EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Antibacterial drug targeting single species

FDA Workshop, 19 July2016

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An agency of the European Union

drug X-1: new class active vs. *P. aeruginosa* only

- Preclinical and clinical pharmacology need to be thoroughly and exhaustively investigated, including:
  - drug-drug interactions
  - Metabolism and excretion
  - distribution at relevant body sites (e.g. ELF)
  - PK in ICU patients and with augmented renal clearance (ARC)
  - PK in renal/hepatic impairment and need for dose adjustment
- Adequate and robust PK/PD profiling is essential and is expected to complement as much as possible any limitation in the clinical efficacy dataset
- E-R analyses to be conducted in efficacy trial(s)

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- Clinical studies:
- In all cases necessary to use (experimental) RDTs to enrich enrolment otherwise feasibility challenging.
- The amount of patients enrolled empirically should be limited to the extent possible
- Up to 24 hours of previous antipseudomonal therapy allowed
- EMA will follow a pragmatic approach in the recommendations for use with respect to RDTs used in clinical trials
- In consideration of the current epidemiology for this pathogen, try to enrol at least some MDR *P. aeruginosa*
- importance of sites selection

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Desired N with illness	100			100		
True rate of illness in the population	10%			15%		
Test sensitivity: TP / (TP + FN)	100%	80%	50%	100%	80%	50%
PPV of test: TP / (TP + FP)	69%	64%	53%	78%	74%	64%
N to screen: Desired N / True rate / Sensitivity	1000	1250	2000	667	833	1333
N to enroll: Desired N / PPV	145	156	190	128	135	157
Specificity	95%	95%	95%	95%	95%	95%

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- Potential options: randomized study in HAP/VAP, with:
  - NI testing with wider than standard margin and alpha level to be discussed
  - Clinical outcome at TOC as primary endpoint
  - Options for testing of nested superiority in subgroups/secondary clinically relevant endpoints
- monotherapy not possible at least initially
- control therapy may be a predefined single combination or may have to be "BAT" (Best Available Therapy)
- If BAT, need to define hierarchy including options for cases of MDR isolates
- An additional uncontrolled study with MDR cases could be considered

drug X-1: new class active vs. *P. aeruginosa* only

- Potential options: "All-comers" randomized study including HAP/VAP, IAI, UTI and bacteremia:
  - infection specific clinical outcome at TOC as primary endpoint
  - not powered for formal inferential testing
  - Superiority is not demanded, but
  - Explore options for testing of nested superiority in subgroups/secondary clinically relevant endpoints
  - Uneven randomization can be considered (e.g. 3:1 or 4:1)
- monotherapy not possible at least initially, maybe except UTI (but not common)
- control therapy may be predefined or be "BAT"
- If BAT, need to define hierarchy including options for cases of MDR isolates

drug X-1: new class active vs. *P. aeruginosa* only

- Potential options: Uncontrolled study including HAP/VAP, IAI, UTI and bacteremia:
  - infection specific clinical outcome at TOC as primary endpoint
  - Need of adequate external/historical control

- monotherapy not possible at least initially, maybe except UTI (but not common)
- In light of likely hurdles in the interpretation of the data, adequate justification should be provided
- Convincing PK/PD package even more critical than in other scenarios

Addendum: labels specific for MDR pathogens

Section 4.1:

For the treatment of infections due to Pseudomonas aeruginosa in patients with limited treatment options. See 4.4 and 5.1.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Section 4.2:

It is recommended that X-1 should be used to treat patients that have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.

Addendum: labels specific for MDR pathogens

Section 4.4:

The limitation of the data would be explicitly stated in the SmPC, mentioning relevant subpopulation for which there are notable uncertainties as e.g. not being included/sufficiently represented in clinical studies or for which PK data are not available or not fully supportive of activity at specific body site.

Thank you for your attention

Further information

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