Authors' Reply to Yu et al.: ""Levothyrox® New and Old Formulations: Are They Switchable for Millions of Patients?"

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LETTER TO THE EDITOR

Authors' Reply to Yu et al.: "Levothyrox® New and Old Formulations: Are They Switchable for Millions of Patients?"

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We thank Yu and Maliepaard [1] for their comments on our article, in which they explain why we have not recommended recourse to an individual bioequivalence (IBE) trial, as proposed historically by the US Food and Drug Administration [2]. From their response, it might be construed that this was our intention, but this is not so, as we made clear in our first publication [3]. There, we stated "IBE has been both extensively discussed and challenged and then, finally, not adopted by regulatory authorities". We respectfully submit that we cannot be criticized for not having discussed the reason for not adopting IBE by regulatory authorities. To re-iterate, we explained in our first article that "It is beyond the scope of this paper to discuss in detail advantages and limitations of IBE". This, we further emphasized in our second article [4] when we suggested that the current Food and Drug Administration approach of assessing the bioequivalence of levothyroxine formulations [5–7], comparing not only the average levothyroxine area under the curve and maximal plasma concentration but also the within-subject variability (WSV) of the two formulations using a replicate design, is the best approach.

Our support for the Food and Drug Administration guideline on levothyroxine is based on the fact that 'what the patient needs to know and be certain of' is the guarantee of reproducibility of treatment. Essentially, this Food and Drug Administration approach is still average but extended average bioequivalence (ABE) and not IBE. Our view was and remains that the *conceptual framework* of IBE should be considered. The IBE concept is highly relevant in this instance because it places the patients and their expectations firmly at the heart of the trial, by considering their individual therapeutic window [8]. We cite the opinion of Munk on IBE trials, "there is a general agreement that the concept of IBE is an important and convincing concept which is in general superior to ABE" [9]. As meaningfully discussed by others [10], the ABE trial does not consider the issue of an individual therapeutic window. These authors reviewed the current 2010 European Medicines Agency guideline [11] when stating, "In fact, those parameters (i.e., area under the curve and maximum plasma concentration) seem to be more sensitive to differences in the formulation or the manufacturing process than clinical end-points and a more 'quality-like' approach has been adopted" (in this guideline). With others, therefore, we do not accept the opinion that, for a narrow therapeutic index drug like levothyroxine, patients are simply members of a statistical distribution, for which it is sufficient to guarantee that the geometric mean (or median) μT/μR ratio of the area under the curve and maximum plasma concentration is equal or close to 1. This opinion fails to fulfill the legitimate expectation of patients, namely that they are entitled to receive treatment with a reproducible formulation.

We do not need to address here the Yu and Maliepaard comment on the interchangeability of generics because the new formulation (NF) of Levothyrox® is not a generic. It is a reformulation of an existing product. Therefore, the issue is not one of interchangeability but of switchability. The two terms are not synonymous because the

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concept of interchangeability for generic drug products also includes drug prescribability [12]. These points were explained in our article when stating "Levothyrox® NF is not a new generic formulation offered as a possible alternative to Levothyrox® OF for a new patient. It is a new formulation designed to replace Levothyrox® OF and the number of patients for which this change was imposed in France between March and June 2017 is estimated to be 2,188,432. Hence, the key question that should have been addressed before the marketing of Levothyrox® NF is: Can a patient already treated with Levothyrox® OF be safely and effectively switched from this no longer available formulation to the new one? A study demonstrating ABE does not answer this question i.e. the demonstration of ABE between Levothyrox® OF and Levothyrox® NF does not ensure their switchability."

We now address two further comments of Yu and Maliepaaed. First, they wrote "With regards to the use of healthy volunteers instead of patients to assess bioequivalence (…) there is no reason to assume that, if two formulations are bioequivalence in healthy subjects, relative exposure of the two formulations in patients would be different. Second, regarding WSV of two formulations, i.e., the original formulation (OF) and the reformulation (NF), they comment that "there is no reason to assume that levothyroxine would be different from other drug". This they conclude because, after reviewing seven trials involving seven drugs (but not levothyroxine), such a difference was not noted [13]. By no standard can levothyroxine be classified as a conventional drug. Whilst the use of healthy volunteers rather than patients is generally acceptable in ABE studies, and indeed sound for most conventional drugs, we submit that further discussion is essential for levothyroxine. Levothyroxine is an endogenous compound. It is a hormone, which can be prescribed as a drug to patients exhibiting varying thyroidal status within a very large range. For the thyroidectomized patient, both the average and the range of internal exposure to T4 depend solely on the prescribed formulation, administered at a relatively high-dose level. The situation differs for those patients receiving treatment for sub-clinical hypothyroidism because they have an elevated thyroid-stimulating hormone level but a normal-range free T4 level. In these patients, the contribution of the low dose of administered levothyroxine to the overall T4 exposure will be minimal and its variability buffered by natural existing feedback mechanisms. We must consider as paramount the patient perspective on two formulations, undeniably bioequivalent in term of ABE but having different WSVs (e.g., 10 vs. 25% for the two formulations). Can the formulations be therapeutically equivalent for these two classes of patient, the thyroidectomized group and the hypothyroid group? It is clear to us that a formulation having a low WSV is highly desirable for patients having no thyroid, whereas a higher WSV would have a much less detrimental impact in the case of sub-clinical hypothyroidism.

These considerations are the basis of our comments expressed on the question of a patient-by-formulation interaction. Those contesting our views challenged the notion of IBE on the ground that such interactions are reported only infrequently. This is true, but what is also true is that physiological or physiopathological factors generating such interactions are very seldom present in the healthy population from which homogeneous volunteers enrolled in an ABE trial are selected. For levothyroxine, the first putative factor to generate a relevant formulation-by-subject interaction is the subjects' thyroid status and the possibility that this was null for Levothyrox® ABE. This was acknowledged by Gottwald-Hostalek et al. when they wrote "The main exclusion criterion was any medical condition or concomitant medication that may have significantly influenced the results" [14].

In conclusion, we respectfully remind Yu and Maliepaard of two key issues. First, that more than 30,000 patients reported adverse drug reactions within 14 months, following the replacement of the OF by the NF of Levothyrox®. Second, in a survey comparing 1,037,553 patients treated in 2016 with the OF vs. 1,037,553 subjects treated in 2017 with the NF, the conclusion was that approximately 20% of patients had ceased using the NF at the end of 2017 compared with 3% for the paired group treated with the OF in 2016 [15]. Attempts to explain what has happened in France as a mere media crisis *due to the greater emotional distress of patients taking thyroxine* are well short of a sound scientific base. At very best, it is a surprising conclusion from those charged with evaluating the licensing submission dossier from an ethical perspective.

Compliance with Ethical Standards

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Conflict of interest Didier Concordet, Peggy Gandia, Jean-Louis Montastruc, Alain Bousquet-Mélou, Peter Lees, Aude A. Ferran, and Pierre-Louis Toutain have no conflicts of interest that are directly relevant to the content of this reply.

References

1. Yu Y, Maliepaard M. Comment on: "Levothyrox® new and old formulations: are they switchable for millions of patients?". Clin Pharmacokinet. 2019. https://doi.org/10.1007/s40262-019-00850-5.
2. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for industry: statistical approaches to establishing bioequivalence. January 2001. https://www.fda.gov/media/70958/download. [Accessed 26 Nov 2019].
3. Concordet D, Gandia P, Montastruc J-L, Bousquet-Mélou A, Lees P, Ferran AA, et al. Authors' reply to Coste et al.: Levothyrox® new and old formulations: are they switchable for millions of patients? Clin Pharmacokinet. 2019;58(7):967–8. https://doi.org/10.1007/s40262-019-00747-3.
4. Concordet D, Gandia P, Montastruc J-L, Bousquet-Mélou A, Lees P, Ferran AA, et al. Why were more than 200 subjects required to demonstrate the bioequivalence of a new formulation of levothyroxine with an old one? Clin Pharmacokinet. 2019. https://doi.org/10.1007/s40262-019-00812-x.
5. Anonymous. Draft guidance on levothyroxine sodium. Food and Drug Administration; 2018: :p. 2. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM428208.pdf. Accessed 4 Oct 2019.
6. Yu L, Jiang W, Zhang X, Lionberger R, Makhlouf F, Schuirmann D, et al. Novel bioequivalence approach for narrow therapeutic index drugs. Clin Pharmacol Ther. 2015;97(3):286–91.
7. Jayachandran P, Okochi H, Frassetto LA, Park W, Fang L, Zhao L, et al. Evaluating within-subject variability for narrow therapeutic index drugs. Clin Pharmacol Ther. 2019;105(2):411–6.
8. Chen ML, Patnaik R, Hauck WW, Schuirmann DJ, Hyslop T, Williams R. An individual bioequivalence criterion: regulatory considerations. Stat Med. 2000;19(20):2821–42.
9. Munk A. Connections between average and individual bioequivalence. Stat Med. 2000;19(20):2843–54.
10. Morais JAG, Lobato Mdo R. The new European Medicines Agency guideline on the investigation of bioequivalence. Basic Clin Pharmacol Toxicol. 2010;106(3):221–5.
11. Anonymous. "Guideline on the investigation of bioequivalence" (EMA, London, 2010). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf. Accessed 26 Nov 2019.
12. Chen M, Chow S-C. Assessing bioequivalence and drug interchangeability. J Biopharm Stat. 2017;27(2):272–81.
13. Yu Y, Teerenstra S, Neef C, Burger D, Maliepaard M. A comparison of the intrasubject variation in drug exposure between generic and brand-name drugs: a retrospective analysis of replicate design trials. Br J Clin Pharmacol. 2016;81(4):667–78.
14. Gottwald-Hostalek U, Uhl W, Wolna P, Kahaly GJ. New levothyroxine formulation meeting 95-105% specification over the whole shelf-life: results from two pharmacokinetic trials. Curr Med Res Opin. 2017;33(2):169–74.
15. Anonymous. Levothyrox et médicaments à base de lévothyroxine: rapport final de l'étude de pharmaco-épidémiologie à partir des données du Système National des Données de Santé (SNDS): point d'Information. ANSM: Agence nationale de sécurité du médicament et des produits de santé. 2019. https://www.ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Levothyrox-et-medicaments-a-base-de-levothyroxine-Rapport-final-de-l-etude-de-pharmaco-epidemiologie-a-partir-des-donnees-du-Systeme-National-des-Donnees-de-Sante-SNDS-Point-d-Information. Accessed 26 Nov 2019.