

Clinical Trial Design Considerations for Antifungal Drug Development

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Presentation

- Discuss some general aspects of clinical trial designs and endpoints for antifungal drug development along with some issues that have recently been considered

Clinical Trial Designs

- Randomized Controlled Trial- preferred
 - Non-inferiority (NI)
 - Must be able to provide a data driven justification of the NI margin
 - Superiority
- External/Historical Control

Non-inferiority Trials

- For typical invasive aspergillosis (IA) and candidemia/invasive candidiasis (IC) trials, have justified NI margins for an endpoint of all-cause mortality (ACM)
 - IA: 10% NI margin for 6 week ACM when control is voriconazole
 - Candidemia/IC: 10% margin for 30 day ACM when control is echinocandin → oral azole
- We have been willing to accept wider NI margins for a limited use indication if a product has the potential to address an unmet medical need

Challenges with NI trial (1)

- An oral only antifungal product that is being studied as an oral step-down from a different IV antifungal
 - To assess the effect of the new oral antifungal and interpret NI, will need to differentiate the treatment effect of the IV antifungal therapy from the oral step down therapy

Challenges with NI trial (2)

- Proposed limited treatment options population including refractory patients
 - NI margins justified are based on initially treated subjects. NI interpretation will need to consider the possibility that the treatment effect for refractory patients may not be the same.

Superiority Trials

- Can be conducted in any situation
- Special case would be an add-on trial

External/Historical Controls

- Needed to interpret the results of uncontrolled studies
- Some issues that need to be considered
 - Availability of patient level data
 - Similarity to the study population (controls can't be found based on autopsies)
 - Assessments made at comparable timepoints in the disease
 - Matching process of external controls to study subjects
 - Pathogen-specific external controls are recommended

Endpoints

- Commonly used endpoints have been ACM or a global/overall response endpoint and assessed at a fixed time point
- Endpoints selected should be well-defined and reliable
 - A clinical endpoint directly measures a therapeutic effect of a drug—an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives
 - A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is likely to predict clinical benefit, but is not itself a measure of clinical benefit

21 CFR 314.126(b)(6)

Role of Diagnostics

- In general, diagnostic tests do not have to be FDA-cleared or FDA-approved for use in a clinical trial if it is being used for enrichment purposes
- Important that the tests adequately detect the disease of interest; especially important in NI trials to ensure that the population studied has the disease of interest
- For candidemia/IC trials, we have allowed use of non-culture based tests for enrollment
- Galactomannan test has been used in IA trials for patient identification and definition of patient populations
- Qualification of an endpoint is not a pre-requisite for use in clinical trials; CDER Biomarker Qualification Program helps to develop biomarkers as drug development tools

Global/Overall Response Endpoint

- Not recommended as a primary endpoint in NI trials due to inability to justify NI margin
- Treatment success: Complete or partial response
 - What about Stable response?
 - Complete/partial/stable(?) vs progression/death

Thanks!