Authors reply to comments of Standing *et al.* to "Effect of Age-Related Factors on the Pharmacokinetics of Lamotrigine and Potential Implications for Maintenance Dose Optimisation in Future Clinical Trials"

Developmental trajectories and clearance: when age also matters.

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In their comments to our recent paper Standing *et al.* raise questions about the plausibility of the (de)maturation function used to describe differences in the clearance of lamotrigine, where patients younger than 2 years show, on average, a higher clearance than adults after correction for body weight. The authors discuss three possible scenarios which could lead to model misspecification. Whilst their arguments highlight important points to consider during model development and evaluation, we contest these points on a case by case basis and provide additional evidence for the increase in clearance and proposed (de)maturation function.

1. The inclusion of elderly subjects does not lead to bias: Whereas we acknowledge that the step function used to describe changes in CL/F in patients > 65 years of age is arbitrary (i.e., the cut-off age was not estimated), the available pharmacokinetic data suggest a clear change relative to the values observed in the younger adult population. It is not uncommon to model this decline as a step function that centres around 65 years [1–3], although a continuous inflection point model has been used before to describe the same phenomenon [4]. Unfortunately, the development of a more elaborate model was not possible with the available data. Nevertheless, the proposed parameterisation should not affect CL/F estimates in adults or children, as a larger portion of our data concerns adults < 65 years (N=208, partially dense sampled data), compared to elderly (N=116, only sparse data). If the use of a step function represented a potential misspecification, we would have expected convergence or boundary issues during the minimization steps or estimates with high imprecision from the covariance step or bootstrap analysis. In fact, the inclusion of the step function was evaluated before extending our modelling exercise to children, and resulted in a statistically significant drop in objective function, with reasonable precision in parameters. CL/F estimates for the adult population based on adult data only were similar to the final model with all data (2.35 vs. 2.23 L/h for a typical 70 kg adult). Furthermore, these results reflect previous findings by Punyawudho *et al.,* who reported a typical value of 1.12 L/h in patients aged 59-92 years [5].

2. Possibility of changes in bioavailability in young children: However unlikely, we accept that changes in oral bioavailability (F) could influence the estimation of the maturation function for CL/F. Given that lamotrigine has negligible first-pass metabolism (absolute bioavailability is 98%), even if one hypothesises the possibility that differences exist in first-pass effect between adults and young children, such differences would have to be very large to result in significant bias. A definitive answer to this point would require further studies in

which pharmacokinetic data are collected from adult and young paediatric patients following intravenous administration. Currently, no suitable formulation is available for this type of investigation.

3. No impact of imbalance in comedication use: Admittedly, the distribution of co-medications is different in subpopulation F (N= 144, age 1-24 months) when compared to the adult population (Table 1S, supplemental material). Few patients received co-medications known to have any impact on the clearance of lamotrigine, i.e. carbamazepine (N=3), phenytoin (N=3) or valproic acid (N=3). Most notably, 24 patients received phenobarbital, which was shown to increase lamotrigine clearance in previous investigations [3,6,7]. Despite these findings, the effect of phenobarbital on CL/F was not statistically significant. Clearance estimates varied by approximately 17%, but this effect resulted in a decrease in the objective function of only 1.46 (p>0.05). In addition, clearance estimates were not significantly affected by phenobarbital even if the maturation function is omitted (3.4 vs. 3.29 L/h, respectively without and with the effect of phenobarbital as covariate).

Further evidence of higher apparent clearance in young children: Our study is not the first to show that lamotrigine clearance may be higher in toddlers and young children, as compared to older children or adults [8,9]. Mikati *et al.* found that *"apparent clearance increased during the first year of life, with a break point at 2 months of age"* [10]. Their estimate for clearance in infants and toddlers was 0.217 L/h. Similarly, He *et al.* has evaluated the pharmacokinetics of lamotrigine in Chinese children and reported even higher values for clearance (i.e. 0.53 L/h for a 1 year old, 10 kg child) [6]. Other publications describe lower peak concentrations (Cmax) and systemic exposure (AUC) in young children [11]. Furthermore, basic research on drug metabolism shows evidence of temporal specific enzyme expression patterns or developmental trajectories, which result in age-dependent changes in the activity of metabolizing enzymes [12,13]. For instance, Miyagi *et al.* have reported a decrease in β-glucuronidase activity with age, whereas UGT activity has been shown to increase with age [14]. Lastly, we also recognise the potential for confounding due other covariate factors, such as genetic polymorphism. It is commonly accepted that lamotrigine is primarily glucuronidated by UGT-1A4. However, UGT2B7 and UGT1A3 have also been suggested to play a (minor) role in the biotransformation of lamotrigine [15-16]. In fact, polymorphism in UGT2B7 has been associated with variability in the clearance of lamotrigine. Clearance was 117% higher (95%-CI 44.8, 247%) in patients with UGT2B7 372 GG genotype, as compared with AA genotype [16]. Unfortunately, genotype data was not available for our analysis.

Given the contribution of different enzyme expression patterns and developmental trajectories to the elimination of lamotrigine, we deem as unlikely that the (de)maturation function results from the imbalance in the number of children between 4 and 12 years of age. This is further highlighted in Figure 1, where individual clearance values estimated by a model without a maturation function and without covariates for the elderly population are presented. It can be seen that clearance in the first two years of life is considerably higher, when adjusted for weight using allometry. Whereas at present we cannot determine the mechanisms underlying the observed developmental trajectory, it cannot be excluded that while UGT-1A4 activity is lower at a younger age, higher activity of the other isozymes (UGT2B7 and UGT1A3) may contribute to the observed increase in clearance. Further studies including genotyping are required to corroborate these findings.
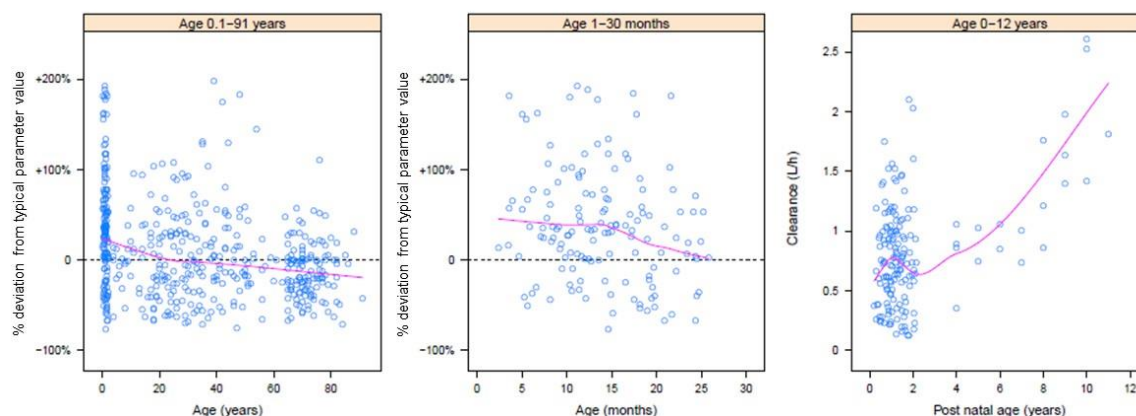

Figure 1. Left panel: Individual clearance estimates (N=494), expressed as percentage (%) deviation from the typical clearance value, based on a population pharmacokinetic model including the effect of body weight (allometry) and comedications, but without maturation function or covariate factors describing the impact of age on pharmacokinetics in elderly patients. Mid panel: Percentage deviation from the typical clearance value in subpopulation F (1-24 months, N=144). Clearance estimates for most patients ≤ 24 months of age show a positive ratio relative to the typical weight-adjusted value for clearance. Despite the gap in data in the age range of 2-4 years, the downward slope that sets in at approximately 1 year is supported by the data in patients aged 1-2 years. The upward trend is evident in older paediatric patients, i.e. > 4 years. Right panel: Individual clearance estimates (L/h) (N=165) obtained with the final model along with the trend line depicting the predicted developmental trajectory.

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