31 January 2019
EMA/CHMP/682121/2018
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Octreotide acetate depot powder and solvent for suspension for injection 10 mg, 20 mg and 30 mg product-specific bioequivalence guidance' (EMA/CHMP/291571/2018)

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

Stakeholder no.	Name of organisation or individual
1	Zentiva, k.s., Czech Republic
2	Novartis
3	Mylan Laboratories Limited, India

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	Novartis welcomes the opportunity to comment of the draft bioequivalence guidance for long-acting octreotide. Briefly, the proposed PK variables and study design are considered necessary to adequately characterize the complex drug release profile of long-action octreotide microparticles. This follows a tri-phasic pattern, consisting of drug burst, lag phase and erosion phase. These PK properties ultimately define the PK profile at steady state and as such the clinical safety and efficacy profile of long-acting octreotide. Although it is a secondary PK parameter, it should be noted that $C_{max\ initial\ release}$ is an important variable as it may be indicative of a "dose dumping" effect, ie too much and/or too quick burst release. The results of $C_{max\ initial\ release}$ in such BE studies therefore merit discussion if they fall outside of the accepted 90% confidence intervals, particularly if $C_{max\ initial\ release}$ would be greater than the actual C_{max}.	Partly accepted. Pharmacokinetic characteristics assigned to be supportive or secondary may not prevent additional queries.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 20 / Table Bioequivalence study design	1	Comments: The waiver of multiple-dose study for this product is considered adequate. However, the requirement for Ctau (concentration at the end of the dosing interval, i.e. day 28) to be the primary parameter for bioequivalence assessment is unjustified and not required by the currently valid EMA Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1) as additional metric for the assessment of the shape of the plasma concentration versus time curve (in a single dose study). Notably, the Ctau metric was not considered to have sufficient scientific evidence to encourage its implementation in the revised EMA/CPMP/EWP/280/96 Corr1 guideline (refer to draft XXIII agreed by PKWP & CHMP for public consultation). Unless there is a documented link between the Ctau metric and efficacy / safety of octreotide, the requirement to pass bioequivalence for this pharmacokinetic metric is unjustified and thus only generates additional barrier for entry of generic products. Proposed change : Table 'Requirements for bioequivalence demonstration (PKWP)': Section 'Main pharmacokinetic variables'	Not accepted. Given the pharmacokinetic characteristics of octreotide acetate and the lack of a multiple dose PK study, the parameter Ctau is considered crucial to estimate the risk of accumulation, which is not considered negligible. Moreover, the bioequivalence of the Ctau would ensure similarity at the end of the dosing interval. The relevance and challenge of inter-subject variability is acknowledged for Ctau. However, this may be addressed by appropriate sample size.

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		delete the corresponding text related to Ctau: AUC(0-28d), AUC(28-56d), AUC(0-∞), Cmax and Ct (concentration at the end of dosing interval, i.e. day 28).	
Line 20	3	Comments: Octreotide acetate product specific bioequivalence draft guidance (Annexure-I) recommends Ct (concentration at the end of the dosing interval, i.e. day 28) to be evaluated as a primary PK parameter. Mylan believes that while Ct contributes to PK comparability, it is not an appropriate PK parameter to demonstrate bioequivalence with conventional BE margins for the following reasons o High inter subject variability observed in reference product study o Extent of accumulation can be derived from comparing the residual concentrations at Day 28 as measured by pAUC o Limited clinical significance considering long duration of pharmacodynamic effect once the octreotide levels are in a plateau range Dose the Agency agree? Proposed change: **Clinical Justification for considering C_{28d}**	Not accepted. Given the pharmacokinetic characteristics of octreotide acetate and the lack of a multiple dose PK study, the parameter Ctau is considered crucial to estimate the risk of accumulation, which is not considered negligible. Moreover, the bioequivalence of the Ctau would ensure similarity at the end of the dosing interval. The relevance and challenge of inter-subject variability is acknowledged for Ctau. However, this may be addressed by appropriate sample size.

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		(concentration at the end of the dosing interval, i.e. day 28) as supportive PK parameter and not primary PK parameter Based on the pharmacokinetic literature of immediate release subcutaneous Sandostatin studies, it is known that octreotide concentrations of around 1 ng/mL are needed to adequately suppress growth hormone (SBOA of Sandostatin LAR; Peter Grass, 1996). In pharmacokinetic studies of Sandostatin LAR 30 mg, the highest average octreotide concentrations were reached between day 26 and day 34 after the injection. However, plateau concentration (defined as 80% of C_{max}) was reached at day 14 and remained stable for up to 19 days, i.e. till day 33. Additionally, from day 21 until day 42, concentrations were quite stable in the range of 900 pg/mL to 1200 pg/mL. Though the range of concentrations remained stable during this period, the inter subject variability for a timepoint like day 28 was significantly high as demonstrated in Mylan's reference product study. Mylan conducted a pilot study which evaluated pharmacokinetics of US Reference Listed Drug (US RLD) and EU reference Medicinal Product (ERMP). Data from 14 patients from US RLD arm and 16 patients from ERMP arm were considered for analysis. The study report (BA16101302-01) can be found in annexure II.	

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		High inter subject variability with reference product: In the BA16101302-01 study, thirty-two healthy adult subjects were randomized (16 subjects per treatment arm) to receive either the USA marketed Sandostatin LAR or the UK marketed Sandostatin LAR. The results from this study confirmed the high inter-subject variability not only at the C_{28d} time point (inter-subject CV > 70%), but also for C_{max} and $AUC_{28\text{-}56d}$ (inter-subject CV > 50% for both). In order to perform sample size calculations, a bootstrapping exercise was performed on the C_{28d} time point data from the pilot study to evaluate the variability. The results are presented below, where Treatment A is the USA marketed Sandostatin LAR, and Treatment B is the UK marketed Sandostatin LAR. **C28 Inter-Subject Variability Observed from a Pilot Study** **Plasma Octreotide PK Parameters C28d estimated inter-subject CV - Bootstrapping analysis (N=200 Rep=5000) (A=US Reference, B=EU Reference Product)**	

Obs	treatment	N	inter_CV
1	US RLD	14	74.529%
2	ERMP	16	74.847%

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Obs	treat	N	MEAN	STD	MIN	P10	P25	MEDIA
1	A	5000	71.03%	12.02%	29.56%	55.57%	62.98%	70.75
2	B	5000	71.76%	7.53%	42.34%	61.94%	66.62%	71.79

Based upon this data, completion of approximately 400 subjects (about 200 subjects per treatment arm) would be necessary for an adequately powered (80%) study with a 5% assumed difference between Test and ERMP to demonstrate bioequivalence of the C_{28d} time point, if it was a primary PK parameter. This product is not suitable for a replicate study design because of the long half life.

Relevance of $pAUC_{28-56d}$ versus C_{28} in assessing bioequivalence:

Pharmacokinetic studies of Sandostatin LAR have demonstrated that mean serum octreotide concentrations at day 28 did not accumulate beyond those expected from addition of residual concentrations from the previous injections (Peter Grass, 1996). Linearity of the pharmacokinetics was maintained. The ratios of average octreotide concentrations assessed at day 28 of the third injection versus the average concentration at day 28 of the first injection indicated an accumulation factor of 1.6. Thereafter, limited accumulation was noted. Since a generic is expected to demonstrate bioequivalence for

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		$pAUC_{28\text{-}56d}$ with the reference product, the equivalence of residual concentrations from first injection at day 28 is known. Hence by demonstrating equivalence on $pAUC_{28\text{-}56d}$, it can be assured, the extent of accumulation is similar between Test and Reference product. This can be further supported by the equivalence demonstrated in $pAUC_{0\text{-}28d}$ which represents the overall drug exposure in the first 28 days. In other words, whatever can be achieved by demonstrating equivalent C_{28d}, can also be demonstrated by comparing residual concentrations as measured by $pAUC_{28\text{-}56d}$. **Limited Clinical Significance of C_{28d} values:** The pharmacodynamic studies of Sandostatin LAR have shown that, from day 14 onwards, GH concentration was consistently reduced to less than 2 ng/mL and remained at this level for the following 34 days (Peter Grass, 1996). Noteworthy are the stable GH concentrations over the 12-hour profiles on each of the profile days evaluated by Grass et al. Considering mean daily average GH concentrations in the acromegalic patients after single injections, the dose-dependency of the effect of octreotide was most prominent, and reached statistical significance in the baseline-corrected parameters, Effect-AUC and plateau duration, defined as the duration of greater than 80%	

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		inhibition. However, maximum inhibition (E_{max}) was already reached with 20 mg Sandostatin LAR. Increasing the dose to 30 mg did not further decrease GH levels relative to baseline, but contributed to the duration of the effect. Based on this data, it can be understood that the concentrations at a range of 800 to 1200 pg/ml is adequate to maintain the treatment effect and the duration of effect stays longer than the pharmacokinetic plateau period. Minor fluctuations in the concentration within the range of plateau concentrations will not impact the pharmacodynamic effect of the drug. Considering the high inter-subject variability, even if the C_{28d} concentrations do not meet the 80.00 to 125.00% conventional margins, but the concentrations are in an acceptable range, the test and reference product are expected to behave similarly. Since the duration of effect is longer, any minor fluctuations in the concentrations at a timepoint like the 28th day during the plateau period should not impact the pharmacodynamic response. In conclusion, given the pharmacokinetic profile of Sandostatin LAR, it appears the octreotide concentrations during the plateau period (between 14 to 33 days after the injection) are in a narrow range of 900 to 1200 pg/ml. Pharmacodynamic studies demonstrate a suppression of maximal GH concentrations around 20 days and maintains this for	

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		up to 40 days after dosing. The duration of pharmacodynamic effect is longer and hence minor fluctuations will not impact the overall treatment effect. Although Mylan acknowledges the requirement of C_{28d} in assessing bioequivalence as outlined in the EMA draft guidance, we believe that if a generic product can show comparable concentrations to reference product over a relevant period, as reflected by pAUCs, instead of at a timepoint like C_{28d}, it should be adequate to demonstrate the equivalence of Test to Reference product. Demonstrating bioequivalence with conventional margins at a timepoint during the plateau period is always challenging because of the high inter-subject variability. Powering the study based on a highly variable timepoint, would require dosing of more than 400 healthy adult volunteers (Refer Annexure III and IV for CI assessment and the sample size calculation) which is clearly unwarranted and would unnecessarily expose such high number of healthy volunteers to a test drug when similar information could be achieved using partial AUCs. This challenge becomes even more relevant especially when the clinical/ PD relevance of the concentration on day 28 might be limited. Hence, Mylan would like to respectfully propose using $pAUC_{28\text{-}56d}$ as one the primary PK parameters to assess bioequivalence and	

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		C_{28d} values as a secondary parameter. **List of References** 1. SBOA of Sandostatin LAR, Clinical Pharmacology and Biopharmaceutics Review(s), FDA, 21008 2. Peter Grass, Peter Marbach, Christian Bruns, and loana Lancranjan, Sandostatin® LAR® (microencapsulated octreotide acetate) in Acromegaly: Pharmacokinetic and Pharmacodynamic Relationships, Metabolism, Vol 45, No 8, Suppl 1 (August), 1996:pp 27-30**.** **List of Annexures** **Annexure I** - EMA **product specific guideline (Draft),** Octreotide acetate LAR powder and solvent for suspension for injection 10, 20 and 30mg, EMA/CHMP/291571/2018 31 May 2018 • **Annexure II -** Reference product comparison biostudy report (BA16101302-01) **Annexure III -** CI Assessment based on BA16101302-01 study **Annexure IV -** Sample Size Calculation based on BA16101302-01 study	