Authors' Reply to Nicolas:"New and Old Formulations: Are they Switchable for Millions of Patients?"

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LETTER TO THE EDITOR

Authors' Reply to Nicolas: "Levothyrox® New and Old Formulations: Are they Switchable for Millions of Patients?"

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We thank Dr. Nicolas for his detailed comments on our article [1]. These we refute from both general and particular perspectives. This response to Dr. Nicholas explains why we do not accept the premises of his reasoning and the deductions he derives, as they lead, in consequence and ineluctably to his wrong conclusions. We reiterate the point made firmly in our article that: when *all patients* in a population (almost 3 million persons in France in 2017) had been treated with the same licensed Levothyrox® formulation; *and when this was administratively and irreversibly switched* to a new Levothyrox® formulation, the conclusion must be that this is a switchability issue. Moreover, as we also made previously clear, switchability cannot be established by a classical average bioequivalence (ABE) trial, especially not for a drug like levothyroxine, which has a narrow therapeutic index (NTI).

In addition, we reiterate that our article does not present a revised and biased statistical analysis of the bioequivalence (BE) study conducted with old and new formulations of Levothyrox®, using the approach of individual bioequivalence (IBE) instead of ABE. To be clear, we did not undertake any such re-analysis; to repeat, we did not develop an IBE model, as suggested by Dr. Nicolas. Had we done so, our approach would indeed be open to fair criticism. In fact, our approach was rather to count the number of subjects for which the individual exposure ratio (IER) [area under the curve new product/area under the curve old product], calculated using both baseline-adjusted and unadjusted T4 concentrations, was outside the *a priori* BE range of 0.90–1.11 for the geometric means [2].

In an old but still valuable paper, which presents the results from BE studies, it is recommended that the IER should be reported as a *descriptive metric* [3]. Such presentation, without any modeling or other testing, reveals the possibility of a *red warning signal* indicating possible non-individual BE, when the percentage of IER exceeds 10% [4], i.e., a much lower percentage than the near 70% IER that we calculated for the adjusted IER of Levothyrox®.

Like Dr. Nicolas, we are acutely aware of the problems and historical vicissitudes relating to the statistical analyses of an IBE study, as reviewed by Endrenyi et al. [5]. Moreover, this point was clearly acknowledged, when we stated "*Individual bioequivalence has been both extensively discussed and challenged and then, finally, not adopted by regulatory authorities*". However, it cannot be asserted that the concept of IBE is either wrong or misplaced, simply because the analysis of IBE studies has, historically, been vigorously debated. Furthermore, it is not correct to claim any inconsistency of IBE because its conclusions may differ from those of an ABE, as previously emphasized by Endrenyi and Midha [6]. The two alternative conclusions, BE or not BE, does not imply any discrepancy, when it is understood that, by their very definitions, ABE and IBE are designed to answer differing questions.

Levothyroxine is classified as a NTI drug by many authorities, including the US Food and Drug Administration (FDA) [7], the World Health Organization [8], and the French regulatory agency [9]. Therefore, it is essential that investigation of any new formulation of levothyroxine requires, as for all

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NTI drugs, an ad hoc BE study to ensure its interchangeability with a reference product. The pivotal information, which is currently absent from the European Union Levothyrox® dossier, is the numerical value of the within-subject variability (WSV). The WSV is of major importance from the patient perspective, especially when treated with a NTI drug because it reflects the day-to-day variability of exposure to the formulation. According to the FDA, one of the characteristics of a NTI drug is that it should possess a low-to-moderate (i.e., not exceeding 30%) WSV [10]. For nine BE trials on levothyroxine, reviewed between 1996 and 2008 by the FDA, an average value of the WSV of 9% (range 3.8–15.5%) has been reported [11]. Estimation of the WSV requires a BE study designed using a fully replicated crossover approach [10, 12]; this approach should comprise a minimal consideration for the Levothyrox® dossier.

Dr. Nicolas proposes, for the Levothyrox® dossier, with 204 subjects (a very large number when one considers that most trials are conducted with 24–36 subjects [13]) that the European Union approach consisting of tightening the *a priori* acceptance interval of an ABE suffices when an ABE analysis is conducted. We beg to differ. This is because it is implicit that a *precautionary intention of the European guideline*, when recommending shortening the *a priori* acceptance interval from 0.80–1.25 to 0.90–1.11, is mitigated or nullified when a large number of subjects is enrolled in this class of BE trial. This is because the width of the computed 90% confidence interval, which should be wholly included in the a priori acceptance range, is directly proportional to the intra-subject coefficient of variation but inversely proportional to the square root of the number of subjects in the trial.

A final point of contention with Dr. Nicolas is our citation of the literature, indicating clinical situations, in which establishing equivalence for thyroxine in healthy volunteers may not translate unequivocally to equivalence in all patients. He alleges that this is "*a redundant but unfounded criticism that has paved the long story of bioequivalence with levothyroxine*". The fact of the matter is, for an endocrine function that is finely tuned by the thyroid-stimulating hormone level, it is not prudent to *a priori* exclude the possibility of a patient-by-formulation interaction. For example, in a peer-reviewed publication entitled "*Generic and branded levothyroxine preparations are not bioequivalent in children with congenital hypothyroidism*" [14], non-equivalence was reported in a sub-group of children, with congenital hypothyroidism, between a brand T4 formulation and a generic product that were considered by the FDA to be interchangeable and it provided evidence that the two formulations were not clinically interchangeable [15].

Finally, we propose that prescriptibility and interchangeability are two distinct issues and that, for a NTI drug such as levothyroxine, the WSV variability must be determined, and this cannot be achieved with a classical ABE approach.

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.

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