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. fibrocavitary
- 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

Co-development guidance: https://www.fda.gov/downloads/drugs/guidances/ucm236669.pdf

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)

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Thank you


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