Development of Antibacterial Drugs for NTM: A Regulatory Perspective

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Background

• There is interest in developing inhaled and oral therapies for the treatment of NTM lung infections

• Approved products:
  – Treatment of MAC lung disease
    • Inhaled amikacin: Treatment of MAC lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy in adults who have limited or no alternative treatment options
  – Treatment of disseminated MAC in patients with advanced HIV infection
    • Clarithromycin: Treatment of mild to moderate infections due to *M. avium* or *M. intracellulare* in patients with advanced HIV infection
    • Azithromycin: Treatment of disseminated MAC in combination with ethambutol in persons with advanced HIV infection; prophylaxis of disseminated MAC disease alone or in combination with rifabutin in persons with advanced HIV infection
Inhaled Amikacin (Arikayce)

• Accelerated approval based on sputum culture conversion

• Limited clinical safety and effectiveness data
  – Indicated for use in a limited population of patients with refractory MAC lung disease with limited or no treatment options

• Clinical benefit has not yet been established
  – Postmarketing requirement to conduct a randomized, double-blind, placebo-controlled clinical trial to assess and describe the clinical benefit of Arikayce in patients with MAC lung disease

Arikayce approval letter: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/207356Orig1s000ltr.pdf
Lessons Learned

• Uncertainty as to the relation of the surrogate endpoint (sputum culture conversion) to clinical benefit in patients with MAC lung disease
  – Inconsistent results in clinical outcomes between the Phase 2 and 3 trials:
    • In Phase 2, improvement in 6-minute walk test distance was seen in the inhaled amikacin arm
    • In Phase 3, lack of a clinical benefit on the measured outcomes (6-minute walk test distance, patient reported outcomes including SGRQ and Quality of Life Questionnaire-Bronchiectasis)

• Comparison between study arms on the long-term endpoint was difficult because a large fraction of patients were allowed to cross over to the test arm

• For inhaled therapies, inclusion of an inhaled placebo/vehicle control may help in attribution of adverse events and for the purposes of blinding trials

https://www.fda.gov/AdvisoryCommittees/Calendar/ucm612659.htm
Surrogate Endpoint

• As discussed at the advisory committee meeting on August 7, 2018, key findings from our review of the literature to support the correlation between the surrogate endpoint and clinical benefit:
  – Retrospective, non-randomized studies suggest higher mortality rate in patients with MAC lung disease who remained culture positive despite treatment compared to those who convert to culture negative
  – Some studies are from single centers/specific subtype of MAC lung disease which limits generalizability to the overall population
  – The main limitation is that it is possible that converters are inherently different from non-converters in certain disease/patient characteristics and hence it is difficult to assess if sputum conversion is a surrogate for clinical outcome

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Some Considerations for Future Development

• At this point, we have more questions than answers, but these are some of the issues that we are thinking about…
  – Patient population heterogeneity
  – Trial design
    • Superiority vs. noninferiority
    • Monitoring patients during the study
  – Clinical endpoints
  – Duration of treatment and follow-up
Patient Population Heterogeneity

- Treatment experience: naïve vs. refractory
- Disease manifestations: nodular bronchiectatic vs. fibro cavitory
- Etiologic organism: MAC vs. non-MAC NTM
- Underlying co-morbid conditions: CF vs. non-CF

*Response to study drugs may vary based on any or all of the above.
Trial Design

• Superiority vs. Noninferiority (NI)
  – Superiority trials are scientifically sound and readily interpretable
  – An evidence-based NI margin needs to be established based on a clinical outcome to have an interpretable non-inferiority trial
Trial Design

• Demonstrating superiority to standard of care (SOC):
  – New drug as add-on therapy (new drug plus SOC vs. SOC plus placebo)
  – Assessment of a new combination regimen vs. SOC or placebo
    • Will need to address the contribution of each component of the combination

Trial Design

• How do we monitor patients to determine clinical benefit?
  – As previously noted, there are limitations to microbiologic results as an outcome measure
  – During the discussion of the cases later today, we will be considering the feasibility/acceptability of:
    • Blinding investigators and patients to culture conversion status during trials
      – Patients could withdraw for clinical reasons (e.g., increased fatigue, worsening respiratory symptoms), but not solely because of failure to convert sputum culture to negative
      – Could allow unbiased assessment of whether culture conversion is an acceptable surrogate for clinical benefit
    • Avoiding cross-over between treatment arms during trials
Clinical Endpoints

• More work needs to be done to define clinically meaningful endpoints/assessments in NTM patients
  – Microbiologic outcomes not linked to how patients feel, function, survive

• Patient-reported outcome (PRO)
  – Is the PRO fit-for-purpose?
    • Assessment of reliability, validity, sensitivity to detect change, and thresholds of meaningful change to the patient

• Would other clinical outcome assessments (e.g., clinician-reported, observer-reported, or performance outcomes) be more feasible/acceptable?
  – Clinically meaningful change would need to be defined for NTM patients
Clinical Endpoints (continued)

• Assuming that the primary endpoint is designed to assess direct clinical benefit (how patients feel, function, survive), when should it be assessed?
  – On therapy vs. off therapy?
  – At 6 months, 12 months, 24 months after initiation of therapy?
  – Does the timing depend on the type of patient?
    • treatment naïve vs. refractory?
    • bronchiectatic nodular vs. fibrocavitary disease?
    • underlying co-morbid conditions (CF vs. non-CF)?
  – Should the assessment be based on a fixed timepoint or on a summary of COA scores over time?
    • If based on a summary of COA scores, how frequently should assessments be made (e.g., daily, weekly, monthly, every 6 months, etc.)?
Duration of Treatment and Follow-up

• What is the evidence to support an optimal duration of treatment?
  – Is evidence based on clinical benefit?
  – In trials, early treatment discontinuations may complicate assessments of long-term follow up

• How long is it acceptable for patients to be on placebo in the control arm?
  – May depend on the study population (e.g., treatment naïve vs. refractory)
Thank you