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Analyst and Investor Day
March 24, 2015

NASDAQ: INSM
Agenda

I. Introduction and Overview – Will Lewis

II. NTM Lung Disease & Clinical Trials –
  Dr. Gina Eagle

III. Regulatory – Peggy Berry

IV. Research and Development INS1009 –
  Dr. Walter Perkins and Dr. Gene Sullivan

I. Global Commercial Plan & Corporate Development –
  Wes Kaupinen, Dr. Olaf Bartsch,
  Drayton Wise and Kevin McDermott

II. Tech Ops, Cash and Tax Planning – Andy Drechsler

III. Q&A
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We are building a self-sustaining biopharmaceutical company focused on patient needs at the intersection of orphan and pulmonary disease.
Insmed’s Orphan Product Portfolio

ARIKAYCE™
liposomal amikacin for inhalation

INS1009
inhaled treprostinil-prodrug

Additional Programs in Orphan Diseases

NTM
PAH
2015 – The Year of the Deliverables

I. Enroll the “212” NTM Global Phase 3 Trial

II. Pursue European Approval of ARIKAYCE – NTM & CF

III. Continue Manufacturing Build-out and Redundancy Planning

IV. Submit IND for INS1009 and Enroll Phase 1 Trial

V. Corporate Development
# Team Introduction

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<th>Role</th>
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<td>Introduction &amp; Overview</td>
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<td>NTM Disease &amp; Clinical Trials</td>
<td>Dr. Gina Eagle</td>
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<td>Regulatory</td>
<td>Peggy Berry</td>
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<td>R&amp;D, INS1009 &amp; IP</td>
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<td>Drayton Wise</td>
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NTM Lung Disease & Clinical Trials
Dr. Gina Eagle
ARIKAYCETM – NTM and CF Indications

ARIKAYCETM
liposomal amikacin for inhalation

INS1009
inhaled treprostinil-prodrug

Additional Programs in
Orphan Diseases
Nontuberculous Mycobacteria (NTM) Lung Infections

No Approved Treatment in US and EU

Progressive Lung Disease and Increased Mortality in High Risk Patient Groups

Common in: COPD, bronchiectasis, asthma and CF

Source: Company website; Clarity Pharma Research; American Journal of Respiratory and Critical Care Medicine; American Lung Association; UCSF Medical Center; Medscape Education; NTM Info and Research; Prevots (2010)
### Nontuberculous Mycobacteria (NTM) Lung Infections

<table>
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<th>Region</th>
<th>Annual Prevalence Increase</th>
<th>Diagnosed Patients</th>
<th>Treatment Resistant Populations (estimate)</th>
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<td>US (^a)</td>
<td>+13%</td>
<td>55-70K</td>
<td>10-20K</td>
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<td>EU (^d)</td>
<td>+6%</td>
<td>30K</td>
<td>5-10K</td>
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<td>Japan (^b)</td>
<td>+11%</td>
<td>30K</td>
<td>5-10K</td>
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<td>Australia (^e)</td>
<td>+9%</td>
<td>5-10K</td>
<td>1-2K</td>
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<tr>
<td>Canada (^c)</td>
<td>+9%</td>
<td>5-10K</td>
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Source: Company website; Clarity Pharma Research; American Journal of Respiratory and Critical Care Medicine; American Lung Association; UCSF Medical Center; Medscape Education; NTM Info and Research; Prevots (2010); (a) Adjemian et al 2012; (b) Yutaki, January 2015 Journal of Infection and chemotherapy; (c) Marras 2007; (d) Ringhausen 2013, Panagiotou 2014; (e) Thomson 2010
Patient Journey Is Long and Difficult for Most
Only a few are diagnosed correctly from the outset

Symptom Presentation

Primary Care Doctor

Seek out Physician

Flu

Bronchitis

COPD

Asthma

Mis-diagnosis

Treatment initiation

Tuberculosis

Lung Cancer

Mis-diagnosis

Symptom persistence

Infectious Disease Dr.

Pulmonary Doctor

Physician Referral/Change

Diagnosis correction

Treatment initiation

Living with NTM
(NTM Management)
NTM Lung Disease
Risk Factors and Mortality
To date >150 identified NTM species

MAC (Mycobacterium avium Complex) is the most common

Ubiquitous organisms: found in soil and water

Animal to human and human to human transmission not widely documented

Asymptomatic infections and symptomatic disease is possible with many NTM species
Nontuberculous Mycobacterial Pulmonary Pathogens

Common
- M. avium
- M. intracellulare
- M. kansasii
- M. abscessus
- M. chelonae

Infrequent
- M. xenopi (zin oh’ pee)
- M. szulgai (sull’ guy)
- M. malmoense
- M. fortuitum
- Rare
- M. celatum (sell ah’ tum)
- M. scrofulaceum
- M. simiae
- M. terrae
- M. immunogenenum
- Never (almost)
- M. gordonae
Risk Factors in MAC Lung Disease

5-year-all-cause overall mortality (Ito et al *): 25.6%

- untreated chronic MAC patients: 33.3%
- treated MAC patients: 22.2%

\[ p = 0.30 \]

Adjusting for clinical, microbiological and radiological confounders, independent factors for 5-year mortality were a high Charlson comorbidity index and presence of cavitary lesions

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<th>Hazard Ratio (HR) Comparisons</th>
<th>High Charlson Comorbidity Index</th>
<th>Presence of Cavitary Lesions</th>
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<tbody>
<tr>
<td>Definite MAC</td>
<td>HR 1.76</td>
<td>HR 1.82</td>
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<tr>
<td>Untreated chronic MAC</td>
<td>HR 3.08</td>
<td>HR 3.91</td>
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</table>

Conclusion: Patients with cavitary lesions require immediate treatment for sputum culture conversion and to improve their chances of survival

*Ito et al INT J TUBERC LUNG DIS 16(3):408–414; A study of 78 patients with definite MAC disease (including treated and untreated chronic MAC patients)*
## Risk Factors in MAC Lung Disease

<table>
<thead>
<tr>
<th>Literature on Risk Factors in MAC Lung Disease</th>
<th>Advanced Stage at Diagnosis</th>
<th>Cavitary Lung</th>
<th>Low BMI</th>
<th>Macrolide-Resistance at Diagnosis</th>
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<tr>
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<td>Masao Okumura et al, Inter Med 47: 1465-1472, 2008 DOI: 10.2169/internalmedicine.47.1114</td>
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*21.0 kg/m² and more than four lung segments involved had a 240-fold increased risk of deterioration (P < 0.001)
High Risk Factor: Cavitary Lung
NTM Lung Disease

Advantages of LAI
Liposomal Amikacin for Inhalation (LAI)

- Amikacin is an aminoglycoside antibiotic with in vitro evidence of activity against NTM
- Novel liposomal formulation for inhalation via nebuliser
  - High lung Cmax, AUC, and t½ improved AUC:MIC ratio
  - Liposomes have a neutral charge and can be taken up by lung macrophages allowing intracellular delivery of drug into infected cells that harbor nontuberculous mycobacteria (NTM) while maintaining normal macrophage function
- Low serum Cmax and low bioavailability (<12%)
  - Decreased potential for systemic toxicity such as renal and ototoxicity
NTM Lung Disease
Recap of Study 112
Study 112: Study Design

Randomized 90 Subjects (1:1):
- Stratified: CF vs non-CF
  - MAC vs M. abscessus

Primary Endpoint: Efficacy
- Change on Semi-Quantitative Scale for mycobacterial culture at Day 84

**Screening period**
- Day –42 to Day –2

**12 Weeks Once-Daily Dosing**
- Background therapy $^d$ + LAI$^e$ once daily by eFlow®

**12 Weeks Once-Daily Dosing, Open-Label**
- LAI once daily by eFlow

**28-Day follow-up**
- No inhaled antibiotics

**4 Weeks**

CF = cystic fibrosis; LAI = liposomal amikacin for inhalation; MAC = *Mycobacterium avium* complex.

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**a** 2007 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria with evidence of nodular bronchiectasis and/or fibrocavitary disease by chest computed tomography scan.

**b** At least 2 documented positive cultures in the prior 2 years, of which at least 1 was obtained in the 6 months prior to screening.

**c** Receiving ATS/IDSA guideline-based treatment for at least 6 months prior to screening with persistently positive cultures.

**d** Continuing on ATS/IDSA guideline-based therapy.
Study 112: Patient Profiles

- **Length of Time on NTM Treatment Regimen Prior to Baseline**

  - >24 Months
  - >12 - 24 Months
  - 6 - 12 Months

- **Lung Lesion Type on HRCT scan at Baseline**

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<th>Lesion Type</th>
<th>N (%)</th>
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<tr>
<td>Cavitary</td>
<td>6 (6.70%)</td>
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<tr>
<td>Nodular and Cavitary</td>
<td>63 (70.0%)</td>
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<tr>
<td>Nodular</td>
<td>21 (23.3%)</td>
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Study 112: Recap of Main Results

- **Reduction** in mycobacterium burden (numerically superior, not statistically significant)

- **Achievement of a negative sputum culture** in 11 out of 44 patients at Day 84 (statistically significant)

- **Safety:** more frequent respiratory events; consistent similar inhaled antibiotics

![Graph showing percent of patients whose sputum culture tested negative for NTM at Day 84 (mITT population).]

ARIKAYCE + Standard of Care: 25.0% (11/44)

Placebo + Standard of Care: 6.7% (3/45)
### Study 112: Patients with at least 1 negative sputum culture for NTM

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>CF Status</th>
<th>NTM Organism</th>
<th>Length of NTM Prior to Baseline (Months)</th>
<th>Baseline</th>
<th>Day 28</th>
<th>Day 56</th>
<th>Day 84</th>
<th>Day 112</th>
<th>Day 140</th>
<th>Day 168</th>
<th>28 Day Follow-Up</th>
<th>Early Term Reason</th>
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<td>Early Term</td>
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</tbody>
</table>
### Study 112: Patients with Sputum Culture Conversion*

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>CF Status</th>
<th>NTM Organism</th>
<th>Length of NTM Prior to Baseline (Months)</th>
<th>Baseline</th>
<th>Day 28</th>
<th>Day 56</th>
<th>Day 84</th>
<th>Day 112</th>
<th>Day 140</th>
<th>Day 168</th>
<th>28 Day Follow-Up</th>
<th>Early Term Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAI</td>
<td>Non-CF</td>
<td>M. abscessus</td>
<td>&gt;24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Broth</td>
<td>Broth</td>
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<tr>
<td>PBO</td>
<td>Non-CF Patient</td>
<td>M. abscessus</td>
<td>&gt;24</td>
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</table>

*ATS definition of conversion = 3 consecutive monthly negative sputum cultures*
Study 112: 6 Minute Walk Test

Change From Baseline in 6MWT Distance
Missing Values Excluded (mITT Population)

Least Squares Mean (SE)

Study Day

Arikayce
Placebo

\( P = .009 \)
## Study 112: Safety Recap

### Treatment-Emergent Adverse Events with >10% occurrence
Through End of Open-label Phase (Safety Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>LAI (n=44)</th>
<th>Placebo (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infective exacerbation of bronchiectasis</td>
<td>45%</td>
<td>40%</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>35%</td>
<td>32%</td>
</tr>
<tr>
<td>Cough</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>20%</td>
<td>12%</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>10%</td>
<td>8%</td>
</tr>
<tr>
<td>Nausea</td>
<td>20%</td>
<td>15%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Wheezeing</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

LAI, liposomal amikacin for inhalation.
NTM Lung Disease
Study 212
# Study 212-Global Sites

**North America**
- United States (34)
- Canada (5)

**Europe**
- UK (15)
- Germany (13)
- Italy (12)
- Spain (7)
- France (6)

**Europe**
- Poland (4)
- Austria (2)
- Netherlands (1)

**Asia-Pac**
- Australia (17)
- Japan (8)
- New Zealand (3)

Goal is to have 80+ sites active in the 1H 2015
Study 212: Study Design Overview

Key Facts: INS-212 Trial
- Randomized ~300 patients (2:1)
- Non-CF MAC Only
- Stratifications: (1) Smokers vs. non-smokers; (2) Background Therapy last 6 months

Key Inclusion Criteria
- Age ≥18 years ≤85 years
- DX of pulmonary NTM lung disease with MAC
- Failed prior treatment
- Multi-drug regimen for at least 6 months; last dose within the prior 12 months

Primary Endpoint at 6 Months for Accelerated Approval
- Percentage of patients that achieve culture conversion
- Secondary: Six-minute walk test

Screening Period
- 8 Months Daily Dosing
  - ~200 patients
  - ARIKAYCE once daily + Background Therapy

Converters Continue Treatment for 12 Months Post Conversion
- 3 Month Off Treatment Follow-Up
  - ARIKAYCE once daily + Background Therapy

Non-converters Enter “312” Follow-on Study
- ARIKAYCE + Background Therapy for 12 Months
- 3 Month Off Treatment Follow-Up

Background Therapy
- ~100 patients
Study 212: Sputum Sampling

Primary Endpoint:
- 3 sputum samples will be collected for each monthly visit (Baseline to Month 6)
- Patients will interrupt LAI administration on day -2 until they visit the clinic

Sputum processing will be
- Performed per standard lab procedures
- Globally aligned
## Central Micro Labs Globally

<table>
<thead>
<tr>
<th>Region</th>
<th>Central Micro Lab</th>
<th>Microbiology Director</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA/Canada</td>
<td>University of Texas at Tyler Health Northeast (USA)</td>
<td>Richard J. Wallace Jr. M.D.</td>
</tr>
<tr>
<td>Europe</td>
<td>Radboud University Medical Center (Netherlands)</td>
<td>Jakko van Ingen, MD, PhD</td>
</tr>
<tr>
<td>Australia/Asia</td>
<td>Queensland Mycobacterium Reference Laboratory (Australia)</td>
<td>Dr. Chris Coulter, Director</td>
</tr>
</tbody>
</table>
# Methodology Across Global Central Micro Labs

<table>
<thead>
<tr>
<th>Methodology/Supplies</th>
<th>Tyler North America</th>
<th>Radbound Europe</th>
<th>QMRL Australia/Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control strain</td>
<td>ATC700898</td>
<td>ATC700898</td>
<td>ATCC700898</td>
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<tr>
<td>Liquid medium</td>
<td>VersaTrek</td>
<td>BD MGIT</td>
<td>BDMGIT</td>
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<tr>
<td>Solid medium</td>
<td>Agar 7H11</td>
<td>Agar 7H11</td>
<td>Agar 7H11</td>
</tr>
<tr>
<td>Mac Growth (ID)</td>
<td>Gen-Probe</td>
<td>Gen-Probe</td>
<td>Hain CM Line Probe</td>
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<tr>
<td>MIC Testing (MAC Susceptibility)</td>
<td>MIC Panel; (Thermofisher)</td>
<td>MIC Panel; (Thermofisher)</td>
<td>MIC Panel; (Thermofisher)</td>
</tr>
<tr>
<td>MAC Mutation Sequencing</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Growth Conditions</td>
<td>35 °C</td>
<td>36°C-37°C</td>
<td>36-37 °C</td>
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<tr>
<td>Standards</td>
<td>CLSI</td>
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Study 212 Sample Size Calculation

● Primary Endpoint
  Proportion of subjects achieving culture conversion by Month 6

● Assumptions
  Month 6 culture conversion rate: 20% for LAI+MDR; 5% for MDR
  Chi-square test at a 2-sided significance level of 0.05
  A 2:1 randomization ratio to either LAI+MDR or MDR
  At least 90% power

● Sample Size
  A total of 261 subjects: 174 for LAI+MDR; 87 for MDR
Study 212 Sample Size Calculation

- **Secondary Endpoint**
  Change from baseline to Month 6 in 6MWT distance

- **Assumptions**
  A common standard deviation (SD) of 100
  A between-treatment difference of 50 meters in mean change
two group t-test at a 2-sided significance level of 0.05
A 2:1 randomization ratio to either LAI+MDR or MDR
At least 90% power

- **Sample Size**
  A total of 192 subjects: 128 for LAI+MDR; 64 for MDR
Study 212 Statistical Methods

● Stratification
Randomization stratified by: Smoking Status (current smoker or not) and Prior Multi-drug Regimen (on treatment or off treatment for at least 3 months)

● Primary Analysis Population
Modified Intent-to-treat population: all randomized subjects who received at least 1 dose of either LAI plus a multi-drug regimen or a multi drug regimen

● Hypothesis – Primary Endpoint
H0: Culture conversion is independent of treatment
H1: Culture conversion is associated with treatment

● Analysis of Primary Endpoint
Cochran-Mantel-Haenszel test adjusting for the 2 stratification variables at a 2-sided significance level of 0.05
Study 212 Statistical Methods

● Hypothesis – Secondary Endpoint
  H0: No between-treatment difference in mean change from baseline to Month 6 in 6MWT distance
  H1: There is a between-treatment difference in mean change

● Analysis of Secondary Endpoint
  Mixed-effects Model for Repeated Measures (MMRM) over Months 4 and 6; The MMRM model includes treatment, month, the treatment-by-month interaction, smoking status, and prior multi-drug regimen (on treatment or off treatment for at least 3 months) as fixed factors, the baseline (Day 1) 6MWT distance as a covariate, as well as the baseline 6MWT distance-by-month interaction.
Cystic Fibrosis Program

TR02-110 Update
Cystic Fibrosis Program Update
LAI for the Management of Pa in Patients with Cystic Fibrosis

Anecdotal Trial Experience

- 8 patients have requested compassionate use of LAI to follow TR02-110
- Very positive feedback from PIs in general regarding slowing of disease progression (even reversal in some cases) and the ‘patient experience’
Cystic Fibrosis Program Update
Reasons for Patient Discontinuation in TR02-110

<table>
<thead>
<tr>
<th>Reason for Early Discontinuation</th>
<th>Prior LAI arm in TR02-108</th>
<th>Prior TOBI arm in TR02-108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Withdrawal of Concent</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Permanent Termination of Study</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>
Regulatory
Peggy Berry
Regulatory Overview

ARIKAYCE
- European update
- US update
- Rest of World activities

INS1009
- US update
- Rest of World activities
European Marketing Application (for NTM Lung Infections and Pseudomonas Aeruginosa CF patients)

Submitted late 2014; Validated February 2015

Expect feedback at Day 120; late June 2015 (preparing responses to potential questions)

Assuming standard response time
- Day 180 (final issues) will be mid-Q4
- Day 210 (opinion) will be late Q4
- Day 277 (final decision) will be mid-Q1 2016
ARIKAYCE – US Update

Reached agreement on protocol INS-212

Anticipate beginning rolling NDA submission in mid-2016 with final at end of 2016 for possible SubPart H approval

- Permits an approval based upon culture conversation & 6-minute walk test (6MWT) distance at the 6 month timepoint
- Requires a commitment to submit additional clinical data when available; discussions with the FDA will occur to determine requirements for full approval to be granted
  - completion of the 212 study through 16+ months of treatment for patients who have converted
  - completion of the 312 safety study through 12 additional months of treatment for those patients who have not converted
- possible additional requirements depending on the data from the studies
SubPart H Approval

● If agreed requirements are met and the data on the final endpoints are achieved, the FDA could issue a full approval of the drug with updated labeling that incorporates information from the study results.

● If agreed requirements are not met or if the clinical data do not succeed on the final endpoints, the FDA may modify the product labeling to include the new data and to specify any limitations of use of the drug based upon the results achieved or they may convene an advisory committee meeting to discuss the data and recommended changes to the product labeling. In rare circumstances, they may also rescind the approval of the drug.
ARIKAYCE – Rest of World Update

Australia
- Orphan drug designation achieved in February 2015 for CF and refractory NTM

Canada
- Held pre-submission meetings with regulatory agencies

Japan
- Reached agreement on clinical study requirements for phase 3 study and PK
INS1009 – US & RoW update

- Reached general agreement on development program

- Agreed that 505(b)(2) is possible – pending review of the data confirming that INS1009 is a prodrug of treprostinil (FDA data review to occur 2Q 2015)
  - Anticipated Benefits of 505(b)(2)
    - No carcinogenicity study
    - Only one phase 3 study required
    - No drug-drug interaction studies required

- Orphan drug application in preparation

- Seeking advice from EU regulators to ensure that the development program will satisfy their requirements
Research and Development
INS1009
Dr. Walter Perkins
Dr. Gene Sullivan
Pulmonary Arterial Hypertension (PAH): Our Next Target Indication

ARIKAYCE™
liposomal amikacin for inhalation

INS1009
inhaled treprostinil-prodrug

Additional Programs in Orphan Diseases
Pulmonary Arterial Hypertension (PAH) Orphan Disease
Progressive Disease Leading to Heart Failure

- No curative treatments
- 15% one-year mortality
- ≈100,000* patients afflicted globally
- ≈25,000 treated patients in the U.S.¹,²,³
- Treatment is progressive combo therapy, including:
  - Calcium channel blockers; Endothelin receptor antagonists (ERAs);
    PDE-5 inhibitors; and Prostacyclins
  - Prostacyclins are perceived to be the most effective class but are limited by
toxicity/tolerability issues
    - 4 to 9x daily inhalations, continuous infusion, or modest efficacy at
      tolerable doses

Source: Company estimates. 1) Yang X, Mardekian J, Sanders KN, Mychaskiw MA, Thomas J. Prevalence of pulmonary arterial hypertension in patients with connective tissue
College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association: developed in collaboration with the American College of Chest
# Current Marketed Prostanoids for Pulmonary Arterial Hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
</table>
| Flolan, Veletri    | Intravenous via continuous    | Continuous drug level              | - Intravenous – central line infection  
| (epoprostenol)     | infusion                      |                                    | - Requires infusion pump                                            |
|                    |                               |                                    |                                                                      |
| Ventavis           | Inhaled with 6-9x daily dosing| Less invasive than infusion        | - Swings in peak/trough plasma levels  
| (iloprost)         |                               |                                    | - Lack of drug overnight                                           |
|                    |                               |                                    | - Inconvenient 6-9x/day dosing                                      |
| Remodulin          | Subcutaneous / Intravenous    | Continuous drug level              | - Subcutaneous -- site pain                                         
| (treprostcinil)    | via continuous infusion       |                                    | - Intravenous – central line infection                              |
|                    |                               |                                    | - Requires infusion pump                                            |
| Tyvaso             | Inhaled with 4x daily dosing  | Less invasive than infusion        | - Swings in peak/trough plasma levels  
| (treprostcinil)    |                               |                                    | - Lack of drug overnight                                           |
|                    |                               |                                    | - Inconvenient 4x daily dosing                                      |
| Orinetram          | Oral with BID/TID dosing      | Convenient dosage form             | - Swings in peak/trough plasma levels  
| (treprostcinil)    |                               |                                    | - Lack of drug overnight                                           |
INS1009: Treprostinil-Prodrug Formulated in a Nanoparticle

24 hour Coverage via Convenient Once-Daily Dosing

without Large Peak/Trough Swings in Plasma Levels

- Hexadecyl-treprostinil (C16TR) Prodrug
- Nanoparticles in aqueous suspension
- Administered by state-of-the-art nebulizer
- Patent applications filed

~100 nm in diameter
A single 6 µg/kg dose administered by inhalation to ventilated rats

*Estimation based on correlation of treprostinil plasma levels with changes in mean pulmonary arterial pressure (mPAP) from multiple experiments in rats

From ERS 2014 Poster 2367.
Mean Pulmonary Arterial Pressure (mPAP) as a % of hypoxic baseline value. mPAP is elevated in rats in response to hypoxia (10% oxygen). Single dose of INS1009 or treprostinil (both at 6 µg/kg treprostinil). Rats are anesthetized and ventilated. The initial time scale is expanded and the dotted line denotes the change in the time scale.
INS1009 Provides Sustained Release of Treprostinil over 24 Hours

With nose-only inhalation plasma levels are higher than those in ventilated rats due to additional deposition/absorption in nasal passages.

*Estimation based on correlation of treprostinil plasma levels with changes in mean pulmonary arterial pressure (mPAP) from multiple experiments in rats.
Inhaled INS1009 Provides Sustained Release of Treprostinil in Dogs

Lung Dose in Ventilated Dogs (Single Inhalation)

Treprostinil Plasma Level (ng/mL) vs Time (hours)

- Tre 5 µg/kg
- Tre 16 µg/kg
- INS1009 7 µg/kg
- INS1009 22 µg/kg
- INS1009 46 µg/kg
- INS1009 95 µg/kg
## INS1009 Better Tolerated in Dogs than Inhaled Treprostinil

<table>
<thead>
<tr>
<th>Compound</th>
<th>Lung Dose (µg/kg)</th>
<th>Observed Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treprostinil</td>
<td>5</td>
<td>0 of 3 dogs</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>4 of 5 dogs</td>
</tr>
<tr>
<td>INS1009</td>
<td>7</td>
<td>0 of 3 dogs</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>0 of 5 dogs</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>0 of 3 dogs</td>
</tr>
<tr>
<td></td>
<td>95</td>
<td>1 of 3 dogs</td>
</tr>
</tbody>
</table>

**Observed side effects after drug delivery:**
- **Treprostinil** -- cough, rapid shallow breathing, pale gums and emesis
- **INS1009** – 1 dog at highest dose exhibited rapid shallow breathing, pale gums, and emesis
INS1009 for PAH: Path to Market

Pursuing 505(b)(2) FDA NDA Approval
- Can be faster to market*
- Lower risk by leveraging prior drug approval
- Lower costs due to fewer studies

FDA IND
- IND: expect to file in 2H 2015

Clinical
- Phase 1 Study: Expect to Start by Year-end 2015
- Phase 2 Study: Expect to Start in 2016
- Phase 3 Study: TBD following completion of Phase 2

* Camargo Pharmaceutical Services
Phase 1
A single ascending dose (SAD) study in healthy volunteers for tolerability and pharmacokinetics

Phase 2
A single 12-week dose exploration study in PAH patients
Insmed’s Orphan Product Portfolio

ARIKAYCE™
liposomal amikacin for inhalation

INS1009
inhaled treprostinil-prodrug

Additional Programs in Orphan Diseases
Global Commercial Plan & Corporate Development

Wes Kaupinen
Drayton Wise
Dr. Olaf Bartsch
### ARIKAYCE: Near-term Commercial Launches

<table>
<thead>
<tr>
<th>Estimated Approval Timing</th>
<th>Diagnosed Patients</th>
<th>Treatment Resistant Populations (estimate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016 EU</td>
<td>30K</td>
<td>5-10K</td>
</tr>
<tr>
<td>2017 US</td>
<td>55-70K</td>
<td>10-20K</td>
</tr>
<tr>
<td>2018 Japan</td>
<td>30K</td>
<td>5-10K</td>
</tr>
</tbody>
</table>

**PARTNERSHIP DISCUSSIONS UNDERWAY**

**LAUNCH ALONE; EXPERIENCED EU LEADERSHIP IN PLACE**

**LAUNCH ALONE; BUILDING AN EXPERIENCED U.S. TEAM**
Europe
Dr. Olaf Bartsch
Targeted EU Build-out to Pursue NTM and CF Indications
Medical Science Liaison Focus

**Phase I**
*Initial Hires In Place*
- Germany
- France

**Phase II**
- UK
- Italy
- Sweden
- Netherlands
Diagnosed NTM Prevalence in EU 5

- Includes both newly diagnosed patients and those with active ongoing disease diagnosed in a previous year
  - Treatment of NTM often extends well into the second year

- Of the ~30k diagnosed NTM patients
  - ~20k are in EU5
  - Germany has the largest population with >5k

Source: Clarity Pharma Chart Audit.
NTM infections mostly occur in patients with underlying pulmonary diseases like COPD, bronchiectasis and asthma and CF.

- No on-label treatment available in Europe
- Cocktail of 3-4 antibiotics used off-label with significant side effects

KOL quote in Europe:

“Make sure you get this product approved for any indication; we are in real need for a safe treatment option for these patients”
CF Patients with Pseudomonas Lung Infections

80% Adults CF patients with chronic Pseudomonas aeruginosa infection

85% Increase in resistance to TOBI

Fatal genetic disease
Life expectancy of 38-40 years

1% to 3% Annual decline in lung function

1 Adapted from Cystic Fibrosis Foundation, Patient Registry Annual Data Reports, 2012.
The Need – CF / *Pseudomonas aeruginosa*

- Several inhaled antibiotics already available with acceptable treatment results

- Market very competitive with downward pressure on prices

- ARIKAYCE adds another treatment option for those patients intolerant or resistant to existing therapies

<table>
<thead>
<tr>
<th>Product</th>
<th>Treatment</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arikayce™</strong></td>
<td>Inhaled, liposomal formulation of amikacin</td>
<td>Phase 3 trial completed in Europe and Canada</td>
</tr>
<tr>
<td><strong>TOBI®</strong> (Novartis)</td>
<td>Inhaled tobramycin</td>
<td>Marketed Combined total sales of $281MM in 2014</td>
</tr>
<tr>
<td><strong>TOBI Podhaler®</strong> (Novartis)</td>
<td>Inhaled tobramycin powder</td>
<td></td>
</tr>
<tr>
<td><strong>Cayston®</strong> (Gilead Sciences)</td>
<td>Inhaled aztreonam</td>
<td>Marketed in Europe and US</td>
</tr>
<tr>
<td><strong>Colimycin and Colobreathe</strong></td>
<td>Inhaled colistimethate sodium</td>
<td>Marketed in Europe</td>
</tr>
<tr>
<td>(Actavis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bramitob®</strong> (Chiesi Group)</td>
<td>Inhaled tobramycin</td>
<td>Marketed in Europe</td>
</tr>
<tr>
<td><strong>BETHKIS®</strong> (Chiesi USA)</td>
<td>Inhaled tobramycin</td>
<td>Marketed in the US</td>
</tr>
<tr>
<td><strong>Aeroquin®</strong> (Actavis)</td>
<td>Inhaled levofloxacin</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
The Addressable Market

**CF / Pseudomonas: slow market penetration foreseen**
- 80% of the adult CF patients have chronic Pseudomonas infections
- The current gold standard is Tobramycin
- ARIKAYCE has some advantages in QoL (once daily) and is just another option for HCP’s

**All NTM: Major unmet need**
- 33% refractory patients represent the primary ARIKAYCE market
- The phase 2 data included patients with MAC and M abscessus
Key Considerations for Insmed Europe

- **Launch strategy** taking into account market sizes & market access possibilities, i.e. start in the 2 major countries (Germany & France), explore the UK and Italy and be opportunistic elsewhere (e.g. NL, Sweden)

- **European launch** provides learning opportunity for US launch: pricing, optimal positioning, patients onboarding and compliance with treatment

- **Insmed enters Europe** with a longer term focus: to broaden its organizational possibilities and enhance the outreach also for future products
EU Launch Preparation

- **Focused build-out of presence in 2015 / 2016**
  - Direct country organizations (Germany & France)
  - 4 markets under evaluation for direct approach (UK, Italy, Sweden, NL)
  - All other EU markets initially mapped through 3rd party consultants
  - Supply & distribution through 3rd party logistics provider

- **Medical Education**
  - Disease Awareness (focus on NTM)
  - Definition and Communication of the unmet need (NTM & CF)

- **KOL Management**
  - Top 5 KOL’s per EU market

- **Market Access preparation**
  - Focus on tier 1 countries (Germany, France)
  - Explore tier 2 markets (UK, Italy, NL, Sweden)
DX Patterns in DE are similar to other EU markets…

- Roughly 20% deemed “severe”
- DE system of referrals drives initial DX at Internal or General Medicine (38%) followed by Pulmonologist (34%)

...while TX Patterns in DE are not.

- Majority of patients seen in academic medical centers or solo private practice (vs UK)
- Only 5% of IV treatments involve amikacin IV vs. 34% amikacin IV in UK
- Very high use of beta agonists (34%)
- DE patients are 3 times more likely to visit the ER than in UK

Country or Region   | Est. Number of NTM Lung Disease Patients | Mild | Moderate | Severe |
---------------------|-----------------------------------------|------|----------|--------|
France              | 3,857                                   | 945  | 2,175    | 737    |
Germany             | 5,373                                   | 1,171| 3,116    | 1,086  |
Italy               | 3,714                                   | 722  | 2,464    | 528    |
Spain               | 2,764                                   | 672  | 1,531    | 561    |
United Kingdom      | 4,103                                   | 845  | 2,437    | 821    |
EU5                 | 19,811                                  | 4,355| 11,723   | 3,733  |
Japan               | 31,745                                  | 21,332| 9,873   | 540    |
EU5 + Japan         | 51,556                                  | 25,687| 21,596  | 4,273  |

Number of times patient visited ER for NTM Lung Disease Patients in past year (mean)

- France: 206 [A]
- Germany: 211 [B]
- Italy: 210 [C]
- Spain: 230 [D]
- UK: 155 [E]
- Japan: 147 [F]
- EU5: 1,012 [G]
- Total: 1,429 [I]

Don’t know responses: France: 23.3%, Germany: 66.1%, Italy: 14.2%, Spain: 29.8%, UK: 31.4%, Japan: 9.3%, EU5: 13.0%, ex-US: 36.1%
Example Germany

Launch possible shortly after approval

Pre launch strategy focused on:

- Medical education
  - Disease Awareness (NTM)
  - Definition of the unmet need
  - (NTM & CF)
- KOL Management
  - Advisory boards
  - PR
- Market Access preparation
  - G-BA consultation process
  - AMNOG Dossier development
German Disease Awareness Campaign NTM Lung Disease

- German Pulmonologist Introductory Mailing
- DA website www.ntmfaaktten.de
- German Advisory boards
- German Ad Campaign
- Medical Education Campaign
NTM Lung Disease Awareness Launch

Disease Awareness Launch Phase 1: Germany

February
- Disease Awareness Microsite Launch
- Banner Ads*
- Insmed Introduction Letter Mailer
- Letter
- Web Key

March
- Banner Ads (Third party vendor)
- Newsletter (Third party vendor)
- DGP Booth
- NTMinfo Literature
- Web Key

April
- Doc Check Email (Third party vendor)
- Banner Ads
- Journal Ad
- Journal Ad**
- Mailing of Disease Awareness Poster

*Banner Ads consist of flash banners and static banners on: doc check, esanum, doc check site seeing.
**Journal ads displayed across 10 publication. The same creative will run from March-June.
US Commercial Planning
Drayton Wise
Key Elements of the U.S. ARIKAYCE Launch Planning

Our Approach

1. Targeted Disease State Awareness, including our key learnings from EU experience
2. SALES + MEDICAL + MARKETING field-oriented and working as one
3. Augmenting therapy with services that maximize patient experience and convenience
4. Voice of the Patient MUST and WILL be represented in everything we do
5. Recruiting talented and experienced people to join this mission
Hallmark of a Successful Orphan Disease Approach:
Begins Early with Highly Targeted Disease State Awareness Campaign

NTM ISN’T WAITING. NEITHER SHOULD YOU.
U.S. ARIKAYCE Launch Planning:
Targeted Sales and Medical Presence Focused on Pulmonologists

30

Field-based pulmonary sales specialists

3,000

Pulmonologists represent over 80% of NTM patients

MSLs

Field Medical Science Liaisons To Convey NTM Medical Story

Patient Centricity

Maximizing convenience:

- 1. Patient services hub
- 2. Specialty pharmacy
US burden of illness study with major US payor confirms NTM is a costly disease:

- Monthly medical + pharmacy expenditures ≈ $5,000 less per month for those diagnosed and treated with existing therapies vs. those diagnosed and untreated/non-compliant

- It “pays” to aggressively treat NTM:
  - The economic impact of treatment is seen immediately in the claims data (reduction in hospitalizations and ER visits)

Treated NTM patients live long enough to recoup investment in therapy
Corporate Development
Wes Kaupinen
Corporate Development Focus: Build on our Commitment to NTM Patients

2015 Corporate Goal: Acquire at least one external asset

Key Corporate Development Criteria:

#1: Product/Product Candidate Serves an Orphan / Pulmonary Orphan Patient Population

#2: Therapeutic Indication is “NTM-Like”
### Differential Criteria Based on Development Stage

<table>
<thead>
<tr>
<th>Commercial</th>
<th>Development</th>
</tr>
</thead>
</table>
| ✓ World-Class Patient Management in Rare Disease(s):  
  ● Enables leverage of successful orphan commercial infrastructure |
| ✓ Affordably Priced:  
  ● Naturally limits pursuit of some therapeutic areas |
| ✓ Minimal Upfront Payment:  
  ● Consideration structured to reward success |
| ✓ Asset Currently “Under the Radar”:  
  ● Proprietary sourced transactions vs. competitive bidding processes |
There is a Broad Spectrum of Pulmonary Orphan Diseases; Many of These Patient Populations are Severely Underserved

<table>
<thead>
<tr>
<th>Auto-Immune Diseases</th>
<th>Genetic Surfactant Disorders</th>
<th>Lung-Limited idiopathic disorders</th>
<th>Trafficking and Lysosomal Storage Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-basement membrane syndrome</td>
<td>ABCA3</td>
<td>Idiopathic eosinophilic pneumonias</td>
<td>Hermansky-Pudlak syndrome</td>
</tr>
<tr>
<td>Pulmonary alveolar proteinosis</td>
<td>SP-A-related lung disease</td>
<td>Tracheobronchopathia osteochondroplastica</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td></td>
<td>SP-B-related lung disease</td>
<td>Tracheobronchomegaly (Mounier-Kuhn syndrome)</td>
<td>Neiman Pick C</td>
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<tr>
<td></td>
<td>SP-C-related lung disease</td>
<td>Idiopathic bronchiolitis</td>
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<tr>
<td>Channelopathies</td>
<td>Infectious Diseases</td>
<td>Neuromuscular disease</td>
<td></td>
</tr>
<tr>
<td>Pulmonary alveolar microlithiasis</td>
<td>Psuedomonas infections associated with CF</td>
<td>Amyotrophic lateral sclerosis</td>
<td>Granulomatosis with polyangiitis (Wegener’s)</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>MRSA lung infections associated with CF</td>
<td>Myasthenia gravis</td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td></td>
<td>Non-tuberculous mycobacterium lung infections</td>
<td>Dermatomyositis.pulmositis</td>
<td>Behçet’s disease</td>
</tr>
<tr>
<td></td>
<td>Fibrosing mediastinitis</td>
<td>Phakomatoses</td>
<td>Takayasu’s arteritis</td>
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<td></td>
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<td></td>
<td>Microscopic polyangiitis</td>
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<tr>
<td></td>
<td>Inherited forms of emphysema</td>
<td></td>
<td>Goodpasture syndrome</td>
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<tr>
<td></td>
<td>Alpha-1 antitrypsin deficiency</td>
<td></td>
<td>Polyarteritis nodosa</td>
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<tr>
<td></td>
<td>Elastin mutations</td>
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<tr>
<td></td>
<td>Salla disease</td>
<td></td>
<td>Other</td>
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<td></td>
<td>Sarcoidosis</td>
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<td>Thoracic endometriosis</td>
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<td>Langerhans’ cell histiocytosis</td>
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<td></td>
<td>Idiopathic pulmonary hemosiderosis</td>
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<td>Sickle Cell anemia</td>
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<td>Bronchiolitis obliterans</td>
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<td></td>
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<td>Hypersensitivity pneumonitis</td>
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<tr>
<td>Ciliary Disorders</td>
<td>Connective Tissue Matrix Disorders</td>
<td>Pulmonary Vascular Disease</td>
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<tr>
<td>Kartagener Syndrome</td>
<td>Marfan syndrome</td>
<td>Pulmonary Arterial Hypertension (PAH)</td>
<td></td>
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<tr>
<td>Primary ciliary dyskinesia</td>
<td>Ehler-Danlos syndrome</td>
<td>Pulmonary veno-occlusive disease (PVOD)</td>
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<td></td>
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<td>Chronic thromboembolic pulmonary hypertension (CTEPH)</td>
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<td>PH-associated with myeloproliferative diseases</td>
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<td>Pulmonary capillary hemangiomatosis</td>
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<td>Hereditary hemorrhagic telangiectasia</td>
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<tr>
<td>Congenital</td>
<td>Disorders of Respiratory Drive</td>
<td></td>
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<tr>
<td>Cystic adenomatoid malformation</td>
<td>Central Alveolar hypoventilation</td>
<td></td>
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<tr>
<td>Pulmonary sequestration</td>
<td>Narcolepsy</td>
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<tr>
<td>Neuroendocrine cell hyperplasia</td>
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<td>Connective Tissue Matrix Disorders</td>
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</tbody>
</table>
Insmed Vision:
Leading Sustainable Pulmonary Orphan Company
Insmed Vision: Leading Sustainable Pulmonary Orphan Company

Today

Future Vision

- CF
- NTM
- PAH
- AATD
- LAM
- NCFB
- SARC
- PAP
Tech Ops, Cash and Tax Planning

Andy Drechsler
Manufacturing and Supply Chain
Producing Product at Scale for Clinical and Commercial Supply

- Multi-sourced supply chain
- Global distribution
- Building out commercial scale manufacturing capabilities
Formulation and Filling of ARIKAYCE
- Current: 50kg Althea (US)
- Future: 50kg Althea (US) & 200kg Therapure (CAN)

Testing
- Covance (UK)

Labelling and Packaging
- For Clinical
  - Xerimis (US) and Biotec (UK)
- For Commercial
  - Almac (US) and Almac (UK)

Device
- PARI (GER)
Manufacturing and Global Supply Chain – ARIKAYCE

Goal: Dual sources throughout the supply chain

#1 - Amikacin (Italy)
#2 - Amikacin (China)
#1 - Cholesterol (France)
#2 - Cholesterol (India)
#1 - DPPC (Germany)
#2 - DPPC (Japan)

Device (Germany)

ARIKAYCE Manufacture (US & Canada)

Testing Sites (UK)

Patients

Almac UK
Almac US
Xerimis US
Biotec UK

Clinical Sites

in smed
Manufacturing and Global Supply Chain – ARIKAYCE

**Althea:**
- Current Clinical and Commercial launch site
- 50kg scale ~ 5,000 vials of ARIKAYCE per batch

**Therapure:**
- Future Commercial production site
  - On-line 2H 2015
- 200kg scale ~ 20,000 vials of ARIKAYCE per batch
Manufacturing and Supply Chain – INS1009

Formulation and Filling
- Toxicology studies
  - Axcellerate (NJ) – 1 liter batch size
- Phase 1 Clinical studies
  - AMRI (MA) – 1 liter batch size

Testing
- PPD (WI)

Labelling and Packaging
- For Clinical
  - Xerimis (PA)

Axcellerate

April  May  June  July  Aug  Sep  Oct

AMRI
Cash Needs from Operations

- Cash Balance at 12/31/14 = $159.2M

- Timing/pace of 2015 spending dependent on:
  - 212 trial enrollment
  - Manufacturing scale up
  - Manufacturing pace/schedule
  - European infrastructure build

- Debt $25M: interest only, due 1/1/16
  - Potentially able to modify
Tax Planning

- Commenced long term tax planning efforts in 2014
- Anticipate that Ireland will be our IP and tax hub for EU
- New entities: Ireland, Germany, France & Netherlands
- Long term plans for manufacturing and distribution
  - Current: Althea (San Diego, California, US)
  - 2015: Addition of Therapure (Toronto, Canada)
  - Future: Addition of Ireland
- Location of intellectual property and manufacturing operations should provide tax rates below current US statutory rates
Key Takeaways

Mission
- Building a patient-focused and sustainable biopharmaceutical company focused on orphan, pulmonary indications

ARIKAYCE
- Significant global NTM market opportunity
- Phase 3 global study in NTM underway
- MAA submitted/validated in EU for NTM and CF

INS1009
- IND to be filed 2H 2015
- Phase 1 enrollment by end of 2015
- Potential 505(b)(2) path to approval
Thank You

www.insmed.com