**Table S2. Parameter Estimates for Pre-Specified LME Applied to Data with No PK/PD Hysteresis and Incorrectly Applied to Data with a 1-h Delay (Misspecified Model)**

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| --- | --- | --- | --- | --- |
|  | **Linear Model Applied to Data with No Delay (Correct Model)** | | **Linear Model Applied to Data with 1-h Delay (Misspecified Model)** | |
| **Parameters** | **Estimate** | **95% CI** | **Estimate** | **95% CI** |
| Placebo(θ0) , ms | -2.76 | [-6.07; -0.555] | -9.54 | [-13.4;-5.66] |
| Active (θ1), ms | -1.80 | [-4.13; -0.534] | -8.89 | [-12.2; -5.59] |
| Time Effect (0.5 h), ms | 3.75 | [0.896; 6.60] | -0.221 | [-3.40; -3.84] |
| Time Effect (1 h), ms | 4.40 | [1.15; 7.64] | 9.95 | [-6.23; 13.7] |
| Time Effect (1.5 h), ms | 6.60 | [3.15; 10.0] | 14.7 | [10.9; 18.4] |
| Time Effect (2 h), ms | 6.98 | [3.49; 10.5] | 15.9 | [12.2; 19.7] |
| Time Effect (3 h), ms | 6.88 | [3.44; 10.3] | 16.2 | [12.5; 19.8] |
| Time Effect (5 h), ms | 2.07 | [-1.21; 5.34] | 11.0 | [7.41; 14.7] |
| Time Effect (8 h), ms | -2.37 | [-5.47; 0.723] | 6.08 | [2.50; 9.66] |
| Time Effect (12 h), ms | 3.42 | [0.453; 6.39] | 11.4 | [7.80; 15.0] |
| Time Effect (16 h), ms | 12.3 | [9.38; 15.2] | 19.9 | [16.3; 23.6] |
| Time Effect (23.5 h), ms | 3.29 | [0.421; 6.15] | 10.6 | [6.92; 14.3] |
| Slope (θ2), ms per concentration unit | 0.867 | [0.609; 1.12] | 0.766 | [0.533; 0.999] |
| Baseline covariate (θ4), ms | -0.0712 | [-0.141; -0.001] | -0.0985 | [-0.185; -0.0116] |
|  |  | |  | |
| **Variance Components** | **Estimate** | | **Estimate** | |
| Variance (Intercept), ms2 | 8.60 | | 12.3 | |
| Variance (Conc), unit2 | 0.291 | | 0.167 | |
| Residual Variance, ms2 | 50.8 | | 79.7 | |
|  |  | |  | |
| **LS mean ΔΔQTcF** | **Estimate (upper 90% CI)** | | **Estimate (upper 90% CI)** | |
| Low (Cmax=7.31), ms | 7.29 (10.1) | | 6.25 (9.55) | |
| Medium (Cmax=15.9), ms | 14.7 (18.6) | | 12.8 (16.6) | |
| High (Cmax=55.3), ms | 48.9 (60.6) | | 43.0 (53.3) | |