Business Assessment of Brensocatib

June 2020

insmed

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Phase 2 Randomized, Double-Blind, Placebo-Controlled Trial of the DPP1 Inhibitor Brensocatib (INS1007) in Patients With Bronchiectasis: The WILLOW Study

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Ninewells Hospital and Medical School, Dundee, UK
Disclosures to Audience

For the three years preceding this presentation:

**Financial Relationships With Relevant Commercial Interests:**

- **Company name:** Insmed Incorporated
- **Type of relationship:** Consultancy and grant funding
Neutrophilic inflammation is key to the pathogenesis of multiple inflammatory diseases

**Neurological**
- Alzheimer's disease
- Stroke

**Lung diseases**
- Bronchiectasis
- COPD
- Severe asthma
- Cystic fibrosis
- Pneumonia
- COVID-19

**Cardiovascular**
- Ischaemic heart disease
- Peripheral vascular disease

**Gastrointestinal disease**
- Inflammatory bowel disease

**Renal disease**
- Chronic renal failure
- Lupus nephritis

**Joint disease**
- Rheumatoid arthritis

**Systemic disease**
- Cancer

**Phagocytosis**

**Bacteria**

**Degranulation**

**NET release**
Clear evidence that neutrophil elastase is involved in bronchiectasis and COPD pathogenesis

Excessive release of neutrophil serine proteases overwhelms natural defences

Key features of disease such as emphysema can be recreated in animal models through elastase administration

Increased infections may be related to disabled antibacterial defence through serine proteases
Neutrophil extracellular traps
Role of Neutrophilic Inflammation in Bronchiectasis

- Bronchiectasis is characterized by frequent exacerbations related to uncontrolled neutrophilic inflammation
- Proinflammatory neutrophil serine proteases (NSPs), including neutrophil elastase, are increased in sputum of patients with bronchiectasis
- Elevated NSPs are associated with exacerbations and poor quality of life

Dipeptidyl Peptidase 1 (DPP1; cathepsin C)

- DPP1 is a lysosomal cysteine protease responsible for activation of neutrophil serine proteases (NSPs) in the bone marrow during the neutrophil maturation cycle.

Brensocatib (INS1007)

- Brensocatib is an oral small molecule inhibitor of DPP1 hypothesized to interrupt the neutrophilic inflammatory processes in the lung
  - Preclinical studies have demonstrated reduction of neutrophil elastase (NE), proteinase 3, cathepsin G
  - Phase 1 studies have demonstrated dose-dependent reduction of NE activity in healthy subjects
- Under investigation for the reduction of exacerbations in patients with non-cystic fibrosis bronchiectasis

DPP1, dipeptidyl peptidase 1
Design of the WILLOW Study (NCT03218917)

- **Primary objective:**
  - Time to first exacerbation over 24 weeks in patients with non–cystic fibrosis bronchiectasis

- **Secondary objectives:**
  - Pulmonary exacerbation rate over 24 weeks
  - Change in QOL-Bronchiectasis questionnaire respiratory symptoms domain over 24 weeks
  - Change in post-bronchodilator ppFEV₁ over 24 weeks
  - Change in sputum NE activity from pretreatment to on-treatment

EOS, end of study; EOT, end of treatment; NE, neutrophil elastase; ppFEV₁, percent predicted forced expiratory volume in 1 second; QD, once daily.
WILLOW Eligibility Criteria

Major inclusion criteria

• Adults (18 to 85 years of age)
• BMI > 18.5 at screening
• Clinical history consistent with non-CF bronchiectasis
• Past chest CT demonstrating bronchiectasis
• At least 2 documented bronchiectasis exacerbations in the past 12 months
• Able to provide sputum sample during screening visit
• Sputum color of mucoid purulent or purulent at screening

Major exclusion criteria

• Underlying diseases:
  – Bronchiectasis due to CF, hypogammaglobulinemia, common variable immunodeficiency, or α1-antitrypsin deficiency
  – Primary diagnosis of COPD or asthma
  – Currently treatment for NTM, ABPA, or TB
  – Clinical diagnosis of Papillon-Lefevre Syndrome, current or recent (< 5 years) skin conditions affecting palms and soles, history of psoriasis or lichen planus, recurrent severe bacterial skin infections, history of recurring gingivitis or periodontitis

BMI, body mass index; CF, cystic fibrosis; CT, computed tomography; ABPA, allergic bronchopulmonary aspergillosis; COPD, chronic obstructive pulmonary disease; NTM, nontuberculous mycobacteria; TB, tuberculosis.
WILLOW Study Flow

416 Patients were screened
- 160 Patients were excluded
  - 256 Patients were eligible for randomization

87 Were randomized to placebo
- 13 Discontinued the study
  - 2 Adverse event
  - 10 Withdraw consent
  - 1 Physician decision
- 74 Completed the study

82 Were randomized to brensocatib 10 mg
- 6 Discontinued the study
  - 3 Adverse event
  - 2 Withdraw consent
  - 1 Lost to follow-up
- 76 Completed the study

87 Were randomized to brensocatib 25 mg
- 12 Discontinued the study
  - 3 Adverse event
  - 4 Withdraw consent
  - 1 Physician decision
  - 1 Nonadherent to study drug
  - 1 Death\(^a\)
  - 2 Other reason
- 75 Completed the study

\(^a\) Death attributed to bronchiectasis progression.
Baseline Demographics and Characteristics

Similar baseline characteristics across treatment groups, representative of a typical bronchiectasis population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 87)</th>
<th>Brensocatib 10 mg (n = 82)</th>
<th>Brensocatib 25 mg (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD), yr</td>
<td>64.0 (11.86)</td>
<td>64.6 (12.42)</td>
<td>63.7 (12.67)</td>
</tr>
<tr>
<td>≥ 65 years, no. (%)</td>
<td>54 (62.1)</td>
<td>48 (58.5)</td>
<td>48 (55.2)</td>
</tr>
<tr>
<td>≥ 75 years, no. (%)</td>
<td>14 (16.1)</td>
<td>20 (24.4)</td>
<td>14 (16.1)</td>
</tr>
<tr>
<td>Female, no. (%)</td>
<td>55 (63.2)</td>
<td>57 (69.5)</td>
<td>62 (71.3)</td>
</tr>
<tr>
<td>White, no. (%)</td>
<td>71 (81.6)</td>
<td>76 (92.7)</td>
<td>78 (89.7)</td>
</tr>
<tr>
<td>History of COPD, no. (%)</td>
<td>17 (19.5)</td>
<td>12 (14.6)</td>
<td>13 (14.9)</td>
</tr>
<tr>
<td>History of asthma, no. (%)</td>
<td>25 (28.7)</td>
<td>18 (22.0)</td>
<td>21 (24.1)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa positive, no. (%)(ab)</td>
<td>29 (33.3)</td>
<td>27 (32.9)</td>
<td>33 (37.9)</td>
</tr>
<tr>
<td>Chronic macrolide use, no. (%)(a)</td>
<td>14 (16.1)</td>
<td>10 (12.2)</td>
<td>16 (18.4)</td>
</tr>
<tr>
<td>Median Bronchiectasis Severity Index (range)(c)</td>
<td>7.0 (0 - 19)</td>
<td>8.0 (1 - 21)</td>
<td>8.0 (0 - 19)</td>
</tr>
<tr>
<td>≥3 Exacerbations in prior 12 months, no. (%)</td>
<td>25 (28.7)</td>
<td>23 (28.0)</td>
<td>36 (41.4)</td>
</tr>
<tr>
<td>Hospitalized for exacerbation in prior 24 months, no. (%)</td>
<td>30 (34.5)</td>
<td>31 (37.8)</td>
<td>31 (35.6)</td>
</tr>
<tr>
<td>Mean FEV(_1), % predicted (SD)</td>
<td>67.3 (23.9)</td>
<td>65.9 (23.9)</td>
<td>70.0 (23.2)</td>
</tr>
<tr>
<td>Neutrophil elastase in sputum, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLQ</td>
<td>18 (20.7)</td>
<td>23 (28.0)</td>
<td>21 (24.1)</td>
</tr>
<tr>
<td>LLQ to &lt; 20 µg/mL</td>
<td>42 (48.3)</td>
<td>28 (34.1)</td>
<td>36 (41.4)</td>
</tr>
<tr>
<td>≥20 µg/mL</td>
<td>24 (27.6)</td>
<td>31 (37.8)</td>
<td>29 (33.3)</td>
</tr>
</tbody>
</table>

\(a\) Stratification criterion, \(b\) Positive culture at the time of randomization, \(c\) Disease severity classified by validated Bronchiectasis Severity Index. BLQ, below the limit of quantification; COPD, chronic obstructive pulmonary disease; LLQ, lower limit of quantification.
Primary Endpoint: Time to First Bronchiectasis Exacerbation

- Significantly longer time to first exacerbation with brensocatib vs placebo
  - Brensocatib 10 mg: HR, 0.58 (95% CI, 0.35-0.95); P = 0.029\(^\text{a}\)
  - Brensocatib 25 mg: HR, 0.62 (95% CI, 0.38-0.99); P = 0.046\(^\text{b}\)

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Chalmers J, Brensocatib in NCFBE: The WILLOW Study

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\(^{a}\) Stratified log-rank test, P value vs placebo; \(^{b}\) Cox proportional hazard analysis, P value vs placebo.
Bronchiectasis Exacerbation Rate Over 24 Weeks of Treatment

Patients With Exacerbations

- Placebo: 48.3%
- Brensocatib 10 mg: 31.7%, P = 0.033\textsuperscript{a}
- Brensocatib 25 mg: 33.3%, P = 0.038\textsuperscript{a}

Annualized Exacerbation Rates

- Placebo: 1.37 (95% CI, 1.02-1.84), \textsuperscript{a}P = 0.033
- Brensocatib 10 mg: 0.88 (95% CI, 0.61-1.26), \textsuperscript{b}P = 0.041
- Brensocatib 25 mg: 1.03 (95% CI, 0.74-1.42), \textsuperscript{b}P = 0.167

\textsuperscript{a} Cochran-Mantel-Haenszel test, P values vs placebo; \textsuperscript{b} Negative binomial model, P values for incidence rate ratio vs placebo.
Change in Sputum Neutrophil Elastase Concentrations

- Least squares means change from baseline to Week 24, P values vs placebo

*Chalmers J, Brensocatib in NCFBE: The WILLOW Study*
Association of Brensocatib Exposure, Achievement of Sputum Neutrophil Elastase Below the Limit of Quantification, and Time to First Exacerbation

- Patients treated with brensocatib (pooled data) who achieved sputum NE BLQ post-baseline had a lower incidence of bronchiectasis exacerbations

HR, 0.28 (95%CI, 0.16-0.50); P < 0.0001a

*Log-rank test applied post hoc to the time-to-event data.

BLQ, below the limit of quantification; HR, hazard ratio; NE, neutrophil elastase.
Chalmers J, Brensocatib in NCFBE: The WILLOW Study

Change in Post-Bronchodilator ppFEV₁ at Week 24

- Placebo-treated patients showed a numerically larger lung function decline than brensocatib-treated patients.

Analysis of Covariance, least squares (LS) mean difference between groups was not significant ppFEV₁, percent predicted forced expiratory volume in 1 second.
## Safety Summary

<table>
<thead>
<tr>
<th>Safety Parameter</th>
<th>Placebo (n = 85)</th>
<th>Brensocatib 10 mg (n = 81)</th>
<th>Brensocatib 25 mg (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE resulting in study discontinuation</td>
<td>3 (3.5)</td>
<td>3 (3.7)</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>TEAE resulting in treatment discontinuation</td>
<td>9 (10.6)</td>
<td>6 (7.4)</td>
<td>6 (6.7)</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>19 (22.4)</td>
<td>11 (13.6)</td>
<td>10 (11.2)</td>
</tr>
<tr>
<td>Serious TEAEs in ≥ 3% of patients in any group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infective exacerbation of bronchiectasis</td>
<td>9 (10.6)</td>
<td>5 (6.2)</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3 (3.5)</td>
<td>0</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>67 (78.8)</td>
<td>75 (92.6)</td>
<td>74 (83.1)</td>
</tr>
<tr>
<td>TEAEs in ≥ 10% of patients in any group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>10 (11.8)</td>
<td>15 (18.5)</td>
<td>12 (13.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (3.5)</td>
<td>8 (9.9)</td>
<td>12 (13.5)</td>
</tr>
<tr>
<td>Sputum increased</td>
<td>6 (7.1)</td>
<td>9 (11.1)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (2.4)</td>
<td>3 (3.7)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Infective exacerbation of bronchiectasis</td>
<td>9 (10.6)</td>
<td>5 (6.2)</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (10.6)</td>
<td>5 (6.2)</td>
<td>3 (3.4)</td>
</tr>
</tbody>
</table>

TEAE, treatment-emergent adverse event.

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Chalmers J, Brensocatib in NCFBE: The WILLOW Study

ATS 2020 | VIRTUAL
### Adverse Events of Special Interest

<table>
<thead>
<tr>
<th>no. (%)</th>
<th>Placebo (n = 85)</th>
<th>Brensocatib 10 mg (n = 81)</th>
<th>Brensocatib 25 mg (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEs of special interest</td>
<td>23 (27.1)</td>
<td>27 (33.3)</td>
<td>35 (39.3)</td>
</tr>
<tr>
<td>Skin(^{a})</td>
<td>10 (11.8)</td>
<td>12 (14.8)</td>
<td>21 (23.6)</td>
</tr>
<tr>
<td>Dental</td>
<td>3 (3.5)</td>
<td>13 (16.0)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Infection</td>
<td>15 (17.6)</td>
<td>11 (13.6)</td>
<td>15 (16.9)</td>
</tr>
<tr>
<td>Change in periodontal pocket depth ≥ 2 mm(^{b})</td>
<td>9 (13.0)</td>
<td>12 (16.9)</td>
<td>14 (19.2)</td>
</tr>
<tr>
<td>Change in periodontal pocket depth ≥ 2 mm and ≥ 5 mm absolute depth(^{b})</td>
<td>8 (11.6)</td>
<td>8 (11.3)</td>
<td>9 (12.3)</td>
</tr>
</tbody>
</table>

\(^{a}\) Includes hyperkeratosis:
- Placebo (n = 1), brensocatib 10 mg (n = 3), brensocatib 25 mg (n = 1)
- Resolved or improved at the end of the study
- No interruption of study drug

\(^{b}\) Change in 3 or more areas, assessed at 3 dental visits. Includes patients with both a baseline and week 24 dental evaluation (placebo, n = 69; brensocatib 10 mg, n = 71; brensocatib 25 mg, n = 73)
Conclusions

• Brensocatib, at doses of 10 and 25 mg, demonstrated a significant effect in prolonging time to first exacerbation; in addition, a significant reduction in the annualized rate of exacerbations was observed with 10 mg

• A dose dependent reduction in neutrophil elastase levels in sputum was observed, which supports the mechanism of action of brensocatib reducing neutrophil serine protease activation

• Both doses of brensocatib were well tolerated; overall safety profile of both doses were comparable with that of placebo

• If these results are confirmed in a phase 3 trial, brensocatib may represent a novel nonantibiotic treatment option for prevention of exacerbations
Vicious Cycle of Bronchiectasis and Opportunities for Intervention

NCFBE, non-cystic fibrosis bronchiectasis
Targeting neutrophilic inflammation

Unmet need across multiple diseases for a neutrophil targeted therapeutic

Transformative potential in lung disease, and beyond

- **Lung diseases**
  - Bronchiectasis
  - COPD
  - Severe asthma
  - Cystic fibrosis
  - Pneumonia
  - COVID-19

- **Cardiovascular**
  - Ischaemic heart disease
  - Peripheral vascular disease

- **Renal disease**
  - Chronic renal failure
  - Lupus nephritis

- **Gastrointestinal disease**
  - Inflammatory bowel disease

- **Systemic disease**
  - Cancer

- **Joint disease**
  - Rheumatoid arthritis

Chalmers J, Brensocatib in NCFBE: The WILLOW Study
Investigator-Initiated STOP-COVID19 Study

Brensocatib (INS1007) represents a first-in-class MOA (DPP1 inhibition) for a broad range of neutrophil-driven inflammatory diseases

- Works by inhibiting the enzyme that activates neutrophil serine proteases, which, when activated excessively, can cause tissue destruction and inflammation
- Positive Phase 2 data in non-cystic fibrosis bronchiectasis (NCFBE), a disease with no approved therapies
- Granted Breakthrough Therapy Designation by FDA in patients with NCFBE
- Global Phase 3 program in bronchiectasis begins 2H 2020

Brensocatib now being evaluated in investigator-initiated STOP-COVID19 study

- Double-blind, placebo-controlled trial in hospitalized patients with COVID-19
- Led by Professor James Chalmers, University of Dundee (Scotland) (lead investigator of Phase 2 WILLOW study in bronchiectasis)
- Up to 300 patients to be enrolled at 10 sites in the UK
- Hypothesis: By blocking damaging neutrophil proteases, brensocatib may reduce the progression to acute respiratory distress syndrome (ARDS)—a severe outcome of COVID-19 associated with high mortality
- Primary endpoint: Clinical improvement on an ordinal scale defined by the WHO
- Sample-size reassessment Q3 2020; final data late 2020/early 2021

PCR-confirmed COVID-19 infection

- Brensocatib 25 mg daily
- Placebo

Clinical status at day 29 (primary endpoint)
- Clinical status during hospitalization
  - National Early Warning Score
  - Oxygenation
  - Mechanical ventilation
  - Duration of Hospitalization
  - Mortality

Exploratory endpoints
Acknowledgments

• We thank the patients and their families for their support and participation, and the study investigators, study coordinators, and support staff across all sites.

• Financial support for this study was provided by Insmed Incorporated.

• Medical writing support was provided by Meditech Media, Ltd (Hamilton, NJ, USA), funded by Insmed Incorporated.
Brensocatib: Pipeline in a product

1. First-in-class neutrophil immunomodulator with potential in a broad range of diseases

2. Lead indication, bronchiectasis, represents significant global opportunity

3. Insmed is uniquely positioned to address current unmet need
Bronchiectasis is only the beginning of what brensocatib may offer to patients

<table>
<thead>
<tr>
<th>Series Unmet Need Conditions</th>
</tr>
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<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
</tr>
<tr>
<td>Granulomatosis with Polyangiitis¹</td>
</tr>
</tbody>
</table>

* AstraZeneca has exercised its option to develop brensocatib in COPD & asthma through Phase 2b. Further development subject to agreement on commercial terms with Insmed.

1: Therapeutic areas with positive in vitro or in vivo data for brensocatib

<table>
<thead>
<tr>
<th>Larger Markets</th>
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<tbody>
<tr>
<td>Indication</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease¹</td>
</tr>
<tr>
<td>Lupus¹</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>COPD*</td>
</tr>
<tr>
<td>Asthma*</td>
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</table>
Preclinical data support potential of brensocatib in Lupus Nephritis, GPA, and IBD

**Lupus Nephritis**
- **Kidney Damage**
- **Kidney Function**

**Inflammatory Bowel Disease (IBD)**
- **Intestinal Damage**
- **Intestinal Function**

**Granulomatosis with Polyangiitis (GPA)**
- Unstained & Isotype Controls
- PR3 Surface Expression (MFI)

- INS1007 also delayed the progression to severe proteinuria, and decreased renal histopathological sum scores and inflammatory cell infiltration into the kidney.
- INS1007 also reduced body weight loss and improved survival rate.
Bronchiectasis patients suffer from chronic respiratory symptoms and lung damage that leads to increased morbidity and mortality.

**US Patient Demographics**

- Mean age: 64
- 79% female
- 63% have NTM infection
- Average approximately 2 exacerbations/year

>60% of patients have Moderate to Severe bronchiectasis

Willow study population included patients with >= 2 exacerbations in 12 months prior to enrollment.

2: Internal Market Research (INS1007 NCFBE Opportunity Assessment – Trinity Jan 2018, Swoop Claims analysis)
FDA recognizes the severity of this disease and degree of unmet need with Breakthrough Therapy designation for brensocatib in non-CF bronchiectasis (NCFBE)

**FDA Breakthrough Therapy designation**

- Intended to treat a serious or life-threatening disease
- Clinical evidence that the drug may provide substantial improvement over existing therapies
- Provides eligibility for Rolling and Priority Review, if relevant criteria are met
- Provides enhanced dialogue with the Agency

MAC= *Mycobacterium avium* complex; IPF=Idiopathic pulmonary fibrosis.
Bronchiectasis is a globally prevalent disease, preliminary data suggest significant need across regions.

- **U.S.**
  - 340K - 520K total diagnosed BE patients*

- **EU5†**
  - 350K - 500K total diagnosed BE patients**

- **Asia-Pacific**
  - ~1M to 5M Total diagnosed BE patients

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*Weycker, et al. Prevalence and incidence of NCFBE among US adults in 2013. Chronic Respiratory Disease. 2017; **Estimates suggest broadly similar per capita prevalence in EU5 as in US; †Asia-Pacific rates 3X to ~10X higher than those in the US; Zhou, YM et al. The prevalence and risk factors of BE in residents aged 40 years old and above in seven cities in China. 2013 †EU5 comprised of France, Germany, Italy, Spain and the United Kingdom.
Current prevalence estimates may underestimate global patient population, given underdiagnosis of bronchiectasis

Between 650,000 to 9 million COPD patients in the US (4%-54%) may also have bronchiectasis

Between 450,000 to 675,000 asthma patients in the US (2%-3%) may also have bronchiectasis

COPD and asthma: Large diagnosed populations exist globally

- **U.S.**
  - 16.5M total diagnosed COPD patients*
  - 22.5M total diagnosed asthma patients*

- **EU5†**
  - 25M total diagnosed COPD patients**
  - 15M total diagnosed asthma patients**

- **China**
  - 161M total diagnosed COPD patients†
  - 49M total diagnosed asthma patients

- **Japan**
  - 12M total diagnosed COPD patients†
  - 3M total diagnosed asthma patients

† EU5 comprised of France, Germany, Italy, Spain and the United Kingdom
Synergy with current US commercial business leverages deeply-held insights, relationships and access

78% of highest-volume BE treaters are current ARIKAYCE called upon universe\(^1\)

High degree of overlap in physicians treating NTM and bronchiectasis (BE)

Modest increase in salesforce would allow us to reach 70% of BE patient opportunity

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\(^1\): 78% of top decile pulmonologists who treat bronchiectasis are T1/T2 ARIKAYCE targets
Insmed is well positioned to support a successful global launch in bronchiectasis

- Proven US launch capabilities with ARIKAYCE®
- Geographic and target HCP overlap with current US Sales structure
- Experience with patient finding and activation
- EU/Japan teams mobilized for launch success
- Advocacy and patient support
Summary

1. The WILLOW study shows potential for brensocatib in bronchiectasis as a Breakthrough Therapy

2. Insmed is positioned for commercial success with brensocatib in bronchiectasis

3. Tremendous global potential for brensocatib beyond bronchiectasis
Thank You