European Federation of Pharmaceutical Industries and Associations

Community-acquired pneumonia (CAP)

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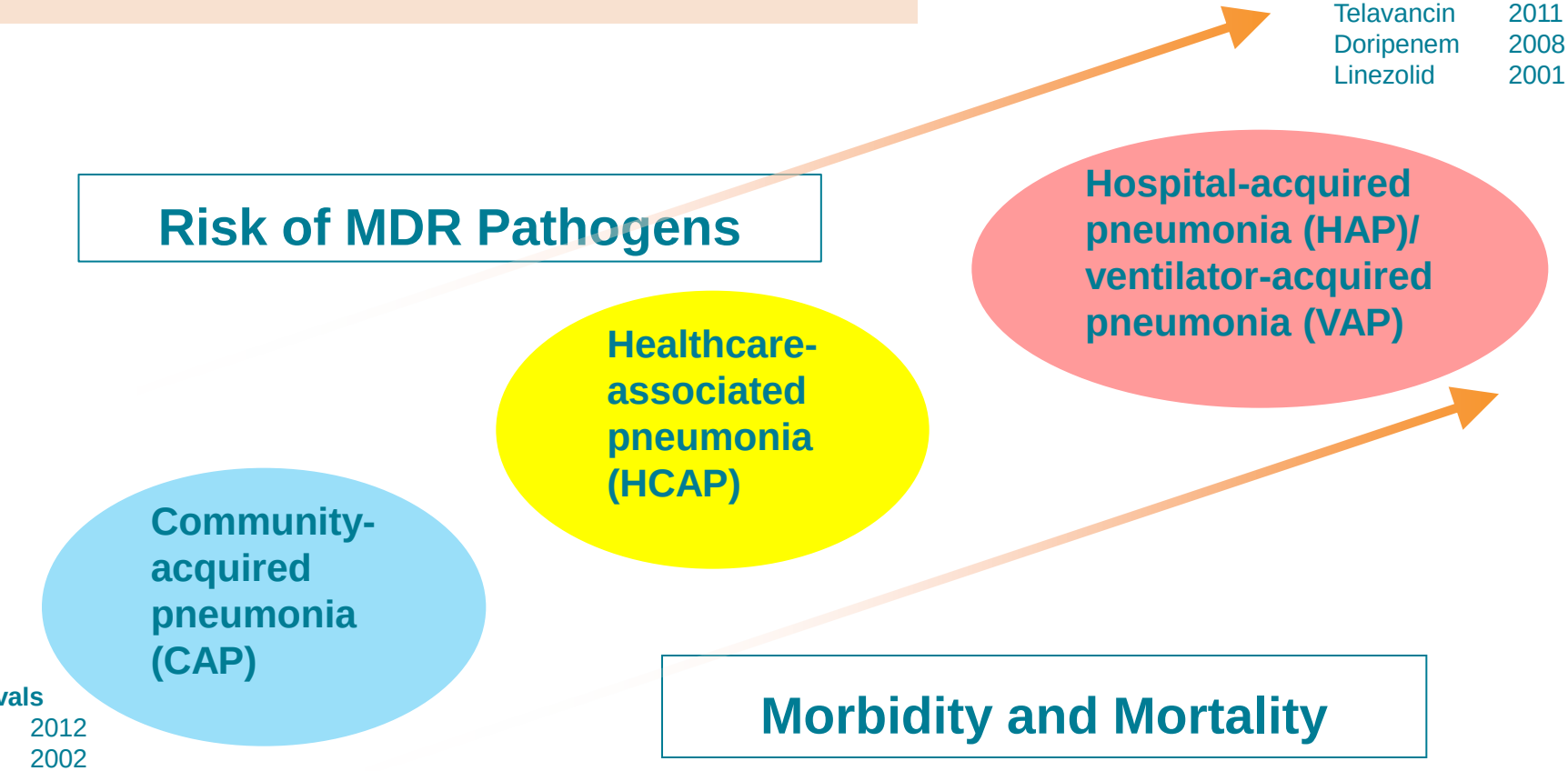
CAP: Key issues

- Definitions and patient population
- Use of prior antibiotics
- Microbiologically Evaluable population
- Efficacy endpoints
- Phase 3 data package
- Use of a patient-reported outcome (PRO) instrument

Types and Spectrum of Pneumonia

- MDR pathogen varies with disease type
- HCAP can be an important source of MDR pathogens for both CAP and HAP-VAP



Craven D. *Curr Opin Infect Dis*. 2006;19:153-160

Definitions and patient population

We agree with these points

- Diagnosis is based on a composite signs/symptoms *plus* labs *plus* vital signs
- Fever is not a requirement for enrolment
- IV: Minimum PORT 3, 25% ≥ PORT 4
  - Is the case that PORT 2 is not allowed in any circumstance for EMA?
- PO: minimum PORT 2, 50% ≥ PORT 3

We are concerned about these points

- Exclusion of HCAP from CAP study population (see prior slide)
- Transition from IV to oral therapy
  - Essential to allow, but with protocol-defined clinical response criteria
- Duration of IV therapy
  - Switch to same drug: should not matter if oral absorption OK
  - Step-down to different oral drug: define minimum IV duration

Use of prior antibiotics

We agree with these points

- Use of prior ABs needs to be practical for the conduct of the study
- Higher PORT scores in proposed study population will drive prior AB use
- Therefore very encouraged by wording in 2012 Addendum:
  - *'up to 24 hours of prior therapy within 72 hours of enrolment may be acceptable'.* In CAP: *'single dose of drug given once daily and 2-3 doses of agents routinely administered more than once a day may be the limit'*
  - failures on existing therapy fine
- Assess effect in subgroup analysis (yes/no prior ABs and by AB type)

We are concerned about these points

- If prior use of > 1 AB, overlapping coverage hours count once only
- Propose that short adjunctive AB for atypicals at study start (with overlapping cover for *Streptococcus pneumoniae* etc.) should be allowed, then exclude proven atypical infections from analysis

Microbiologically Evaluable (ME) population

We agree with these points

- Flexibility to consider ITT population as primary rather than the ME population

We are concerned about these points

- ME is typically ~30% in CAP
- Enrichment techniques (e.g. Gram stain, urinary *Streptococcus pneumoniae* / *Legionella pneumophila* antigen testing, PCR) are employed but historically agencies have still required positive culture and/or atypical serology for inclusion in the ME population
- Propose urinary SP/LP antigen testing (e.g. Binax NOW®) alone can be used as evidence of bacterial infection and inclusion in the ME population. Sponsors will clearly state in reports numbers without culture/serology confirmation
- Criteria for atypical diagnosis should allow inclusion in the ME population
- **Guidance should leave room for future evolution in this area as new approaches (e.g. combinations of biomarkers) are created and evolve**

Efficacy endpoints

We agree with these points

- to continued use of TOC as the timing for a primary efficacy assessment
  - 30d mortality is too low in study populations for use an endpoint in CAP (2% in ceftaroline P3)
- to use of a co-primary endpoint for EMA and FDA with sponsor powering on the endpoint requiring the most subjects

We are concerned about these points

- current lack of harmonisation in CAP endpoints
  - FDA Draft Guidance (Mar 2009), FNIH recommendations to FDA (Nov 2011), EMA Draft Addendum (Jun 2012) all differ
  - key issue is use of clinical outcome at TOC (EMA) *vs*. earlier Day 4 time point (FNIH/FDA)
  - accept that Day 4 may separate drugs (e.g. ceftaroline from ceftriaxone in post-hoc FDA-defined micro-ITT) but not the full story (i.e. meaningless in isolation)
  - early endpoint incorporated into traditional TOC endpoint

Phase 3 data package

We accept that

- the case for a single Phase 3 study per indication has to be compelling
- that unmet medical need must drive innovative regulatory pathways

We seek clarification on

- pooling of data across Phase 3 studies
  - e.g. use of single CAP study with a HAP/VAP study to secure the CAP indication
- use of only a single CAP study with p = 0.01
- implication of increasing the size of the ME population
  - e.g. acceptability of a wider non-inferiority margins such as 15%

Use of a PRO in CAP

- Nothing currently validated
- Intention for the FNIH to pursue in CAP (after the SSTI indication)

- EFPIA believe a PRO in CAP is likely to have limited utility
  - a short term acute condition, very different to ABECB
  - as patient population shifts to more severe PORT 3+ may be issues in PRO completion (e.g. altered mental status)

- EFPIA recommend clinical outcome based on
  - pre-defined resolution of symptoms and signs at a fixed time point (EMA and FDA), or
  - one point improvement in ≥ 2 symptoms and no worsening of other symptoms (FNIH)

already combine patient-reported information with objective clinical measures

Summary

EFPIA

- Agree with focus on more severe spectrum of disease (PORT 3+), with inclusion of PORT 2 for drugs only given orally
- Acknowledge the position of different regulators in terms of efficacy endpoints and accept the challenge in incorporating multiple efficacy endpoints into pivotal studies
- Agree that defined prior AB use must be acceptable to reflect real world clinical practice and to operationalise studies
- Seek discussion and flexibility in
  - agreeing the ME population
  - use of a single Phase 3 study
- Are not supportive of PRO use in CAP