30 July 2019

Submission of comments on 'Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3 (EMA/844951/2018 Rev. 3)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	. General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through postapproval and pharmacovigilance research. In 2018, ACRO member companies managed or otherwise supported a majority of all biopharmaceutical-sponsored clinical investigations worldwide. With more than 130,000 employees, including 57,000 in Europe, engaged in research activities in 114 countries the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. ACRO thanks the Agency for this important draft guideline. According to the European Commission, antimicrobial resistance is responsible for 25,000 deaths per year in the European Union and 700,000 deaths per year globally. And, at least 23,000 people die each year from antibiotic-resistant infections in the US according to the Centers for Disease Control. This revised guideline on the evaluation of human medicines indicated for the treatment of bacterial infections plays an important role	

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	in the fight against AMR through the application of regulatory science to support the development of new medicines and treatment approaches, especially for patients with infections caused by multi-drug resistant bacteria and limited therapeutic options. ACRO represents the leading clinical research and technology organizations with global operations, and we engage with regulators around the world. Because of this, ACRO thanks the Agency for the global approach of this guidance document, which is the outcome of discussions between regulators in the EU, US, and Japan aimed at aligning respective data requirements so that industry can design clinical trials that meet the evidence needs of multiple regulatory agencies. Section 5.6: The requirement to conduct 2 pivotal trials in cUTI when the IMP has not been developed for another indication does not make sense. The sample size should be sufficient to reach the endpoints in a non-inferiority design and provide sufficient numbers for the safety data base (e.g. n=700 as recommended by the FDA). The current guidelines result in 2 identical clinical trials which are more costly and potentially takes more time without providing any additional benefit compared to a single trial. This does not serve the purpose to deliver new antibiotics for serious bacterial infections in	

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	the face of increasing bacterial resistance	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
652-662		Comment: 6.1.1. The criteria for patient selection seem vague and there is a need in clarity in the defined criteria Proposed change (if any): Suggested intervention would be the definition of the lesion size measured as the minimum surface area of redness, oedema, or induration. This area should be chosen and defined to select the patients with acute bacterial skin infections for which a reliable control drug treatment can be estimated. A sufficiently large lesion size also differentiates between *minor cutaneous abscesses* (smaller than a predefined surface area) and *major cutaneous abscess (*greater than the predefined surface area). This definition might be important as studies have shown that there appears to be insufficient information to reliably estimate a quantitative treatment effect of an antibacterial drug for patients who have undergone surgical incision and drainage for minor cutaneous abscesses. Also, the methods of measuring the lesion size should be unified across all trial sites.	
665-672		Comment: 6.1.2. The patient selection criteria should be based upon the	

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		clinical, radiographic and microbiological aspects. The criteria as defined at the moment are vague and can be subject to subjective interpretation- "at least one characteristic finding on percussion and/or auscultation associated with induration", are mostly symptoms and are insufficient in the declaration of objective signs and laboratory and radiograph changes. Proposed change (if any): The assessment of CAP severity through the PORT system should be clearly listed in this paragraph, as the way the score will be obtained, before proceeding to the assignment and stratifications of patients to a particular class	
716-735		Comment: 6.1.5. As one of the signs that accompany the conditions encompassed under this indication is fever, it should be listed as a sign that can be used when evaluating the criteria for patient selection. Proposed change (if any): Considering the indication is cUTI, a parallel haemoculture should always be obtained for microbiological analysis, together with the urine culture. Also, follow up visits should be defined across all trials in a given interval, with concomitant urine culture analysis (not only of the pathogen species, but also the profile of resistance of the pathogen), to capture the persistence, re-infection (new	

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		infection with a different pathogen) or resistance of a particular pathogen. This is also valuable to recognise the importance of asymptomatic bacteriuria, and special considerations should be made for the statistical analysis of this population, as asymptomatic bacteriuria without signs and symptoms should not be treated	
795-803		Comment: 6.3. There appears to be a need for better definition of the antibacterial agents for this particular patient population.	
		Proposed change: It would be good to define the antibacterial drugs in this section as drugs likely to have a new mechanism of action that preserves antibacterial activity in resistant pathogens, or a potential alteration in the structure of the molecule of the drug that makes the antibiotic no longer susceptible to the existing mechanisms of resistance, or other characteristic that has a potential to create enhanced effectiveness. Also, it should be clearly stated that a drug that has slightly great potency (the value for this should be clearly defined as the number of dilutions in in-vitro testing) should undergo a traditional development program as it will not be considered a drug that would address the unmet needs of this population with limited treatment options. In this section it would also be good to address the need of co-development and use of novel and rapid diagnostic tests for prompt identification of patients with the pathogen of	

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		interest as the cause of the infection in this group of patients with limited treatment options.	
		ACRO thanks the Agency for the opportunity to provide these comments on its 'Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev. 3 (EMA/844951/2018 Rev. 3). Please do not hesitate to contact ACRO if we can answer any questions or provide additional details (knoonan@acrohealth.org).	

Please add more rows if needed.