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**Supplemental Table 1: Continuous glucose monitoring data.** CGM data for the pediatric cohort is shown with summary statistics including mean glucose, SD, CV, and percent of reading in various glucose ranges shown.

|                                             | Pediatric (N=81)   |                |
|---------------------------------------------|--------------------|----------------|
|                                             | Tocilizumab (N=54) | Placebo (N=27) |
| Baseline                                    |                    |                |
| n                                           | 6                  | 7              |
| Mean: Mean (SD)                             | 165.7 (35.19)      | 159.5 (23.73)  |
| SD: Mean (SD)                               | 54.4 (14.34)       | 54.3 (16.86)   |
| CV: Mean (SD)                               | 32.7 (5.32)        | 33.4 (6.91)    |
| % Readings in Range >180 mg/dL: Mean (SD)   | 33.4 (22.73)       | 28.1 (16.11)   |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 65.5 (22.00)       | 71.3 (16.24)   |
| % Readings in Range <70 mg/dL: Mean (SD)    | 1.1 (0.80)         | 0.6 (0.51)     |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 0.9 (0.72)         | 0.5 (0.46)     |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.1 (0.12)         | 0.1 (0.09)     |
| Week 4                                      |                    |                |
| n                                           | 15                 | 6              |
| Mean: Mean (SD)                             | 148.0 (32.44)      | 170.2 (22.14)  |
| SD: Mean (SD)                               | 46.6 (15.90)       | 61.0 (7.46)    |
| CV: Mean (SD)                               | 30.9 (6.12)        | 36.2 (4.78)    |
| % Readings in Range >180 mg/dL: Mean (SD)   | 22.6 (19.18)       | 38.6 (14.06)   |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 76.1 (18.49)       | 59.7 (12.01)   |
| % Readings in Range <70 mg/dL: Mean (SD)    | 1.2 (1.33)         | 1.7 (2.62)     |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 1.1 (1.19)         | 1.5 (2.17)     |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.1 (0.17)         | 0.2 (0.46)     |
| Week 8                                      |                    |                |
| n                                           | 12                 | 7              |
| Mean: Mean (SD)                             | 156.4 (29.69)      | 180.0 (31.51)  |
| SD: Mean (SD)                               | 49.7 (15.07)       | 62.7 (16.48)   |
| CV: Mean (SD)                               | 31.6 (7.04)        | 34.5 (6.62)    |
| % Readings in Range >180 mg/dL: Mean (SD)   | 28.7 (18.14)       | 43.3 (19.77)   |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 70.1 (17.87)       | 55.6 (19.57)   |
| % Readings in Range <70 mg/dL: Mean (SD)    | 1.2 (1.70)         | 1.1 (1.26)     |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 1.0 (1.21)         | 0.9 (0.93)     |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.2 (0.59)         | 0.2 (0.34)     |
| Week 12                                     |                    |                |
| n                                           | 17                 | 8              |
| Mean: Mean (SD)                             | 156.3 (27.22)      | 180.0 (29.78)  |
| SD: Mean (SD)                               | 49.2 (11.58)       | 65.1 (18.01)   |

|                                             |               |               |
|---------------------------------------------|---------------|---------------|
| CV: Mean (SD)                               | 31.4 (5.45)   | 35.8 (5.88)   |
| % Readings in Range >180 mg/dL: Mean (SD)   | 29.2 (19.29)  | 42.9 (17.59)  |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 69.8 (18.97)  | 55.6 (17.59)  |
| % Readings in Range <70 mg/dL: Mean (SD)    | 0.9 (0.90)    | 1.5 (1.53)    |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 0.8 (0.75)    | 1.2 (1.23)    |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.1 (0.23)    | 0.3 (0.33)    |
|                                             |               |               |
| Week 16                                     |               |               |
| n                                           | 24            | 9             |
| Mean: Mean (SD)                             | 157.7 (30.35) | 163.4 (38.64) |
| SD: Mean (SD)                               | 51.8 (17.35)  | 57.8 (17.10)  |
| CV: Mean (SD)                               | 32.3 (5.68)   | 35.3 (7.27)   |
| % Readings in Range >180 mg/dL: Mean (SD)   | 28.8 (18.69)  | 33.8 (22.81)  |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 69.6 (18.54)  | 64.3 (21.93)  |
| % Readings in Range <70 mg/dL: Mean (SD)    | 1.6 (1.93)    | 1.9 (1.67)    |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 1.2 (1.10)    | 1.6 (1.41)    |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.4 (0.90)    | 0.3 (0.29)    |
|                                             |               |               |
| Week 20                                     |               |               |
| n                                           | 25            | 7             |
| Mean: Mean (SD)                             | 159.2 (29.84) | 156.5 (21.46) |
| SD: Mean (SD)                               | 51.4 (14.60)  | 58.0 (12.94)  |
| CV: Mean (SD)                               | 31.9 (5.05)   | 37.0 (5.76)   |
| % Readings in Range >180 mg/dL: Mean (SD)   | 29.3 (18.40)  | 31.0 (12.72)  |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 69.7 (18.29)  | 66.5 (12.58)  |
| % Readings in Range <70 mg/dL: Mean (SD)    | 1.0 (1.28)    | 2.5 (2.22)    |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 0.8 (0.85)    | 1.9 (1.73)    |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.2 (0.48)    | 0.5 (0.68)    |
|                                             |               |               |
| Week 24                                     |               |               |
| n                                           | 22            | 11            |
| Mean: Mean (SD)                             | 159.9 (25.89) | 167.4 (28.35) |
| SD: Mean (SD)                               | 53.1 (15.13)  | 62.3 (15.39)  |
| CV: Mean (SD)                               | 32.8 (5.12)   | 36.9 (4.84)   |
| % Readings in Range >180 mg/dL: Mean (SD)   | 29.8 (15.20)  | 35.1 (17.44)  |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 69.3 (15.00)  | 63.6 (17.41)  |
| % Readings in Range <70 mg/dL: Mean (SD)    | 0.9 (0.90)    | 1.3 (0.86)    |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 0.8 (0.82)    | 1.1 (0.68)    |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.1 (0.13)    | 0.2 (0.22)    |
|                                             |               |               |
| Week 39                                     |               |               |
| n                                           | 28            | 10            |
| Mean: Mean (SD)                             | 164.7 (22.22) | 183.7 (50.90) |
| SD: Mean (SD)                               | 58.6 (13.93)  | 65.9 (18.39)  |
| CV: Mean (SD)                               | 35.5 (6.36)   | 36.3 (6.72)   |
| % Readings in Range >180 mg/dL: Mean (SD)   | 34.7 (14.51)  | 42.1 (24.30)  |

|                                             |               |               |
|---------------------------------------------|---------------|---------------|
| % Readings in Range 70-180 mg/dL: Mean (SD) | 63.1 (14.26)  | 56.2 (23.51)  |
| % Readings in Range <70 mg/dL: Mean (SD)    | 2.2 (2.98)    | 1.7 (2.04)    |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 1.8 (2.37)    | 1.4 (1.57)    |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.4 (0.67)    | 0.3 (0.51)    |
|                                             |               |               |
| Week 52                                     |               |               |
| n                                           | 32            | 9             |
| Mean: Mean (SD)                             | 167.1 (28.11) | 182.0 (46.43) |
| SD: Mean (SD)                               | 58.4 (15.00)  | 67.6 (16.61)  |
| CV: Mean (SD)                               | 34.8 (4.96)   | 37.6 (6.97)   |
| % Readings in Range >180 mg/dL: Mean (SD)   | 35.4 (16.40)  | 42.3 (20.11)  |
| % Readings in Range 70-180 mg/dL: Mean (SD) | 63.0 (16.01)  | 55.2 (19.37)  |
| % Readings in Range <70 mg/dL: Mean (SD)    | 1.6 (1.66)    | 2.5 (2.66)    |
| % Readings in Range 54-<70 mg/dL: Mean (SD) | 1.3 (1.07)    | 2.1 (2.05)    |
| % Readings in Range <54 mg/dL: Mean (SD)    | 0.3 (0.69)    | 0.4 (0.64)    |

**Supplemental Table 2:** Genotype frequencies in both adult and pediatric cohorts.

| Pediatric Patients            |              |       |       |       |
|-------------------------------|--------------|-------|-------|-------|
| Treatment Group               | (rs61812598) |       |       |       |
|                               | AA           | AG    | GG    | Total |
| Placebo                       | 5            | 10    | 9     | 24    |
| Tocilizumab                   | 5            | 27    | 20    | 52    |
| Total                         | 10           | 37    | 29    | 76    |
|                               | 13.16        | 48.68 | 38.16 | 100   |
| Fisher's exact p-value: 0.405 |              |       |       |       |

| Pediatric Patients            |             |       |       |       |
|-------------------------------|-------------|-------|-------|-------|
| Treatment Group               | (rs4129267) |       |       |       |
|                               | TT          | CT    | cc    | Total |
| Placebo                       | 5           | 10    | 9     | 24    |
| Tocilizumab                   | 5           | 27    | 20    | 52    |
| Total                         | 10          | 37    | 29    | 76    |
|                               | 13.16       | 48.68 | 38.16 | 100   |
| Fisher's exact p-value: 0.405 |             |       |       |       |

| Pediatric Patients            |             |       |       |       |
|-------------------------------|-------------|-------|-------|-------|
| Treatment Group               | (rs4129267) |       |       |       |
|                               | TT          | CT    | CC    | Total |
| Placebo                       | 5           | 10    | 9     | 24    |
| Tocilizumab                   | 5           | 27    | 20    | 52    |
| Total                         | 10          | 37    | 29    | 76    |
|                               | 13.16       | 48.68 | 38.16 | 100   |
| Fisher's exact p-value: 0.405 |             |       |       |       |

| Adult Patients                |             |      |       |       |
|-------------------------------|-------------|------|-------|-------|
| Treatment Group               | (rs4129267) |      |       |       |
|                               | TT          | CT   | CC    | Total |
| Placebo                       | 3           | 9    | 8     | 20    |
| Tocilizumab                   | 10          | 16   | 8     | 34    |
| Total                         | 13          | 25   | 16    | 54    |
|                               | 24.07       | 46.3 | 29.63 | 100   |
| Fisher's exact p-value: 0.341 |             |      |       |       |

**Supplemental Table 3:** Participants studied for each mechanistic assay

| <b>Cell population</b>               | <b>Treatment</b>                         | <b><u>Week</u><br/><u>0</u></b> | <b><u>Week</u><br/><u>4</u></b> | <b><u>Week</u><br/><u>12</u></b> | <b><u>Week</u><br/><u>24</u></b> | <b><u>Week</u><br/><u>52</u></b> |
|--------------------------------------|------------------------------------------|---------------------------------|---------------------------------|----------------------------------|----------------------------------|----------------------------------|
| MFI pSTAT3 of CD4 Teff               | Placebo                                  | 22                              | 19                              | 22                               | 22                               | 22                               |
| MFI pSTAT3 of CD4 Teff               | Tocilizumab                              | 43                              | 41                              | 43                               | 43                               | 42                               |
| % total pSTAT3 of Tregs              | Placebo                                  | 22                              | 18                              | 21                               | 21                               | 22                               |
| % total pSTAT3 of Tregs              | Tocilizumab                              | 42                              | 40                              | 40                               | 42                               | 41                               |
| %pSTAT3 of CD4 Memory Teff           | Placebo                                  | 21                              | 18                              | 21                               | 21                               | 21                               |
| %pSTAT3 of CD4 Memory Teff           | Tocilizumab                              | 43                              | 41                              | 43                               | 43                               | 42                               |
| MFI IL6 of Total CD4                 | Placebo                                  | 22                              | 19                              | 22                               | 22                               | 22                               |
| MFI IL6 of Total CD4                 | Tocilizumab                              | 43                              | 41                              | 43                               | 43                               | 42                               |
| % CD45RO+ (memory) of CD4 Teff       | Placebo                                  | 25                              | 23                              | 25                               | 25                               | 24                               |
| % CD45RO+ (memory) of CD4 Teff       | Tocilizumab                              | 49                              | 47                              | 49                               | 49                               | 48                               |
| %CCR7+ (CM) of memory CD4 Teff       | Placebo                                  | 25                              | 23                              | 25                               | 25                               | 24                               |
| %CCR7+ (CM) of memory CD4 Teff       | Tocilizumab                              | 49                              | 47                              | 49                               | 49                               | 48                               |
| %CCR7- (EM) of CD4 Teff              | Placebo                                  | 25                              | 23                              | 25                               | 25                               | 24                               |
| %CCR7- (EM) of CD4 Teff              | Tocilizumab                              | 49                              | 47                              | 49                               | 49                               | 48                               |
| %Treg (FoxP3+) of CD4 T cells        | Placebo                                  | 25                              | 23                              | 25                               | 25                               | 24                               |
| %Treg (FoxP3+) of CD4 T cells        | Tocilizumab                              | 49                              | 47                              | 49                               | 49                               | 48                               |
| % IL-21+ of FoxP3-CD45RO+            | Placebo                                  | 26                              | 24                              | 26                               | 26                               | 25                               |
| % IL-21+ of FoxP3-CD45RO+            | Tocilizumab                              | 53                              | 50                              | 53                               | 53                               | 52                               |
| % IL-17a of FoxP3-CD45RO+            | Placebo                                  | 26                              | 24                              | 26                               | 26                               | 25                               |
| % IL-17a of FoxP3-CD45RO+            | Tocilizumab                              | 53                              | 50                              | 53                               | 53                               | 52                               |
| cDC1                                 | Placebo                                  | 25                              | 25                              | 25                               | 23                               | 24                               |
| cDC1                                 | Tocilizumab                              | 49                              | 49                              | 48                               | 47                               | 48                               |
| cDC2                                 | Placebo                                  | 25                              | 25                              | 25                               | 23                               | 24                               |
| cDC2                                 | Tocilizumab                              | 49                              | 49                              | 48                               | 47                               | 48                               |
| pDC                                  | Placebo                                  | 25                              | 25                              | 24                               | 23                               | 24                               |
| pDC                                  | Tocilizumab                              | 49                              | 49                              | 48                               | 47                               | 48                               |
| Classical Monocytes                  | Placebo                                  | 25                              | 25                              | 25                               | 23                               | 24                               |
| Classical Monocytes                  | Tocilizumab                              | 49                              | 49                              | 48                               | 47                               | 48                               |
|                                      |                                          |                                 |                                 |                                  |                                  |                                  |
| <b><u>Treg Suppression Assay</u></b> | -                                        | -                               | -                               | -                                | -                                | -                                |
| <b><u>Treatment</u></b>              | <b><u>TReg:teff</u><br/><u>Ratio</u></b> | <b><u>Week</u><br/><u>0</u></b> | <b><u>Week</u><br/><u>4</u></b> | <b><u>Week</u><br/><u>12</u></b> | <b><u>Week</u><br/><u>24</u></b> | <b><u>Week</u><br/><u>52</u></b> |
| Placebo                              | 1:4                                      | 8                               | 10                              | 10                               | 10                               | 9                                |
| Tocilizumab                          | 1:4                                      | 10                              | 10                              | 10                               | 10                               | 10                               |
| Placebo                              | 1:8                                      | 10                              | 10                              | 10                               | 10                               | 10                               |
| Tocilizumab                          | 1:8                                      | 10                              | 10                              | 10                               | 10                               | 10                               |
| Placebo                              | 1:16                                     | 10                              | 10                              | 10                               | 10                               | 10                               |
| Tocilizumab                          | 1:16                                     | 10                              | 10                              | 10                               | 10                               | 10                               |
| Placebo                              | 1:32                                     | 9                               | 10                              | 10                               | 10                               | 9                                |
| Tocilizumab                          | 1:32                                     | 10                              | 10                              | 10                               | 10                               | 10                               |

| <u>Serum Analyte</u> | <u>Treatment</u> | <u>Week</u><br><u>0</u> | <u>Week</u><br><u>4</u> | <u>Week</u><br><u>12</u> | <u>Week</u><br><u>24</u> | <u>Week</u><br><u>52S</u> |
|----------------------|------------------|-------------------------|-------------------------|--------------------------|--------------------------|---------------------------|
| CRP                  | Placebo          | 25                      | 25                      | 25                       | 25                       | 25                        |
| CRP                  | Tocilizumab      | 49                      | 49                      | 49                       | 49                       | 49                        |
| IL6                  | Placebo          | 23                      | 23                      |                          | 23                       | 21                        |
| IL6                  | Tocilizumab      | 43                      | 47                      |                          | 47                       | 40                        |
| sIL6-R               | Placebo          | 23                      | 23                      |                          | 22                       | 22                        |
| sIL6-R               | Tocilizumab      | 47                      | 47                      |                          | 47                       | 46                        |

**Supplemental Table 4:** Flow cytometry staining panels used for immunophenotyping

| ITN X-trial T cell panel |               |          |
|--------------------------|---------------|----------|
| Marker                   | Fluorochrome  | Clone    |
| CD3                      | BV605         | OKT3     |
| CD4                      | BB515         | RPA-T4   |
| CD8                      | AlexaFluor700 | SK1      |
| CD56                     | BUV395        | NCAM16.2 |
| CCR7                     | BV510         | G043H7   |
| CD45RA                   | BUV737        | HI100    |
| CD45RO                   | BV786         | UCHL1    |
| CD127                    | BV711         | A019D5   |
| FoxP3                    | PE-CF594      | 259D/C7  |
| PD1                      | BV650         | EH12.2H7 |
| CD57                     | APC-Vio770    | REA769   |
| KLRG1                    | PE-Cy7        | SA231A2  |
| Eomes                    | PE            | WD1928   |
| TIGIT                    | APC           | MBSA43   |
| Ki67                     | BV421         | Ki67     |
| CD95                     | BB700         | DX2      |
| viability                | BUV496        |          |

| ICS panel |                 |          |
|-----------|-----------------|----------|
| Marker    | Fluorochrome    | Clone    |
| CD3       | Alexa Fluor 700 | OKT3     |
| CD4       | BV650           | SK3      |
| CD8       | BUV737          | SK1      |
| CD45RA    | BV605           | HI100    |
| CXCR5     | BV785           | J252D4   |
| PD1       | BV421           | EH12.2H7 |
| CD56      | PE-CY7          | NCAM16.2 |
| CD161     | BV510           | HP-3G10  |
| FoxP3     | PE-CF594        | 259D/C7  |
| CRTH2     | BV711           | BM16     |
| CD45RO    | BB515           | UCHL1    |
| IFNg      | BUV395          | B27      |
| TIGIT     | APC             | MBSA43   |
| IL21      | PE              | 3A3-N2.1 |
| IL17A     | APC-Cy7         | BL168    |
| viability | BUV496          |          |

| IL6-R / APC panel |              |          |
|-------------------|--------------|----------|
| Marker            | Fluorochrome | Clone    |
| CD19              | BV421        | HIB19    |
| CD141             | BB700        | 1A4      |
| CD3               | BUV737       | UCHT1    |
| HLADR             | BV510        | G46-6    |
| CD123             | PE           | 7G3      |
| CD1c              | BV650        | F10/21A3 |
| CD16              | APC-H7       | 3G8      |
| CD8               | FITC         | RPA-T8   |

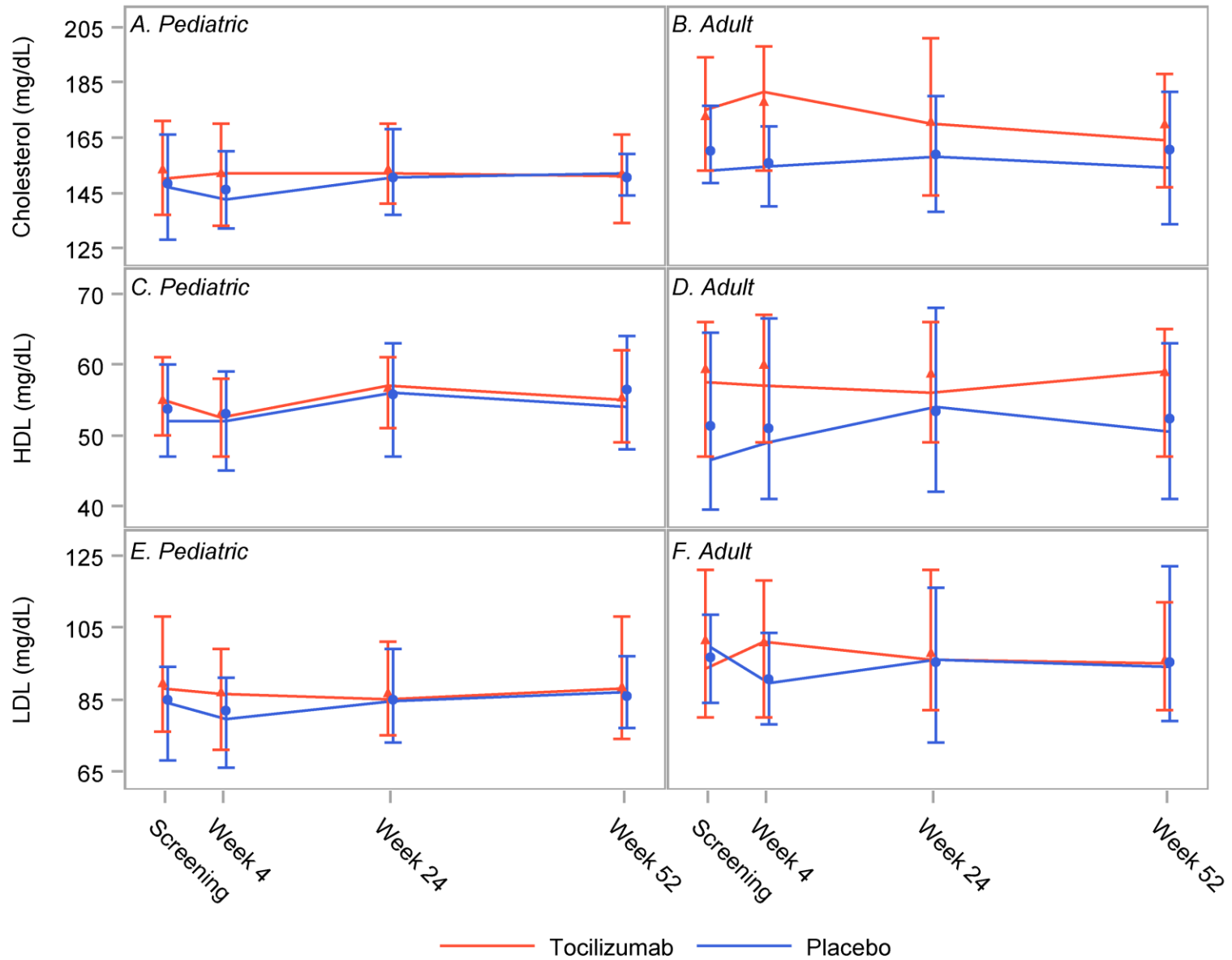
|           |          |          |
|-----------|----------|----------|
| CD4       | AF700    | RPA-T4   |
| CD14      | BV786    | M5E2     |
| IgD       | BV605    | IA6-2    |
| CD56      | PE-CF594 | NCAM16.2 |
| CD38      | APC      | HIT2     |
| CD27      | BV711    | M-T271   |
| IL6-R     | PE-Cy7   | UV4      |
| viability | BUV496   |          |

| Phospho-flow Panel |               |          |
|--------------------|---------------|----------|
| Marker             | Fluorochrome  | Clone    |
| CD3                | PerCP-Cy5.5   | UCHT1    |
| CD4                | BV605         | RPA-T4   |
| CD8                | BUV395        | RPA-T8   |
| CD45RA             | BUV737        | HI100    |
| CD27               | BV510         | O323     |
| CD56               | PE-CY7        | NCAM16.2 |
| CD33               | APC           | P67.6    |
| CD25               | PE-CF594      | M-A251   |
| CD127              | APCef780 (H7) | RDR5     |
| pSTAT3 (Y705)      | PE            | 4/pSTAT3 |
| pSTAT1 (Y701)      | AF488         | 4a       |
| CD45RO             | BV786         | UCHL1    |
| viability          | BUV496        |          |

**Supplemental Table 5:** Flow cytometry staining panel used for Treg suppression assay

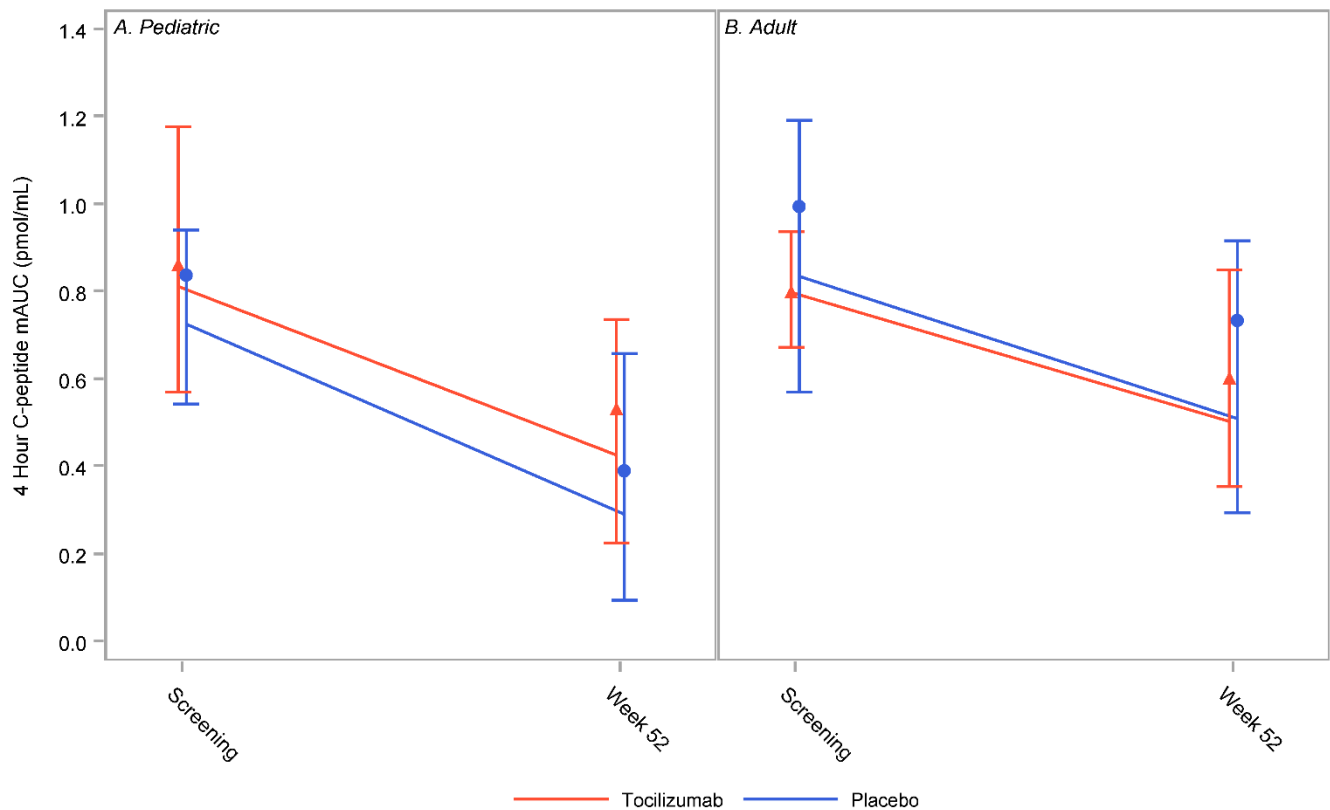
| <u>Marker</u> | <u>Fluorochrome</u> | <u>Catalog #</u> |
|---------------|---------------------|------------------|
| CD3           | BV421               | Biolegend 300434 |
| CD4           | APC-Cy7             | BD 557871        |
| CD45RO        | BV605               | BD562790         |
| CD45RA        | FITC                | Biolegend 983002 |
| CD25          | PE-Cy7              | BD557741         |
| CD134         | PE                  | BD555838         |

**Supplemental Figure 1: Lipid levels.** Markers represent the means, lines connect the medians, and error bars represent the 25th and 75th percentiles. Longitudinal lipid levels observed in both cohorts for total cholesterol (A and B), HDL (C and D), and LDL (E and F).



### Supplemental Figure 2: Longitudinal changes in 4-hour C-peptide mAUC.

4-hour C-peptide mAUC. Markers represent the means, lines connect the medians, and error bars represent the 25th and 75th percentiles of C-peptide mAUC collected during the 4-hour MMTT for participants  $\geq 12$  years of age. Data shown at screening and week 52 for (A) the pediatric cohort and (B) the adult cohort. Not all pediatric subjects received a 4-hour MMTT; in the pediatric cohort a total of 27 tocilizumab treated participants had a 4-hour MMTT at screening and 26 had a 4-hour MMTT at week 52. In the placebo group, 9 patients had a 4 hour MMTT at screening and 12 at week 52.



### Supplemental Figure 3:

Insulin sensitivity (SI) from FSIVGTT. SI over time is displayed for each subject who participated in the FSIVGTT assessments.

