EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2012
Addendum to the EU Guideline on Antibacterial Agents

EMA Workshop on development of new antibacterial medicines October 2012

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An agency of the European Union

Current guidance

- Guideline on evaluation of medicinal products indicated for treatment of bacterial infections

  (= *Core Guidance)*

  CPMP/EWP/558/95 rev 2; January 2012

- Refers to *Addendum* under development

- *Addendum* was released for consultation 4 July 2012 until 31 January 2013

Aims of the meeting

Obtain input on the proposals made in the Addendum.

In particular:

- Discuss feasibility of proposals
- Discuss alternative proposals
- Identify issues not yet covered
- Identify areas requiring more detail
- Consider implications for WW clinical development programmes

Antibacterial agents targeting rare / very rare pathogens including MDR / XDR / PDR pathogens

Core guidance

- Efficacy may be evaluated in infection type-specific studies and/or in separate studies of infections due to selected pathogens
- May be necessary to obtain clinical efficacy data vs. specific pathogens in studies of documented infections regardless of body site(s) affected
- Randomised preferred vs. uncontrolled studies
- External controls preferred vs. historical controls

Core guidance

- Minimum treated cases to support specific claim to be judged on a case by case basis
- A pathogen-specific indication may be appropriate if an agent has been shown to have clinical efficacy against organisms that express certain types or patterns of resistance when causing infections at a range of body sites

Addendum

- Aim is to provide guidance on minimum evidence needed for an initial approval of an antibacterial agent/FDC that addresses an unmet clinical need
- Need to clarify the criteria for concluding that an agent qualifies for a reduced programme
- Depends on whether it is an new agent within an existing class or a new agent of a new class

Addendum

- Uses example of new agent potentially effective vs. MDR Gram-negative aerobes/facultative anaerobes
- Develop robust PK/PD programme to strongly support expectation of efficacy vs. target pathogens
- Consider impact of multiple resistance mechanisms in the same organism (e.g. enzymic + permeability or efflux)

Addendum

Scenario 1 – Broad Spectrum Agent

- At least one standard pivotal NI study in at least one infection type
- Supplement with efficacy vs. selected infection types due to “target pathogens”

  May be non-comparative assessment
- Support with updated PK/PD analysis using PK data collected from patients

Addendum

Scenario 2 – Narrow Spectrum Agent

- If possible - at least one standard pivotal NI study using monotherapy plus data as suggested in Scenario 1
- If not possible – as above + 2nd agent

  - To cover expected non-target pathogens (i.e. effective monotherapy vs. target pathogens)

  OR

  - To cover target pathogens (i.e. no monotherapy efficacy data except vs. few PDR organisms)

Addendum

SmPC

- Programmes could lead to infection type indication if studied as usual
- And/or pathogen-specific indication depending on evidence provided
- Specific wording to be qualified in light of level of evidence

Not in Addendum

- Pivotal study in one or multiple infection types that aims to demonstrate superiority
- Pivotal study in one or multiple infection types that aims to demonstrate superiority within a subset;

  Possibly in the setting of an adequately powered or under-powered NI study
- Superiority not based on cure rates but on time to reach milestones or on death rates
- Non-inferiority study in multiple infection types due to target pathogens (only or enriched)
- Pivotal study in bacteraemic patients regardless of known/unknown primary focus

All raise issues regarding the comparator (s)

All potentially difficult to interpret

Points for Discussion

Points for Discussion

- Is the suggested scenario for a new broad spectrum agent feasible?
- Do we always need a supplementary study for a pathogen-specific indication to collect information on “target pathogens”? What could be the design?
- Would investigators be willing to use the new agent alone against MDR/XDR pathogens?
- If a comparative study is performed that includes MDR/XDR pathogens how to select and handle the comparator (s)?

Points for Discussion

- Is the suggested scenario for a new narrow spectrum agent feasible?
- What if the new agent can only be studied as monotherapy in cUTI?
- What if the new agent can only be studied in a combination regimen that includes another active agent?
- Could we supplement with observational data on use as effective monotherapy vs. PDR organisms?

Points for Discussion

- Superiority study in a single infection type or multiple infection types or bacteraemia in patients infected with target pathogens or with enrichment for such patients?
  - Test agent vs. SOC; alone or in combination
  - Add-on to SOC vs. SOC
  - Substitution with test for available agent within SOC vs. SOC?
- Non-inferiority study that shows superiority in a subset infected with target pathogens?
- Non-inferiority study that shows superiority based on an endpoint other than cure rate either overall or in a subset infected with target pathogens?
  - What could those alternative endpoints be?

Points for Discussion

- Are there scenarios in which only the following types of study could be considered feasible?
- Non-inferiority study in multiple infection types due to target pathogens or enriched for target pathogens
- Non-inferiority study in patients with bacteraemia of known and unknown sources due to target pathogens
- How to determine non-inferiority in such examples when the absolute treatment effect is not known or is anticipated to differ between infection types?

Points for Discussion

- What are the relative merits of cure vs. mortality endpoints?
- Is it possible to define the nature and dose of comparative therapy in an hierarchical fashion
  (e.g. depending on susceptibility and patients)?
- Could Bayesian approaches be considered?
- What could be provided after an approval for use in the limited treatment option setting?
- Should paediatric cohorts be included at an early stage?

Indication-specific guidance

General Approach

- Major patient selection criteria have been proposed for 5 major infection types
- Clinical and/or microbiological primary endpoints at post-treatment TOC
- Non-inferiority margins have taken into account ability to differentiate treatment vs. placebo and likely feasibility

HAP, VAP and HAP / VAP

HAP/VAP

- Confine to HAP or VAP preferred; mixed should stratify (eg. at least 30% with VAP)
- 48 h post-admission or within 7 days post-discharge
- VAP for ≥ 48 h ± CPIS, SOFA, MODS and/or APACHE II
- Clinical outcome 7-14 days post-treatment;
  Co-primary all treated and clinically evaluable
- Non-inferiority margin should not exceed -12.5%
  (whether HAP or VAP only or mixed)

CAP
[PORT III +]

CAP

- CXR plus 3-4 signs/symptoms plus signs of consolidation
  Urinary antigen for S. *pneumoniae* + *L. pneumophila*
- IV – PORT III - V; ≥ 25% IV-V (not immediate ICU)
  PO – PORT II-III; ≥ 50% III
- Capture CURB scores to document baseline status
- Clinical outcome 5-10 days post-treatment;
  Co-primary all treated and clinically evaluable
- Non-inferiority margin -10%;
- Wider margin may be justifiable if large percent are IV-V

IAI
ABSSSI
UTI

IAI

- Diagnosis based on an intervention
  Surgery, laparoscopy, percutaneous drainage
- Limit percent with appendicitis (perforated);
  Stratify by appendix vs. other primary foci
- Avoid upper GI perforation unless clear evidence of peritoneal infection rather than inflammation
- Clinical outcome 7-14 days post-treatment; Co-primary all treated and clinically evaluable
- Non-inferiority margin -12.5%

ABSSSI

- Cellulitis, erysipelas, wound infections, major abscesses
- May choose to avoid burns; prefer separate DFI study
- Superficial SSSI are dealt with separately (superiority)
- Define minimum area affected in inclusion criteria
- Define minimum signs and symptoms compatible with an ongoing infectious process
- Clinical outcome 7-14 days post-treatment;
  Co-primary all treated and clinically evaluable
- Non-inferiority margin -10%

UTI + initial IV

- Catheter, retention, obstruction, neurogenic bladder
- Avoid percutaneous drainage and reflux
- Prefer that acute pyelonephritis is studied separately

- ME minimum cfu/mL > 1 x 105 single morphology

- Speciate baseline and failure pathogens

- Microbiological outcome 7-14 days post-treatment;
- Microbiological success < 1 x 103 cfu/ml
- Co-primary - all with pathogen and ME
- Document and investigate all with microbiological success but lack of clinical response

- Non-inferiority margin -10%

BACTERAEMIA

Bacteraemia

Pathogen-specific

- Studies in patients presenting with bacteraemia and known/unknown foci are not usually encouraged
- Qualification only by pathogen implies treatment of any infection focus; such studies cannot support this

As discussed Day 1:

- Exception may be agents active against rare and/or MDR pathogens, with qualification regarding circumstances of use

Bacteraemia

Non-pathogen specific

- Usual approach is not to preclude or specifically endorse use for indicated infections when associated with bacteraemia
- Based on cumulative clinical experience of treatment when associated with various types of infections
  eg. > 50 cases across infections and no concern raised
- A qualified indication could be considered for:

  Treatment of bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above (i.e. list of indications)

ERADICATION OF CARRIAGE

Eradication of carriage

- Indications that relate to the reduction or eradication of a pathogen from a specified body site are not acceptable unless the microbiological findings were shown to result in a measurable clinical benefit
- Require placebo-controlled studies to show superior eradication rates" unless usage has become widely accepted as SOC; examples of exceptions given
- Use of published data to substantiate link between eradication and clinical benefit not usually acceptable;
  possible exception nasal *S. aureus*

Eradication of carriage

- Fully validated microbiological techniques must be used to detect and quantify pathogens (may need pilot study)
- “Apparent eradication” = no growth Need to define success and failure based on serial sampling and duration of effect
- Extent and duration of effect should be sufficient to cover the intended mode of use (e.g. until wound healed)

INHALED AGENTS FOR NON-CF INDICATIONS

Inhaled agents for non-CF uses

- Efficacy not yet established in prophylaxis or treatment settings (e.g. COPD, NCBE, pneumonia)
- Need to show superiority vs. placebo
- Prevention of exacerbations - Assess underlying chronic lung disease and adequate definitions of exacerbations; follow ≥ 12 months from start of regimen
- Treatment uses - May be investigated as add-on or alternative to systemic treatment
  Add-on could show superiority in alternative endpoints
  Alternative could be designed as a non-inferiority study if sole reliance on inhaled treatment can be supported

SUMMARY

Major issues for further consideration before finalising the Addendum

Day 1

- Pharmacometric methods available to better support the selection of dose regimens that minimise the risk of selecting for resistance to new drug
- Pharmacometric methods available to maximise the information that can be gained from small numbers of treated cases
- Critical to obtain adequate PK data from treated patients and to collect all the information required to support these analyses
- These approaches can allow integration of all the non-clinical and clinical information obtained across the entire development programme to strengthen the total level of evidence

Day 1

Outline a range of programmes from highest level of evidence to lowest level of evidence that can be provided and then discuss which scenario best fits to the properties of the individual agent

It may be that a single drug could fit more than one of the programmes outlined so need to discuss relative merits

Small non-inferiority studies and non-randomised studies will require special/additional consideration in the guidance

Superiority for usual efficacy endpoint has low feasibility even now and even less feasible once new drugs approved

Explore alternative endpoints; improved safety has merit

Day 1

- Expectation is that monotherapy will not be possible for MDR/XDR pathogens unless there are patient reasons precluding use of agents to which the organism is susceptible
- Enrolment of patients with a range of infection types seems inevitable to collect data on treatment of MDR/XDR cases
- Both underline the need for strong PK/PD package
- EU regulatory pathways exist to discuss non-drug specific approaches to various issues (e.g. use of Bayesian methodologies, construction of appropriate control populations)

Day 2

- Diagnostic development should take into account how they will be used
- A predictive diagnostic could facilitate patient selection and appropriate use of a new agent in routine use
- Cost may preclude a test in routine use that is feasible for trials

- HAP/VAP some requests for more specificity and alignment in EU
- Day 28 mortality good for safety but Day 14 better for efficacy
- Concomitant agents at least from outset; adjust later; evaluability
- Underpowered study as add-on to standard studies in other indications?

Day 2

- CAP discussion should include additional consideration of HCAP and the definition/handling of these subgroups
- May need combination treatment at least to cover Legionellae not detected by urinary antigen test
- Acceptance of additional RDTs for ME eligibility

- IAI stress is on diagnosis of bacterial infection process
- UTI could include pyelonephritis requiring IV initially but

Day 2

- Bacteraemia NPS pooled analyses could improve on min #
- Special case made for SAB and MDR/XDR with adequate supporting information to add confidence to expectations
- Address carriage beyond current addendum examples suggested
- Consider how to obtain the clinical impact data needed
- Considerable potential for inhaled agents to prevent and treat
- Treatment of HAP/VAP needs endpoint identification
- Superiority studies in NCBE and COPD; unsure which endpoint