

## Supplementary tables

**Table S1a: Association of steroid-free remission at week 16 and therapies used before inclusion in MERIT-UC**

|                              | Week 16 Remission |
|------------------------------|-------------------|
| 5-ASA Only                   | 15/65 (29%)       |
| 6-MP or AZA only             | 15/33 (45%)       |
| Any biologic only            | 8/20 (40%)        |
| 6-MP or AZA and any biologic | 14/61 (23%)       |

p-value=0.05

**Table S1b Association of steroid-free remission at week 16 and previous exposure to anti-TNF therapy.** \*includes 8 patients, who had failed both anti-TNF and vedolizumab

|                        | Week 16 Remission |
|------------------------|-------------------|
| No prior TNF           | 30/98 (31%)       |
| Any Prior TNF Exposure | 22/81* (27%)      |

p-value=0.625

**Table S2: Extent of disease at baseline (left vs pancolitis) and steroid free clinical remission at a) week 16 and b) week 48**

**a)**

|  | Left-sided  | Pan-colitis | p-value |
|--|-------------|-------------|---------|
| Steroid free clinical remission at week 16 | 26/86 (30%) | 26/93 (28%) | 0.738   |

**b)**

|  | Left-sided Placebo | Left-sided MTX | p-value |
|--|--------------------|----------------|---------|
| Steroid free clinical remission at week 48 | 7/23 (30%)         | 7/19 (37%)     | 0.661   |

|  | Pancolitis Placebo | Pancolitis MTX | p-value |
|--|--------------------|----------------|---------|
| Steroid free clinical remission at week 48 | 5/17 (29%)         | 5/25 (20%)     | 0.482   |

**Table S3: Total Mayo score at baseline (total Mayo score <9 and ≥ 9) and steroid-free remission at a) week 16 and b) week 48**

**a)**

|  | Mayo <9      | Mayo ≥ 9    | p-value |
|--|--------------|-------------|---------|
| Steroid free clinical remission at week 16 | 36/104 (35%) | 16/75 (21%) | 0.05    |

**b)**

|  | Mayo <9<br>Placebo | Mayo < 9<br>Methotrexate | p-value |
|--|--------------------|--------------------------|---------|
| Steroid free clinical remission at week 48 | 10/27 (37%)        | 7/25 (28%)               | 0.48    |

|  | Mayo ≥9<br>Placebo | Mayo ≥ 9<br>Methotrexate | p-value |
|--|--------------------|--------------------------|---------|
| Steroid free clinical remission at week 48 | 2/13 (15%)         | 5/19 (26%)               | 0.67    |

**Table S4: Steroid free clinical remission at week 48 and disease activity status at week 16 (remission or response at week 16 as assessed by partial Mayo  $\leq 2$  (n=52) vs  $>2$  (n=32)).**

|  | Clinical Mayo $\leq 2$ at week 16<br>Placebo | Clinical Mayo $\leq 2$ at week 16<br>Methotrexate | p-value |
|--|--|---|---------|
| Steroid free clinical remission at week 48 | 11/25 (44%)                                  | 8/27 (30%)  | 0.28    |

|  | Clinical Mayo $>2$ at week 16<br>Placebo | Clinical Mayo $>2$ at week 16<br>Methotrexate | p-value |
|--|--|---|---------|
| Steroid free clinical remission at week 48 | 1/15 (7%)                                | 4/17 (24%)                                    | 0.34    |

**Table S5: Steroid free clinical a) clinical remission at week 16 and b) steroid free clinical remission week 48 stratified by smoking status.**

**a)**

|   | Current Smoker<br>(n=8) | Former Smoker<br>(n=59) | Non Smoker<br>(n=112) |
|---|-------------------------|-------------------------|-----------------------|
| Steroid free clinical remission week 16 | 3/5 (60%)               | 19/40 (48%)             | 30/82 (37%)           |

p-value =0.66

**b)**

|  | Smoker<br>Placebo | Smoker<br>MTX | p-value |
|--|-------------------|---------------|---------|
| Steroid free clinical remission at week 48 | 1/1 (100%)        | 1/3(33%)      | 0.25    |

|  | Former smoker<br>Placebo | Former smoker<br>MTX | p-value |
|--|--------------------------|----------------------|---------|
| Steroid free clinical remission at week 48 | 5/13(38%)                | 4/16(25%)            | 0.44    |

|  | Non-smoker<br>Placebo | Non smoker<br>MTX | p-value |
|--|-----------------------|-------------------|---------|
| Steroid free clinical remission at week 48 | 6/26(23%)             | 7/25(28%)         | 0.69    |

**Table S6** Outcomes following 32 weeks of therapy with methotrexate 25 mg weekly or placebo during the maintenance phase of the study in anti-TNF naïve (n=48) and anti-TNF experienced (n=36) patients (includes 2 patients exposed to anti-TNF and vedolizumab).

| <b>anti-TNF naïve</b>        | Placebo<br>(n=27) | MTX<br>(n=21) | p value |
|------------------------------|-------------------|---------------|---------|
| Remission week 48            | 7 (26%)           | 6 (29%)       | 0.84    |
| Relapse between week 16 - 48 | 17 (63%)          | 13 (62%)      | 0.94    |
| <b>anti-TNF experienced</b>  | Placebo<br>(n=13) | MTX<br>(n=23) | p value |
| Remission 48                 | 5 (38%)           | 6 (26%)       | 0.44    |
| Relapse between week 16 - 48 | 8 (62%)           | 16 (70%)      | 0.62    |

**Table S7** Outcomes following 32 weeks of therapy with methotrexate 25 mg weekly or placebo during the maintenance phase of the study in patients after a low steroid induction taper (starting at 20 mg; n=42) vs a high steroid induction taper (starting at 40 mg; n=42).

| <b>Low steroid taper</b>            | Placebo (n=18) | MTX (n=24) | p value |
|-------------------------------------|----------------|------------|---------|
| Remission week 48                   | 6 (33%)        | 8 (33%)    | 1.00    |
| Relapse between week 16 and week 48 | 12 (46%)       | 14 (58%)   | 0.58    |
| <b>High steroid taper</b>           | Placebo (n=22) | MTX (n=20) | p value |
| Remission 48                        | 6 (27%)        | 4 (20%)    | 0.58    |
| Relapse between week 16 and week 48 | 13 (59%)       | 15 (75%)   | 0.27    |

**Table S8: Remission, response and clinical Mayo subscores for rectal bleeding score =0, and stool frequency score =0 following 32 weeks of therapy with methotrexate 25 mg weekly or placebo during the maintenance phase of the study. Thirty patients (16 and 15 in the placebo and MTX group, respectively) completed the study visit at week 48.**

| Week 48 outcome                         | Placebo     | Methotrexate | p-value |
|---|-------------|--------------|---------|
| Remission and no steroids               | 12/40 (30%) | 12/44 (27%)  | 0.91    |
| Response only and no steroids           | 3/40 (8%)   | 2/44 (5%)    | 0.66    |
| Rectal Bleeding score 0 and no steroids | 15/40 (38%) | 14/44 (32%)  | 1.00    |
| Stool Frequency score 0 and no steroids | 10/40 (25%) | 12/44 (27%)  | 0.75    |

**Table S9: Endoscopy score at baseline, stratified by baseline fecal calprotectin:**

|                                | Endo score 2<br>n=106 | Endo Score 3<br>n=73 |
|--------------------------------|-----------------------|----------------------|
| <50 mg/kg; n=13                | 9 (9%)                | 4 (6%)               |
| >50 mg/kg and <250 mg/kg; n=32 | 25 (24%)              | 7 (10%)              |
| ≥250 mg/kg; n=134              | 72 (68%)              | 62 (85%)             |

p-value = 0.03



## Supplementary figures

Figure S1: Kaplan-Meier survival plot of the rate of relapse in the maintenance period after achieving steroid-free response or remission to open label MTX 25 mg/week after a 16-week induction period were randomized to placebo or continuing MTX therapy the MTX in patients with previous exposure to anti-TNF agents (n=36, S1a) and anti-TNF naïve patients (n =48; S1b).

Figure S1a previous exposure to anti-TNF agents

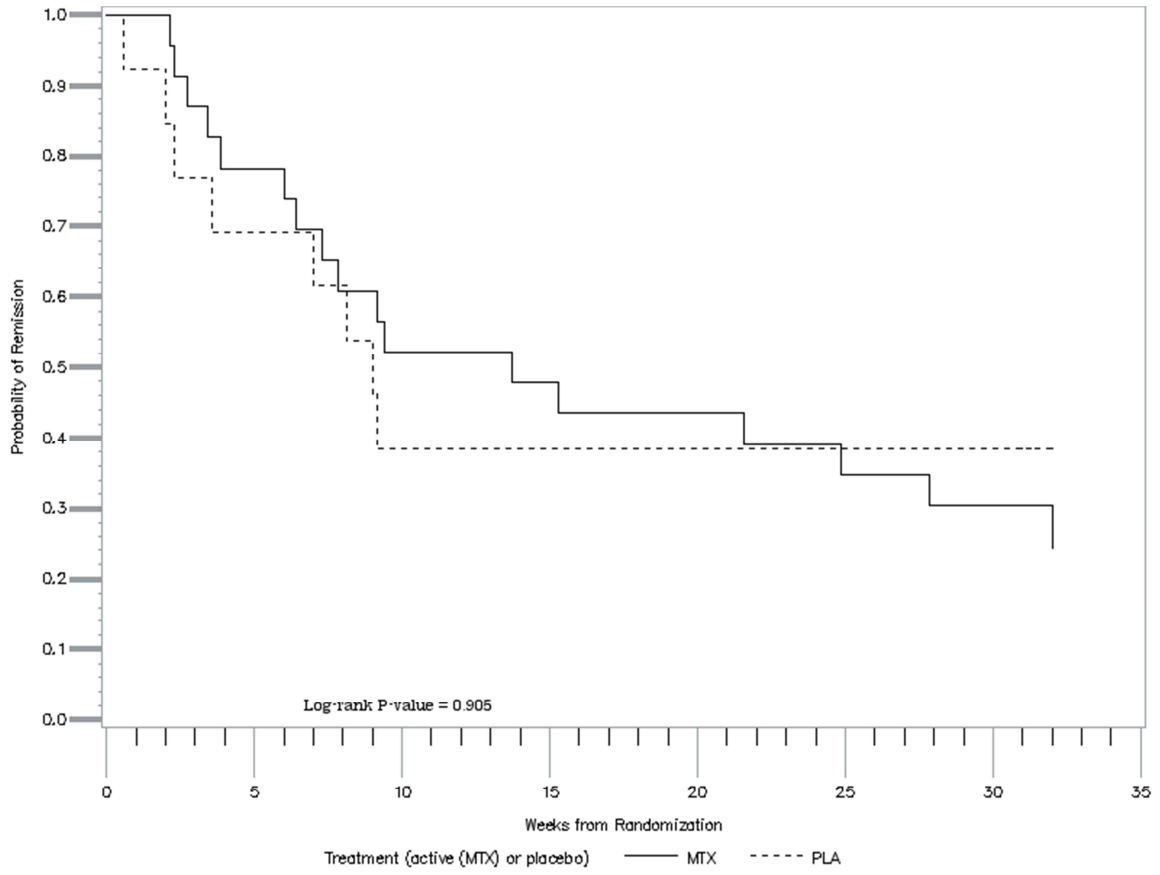


Figure S1b anti-TNF naïve patients

