Public Meeting on Non-Tuberculous Mycobacterial (NTM) Lung Infections
Patient-Focused Drug Development

October 15, 2015
Welcome

Soujanya Giambone, MBA
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 15, 2015
Agenda

• **Setting the context**
  – Opening Remarks
  – Overview of FDA’s Patient-Focused Drug Development Initiative
  – Background on NTM and Therapeutic Options
  – Overview of Discussion Format

• **Discussion Topic 1**: Disease symptoms and daily impacts that matter most to patients

• **Discussion Topic 2**: Patients’ perspectives on current approaches to treating NTM

• Lunch

• **Scientific Discussion**
Opening Remarks

John Farley, MD MPH
Deputy Director, Office of Antimicrobial Products (OAP)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 15, 2015
FDA’s Patient-Focused Drug Development Initiative

Theresa Mullin, PhD
Director, Office of Strategic Program
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 15, 2015
Patient-Focused Drug Development under PDUFA V

• FDA is developing a more systematic way of gathering patient perspective on their condition and available treatment options
  – Patient perspective helps inform our understanding of the context for the assessment of benefit-risk and decision making for new drugs
  – Input can inform FDA’s oversight both during drug development and during our review of a marketing application

• Patient-Focused Drug Development is part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V)
  – FDA will convene at least 20 meetings on specific disease areas over the next five years
  – Meetings will help develop a systematic approach to gathering patient input
Identifying Disease Areas for the Patient-Focused Meetings

- In September 2012, FDA announced a preliminary set of diseases as potential meeting candidates
  - Public input on these nominations was collected. FDA carefully considered these public comments and the perspectives of our drug review divisions at FDA

- FDA identified a set of 16 diseases to be the focus of meetings for fiscal years 2013-2015
  - Another public process was initiated and 8 diseases were determined as the disease set for fiscal years 2016-2017
Disease Areas to be the focus of meetings for FY 2013-2017

<table>
<thead>
<tr>
<th>Fiscal Year 2013</th>
<th>Fiscal Year 2014</th>
<th>Fiscal Year 2015</th>
<th>Fiscal Year 2016-2017</th>
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<tr>
<td>Chronic fatigue syndrome/myalgic encephalomyelitis</td>
<td>Sickle cell disease</td>
<td>Female sexual dysfunction</td>
<td>Non-tuberculous mycobacterial lung infections</td>
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<td>HIV</td>
<td>Fibromyalgia</td>
<td>Breast cancer</td>
<td>To be announced</td>
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<td>Pulmonary arterial hypertension</td>
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<td>Alopecia areata</td>
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<td>Inborn errors of metabolism</td>
<td>Functional gastrointestinal disorders</td>
<td>Autism</td>
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<td>Hemophilia A, B, and other heritable bleeding disorders</td>
<td>Huntingdon’s disease and Parkinson’s disease Alpha-1 antitrypsin deficiency</td>
<td>Hereditary angioedema</td>
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<td>Idiopathic pulmonary fibrosis</td>
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<td>Patients who have received an organ transplant</td>
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<td>Neuropathic pain associated with peripheral neuropathy</td>
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<td>Sarcopenia</td>
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Tailoring Each Patient-Focused Meeting

• Each meeting focuses on a set of questions that aim to elicit patients' perspectives on their disease and on treatment approaches
  – We start with a set of questions that could apply to any disease area; these questions are taken from FDA’s benefit-risk framework and represent important considerations in our decision-making
  – We then further tailor the questions to the disease area of the meeting (e.g., current state of drug development, specific interests of the FDA review division, and the needs of the patient population)

• Focus on relevant current topics in drug development for the disease at each meeting
  – E.g., focus on HIV patient perspectives on potential “cure research”

• We’ve learned that active patient involvement and participation is key to the success of these meetings.
“Voice of the Patient” Reports

• Following each meeting, FDA publishes a Voice of the Patient report that summarizes the patient testimony at the meeting, perspectives shared in written docket comments, as well as any unique views provided by those who joined the meeting webcast.

• These reports serve an important function in communicating to both FDA review staff and the regulated industry what improvements patients would most like to see in their daily life.

• FDA believes that the long run impact of this program will be a better, more informed understanding of how we might find ways to develop new treatments for these diseases.
NTM Lung Infections

Hala Samsuddin, MD

Division of Antimicrobial Products (DAIP)
Center for Drug Evaluation and Research
FDA
Outline

• What are non-tuberculous mycobacteria (NTM)?
• Who is at risk for NTM lung infections?
• What are the clinical manifestations?
• How many people are affected in the US?
• Treatment?
• Challenges in drug development for NTM lung infections
Non-Tuberculous Mycobacteria

- More than 150 species recognized
- Examples: *M. avium* complex (MAC), *M. abscessus*, *M. kansasii*, *M. xenopi*, etc.
- In the US, MAC accounts for approximately 70-80%, *M. abscessus* group for most of the remainder
- Acquired by inhalation from environment
- Water thought to be the main source
Lung NTM Distribution and Prevalence in the United States

Adjemian et al. AJRCCM 2012
Who is at Risk?

- Underlying lung disease and/or genetic predisposition
- Bronchiectasis (damage and scarring of airways)
  - Body type: thin, chest cage abnormalities, mainly women
- Cystic Fibrosis
- COPD (chronic obstructive pulmonary disease)
- Prior tuberculosis
- Alpha-one antitrypsin deficiency
- Primary ciliary dyskinesia
- Immunosuppressive therapy
Clinical Manifestations

- Cough
- Shortness of breath
- Sputum production
- Hemoptysis (coughing up blood)
- Chest pain
- Fatigue
- Weight loss
- Fever
- Findings of cavity or lung nodules on X-ray or CT scan of lungs
- Positive sputum cultures
How Common are NTM Lung Infections

• Increasing in the general population and in CF
• In the US, estimated to be present (prevalence) in approximately 8-9 per 100,000 people
  \(^1\)
• Approximately 20 per 100,000 people older than 50 years of age\(^1,2\)
• Approximately 47 per 100,000 in people older than 70 years of age\(^3\)
• Approximately 10-15% of CF patients\(^4\)

\(^1\) Winthrop et al. AJRCCM 2010, 2 Prevots et al. AJRCCM 2010, 3 Adjemian et al. AJRCCM 2012,
4Leung et al. Curr Opin Pulm Med 2013
Increase in NTM Lung Infections - Medicare

Adjemian et al. AJRCCM 2012
Why are NTM Lung Infections Increasing

• Increased awareness
• Increased number of susceptible individuals
  – Older population
  – More chronic lung disease
  – More immunocompromised
  – Improved survival among CF patients
• Possibly increased exposure
Treatment

• No FDA-approved drugs for NTM lung infections
• Physicians use antibiotics that are approved to treat tuberculosis or other bacterial infections
• Antibiotic combinations recommended:
  – 3 or more drugs, may include an injectable
• Optimal combination and duration of injectable and overall therapy are not clearly defined
• Treatment is lengthy
  – goal is culture negative sputum for 12 consecutive months\(^1\)

\(^1\) Griffith et al. AJRCCM 2007
Treatment

• Study 2004-2005\(^1\):
  – Median 5 antibiotics (range 1-10)
  – Median treatment 2638 drug days (range 84-7689)
  – Median cost per patient $19,876 (range 389-70,917)
  – \textit{M. abscessus} associated with higher treatment cost

• Adverse reactions (side effects) are common:
  – 50\% for “commonly used” drugs
  – 100\% for “less commonly” used drugs

\(^1\) Ballarino et al. Resp. Med. 2009
Challenges to Drug Development

- Disease progression varies by underlying lung disease and appearance on X-rays
- Response to treatment varies by species
- Therefore a drug that may treat one NTM species or one affected patient population may not treat other NTM or other patient populations
- Treatments (and therefore trials) are lengthy
- Need to define early assessments that may lead to faster drug approval (will be discussed further this afternoon)
Conclusions

• NTM lung infections are increasing in the US
• Affected population in the US are mainly patients with bronchiectasis, and individuals with underlying lung disease
• No FDA-approved drugs for lung NTM
• Currently used treatments are multiple drugs for lengthy periods and with significant side effects
• **Unmet** medical need
• Many challenges to drug development
Thank You
Overview of Discussion Format

Soujanya Giambone, MBA
Office of Strategic Programs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 15, 2015
Discussion Overview

Topic 1: The symptoms that matter most to you
   – Which symptoms have the most significant impact on your life?
   – How do these symptoms affect your ability to do specific activities?
   – How have your symptoms changed?

Topic 2: Current approaches to treating NTM lung infections
   – What are you doing to treat NTM lung infections?
   – How well is/are the treatment(s) treating your significant symptoms?
   – What are the biggest downsides to your treatments?
   – What would you look for in an “ideal” treatment?
Discussion Format

• We will first hear from a panel of patients and caregivers
  – The purpose is to set a good foundation for our discussion
  – They reflect a range of experiences with NTM lung infections

• We will then broaden the dialogue to include patients and patient representatives in the audience
  – The purpose is to build on the experiences shared by the panel
  – We will ask questions and invite you to raise your hand to respond
  – Please state your name before answering
Discussion Format, continued

• You’ll have a chance to answer “polling” questions
  – Their purpose is to aid our discussion
  – In-person participants, use the “clickers” to respond
  – Web participants, answer the questions through the webcast
  – Patients and patient representatives only, please

• Web participants can add comments through the webcast
  – Although they may not all be read or summarized today, your comments will be incorporated into our summary report
  – We’ll occasionally go to the phones to give you another opportunity to contribute
Send us your comments!

• You can send us comments through the “public docket”
  – The docket will be open until December 15, 2015
  – Share your experience, or expand upon something discussed today
  – Comments will be incorporated into our summary report
  – Anyone is welcome to comment

Visit: http://www.regulations.gov/#!documentDetail;D=FDA-2012-N-0967-0748
Click Comment Now!
Resources at FDA

• FDA Office of Health and Constituent Affairs
  – Contact: PatientNetwork@fda.hhs.gov, (301) 796-8460
  – Liaison between FDA and stakeholder organizations
  – Runs the Patient Representative Program
    • Patient Representatives advise FDA at Advisory Committee meetings

• CDER Office of Center Director
  – Professional Affairs and Stakeholder Engagement (PASE)
  – Contact: Francis Kalush, francis.kalush@fda.hhs.gov
  – Facilitates communication and collaboration between CDER and patient and healthcare professional stakeholders and others on issues concerning drug development, drug review and drug safety.
Discussion Ground Rules

• We encourage patients to contribute to the dialogue—caregivers and advocates are welcome too

• FDA is here to listen

• Discussion will focus on symptoms and treatments
  – Open Public Comment Period is available to comment on other topics

• The views expressed today are personal opinions

• Respect for one another is paramount

• Let us know how the meeting went today; evaluation forms at registration desk
Discussion Topic 1

Disease symptoms and daily impacts that matter most to patients

Soujanya Giambone
Facilitator
Topic 1 Panel Participants

• Marilyn Lundy
• Philip Leitman
• Barbara Hudson
• Kathleen Keating
Topic 1 Discussion: Disease symptoms and daily impacts that matter most to patients

- Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life?

- Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition?

- How has your condition and its symptoms changed over time?

- What worries you most about your condition?
BREAK
Discussion Topic 2

Patients’ perspectives on current approaches to treating NTM Lung Infections

Soujanya Giambone
Facilitator
Topic 2 Panel Participants

• Jennifer Bogenrief
• Betsy Glaeser
• Gaby Chien
• Mary Fisher
• Patricia Yost
Topic 2 Discussion: Patients’ perspectives on current approaches to treating NTM

- What are you currently doing to help treat your condition or its symptoms?
  - What specific symptoms do your treatments address?
  - How has your treatment regimen changed over time, and why?
- How well does your current treatment regimen treat the most significant symptoms of your disease?
- What are the most significant downsides to your current treatments, and how do they affect your daily life?
- Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?
Scenario

Imagine that...

- You have been invited to participate in a clinical trial to study an experimental antibiotic treatment for NTM lung infections
- The purpose of the study is to better understand how well this treatment works and its safety
- This clinical study lasts 2 years, and clinical visits will occur every month for 2 years, in addition to regular doctor’s visits
- Visits will involve monthly sputum collections, lab tests, lung function tests, and other laboratory tests as needed
- Treatments may involve either IV medication (administered via catheter) or inhaled therapy (administered for 1-2 hours)
- Treatment will be given in addition to standard of care

What thoughts and questions come to mind as you hear this scenario?
LUNCH
Scientific Discussion on Non-tuberculous Mycobacterial (NTM) Lung Infections

October 15, 2015
Welcome

John Farley, MD MPH
Deputy Director, OAP
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

October 15, 2015
Epidemiology & Natural History of NTM Lung Infections

Kenneth N Olivier, MD, MPH
Cardiovascular & Pulmonary Branch/NHLBI
Oct 15, 2015
NTM Epid...historic

Fig. 11. Geographic variation in the frequency of reactors to 0.0001 mg PPD-B.
NTM Epid...historic

Prevalence *M. avium* complex/100,000 by state
Good. J Infect Dis 1982; 146:829-833
Nontuberculous Mycobacterial Lung Disease Prevalence at Four Integrated Health Care Delivery Systems

D. Rebecca Prevots¹, Pamela A. Shaw², Daniel Strickland³, Lisa A. Jackson⁴, Marsha A. Raebel⁵, Mary Ann Blosky⁶, Ruben Montes de Oca¹, Yvonne R. Shea⁷, Amy E. Seitz¹, Steven M. Holland¹, and Kenneth N. Olivier¹

- Avg age adj period prevalence
  2004-2006: 5.5/100K ~ 16K
  - Increasing 3% per year
  - NTM >> TB over age 60
  - Women > Men
Retrospective study Ontario
Case = ≥2 pos sputum or 1 bronch/bx
Species in 2010
- Mac 12.2/100K
- M. xenopi 3.9/100K
- M. abscessus 0.6/100K

6.3% annual increase
6.5% annual increase
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D. Rebecca Prevots¹, Pamela A. Shaw², Daniel Strickland³, Lisa A. Jackson⁴, Marsha A. Raebel⁵, Mary Ann Blosky⁶, Ruben Montes de Oca¹, Yvonne R. Shea⁷, Amy E. Seitz¹, Steven M. Holland¹, and Kenneth N. Olivier¹

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US Medicare: Bronchiectasis Prevalence
Seitz A. Chest 2012

US Medicare: NTM Prevalence
Adjemian J. AJRCCM 2012
The Burden of Pulmonary Nontuberculous Mycobacterial Disease in the United States

Sara E. Strollo¹, Jennifer Adjemian¹,², Michael K. Adjemian³, and D. Rebecca Prevots¹

¹Epidemiology Unit, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; ²Commissioned Corps, United States Public Health Service, Rockville, Maryland; and ³Market and Trade Economics Division, Economic Research Service, United States Department of Agriculture, Washington, DC

- Estimated annual medical costs
  - Extrapolated data from US Medicare and practice survey studies
  - Assumed
    - 73% cases missed based on ICD9 coding
    - 31% NTM cases are younger than age 65
    - 8.2% annual increase in prevalence
  - 2010 US Census Bureau data

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<tr>
<th>National Nontuberculous Mycobacterial Disease Estimates</th>
<th>National Nontuberculous Mycobacterial Disease Estimates Assuming 1 Additional Outpatient Visit per Year</th>
<th>National Nontuberculous Mycobacterial Disease Estimates Assuming 2 Additional Outpatient Visits per Year</th>
<th>National Nontuberculous Mycobacterial Disease Estimates Assuming 3 Additional Outpatient Visits per Year</th>
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<tbody>
<tr>
<td>Annual medical encounters*</td>
<td>86,244</td>
<td>172,487</td>
<td>258,731</td>
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<td>Annual cost†</td>
<td>$815,098,690</td>
<td>$937,491,959</td>
<td>$1,059,885,228</td>
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</table>

- 80% costs attributed to prescription medication costs

Bronchiectasis
Seitz A. Chest 2012

NTM
Adjemian J. AJRCCM 2012

Bronchiectasis Period Prevalence
cases per 100,000 individuals:
- 488 - 564
- 565 - 784
- 795 - 940
- 941 - 1076
- 1077 - 1291
- 1292 - 1692

NTM Cases/100,000 Persons:
- 0-29
- 27-77
- 78-121
- 122-192
- 193-396

NIH National Heart, Lung, and Blood Institute
Spatial Clusters of Nontuberculous Mycobacterial Lung Disease in the United States

Jennifer Adjemian¹,², Kenneth N. Olivier², Amy E. Seitz¹,², Joseph O. Falkingham III³, Steven M. Holland², and D. Rebecca Prevots¹,²

¹Epidemiology Unit and ²Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and ³Virginia Polytechnic Institute and State University, Blacksburg, Virginia

High risk counties
- > surface water (OR 4.6)
- > evapotranspiration (4.0)
- > copper (1.2) & Na⁺ (1.9)
- < manganese (0.7)
Nontuberculous Mycobacteria among Patients with Cystic Fibrosis in the United States
Screening Practices and Environmental Risk

Jennifer Adjemian¹,², Kenneth N. Olivier³, and D. Rebecca Prevots¹

¹Epidemiology Unit and ³Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and ²United States Public Health Service, Rockville, Maryland

- CF Patient Registry 2010 & 2011
- 18,003 pts >12 yrs
  - 14% pos Mac/Mab
  - 4 significant geospatial clusters
    - Saturated vapor pressure specific climatic risk

Prevalence of NTM among CF Patients

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<th>Prevalence</th>
<th>Spatial Clusters of NTM</th>
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<td>0 - 10</td>
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<td>10 - 15</td>
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Adjemian. Am J Respir Crit Care Med 2014
Significance of *M. abscessus*

- *M. abscessus* excess decline of -0.78% per year vs no NTM (p=0.02)
- Other NTM were intermediate between *M. abscessus* and no NTM
A Steady Increase in Nontuberculous Mycobacteriosis Mortality and Estimated Prevalence in Japan

Kozo Morimoto\(^1\), Kazuro Iwai\(^2\), Kazuhiro Uchimura\(^2\), Masao Okumura\(^1\), Takashi Yoshiyama\(^1\), Kozo Yoshimori\(^1\), Hideo Ogata\(^1\), Atsuyuki Kurashima\(^1\), Akihiko Gemma\(^3\), and Shoji Kudoh\(^1\)

\(^1\)Respiratory Disease Center, Fukuiji Hospital, Japan Anti-Tuberculosis Association. \(^2\)Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, and \(^3\)Division of Pulmonary Medicine, Infectious Diseases, and Oncology, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan

- Increasing mortality for both sexes through 2000, then only in women
  - Increased in warm areas, high rainfall

- Estimated prevalence 33-65/100K
  - >50% dx with Mac remained cx pos at 2yr; 36% cx pos at 5 yr

Several studies have reported 5-year mortality:

- Hayashi AJRCCM 2012 – Japan: 25%
- Ito IJTLD 2012 – Japan: 28%
- Andrejak AJRCCM 2010 – Denmark: 40%
- Kotilainen SJID 2013 – Finland: 28% (4yr)
- Strollo (unpub 2015) – NIH cohort: 25%
Mortality risk factors

Fibrocavitary Disease

- Median survival
  - FCD = 9.0 years
  - No FCD = 13.1 years
  - $p = 0.006$

Pulmonary Hypertension

- Median survival
  - PH = 6.8 years
  - No PH = >18 years
  - $p = 0.48$
Summary

- US prevalence difficult to assess
  - ~16K – 84K
- Increased in women and age >60
- Considerable geographic variability
  - Likely reflects environmental influences
- Disease burden and costs are substantial
- Adversely effects lung function
- Associated with increased mortality
Review Considerations for New Drugs

Hala Shamsuddin, MD
Patient Focused Drug Development
NTM Lung Infections
October 15, 2015
Outline

- Adequate and Well Controlled Clinical Trials
- Drugs in Combination
- Trial Endpoints
Drug Development

• Non-Clinical
  – Chemistry and Manufacturing
  – Toxicology
  – Pharmacology
  – In vitro activity
  – Animal models of infection (if any)
Clinical Trials

• For market authorization/approval, drug must show substantial evidence of efficacy
  – Section 505(d) of the FD&C act: adequate and well-controlled investigations

• 21 CFR 314.126
  – Adequate and well controlled clinical trials
  – To distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo-effect, or biased observation.
Types of A &WC Clinical Trials

• Placebo concurrent control
  – Randomized trial in which test drug is compared to inactive drug that is similar in appearance

• No treatment concurrent control
  – Randomized trial in which test drug is compared to no treatment

• Dose-comparison concurrent control
  – Randomized trial in which two or more doses of the test drug are compared
Types of A &WC Clinical Trials

• Active treatment concurrent control
  – Randomized trial in which test drug is compared to known effective therapy (active control)

• Historical control
  – Test drug is compared to historical experience
  – Reserved for special circumstances (e.g., disease with high mortality, course of illness predictable, or where drug effect is self-evident such as in general anesthetics)
Types of Clinical Trials

• Superiority Trials: test drug better than comparator
  – Placebo, no treatment, dose-comparison, active control or historical trials

• Advantage: Can assess any outcome of interest regardless of what previous trials had assessed
Clinical Trials

• Non-inferiority trials: test drug no worse than an active comparator by a certain pre-specified degree (non-inferiority margin)

• Disadvantages
  – The effect of the active comparator compared to placebo needs to be estimated in the particular population and for the particular outcome of interest
  – May limit choice of study population and study outcome measures
  – Possible that study cannot support efficacy if no historical evidence of active comparator exists
NTM Lung Infection Trials

• Monotherapy is not recommended
• Complicates trial design for a new regimen; For diseases that require use of drugs in combination, the new drug(s) must be demonstrated to make a contribution to the overall regimen
  – The contribution may be additive treatment effect, prevention of emergence of resistance or mitigation of toxicity
  – Demonstrating the contribution of a drug in a combination regimen may be difficult unless the clinical trial is an add-on trial
• In some instances, drugs in a combination regimen can be co-developed.
Drugs in Combination

- Guidance for Industry – Co-development of two or more new investigational drugs for use in combination
  - Treatment of serious disease (lung NTM is)
  - Compelling reasons why the drugs cannot be developed independently (monotherapy is not recommended)
  - Strong biologic rationale for the combination (e.g., drugs act on different microbial targets)
  - Nonclinical evidence that combination provides significant therapeutic advance over available therapy and is superior to the individual drugs (in vitro synergy or prevention of resistance; effects in animal model)

NTM Lung Infection Trials

• Superiority trials
  – Add-on trials: Test drug or test drug combination added to background regimen (BR) compared to placebo or no treatment added to BR
    • Test drug plus BR vs. BR used in TB trials
  – New Regimen
    • Test drug combination compared to placebo or no treatment (no BR) in patients in whom delaying treatment may be clinically acceptable
    • Test combination regimen compared to another combination that does not include the same drugs
    • Contribution of each component may be demonstrated in vitro or animal model
NTM Lung Infection Trials

• Non-inferiority trials
  – Test drug substitutes for a drug in the BR (has been used in TB to allow treatment shortening)
  – If feasible, compare new combination regimen to another combination regimen for treatment shortening or mitigation of toxicities

• NI trials are likely to be extremely challenging
  – Treatment effect of single drug substitution for efficacy or to allow shorter treatment duration is not known to allow derivation of NI margin
Trial Endpoints (Outcome Measures)

- Assess a clinically meaningful endpoint that is a direct measure of how a patient feels, functions or survives
  - Federal Register/Vol. 57, No.73/April 15, 1992
- Include:
  - Improved survival
  - Improvement of symptoms or functional capacity
  - Prevention of disease complication (e.g., treatment of latent TB)
Biomarkers and Surrogates

• Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to an intervention.

• A surrogate is a laboratory measurement or physical sign that is used as a substitute for a clinically meaningful outcome
  – Reasonably likely to predict clinical benefit [21 CFR 314.500 (subpart H)]
  – Examples: BP, HIV viral load
Surrogate Endpoints

• A surrogate is a biomarker, but not every biomarker is a surrogate

• However, for a biomarker to be established as a surrogate that is predictive of clinical outcome, evidence that changes in the biomarker correlate with changes in the clinical outcome should be established.

• Once established, surrogates allow faster drug development

• If accelerated approval on the basis of surrogate biomarker, a confirmatory trial that assesses the clinical outcome is required
  – Example: TB drugs may receive accelerated approval based on culture conversion to negative but a confirmatory trial showing relapse free survival is required
Endpoints in NTM Lung Infections Trials

• Endpoints under consideration in NTM lung infection trials

1. Survival

2. Measures of symptoms or function
   - Clinician reported outcomes: may be difficult for some symptoms
   - Patient reported outcomes (PRO): require validation
   - 6MWT or other functional assessment: degree of change that is meaningful to the patient should be defined
Endpoints in NTM Lung Infections Trials

3. Surrogate biomarkers to consider

- Microbiologic: Sputum culture conversion to negative
  - Similar to TB trials, but
    - Number of consecutive negative cultures not established
    - Timing of determining conversion during therapy not established
    - Correlation with clinical outcomes needs to be established

- Other surrogates? (e.g., radiologic – same considerations as microbiologic endpoints):
Conclusions

• Drugs need to show evidence of *efficacy for a clinically meaningful outcome* evaluated in *adequate and well controlled trials*

• Surrogate markers can be used for approval if the surrogate has been shown to *predict/correlate with* a meaningful clinical outcome

• PROs, if validated, can be used for approval

• Co-development of a new test drug combination may be possible in certain situations
The Road from Patient-Focused Drug Development Public Meetings to Clinical Study Endpoints

Selena R. Daniels, Pharm.D., M.S.
Clinical Outcome Assessments Staff (formerly SEALD)
Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Disclaimer

The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.
PATIENT-FOCUSED DRUG DEVELOPMENT (PFDD) MEETINGS

WHERE DO WE GO FROM HERE
I need a valid assessment.
Two Pathways for FDA Clinical Outcome Assessment Review & Advice

1. **Within** an individual drug development program
   - Investigational New Drug (IND) submissions to FDA
   - Potential to result in labeling claims

2. Within the Drug Development Tool (DDT) qualification program; **outside** of an individual drug development program
   - Potential to result in qualification

*In the future, we anticipate there will be tools that are both qualified and in labeling.*
Key Takeaways

• PFDD meetings are a “starting point” for developing patient-focused outcome measures and endpoints

• The outcomes of PFDD meetings will support and guide FDA risk-benefit assessments in drug reviews

• Patients’ input ultimately helps determine:
  – **WHAT** is measured to provide evidence of treatment benefit
  – **HOW** best to measure concepts in a clinical study
  – **WHAT** a meaningful improvement is in treatment benefit
The Road from Patient-Focused Drug Development Public Meetings to Clinical Study Endpoints

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Office of New Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Quality of Life-NTM Module

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UNIVERSITY OF MIAMI

ACKNOWLEDGEMENTS: KEN OLIVIER, KEVIN WINTHROP, MATTHIAS SALATHE

Acknowledgements

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Collaboration with:
- Dr. Ken Olivier, NIH
- Dr. Matthias Salathe
- Dr. Kevin Withrop
Objectives

- Nontuberculous mycobacteria (NTM) is a substantial cause of pulmonary infections and can affect those with chronic respiratory diseases, such as cystic fibrosis (CF) and bronchiectasis.

- NTM is rare, poorly understood, and difficult to treat, with few clear identified endpoints to evaluate new medications in randomized, controlled trials.

- We are developing a patient-reported outcome (PRO) that identifies key symptoms, tracks the progression of disease, and can serve as an important end-point in clinical trials of new therapies (FDA Guidance, 2009)

- The aim of this study was to develop an instrument for NTM symptoms; this can be used with existing PROs measures for CF (CFQ-R) and bronchiectasis (QOL-B)
Methods

• We followed the FDA Guidance on PROs (2009)
• Reviewed published literature on NTM to identify critical symptoms and challenges of living with NTM
• Focus groups, moderated by a psychologist, were conducted with adults with NTM + bronchiectasis at 2 sites, N=31
• A consensus panel of 9 pulmonologists with expertise in NTM provided input on how NTM and its treatment affects their patients
• Open-ended interviews were conducted with 13 patients: asked how NTM affects their daily lives; including frequent and difficult symptoms, effects on physical, emotional, and social functioning. Patients then completed the QOL-B; coded in Atlas.ti
• Cognitive testing, using a standard “think aloud” procedure conducted with 53 adults; input on the preliminary items & rating scale options
• We completed an initial psychometric validation of the module in 148 patients
Measurement Development Process

Focus groups of adults with bronchiectasis and NTM (N=31)

Focus group with medical experts treating NTM (N=9)

Open-ended interviews with patients to identify key symptoms and impact of disease on daily functioning (N=13)

Interviews coded in Atlas.ti to identify critical concepts

Instrument Created

Cognitive testing (N=53) of draft instrument to assess clarity, relevance, and completeness, administered NTM Module

NTM Module completed by total of 148 individuals – preliminary psychometric analyses completed
## Patient Demographics

<table>
<thead>
<tr>
<th>Gender N (%)</th>
<th>Focus Groups (N=31)</th>
<th>Open-Ended Interviews (N=13)</th>
<th>Cognitive Testing (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>29 (93.5%)</td>
<td>12 (92.3%)</td>
<td>45 (83.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>2 (6.5%)</td>
<td>1 (7.7%)</td>
<td>8 (14.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>31 (100%)</td>
<td>13 (100%)</td>
<td>47 (87%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>0</td>
<td>5 (9.3%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>0</td>
<td>0</td>
<td>2 (3.8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean (Range)</th>
<th>Focus Groups (N=31)</th>
<th>Open-Ended Interviews (N=13)</th>
<th>Cognitive Testing (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67.8 years (54.9 – 91.1 years)</td>
<td>65.9 years (42 – 82 years)</td>
<td>66.3 years (28 – 86 years)</td>
<td></td>
</tr>
</tbody>
</table>
**Key Themes**

### Main themes from Focus Groups (N=31)
- Frequent pain (dull, aches, pressure in chest)
  - Metal taste in mouth
- Fever
  - Lack of sleep

### Main themes from Open-Ended Interviews (N=13)
- Fatigue
  - Sensitivity to smell
- Sensitivity to cold/chills
  - Hot flashes/sweats

### Main themes from Physician Panel (N=9)
- Memory loss
  - Body Image issues
- Side effects from medications: GI problems
- Weight loss with greater disease severity
Results

• Focus groups and open-ended interviews identified eating issues, sleep quality, fever, and chills; physicians also identified body image as a concern

• The new NTM Module consists of eight unique symptoms; administered to 148 patients ($\alpha = .73$); very good reliability

Sample items from NTM module

“Bothered by cold weather?”

“Have you experienced problems with memory?”
## Internal consistency of NTM module (N = 148)

<table>
<thead>
<tr>
<th>Scale Name</th>
<th>Cronbach's Alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTM Symptoms</td>
<td>0.73</td>
</tr>
<tr>
<td>Body Image</td>
<td>0.76</td>
</tr>
<tr>
<td>Eating Problems</td>
<td>0.89</td>
</tr>
<tr>
<td>Digestive Symptoms</td>
<td>0.75</td>
</tr>
</tbody>
</table>
Multitrait analysis of NTM module (N = 148)

<table>
<thead>
<tr>
<th>Item</th>
<th>Abbreviated Item Content</th>
<th>NTM Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTM48</td>
<td>Feverish (chills, sweating)</td>
<td>0.42(^a)</td>
</tr>
<tr>
<td>NTM49</td>
<td>Problems sleeping</td>
<td>0.39(^a,b)</td>
</tr>
<tr>
<td>NTM50</td>
<td>Pain</td>
<td>0.41(^a)</td>
</tr>
<tr>
<td>NTM51</td>
<td>Bothered by cold weather</td>
<td>0.51(^a)</td>
</tr>
<tr>
<td>NTM52</td>
<td>Sensitivity to smell</td>
<td>0.37(^a,b)</td>
</tr>
<tr>
<td>NTM53</td>
<td>Sensitivity to taste</td>
<td>0.39(^a)</td>
</tr>
<tr>
<td>NTM54</td>
<td>Bad taste in mouth</td>
<td>0.48(^a)</td>
</tr>
<tr>
<td>NTM55</td>
<td>Memory problems</td>
<td>0.45(^a)</td>
</tr>
</tbody>
</table>

\(^a\) Item-scale correlation adjusted for overlap (item removed from its scale for correlation)

\(^b\) Item-scale correlation is <.40
Algorithm for administering NTM module with QOL-B or CFQ-R

- Individual with NTM
  - Bronchiectasis
    - Completes QOL-B
    - NTM Module
      - NTM Module + Additional Scales
        - Digestive Symptoms
        - Eating Issues
        - Body Image
        - NTM Symptoms
  - CF
    - Completes CFQ-R
      - CFQ-R contains Body Image, Digestive Symptoms, & Eating Issues Scales
      - Only fill out NTM Module
Summary & Future Directions

• Cognitive testing indicated that the draft items were relevant, clear, and easy to understand

• Strong reliability

• When utilizing NTM module with non-CF bronchiectasis: use module + Body Image, Eating Issues, & Digestive Symptoms scale (elicited from those with bronchiectasis)

• Next steps include additional psychometric testing, and identification of the meaningful change on this instrument
Challenges in design of clinical trials for NTM lung infections

Anne E. O’Donnell MD
October 15, 2015
Disclosures

- Principal Investigator/Grant support to GU for clinical trials
  - Insmed (inhaled liposomal amikacin)
- Foundation support to GU for Bronchiectasis Registry
  - COPD Foundation
- Consultant/Advisor
  - Insmed (inhaled liposomal amikacin): in Jan 2014
  - Xellia Pharmaceuticals (manufactures amikacin and colistin)

- No FDA approved therapies
In a perfect world
- Medications are simple
- Medications are tolerable
- Results are easy to evaluate:
  - Patient feels better
  - Infection is cured
  - Lung damage reversed
- Infection never recurs

Reality
- Regimen is complex
- Side effects are troublesome
- What constitutes response?
  - Microbiology
  - Imaging
  - Lung function
  - Patient’s symptoms
- “Cure” is elusive
NTM and clinical trials

• Microbiologic results
  – Reduction in organism counts
  – Eradication of organism
  – Duration of response
  – Presence or development of resistance

• Imaging results

• Lung function results

• Patient reported outcomes
  – Exacerbations are not a clinical feature in NTM
NTM and clinical trials
Microbiology

• Current “gold standard”
  – 12 months of negative cultures while receiving Rx
• How are cultures processed?
  – Routine practice
    • Haphazard, standard lab evaluation
  – Tyler
    • Monthly
    • Semiquantitative cultures
    • Macrolide susceptibility testing
    • Genotyping

  • Griffith DE et al. Am J Respir Crit Care Med 2015;192:754-760
• Tyler results
  – 180 patients with MAC and nodular bronchiectasis
  – Greater than 12 months of three drug therapy
    • 82% had culture conversion to negative
    • Microbiologic recurrences during therapy in 14%
      – 73% reinfection
      – 27% true relapse
    • Microbiologic recurrences after therapy in 48%
      – 75% reinfection
      – 25% true relapse
  • Wallace RJ et al. Chest 2014;146:276-282
NTM and clinical trials
Microbiology

• South Korean results
  – 217 patients with MAC and nodular bronchiectasis
  – Daily or intermittent three drug therapy
    • 71-72% sputum culture conversion to negative
    • Only 4 patients had recurrence while on therapy
    • No post therapy results
      • Jeong B et al.  Am J Respir Crit Care Med 2015;191:96-103

• Cavitary MAC disease
  – 49 subjects with MAC and cavitary disease
    • Thrice weekly regimen
    • 4.1% culture conversion
      • Lam PK et al.  Am J Respir Crit Care Med 2006;173:1283-1289
NTM and clinical trials
Microbiology

• MAC and M. abscessus refractory to treatment
  – Salvage with bedaquiline
    • 10 subjects
      – 8 macrolide resistance
      – 6/10 had microbiologic response
  – Salvage with inhaled liposomal amikacin
    • 90 patients: MAC 64%, m. abscessus 36%
      – 10/44 MAC patients converted at day 56; 11/44 at day 84
      – 0/15 M. abscessus converted at day 56; 1/15 at day 84
        • Biller JA et al. Am J Respir Crit Care Med 2015;191:A6295
NTM and clinical trials
Microbiology endpoint

- **Advantages**
  - Hard end point
  - Reproducible if done in advanced mycobacterial lab

- **Problems**
  - How to define success?
    - Three negative cultures while on therapy
    - One positive culture “doesn’t count”
    - What about after the conclusion of therapy
      - Defining relapse vs new infection
      - How long to monitor
NTM and clinical trials
Imaging

• Heterogeneous findings
• Nodular vs cavitary disease
  – Waxing and waning bronchiolitis
• Lack of standardized CXR or CT scoring
• Radiation dosing and exposure
  – McCunney RJ. Chest 2015;147:872
  – Doss M. Chest 2015;147:874
• Two trials that reported serial imaging findings
  – Lam PK et al Am J Respir Crit Care Med 2006;173:1283-89
NTM and clinical trials
Lung function testing

- Lung function results
  - Pulmonary function tests
  - 6 min walk test
- Paucity of published data
- Heterogeneous patient population
- Probably only helpful for monitoring adverse effects of inhaled medications
NTM and clinical trials
Patient reported outcomes

• Mortality
  – Fortunately, a rare outcome

• Morbidity
  – Fatigue
  – Fever
  – Cough
  – Hemoptysis
  – Weight loss
  – Night sweats
  – Shortness of breath
  – Sputum production

  • Olivier KN et al. Annals ATS 2014;11:30-35
NTM and clinical trials
Patient reported outcomes

• 20 patients with refractory NTM infection
  – 15 m. abscessus, 5 MAC
  – Inhaled amikacin added to regimen
    • 8/20 had at least one negative culture
    • 5/20 had persistently negative cultures
    • 9/20 had improved symptom scores
    • 7 unchanged, 4 worsened symptom scores
      » Olivier KN et al. Annals ATS 2015;11:30-35

• Quality of life bronchiectasis with NTM specific questions
  » Quittner A et al. ERJ 2015;46:A2635
NTM and clinical trials
Confounding factors

• Heterogeneous disease
  – MAC vs M. abscessus
  – Nodular bronchiectasis vs cavitary disease
    • NTM causing the structural damage
      – Female predominant
    • NTM superimposed on chronic disease
      – Males and females affected
      – Cystic fibrosis
      – Emphysema

• Co-infections with other bacteria
  – Pseudomonas, staphylococcus, nocardia, aspergillus
65 year old male with MAC and pseudomonas aeruginosa
59 year old female with MAC
56 year old female with MAC
72 year old female with m. abscessus
NTM and clinical trials
Conclusions/Discussion

- Imaging endpoints
  - Not currently feasible
- Pulmonary function endpoints
  - Not predictive of overall outcomes
  - Helpful for monitoring inhaled antibiotic toxicity
- Patient reported outcomes
  - Vital, need to be in all trials
  - Need to continue after conclusion of therapy
  - Assess adverse treatment effects vs disease effects
NTM and clinical trials
Conclusions/Discussion

- Microbiologic endpoint probably best
  - Standardization of culture collection and processing
  - Consider Stratifying trials
    - MAC only: M. avium vs M. intracellularre vs others
      - Virulence issues
        - Boyle DP et al. Am J Respir Crit Care Med 2015;191:1310-1317
    - M. abscessus only: M. abscessus abscessus vs others
  - Nodular vs cavitary disease
    - Evaluate impact on co-infecting organisms, if present
      - Prolonged microbiologic follow up after therapy
Serological monitoring?

- Serodiagnosis of MAC reported from Japan
  - IgA antibodies against mycobacterial glycopeptidolipid
    - Potentially supportive for confirming diagnosis
    - Possibly helpful for monitoring response to disease
  - Not commercially available in US
  - Not validated as a diagnostic or monitoring tool
  - May be helpful in the future/may warrant further evaluation

  - Shigeki K et al. Eur Respir J 2015;46:PA2675
NTM and clinical trials

• Questions for the panel and the FDA
  – Microbiologic endpoint AND clinical outcome

• Acknowledgments:
  – Work done to date
  – FDA and pharma
  – Patients
    • NTM Info and Research
    • US Bronchiectasis Registry
Panel Discussion
Clinical Trial Considerations

- Eligible population: CF vs. non-CF, Rx naïve vs. Rx experienced, MAC vs. other NTM (especially M. abscessus)

- Use of Control: active or placebo: Add-on therapy vs. new regimen, how to choose optimized background regimen if there is no correlation between the results of susceptibility testing and clinical activity
Clinical Trial Considerations

Trial endpoints

- Microbiologic endpoint:
  - Effect of inhaled therapies?
  - Sputum Conversion and Clearance: definitions, timing and durability – how many consecutive cultures define sputum conversion to negative? Sputum clearance?
  - How many months after sputum clearance is a “cure” declared?
  - Correlation of microbiologic endpoints with clinical outcomes

- Patient Reported Outcome endpoint: which PRO, when to assess, effect of other concomitant interventions for underlying lung disease

- Assessments of exercise tolerance: 6MWT: what change is clinically meaningful, effect of other interventions for underlying lung disease

- Other endpoints
Clinical Trial Considerations

Trial Feasibility

- Trial feasibility: frequency of visits, frequency of labs, available treatment centers, length of study, possible need for equipment (IV or inhaled therapies)
Open Public Comment Period
Closing Remarks