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LETTER TO THE EDITOR

Comment on: "Why Were More Than 200 Subjects Required to Demonstrate the Bioequivalence of a New Formulation of Levothyroxine with an Old One?"

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In their article, Concordet et al. [1] deliver a second set of criticisms against the study by Gottwald-Hostalek et al. [2]. In this letter, I would like to challenge this additional argumentation that has already reboosted sensational headlines about the French 'Levothyrox® scandal'.

In my previous response [3], I pointed out that it was a wrong reasoning to apply the tighter acceptance range (0.90–1.11) to individuals because this criterion has been only validated for an average bioequivalence (ABE) purpose. Still promoting individual bioequivalence (IBE), Concordet et al. now presume that a planned ABE study with 204 subjects was intentionally masking or anticipating greater within-subject variability (WSV) with Levothyrox® NF. As proof, they put forward a mean WSV of 9.3% for levothyroxine area under the plasma concentration-time curve (AUC) [US FDA data[1]], compared with 23.7% reported for Levothyrox® NF. As shown in Table 1, from representative publicly available studies, WSVs and widths of 90% confidence intervals (CIs) may really differ according to the mode of calculation. On baseline-adjusted data, mean WSV is twofold greater. The reason for this is well known. Even after a high oral dose of levothyroxine 0.600 mg, endogenous T4 secretion turns preponderant within 48 h postdosing. Without adjustment, a difference between two formulations can be lost and the resulting lower variability is mainly that of endogenous T4. Therefore, I assume that the mean WSV of 9.3% [4] was based on 'non-adjusted' data, as previously recommended by the US FDA. Today, all regulatory authorities require baseline-adjusted data. Interestingly, Gottwald-Hostalek et al. [2] also reported a second study comparing Levothyroxine® NF versus itself at three different strengths administered to 37 subjects, in a quasi-replicate crossover design based on the standard acceptance range. WSV of Levothyrox® NF was moderate on baseline-adjusted data (15.5% on maximum plasma concentration [C_{max}], 17.1% on AUC; see Table 1). By missing all these facts, Concordet et al. leave wide open the false idea that Levothyrox® NF is a bad formulation with too large a WSV for a narrow therapeutic index drug. They argue that a standard ABE study with 24–36 subjects would have failed, which is obvious due to the tighter acceptance range of bioequivalence (regulatory requirement) and the true level of WSV for baseline-adjusted levothyroxine. Therefore, claiming that "an atypically very large number of subjects" forced the decision of bioequivalence is unfair, casting detrimental doubt in patients and in public opinion.

Levothyrox® NF not only has moderate WSV, but its WSV is also possibly lower than that of Levothyrox® OF. When an ABE study ends up with point estimates close to 100%, with 90% CIs easily within the 0.90–1.11 range, a high sample size effectively decreases type II error (producer risk), but type I error (consumer risk), a critical point checked during regulatory assessment, remains strictly controlled. Concordet et al. do not consider this reasoning but call for a 'scientific' revision of the European policy on bioequivalence standards.

Another disagreement is the caricature that healthcare professionals and regulatory authorities would consider switchability as a 'byproduct' of an ABE trial. Switchability is linked to WSV and subject-by-formulation interaction (SBFI), an expression meaning that some patients might react differently when switched from one formulation to

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[1] The reference [13] quoted by Concordet et al. does not contain such data.

Table 1 Within-subject variability on maximum plasma concentration and area under the plasma concentration–time curve based on non-adjusted or baseline-adjusted levothyroxine (0.600 mg single oral dose in healthy subjects)

Studies	Point estimate (%)	Width 90% CI	*N*	WSV (%)	References
Calculations based on non-adjusted levothyroxine					
Di Girolamo et al. [8] Test: tablet Ref: Synthroid® tablet	C_{max}: 95.06 AUC_{48}: 96.10	6.37 4.18	24	8.07[a] 5.23[a]	[8]
CBGMEB, NL/H/2567/001-004/DC (2014) Test: tablet Ref: Euthyrox® tablet	C_{max}: 100.xx AUC_{72}: 99.xx	11.xx 10.xx	36	13.5 11.6	[9]
Australian TGA, PM-2012-04477-1-5 (2014) Test: tablet (Eltroxin) Ref: Oroxine® (Eutroxsig®) tablet	C_{max}: 86.21 AUC_t: 89.09	8.52 8.94	31	19.26[a] 19.56[a]	[10]
Gottwald-Hostalek et al. [2] Levothyrox® NF vs. itself (12 × 0.050 vs. 6 × 0.100 vs. 3 × 0.200 mg)	C_{max}: 99.9–101.8 AUC_{72}: 100.1–101.7	6.7 to 6.9 5.1	37	7.3 5.4	[2]
Average WSV on C_{max}: 12.03% Average WSV on AUC: 10.45%					
Calculations based on baseline-adjusted levothyroxine					
Di Girolamo et al. [8] Test: tablet Ref: Synthroid® tablet	C_{max}: 93.13 AUC_{48}: 92.39	17.27 15.00	24	22.55[a] 19.69[a]	[8]
BfArM DE/H/2580/01-12/DC (2011) Test: soft capsule Ref: Euthyrox® tablet	C_{max}: 114.80 AUC_{72}: 109.06	15.40 15.17	32	21.6[a] 20.8[a]	[11]
CBGMEB, NL/H/2700/001-011/DC (2015) Test: tablet Ref: Euthyrox® tablet	C_{max}: 87.90 AUC_{48}: 90.25	6.92 5.91	71	14.25[a] 16.27[a]	[12]
CBGMEB, NL/H/2700/001-011/DC (2015) Test: tablet Ref: Eltroxin® tablet	C_{max}: 104.52 AUC_{48}: 107.24	12.58 14.71	75	26.53[a] 30.39[a]	[12]
MHRA PL00289/1971-73 (2016) Test: tablet Ref: Eltroxin® tablet	C_{max}: 103.05 AUC_{72}: 106.91	16.50 12.86	NA	NA	[13]
Gottwald-Hostalek et al. [14] Test: Levothyrox® NF Ref: Levothyrox® OF	C_{max}: 101.70 AUC_{72}: 99.30	5.80 7.60	204	17.70 23.70	[2]
Gottwald-Hostalek [2] Levothyrox® NF vs. itself (12 × 0.050 vs. 6 × 0.100 vs. 3 × 0.200 mg)	C_{max}: 99.4–103.8 AUC_{72}: 99.30–104.8	14.2–14.8 15.7–16.6	37	15.50 17.10	[2]
Tanguay et al. [14] Test: oral solution Ref: Tirosint® soft capsule	C_{max}: 98.47 AUC_{48}: 95.33	7.14 6.85	36	10.81[a] 10.72[a]	[14]
Average WSV on C_{max}: 18.42% Average WSV on AUC: 19.81%					

AUC area under the plasma concentration-time curve, AUC_{48} AUC from time zero to 48 h, AUC_{72} AUC from time zero to 72 h, AUC_t AUC during a dosing interval, C_{max} maximum plasma concentration, *CI* confidence interval, *NA* not available, *Ref* reference compound, *WSV* within-subject variability

[a]Recalculated by Nicolas

another. It would be out of scope to review two decades of dedicated scientific literature. However, when two products have similar WSV without SBFI, Concordet et al. should know that the connection between ABE and IBE is mathematically demonstrated [5, 6]. While theoretically conceivable, the clinical reality of SBFI with generic drugs has been regularly questioned. In a recent analysis of nine replicate design trials between generic and brand name products from six drug classes, the variance related to SBFI was considered negligible [7]. In fasting healthy subjects, the absorption phase of an oral immediate-release formulation of levothyroxine is easily predictable. Nevertheless, pretending that subjects enrolled in an ABE trial can be regarded as 'running chromatograph columns' is a strange conception of human

physiology. What about same subjects participating in an IBE trial?

To conclude, Levothyrox® NF shows moderate WSV with no proven SFBI. Therefore, the great obstinacy of Concordet et al. to disqualify this product by all means remains puzzling.

Compliance with Ethical Standards

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Conflict of interest Patrick Nicolas declares no potential conflicts of interest that might be relevant to the contents of this letter.

References

1. Concordet D, Gandia P, Montastruc J-L, Bousquet-Melou A, Lees P, Ferran A, Toutain P-L. Why were more than 200 subjects required to demonstrate the bioequivalence of a new formulation of Levothyroxine with an old one? Clin Pharmacokinet. Epub 21 Aug 2019. https://doi.org/10.1007/s40262-019-00812-x.
2. 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;33:169–74.
3. Nicolas P. Comment on: "Levothyrox® new and old formulations: are they switchable for millions of patients? Clin Pharmacokinet. 2019;58:959.
4. Yu LX. Quality and bioequivalence standards for narrow therapeutic index drugs. GPhA 2011 Fall Technical Workshop. Available at: https://www.fda.gov/media/82940/download. Accessed 22 Sep 2019.
5. Munk A. Connections between average and individual bioequivalence. Stat Med. 2000;19:2843–54.
6. Chow S-C., Endrenyi L, Chi E, Yang L-L., Tothfalusi L. Statistical issues in bioavailability/bioequivalence studies. J Bioequiv Availab. 2011;S1. https://doi.org/10.4172/jbb.s1-007.
7. 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. 2015;81(4):667–78.
8. Di Girolamo G, Keller GA, de los Santos AR, Schere D, Gonzalez CD. Bioequivalence of two levothyroxine tablet formulations without and with mathematical adjustment for basal thyroxine levels in healthy Argentinian volunteers: a single-dose, randomized, open-label, crossover study. Clin Ther. 2008;30(11):2015–2023.
9. Levothyroxine (as sodium). EU-procedure number: NL/H/2567/001-004/DC, 2014. Available at: https://www.geneesmiddeleninformatiebank.nl/Pars/h111900.pdf. Accessed 22 Sep 2019.
10. Australian public assessment report for thyroxine sodium, 2014. Available at: https://www.tga.gov.au/sites/default/files/auspar-thyroxine-sodium-140612.pdf. Accessed 22 Sep 2019.
11. Levothyroxine sodium soft capsules. Procedure number DE/H/2580/01-12/DC, 2011. Available at: http://mri.cts-mrp.eu/download/DE_H_2580_011_PAR.pdf. Accessed 22 Sep 2019.
12. Levothyroxine sodium. Procedure NL/H/2700/001-011/DC, 2015. Available at: https://db.cbg-meb.nl/Pars/h112415.pdf. Accessed 22 Sep 2019.
13. Levothyroxine sodium. UK Licence no. PL00289/1971-73, 2016. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con738143.pdf. Accessed 22 Sep 2019.
14. Tanguay M, Girard J, Scarci C, Mautone G, Larouche R. Pharmacokinetic and comparative bioavailability of a levothyroxine sodium oral solution and soft capsule. Clin Pharmacol Drug Dev. 2019;8(4):521–8.