiotics and thus could be used as adjunctive therapy on top of standard-of-care.


\(^{13}\) Burgner, D, 1999. Nitric oxide and infectious diseases. *Archives of Disease in Childhood*, 81(2), pp185-188.
The Company’s lead indication is bronchiolitis and the Company is currently conducting a Phase III study that is expected to read out in later this year. AIT is also evaluating NO delivery as a therapy for patients with infections due to non-tuberculosis mycobacteria (NTM) and has treated a small number of patients on a compassionate use basis in this indication. The drug-device combo has potential applications across a wide range of lung diseases, and AIT may also choose to evaluate their technology in patients with chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) exacerbations, although this will be dependent on securing funding.

**Safety Profile.** To date, AIT has generated safety data in more than 60 patients across three indications in 4 separate clinical trials. The treatment regimen is designed to provide antimicrobial therapy via intermittent delivery, which can mitigate the risks of adverse events associated with continuous NO delivery. The device is designed to monitor a wide range of important safety parameters, including inhaled NO concentration, NO\(_2\) concentration, methemoglobin and the fraction of inspired oxygen (FiO\(_2\)), blood oxygen saturation, and heart rate.

In the Company’s Phase II study, which evaluated intermittent high-dose NO therapy as an add-on to standard-of-care (vs. SOC), AIT’s device was considered safe and well-tolerated with a similar incidence of AEs between the two treatment groups. There were 10 subjects in the NO treatment group reporting 22 AEs and 13 subjects in the SOC group reporting 22 AEs. Serious adverse events were reported by 4 subjects in each group, although none of the SAEs in the NO treatment group were deemed drug-related. The trial also assessed MetHb levels as a safety measure, since inhaled NO can lead to the formation of MetHb in a time-dependent and concentration-dependent manner. At excessive levels, MetHb can cause tissue hypoxia. In the NO-treated group, 29% (6/21) of subjects had at least one MetHb measurement exceed 5%, and three of these patients had multiple MetHb readings over 5%. The maximum MetHb measurement observed in the study was 5.6%. One patient in the NO-treated group discontinued the study due to repeated MetHb measurements over 5%. MetHb levels above 10% can lead to complications, but the use of intermittent 30 minute treatment periods and allowing at least 3 hours to lapse between cycles is expected to mitigate the risk of MetHb elevations to unsafe levels.

**Bronchiolitis**

Bronchiolitis is an acute respiratory infection characterized by obstruction, inflammation and damage to the distal airways known as the bronchioles. It is most common in infants and children less than two years of age, although the elderly and immunocompromised are also susceptible to severe infection. Rhinoviruses, coronaviruses, paramyxoviruses and influenza viruses are all able to replicate and spread in the epithelial cells of the respiratory tract mucosa to cause infection. Of these viruses, respiratory syncytial virus (RSV) is the most often implicated pathogen in bronchiolitis in children. Bronchiolitis secondary to respiratory syncytial infection is a leading cause of hospitalization in previously healthy infants less than 1 year. In fact, globally, more children less than 1 year of age die from RSV infection than any other single pathogen besides malaria. While RSV distal airway infection has more devastating effects in the developing world, infection is as common in young children in the developed world, with an estimated 100 percent of children in the United States suffering from RSV bronchiolitis at least once by the age of 3.

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Causes & Pathogenesis. Bronchiolitis secondary to RSV accounts for 60-80% of all cases of bronchiolitis. RSV is an enveloped pneumovirus belonging to the paramyxovirdae family. It is composed of several proteins that allow the virus to replicate within host epithelial cells of the airways and descend through the pulmonary tract to produce bronchiolitis. Relevant RSV proteins include attachment glycoprotein (G), fusion glycoprotein (F), nucleocapsid (N), small hydrophobic (SH) and two nonstructural proteins (NS1 and NS2). G protein is involved in viral attachment to host cells. Once a virion has attached to a host cell, F protein mediates the fusion of the virus with the host cell membrane allowing the virus to penetrate the cell. Inside the host cell, the virus uses cellular organelles to replicate its genome. The viral genome is protected from host cell defenses by N protein which encapsidates the viral RNA. SH1 protein has a poorly defined role in viral replication, but is thought to be involved in the formation of a transmembrane selective ion channel. Similarly, NS1 and NS2 are not required for replication, although deletion of either gene significantly reduces viral replication in animal models.

The pathogenesis of RSV bronchiolitis is based not only on how the virus infects host cells and spreads, but also on how the virus interfaces with the host immune system. As RSV viral particles enter host cells, replicate and spread, the host immune system responds. Initially components of the innate immune system are activated to limit the replication and spread of infection. Ciliated epithelial cells, macrophages and dendritic cells dwelling in the airways and alveoli have surface and intracellular receptors known as pattern recognition receptors (PRRS). When these receptors make contact with viral particles such as F protein, as a virion infects a cell, a signaling cascade is initiated. This cascade consists of a series of reactions that sequentially activate cytoplasmic proteins. The final reaction in the cascade activates IFR3, a transcription factor that translocates to the host cell nucleus and upregulates the gene transcription of proinflammatory cytokines and chemokines. These molecules include interleukins (IL-), tumor necrosis factor-alpha (TNF-α), and interferons among others. They recruit and activate circulating innate immunity cells such as monocytes, macrophages, natural killer cells, neutrophils and dendritic cells. Each of these cell types functions to kill cells infected with RSV, release additional pro-inflammatory cytokines or activate the adaptive immune system.

Only after innate immune defenses have been mobilized, are the adaptive immune defenses activated. Dendritic cells (DCs) recruited to areas surrounding infected cells recognize viral particles with PRRs and uptake viral antigens. Carrying these antigens, they migrate to lung lymph nodes and activate specific cellular subsets of T and B cells. CD8, or cytotoxic T cells participate in viral clearance by directly killing infected host cells. CD4 cell subtypes- Th1, Th2, Th17 and Tregs—support viral clearance via cytokine production and regulate inflammation to protect surrounding lung tissue. Activated B cells produce antibody subtypes, IgG and mucosal IgA, against viral proteins F and G to help protect against subsequent RSV infection.

RSV Modulation of Host Immunity. The innate and adaptive immune components that act on virions to sequester and eradicate infection are also acted upon by virions to prolong infection. RSV modulates the host immune response to limit its efficacy and promote survival of the virus. Of the aforementioned proteins, G, N, SH, NS1 and NS2 are all implicated in modulating host immunity and contributing to the pathogenesis and severity of RSV infection.

G protein, which facilitates viral attachment to host lung epithelial cells, interacts with the immune system to reduce recruitment of immune cells and influence cytokine profile. The protein’s CX3C motif is similar to fractalkine (CX3CL1), a chemokine that binds to leukocyte CX3CR1 receptor inducing the migration of leukocytes to the lung. RSV G protein’s CX3C motif binds to the leukocyte receptor instead of fractalkine, reducing leukocyte chemotaxis. In addition to leukocyte receptors, G protein’s CX3C motif binds to DCs responsible for antigen presentation in lung lymph nodes. This binding limits the production of type I and type III interferons, critical antiviral cytokines for
immune and inflammatory response. Through other motifs, G protein binds to DCs to prevent their maturation and production of interferon alpha (IFN-α). Finally, G protein promotes the activity of Th2 CD4 cells and suppresses Th1 CD4 cells. Consequently, there is less Th1 cell produced IFN-γ and more Th2 cell produced IL-4, IL-5, and IL-13. This cytokine bias is associated with more severe clinical disease.

On a cellular level, RSV enters cells, replicates, exits and spreads to other cells in a specific sequence of cellular events. The virus also interacts with a variety of molecules and immune cells to circumvent host defenses and sustain viral replication. These individual cellular processes clinically manifest as bronchiolitis, or pneumonia if the virus is able to spread more distally. On a systems level, specifically within the pulmonary tract, RSV infection progresses from the upper airway to the distal airways breeding the syncytia formation and inflammation that characterize bronchiolitis.

Initially, RSV is inhaled in droplets from the air, likely from those infected sneezing, coughing, or breathing. Upon inhalation, RSV infects the epithelial cells of the mucosa lining the upper airways. RSV disrupts the epithelial cell morphology, creating large, multinucleated polyploid cells that project and slough off into the airway lumen. These shed RSV containing epithelial cells retain their infectivity and mechanical inhalation of this airway debris allows the infection to spread to the distal airways causing bronchiolitis. Furthermore, this shed material, often necrotic, obstructs the lumen and contributes to the ongoing inflammation that characterizes the disease. This inflammation results in a cellular infiltrate, excessive mucus secretion, fibrin deposition and accumulation of other non-cellular material, all of which compound the obstruction of the bronchiolar lumen.

Risk factors for disease include young age, premature birth, immunodeficiency and underlying cardiopulmonary disease with the most significant being young age. For one, the innate immune system in children is underdeveloped, and there is insufficient transfer of maternal RSV antibody in utero. Perhaps more importantly, the dimensions of infant pulmonary systems, with airway lumens measuring 120 µm compared to an adult’s 250µm, cannot accommodate the presence of obstructive material. Hence, RSV infection causes much more severe disease in children than it does in adults.

**Symptoms & Diagnosis.** Obstruction and inflammation of the distal airways results in reduced airflow through the bronchioles producing the classic symptoms of bronchiolitis. Initially, infection of the upper airways precipitates symptoms of the common cold—nasal inflammation and discharge, mild cough, fever and ear infection. As the infection spreads to the lower airways, symptoms worsen to rapid, difficult breathing, wheezing, severe persistent cough, and difficulty feeding due to nasal congestion and breathing rate. Furthermore, airway obstruction prevents air from being adequately expelled resulting in chest hyperexpansion and worsened breathing. Infants with severe bronchiolitis may show signs of labored breathing during inhalation including grunting, nasal flaring, and skin retraction around the ribs and base of the throat. While bronchiolitis secondary to other respiratory viruses results in similar symptoms, RSV infection produces the worst clinical picture, which is likely related to the inflammatory cytokine profile of RSV infection. Furthermore, infection of the distal airways with more than one virus, but including RSV, will result in a clinical picture more or less identical to an isolated RSV infection.15

The typical clinical presentation of the aforementioned symptoms, during the months between November and April is easily identified as an acute respiratory infection of the lower airways. Because an overwhelming majority of bronchiolitis cases are due to RSV infection, a clinical diagnosis is often made and the pathogen is assumed to be RSV.

Chest radiography signs of gas trapping and peri-bronchial thickening with or without evidence of interstitial pneumonia usually support the diagnosis. Laboratory identification of RSV antigens from patient airway samples can be used as confirmation, although this is not typically done. The most important aspect of diagnosis is determining how severe the infection is, because hospitalization and subsequent mechanical ventilation may be required.

**Treatment.** Current treatment is based on supportive care measures, mainly oxygen supplementation and fluid replacement. Treatment for symptom relief including nasal sprays and fever control is also common. Patients with severe disease are often hospitalized for close monitoring. Among these hospitalized patients, 15-35% require intensive care and 8-21% require mechanical ventilation. Current treatment options have not resulted in decreased morbidity or mortality. This treatment, palivizumab is an RSV fusion protein-specific monoclonal antibody that provides short-term, passive immunity. It significantly reduces disease severity and hospitalization rates in children, however its cost limits its use to high-risk infants or infants with a gestational age greater than 29 weeks.

**Synagis (palivizumab) – AstraZeneca (NYSE: AZN).** Palivizumab is a monoclonal antibody that is used to prevent RSV infection in high-risk infants like those born prematurely. The half-life of the monoclonal antibody is approximately 20 days, enabling once-monthly administration for the duration of the flu season. Prophylactic use of palivizumab has been shown to reduce the rate of RSV-related hospitalizations by 55% in high-risk infants. It has also been demonstrated the palivizumab prophylaxis decreases hospital length of stays, ICU use, and oxygen supplementation. The cost of palivizumab is fairly high, which limits use of this antibody to only high-risk infants; its dosing by weight precludes use in elderly or immunocompromised adults. For these patients, there are no approved treatment options. As a form of prophylaxis, palivizumab must be given very broadly despite the fact that only a small percentage of infants will ultimately contract RSV and become severely sick. However, even with the availability and use of palivizumab, a substantial number of hospitalizations occur each year for RSV infection.

**Ribavirin.** Ribavirin is an amino acid homologue that was approved in 1986 as a broad-spectrum antiviral drug. Ribavirin is speculated to inhibit RSV replication by both direct (interference of RNA capping, polymerase inhibition, lethal mutagenesis) and indirect (inosine monophosphate dehydrogenase inhibition and immunomodulatory effects) mechanisms. Ribavirin is used as a last-line therapy in some patients, although lingering concerns about its safety and efficacy limit its use to only the most dire, life-or-death situations, typically in intensive care settings.

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RSV Market Information

**Epidemiology.** Respiratory syncytial virus (RSV) is an RNA virus that primarily infects the airway of infants. Roughly 66% of infants are infected with RSV by 1 year of age, and by the age of 2, RSV will have infected nearly all children at least once. Roughly 25-40% of children younger than 1 year old infected with RSV will develop initial signs of bronchiolitis or pneumonia, the 2 most common conditions associated with RSV infection. Typically, infected individuals recover within 7 days of infection only presenting symptoms of fever and coughing; however, 0.5-2% will be hospitalized and diagnosed with bronchiolitis (50-90%) or pneumonia (5-40%). Interestingly, residual antibodies and adaptive immune responses fail to prevent future infections, causing a severe problem for immunocompromised individuals, such as the elderly, with an estimated prevalence of approximately 13.7% and 10.0% in the US and EU, respectively.

RSV infection remains a leading cause of hospitalization for infants less than 1 year. Worldwide, there are an estimated 34 million new pediatric cases, leading more than 3.4 million hospitalizations and 200,000 pediatric deaths annually. Mortality is significantly lower in developed countries due to increased access to supportive care. However, annually in the US, there are 1.5 million outpatient visits for children less than 5 years and an estimated 146,000 hospitalizations for RSV infection. With an average hospital stay of 3.5 days per patient, up to approximately 511,000 days are spent in the hospital for RSV infection in the US each year. Of these hospitalizations 1.5% requires treatment in a pediatric intensive care unit.

**Market Size.** While RSV infection can occur at any time in an individual’s life, infants younger than the age of 2, adults over 65 years of age, and the immunocompromised are at the greatest risk. It is estimated that treating RSV infections results in over $1 billion in annual healthcare expenditure. This is driven in part by hospital length of stays, which averages 3.2 days for infants. In Figure 2, we estimate the number of hospitalizations due to RSV infection in infants and elderly populations. AIT anticipates use of their NO delivery device exclusively in the hospital setting for RSV, so this likely reflects their target patient population. There are roughly 146,000 infants and 164,000 elderly individuals who are hospitalized each year for RSV infections, which translates into a potential market opportunity for AIT that likely exceeds $2 billion. It is worth noting that AIT plans to pursue the infant bronchiolitis segment first. We based our estimates on the following assumptions:

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- **Infant and Elderly Populations** – Based on data from the US Census Bureau, we estimate that there are 22.4 million infants under the age of 5 and 109.6 million individuals 50 years or older.

- **Hospitalization Rates** – We assume a hospitalization rate for RSV of 6.5 per 1,000 for infants and 15 per 10,000 in elderly adults.\textsuperscript{25,26}

- **Dosage** – We assume that NO therapy in bronchiolitis patients is used 5 times a day for an average of 3 days.

- **Price per Dose** – We assume low and high price points of $250 and $750. The Company has previously discussed the possibility of using a price per dose in this range. The exact pricing that the Company ultimately chooses will be based on the potential for reduced hospitalizations.

**Figure 2. Market Opportunity for AIT in Treating Bronchiolitis in Infants and Elderly Patients**

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*Source: LifeSci Capital*

The current Phase III trial that is being conducted in Israel is testing hospital length of stay as the primary endpoint. If AIT is able to show that high-dose NO therapy can meaningfully reduce hospitalization time, then this could have a significant impact on total treatment costs for RSV and provide a strong pharmacoeconomic rationale for the broad adoption of their device.

**Clinical Data Discussion**

To date, AIT has completed a Phase I safety study in healthy volunteers as well as a Phase II study in bronchiolitis patients. The Company has conducted additional trials in other indications, including NTM infections, which we discuss in subsequent sections of the report. The Company is currently conducting a Phase III trial in Israel evaluating


NO therapy in bronchiolitis patients and expects to report topline results in the first half of 2018. Following this readout, AIT plans to file and IND with the FDA in 2018 to support a pivotal Phase III study in the US. **Figure 3** highlights the clinical program in bronchiolitis.

**Figure 3. Clinical Trials to Date for Bronchiolitis Indication**

<table>
<thead>
<tr>
<th>Study</th>
<th>Target Indication</th>
<th>Focus</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>All comers</td>
<td>Safety and tolerability</td>
<td>2011</td>
</tr>
<tr>
<td>Phase II</td>
<td>Bronchiolitis patients</td>
<td>Safety and efficacy</td>
<td>2013-2014</td>
</tr>
<tr>
<td>Phase III</td>
<td>Bronchiolitis patients</td>
<td>Safety and efficacy</td>
<td>2017-</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

**Phase I Trial**

This open-label, controlled Phase I study assessed the safety and tolerability of add-on NO therapy in 10 healthy adult volunteers between the ages of 20 and 62. Subjects were administered NO therapy at a dose strength of 160 ppm for 30 minutes 5 times per day for 5 days. The primary endpoint was the safety and tolerability of NO therapy including measurements of NO, NO2, and methemoglobin (MetHb) concentrations, as well as inhaled fraction of inspired oxygen (FiO2) and oxygen saturation (SaO2). The study also assessed vital sign, lung function, blood chemistry, hematology, prothrombin time, inflammatory cytokine and chemokine levels, and endothelial activation.

In the subjects enrolled in the study, NO therapy was well-tolerated and there were no significant adverse events (AE). There were no changes in forced expiratory volume in one second (FEV1) or other lung function parameters between baseline and day 5 of therapy. In addition, no changes were observed in serum nitrites/nitrates, prothrombin, and inflammatory markers. MetHb increased to 0.9% during the study period, which is within a safe range, indicating that 30-minute dosing of 160 ppm NO therapy can be safely used to treat a range of respiratory conditions.

**Phase II Trial**

AIT conducted this proof-of-concept Phase II study at the Soroka University Medical Center and demonstrated that NO therapy was safe, well-tolerated and effective at treatment acute cases of bronchiolitis. There were no NO-related serious adverse events in the trial and NO therapy shortened hospital stays by 24 hours and reduced the time to normal oxygenation. Based on these results, AIT decided to move into a Phase III study.

**Trial Design.** This was a randomized, double-blind, placebo controlled Phase II study evaluating the safety, tolerability, and efficacy of high-dose NO administered 5 times per day to 43 bronchiolitis patients between 2 and 12 months of age.\(^\text{27}\) Patients were randomized to receive NO therapy at 160 PPM or placebo on top of standard-of-care (SOC) until their release from the hospital. Primary endpoints were the methemoglobin (MetHb) percentage over 21 days and the number of subjects with adverse events (AE) over 5 days. A key secondary endpoint was the percentage of subjects that discontinued due to an AE, and the trial also assessed the length of hospital stay as an exploratory

\(^{27}\) https://clinicaltrials.gov/ct2/show/record/NCT01768884
endpoint. Subjects returned for follow-ups on day 7(+5) and day 14(+5) and were contacted by phone for a follow-up on day 30 (+5) from the day of admission.

**Trial Results.** Overall, NO therapy was considered safe and well-tolerated in the study with a similar incidence of AEs between the two treatment groups. There were 10 subjects in the NO treatment group reporting 22 AEs and 13 subjects in the SOC group reporting 22 AEs. Serious adverse events were reported by 4 subjects in each group, although none of the SAEs in the NO treatment group were deemed drug-related.

The trial also assessed MetHb levels as a safety measure, since inhaled NO can lead to the formation of MetHb in a time-dependent and concentration-dependent manner. At excessive levels, MetHb can cause tissue hypoxia. In the NO-treated group, 29% (6/21) of subjects had at least one MetHb measurement exceed 5%, and three of these patients had multiple MetHb readings over 5%. The maximum MetHb measurement observed in the study was 5.6%. One patient in the NO-treated group discontinued the study due to repeated MetHb measurements over 5%.

**Figure 4** shows the time to reach normal oxygenation, defined as 92% oxygen saturation, for patients treated with NO therapy and SOC (blue) or SOC alone (red). Subjects receiving add-on NO therapy took 35 hours to reach normal oxygenation, compared with 63 hours in the SOC group (p=0.0275), reflecting a 44% reduction in the time to reach normal oxygen levels.

![Figure 4. Time to Reach Normal Oxygenation](image)

**Source:** Corporate Presentation

---

Figure 5 shows the overall length of hospital stays for infants treated with NO therapy and SOC (blue) or SOC alone (red). Infants who received NO add-on therapy had a roughly 34% reduction in the length of hospital stays compared with the SOC control group, reflecting a one day shorter hospital stay on average (p=0.0587). This result is particularly important since length of hospital stay is a validated FDA endpoint that could be used in pivotal studies and it also suggests that potential cost-savings could be a pharmacoeconomic driver for the use of NO therapy in treating bronchiolitis.

Figure 5. Total Hospitalization Time

Source: Corporate Presentation

Figure 6 shows the time to achieve a normal clinical score of less than or equal to 5, using the Modified Tal scoring system. The mean baseline score in both groups was roughly 8. The mean time to reach a normal clinical score was 31 hours in the NO therapy group and 56 hours in the SOC group (p=0.0125), which translates into an 80% reduction in the time to reach a normal clinical score.
Phase III Trial

Following positive results in Phase II, AIT launched a Phase III trial in Israel that is evaluating AIT’s drug-device combo in 120 infants hospitalized for acute bronchiolitis. The Company expects to report topline results in the first half of 2018 and file an IND in 2018 to support a Phase III trial in the US.

**Trial Design.** This randomized, double-blind, placebo controlled Phase III trial evaluating the safety, tolerability, and efficacy of intermittent inhaled NO therapy in the treatment of 120 infants with bronchiolitis. This trial is enrolling infants between 0 and 12 months of age that were born at greater than 28 weeks of gestation and have acute bronchiolitis requiring inpatient hospitalization for at least 24 hours. Subjects enrolled into the trial are randomized to receive either 160 PPM NO therapy for 30 minutes five times per day for up to 5 days on top of standard-of-care or standard-of-care alone. The primary endpoint is the difference in hospital length of stay (LOS) over 30 days. Secondary endpoints include time to achieve a Modified Tal clinical score less than or equal to 5, time to achieve a 92% oxygen saturation (SaO2), and the rate of NO-related adverse events (AE). Subjects are returning for follow-up visits on day 14±5 and 21±5 and will be contacted by phone for a follow-up 30 days after the day of admission to the hospital.

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29 https://clinicaltrials.gov/ct2/show/record/NCT03053388
Other Drugs in Development

There are multiple treatments in development, although very few are likely to meaningfully impact the market segment targeted by AIT. The existing development pipeline of prophylactic treatments is shown in Figure 7. Regeneron’s (NasdaqGS: REGN) suptavumab, AstraZeneca/Sanofi’s (NYSE: AZN; SNY) MEDI8897, and Ablynx’s (Euronext Brussels: ABLX.BR) ALX-017 are anti-F protein antibodies that are being developed for prophylaxis and are intended to be successors to AstraZeneca’s Synagis (palivizumab). In addition, there are multiple prophylactic vaccines in development for immunization of older adults and pregnant women. However, there have been many challenges to RSV vaccine development, and some of the most advanced programs have stumbled, including Novavax’s (NasdaqGS: NVAX) Phase III failure in elderly patients. Approval of any of the antibodies or vaccines could reduce the overall number of patients that develop bronchiolitis and could be treated with NO therapy, although the large number of infants and older adults that are hospitalized each year suggest that this would not have too much of an impact on AIT’s commercial prospects.

Figure 7. RSV Treatments in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Mechanism</th>
<th>Route</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>suptavumab (REGN2222)</td>
<td>Regeneron</td>
<td>Anti-F protein antibody</td>
<td>IM</td>
<td>III</td>
</tr>
<tr>
<td>MEDI8897</td>
<td>AstraZeneca/Sanofi</td>
<td>Anti-F protein antibody</td>
<td>IM, IV</td>
<td>IIb</td>
</tr>
<tr>
<td>ALX-017</td>
<td>Ablynx</td>
<td>Anti-F protein nanobody</td>
<td>IN, IV</td>
<td>IIb</td>
</tr>
<tr>
<td>Vaccines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV F Vaccine</td>
<td>Novavax</td>
<td>Recombinant F protein nanoparticle vaccine</td>
<td>IM</td>
<td>III</td>
</tr>
<tr>
<td>GSK3003891A</td>
<td>GlaxoSmithKline</td>
<td>F protein vaccine</td>
<td>IM</td>
<td>II</td>
</tr>
<tr>
<td>MVA-BN RSV</td>
<td>Bavarian Nordic</td>
<td>Attenuated multivalent vaccine</td>
<td>IM, IN, SC</td>
<td>II</td>
</tr>
<tr>
<td>RSV001</td>
<td>GlaxoSmithKline</td>
<td>Attenuated multivalent vaccine</td>
<td>IM</td>
<td>II</td>
</tr>
</tbody>
</table>

IM: intramuscular; IN: intranasal; IV: intravenous; SC: subcutaneous

Source: Mejias A. et al. 2017

NO Therapy to Address NTM Infections

People with severe pulmonary diseases, such as cystic fibrosis (CF), chronic obstructive pulmonary diseases (COPD), or α-1 antitrypsin deficiency, are particularly vulnerable to persistent infections by non-tuberculosis mycobacteria.

(NTM), which are found everywhere but normally don’t pose much threat to healthy individuals. For a therapy to be effective against NTM, it must be capable of killing bacteria in its three forms: planktonic (freely suspended as single cells in water), engulfed into macrophages, and biofilms, which are aggregation of bacterial cells in a self-produced extracellular matrix. AIT has demonstrated proof-of-concept in a small, open-label Phase II study and plans to launch a second Phase II trial in the near-term. This new trial will test the safety and efficacy of 21 days of NO therapy to account for the difficulty in treating *M. abscessus* infections. The Company expects to report data from the trial in the fourth quarter of 2017, which could permit a subsequent Phase III trial launch by the middle of 2018. The clinical program currently focuses on *M. abscessus*, the most difficult-to-treat subtype of infection, due to the lack of expected competition and thus greater commercial prospects.

**NTM Infections**

Nontuberculous mycobacteria (NTM) are a group of naturally occurring bacteria, found in water and soil that can cause severe pulmonary disease. The most prevalent strain of NTM is *Mycobacterium avium complex* (MAC) followed by *Mycobacterium abscessus*. Although MAC is the most common bacteria, *M. abscessus* is more difficult to treat because of its antimicrobial multidrug resistance. Among *M. abscessus*, there are three subspecies: *M. abscessus subsp. abscessus, M. abscessus subsp. massiliense*, and *M. abscessus subsp. bolletii*. The subspecies are characterized by the differentiation in their erm gene patterns, which cause varying resistance to macrolides and consequently result in different treatment outcomes. The distinction between subspecies has been significant in managing NTM disease because it has led to further development of macrolide susceptibility profiles, which ultimately helps physicians prescribe more effective medicine.

**Causes and Pathogenesis.** NTM is thought to be transmitted through the environment, either by inhaling the bacteria or drinking contaminated water sources. Because *M. abscessus* is resistant to disinfectants, it can also be transmitted during invasive medical procedures that use contaminated equipment. While many people are exposed to NTM, only a small percentage develop clinical signs of infection. It remains unclear why only certain individuals develop infections, but there are recognized risk factors such as immunosuppression and structural lung disease.

*M. abscessus* primarily causes pulmonary disease in susceptible individuals, but the bacteria can cause disease in almost all organs. Patients with pre-existing lung conditions, such as cystic fibrosis (CF), bronchiectasis, and prior tuberculosis, are at increased risk of developing infections. This is most likely due to the underlying disease that leads to damaged substrates and altered mucociliary clearance (MCC). Furthermore, there is a known correlation between abnormalities in the CF gene (CFTR) and NTM infections. However, the etiology remains largely unknown.

These low-virulence bacteria most commonly cause opportunistic infections in immunocompromised patients, but there have been increasing rates of infection in immunocompetent patients as well. Although the immunologic mechanism that predisposes individuals to NTM remains unclear, defects in interleukin-12 (IL-12) or interferon-γ (IFN-γ) production are thought to increase risk of developing NTM disease. There is a positive feedback loop between IL-12 and IFN-γ that controls the progression of NTM and other infections through the up-regulation of tumor necrosis factor (TNF-α), so patients treated with therapies that inhibit TNF-α often have weakened immune systems.

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The cases that support the link between NTM infection and therapies involving TNF-α inhibitors suggest that compromised immune systems increase NTM susceptibility.²

In broad terms, the progression of *M. abscessus* lung infections depends on the variant of the bacteria. The soft (S) variant usually causes a slower progression, and it is not immediately problematic. However, the rough (R) variant is more virulent and leads to a more aggressive development of NTM infection.³³ Without treatment, both types eventually cause a decline in lung function and lead to an impaired quality of life. In some severe cases of disease, the patient experiences acute respiratory failure.

**Diagnosis and Symptoms.** Because NTM exists naturally in the environment, it is difficult to diagnose NTM pulmonary disease. A positive culture from a nonsterile respiratory source does not necessarily provide clinical significance because bacteria can colonize in the lungs without invading the cells. The diagnosis of NTM lung disease must therefore meet multiple criteria, including the presence of clinical symptoms, radiologic abnormalities, and microbiologic cultures.³

Clinical symptoms often vary from person to person, but chronic cough and purulent sputum is common in most individuals. Other symptoms include fever, weight loss, fatigue, and malaise. Chest radiographs and high resolution computed tomography (HRCT) scans reveal various characteristic patterns of NTM infections, including nodular opacities and multifocal bronchiectasis.³ However, a diagnosis cannot be made based upon clinical and radiographic evidence alone. Although isolation of NTM culture is not a sufficient means of identifying NTM infections, it is nonetheless essential in preventing misdiagnosis. It is recommended that physicians test for positive culture results multiple times.²

In general, the diagnostic criteria for NTM lung disease applies to patients with pre-existing CF as well. However, it can be difficult to diagnose NTM disease in such patients due to the overlapping symptoms and radiographic changes that occur as a result of the underlying CF.² Due to the limited clinical data pertaining to *M. abscessus* in patients with CF, diagnosis and treatment primarily relies on expert opinion.

**Treatment.** The treatment of *M. abscessus* usually begins with combination therapy involving antimicrobials and intravenous (IV) agents. Physicians administer several different antimicrobials at once to combat antimicrobial multidrug resistance. The initial antimicrobials used are macrolides, clarithromycin and azithromycin, and the drugs of choice for IV administration are amikacin combined with either cefoxitin or imipenem. However, the appropriate treatment specifications depend on individual macrolide susceptibility profiles. The duration of this treatment lasts two weeks to several months and is followed by further oral antibiotics, which continue for an additional 12 plus months. When drug therapy alone cannot control the progression of the disease, or, in acute initial cases, surgical resection is required. Once surgery has been performed, the patient must undergo further antibiotic treatment until he or she has shown negative sputum cultures for at least 12 months.

There are several unsolved problems regarding the treatment of *M. abscessus* infections, including high frequency of side effects and toxicities, a lack of consensus on the optimal antimicrobial agents, and treatment duration.² A potential consequence of the broad adoption of the low-dose, long-term antimicrobial treatment is the evolution of macrolide-resistant NTM, which has created a perpetual need for novel antimicrobial treatments.

Furthermore, there is no antibiotic regimen that has proven to consistently treat NTM pulmonary infections.\textsuperscript{34} The American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) have provided guidelines for treatment based on the limited data and case studies available; however, they have also acknowledged that there are no current drug combinations with proven efficacy.

**NTM Market Information**

**Epidemiology.** There are more than 150 species of NTM that are found prevalently throughout the environment. Those with underlying lung disease and/or genetic dispositions are the most likely to develop an NTM infection. While \textit{M. avium complex} (MAC) is the most common pathogen underlying NTM infection, \textit{M. abscessus} infections are the most difficult to detect and treat due its rapid growth and multidrug resistance.\textsuperscript{35} In the US, there are thought to be roughly 181,000 cases each year.\textsuperscript{36} Consistent with most infections, elderly patients are also more susceptible, as approximately 69% of NTM infections occur in those 65 years of age or older.

**Market Size.** NTM infections in the US accounted for a healthcare burden of $1.7 billion, corresponding to approximately $9,400 per patient. Of the total treatment costs, 87% is associated with inpatient expenses. Approximately two-thirds of these costs were attributable to adults 65 years of age and older. We also note that 76% of all costs were related to prescription medications.

Based on the annual pulmonary NTM cases above, percentage of patients that are currently receiving inhaled therapeutics, and product pricing strategies, we estimated in Figure 8 a total market to range between $1.0 billion to $3.1 billion in the US. Our analysis is based on the following assumptions:

- **Annual Pulmonary NTM Cases** – We assume that there are approximately 181,000 NTM cases in the US each year.
- **\textit{M. Abscessus} Cases** – We assume that roughly 25% of NTM cases are due to \textit{M. abscessus}.\textsuperscript{37}
- **Dosage** – We assume that NO therapy in NTM patients mirrors what AIT plans to use in their Phase II trial. This includes 91 sessions of 30 minutes over a period of 21 days.
- **Price per Dose** – We assume low and high price points of $250 and $750. The Company has previously discussed the possibility of using a price per dose in this range. The exact pricing that the Company ultimately chooses will be based on the potential for reduced hospitalizations.


\textsuperscript{36}Strollo SE. et al. 2015. The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States. \textit{Ann Am Thorac Soc.} 12(10): 1458-1464

Figure 8. Total Market Opportunity for Treating M. Abscessus Infections in the US

<table>
<thead>
<tr>
<th></th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with Pulmonary NTM Infections</td>
<td>181,000</td>
</tr>
<tr>
<td>Cases of <em>M. abscessus</em> (25%)</td>
<td>45,250</td>
</tr>
<tr>
<td>Price – Low ($250 per dose)</td>
<td>$22,750</td>
</tr>
<tr>
<td>Annual Sales - Low</td>
<td>$1,030 M</td>
</tr>
<tr>
<td>Price – High ($750 per dose)</td>
<td>$68,250</td>
</tr>
<tr>
<td>Annual Sales - High</td>
<td>$3,090 M</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

We estimate a total US market opportunity in treating respiratory infections caused by *M. abscessus* of between $1.0 billion and $3.1 billion. Capturing just 25% of these patients, which may be fairly conservative considering the lack of approved treatment options and the severity of the infection, would translate into sales for AIT of between $250 million and $770 billion, depending on the chosen pricing. There would also likely be some amount of off-label use in treating MAC and other NTM infections, which could increase the market potential for AIT’s therapy. In addition, the ex-US market is thought to be roughly the same size as the opportunity in the US, providing for an even larger market potential for AIT’s device if they choose to push into additional territories.

**Clinical Data Discussion**

AIT has evaluated the use of high-dose NO therapy in a Phase IIa study in CF patients as well as a compassionate use study in 2 CF patients infected with *M. abscessus*. Although the trial was small, the compassionate use study achieved a 99% reduction in bacterial load by utilizing a 21-day treatment regimen. AIT plans to launch a Phase II study in individuals infected with NTM infections with a specific focus on *M. abscessus*. The Company expects to report data from the trial in the fourth quarter of 2017, which could permit a subsequent Phase III trial launch by the middle of 2018.

**Phase IIa Study in CF Patients**

Between 2013 and 2014, AIT conducted a small open-label, proof-of-concept study evaluating NO therapy in the treatment of infections in 9 CF patients over the age of 10. The enrolled subjects included 6 individuals who were infected with *Pseudomonas aeruginosa*. The subjects received intermittent NO therapy (160 ppm) for 30 minutes three times per day for a total of 9 days. The primary endpoints were the MetHb percentage, adverse events (AE) associated with inhaled NO, and the percentage of subjects discontinuing due to AEs. Secondary endpoints included forced expiratory volume in 1 second (FEV1) before and after therapy. Following 9 days of NO therapy, none of the subjects reached a MetHb level that exceeded the study threshold. Overall, treatment was considered safe and well-tolerated.

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38 [https://clinicaltrials.gov/ct2/show/NCT01958944](https://clinicaltrials.gov/ct2/show/NCT01958944)
There were 31 AEs reported with 24 deemed possibly related to the treatment. There were no serious AEs (SAE) reported during the study. In addition, all of the AEs that were potentially related to treatment occurred in only 2 of the patients. In terms of bacterial load, the enrolled subjects experienced a roughly 60% decrease in bacterial load as measured at the end of the treatment period compared to baseline.

**Compassionate Use Study in CF Patients Infected with *M. abscessus***

AIT has also evaluated NO therapy in 2 CF patients infected with *M. abscessus*, a particularly difficult-to-treat form of NTM infection, on a compassionate use basis. Due to the difficulty in treating *M. abscessus*, AIT decided to treat for 21 days in this study. These 2 individuals experienced a 99% reduction in bacterial load from baseline, as well as improvements in the 6-minute walk distance (6MWD) test and reductions in inflammation.

**Phase II Study in Patients Infected with *M. abscessus***

AIT plans to launch an open-label Phase II study evaluating the safety and efficacy of NO therapy in patients infected with *M. abscessus*.39 The trial will enroll 10 patients over 6 years old with a confirmed pulmonary NTM infection caused by *M. abscessus*. Enrolled patients will receive 91 30-minute sessions of 160 ppm NO therapy with at least 3 hours between each session. The primary endpoint is safety, as measured by NO-related serious adverse events (SAE). Secondary endpoints include the six-minute walk test, *M. abscessus* bacterial load, NO-related AEs including Met-hemoglobin and NO2 levels, and type and frequency of NO-related AEs. AIT expects to report results from the trial in the fourth quarter of 2017, which could position the Company for a pivotal Phase III trial launch as early as the middle of 2018.

**Other Drugs in Development***

There is a pressing need for effective treatments for NTM infections and the FDA considers this a major priority. The other drugs in development for NTM infections are shown in Figure 9. Currently, there are two inhaled antibiotic formulations in development for respiratory infections: Insmed’s (NasdaqGS: INSM) *Arikayce* (liposomal amikacin) and Aradigm’s (NasdaqCM: ARDM) *Linhaq* (liposomal ciprofloxacin). These products are often used in 28 days on/28 days off treatment sequences and could likely be used in a complimentary manner with AIT’s drug-device combo. Insmed is currently conducting Phase III trials for Arikayce and expects to report data and file their NDA in the second half of 2017. However, it is important to note that Insmed is only pursuing NTM infections due to *M. avium complex* (MAC) due to a lack of efficacy against *M. abscessus*. As a result, Insmed and AIT end up targeting entirely different subsets of the patients infected with NTM. While Aradigm has shown preclinical results indicative of efficacy against *M. abscessus*, the lead indication for Linhaliq non-CF bronchiectasis (nCFBE) and would have to conduct additional trials, likely one Phase II study as well as a pivotal Phase III study, to support an NDA filing for NTM infections.

39 https://clinicaltrials.gov/ct2/show/NCT03208764
Nitric Oxide Therapy for Chronic Obstructive Pulmonary Disease (COPD)

AIT believes that patients with COPD could benefit from treatment with high-dose NO therapy as well and plans to pursue this indication if the Company can secure further financing. These patients’ lungs are prone to chronic bacterial infection, so the use of NO therapy could provide an important add-on therapy to help control bacterial load in the lungs and reduce the chances of disease exacerbations.

**Disease Background.** Chronic obstructive pulmonary disease is a progressive diminishing of pulmonary function, causing constant shortness of breath, due to a narrowing of the airways. No treatments currently exist to reverse the progression of the disease, and complications related to COPD are a very common cause of death. By far, the most common cause of COPD has been smoking cigarettes, pipes, and cigars, but air pollution, especially in countries with rapid industrialization, is beginning to compete with tobacco smoking as the chief cause of COPD. Although decline in lung function is gradual, patients often experience sudden worsening of symptoms, called acute exacerbations, due to air pollution or infections.

The development of COPD happens on two parallel tracks, with most patients experiencing more dramatic disease in one area or the other. In the large airways, the bronchi, inflammation and lung damage result in a condition called chronic bronchitis. When the same processes affect the tiny air sacs, or alveoli, in the lungs the condition is referred to as emphysema. Chronic bronchitis is clinically defined as a cough with sputum production on most days for 3 months of the year for 2 years. Along with increased goblet cells and mucus glands, there is also inflammation that causes scarring and thickening of bronchial walls, resulting in narrowing of the airways. People with COPD primarily caused by chronic bronchitis sometimes have bluish skin and lips due to a lack of oxygen.

Emphysema occurs when the lung damage is concentrated in the alveoli. The air sacs become enlarged and the walls begin to break down, reducing the surface area available for gas exchange. Since the alveoli make up the major mass of the lung, as they break down the smaller bronchi lose support and can collapse, further limiting airflow. Patients suffering from emphysema sometimes have a pink color in their faces caused by the extra effort they expend during exhalation. The pathogenesis of COPD is less well understood than that of BE or CF. Although inflammation clearly plays an important role in the degradation of the lungs, it is not clear that bacterial infection acts in a vicious cycle as in BE.

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**Figure 9. Therapies in Development for NTM Infections**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arikayce (liposomal amikacin)</td>
<td>Insmed</td>
<td>III</td>
</tr>
<tr>
<td>Linhaliq (liposomal ciprofloxacin)</td>
<td>Aradigm</td>
<td>Phase II ready</td>
</tr>
</tbody>
</table>

* Aradigm has completed two Phase III trials in non-CF bronchiectasis

Source: LifeSci Capital
**COPD Treatment.** The first step in the treatment of COPD is to limit exposure to any factors that are causing the disease – usually, this means to quit smoking. As the disease progresses, measurement of FEV₁, which is measured in percentage of normal capacity, gets worse and worse, and stronger interventions are needed. For severe cases of COPD, surgery is sometimes needed. Surgical interventions include bullectomy, removal of an air-filled space that can crush functioning lung, and lung volume reduction, removal of heavily damaged portions of the lung so healthier portions have room to work. Lung transplantation is sometimes performed, especially in younger patients.

There are no drugs approved for the treatment of disease progression in COPD; however a number of drugs are used to manage the disease. The primary focus for pharmaceutical interventions is control of a patient’s symptoms. Some of the drugs used are β-2 agonists such as Ventolin (albuterol) or Foradil (formoterol); anticholinergics like Spiriva (tiotropium) or Atrovent (ipratropium); and corticosteroids, including prednisone, fluticasone, and Pulmicort (budesonide). Many of the hospitalizations and deaths related to COPD are due to acute exacerbations caused by bacterial infections, so there is definitely a need for drugs in this area.

**COPD Market Information.** COPD is currently the third most prevalent cause of death in the United States. According to the National Heart, Lung, and Blood Institute of the NIH, approximately 24 million Americans have COPD, and half of the cases are undiagnosed. So there are 12 million people in the US actively seeking treatment for the disease, and the incidence is increasing, mostly due to the cumulative nature of lung damage. More than 1.5 million emergency room visits per year are attributed to COPD each year. According to the Institute, the estimated cost of COPD in the US in 2010 was $50 billion, which included $30 billion in direct medical costs and $20 billion in indirect costs.

The overall market for COPD treatments is huge, with increasing need for medication as patients get older. Controlling bacterial infections is a key component to successfully managing COPD, and if safe inhaled therapies that can reduce bacterial load were available, they would be widely adopted. Acute exacerbations in COPD patients are a major source of hospitalizations for COPD, incurring large costs. Prophylactic antibacterial treatment in at-risk patients should reduce exacerbations, and thereby shorten hospital stays and reduce the rate of COPD-related mortality. This creates clear cost/benefit incentives for doctors to aggressively treat COPD with inhaled therapies.

**Intellectual Property & Licensing**

As of May 23, 2017, AIT’s intellectual property suite includes 24 issued patents and 22 pending applications. Of the 24 issued patents, 7 were obtained via a non-exclusive worldwide license from SensorMedics Corporation, and the remaining 17 were acquired through an option granted to AIT by Pulmonox Technologies Corporation. The 22 pending applications were developed internally.
Management Team

Steve Lisi
CEO and Chairman of the Board

Steven Lisi has served on our Board since January 2017 and on the Board of AIT Ltd., our wholly-owned subsidiary, since June 2016. Mr. Lisi was previously Senior Vice President of Business and Corporate Development at Avadel Pharmaceuticals (AVDL) where he was instrumental in restructuring the company, raising $121m and transforming it from $100m enterprise value to $1b in three years. Prior to his position at Avadel, Mr. Lisi spent 18 years investing in the global healthcare industry at Mehta and Isaly (now Orbimedi), SAC Capital, Millennium Management, Panacea Asset Management and as a Partner at Deerfield Management. Mr. Lisi serves as Chairman of the Board of Mico Innovations, a next generation coronary and neurovascular stent company. He received his Master in International Business from Pepperdine University.

Amir Avniel
President and Chief Operating Officer

Amir Avniel is the COO and co-founder of AIT. He has over 20 years of experience leading biotechnology companies. Prior to AIT, he co-founded Rosetta Green, which was eventually acquired by Monsanto. Prior to Rosetta Green, he served as the president and the Chief Executive Officer of Rosetta Genomics, a NASDAQ company. He studied computer science at the Academic College of Tel Aviv – Jaffa Israel and earned a Bachelor’s degree in Social Sciences and Humanities – from Open University in Israel. Prior to his academic studies, he served as an officer in the Israel Defense Force, where he was awarded four commendations for excellence.

Hai Aviv
Chief Financial Officer

Mr. Aviv brings over 10 years of accounting and financial management practice in publicly traded companies. He was previously the CFO at Babylon Ltd., a publicly-traded Israeli company listed on the Tel Aviv Stock Exchange and operating in the fields of internet, risk capital investments and software. In his role he was actively involved in mergers, acquisitions, and investments. From 2010 to 2013, Mr. Aviv was Babylon’s Corporate Controller. From 2005 to 2010, he was a manager at the Ernst & Young Accounting Firm of Kost Forer, Gabbay & Kasierer, in Tel Aviv, working predominantly with the high-tech team. Mr. Aviv is a Certified Public Accountant, and holds a Bachelor of Arts degree in Business and Accounting, and an MBT in Business and Taxation from The College of Management, Israel

Ali Ardakani
Senior VP Device & Business Development

For the past 18 years, Ali Ardakani has been pivotal in start-up and development of several biotech companies, drugs and medical devices, for which he has raised millions of dollars in private and grant financing. Most recently, he co-founded virtual biotech Niiki Pharma Inc in NYC, where he acquired two first-in-class oncology drugs from Europe and took them through US IND, UK CTA and Phase 1 and 2 clinical trials within 3 years. Prior to Niiki Pharma, he was the director of corporate development at iCell Therapeutics, a drug delivery platform company. Prior to iCell he led operations of PulmoNOx Medical Inc, a medical device company responsible for 510(k) approval of two novel medical devices. At the same time, he was VP of Operations of EquaTec, a virtual med-tech veterinary company
developing novel therapies for the equine, where he led global operations and trials in Canada, US and Hong Kong. He also managed the global alliance of EquATec with a large pharma partner.

Risk to an Investment

We consider an investment in AIT to be a high-risk investment. AIT has generated positive clinical data, but early signs of safety and efficacy may not necessarily translate into late-stage success. There are clinical and commercialization risks associated with their programs as well. As with any company, AIT may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any device, and AIT may not receive FDA or EMA approval for its therapies despite significant time and financial investments. Regulatory approval to market and sell a device does not guarantee that the device will penetrate the market, and sales may not meet expectations.
Analyst Certification

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