NTM Drug Development: An Industry Perspective

Angela Talley, MD

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Conflict of Interest Disclosure

• Angela Talley is a full time employee of Spero Therapeutics, Inc.
Opportunity

• Multiple candidate agents in existing and novel classes
  ― Gyrase inhibitors, macrolides, rifamycins, ethambutol, oxazolidinones, aminoglycosides, tetracyclines, BL-BLIs, others

• Increasing recognition of NTM as a chronic debilitating disease state

• Current SOC is inadequate, poorly tolerated

• Effective regimen(s) are urgently needed (can’t wait 10 years)

• Unique opportunity to catalyze new development approach to get these agents to patients in need faster
Drug X: Clinical Development Path

- **3-4 years**
  - Nonclinical efficacy, PK/PD:
    - *in vitro* activity vs. NTM isolates;
    - Animal models: mono/combination therapy, PK/PD
  - PK/PD hollow fiber models including combination therapy
  - Phase 1 PK (SAD/MAD) study in healthy volunteers

- **1-2 years**
  - Selection of potential therapeutic doses to be interrogated
  - Additional Phase 1 Clinical Pharmacology Studies:
    - (eg DDI, special populations)
  - Subchronic & Chronic toxicology studies

- **2-3 years**
  - Compilation of Data Provides Early POP
    (animal models, hollow fiber, SAD/MAD, DDI)

- **5-8 years**
  - Phase 2 dose-ranging study
    N ~60
  - Phase 3 Pivotal Trial
    N~ 200-300
  - Evaluation in Patients with NTM
  - Registration

- **3-4 years**
  - Registration
  - 3-4 years

- **1-2 years**
  - 1-2 years

- **2-3 years**
  - 2-3 years

- **5-8 years**
  - 5-8 years
Drug X: NTM Clinical Development

• Current status/understanding:
  – The definitive efficacy endpoint(s) for NTM clinical trials are unclear
  – Sputum culture conversion as a surrogate endpoint may not be predictive of clinical benefit
  – Important to demonstrate a benefit to the patient via a clinically meaningful endpoint
  – Patient reported outcomes could be one method to evaluate clinical benefit, but the specific elements of the tool need to be defined
  – Need for placebo in order to understand safety

→ Development of clinical endpoints that reflect the early objectives of therapy may be more appropriate primary efficacy measures or part of a composite endpoint
Drug X Clinical Development: Key Questions

What are the objectives of treatment of pulmonary NTM?

- **Cure?**
  - Is durable microbiological response at 12, 18, 24 months an appropriate objective of therapy?

- **Symptomatic improvement on therapy?**
  - Which symptoms? How to measure?
    - daily QoL: patient reported (PRO assessment tool) which one?, objective assessments
    - functional status: FEVI/ 6MWT, other objective assessment?

- **Improvement or delay of disease progression?**
  - Is the duration of progression-free survival as compared with SOC a reasonable endpoint? If so, what is the appropriate measurement?

- **What is the appropriate timing for assessment of response?**
  - Should the primary endpoint reflect the early objectives of treatment on or at completion of therapy rather than durable response?
Drug X Clinical Development: Key Questions

• **Whom should we study?**
  – Salvage therapy in treatment-refractory patients or treatment-naïve/inexperienced patients at the cusp of starting therapy?
  – Pulmonary MAC or Pulmonary NTM? Subtypes?
  – Are different populations appropriate for early (Phase 2) vs. pivotal trials?

• **Which endpoints are appropriate to assess benefit?**
  – What are the clinical outcome measures to assess “objective improvement of symptoms” (per consensus definition)?
  – Which outcomes (clinical or microbiologic) are most appropriate as a primary efficacy endpoint?
  – Are there population/patient-specific differences in endpoints?
  – How do we evaluate a new NME vs. a new regimen?

• **Timing/Feasibility:** What is minimum treatment duration for a specific clinical or micro endpoint (or population) at which we might detect a meaningful difference?
Drug X: Efficacy vs. Comparators

- How do you standardize a background regimen in a treatment-refractory population particularly in an early efficacy assessment?
- Is it appropriate to add a single agent to a potentially failing SOC regimen?
- In what settings is a monotherapy vs. placebo trial design appropriate?
- Given the recruitment and feasibility challenges, are there the opportunities for platform trial collaboration to increase efficiency?
- What lessons can we learn from the MDR-TB experience? From regimen-building in HIV? Oncology?
More questions than answers...

The heterogeneity in the patterns of disease and the response to therapy may reflect our limited understanding of the pathophysiology of NTM-LD.

Colonization

Define host and microbiological risk factors for progression

Inflammatory disease (tissue burden drives an inflammatory response)

When to start therapy?
Desire to defer long term antibiotic exposure drives late intervention

Anatomical disease (fixed lung injury)

Limited reversibility?
Impacts the objectives of treatment

Objectives of therapy:
• decrease tissue burden to control inflammation and prevent progression
• Symptomatic improvement
• Quality of life improvement

Trial designs and endpoints may differ across the spectrum of NTM-LD
NTM Drug Development: Addressing Barriers and Challenges

- Better understanding of pathophysiology of NTM lung disease and factors associated with disease progression/treatment response
  - Collaboration to optimize the utility of existing data
- Better translation of preclinical data to clinically effective new combination regimens
  - Technology to identify promising compounds based on preclinical data (e.g. validation of hollow fiber)
  - Early identification of combination partners
- Feasible trial designs with earlier definitive primary endpoints
- Feasible development path for accelerated approval
- Development of validated Patient Reported Outcome measures
- Pathway for regimen-based development (MDR-TB parallels)