# Effect of low-dose methotrexate on estimated glomerular filtration rate and kidney adverse events: A randomized clinical trial

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**Supplemental Material:**

**Supplemental Table 1**. Difference in ΔeGFR and eGFR slope change low-dose methotrexate compared to placebo during the acute and chronic periods of follow-up after randomization (n=4,786).

**Supplemental Table 2**. Rates and hazard ratios for alternative definitions of kidney adverse events for low-dose methotrexate compared to placebo (n=4,786).

**Supplemental Table 3**. Worsening of chronic kidney disease (CKD) stage at final visit for low-dose methotrexate compared to placebo, restricted to participants with CKD Normal/Stage 1 or Stage 2 (≥60 mL/min/1.73m$^2$) at baseline (n=3,789).

**Supplemental Table 1**. Difference in ΔeGFR and eGFR slope change low-dose methotrexate compared to placebo during the acute and chronic periods of follow-up after randomization (n=4,786).

| | Acute (≤3 months) | Chronic (>3 months) |
|---|---|---|
| Difference in ΔeGFR (mL/min/1.73m$^2$) | 0.70 (95%CI 0.14, 1.25), p=0.015 | 1.00 (95%CI 0.47, 1.52), p=0.0002 |
| eGFR slope difference (mL/min/1.73 m$^2$/yr) | 0.83 (95%CI 0.29, 1.38), p=0.0026 | 1.12 (95%CI 0.62, 1.63), p<0.0001 |

CI, confidence interval; eGFR, estimated glomerular filtration rate.

**Supplemental Table 2**. Rates and hazard ratios for alternative definitions of kidney adverse events for low-dose methotrexate compared to placebo (n=4,786).

| | Low-dose methotrexate (n=2,391) | | Placebo (n=2,395) (reference group) | | |
|---|---|---|---|---|---|
| | Events | Rate per 100 person-years (95%CI) | Events | Rate per 100 person-years (95%CI) | HR (95%CI) |
| *Composite clinical kidney failure and sustained decline** in eGFR* | | | | | |
| Composite kidney failure with sustained decline in eGFR of ≥40% | 18 | 0.39 (0.24, 0.62) | 23 | 0.50 (0.33, 0.75) | 0.77 (0.42, 1.43) |
| Composite kidney failure with sustained decline in eGFR of ≥50% | 6 | 0.13 (0.06, 0.29) | 7 | 0.15 (0.07, 0.32) | 0.83 (0.28, 2.45) |
| Composite kidney failure with sustained decline in eGFR of ≥57% | 3 | 0.06 (0.02, 0.20) | 3 | 0.06 (0.02, 0.20) | 0.99 (0.20, 4.84) |
| | | | | | |
| *Sustained decline in eGFR* | | | | | |
| Sustained decline in eGFR of ≥40% | 17 | 0.37 (0.23, 0.59) | 21 | 0.46 (0.30, 0.70) | 0.80 (0.42, 1.51) |
| Sustained decline in eGFR of ≥50% | 5 | 0.11 (0.04, 0.26) | 5 | 0.11 (0.05, 0.26) | 0.95 (0.27, 3.27) |
| Sustained decline in eGFR of ≥57% | 2 | 0.04 (0.01, 0.17) | 1 | 0.02 (0.003, 0.15) | 1.95 (0.18, 20.83) |
| Sustained eGFR <15 mL/min/1.73m$^2$ | 2 | 0.04 (0.01, 0.17) | 0 | 0 | N/A |
| | | | | | |
| *SCr at final study visit* | | | | | |
| Any event | 38 | 0.82 (0.60, 1.12) | 50 | 1.09 (0.82, 1.43) | 0.76 (0.50, 1.16) |
| Mild (SCr 1.5-1.9x baseline) | 33 | 0.71 (0.51, 1.00) | 42 | 0.91 (0.68, 1.23) | 0.79 (0.50, 1.25) |
| Moderate (SCr 2-2.9x baseline) | 4 | 0.09 (0.03, 0.23) | 5 | 0.11 (0.05, 0.26) | 0.79 (0.21, 2.94) |
| Severe (SCr ≥3x baseline) | 1 | 0.02 (0.003, 0.15) | 3 | 0.07 (0.02, 0.20) | 0.33 (0.03, 3.12) |
| | | | | | |
| *eGFR decline at final study visit* | | | | | |
| Decline in eGFR of ≥40% | 26 | 0.56 (0.38, 0.82) | 39 | 0.85 (0.62, 1.16) | 0.66 (0.40, 1.08) |
| Decline in eGFR of ≥50% | 9 | 0.19 (0.10, 0.37) | 14 | 0.30 (0.18, 0.51) | 0.63 (0.27, 1.46) |
| Decline in eGFR of ≥57% | 5 | 0.11 (0.04, 0.26) | 7 | 0.15 (0.07, 0.32) | 0.71 (0.23, 2.22) |

*The composite kidney failure outcome was defined as the first of any of these events: new dialysis, eGFR <15 mL/min/1.73m$^2$ on two consecutive safety labs, or decline from baseline eGFR of ≥40, 50, or 57% on two consecutive safety labs.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SCr, serum creatinine.

**Supplemental Table 3**. Worsening of chronic kidney disease (CKD) stage at final visit for low-dose methotrexate compared to placebo, restricted to participants with CKD Normal/Stage 1 or Stage 2 ($\geq 60$ mL/min/1.73m$^2$) at baseline (n=3,789).

| n (%) | Low-dose methotrexate (n=1930) | Placebo (n=1859) | p-value |
|---|---|---|---|
| CKD Stage 3 or worse at final visit (eGFR <60 mL/min/1.73m$^2$) | 144 (7.5%) | 194 (10.4%) | 0.004 |
| CKD Stage 3b or worse at final visit (eGFR <45 mL/min/1.73m$^2$) | 17 (0.9%) | 32 (1.7%) | 0.029 |
| CKD Stage 4 or worse at final visit (eGFR <45 mL/min/1.73m$^2$) | 4 (0.2%) | 4 (0.2%) | 0.99 |

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate