22 April 2021
EMA/CHMP/89249/2021
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Lapatinib film-coated tablet 250 mg product-specific bioequivalence guidance' (EMA/CHMP/257298/2018)

First and second public consultations

Interested parties (organisations or individuals) that commented on the first draft document as released for consultation from 27 June 2018 to 30 September 2018 and on the second draft as released for consultation from 6 July 2020 to 31 January 2021.

Stakeholder no.	Name of organisation or individual
1	Zentiva, k.s., Czech Republic (draft 1)
2	Pharmaceutical Research Institute (Instytut Farmaceutyczny), Warsaw, Poland (draft 1)
3	Novartis (draft 1)
4	Medicines for Europe (draft 2 – submitted in 2 sets)

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1 **Draft 1**	We welcome the EMA initiative to issue product-specific guidance(s) to clarify the regulatory expectations regarding bioequivalence of certain products. Companies and other stakeholders also appreciate publication of received comments along with the PKWP feedback (outcome). However, for some products (namely ibuprofen and dimethylfumarate) neither the stakeholders' comments nor the feedback (outcome) from PKWP were published. The publication of comments as well as PKWP feedback (outcome) is considered essential to understand the rationale based on which the final requirements are laid. Also, in some cases, there were major changes introduced from draft to the final version of guidance (e.g., dabigatran etexilate or paliperidone palmitate) without the possibility of stakeholders to comment on the additional requirements. Therefore, the consultation process could be improved to enable at least 2 rounds of public comments in case of major changes (e.g., additional in-vivo studies are added). We believe this would be helpful for sponsors and would contribute to regulatory efficiency which translates to better access to affordable high-quality medicines for European patients.	Only where comments are received is it possible to publish an overview document. However, overview documents for the products cited (namely ibuprofen and dimethylfumarate) were not published in error and have now been published. While generally 2 rounds of public consultation are not envisaged, guidelines may be updated in light of increasing scientific knowledge (e.g. revision of paliperidone prolonged-release tablet 1.5 mg, 3 mg, 6 mg, 9 mg and 12 mg product-specific bioequivalence guidance regarding requirements for the multiple dose fasting study) and companies are invited to submit comments on existing guidelines at any stage to this effect. Exceptionally, for this lapatinib guideline 2 rounds of public consultation have been conducted due to the significant changes between the original and next version i.e. change from studies in healthy volunteers to patients with implications for requirements on food intake.
2 **Draft 1**	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 65 years of experience in pharmaceutical R&D (technology of API synthesis, drug dosage form, analytical services, registration). Pharmacokinetics Department (previously Pharmacology Department) of	Not accepted. The input is appreciated. However, the aim of developing the product specific guidance document is to enable a consistent approach to the assessment of applications based on bioequivalence data. As such they focus on general principles and major aspects on study design.

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	PRI conducts GLP compliant pharmacokinetic studies, including bioavailability and bioequivalence. The product specific bioequivalence guidances 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 recommended by the EMA for adoption by the applicant in specific cases. It is appreciated that the guideline deals with lapatinib, because its dosing regarding to meal intake does not follow standard approach. The EMA advise on selecting fasting and/or fed conditions for the bioequivalence study is appreciated.	
3 **Draft 1**	Novartis welcomes the opportunity to comment on the draft lapatinib product-specific bioequivalence guidance. In a nutshell, Novartis proposes the BE study to be conducted in naive patients eligible for lapatinib treatment or patients who are already on a regimen of oral lapatinib tablets within the approved combinations with the multiple dose, two-way, cross over study design. Further details are provided in the following comments section.	Accepted. The feasibility of conducting studies in healthy volunteers has been reconsidered. As a precautionary matter, considering the safety profile of lapatinib, bioequivalence studies in patients are now recommended.
4 **Draft 2**	Medicines for Europe welcomes the public consultation on Draft 2 of the product-specific guidance since there are relevant differences vs. the first draft document.	Accepted
4 **Draft 2**	It is stated (lines 11-12) that this draft is the second public consultation after significant revision of the draft requirements in response to the comments from the first public consultation. However, the comments to	Accepted. A draft Overview of comments was published on the EMA website on 23 November 2020 and the public consultation further extended accordingly.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	the first draft are not published. Could the agency kindly publish the comments before the guideline is finalized?	
4 **Draft 2**	Regulatory guidelines should focus mainly on the scientific value and reliability of data submitted to regulatory agencies. On safety considerations, ECs/IRBs as well as sponsor assessments are important as well and sometimes even regional differences exist between countries where studies are performed. We therefore suggest that the PSG provides flexibility to submit either single dose studies in healthy volunteers or multiple dose studies in patients, based on the critical analysis conducted by the aforementioned stakeholders during trial feasibility.	As per the Concept paper on development of product specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013), the aim of developing such guidance is to enable a consistent approach to the assessment of applications based on bioequivalence data, particularly generic applications, across all submission routes, i.e. submitted centrally, via the decentralised procedure or mutually recognition procedure, or purely nationally. For companies it is intended that such product-specific guidance will facilitate the design of study programmes that meet the expectations of European Union regulators hence allowing for better predictability in terms of the assessment during the authorisation process. Such guidelines are not legally binding, but it is expected that any deviations from the guidelines or indeed any choices where alternatives are offered are robustly scientifically justified.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Draft 1 – Table Bioequivalence study design	1	**Comments:** We consider the proposed single-dose, cross-over study in healthy volunteers as well as the choice of primary pharmacokinetic metrics, study strength, analyte and achiral analytical method adequate for demonstration of bioequivalence for lapatinib. However, we have comments to the proposal to conduct studies both under fasting and fed conditions. Our position is summarized in the below paragraphs. Systemic exposure to lapatinib (Tyverb, EMEA/H/C/000795) is increased when administered with food. The bioavailability is approximately 2-3 times higher when lapatinib is taken 1 hour after food compared with 1 hour before the first meal of the day (SmPC of Tyverb). These were the conditions under which the drug was tested in pivotal efficacy and safety trials (Devriese, et al., 2014, Invest New Drugs 32: 481–488) and thus identical posology has been reflected in the prescribing information. Patients are instructed to standardise the drug administration in relation to food intake, for example always take the drug one hour before a meal (SmPC of Tyverb). As per EMA Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), in those situations where SmPC allows the intake of reference medicinal product under fasting or fed conditions, the bioequivalence	Partly accepted. The situation when a drug should be administered in a standardised way either always with or always without food is not covered by the Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). Lapatinib should be administered in a standardised way either at least 1 h before or at least 1 h after a meal due to the large effect of food on lapatinib bioavailability. It is therefore important to detect possible differences in food effect between formulations. Regarding the reference to imatinib, this example is not applicable to the current case, as imatinib is administered in the fed state for tolerability reasons and not for pharmacokinetic reasons. Therefore, either a fed or a fasted study is acceptable according to the PSBGL for imatinib. The feasibility of conducting studies in healthy volunteers has been reconsidered. As a precautionary matter, considering the safety profile of lapatinib, bioequivalence studies in patients are now recommended: one study in the fasting state (or semi-fasting 1 hour before a meal) and one study in a semi-fed state, i.e. 1 hour after a meal.

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		study should be conducted under fasting conditions as this represents the most sensitive condition to detect potential difference between formulations. Indeed, fasting conditions are most discriminative for lapatinib since factors like partitioning into fat, increased bile salts solubilisation and delayed gastric emptying under fed conditions will not interfere with the absorption process (Koch et al., 2000 J Clin Oncol 27: 1191-1196). Notably, to increase the sensitivity to detect differences between products, a fasting study is preferred over a fed one for another drug from the group of tyrosine kinase inhibitors, namely for imatinib (Glivec, EMEA/H/C/000406), even if the drug should be administered only with meal (Imatinib hard capsules 50 and 100 mg, film-coated tablets 100 and 400 mg product-specific bioequivalence guidance, EMA/CHMP/315242/2014). The safety profile of lapatinib was assessed in pivotal clinical trials where the drug was administered either 1 hour before or 1 hour after food. Additional safety data were generated in smaller trials, where lapatinib was generally well-tolerated when administered with low or high-fat meal (Koch et al., 2000 J Clin Oncol 27: 1191-1196; Smith et al., 2003 Eur J Cancer 1:S169 (suppl; abstr 558); Devriese, et al., 2014, Invest New Drugs 32: 481–488). Should the conduct of fed study be enforced by PKWP due to safety concerns, the posology in this safety study needed to be aligned to the SmPC recommended conditions, i.e., lapatinib dose given at least one hour after meal. Moreover, the	

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		acceptance criteria would have to be modified: it shall be demonstrated that the systemic exposure is not higher for the test product than for the reference product, i.e. the upper limit of the 90% confidence interval should not exceed the upper bioequivalence acceptance limit. **Proposed change:** Table 'Requirements for bioequivalence demonstration (PKWP)': Section bioequivalence study design, in the recommendation regarding posology modify to: (1) ☒ fasting, ☐ fed, ☐ either fasting or fed, and (2) in the section Number of studies, modify to: one single dose study.	
Draft 1 - *Bioequivalence study design* row in the table, fasting/fed conditions cell	2	**Comments:** Recommendation on evaluating bioequivalence in both fasting and fed conditions seems to be unnecessary. 1. According to the EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) single fasting study should be performed for lapatinib because: a) The SmPC of the reference medicinal product recommends intake on an empty stomach ("at least one hour before food") or after meal ("at least one hour after food"). Thus, reference product administration is irrespective of food intake and the	See previous comment.

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		bioequivalence study should be conducted under fasting conditions. b) The reference medicinal product is not product with specific formulation characteristics (e.g. microemulsions, solid dispersions). Thus, it is not necessary to perform bioequivalence studies under both fasted and fed conditions. 2. Unnecessary exposure during second BE study rises serious ethical questions, because administration of lapatinib to healthy subjects results in high frequency of adverse events, see for example: a) Koch K. M. et al., J Clin Oncol. 2009; 27(8):1191-6 b) Burries III H. A. et al., Clin Cancer Res. 2009; 15(21): 6702–6708, c) Burries III H. A. et al., J Clin Oncol. 2005; 23(23):5305-13, d) Nakagawa K. et al., Jpn J Clin Oncol. 2009; 39(2):116-23). 3. Recommendation to conduct both fasting and fed studies seem to be not justified scientifically and it may negatively influence Patients' access to different products containing lapatinib. Due to rather high intra-subject variability of lapatinib (over 28%) and its BCS class II properties the number of subjects in bioequivalence study is predicted to exceed 70 for each	

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		study. Thus, cost of bioequivalence studies may limit development of generic drugs and decrease competition. **Proposed change (if any):** ☒ fasting ☐ fed ☐ both ☐ either fasting or fed ~~The fed study should be a conventional fed study (high-fat high-calorie meal given 30 minutes prior to administration of drug product and finished within 30 minutes).~~ **Background:** ~~Both fasting and fed are necessary since lapatinib should be administered in a standardised manner with regards to food as systemic exposure to lapatinib is significantly increased when administered with food.~~ Lapatinib is administered in fasting (at least one hour before food) or fed conditions (at least one hour after food). Fasting conditions are more sensitive to detect potential difference between formulations and are related to less adverse events.	
Draft 1 - Bioequivalence study design: Single dose	3	**Comments:** Lapatinib is not recommended to be administered in healthy volunteers due to its hepatotoxicity (see comment no.3), thus the BE study needs to be conducted in patients for whom lapatinib is indicated (naive or already on lapatinib treatment).	Partly accepted. The feasibility of conducting studies in healthy volunteers has been reconsidered. As a precautionary matter, considering the safety profile of lapatinib, bioequivalence studies in patients are now recommended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Therefore, one multi-dose study is proposed considering the adverse effects of lapatinib, and to measure the concentration of lapatinib after attaining steady-state. **Proposed change:** Add 'Multiple Dose once daily for 14 days' to replace 'single dose'. Add 'Dose of lapatinib depends on the indication that is being treated. For combination with capecitabine, lapatinib dose will be 1250 mg (5 tablets); for combination with trastuzumab, lapatinib dose will be 1000 mg (4 tablets); and for combination with aromatase inhibitor, lapatinib dose will be 1500 mg (6 tablets) (see section 4.2 of Tyverb SmPC). Consecutive lapatinib trough levels are recommended to establish attainment of steady state.'	The studies should be conducted in patients with breast cancer, whose tumours overexpress HER2 (ErbB2), for whom the drug is indicated. If the study is performed in patients who are treated with lapatinib in combination with capecitabine, pharmacokinetic sampling in each cycle is recommended during the latter part of the 7-day period when capecitabine is not administered.
Draft 1 - Bioequivalence study design: Cross-over	3	**Comments:** Novartis proposes to add 'Two-way' to the study design for clarity. **Proposed change:** Add 'Two-way' in addition to 'cross-over' study design. Add 'Each patient would receive their dose of lapatinib using either the test or reference product in a crossover design.'	Not accepted. This clarification is not considered necessary. Other study designs, e.g. a four-way replicated design could also be acceptable.
Draft 1 - Bioequivalence study design:	3	**Comments:** Novartis proposes that subjects should be naive patients eligible for lapatinib treatment or patients who are already	Accepted.

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Healthy volunteers		on a regimen of oral lapatinib tablets in combination with capecitabine, trastuzumab or aromatase inhibitors as indicated for the treatment of metastatic breast cancer whose tumours overexpress HER2 (ErBb2) (Tyverb SmPC section 4.1.) Due to the potential hepatotoxicity, lapatinib is not recommended to be administered in healthy volunteers. The hepatotoxicity-related warning & adverse reactions are included in the Tyverb EU SmPC. The recommendation also corresponds to the EMA guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr, Jan-2010) section 4.1.3 that '*If the investigated active substance is known to have adverse effects, and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to include patients instead, under suitable precautions and supervision*.' **Proposed change:** Please replace "Healthy Volunteers" by "Patients" in the Bioequivalence Study Design section.	
Draft 1 - Bioequivalence study design: Both (fasting/fed)	3	**Comments:** Following the proposed study design in patients with multiple dose daily for 14 days and consistent with Tyverb SmPC labelling, Novartis suggests that lapatinib should be	Partly accepted. Two patient studies are recommended, one study in the fasting state (or semi-fasting 1 hour before a meal) and one study in a semi-fed state, i.e. 1 hour after a meal.

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		administered either at least one hour before or at least one hour after food. **Proposed change:** ☒ Either fasting or fed Add 'lapatinib should be administered at least either one hour before or at least one hour after food' **Background:** ~~Both fasting and fed are necessary since~~ Lapatinib should be administered in a standardised manner with regards to food as systemic exposure to lapatinib is significantly increased when administered with food.	
Draft 1 - Bioequivalence study design: Number of studies Two single dose studies	3	**Comments:** Following the proposed study design, the fasting and fed condition are not applicable as well as two single dose studies. Fourteen days of dosing are proposed to ensure that patients have reached steady state of lapatinib. The PK matrix for BE assessment is AUC_{tau} (where tau = 24 hr) and C_{max} at steady state. Therefore, 24 hr sampling is adequate. **Proposed change:** Add 'One multiple dose study' to replace 'two single dose studies'; Add 'Collect 24-hour blood samples for steady state PK assessment from the last dose of 14 days of dosing'	Partly accepted. If the study is performed in patients who are treated with lapatinib in combination with capecitabine, pharmacokinetic sampling in each cycle is recommended during the latter part of the 7-day period when capecitabine is not administered (days 14-21), i.e. 3-5 lapatinib half-lives after the last dose of capecitabine in that cycle of treatment.

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		Remove 'Background: both a fasting and a fed study are needed.'	
Draft 2 - table	4	**Comments:** The new draft states that a multiple dose study in patients is recommended due to safety reasons. Several studies included in the GSK Clinical Study Register performed with laptinib following single dose in healthy volunteers resulted in no serious adverse events or death and they concluded that the products were found to be safe and well tolerated. These studies are: • A single dose, open label, randomized, three-way cross-over study in healthy subjects to evaluate the relative bioequivalence of two new small tablet formulations of lapatinib (GW572016) • A Single Dose, Open Label, Randomized, Five-way, Crossover Study in Healthy Subjects to Evaluate the Effect of Food on the Pharmacokinetics of GW572016 and to Evaluate the Relative Bioavailability of GW572016 as a Salt (F) versus Base (X) and Capsule (F) versus Tablet (F) • A Phase I, Open Label, Randomized, Four-way, Crossover Study in Healthy Subjects to Evaluate the Relative Bioavailability of Three Batches of Oral	Not accepted. As a precautionary matter, considering the safety profile of lapatinib, bioequivalence studies in patients are recommended. It is acknowledged that several studies have been performed in healthy volunteers with the originator. However, issues with liver toxicity were discovered rather late in the clinical development and were not fully known at the time these studies were performed. Although these effects are rare, they may occur suddenly and are difficult to control. Even though small studies can be done without signs of hepatoxicity, there is still a risk that such toxicity could occur, and for this reason studies in patients are recommended.

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		GW572016 Tablets with Varying Dissolution Rates Compared to Oral GW572016 as a Suspension • A Phase I, Open Label, 4-Period, Crossover Study in Healthy Subjects to Evaluate the Bioequivalence of 2 Oral Tablet Formulations of GW572016 Ditosylate Monohydrate Experience with single dose fast and fed studies in healthy volunteers from one of our member companies resulted in only mild adverse events and concluded that the products were found to be safe and well tolerated. Further safety data from these studies can be provided on request confidentially. Together, the literature data and the data available from one of our member companies documents the safety of single dose studies in healthy volunteers. As per the general EMA guideline on bioequivalence, single dose bioequivalence studies in healthy volunteers are most sensitive to detect differences between formulations. Only if dosing in healthy volunteers is not feasible due to tolerability reasons, multiple dose studies in patients are to be considered. As per the abovementioned data (from published literature and from of our member companies), the studies in healthy volunteers are feasible. **Proposed change:**	

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		Single dose bioequivalence studies in healthy volunteers are most sensitive to detect differences between formulations. However, multiple dose bioequivalence studies in patients with breast cancer, whose tumours overexpress HER2 (ErbB2), for whom the drug is indicated may be acceptable in lieu of the single dose studies in case of safety concerns.	
Draft 2 - table	4	**Comment:** As per the new draft guidance, bioequivalence needs to be shown both under (semi-)fasting and semi-fed (1 hour after food) conditions. These conditions are relevant for bioequivalence studies in patients. In case previous comment is accepted, then single dose bioequivalence studies in healthy volunteers are not only more sensitive, but would also better cover the range of meals by use of the extremes i.e. 1. conventional fasting study (at least 8 hours), 2. and a fed study which could follow one of the following two options: a. a conventional fed study (high-fat high-calorie meal given 30 minutes prior to administration of drug product and finished within 30 minutes) or b. a semi-fed study (in accordance with the SPC recommendations, a high-fat high-calorie meal	Previous comment not accepted, thus the recommendation to perform patient studies remains. Two studies are recommended, one study in the fasting state (or semi-fasting 1 hour before a meal) and one study in a semi-fed state, i.e. 1 hour after a meal.

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		given 1 hour prior to administration of drug product and finished within 30 minutes) These are considered more discriminative conditions which could be applied for healthy volunteers' single dose studies. **Proposed change:** Both fast and fed bioequivalence studies are required. The fed study should be either: • a conventional fed study (high-fat high-calorie meal given 30 minutes prior to administration of drug product and finished within 30 minutes) or • a semi-fed study (in accordance with the SPC recommendations, a high-fat high-calorie meal given 1 hour prior to administration of drug product and finished within 30 minutes). These are considered the most discriminative conditions. In case applicant chooses to perform multiple dose studies in patients, bioequivalence needs to be shown both under (semi-)fasting and semi-fed (1 hour after food) conditions.	
Draft 2 - table	4	**Comments:** Considering the details provided in the Draft 1 Overview of comments, in order to evaluate the possible hepatotoxic effect of the drug (Lapatinib 250 mg) on the study participants (healthy subject), one of our company	Not accepted. As a precautionary matter, considering the safety profile of lapatinib, bioequivalence studies in patients are recommended. It is acknowledged that several studies have been performed in healthy volunteers with the originator. However, issues with liver toxicity were discovered rather late in the clinical

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		members who has previously performed pilot studies with lapatinib in healthy subjects compiled and reviewed the following: 1. The data of liver function test which was performed at screening and at the end of the study. 2. Adverse events experienced by the subjects. <u>Conclusion:</u> The data suggest that none of the subjects who had participated in these two studies had evidence of hepatocellular injury (indicated by leakage of aminotransferase (AT) enzymes (SGOT & SGPT) from injured liver cells) nor hepatobiliary obstruction or intrahepatic cholestasis (indicated by elevation of Total Bilirubin). Also, none of the study subjects had AE's suggestive of hepatocellular injury, hepatobiliary obstruction or intrahepatic cholestasis nor any hepatic involvement. Additional data from public domain demonstrate that single and multiple doses of lapatinib were safe and well-tolerated in studies performed in healthy volunteers. In brief, in bioavailability studies included in the GSK Clinical Trial Register (available at www.gsk-studyregister.com under following study identifiers: EGF102587, EGF10008, EGF10012 and EGF10024), changes in laboratory results related to liver function (namely, increase in levels of alanine and aspartate aminotransferases) were observed only in one subject out of total 270 subjects enrolled in	development and were not fully known at the time these studies were performed. Although these effects are rare, they may occur suddenly and are difficult to control. Even though small studies can be done without signs of hepatoxicity, there is still a risk that such toxicity could occur, and for this reason studies in patients are recommended.

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		4 multi-period cross-over studies. In another placebo-controlled, double-blind study that combined single and multiple-doses of lapatinib, the study treatments were well tolerated and there were no serious adverse events (Bence et al. 2005, Invest New Drugs. 23(1): 39-49). During the multiple-dose part of the study (lapatinib administered once daily for 8 consecutive days), elevated liver function tests (AST, ALT, or bilirubin) were observed in 3 subjects from the lapatinib group (N=18) and 3 subjects from the placebo group (N=9). Elevations were resolved without the need for additional treatment. Overall, the analysis of safety data collected in previous studies does confirm feasibility of dosing of lapatinib to healthy volunteers. **Background information**; In general, the type of liver injury that leads to severe drug induced liver injury (DILI) is a predominantly hepatocellular injury. Hepatocellular injury is indicated by rises in aminotransferase (AT) activities in serum reflecting release of alanine or aspartate aminotransferase (ALT/SGPT or AST / SGOT) from injured liver cells. The ability to cause some hepatocellular injury, however, is not a reliable predictor of a drug's potential for severe DILI. Many drugs that cause transient rises in serum aminotransferase (AT) activity do not cause progressive or severe DILI, even if drug administration is continued. It is only those drugs that can cause hepatocellular injury	

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		extensive enough to reduce the liver's functional ability to clear bilirubin from the plasma or to synthesize prothrombin and other coagulation factors that cause severe DILI. Hence it is important to identify those drugs as early as possible. Detecting drug induced liver injury (DILI) in clinical trials (https://www.fda.gov/media/116737/download); In a clinical trial, DILI should be suspected if – with liver chemistry results being normal at baseline – aminotransferases (SGPT & SGOT) exceed 3 times the upper limit of normal (ULN) (which indicates hepatocellular injury). Elevations of ALT and/or AST less than 3 ULN are much less specific for DILI, **as in the member company's study subjects** and this can be also observed in placebo treated patients or healthy individuals. In particular, during phase I studies with healthy individuals or subjects being kept on a ward for days or weeks, aminotransferase elevations are often confounded by the effects of physical exercise or diets. With abnormalities being present at baseline already, doubling of baseline values may be considered a threshold warranting close observation, which is not the case in the member company's studies as their SOP does not allow us to include subjects with clinically abnormal liver function tests.	

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		Further, Hy's law is a sensitive and specific predictor of a drug's potential to cause severe hepatotoxicity. If observed, it indicates hepatocellular injury severe enough to impair hepatic function, which is anticipated to result in study subjects experiencing liver failure that is fatal or requires liver transplantation in at least 10% of cases. Hy's law consists of 3 components: 1. A statistically significant higher incidence of 3-fold or greater elevations above ULN of ALT or AST compared to (non-hepatotoxic) control or placebo. 2. Individuals showing ALT or AST >3 ULN, combined with elevation of serum TBL >2 ULN, without initial findings of cholestasis, indicated by elevated ALP. 3. Absence of any alternative cause likely to explain the combination of increased ALT or AST and TBL, such as viral hepatitis A, B, C, or E, pre-existing or acute liver disease, or another drug capable of causing the observed injury. In the member company's studies, at screening they have enrolled subjects with labs values in acceptable limits of biological reference interval and excluded subjects with viral hepatitis and pre-existing or acute liver disease. These subjects were dosed with lapatinib 250 mg (4 times overall) with wash out of 5 days. At the end of 4th period, the safety labs were performed and were also found to be within the	

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		biological reference interval. This possibly explains that the drug may not have significant effect on the liver function. *References;* https://easl.eu/wp-content/uploads/2019/04/EASL-CPG-Drug-induced-liver-injury-2019-04.pdf https://www.fda.gov/media/116737/download The feasibility to dose healthy volunteers was also further confirmed via one of our CRO members. Their principal investigator has suggested that in order to reinforce safety considerations, females of non-childbearing potential and males could be included. **Proposed change**: Single dose bioequivalence studies in healthy volunteers are most sensitive to detect differences between formulations. In order to mitigate safety risks, the study should include females of non-childbearing potential and males. However, multiple dose bioequivalence studies in patients with breast cancer, whose tumours overexpress HER2 (ErbB2), for whom the drug is indicated may also be acceptable.	
Draft 2 - table	4	**Comment:** In addition to these considerations, according to the SmPC "Patients who carry the HLA alleles DQA1*02:01 and DRB1*07:01 have increased risk of Tyverb-associated hepatotoxicity."	Not accepted. It is assumed that this recommendation refers to studies in healthy subjects, and as discussed in previous comment, studies in patients are recommended.

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		Therefore, as a risk mitigation strategy it would also be possible to include a test during screening to avoid inclusion of such subjects who are at increased risk. **Proposed change:** Consider the optional inclusion of: HLA allele DQA1*02:01 and DRB1*07:01 testing could be used during screening to avoid inclusion of subjects who carry these alleles who may be at increased risk as an additional precautionary measure.	