1 April 2016
EMA/CHMP/162888/2016
Committee for medicinal products for human use (CHMP)

Overview of comments received on 'Prasugrel film-coated tablets 5 and 10 mg product-specific bioequivalence guidance' (EMA/CHMP/PKWP/36761/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Eli Lilly and Company
2	Pharmaceutical Research Institute (Instytut Farmaceutyczny), Warsaw, Poland

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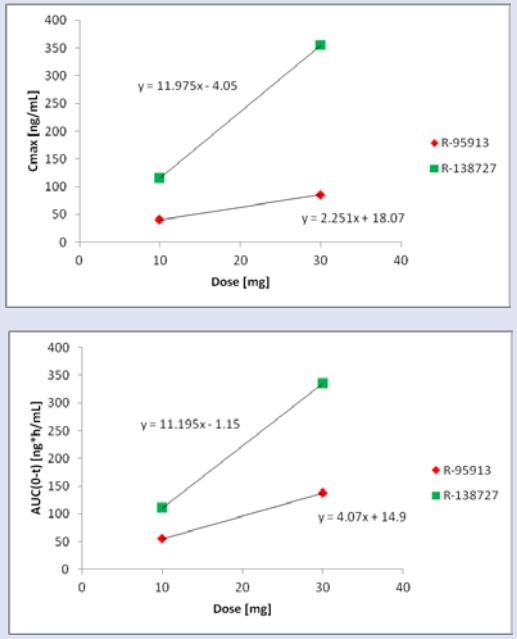
1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	**Reason that we believe basing Bioequivalence on the active metabolite, instead of the first metabolite R-95913, is a better approach:** We understand that the EMA recommends in general that when the parent drug cannot be measured, the first metabolite should be. Although it is a good general rule, for prasugrel we believe the best clinical approach would be to base Bioequivalence on the active metabolite for the following reasons: 1. The active metabolite is the only moiety which is clinically relevant. 2. The EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98) states that: “However, some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compound. In this situation it is acceptable to demonstrate bioequivalence for the main active metabolite without measurement of parent compound”.	Refer to specific comments on text below.
2	The Pharmaceutical Research Institute (PRI) is pleased to have the opportunity to comment on the draft Product-Specific BE Guidance released by the EMA. PRI has over 60 years of experience in pharmaceutical R&D (technology of API synthesis, drug dosage form, analytical services,	Inclusion of more details in the product specific guidance is not accepted. For such details, refer to the “Guideline on the investigation of bioequivalence” (CPMP/EWP/QWP/1401/ 98 Rev. 1/ Corr).

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	and registration). Pharmacology Department of PRI conducts GLP compliant pharmacokinetic studies, including bioavailability and bioequivalence. The general idea of a product specific bioequivalence guidance is definitely a good proposal. It will facilitate both preparation and evaluation of drug registration documentation. The presentation of data in the form of a table greatly facilitates reading. However, it would be appreciated if some more details, e.g. number of subjects and sampling schedule, would be suggested in the EMA proposal, which may be adopted by the applicant in specific cases.	
	It is appreciated that the guideline deals with prasugrel, because selection of analyte for this drug does not follow standard approach. EMA statement which analyte is acceptable is clearly needed.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
16 (analyte row in the table)	2	Comment: Pharmacokinetics of prasugrel indicates that detection of parent drug is not possible. In this situation bioequivalence should be based on the metabolite. However, in our opinion active metabolite (R-138727) may be a better choice than inactive one (R-95913). 1. In case of prasugrel it seems appropriate to follow specific requirement of CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** (Page 10): *"some pro-drugs may have low plasma concentrations and be quickly eliminated resulting in difficulties in demonstrating bioequivalence for parent compound. In this situation it is acceptable to demonstrate bioequivalence for* ***the main active metabolite*** *without measurement of parent compound*". Selection of analyte proposed in the product specific guideline (inactive metabolite) is not in line with bioequivalence guideline, which recommends active metabolite as an analyte. 2. The assessment report for Efient (EMEA/117561/2009, pages 19-24) shows that most of pharmacokinetic studies (including 16 trials of phase 1, in total of 506 subjects) to obtain regulatory approval for the original drug used	Not accepted. The first metabolite (R-95913) should be measured as this metabolite best reflects the exposure of the parent compound.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		active metabolite R-138727 as an analyte. It seems appropriate to select the same analyte for assessment of both original and generic drug. 3. It seems that R-138727 reflects better parent drug exposure than R-95913. The dose increase leads to proportional increase in C_{max} and $AUC_{(0-t)}$ for R-138727 and less than proportional increase for R-95913, particularly for C_{max} (see H-S Jeon et al. in Clin. Ther. 37 (3) 2015, 563-573, Figure 1).  *Figure 1. Dose proportionality for C_{max} and $AUC_{(0-t)}$ -*	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		adopted from H-S Jeon et al. in Clin. Ther. 37 (3) 2015, 563-573). The bioequivalence study should be designed to show the difference between products if any. Using R-138727 as an analyte seems to be a more sensitive tool to detect difference between products than using R-95913. Products bioequivalent basing on R-95913 data may not be bioequivalent basing on R-138727 data. The opposite situation is rather unlikely. Proposed change (if any): Bioequivalence should be based on ~~the first metabolite, R-95913~~ active metabolite, R-138727	
Line 17 – table Analyte - Background	1	Comment: We suggest the following changes since the parent drug does not appear in the plasma. Proposed change (if any): **"Background:** the parent compound is not detected in human or animal plasma (or other biological matrix). Bioequivalence should be based on the ~~first~~ active metabolite ~~R-95913~~. ~~However, the parent drug should be studied if feasible."~~	Not accepted. The first metabolite (R-95913) should be measured as this metabolite best reflects the exposure of the parent compound.
Line 20	1	Comment: editorial Proposed change (if any): "in vivo studies seem~~s~~ to be	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		mandatory”	