LETTER TO THE EDITOR

Author’s Reply to Petersen: “Differences in In Vitro Properties of Pancreatin Preparations for Pancreatic Exocrine Insufficiency as Marketed in Russia and CIS”

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Referring to the Letter to the Editor by Prof. Dr. Karl-Uwe Petersen [1] regarding our article entitled Differences in In Vitro Properties of Pancreatin Preparations for Pancreatic Exocrine Insufficiency as Marketed in Russia and CIS [2], we would like to provide further information and feedback.

Our investigation has indeed focused on Feret max X50 as the selected representative parameter for particle size measurements. As explained in the publication, this was used as a representative parameter for the overall particle size diameter (PSD), for which the cumulative distribution Q3 (volume-based) assumes a value of 50%, where X50 represents the particle size at which 50% of particles in the material are smaller than this. Within the study, X10 and X90 have also been determined (data on file). For the X90 max assessments, Kreon has the lowest PSD (approximately 2000 µm) compared with all other pancreatin preparations (approximately 3000 µm). Upon evaluation of the X10 results, the preparations meeting a particle size smaller than 2000 µm are Kreon 25000, Kreon 40000, and Micrazim 25000 and 40000. All other preparations, including Ermytal (both strengths), Pangrol, and Panzytrat, still do not meet a particle size smaller than 2000 µm. Even when assessing the Feret min X50 data, only Kreon and Micrazim preparations are below 1500 µm, with averages of 1121 µm for Kreon and 1389 µm for Micrazim. The authors therefore believe that the choice of X50 is justified and supportive of the United European Gastroenterology Diagnosis and Treatment of Chronic Pancreatitis (UEG/HaPanEU) guideline consensus statement [3] and previously published comparative studies assessing the in vitro properties of different pancreatin preparations.

Prof. Dr. Karl-Uwe Petersen mentions that the conclusion of the abovementioned HaPanEU guideline [3] has been challenged, particularly in his systematic review from March 2021 [4], which succeeds our publication; however, the authors would like to point out that the systematic review is based on publications currently in the public domain and is not reflective of the full dataset for our particular study and the pancreatin preparations available in Russia/Commonwealth of Independent States (CIS). Additionally, contrary to what is being postulated and as mentioned in the publication by Prof. Dr. Karl-Uwe Petersen; the pancreatin preparations assessed, including Kreon, do not have a round shape but rather a more cylindrical shape, where the Feret min diameter represents the diameter of the cylinder and the Feret max represents the maximum size of the particle in any dimension, thereby being indicative of the probability of the particle passing the pylorus together with the chyme.

We also note that Prof. Dr. Karl-Uwe Petersen only addresses the PSD and the max Feret X value in his Letter to the Editor [4], and does not comment on the other differences between the specific pancreatin preparations identified in our in vitro investigation, particularly the differences observed regarding lipase activity (with Micrazim 40000 being a significant outlier at 79% of the declared lipase content) and (associated) dissolution [2] - variables likely having an even greater impact on digestive potency and clinical efficacy.

We therefore re-emphasize the conclusion drawn in our publication - aligned with the HaPanEU guidelines and previous investigations - that pancreatin preparations with a diameter of < 2 mm should be regarded as optimal for the treatment of pancreatic exocrine insufficiency (PEI), combined with clinical efficacy data generated with said

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preparations as well as enzyme activity and optimal dissolution characteristics.

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**Declarations**

**Conflicts of interest**  Igor V. Maev, Yury A. Kucheryavyy, and Natalya B. Gubergrits have no conflicts of interest that are directly relevant to the content of the original article or the Reply to the Letter to the Editor. Dr. J. Enrique Domínguez-Muñoz has received research grants from Abbott Pharmaceuticals and Mylan; payment for lectures from Abbott and Mylan; and paid consultancy from Mylan. Ingo Bonnacker, Ekaterina A. Shelest, and Gwendolyn P. Janssen-van Solingen are employed by Abbott Pharmaceuticals.

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