



Possible Clinical Trial Approaches for Areas of Unmet Need

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Possible Approaches

Points for Discussion

- Are there more streamlined drug development programs that can provide appropriate levels of information for an antibacterial drug intended for use in patients who lack or who have few therapeutic options?
- In general, what are some of the possible approaches? (for purposes of discussion)
- What are the Pros and Cons of each of the approaches?

General Information

- In vitro activity data
- Preclinical data
- Data from animal models of infection
- Pharmacokinetic data / tissue distribution data
- Pharmacodynamic information
- Characteristics that make the molecule an appropriate choice for an unmet need pathway
 - New mechanism of action
 - Activity preserved in setting of resistance to other drugs (e.g., paired with an inhibitor)

Option 1

- Randomized, concurrent controlled, clinical trial designed to show superiority of the test drug over best available standard of care in patients with infections at each of several different body sites.
- Other variants of this
 - Nested superiority NI trial (see option 1 and option 2)
- Pros
 - Superiority could provide clear evidence of efficacy
 - Study in the unmet need population
 - Addresses issue of varying degree of severity of infection and underlying conditions affecting outcomes for patients in a particular trial

Option 1 (cont'd)

- Cons
 - Difficult if resistant pathogens of low prevalence prevalence (and ability to enroll) patients who are likely to have resistance / less than ideal outcome when given standard of care
 - Approaches to and interpretation of data from infections at different body sites
 - Background events and small numbers may obscure safety signals

Option 2

- An NI Study in a traditional indication (single body site in patients with more severe disease) with a less precise characterization of efficacy and safety
 - would not lead to receiving this indication
 - study would support use in the unmet need pop.

and

- A study in patients with unmet need and or patients with similar level of acuity / severity of illness with infections at each of several different body sites
 - get PK information
 - not for inferential testing
 - assess patient response (could still consider a limited control pop.)

Option 2 (cont'd)

- Pros
 - Traditional indication study could provide an interpretable and feasible means to evaluate safety and efficacy
- Cons
 - efficacy in one indication in a population that might not be as acutely ill or have as many co-morbidities as the unmet need population
 - more limited data in population of interest
 - Would need to evaluate mechanisms of action of test drug / mechanisms of resistance leading to unmet need to other drugs to understand likelihood of preserved activity

Option 3

- In patients with infections at each of several different body sites with resistant organisms, show superiority of the test drug over an external control comprised of similar patients
- Pros
 - Study in population of patients with unmet need
- Cons
 - Well known challenges of externally controlled studies
 - Heterogeneity of outcomes in patients based on a variety of patient factors (known and unknown)

Option 4

- An option in need of much more discussion
 - In settings in areas of immediate unmet need
 - Accelerated Approval based on matching/exceeding exposure in relevant animal animals models of infection
- and
- A single arm study in patients with unmet need and or patients with similar level of acuity / severity of illness with infections at each of several different body sites
 - get PK information
 - not for inferential testing
 - assess patient response (could still consider a limited control pop.)
 - Confirmatory trial in one or more of the specific body sites (probable NI design)

Option 4 (cont'd)

- Pros
 - Feasibility
 - Possible earlier availability in situations of immediate unmet need
- Cons
 - Greater uncertainty when relying on a surrogate
 - Difficulty of interpreting safety information from the single arm study in a population likely to have a high background rate for events
 - Confirmatory trial not specifically in population of unmet need

Additional Considerations

- If a drug is approved for a population of patients with unmet need based on a smaller database with greater uncertainty...
- Means to identify important findings for the drug in the postmarketing setting
- Further study in “traditional” indications possible
 - risk/benefit for these other indications would be evaluated based on findings from studies
- Role of the healthcare community in choosing to use the drug in situations where risk / benefit appropriate



Thank you