Lessons Learned from Completed NTM Lung Disease Trials & Implications for Future Trials

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Chief Product Strategy Officer
Insmed Incorporated

Development of Antibacterial Drugs for the Treatment of Nontuberculous Mycobacterial Disease
FDA Public Workshop, April 8 2019

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<table>
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Insmed’s NTM Lung Disease Trials
Three Studies of ALIS in Patients with NTM Lung Disease

Supportive Phase 2

Study 112
Randomized, double-blind, placebo-controlled
ALIS 590 mg QD + Background Regimen vs Placebo + Background Regimen

Pivotal Phase 3

Study 212
Randomized controlled open-label
ALIS 590 mg QD + Background Regimen vs Background Regimen Alone

Supportive Phase 3

Study 312
Open-label extension for Study 212 non-converters
ALIS 590 mg QD + Background Regimen

ALIS, amikacin liposome inhalation suspension
Study 112 (Ph 2): Randomized, Double-Blind, Placebo-Controlled Study in Refractory NTM Lung Disease

Double-Blind (84 days)

- ALIS + Background Regimen
- Placebo + Background Regimen

Open-Label (84 days)

- ALIS + Background Regimen
- ALIS + Background Regimen

All Patients 12 Month Follow-up

Day 84
Primary and Secondary Endpoint Assessments

Day 168
Primary and Secondary Variable Assessments

ALIS, amikacin liposome inhalation suspension
Study 212: Randomized, Open-Label, Multicenter Study of ALIS + Background Regimen

Primary Endpoint
Negative sputum for 3 consecutive months

Randomization (2:1)
Adults with MAC NTM lung disease failing ≥ 6 months guideline-based treatment

By Month 6
ALIS + Background Regimen
Background Regimen Alone

Non-converters exit into Study 312

12 months following first of 3 consecutive negative sputum cultures
ALIS + Background Regimen Patients who Achieved Culture Conversion
Background Regimen Alone Patients who Achieved Culture Conversion

Off-treatment 12 months
Off All MAC Treatments

Durability Endpoint
Negative culture at 3 months off all MAC treatment

ALIS, amikacin liposome inhalation suspension; MAC, *Mycobacterium avium* complex
Study 212: Primary Endpoint - Higher Proportion of ALIS Patients Achieved Culture Conversion

Proportion of Patients Achieving Culture Conversion by Month 6

- ALIS + Background Regimen (N=224): 29.0%
- Background Regimen Alone (N=112): 8.9%

LS Mean Difference: 20.1%
p < 0.0001

ALIS, amikacin liposome inhalation suspension
# Most common Adverse Events in Study 212

## Study 212: Most Common AEs (ALIS + Background Regimen, ≥ 10%)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ALIS + Background Regimen (N=223)</th>
<th>Multidrug Background Alone (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphonia</td>
<td>47%</td>
<td>1%</td>
</tr>
<tr>
<td>Cough</td>
<td>39%</td>
<td>17%</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>29%</td>
<td>11%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>17%</td>
<td>10%</td>
</tr>
<tr>
<td>Upper airway irritation</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>17%</td>
<td>8%</td>
</tr>
<tr>
<td>Fatigue and asthenia</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Exacerbation of underlying pulmonary disease</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
<td>5%</td>
</tr>
</tbody>
</table>

ALIS, amikacin liposome inhalation suspension
Culture Conversion at Month 6 Predicts Durable Conversion
Study 212: Randomized, Open-Label, Multicenter Study of ALIS + Background Regimen

**Primary Endpoint**
Negative sputum for 3 consecutive months

**Randomization (2:1)**

- Adults with MAC NTM lung disease failing ≥ 6 months guideline-based treatment

**By Month 6**
- ALIS + Background Regimen
- Background Regimen Alone

**Non-converters exit into Study 312**

**12 months following first of 3 consecutive negative sputum cultures**
- ALIS + Background Regimen Patients who Achieved Culture Conversion
- Background Regimen Alone Patients who Achieved Culture Conversion

**Off-treatment 12 months**
- Off All MAC Treatments

**Durability Endpoint**
Negative culture at 3 months off all MAC treatment

ALIS, amikacin liposome inhalation suspension; MAC, *Mycobacterium avium* complex
Study 212 Interim Data: Month 6 Results Predict for Durable Culture Conversion

Proportion of Patients with Durable Conversion
3 Months After Stopping all MAC Treatment

*Data as of April 2018 in patients with samples

Data on File. Insmed Incorporated.
ALIS, amikacin liposome inhalation suspension; MAC, Mycobacterium avium complex
Heterogeneous Study Population, Even Among Refractory Patients, Introduces Noise
**Study 212: Number of Drugs and Drug Class in Regimen at Baseline**

<table>
<thead>
<tr>
<th>Number of drugs in regimen</th>
<th>ALIS + Background Regimen Total (N=223)</th>
<th>Background Regimen Alone Total (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>2</td>
<td>39 (18)</td>
<td>14 (13)</td>
</tr>
<tr>
<td>3</td>
<td>148 (66)</td>
<td>84 (75)</td>
</tr>
<tr>
<td>4+</td>
<td>34 (15)</td>
<td>11 (10)</td>
</tr>
</tbody>
</table>

**Drug class**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>ALIS + Background Regimen Total (N=223)</th>
<th>Background Regimen Alone Total (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>184 (83)</td>
<td>85 (76)</td>
</tr>
<tr>
<td>Macrolide</td>
<td>207 (93)</td>
<td>101 (91)</td>
</tr>
<tr>
<td>Rifamycin</td>
<td>191 (86)</td>
<td>94 (84)</td>
</tr>
<tr>
<td>Other</td>
<td>69 (31)</td>
<td>39 (35)</td>
</tr>
</tbody>
</table>

In drug combinations, ‘Other’ may include medications deemed to be a component of background regimen by the investigator.
## Study 212: Combinations of Background Regimen at Baseline

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>ALIS + Background Regimen Total (N=223)</th>
<th>Background Regimen Alone Total (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/M/R/O</td>
<td>30 (14)</td>
<td>8 (7)</td>
</tr>
<tr>
<td>E/M/R</td>
<td>123 (55)</td>
<td>61 (55)</td>
</tr>
<tr>
<td>E/M/O</td>
<td>6 (3)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>E/M</td>
<td>13 (6)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>E/R/O</td>
<td>8 (4)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>E/R</td>
<td>3 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>E/O</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>M/R/O</td>
<td>13 (6)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>M/R</td>
<td>13 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>M/O</td>
<td>9 (4)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>R/O</td>
<td>1 (0.4)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>O</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

In drug combinations, letter ‘E’ stands for Ethambutol, ‘M’ for macrolide class, ‘R’ for rifamycin class, and ‘O’ for other which may include medications deemed to be a component of background regimen by the investigator.
## Study 212: Duration of NTM Diagnosis Prior to Baseline (Years)

**Years**

<table>
<thead>
<tr>
<th></th>
<th>ALIS + Background Regimen (N=223)</th>
<th>Background Regimen Alone (N=112)</th>
</tr>
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<tbody>
<tr>
<td><strong>n</strong></td>
<td>221</td>
<td>112</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>6.18</td>
<td>4.54</td>
</tr>
<tr>
<td><strong>Standard deviation</strong></td>
<td>5.525</td>
<td>3.858</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>4.45</td>
<td>3.26</td>
</tr>
<tr>
<td><strong>Minimum</strong></td>
<td>0.0*</td>
<td>0.0*</td>
</tr>
<tr>
<td><strong>Maximum</strong></td>
<td>32.5</td>
<td>20.3</td>
</tr>
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*6 subjects reported unknown NTM diagnosis date; all subjects reported at least 6 months of prior multidrug treatment.

**ALIS**, amikacin liposome inhalation suspension
Baseline SGRQ Stratified by Quartiles

Study 212

SGRQ total score

SGRQ symptom score

Data on File. Insmed Incorporated
SGRQ, Saint George's Respiratory Questionnaire
Baseline QoL-B Respiratory Symptom Scores

Study 112

Data on File. Insmed Incorporated
QoL-B, The Quality of Life-Bronchiectasis
Very large range of baseline 6-Minute Walk Distance, ranging from severely impaired (<200m) to values seen in healthy subjects (>550m)
Six-Minute Walk Test Not a Reliable Endpoint for NTM Lung Disease Trials
Study 112: 6-Minute Walk Test Distance (Exploratory Endpoint)

Mean distance walked in the 6-minute-walk test (last observation carried forward; modified ITT population).

Study 212: Secondary Endpoint Change from Baseline in 6MWT at Month 6

LS Mean Change from Baseline in 6MWT Distance Meters (SE)

LS Mean Difference: -3.0m
p = 0.7394

ALIS + Multidrug Regimen (N=224)
Multidrug Regimen Alone (N=112)

6MWT = 6-minute walk test

ALIS, amikacin liposome inhalation suspension
6-Minute Walk Test Distance: Baseline and Change from Baseline to Month 6

Data on File. Insmed Incorporated
CFB, Change From Baseline
Other Potential Challenges with the 6MWT

• Implementation at study sites
• Influence of underlying lung disease
  - Underlying structural lung disease may contribute to exercise impairment
  - Status of underlying lung disease (e.g. COPD, bronchiectasis) may vary during the course of the trial
• Potential blunting of effect size in a refractory population if benefit is present only in culture converters
• Physiologic benefit may occur later in the course of treatment, or following completion of treatment
Drug Tolerability Issues May Confound Assessment of Clinical Benefit During Treatment
Tolerability of Multidrug NTM Lung Disease Regimens

- Multidrug NTM lung disease regimens are often poorly tolerated
- Adverse effects of multidrug regimens may impact patient quality of life
- Nevertheless, the safety and tolerability profile of NTM lung disease regimens are accepted in order to ameliorate the disease or achieve microbiologic cure
Study 212: Achievement of MID (> -4 Unit Change) for SGRQ scores

Adults with Refractory MAC Lung Disease

Data on File. Insmed Incorporated.
ALIS, amikacin liposome inhalation suspension; MAC, *Mycobacterium avium* complex; SGRQ, Saint George’s Respiratory Questionnaire; MID, minimally important difference; EOT, end of treatment
Study 112: Mean QoL-B Respiratory Symptom Scores

End of Treatment (Day 168) and 28 Days Later (Day 196)

Data on File. Insmed Incorporated.
ALIS, amikacin liposome inhalation suspension; QoL-B, Quality of Life-Bronchiectasis
Timing of Patient Reported Outcome Assessments May be Important

• Similar to the existing drugs, investigational drugs may be associated with certain tolerability issues

• Tolerability issues may impact Patient Reported Outcome scores during treatment

• If the goal is to understand the ultimate clinical benefit of an investigational drug, Patient Reported Outcome assessment following completion of therapy may be more relevant
## Lessons Learned

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Thank You