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Response to commentary: Head-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomised phase III BALANCE study – determination of immunogenicity

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We appreciate the commentary by Lenders and Brand[1] that addressed the determination of immunogenicity of pegunigalsidase alfa in our recent publication in the journal.[2] Determination of the immunogenicity of pegunigalsidase alfa is important, and the possible interference of residual drug with antidrug antibody (ADA) detection has been previously addressed[3 4] and also acknowledged in our manuscript.[2] It should be noted that the primary outcomes analysis of the BALANCE study focused on the non-inferiority assessment of pegunigalsidase alfa compared with agalsidase beta with respect to the annualised change in the estimated glomerular filtration rate in both treatment arms and not on the ADA assays.

We wish to correct an apparent misinterpretation of a statement in the online supplemental materials concerning the impact of sample collection on assay drug tolerance level. Lenders and Brand[1] state:

> In case of low or medium antibody titers, this might result in false negative results. Since this effect is likely to be stronger the closer the time of blood collection is to the last infusion, it would be most useful to measure antibody titers immediately before the next infusion. This general methodological problem might explain why in some patients reduced titers or even no free antibodies/no ADA-mediated inhibition was detected in between or at the end of the study (at 24 months).

In all pegunigalsidase alfa trials, samples for ADA titres were done on the day of and immediately preceding the next infusion of study drug and 14 days following the previous infusion. This approach was specifically implemented in order to reduce the risk of drug interference. Yet, to be cautious, since some amount of pegunigalsidase alfa may be present in the blood at the time of ADA sampling given its half-life, we cannot completely rule out the possibility that part of the drug remains bound to the ADA and therefore interferes with low titre ADA detection. The ADA assays have shown good correlation with pharmacokinetic findings,[5 6] and the plasma half-life of pegunigalsidase alfa is reduced in patients with ADAs and this effect is directly related to the ADA titre at the time of sampling.[6]

Nevertheless, we fully ascribe to the conclusion of Lenders and Brand that[1] '… the results presented concerning the immunogenicity of pegunigalsidase-alfa should be interpreted with caution'. As we state in the penultimate paragraph of our paper[2]:

> BALANCE is the first clinical trial in Fabry disease to be conducted with a double-blind, active-control design. Pegunigalsidase alfa was comparable to agalsidase beta based on the annualised estimated glomerular filtration rate (eGFR) slope, an accepted surrogate for progression to end-stage kidney disease. Results demonstrated the potential for improved tolerability with less infusion-related reactions in some patients. *Further detailed analysis of pegunigalsidase alfa immunogenicity is warranted.*

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REFERENCES

1 Lenders M, Brand E. Comment to: head-to-head trial of Pegunigalsidase Alfa versus Agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year

randomised phase III BALANCE study—determination of Immunogenicity. *J Med Genet* 2024;61:531–3.
2 Wallace EL, Goker-Alpan O, Wilcox WR, *et al*. Head-to-head trial of Pegunigalsidase Alfa versus Agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomised phase III BALANCE study. *J Med Genet* 2024;61:520–30.
3 Lenders M, Pollmann S, Terlinden M, *et al*. Pre-existing anti-drug antibodies in Fabry disease show less affinity for pegunigalsidase alfa. *Mol Ther Methods Clin Dev* 2022;26:323–30.
4 van der Veen SJ, Langeveld M. Antibodies against recombinant enzyme in the treatment of Fabry disease: Now you see them, now you don't. *Mol Ther Methods Clin Dev* 2022;27:324–6.
5 Kizhner T, Azulay Y, Hainrichson M, *et al*. Characterization of a chemically modified plant cell culture expressed human α-Galactosidase-A enzyme for treatment of Fabry disease. *Mol Genet Metab* 2015;114:259–67.
6 Schiffmann R, Goker-Alpan O, Holida M, *et al*. Pegunigalsidase alfa, a novel PEGylated enzyme replacement therapy for Fabry disease, provides sustained plasma concentrations and favorable pharmacodynamics: a 1-year phase 1/2 clinical trial. *J Inherit Metab Dis* 2019;42:534–44.