European Federation of Pharmaceutical Industries and Associations

HAP-VAP

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Overview

- Key points from previous workshop (Feb 2011)
- Two new ideas not covered in the addendum
- Other points from the addendum

Key Points from Feb 2011 Workshop

EFPIA: Inclusion of HAP and VAP in one study

Addendum:

- minimum of 30% VAP

Further notes from EFPIA:

- This may be impractical
  - Theravance study had 29% VAP (circa 2005-2007)
  - Incidence of VAP is decreasing
    - Preventative measures more ubiquitous[1,2,3,4]
    - In 2013 in US, ventilator-associated events reported by hospital; may affect pay-for-performance
- EFPIA recommendation: set minimum at 25%

1 *Bird D., et al. Arch Surg. 2010;145(5):465-470;* 3 *Morris AC, et al. Crit Care Med. 2011; 39:2218–2224*

2 *Koeman M, et al. Am. J. Respir. Crit. Care Med. 2006; 173(12): 1348-55;* 4 *Kollef MH. Surg Inf. 2011; 3(12):211-220*

Key Points from Feb 2011 Workshop

NI margin up to 15% can be supported

Addendum:

- NI margin of 12.5%

Further notes from EFPIA:

- M1 is 29%, thus supporting higher M2 than 12.5%
- Due to size and complexity, only one trial should be required; 12.5% is supported by EFPIA
  - E.g., Sample size will be 973 subjects
    - Assumes 80% cure rate for CE (45% evaluability), 90% power, 1-sided alpha of 0.025 [ITT population requires similar size]
- If 2 studies are required, then 15% for each study should be acceptable
  - Sample size 680 subjects per study – 1360 subjects total

Key Points from Feb 2011 Workshop

EFPIA: Allow up to 24 h of prior antibiotics

Addendum:

- Supportive of up to 24 h of prior antibiotics

EFPIA: Micro population should not be primary

Addendum:

- No specific mention of primary population(s)
- Dec 2011 guideline states ITT and CE as coprimary

Further notes from EFPIA:

- We agree with the ideas in the Dec 2011 guideline

Key Points from Feb 2011 Workshop

EFPIA: Mortality (Day 14) only as secondary endpoint

Addendum:

- Day 28 mortality as secondary endpoint

Further notes from EFPIA:

- TOC could be before Day 28
  - Could be clinical cure but still “failure” in secondary endpoint
- Day 28 mortality good for safety assessment
- Day 14 mortality is a better measure of efficacy
  - More contemporary to antibiotic therapy
  - Less “noise” due to comorbidities

New ideas not covered in the addendum

EFPIA: Initial concomitant study antibiotics

- If new agent predominately Gram-negative
  - May need dual *P. aeruginosa* coverage
  - Will need Gram-positive coverage
- If new agent predominately Gram-positive
  - Will need double coverage for *P. aeruginosa*
  - Gram-negative coverage likely to have overlapping gram-positive coverage
    - Result: monotherapy study drug against MRSA only

– Need for mid-course adjustment based on culture results

EFPIA recommendation:

- Requirement for concomitant study antibiotics should not affect evaluability

New ideas not covered in the addendum

EFPIA: Development of antibiotic for MDR pathogens

- Using 12.5% margin requires 973 subjects
- Only 25 MDR Gram-negatives enrolled
  - Assumes 33% ME, 40% G-neg pathogen, 20% MDR rate

EFPIA recommendation:

- Can we approach as add-on to “Tier B”?
  - Approval in another indication using standard NI studies (assumes study drug works equally well for non-MDR pathogens)
  - Non-statistically powered HAP/VAP study enriching for population of interest (e.g., a few hundred subjects)
    - Enrollment will be significantly slower (subject/site/month basis)
  - Restricted label for HAP/VAP (discussed yesterday)

Other points from the addendum

No mention of PRO for HAP/VAP

- *EFPIA:* We agree – a PRO makes no sense here
  - Patients are intubated, critically ill, etc.

Should HCAP be allowed?

- Addendum seems to exclude
  - *EFPIA:* Could be excluding MDR pathogens (see CAP talk)

Use of CPIS ≥ 6 as inclusion criterion for VAP

- Addendum not clear if this is required for VAP or can be used if subject doesn't meet other criteria
  - Theravance studies: 32 – 57% subjects ≥ 6 (CE populations)
  - CPIS use controversial; "CPIS has a limited role both clinically and as a research tool" (Zilberberg and Shorr, CID 2012)
- *EFPIA:* CPIS ≥ 6 should not be a requirement for VAP

Summary

- EFPIA acknowledges the progress EMA has made with the new guidances
- For broad spectrum agents, path forward is relatively clear
  - Caveats: concomitant study antibiotics should be allowed and not affect evaluability
  - Single trial should be adequate for HAP/VAP indication
- For new agents targeting MDR pathogens, we need a different path forward
  - Proposal for “Tier B” approach: Treat HAP-VAP as one of the add-on site in a Tier B program