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## Authors' Reply to Coste et al.: "Levothyrox<sup>®</sup> New and Old Formulations: Are they Switchable for Millions of Patients?"

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We are pleased to respond to the letter of Coste et al. [1] as follows. Nowhere in our article is any claim made to analyse the problem of symptoms reported with the new formulation of Levothyrox<sup>®</sup>. Our sole aim was to challenge scientifically the principle of using an average bioequivalence (ABE) approach to document a switchability issue. This is a particular concern, given that substitution of a new formulation was *imposed on* several million patients.

*First*, we address the question of correcting (or not) the raw data for basal values of thyroxine (T4). Our article is neither misplaced nor misleading in this regard, and, for the avoidance of doubt, we direct readers to the 2010 European Union (EU) guideline [2]. It is a requirement of this guideline that a baseline correction should be applied to the variable area under the curve for products containing endogenous compounds as active constituents. The guideline states explicitly "*If the substance being studied is endogenous, the calculation of pharmacokinetic parameters should be performed using baseline correction so that the calculated pharmacokinetic parameters refer to the additional concentrations provided by the treatment*". Moreover, the

guideline further qualifies this requirement in stating: "*The exact method for baseline correction should be pre-specified and justified in the study protocol. In general, the standard subtractive baseline correction method, meaning either subtraction of the mean of individual endogenous pre-dose concentrations or subtraction of the individual endogenous predose AUC, is preferred*". We have followed the guideline to the letter and note that the US Food and Drug Administration guideline [3] gives a similar direction.

Furthermore, we draw attention to the fact that the French Regulatory Authorities' evaluation dossier for Levothyrox<sup>®</sup> explicitly endorsed this baseline correction [4]. Nevertheless, it is the case that the actual methods used to correct baseline concentrations of endogenous compounds have been debated in the literature. In a review on the methodology adopted to assess the bioequivalence of levothyroxine [5], it was concluded that the so-called correction Method 1, comprising subtraction from each T4 concentration of the mean of control concentrations, is the most appropriate and was, indeed, cited in the US Food and Drug Administration guideline [3]. This method we followed precisely.

*Second*, in their letter to the Editor, Coste et al. stated "*Furthermore, the authors use results obtained from adjusted IER, rather than from unadjusted IER, to affirm the "fact that more than 50% of individuals were outside the a priori bioequivalence range (0.90–1.11)"*". In response, we confirm the soundness of this approach, as the EU guideline indicates that it is only "*In rare cases where substantial increases over baseline endogenous levels are seen, baseline correction may not be needed*". Even when considering only the unadjusted baseline area under the curve, the number of subjects outside the *a priori* acceptance interval of 0.90–1.11 is still sufficiently high (17%) to constitute a *red warning signal* of possible non-individual bioequivalence. This might be suspected when the percentage exceeds 10% [6]. In addition, it has been alleged that the application of criteria for determination of bioequivalence, without

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accounting for endogenous T4 levels, resulted in a failure to identify products that differed by as much as 25–33% [7].

We question this technical polemical argument, which fails to address the main messages conveyed by our article. The article did not challenge the data analysis, as conducted by the company; in fact, we endorsed this when stating, “*it is acknowledged that the trial and analyses were conducted professionally according to current EU guidelines*” [8].

To be clear, what we are challenging is the validity of an ABE investigation to impose, administratively, substitution of an older by a newly formulated product for almost 3 million patients. We make this challenge because an ABE study is not intended for and therefore should not be used to guarantee the switchability within patients of two formulations.

In summary, what must be questioned is that a new formulation, possibly highly variable in its pharmacokinetic profile (implicitly indicated by the 216 subjects planned and used to demonstrate the ABE [9]), should be marketed on the basis of an ABE, for a drug like levothyroxine, with a narrow therapeutic index [10–12], without any further evaluation or precautions.

In a future publication, we shall challenge this use of an atypically large number of subjects (204 for the present ABE trial). Further, we will propose that this effectively nullifies the necessarily precautionary intention of the EU guideline, when recommending shortening the a priori acceptance interval from 0.80–1.25 to 0.90–1.11.

Finally, we accept that there is neither conspiracy nor malice on either side of this debate, but rather a difference of judgement on data derived and conclusions drawn. It is scientific argument that must fuel this crucial debate, with its welfare considerations, and not media opinions, when these are not based on sound science.

## 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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