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

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

# Outline

| | |
|---|---|
| 1 | Insmed’s NTM Lung Disease Trials |
| 2 | Culture Conversion at Month 6 Predicts Durable Conversion |
| 3 | Heterogeneous Study Population, Even Among Refractory Patients, Introduces Noise |
| 4 | Six-Minute Walk Test Is Not a Reliable Endpoint for NTM Lung Disease Trials |
| 5 | Drug Tolerability Issues May Confound Assessment of Clinical Benefit During Treatment |

# 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**

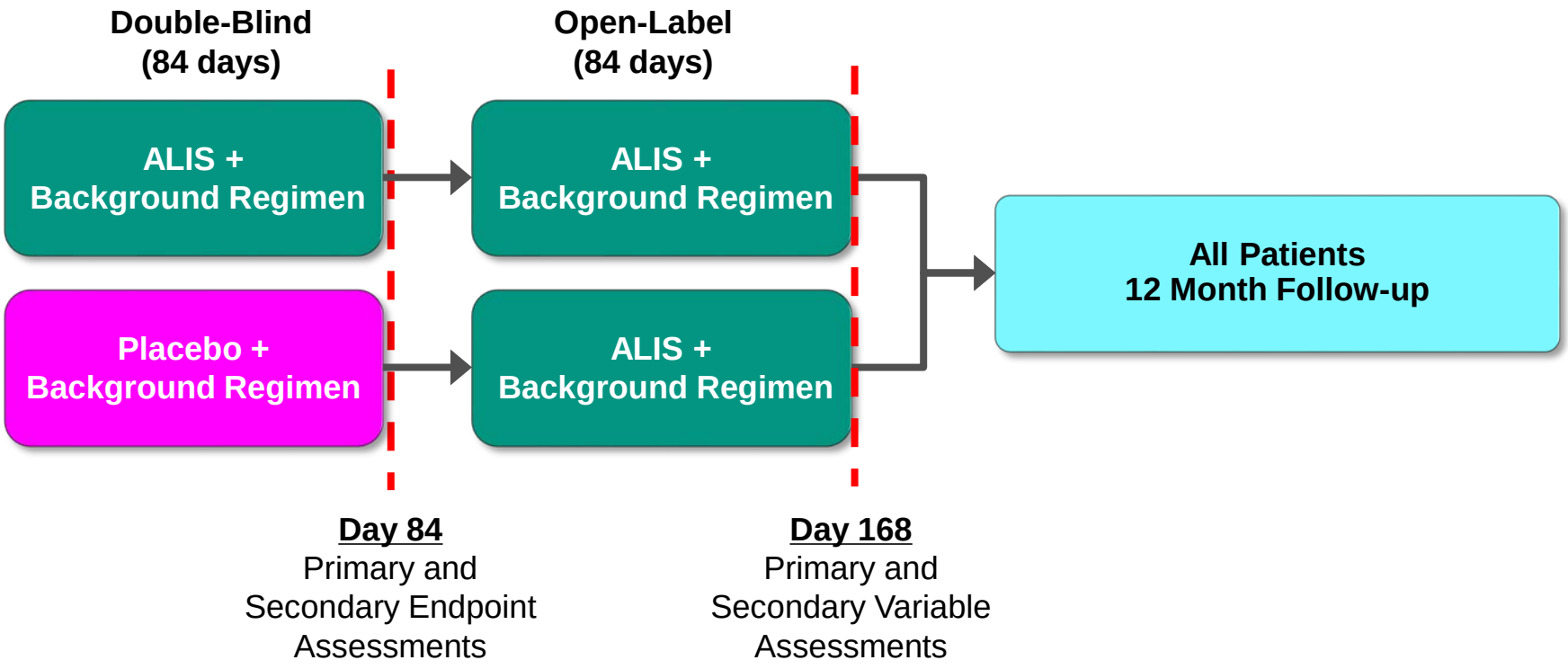
**Study 312**

**Open-label extension for Study 212 non-converters**

**ALIS 590 mg QD + Background Regimen**

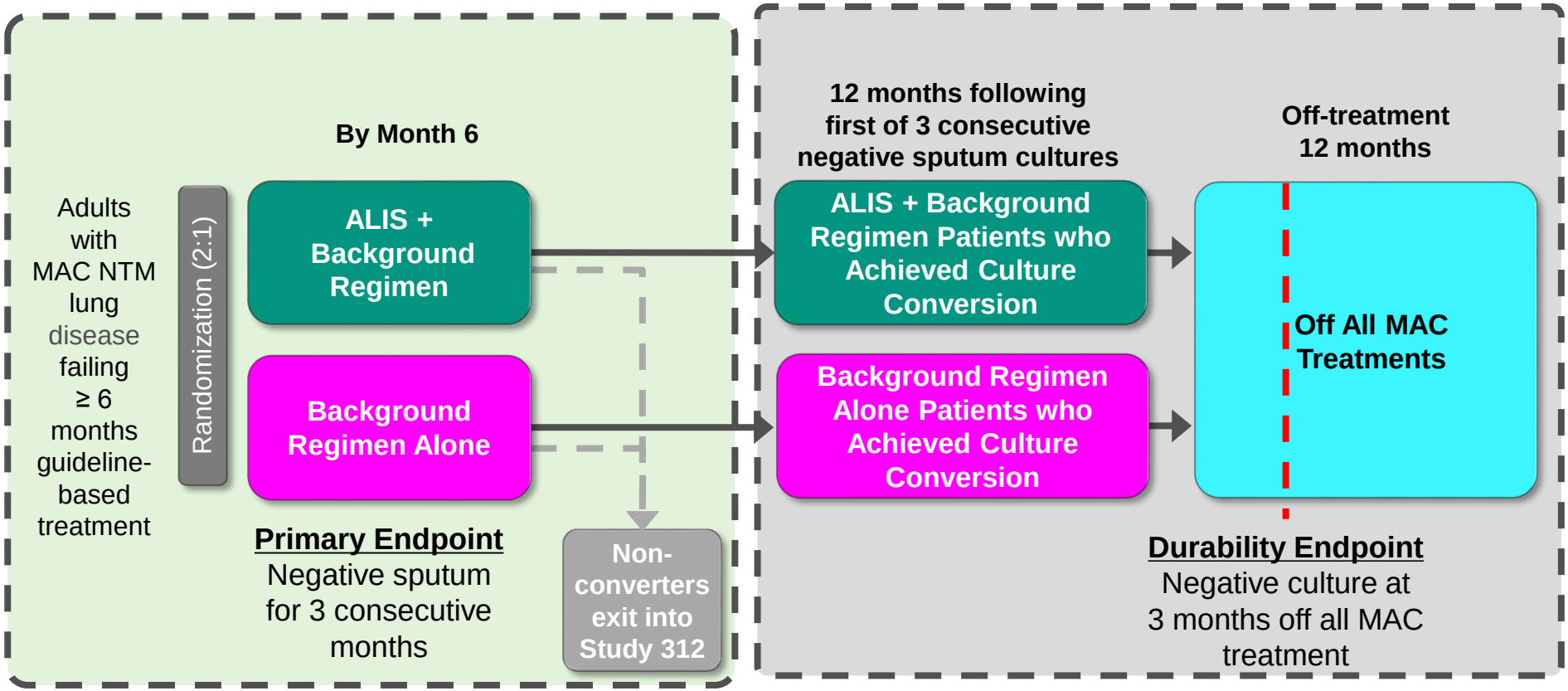
ALIS, amikacin liposome inhalation suspension

# Study 112 (Ph 2): Randomized, Double-Blind, Placebo-Controlled Study in Refractory NTM Lung Disease



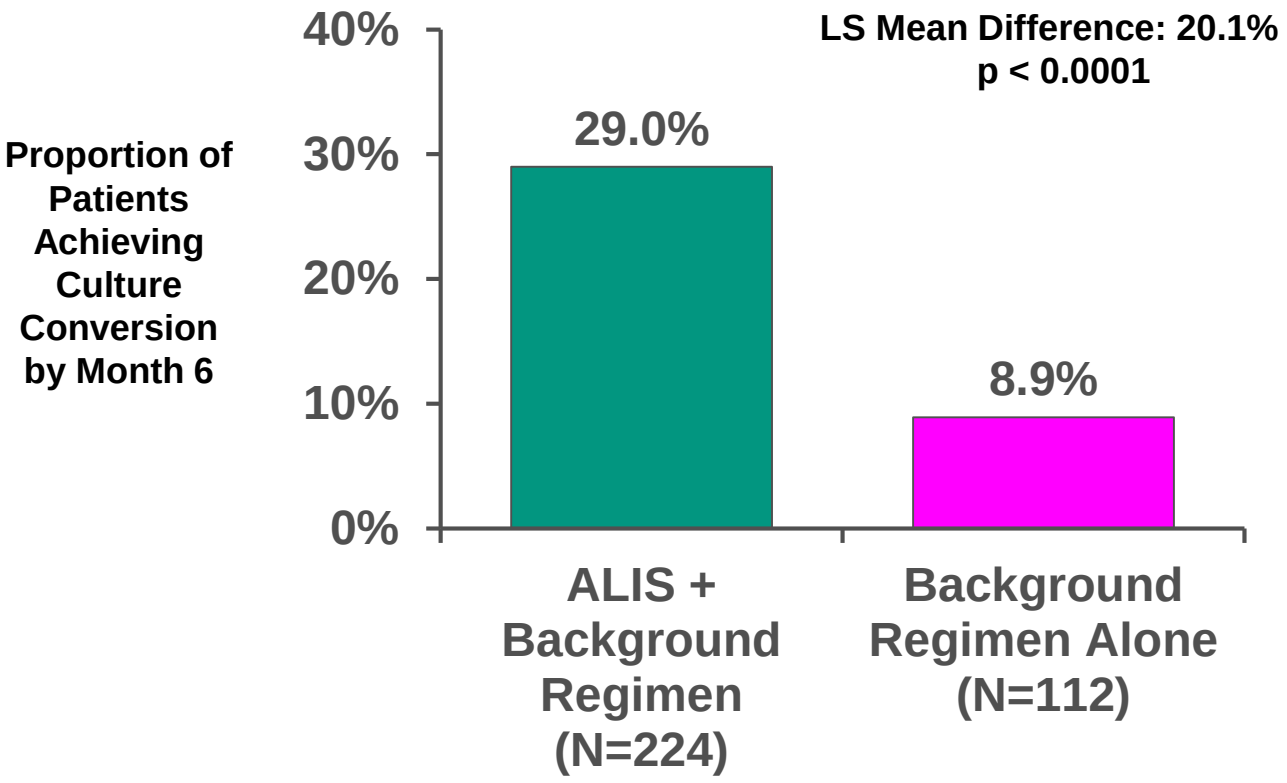

ALIS, amikacin liposome inhalation suspension

# Study 212: Randomized, Open-Label, Multicenter Study of ALIS + Background Regimen




ALIS, amikacin liposome inhalation suspension; MAC, *Mycobacterium avium* complex

# Study 212: Primary Endpoint - Higher Proportion of ALIS Patients Achieved Culture Conversion




ALIS, amikacin liposome inhalation suspension

ARIKAYCE [prescribing information]. Bridgewater, NJ: Insmed Incorporated; 2018.

# Most common Adverse Events in Study 212

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

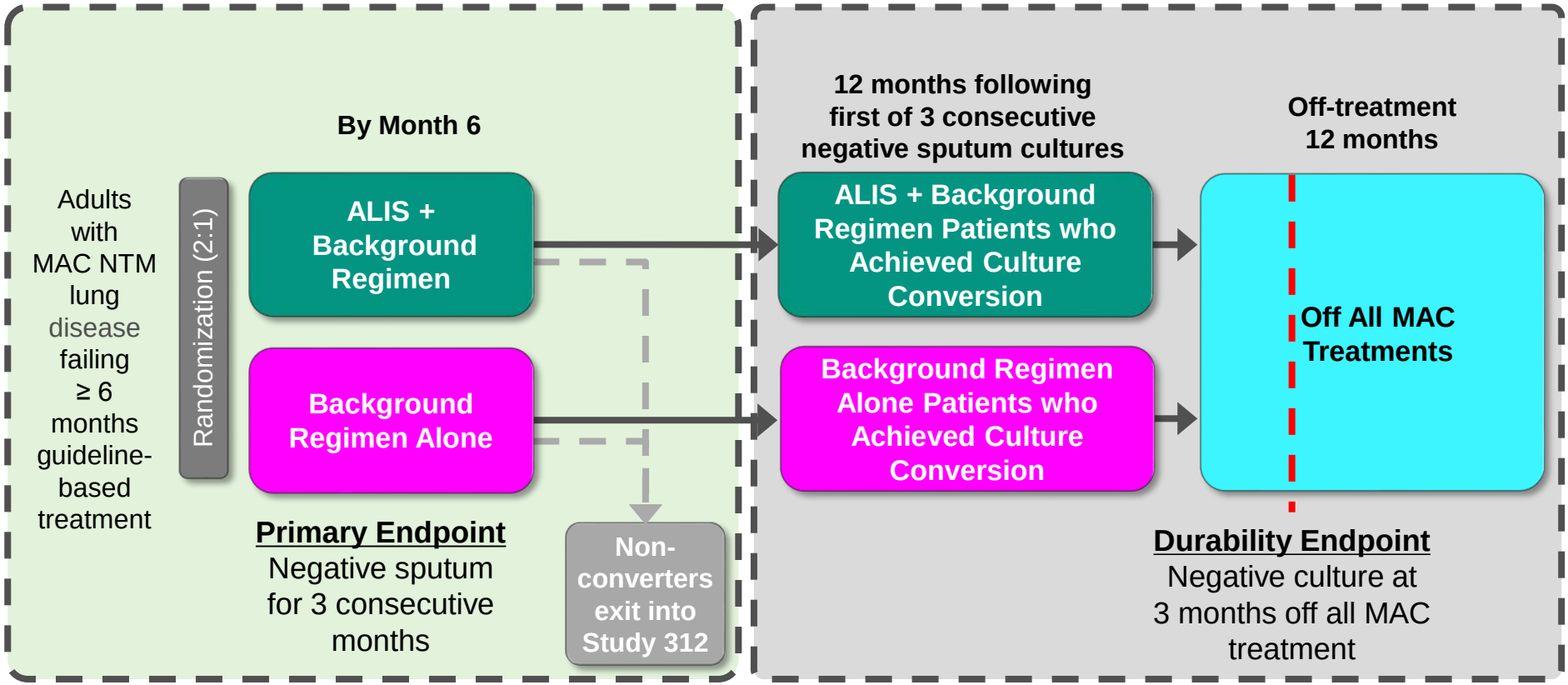
| Preferred Term | ALIS + Background Regimen (N=223) | Multidrug Background Alone (N=112) |
|---|---|---|
| Dysphonia | 47% | 1% |
| Cough | 39% | 17% |
| Bronchospasm | 29% | 11% |
| Hemoptysis | 18% | 13% |
| Ototoxicity | 17% | 10% |
| Upper airway irritation | 17% | 2% |
| Musculoskeletal pain |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

ALIS, amikacin liposome inhalation suspension

ARIKAYCE [prescribing information]. Bridgewater, NJ: Insmed Incorporated; 2018.

# Culture Conversion at Month 6 Predicts Durable Conversion

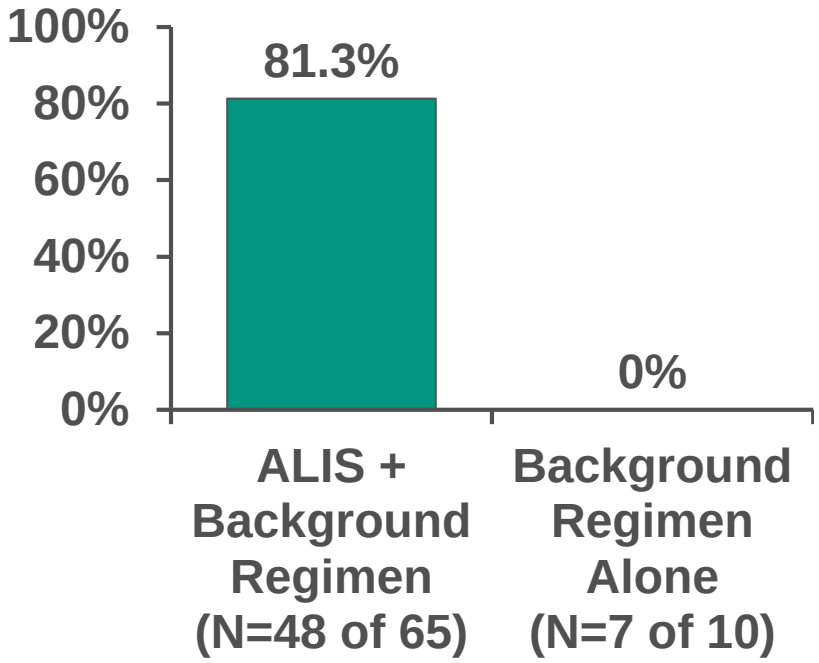
# Study 212: Randomized, Open-Label, Multicenter Study of ALIS + Background Regimen




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

| | ALIS + Background Regimen Total (N=223) | Background Regimen Alone Total (N=112) |
|---|---|---|
| Number of drugs in regimen | | |
| 0 | 2 (1) | 3 (3) |
| 2 | 39 (18) | 14 (13) |
| 3 | 148 (66) | 84 (75) |
| 4+ | 34 (15) | 11 (10) |
| Drug class | | |
| Ethambutol | 184 (83) | 85 (76) |
| Macrolide | 207 (93) | 101 (91) |
| Rifamycin | 191 (86) | 94 (84) |
| Other | 69 (31) | 39 (35) |

**In drug combinations, 'Other' may include medications deemed to be a component of background regimen by the investigator**

ALIS, amikacin liposome inhalation suspension

Griffith DE et al. Am J Respir Crit Care Med. 2018;198:1559-1569.Online Supplement

# Study 212: Combinations of Background Regimen at Baseline

| Drug combination | ALIS + Background Regimen Total (N=223) | Background Regimen Alone Total (N=112) |
|---|---|---|
| E/M/R/O | 30 (14) | 8 (7) |
| E/M/R | 123 (55) | 61 (55) |
| E/M/O | 6 (3) | 6 (5) |
| E/M | 13 (6) | 3 (3) |
| E/R/O | 8 (4) | 6 (5) |
| E/R | 3 (1) | 1 (1) |
| E/O | 1 (0.4) | 0 |
| M/R/O | 13 (6) | 12 (11) |
| M/R | 13 (6) | 5 (5) |
| M/O | 9 (4) | 6 (5) |
| R/O | 1 (0.4) | 1 (1) |
| O | 1 (0.4) | 0 |

**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**

ALIS, amikacin liposome inhalation suspension

Griffith DE et al. Am J Respir Crit Care Med. 2018;198:1559-1569.Online Supplement

# Study 212: Duration of NTM Diagnosis Prior to Baseline (Years)

| Years | ALIS + Background Regimen (N=223) | Background Regimen Alone (N=112) |
|---|---|---|
| n | 221 | 112 |
| Mean | 6.18 | 4.54 |
| Standard deviation | 5.525 | 3.858 |
| Median | 4.45 | 3.26 |
| Minimum | 0.0* | 0.0* |
| Maximum | 32.5 | 20.3 |

*6 subjects reported unknown NTM diagnosis date; all subjects reported at least 6 months of prior multidrug treatment

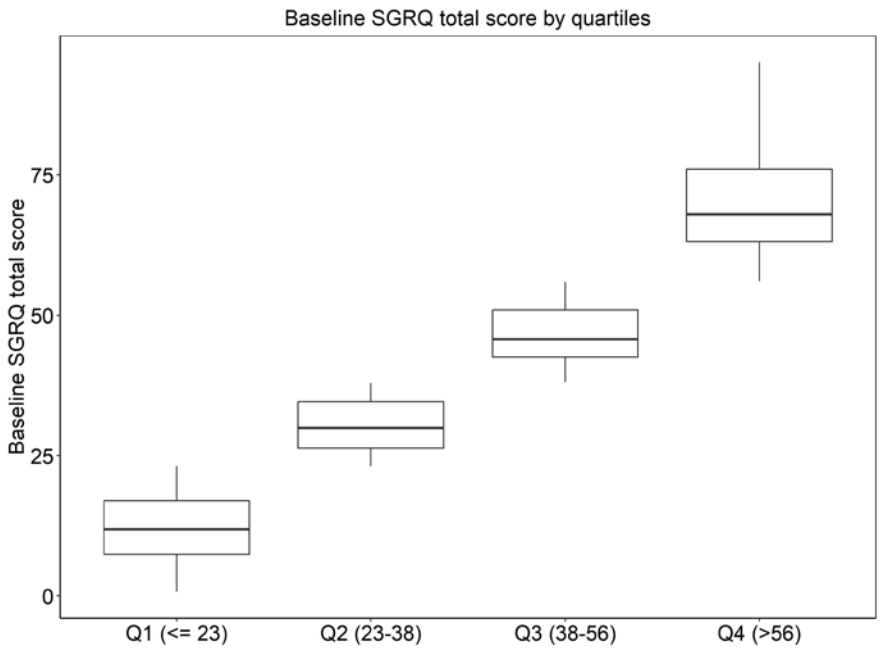
ALIS, amikacin liposome inhalation suspension

Data on File. Insmed Incorporated; Griffith DE et al. Am J Respir Crit Care Med. 2018;198:1559-1569.Online Supplement

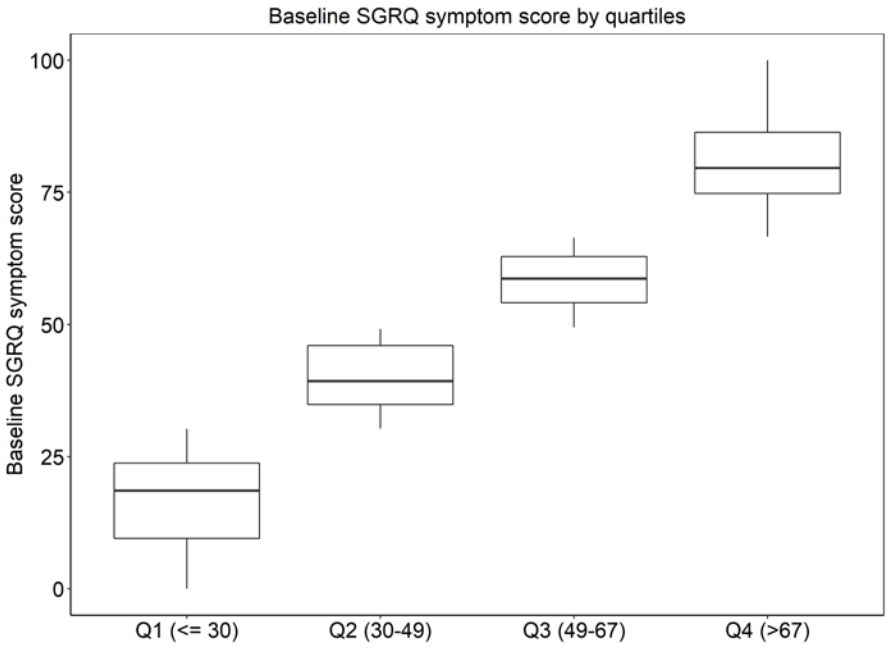
# Baseline SGRQ Stratified by Quartiles

*Study 212*

SGRQ total score




SGRQ symptom score




Data on File. Insmed Incorporated
SGRQ, Saint George's Respiratory Questionnaire

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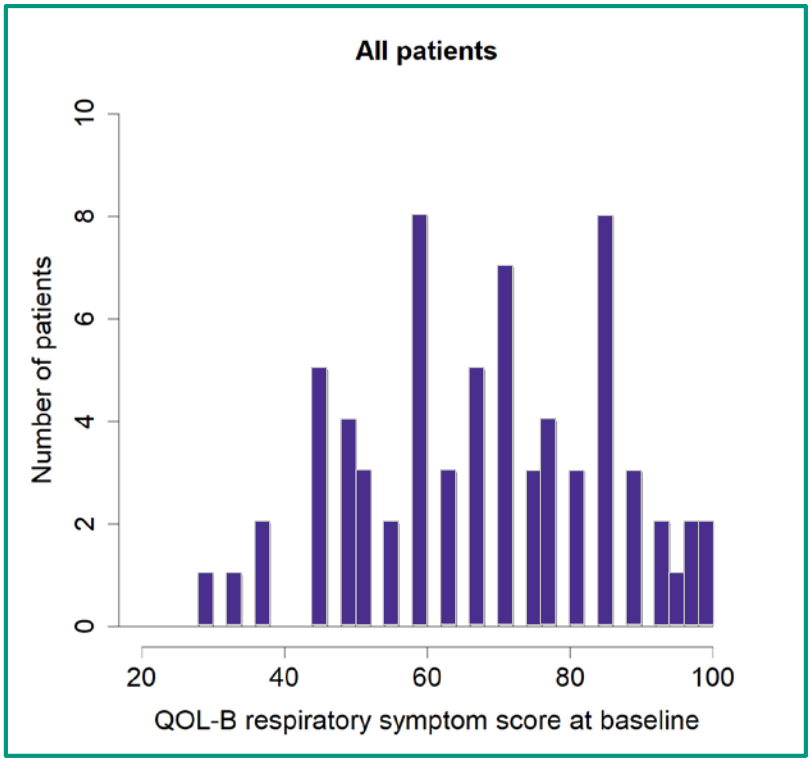
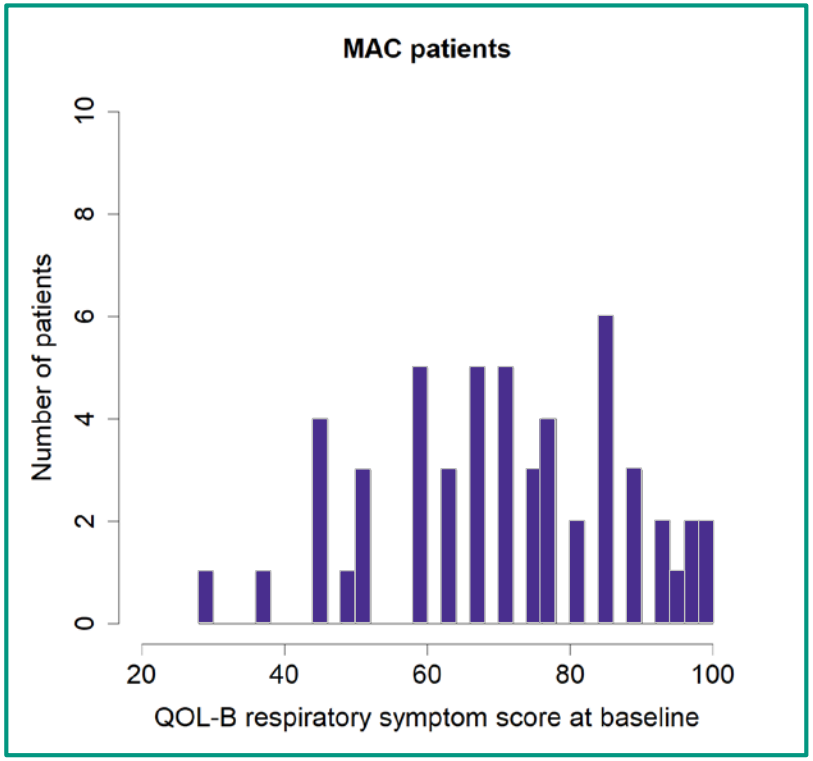
# Baseline QoL-B Respiratory Symptom Scores

*Study 112*



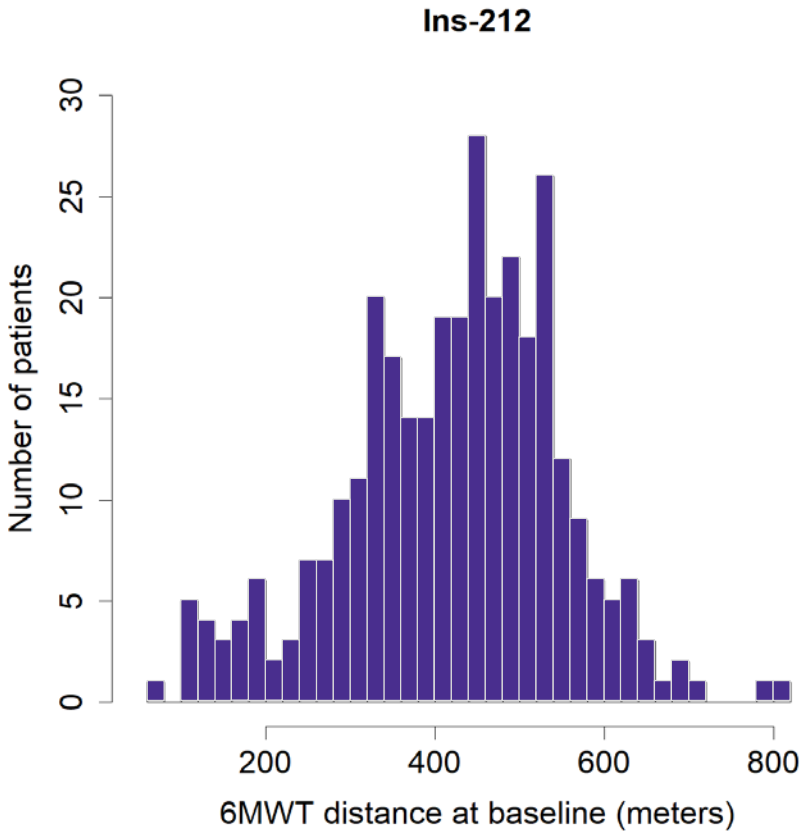




Data on File. Insmed Incorporated
QoL-B, The Quality of Life-Bronchiectasis

# Baseline 6-Minute Walk Test Distance

*Study 212*

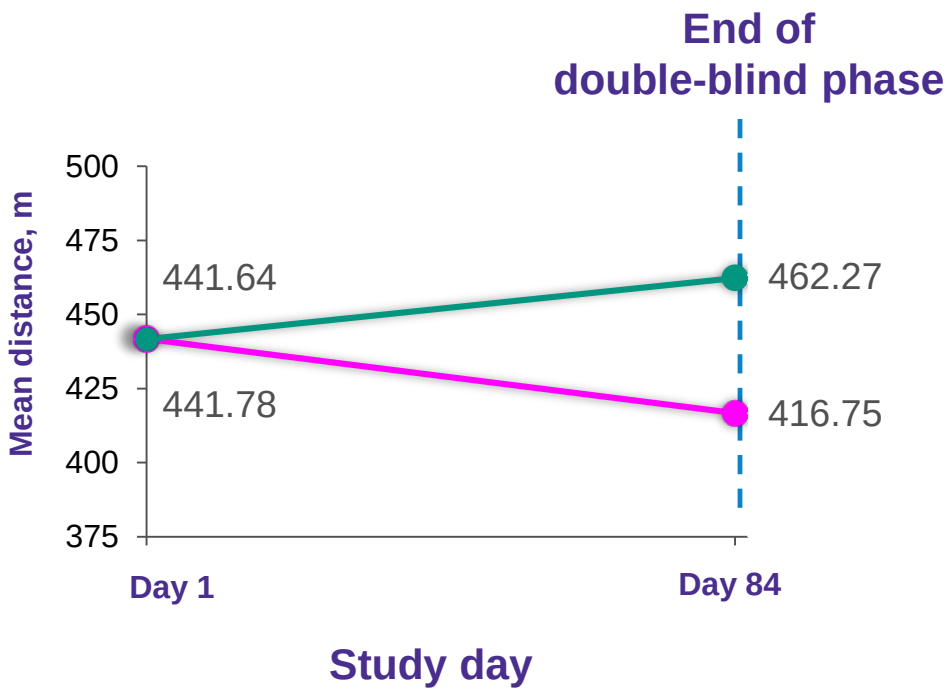
Very large range of baseline 6-Minute Walk Distance, ranging from severely impaired (<200m) to values seen in healthy subjects (>550m)




Data on File. Insmed Incorporated

# Six-Minute Walk Test Not a Reliable Endpoint for NTM Lung Disease Trials

# Study 112: 6-Minute Walk Test Distance (Exploratory Endpoint)

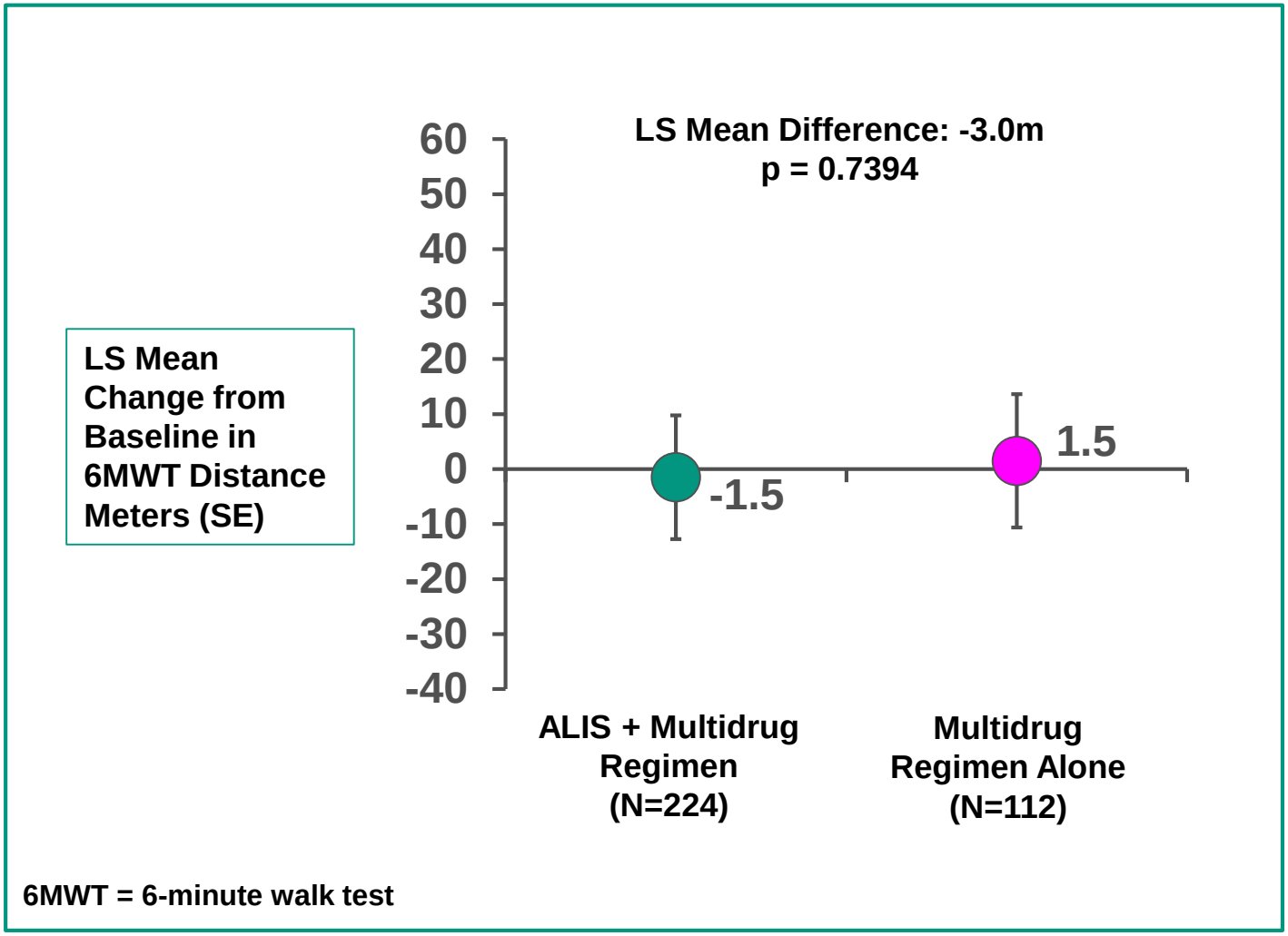



| | ALIS + Background Regimen (n=44) | Placebo + Background Regimen (n=45) |
|---|---|---|
| Change from Baseline at Day 84 | 20.64 | -25.03 |
| Mean Difference | 47 (P=0.01) | |

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

Olivier KN et al. *Am J Respir Crit Care Med.* 2017;195(6):814-823.

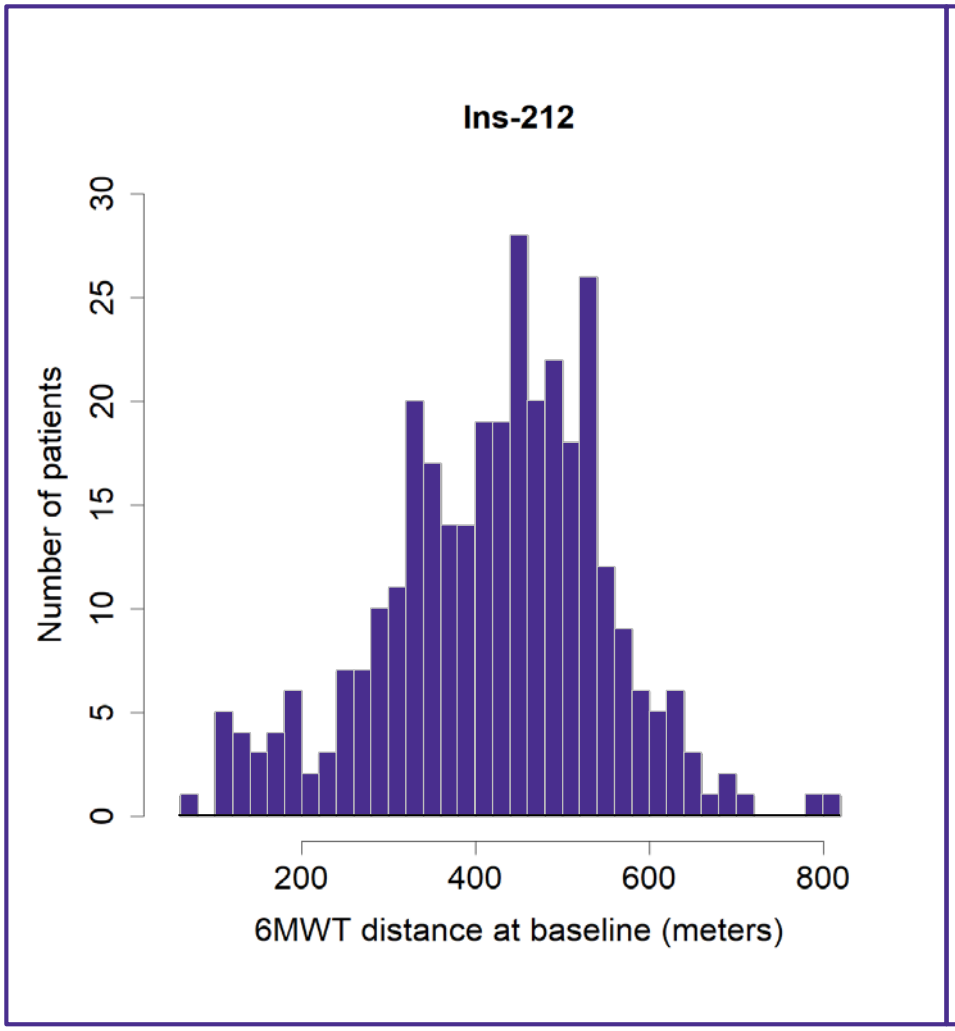
# Study 212: Secondary Endpoint Change from Baseline in 6MWT at Month 6

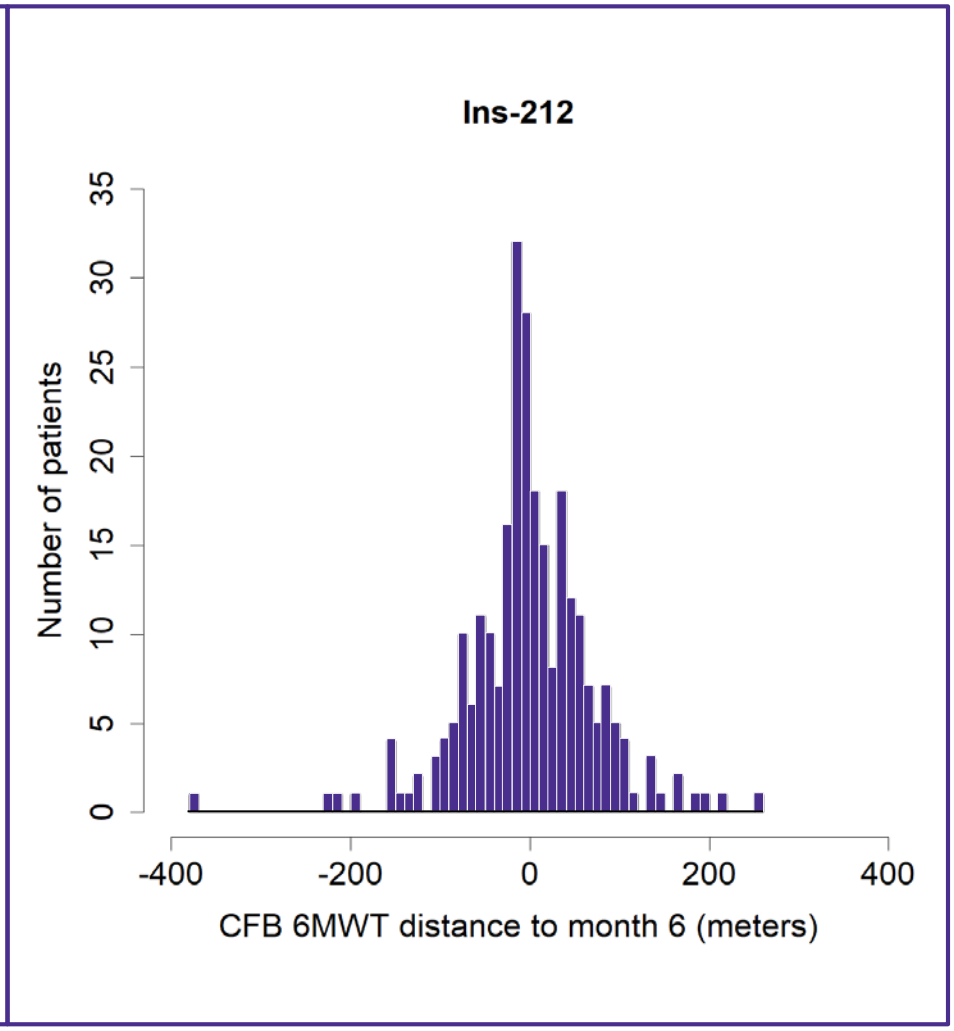



ALIS, amikacin liposome inhalation suspension

Griffith DE et al. Am J Respir Crit Care Med. 2018;198:1559-1569.

# 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

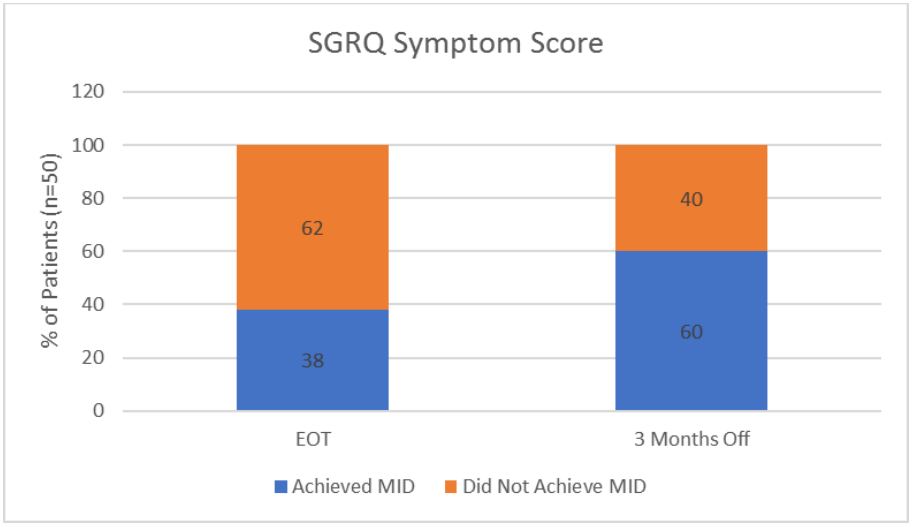
# Drug Tolerability Issues May Confound Assessment of Clinical Benefit During Treatment

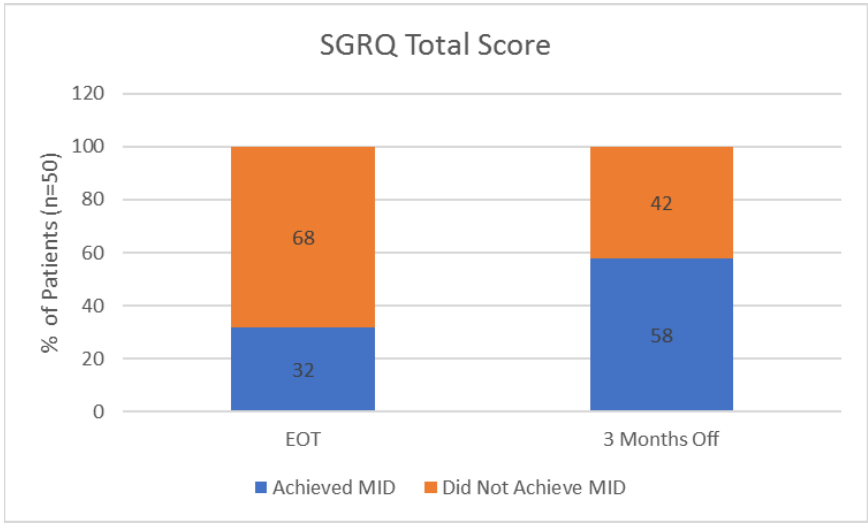
# Tolerability of Multidrug NTM Lung Disease Regimens

- 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*



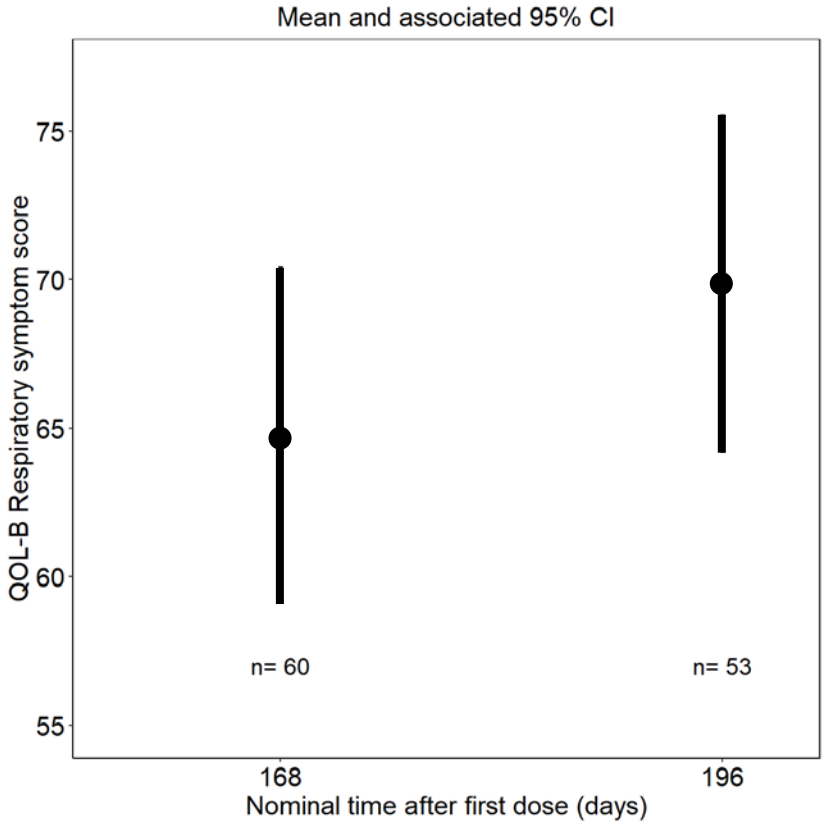




Data on File. Insmed Incorporated.

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

| | |
|---|---|
| 1 | Culture Conversion at Month 6 Predicts Durable Conversion |
| 2 | Heterogeneous Study Population, Even Among Refractory Patients, Introduces Noise |
| 3 | Six-Minute Walk Test Is Not a Reliable Endpoint for NTM Lung Disease Trials |
| 4 | Drug Tolerability Issues May Confound Assessment of Clinical Benefit During Treatment |

# Thank You