

**Table S6: Meta-analysis pooled estimates for the composite and individual outcomes comparing fixed and random effects models.**

| Outcomes                                                                                                        | Reduced function CYP2D6 allele § | No. of studies | Events | Participants | Fixed effects RR | 95% CI    | Random effects RR | 95% CI     | $I^2$ | Cochrane's Q P-value |
|-----------------------------------------------------------------------------------------------------------------|----------------------------------|----------------|--------|--------------|------------------|-----------|-------------------|------------|-------|----------------------|
| <b>COMPOSITE OUTCOMES</b>                                                                                       |                                  |                |        |              |                  |           |                   |            |       |                      |
| All-cause mortality                                                                                             | Any vs. none                     | 6              | >307   | 4936         | 1.11             | 0.94-1.31 | 1.12              | 0.90-1.41  | 19.6% | 0.286                |
|                                                                                                                 | 1 vs. none                       | 3              | 250    | 1429         | 1.16             | 0.88-1.53 | 1.19              | 0.85-1.68  | 5.4%  | 0.348                |
|                                                                                                                 | 2 vs. none                       | 3              | 142    | 778          | 1.71             | 1.00-2.95 | 3.23              | 0.73-14.21 | 47.5% | 0.149                |
| All-cause mortality & surrogate endpoints for overall survival (including non-fatal events)                     | Any vs. none                     | 10             | >307   | 6721         | 1.27             | 1.11-1.45 | 1.34              | 1.06-1.69  | 55.8% | 0.016                |
|                                                                                                                 | 1 vs. none                       | 4              | >250   | 1635         | 1.23             | 0.96-1.59 | 1.28              | 0.95-1.71  | 7.8%  | 0.354                |
|                                                                                                                 | 2 vs. none                       | 3              | 142    | 778          | 1.71             | 1.00-2.95 | 3.23              | 0.73-14.21 | 47.5% | 0.149                |
| All-cause mortality, surrogate endpoints for overall survival (including non-fatal events) & non-fatal outcomes | Any vs. none                     | 17             | >1088  | 9555         | 1.19             | 1.07-1.33 | 1.22              | 1.01-1.46  | 53.4% | 0.005                |
|                                                                                                                 | 1 vs. none                       | 9              | >956   | 4624         | 1.16             | 0.99-1.34 | 1.16              | 0.99-1.34  | 0.0%  | 0.477                |
|                                                                                                                 | 2 vs. none                       | 8              | >802   | 3405         | 1.33             | 1.00-1.77 | 1.36              | 0.93-1.97  | 29.4% | 0.194                |
| <b>INDIVIDUAL OUTCOMES</b>                                                                                      |                                  |                |        |              |                  |           |                   |            |       |                      |
| Breast-cancer specific mortality                                                                                | Any vs. none                     | 2              | >35    | 3240         | 1.12             | 0.89-1.40 | 1.44              | 0.65-3.20  | 68.7% | 0.074                |
| Overall survival/ All-cause mortality                                                                           | Any vs. none                     | 6              | >272   | 5057         | 1.11             | 0.95-1.29 | 1.11              | 0.95-1.29  | 0.0%  | 0.442                |
| Surrogate endpoints for overall survival (including non-fatal events)                                           | Any vs. none                     | 6              | >385   | 3270         | 1.43             | 1.22-1.68 | 1.37              | 1.01-1.85  | 66.3% | 0.011                |
| Non-fatal outcomes                                                                                              | Any vs. none                     | 11             | >989   | 5445         | 1.34             | 1.17-1.54 | 1.32              | 1.02-1.71  | 63.9% | 0.002                |
| Hot flush                                                                                                       | Any vs. none                     | 1              | 36     | 190          | 0.83             | 0.36-1.91 | 0.83              | 0.36-1.91  | 0.0%  | NA                   |

**Footnotes:** CI: confidence interval,  $I^2$ : I-squared heterogeneity statistic, NA: not applicable, RR: relative risk. § represents genotype comparison used for analysis