The unmet need for an inhaled antibiotic in the treatment of non-cystic fibrosis bronchiectasis (NCFB)

Professor James D Chalmers, MD PhD
British Lung Foundation Chair of Respiratory Research
University of Dundee, Scotland, UK
What is Bronchiectasis?

◆ Characterized pathologically by airway inflammation and permanent bronchial dilatation, and clinically by productive cough and recurrent respiratory infections

◆ Etiology
  – Idiopathic
  – Post-infectious
  – Endobronchial obstruction
  – Congenital syndromes
  – Immunodeficiency states
  – Immune mediated diseases
  – Non-tuberculous Mycobacterial infection

Pathogenesis of Bronchiectasis is a Vicious Cycle

- **Initiating Event**
- **Chronic Bacterial Infection**
- **Abnormal Mucus Clearance**
- **Neutrophil Inflammation (Proteases)**
- **Airway” Destruction and Distortion (Bronchiectasis)**

Disrupting the cycle with inhaled antibiotics

NCFBE Rates are Increasing

- Prevalence is unclear
  - >110,000 patients in the United States\(^1\)

- Increasing at a rate of ~9% annually\(^2\)

- Potential reasons for increases include
  - Increased use of chest CT scans as a diagnostic tool
  - Changes in the prevalence of diseases causing bronchiectasis
  - Increasing awareness that asthma and COPD may be closely linked with bronchiectasis

1. Weycker 2005
2. Seitz 2012
3. Quint 2016
NCFBE: Impact of *Pseudomonas Aeruginosa* (PsA)

- 3× higher mortality
- 7× higher risk of hospitalization
- Average of 1 additional exacerbation per patient per year

PsA Results In More Hospitalizations and Higher Mortality Rates Than Other Infections

Chalmers et al, AJRCCM 2014
BE with PsA Results in Worse Quality of Life than Patients with Other Severe Respiratory Diseases

SGRQ total score

Worsening QoL

Acute Pulmonary Exacerbations

- Increased cough and sputum volume
- Increased sputum purulence and viscosity
- Worsened dyspnea
- Fever
- Malaise
- Pleuritic chest pain
- Wheezing
- Hemoptysis
Why are Pulmonary Exacerbations Important?

- Median duration is 16 days
- Symptoms can persist for weeks; 16% had not recovered by 35 days
- Some patients may not return to baseline – “irreversible morbidity”
- Breathlessness is the second most common symptom of exacerbation (after cough)
- Functional ability is an independent predictor of long term mortality and exacerbation frequency

Current Clinical Practice

- No approved treatments, including for prevention of PEs
- Variability and limitations of treatment
  - Use of antibiotics for exacerbation only - 41%
  - Suppressive antibiotics - 39%: 10% aerosol, 7% rotating regimen
  - Inhaled bronchodilators - 61%
  - Inhaled steroids - 39%, systemic steroids - 13%
  - Airway clearance - 56%

Case Study

- **57 y.o. man:**
  
  Diagnosed with bronchiectasis at age 8 after a respiratory tract infection (negative tests for CF and primary ciliary dyskinesia)

- Excellent health during his 20’s and 30’s (ran 10k races and rowed at a high level).

- Presented just over 5 years ago with worsening symptoms

- *P. aeruginosa* acquired in sputum for the first time
Clinical Course

- Initially treated with sequential oral ciprofloxacin, intravenous ceftazidime and tobramycin.
- *P. aeruginosa* failed to clear from sputum
- Frequent exacerbations (up to 8 per year) requiring antibiotics
- TRIaled on long-term macrolide but exacerbations persisted
- Various off-label long term inhaled antibiotics trialed. Unable to tolerate due to worsening of respiratory symptoms when on inhaled therapy.
- Very poor quality of life
- Ultimately managed with 6-8 weekly intravenous antibiotic courses
The new European Guidelines recommend the use of inhaled antibiotics for bronchiectasis patients with frequent exacerbations and chronic infections with *Pseudomonas aeruginosa*

- Aradigm’s clinical development program focused on this patient population
Bronchiectasis Patients with Chronic Lung Infections with *P. aeruginosa* and >1 Pulmonary Exacerbation per Year Have Strikingly Higher Mortality and Morbidity

**Mortality**

- **No PA, <2 exacerbations**
- **No PA - 2 or more exacerbations**
- **PA < 2 exacerbations**
- **PA and 2 or more exacerbations**

**Exacerbations**

- **PA and 2 or more exacerbations**
- **No PA 2 or more exacerbations**
- **PA < 2 exacerbations**
- **No PA < 2 exacerbations**
Reducing the frequency of pulmonary exacerbations is the key objective of bronchiectasis therapy

- Pulmonary exacerbations have a key role in disease progression and morbidity
- Some patients may never recover from exacerbations – “irreversible morbidity”
- The major driver in clinical guidelines and clinical practice for the use of prophylactic antibiotic therapies is annual frequency of exacerbations and severity of exacerbations
- Time to first exacerbation is not used for clinical decision making, but is regarded as a surrogate of annual exacerbation frequency
- The unmet medical need in bronchiectasis is to identify a safe therapy that can reduce exacerbation frequency and severe exacerbations

# PE Endpoints in 1202 (ORBIT-4) and 1201 (ORBIT-3)

## Frequency of PEs

<table>
<thead>
<tr>
<th></th>
<th>Study 1202</th>
<th>Study 1201</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All PEs</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>HR=0.63, p=0.0006</strong></td>
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<tr>
<td><strong>Severe PEs</strong></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td><strong>RR=0.40, p=0.0031</strong></td>
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</table>

## Relative Risk

<table>
<thead>
<tr>
<th></th>
<th>Study 1202</th>
<th>Study 1201</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All PEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HR=0.63, p=0.0006</strong></td>
<td></td>
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<tr>
<td><strong>PP=0.22</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study 1201</strong></td>
<td></td>
<td></td>
<td><strong>HR=0.85, p=0.26</strong></td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td><strong>HR=0.73, p=0.0011</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Study 1202</th>
<th>Study 1201</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe PEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RR=0.80, p=0.48</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PP=0.22</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sustained antipseudomonal activity over 48 weeks and high rates of treatment completion

**Average Change in Log$_{10}$ CFUs (LS Mean)**

- **1201 Linhaliq**
- **1201 Placebo**
- **1202 Linhaliq**
- **1202 Placebo**

**Rates of completion of double-blind treatment period**

- **Study 1201**
  - Linhaliq: 86%
  - Placebo: 83%
- **Study 1202**
  - Linhaliq: 78%
  - Placebo: 81%
What are the alternatives to Linhaliq?

- There is no inhaled antibiotic available on the US market for non-CF Bronchiectasis Patients

- Off label inhaled antibiotic use (10% of patients in the United States bronchiectasis registry)
  - Lack of proven efficacy
  - Poor tolerability
  - Lack of approval means many patients cannot access to therapy
  - Compliance is poor (estimated that only 41% of patients adhere to treatment, many discontinue due to side-effects)
High Rates of Bronchospasm and other Respiratory Adverse Effects with Off-label Inhaled Antibiotics

Inhaled Tobramycin (TSI, TOBI) (Rubin, 2008)
- Barker et al. (2000): Respiratory AEs by 70% TSI vs. 51% placebo patients
- Drobnic, et al.(2005): 10% of subjects had bronchospasm while on TSI
- Bilton et al.(2006): 50% on TSI “wheeze” vs. 15% on placebo

Inhaled Gentamicin
- Murray et al. (2011):
  - 7 of the original 32 patients subsequently developed bronchospasm during the trial

Inhaled Aztreonam (Cayston, AZLI)
- Barker et al. (2014):
  - AZLI treatment did not provide significant clinical benefit
  - Adverse events leading to study drug discontinuation 22% vs 6% in AIR-BX1, 10% vs 5% in AIR-BX2
Linhaliq shows very good respiratory tolerability:
Pre-specified Adverse Effects of Special Interest (AESI) <5%

Bronchospasm reported in a very small number of patients in the Phase 3 Linhaliq clinical trials:

1.3% in the Linhaliq group and 1.0% in the placebo group
Pre-specified Adverse Events of Special Interest ≥5%: Similar Rates in Placebo and Linhaliq Groups

<table>
<thead>
<tr>
<th>Events</th>
<th>Linhaliq, %</th>
<th>Placebo, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>64.5</td>
<td>65.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>54.2</td>
<td>53.4</td>
</tr>
<tr>
<td>Wheezing</td>
<td>39.3</td>
<td>43.5</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>4.9</td>
<td>10.4</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>4.9</td>
<td>5.2</td>
</tr>
</tbody>
</table>
Efficacy and Safety Conclusions for Linhaliq

- The benefits demonstrated in the ORBIT trials are clinically meaningful to physicians and patients
- Good safety and tolerability profile, high compliance

Linhaliq could have a transformative effect on the field of bronchiectasis
NCFBE PATIENT POPULATION AND MARKET ANALYSIS

TREVOR SELL
NOVEMBER 9TH, 2017
The Weycker study is the most commonly cited source for NCFBE patient population estimates\(^{(1)}\)

### NCFBE Diagnosed Prevalence Rate by Age Group (31,122 patients with NCFBE identified in study database)\(^{(1)}\)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>18-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
<th>&gt;=75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate per 100,000</td>
<td>7</td>
<td>18</td>
<td>43</td>
<td>122</td>
<td>373</td>
<td>812</td>
</tr>
</tbody>
</table>

- Source based on claims data from Truven Health Analytics database covering a total of ~33.2M lives\(^{(1)}\)
- Academic studies have estimated prevalence growth rates between 2.0 – 8.7%\(^{(1,2,3,4)}\)
- Studies indicate the historical prevalence rate increased significantly (~8% p.a.) from 2000 – 2013\(^{(1,2)}\) driven by increased HRCT scan utilization, but may be moderated going forward as growth in HRCT usage slows\(^{(3)}\)
- Based on these estimates, 5.0% p.a. overall prevalence growth rate is projected through 2021, tapering to 2.5% by 2025, in line with demographics

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\(^{(4)}\) Sanchez-Munoz et al. PLOS ONE 2016; DOI:10.1371.
# Prevalence of NCFBE

Prevalence of NCFBE increases substantially with age and with an aging population.

## US Prevalence (2017 est.)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pop.(1)</th>
<th>Prevalence Rate(2)</th>
<th>=</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 34</td>
<td>66M</td>
<td>7 / 100K</td>
<td>=</td>
<td>4,648</td>
</tr>
<tr>
<td>35 – 44</td>
<td>41M</td>
<td>18 / 100K</td>
<td>=</td>
<td>7,354</td>
</tr>
<tr>
<td>45 – 54</td>
<td>43M</td>
<td>43 / 100K</td>
<td>=</td>
<td>18,670</td>
</tr>
<tr>
<td>55 – 64</td>
<td>42M</td>
<td>122 / 100K</td>
<td>=</td>
<td>50,713</td>
</tr>
<tr>
<td>65 – 74</td>
<td>29M</td>
<td>373 / 100K</td>
<td>=</td>
<td>108,349</td>
</tr>
<tr>
<td>&gt;=75</td>
<td>21M</td>
<td>812 / 100K</td>
<td>=</td>
<td>174,453</td>
</tr>
<tr>
<td>Total</td>
<td>243M</td>
<td>150 / 100K</td>
<td>=</td>
<td>364,187</td>
</tr>
</tbody>
</table>

## EU Prevalence (2017 est.)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pop.(1)</th>
<th>Prevalence Rate(2)</th>
<th>=</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 34</td>
<td>95M</td>
<td>7 / 100K</td>
<td>=</td>
<td>6,634</td>
</tr>
<tr>
<td>35 – 44</td>
<td>72M</td>
<td>18 / 100K</td>
<td>=</td>
<td>12,963</td>
</tr>
<tr>
<td>45 – 54</td>
<td>75M</td>
<td>43 / 100K</td>
<td>=</td>
<td>32,415</td>
</tr>
<tr>
<td>55 – 64</td>
<td>67M</td>
<td>122 / 100K</td>
<td>=</td>
<td>81,693</td>
</tr>
<tr>
<td>65 – 74</td>
<td>52M</td>
<td>373 / 100K</td>
<td>=</td>
<td>193,853</td>
</tr>
<tr>
<td>&gt;=75</td>
<td>48M</td>
<td>812 / 100K</td>
<td>=</td>
<td>388,561</td>
</tr>
<tr>
<td>Total</td>
<td>409M</td>
<td>150 / 100K</td>
<td>=</td>
<td>716,120</td>
</tr>
</tbody>
</table>

## Asia(3) (non-Japan) Prevalence (2017 est.)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pop.(1)</th>
<th>Prevalence Rate(2)</th>
<th>=</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 34</td>
<td>457M</td>
<td>7 / 100K</td>
<td>=</td>
<td>31,964</td>
</tr>
<tr>
<td>35 – 44</td>
<td>288M</td>
<td>18 / 100K</td>
<td>=</td>
<td>51,918</td>
</tr>
<tr>
<td>45 – 54</td>
<td>301M</td>
<td>43 / 100K</td>
<td>=</td>
<td>129,545</td>
</tr>
<tr>
<td>55 – 64</td>
<td>210M</td>
<td>122 / 100K</td>
<td>=</td>
<td>255,867</td>
</tr>
<tr>
<td>65 – 74</td>
<td>123M</td>
<td>373 / 100K</td>
<td>=</td>
<td>459,613</td>
</tr>
<tr>
<td>&gt;=75</td>
<td>72M</td>
<td>812 / 100K</td>
<td>=</td>
<td>587,877</td>
</tr>
<tr>
<td>Total</td>
<td>1,452M</td>
<td>150 / 100K</td>
<td>=</td>
<td>1,516,784</td>
</tr>
</tbody>
</table>

## Japan (2017 est.)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Pop.(1)</th>
<th>Prevalence Rate(2)</th>
<th>=</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 – 34</td>
<td>18M</td>
<td>7 / 100K</td>
<td>=</td>
<td>1,294</td>
</tr>
<tr>
<td>35 – 44</td>
<td>15M</td>
<td>18 / 100K</td>
<td>=</td>
<td>2,712</td>
</tr>
<tr>
<td>45 – 54</td>
<td>18M</td>
<td>43 / 100K</td>
<td>=</td>
<td>7,702</td>
</tr>
<tr>
<td>55 – 64</td>
<td>15M</td>
<td>122 / 100K</td>
<td>=</td>
<td>18,888</td>
</tr>
<tr>
<td>65 – 74</td>
<td>18M</td>
<td>373 / 100K</td>
<td>=</td>
<td>66,996</td>
</tr>
<tr>
<td>&gt;=75</td>
<td>25M</td>
<td>812 / 100K</td>
<td>=</td>
<td>202,195</td>
</tr>
<tr>
<td>Total</td>
<td>110M</td>
<td>150 / 100K</td>
<td>=</td>
<td>299,787</td>
</tr>
</tbody>
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(1) US Census Bureau, International Data Base.
(3) Includes: Australia, China, Hong Kong, Indonesia, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, Thailand.
The NCFBE patient population is expected to grow ~5.0% p.a. in the coming years as growth in diagnosis rates slows.

Growth in the prevalent population is estimated at 5.0% p.a., tapering to 2.5% post-2024(2), and is driven by:

- Growth in the underlying diagnosed prevalence rate per 100,000 people
- Population growth, particularly in the elderly population, given >75% of patients are >65 years old

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Asia-Pacific markets offer very large upside potential to US and EU market forecasts.

Prevalence of NCFBE

- **Asia-Pacific** markets present a large additional revenue opportunity.
- **ORB**IT-3 and **ORB**IT-4 Phase 3 Studies included clinical sites in key target Asian geographies including South Korea, Taiwan, Australia and New Zealand.

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PREVALENCE OF CHRONIC PA INFECTION IN NCFBE PATIENTS

The prevalence of PA infection among NCFBE patients is not well defined; however, a number of studies suggest it may range between 15 – 58%.

Academic literature¹-⁶,⁸

- Various studies have been conducted to determine the prevalence of PA infection among NCFBE patients.
- The true prevalence remains unclear, and may differ regionally driven by climate, diagnostic techniques and other factors.
- Blanchette et al. (2017) suggests a range from 15 – 58%⁷ of NCFBE patients may be chronically infected with PA.
- Finch et al. (2015) performed an extensive meta-analysis of key studies and estimated a prevalence rate of 21.4%⁸ of NCFBE patients PA infected across all studies.

Authors of academic studies note a number of potential limitations:
- Differences in classification of NCFBE as a primary vs. secondary diagnosis across studies.
- Data sets limited to local or regional populations.
- Lack of radiologic (CT) data to confirm true NCFBE diagnoses.

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⁶ Sanchez-Munoz et al. PLOS ONE 2016; DOI:10.1371.
Based on a study of inhaled medication usage in 55,076 COPD patients, Toy et al found that patient compliance was "strongly correlated with dosing frequency" (2).

Patient compliance in CF patients using TOBI (2x daily) and Cayston (3x daily) is estimated at around 50%.

Studies confirm long-term compliance of inhaled medications (including home nebulizers (3)) may range from 40 – 80% (3,4).

Studies suggest that 1x daily dosing has a significant impact on patient compliance (5):

- 13 – 26% higher compliance compared to 2x daily dosing
- 22 – 41% higher compliance compared to 3x daily dosing

Linhaiq forecast assumes 70% patient compliance, given improved dosing relative to comparable inhaled antibiotics.

(1) ORBIT-3 / ORBIT-4 Phase 3 Study Results.
Currently there are no approved agents for NCFBE, but as a reference point, inhaled antibiotics TOBI Podhaler and Cayston (approved for cystic fibrosis) were priced at an average $8,427 (WAC) per cycle, equating to $35,396 for annual treatment.

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</tr>
</thead>
<tbody>
<tr>
<td>Cayston (aztreonam)</td>
<td>Gilead</td>
<td>2010 (Dec’21)</td>
<td>PA in cystic fibrosis</td>
<td>75mg TID; 28 days on + 28 off</td>
<td>$7,992 (10% CAGR)</td>
<td>$33,566 / year</td>
<td>$174M</td>
</tr>
<tr>
<td>TOBI Podhaler (tobramycin dry powder for inhalation)</td>
<td>Novartis</td>
<td>2013 (Sep’24)</td>
<td>PA in cystic fibrosis</td>
<td>112mg BID, 28 days on + 28 off</td>
<td>$8,863 (10% CAGR)</td>
<td>$37,225 / year</td>
<td>$167M</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>$8,427</strong></td>
<td><strong>$35,396</strong></td>
<td></td>
</tr>
</tbody>
</table>

TOBI Podhaler and Cayston generated >$340M in combined global sales in 2015 in cystic fibrosis, a much smaller indication compared to NCFBE.

(2) Net cost, assumes discounts of 30% from ASP accounting for rebates and contracting.
(3) EvaluatePharma.
(4) Company 10Ks (Gilead and Novartis).
Currently available branded nebulized and dry powder antibiotics (Cayston and TOBI Podhaler) are priced at an average of $8,427.41 (per cycle) in US\(^{(1)}\)

- Ex-US geographies modeled to assume pricing set 25\% below US ($6,320.56 per cycle) based on EU orphan drug price comps\(^{(3)}\)
- Modeled forecast assumes price increases of 10\% p.a. in US through 2021, in-line with historical Cayston and TOBI Podhaler price increases\(^{(1)}\); post-2021 prices increase in-line with inflation (2\% p.a.)\(^{(2)}\)
- No price growth (0\% p.a.) assumed in EU territories based on historical Cayston price growth in EU\(^{(3)}\)
- Asia and Japan price growth modeled in-line with inflation (2\% p.a.)\(^{(2)}\)
- Modeled forecast assumes additional 30\% discounts in all geographies to allow for rebates/contracting based on average 2015 gross-to-net discounts across select comparable biopharma companies\(^{(4)}\)

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\(^{(2)}\) OECD Long-term Forecast Inflation.
\(^{(3)}\) Mycka J et al. 2015; ISPOR Orphan Drug Pricing Study.
\(^{(4)}\) Company 10Ks (Grifols S.A., Gilead, BioMarin and Novartis).
Acute pulmonary exacerbations impact quality of life and drive expensive hospital admissions

Exacerbations Drive the Health and Economic Impacts of NCFBE

- ~40% of patients experience 2+ exacerbations per year and these patients have >15% 4-year mortality\(^1\)
- Pulmonary exacerbations are a key reason for the high morbidity and mortality of the disease, and a high rate of hospitalizations
- Average cost: $30-40K+ per hospitalized event\(^2,3,4\)
  - Most exacerbations due to respiratory infections result in admission to ICU\(^2\)
  - Average ICU costs estimated between $4K - $5K per day with an average stay of 8 – 14 days\(^3\)
- Agency for Healthcare Research and Quality (AHQR)\(^4\):
  - Annual age-adjusted hospitalization rate: 16.5 per 100,000 population
  - Rate increased from 1993 to 2006: 2.45% for men, 3.0% for women
  - Women >60 had highest admission rates
- When comparing all-cause healthcare costs between PA and non-PA NCFBE patients, Blanchette et al. estimated PA-infected patients cost 87% or $31,551 more on average compared to non-PA patients\(^5\)

No specific treatment is currently approved for chronic treatment to prevent or reduce the number of pulmonary exacerbations

\(^1\) American Journal of Respiratory and Critical Care Medicine Volume 189 Number 5 | March 1 2014.
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**Investment Inflection Points**

Linhaliq™ is a first in class/best in class product candidate. Linhaliq received Orphan Drug and Qualified Infectious Disease Product (QIDP) designations with Fast Track Review for the treatment of a severe respiratory disease with unmet medical need: Non-Cystic Fibrosis Bronchiectasis (NCFBE)

### Accomplished and Near-term Milestones

<table>
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<tr>
<th>Date</th>
<th>Milestone</th>
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<tr>
<td>Sept 2017</td>
<td>▪ NDA accepted for filing with Priority Review (PDUFA date Jan 26 2018)</td>
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<tr>
<td>Q4’17/Q1’18</td>
<td>▪ Advisory Committee possible</td>
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<td>Q1/Q2’18</td>
<td>▪ Anticipated US approval, commercial launch in US</td>
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<tr>
<td>Q1’18</td>
<td>▪ Planned submission to EMA for regulatory approval</td>
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<tr>
<td>Q4’18/Q1’19</td>
<td>▪ Anticipated EU approval, commercial launch in EU</td>
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Linhalig is a proprietary combined formulation of encapsulated and un-encapsulated ciprofloxacin that is designed to be inhaled once daily using a common and easy to use nebulizer that even patients with severely impaired lung function can use.
Key Goals for Linhaliq

➢ Linhaliq was designed to treat NCFBE patients with chronic lung infections with *Pseudomonas aeruginosa* (PA) and at least 2 pulmonary exacerbations (PEs) in the prior year treated with antibiotics
  • These are the patients at the highest risk, with much higher morbidity, mortality and healthcare costs.

➢ The primary and secondary endpoints focused on the ability of Linhaliq to prevent and reduce the number of PEs – the key goals of treatment of these patients

➢ Safety, tolerability, convenience
  • Use liposomes to minimize irritation of airways and facilitate once daily dosing
US: FDA MODERNIZATION ACT

- ORBIT- 4 (ARD-3150-1202) provides substantial evidence of efficacy, met the primary and key secondary endpoints
  - ORBIT- 3 (ARD-3150-1201) and ORBIT- 2 provide supporting evidence
  - Integrated safety supports Linhaliq’s positive risk/benefit

EU: Totality of evidence including assessment of benefits of Linhaliq to reduce and prevent pulmonary exacerbations

- Focus on PEs requiring intervention with antibiotics
Time to First PE prolongation similar between 1202 and 1201

Stratified Unweighted Log rank Test

Hazard Ratio

Study 1202  p=0.032
Study 1201  p=0.97
Pooled      p=0.074
Frequency of all and severe PEs

**Stratified Negative Binomial Regression**

**All PEs**

- Study 1202: Relative Risk, p=0.0006
- Study 1201: Relative Risk, p=0.26
- Pooled: Relative Risk, p=0.0011

**Severe PEs**

- Study 1202: Relative Risk, p=0.0031
- Study 1201: Relative Risk, p=0.48
- Pooled: Relative Risk, p=0.014
Reduced Risk of PEs Requiring Intervention with Antibacterials (Moderate or Severe PEs)

Stratified Negative Binomial Regression

- Study 1202: p=0.0001
- Study 1201: p=0.10
- Pooled: p=0.0001

Risk Ratio for PEs Requiring Intervention
Patients with NCFBE are often chronically infected with *Pseudomonas aeruginosa* (PA), requiring multiple courses of oral and IV antibiotics including quinolones for treatment of pulmonary exacerbations (PEs)

- Repeated antibiotic treatment of PEs often results in ciprofloxacin resistant PA isolates from sputum

Linhaliq produces high concentrations of ciprofloxacin within the airway and minimizes systemic exposure

- Expected to be effective even against PA that are deemed to be resistant to oral and IV ciprofloxacin
1202 and 1201: Sputum and Plasma Ciprofloxacin Exposures

- *MIC ≥ 4mcg/mL is deemed to be resistant to oral and IV ciprofloxacin*
Treatment with Linhaliq reduced the number of PEs compared with the prior year in patients with resistant isolates at baseline (MIC≥ 4 mcg/mL), shifting the exacerbation profile (ORBIT-3 = 1201, ORBIT 4 =1202)
Partnership with Grifols, S.A.

GRIFOLS

Grifols (BME:GRF) is a biopharmaceutical company that develops, manufactures and distributes plasma derivative and respiratory products in the US and internationally.

Key Statistics

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<tr>
<td>Founded</td>
<td>1940</td>
</tr>
<tr>
<td>Headquarters</td>
<td>Barcelona, Spain</td>
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<tr>
<td>Employees</td>
<td>~ 15,000</td>
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<td>Strengths</td>
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<td>Significant specialty respiratory salesforce in place in both US and Europe</td>
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<td>Prolastin (for α-1 antitrypsin deficiency respiratory orphan disease) has 67% global market share and leading market share in the US</td>
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<td>10 plus years detailing Prolastin to pulmonologists</td>
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Key financials in the licensing agreement:

- The royalty rate is 12.5% on the first $300 million of annual sales for all territories and all indications, and 20% for annual sales in excess of $300 million
- $15 million in pre-approval and approval milestones remaining
- Aradigm responsible for the product supply
  - Sale to Grifols at “Cost of goods + mark-up”
  - Use US-based contract manufacturer Exelead who produced Phase 3 supplies at commercial scale
**Key Investment Highlights:**
NDA accepted for filing with Priority Review – PDUFA date Jan 26 2018

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**Aradigm is well-positioned to start generating in 2018 double digit royalty revenues from sales of Linhaliq in Non-Cystic Fibrosis Bronchiectasis (NCFBE), with potential upside from other indications**

- **Aradigm believes the NCFBE indication for Linhaliq will exceed $500MM of sales by 2021**
  - Ladenburg analysts project $1B sales by 2022, Nektar projected $750 million for their NCFBE product with Bayer

- **Important objectives achieved in Phase 3**
  - Prevention and reduction in frequency of pulmonary exacerbations
  - High persistent drug concentrations in sputum, low in blood
  - Sustained powerful antipseudomonal activity even for patients with resistant isolates
  - Good safety and tolerability

- **US Orphan Drug Designation with no existing approved therapies**

- **QIDP Designation and Fast Track received**
  - FDA priority review accompanies QIDP designation

- **Commercial Launch in US expected in Q2’18**
  - EU approval expected Q4’18/Q1’19

- **Sole competitor: Bayer’s twice daily, dry powder inhaled ciprofloxacin**
  - “Unencapsulated” inhaled antibiotics TOBI, Cayston and colistin have failed in all NCFBE trials
  - Bayer’s first Phase 3 showed efficacy with 14 day BID cycles and failed with 28 day cycles; second Phase 3 trial failed criteria agreed with FDA

- **Strong IP protection to 2031**
  - 8 patents issued in US; 41 issued patents in 37 countries outside the US

- **Linhaliq is administered once daily:**
  - Active in biofilms, uptake by macrophages
Any questions?
Oral Ciprofloxacin PK and *In Vitro* Susceptibility Breakpoint

* MIC ≥ 4mcg/mL is deemed to be resistant to oral and IV ciprofloxacin
Oral Ciprofloxacin PK and *In Vitro* Susceptibility Breakpoint

* MIC ≥ 4mcg/mL is deemed to be resistant to oral and IV ciprofloxacin