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European Federation of Pharmaceutical Industries and Associations

Development of Drugs for HAP-VAP

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Hospital-Acquired & Ventilator-Associated Pneumonia (HAP-VAP)

- The EMA 2015 roadmap recognizes the need for new antibiotics
  - New drugs for HAP-VAP are urgently needed
  - HAP-VAP is a key testing ground for new Gram-negative agents
- Critical need for updated and clear guidance that encourages:
  - Informative clinical trial designs
  - Feasible clinical trial designs that encourage industry investment
  - Endpoints that are relevant to patients and physicians and that clearly assess the effectiveness of a new antibiotic
  - Need for uniform criteria for diagnosis of pneumonia among regulatory guidances and clinical treatment guidelines

Key Issues for Today

- Endpoint
  - Is All-Cause Mortality the correct endpoint?

    What is the appropriate time to assess the endpoint?
- Margin: Needs to be clinically meaningful and realistic
- mMITT (microbiologically proven) vs. ITT (all patients)
  - What level of microbiologic proof is needed?
- Can HAP and VAP be in the same trial with stratification vs. separate studies?
- Can antibiotics be used prior to trial entry?

Realistic & Informative Trial Design

- Acceptable trials must assess efficacy and safety in a fully representative patient population
  - Active-control, non-inferiority designs are required
  - Enroll patients only with strong HAP-VAP syndrome
  - In such patients, increased mortality seen with inadequate therapy e.g., there is a low spontaneous response rate
- Measure response before underlying disease influences outcome: early (7-14 d) likely better than late (28d)
- Margin & inclusions should be scientifically justifiable and lead to achievable trial size
- Limit prior antibiotics but do not exclude entirely
- Patients from all relevant extended health care settings (hospitals, nursing homes, ICU) should be permissible

What is the Correct Endpoint?

- Issue: All-cause mortality (ACM) has many limitations
  - As antibiotics have a clear effect on 28-day ACM, a recent position paper endorsed by 4 societies (IDSA, ATS, ACCP, & SCCM) suggests ACM be used the primary endpoint for HAP-VAP[1]
  - But, attributable mortality would be preferred[1] as the linkage of ACM is reduced by supportive care and underlying disease[1,2]
  - Further, ACM "is not consistent with clinical practice."[1]
  - Finally, fever, oxygenation, etc. are routinely assessed. "Failure to consider (these) decreases clinical relevance and creates a risk that results of registration studies will not extrapolate well to post-approval use"
- Suggestion: ACM could be used, but clinical response based on fever, oxygenation, and survival is also plausible
  - Combes (Crit Care Med 2007; 35:146-54) showed changes in PaO_2/FiO_2 were linked to mortality

[1]Spellberg et al. Clin Infect Dis 51:S150-70 2010; [2]Wenzel AAC 54:4956-60, 2010

Statistical Analysis - Margin

- Issue: What is an appropriate margin for HAP/VAP?
- Concerns:
  - Non-inferiority margin up to 15% is:
    - Reasonable vs. strong historical data with effect of ~30%
    - Consistent with prior clinical studies and guidances
    - Provides some flexibility in study design
    - Reasonable if paired (2 confirmatory) studies are conducted
- Suggestion: Historical data estimates ~30% effect, so margins of up to 15% are supportable.
  Such margins are clinically reasonable and will greatly improve the success of enrolling studies and moderate the size of clinical studies.

mMITT vs. ITT (1 of 2)

- Issue: What level of bacteriologic confirmation is needed?
- Merits of ITT (Clinical diagnosis) population
  - Antibiotics give mortality benefit in ITT populations[1]
  - ITT population is more representative of the future use of the drug
  - Uses all patients: Pathogen shown in only 30-40% of HAP-VAP cases[2]
  - If mMITT is primary analysis, need 2,200 patients for 10% margin[3]
    - 1000 for 15%
  - Avoids uncertainties of cultures (e.g., defining proper CFU cutoff)
- Merits of mMITT (microbiological proof) population
  - Seems logical to want to have an organism for a clinical trial
  - Is required for a narrow-spectrum agent
  - May reduce enrollment with syndromes mimicking pneumonia (confirm true HAP-VAP syndrome)

[1]Sorbello, Drug Info J 2010; 44:165-176; [2]Telavancin vs. vancomycin for HAP: ATTAIN: 31% of randomized patients were in mMITT; [3]Presumes 30% mMITT rate, 80% response rate.*

mMITT vs. ITT (2 of 2)

- EFPIA suggests
  - Primary analysis would be of ITT population
  - This would be followed by a subset analysis for microbiologically proven cases
  - Minimum numbers (or percentages) of microbiologically proven cases could be agreed upon
- If mMITT required, must accept all types of microbiological proof
  - We should consider & employ all diagnostic tools possible, both cultures (blood, sputum, BAL) and non-culture-based methodologies

HAP-VAP: Separate Studies?

- Issue: Should HAP and VAP be studied separately or can they be studied together with proper sub-analysis?
- Concerns:
  - The syndromes are similar; VAP patients tend to have more severe infections than HAP patients (higher incidence of MDR organisms)
  - Prior studies allowed both (with stratification) → ATTAIN* had 70% HAP & 30% VAP
  - Feasibility issue for separate study of VAP
    - VAP represents about 32% of HAP-VAP patients - it will be difficult to impossible to enroll a VAP-only study with proper patient numbers
  - There is a concern of creating orphan "body-site" diseases
- Suggestion: Permit either separate studies or combined study with stratification (review design strategy via Scientific Advice)

**Telavancin vs. vancomycin for HAP*

Prior Antibiotic Therapy

- Issue: Should prior antibiotic therapy be allowed?
- Concerns:
  - Prior antibiotics are common in this setting and lead to higher MIC values and more resistant pathogens
  - Very restrictive approaches (e.g., prior 30 days) will make enrollment very difficult
  - By excluding prior antibiotics, one narrows the generalisability of the enrolled population & the results
  - ATTAIN permitted prior antibiotic therapy: ~55% received prior antibiotics, including 30% failing prior antibiotics
- Suggestion:
  - Allow antibiotics within the 48 hours prior to enrollment
  - Stratification based on receipt of prior antibiotic therapy could be used to maintain balance across groups

Conclusion

- Critical need for updated and clear guidance that encourages:
  - Informative clinical trial designs
  - Feasible clinical trial designs that encourage industry investment
  - Endpoints that are relevant to patients and physicians and that clearly assess the effectiveness of a new antibiotic
  - Need for uniform criteria for diagnosis of pneumonia among regulatory guidances and clinical treatment guidelines
- EFPIA is concerned that overly restrictive guidance will make this area so unmanageable that no work will be done
  - Case in point: Developing a narrow-spectrum anti-pseudomonal agent via a fully powered mMITT-based analysis may not be possible