EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2018

Submission of comments on Draft reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population (EMA/CHMP/535116/2016)

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, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices – from discovery, pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the draft reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population. ACRO considers this to be a useful document to help facilitate appropriate dosing of obese patients. In particular, ACRO welcomes the guidance on when to investigate the effects of obesity, and the currently acceptable	

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	methodological approaches to do so. With the increasing incidence of obesity in the paediatric population, ACRO also welcomes the acknowledgement within the reflection paper of the different criteria for children. ACRO notes, however, that the title of this reflection paper speaks of the investigation of pharmacokinetics (PK) and pharmacodynamics (PD) whereas the objective statements do not mention PD, and no specific guidance is provided on investigation of the effect of obesity on PD, or on PK/PD correlation. ACRO recommends that either the title and scope of the document should be limited to PK, or that specific guidance on the investigation of PD and the PK/PD correlation in obese patients is included. Additionally, ACRO cautions that it is important that the reflection paper provides practical and pragmatic guidance with regard to dosage recommendations. For instance, prescribers may need guidance regarding dose adjustment on a dynamic basis, e.g., when subjects move from, for example, WHO Class III obesity to Class II; this will impose a greater burden on prescribers, as it may entail checking the patient's weight/BMI at every visit, rather than simply providing a repeat prescription. Care will also need to be taken to avoid "salami slicing" dose recommendations by taking account of variations in	

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	exposure and level of effect in non-obese patients to determine whether an additional dosage-form is truly required. For example, if a product is authorised at dosage-forms of 20, 40 and 80 mg for use in a non-obese population, would additional dosage-forms of, e.g., 30, 50 and 90 mg then be expected for use in obese subjects? Moreover, similar arguments to those supporting the assessment of new drugs in the obese population could also be developed for the lean population, extending to patients with anorexia. If so, the “salami-slicing” concern becomes greater, with the same drug as exemplified above now also needing to be made available at doses of, e.g., 15, 35 and 70mg.	

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)*
6-7		Comment: As noted above, no specific guidance is provided on investigation of the effect of obesity on PD, or on PK/PD correlation. If none is to be included, ACRO recommends that the title of the document should be limited to PK. Proposed change (if any): Change the title to "Reflection paper on investigation of pharmacokinetics in the obese population" or include specific guidance on the investigation of the effect of obesity on PD and PK/PD correlation.	
39-40		Comment: The following information does not seem to appear in reference 1 (to which it is attributed): "The alteration of body composition and physiology as well as steatosis and a chronic state of inflammation" Proposed change (if any): Revise the statement to reflect the reference or provide the relevant reference to support the statement.	
48 254 309 (Table 1)		Comment: The statement "According to the WHO, BMI between 25 and 29.9 kg/m^2 represents overweight" (line 48) is not consistent with the table following line 254, where this range is described as "pre-obesity" and Table 1, which states that "overweight" applies to any BMI ≥25 kg/m^2.	

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		Proposed change (if any): ACRO recommends that the WHO terminology is used consistently throughout the document in order to avoid confusion.	
68		Comment: As noted earlier, no specific guidance is provided on investigation of the effect of obesity on PD, or on PK/PD correlation. If none is to be included, ACRO recommends that the title and scope of the document should be limited to PK. Proposed change (if any): Change the title to “Reflection paper on investigation of pharmacokinetics in the obese population” or include specific guidance on the investigation of the effect of obesity on PD and PK/PD correlation.	
108		Comment: The statement “glomerular filtration rate (GFR) is approximately 60 % higher in obese subjects” is presumably based on comparison with lean subjects. This should be clarified. In practice, it is more likely that obese subjects will show a range of GFR values and it would be more helpful to quote the range rather than an average (or mean or median?) increase that may not apply to the majority of individual subjects. Further, the total enrolment in the cited study (Chagnac 2008) was N=31 (12 obese subjects, 19 ‘lean’ subjects). ACRO cautions against the use of a wide-sweeping statement, regardless of significant p-values, given the small size of the study (or the reflection paper should state explicitly	

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		that the statement is based on a small sample size). Proposed change (if any): Provide the ranges of GFR values shown in obese and lean subjects in the referenced study and make clear the small sample size of the study.	
143-149		Comment: The inclusion of specifically bariatric surgery seems odd, even though it is associated with obesity. Other types of gastrointestinal surgery that are unrelated to obesity (e.g., small bowel resection) could also affect drug absorption and metabolism. Proposed change (if any): ACRO recommends expanding the scope of the section to include any gastrointestinal surgery that might affect drug absorption.	
150		Comment: The current content of section 2.5 is not really related to PK/PD correlation. Proposed change (if any): Change the title of Section 2.5 to Pharmacology Considerations. Consider if more recent publications add valuable information for this section, eg. Expert Opin Drug Metab Toxicol. 2018 Mar;14(3):275-285.	
170 176 179		Comment: ACRO recognises that there needs to be flexibility in the reflection paper, but the statement “obese patients are a reasonably large part of the target patient population” (line	

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		170) seems vague and may not provide adequate guidance. For example, it is not clear what “reasonably large” (also used in line 176) means relative to the proportion of the population as a whole who are obese, nor is it clear whether a “reasonably large” part (line 170) or proportion (line 176) of the population is the same as “a significant proportion” (line 179). Overall, it is not clear if the statements in lines 170, 176 and 179 relate to the same or different groups of patients. Proposed change (if any): ACRO recommends revising this section to provide greater clarity of the situations in which obese patients should be included in (a) dose-finding studies and (b) confirmatory clinical trials, and how dosage recommendations should be addressed. Reference to additional source documentation (references) might reduce the ambiguity, as would consistent use of terminology.	
186		Comment: The term “(morbidly) obese” is not one of the categories defined by the WHO in Section 1. In order to provide clarity and to aid international recognition, ACRO recommends the use of the WHO classification and terminology throughout the reflection paper. Additionally, although information on PK/PD relationships in obese patients is currently limited, this does not mean that such information should not be sought when relevant and practical. Consequently, ACRO recommends revising the paper as described below.	

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		Proposed change (if any): Use WHO classification and terminology throughout the document. Change the statement "…additional dedicated PK studies…" to "…additional dedicated PK/PD studies…"	
192		Comment: If specific guidance on the investigation of PD and the PK/PD correlation in obese patients is to be included in the reflection paper (see ACRO's General Comments above), the section heading should be changed from "Investigation of the effect of obesity on PK" to "Investigation of the effect of obesity on PK and PD", and section 4 should provide guidance on how the PD effect in obese patients should be studied. Proposed change (if any): As stated above.	
201-202		Comment: The population studied in clinical trials should be representative of the population that will be treated with the medicinal product when marketed. It may not be necessary, therefore, to "collect data in all classes of obesity" as not all classes may be relevant to the target population. However, in view of the global obesity epidemic, most medicinal products will ultimately be administered to patients meeting the definition of Class I for obesity. Therefore, it is suggested to include Class I obesity patients early in product development so that effects on PK/PD can be studied. The PK/PD results from these early studies in Class I obesity patients could	

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		inform, along with the expected target population, the need for additional studies in obesity classes II and III. In addition to studying the different classes of obesity, ethnic differences in body composition should also be a consideration. According to research, and as stated by the WHO, “BMI may not correspond to the same degree of fatness in different populations due, in part, to different body proportions. The health risks associated with increasing BMI are continuous and the interpretation of BMI gradings in relation to risk may differ for different populations.” http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (accessed 05 July 2018). Linear BMI-based risk factor and drug distribution relationships may differ based upon ethnically (and genetically) determined differences in fat distribution and body composition. ACRO therefore recommends that the reflection paper should reference this WHO paper and include a recommendation to consider the effects of ethnic differences in body composition. Proposed change (if any): Revise the sentence to read “Sufficient data should, if possible, be collected in those categories of obesity (pre-obese and BMI I, II, and III classes) that are relevant to the target patient population.” Add a recommendation to include Class I obesity patients early in product development, and a recommendation to consider the effects of ethnic differences in body composition.	

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219		Comment: ACRO believes the correct reference is reference 5 (population PK analyses guidance) rather than the stated reference 4 (addendum on weight control in children). Proposed change (if any): Check references.	
228		Comment: ACRO recommends that t_{max} should also be included in the list of parameters to be estimated and compared. Proposed change (if any): Add t_{max}.	
236-262		Comment: ACRO recommends that section 5 “Presentation and discussion of data” should also discuss the impact of changes in the exposure-response relationship on dose selection, if any. Additionally, with the exception of the summary data and conclusions that will be described in section 5.2 of the SmPC (lines 260-262), it is not clear where the discussion and presentation of data described in this part of the draft reflection paper should be placed in the Common Technical Document (CTD) supporting a marketing authorisation application. ACRO recommends that this should be stated clearly at the start of section 5. Proposed change (if any): As noted above.	

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		ACRO thanks the Agency for the opportunity to provide comment on this Draft reflection paper on investigation of pharmacokinetics and pharmacodynamics in the obese population (EMA/CHMP/535116/2016). Please contact ACRO if we can answer questions or provide additional details (knoonan@acrohealth.org).	

Please add more rows if needed.