**Supplemental Material**

**Material and methods**

*Clinical pathology parameters*

Table 1. Hematology and coagulation parameters

| **Hematology parameters** | **Abbreviation** | **Units** |
| --- | --- | --- |
| **Red blood cell** |  |  |
| Reticulocyte count | RETI. | 0/00 |
| Absolute reticulocyte count | TRET. | 10E12/L |
| Red blood cell count | RBC. | 10E12/L |
| Hemoglobin | HGB. | mmol/L |
| Hematocrit | HCT. | % |
| Mean corpuscular volume | MCV. | fL |
| Mean corpuscular hemoglobin | MCH. | fmol |
| Mean corpuscular hemoglobin concentration | MCHC. | mmol/L |
| **White blood cell** |  |  |
| White blood cell count | WBC. | 10E9/L |
| Neutrophils | NEUT. | % |
| Lymphocytes | LYM. | % |
| Monocytes | MONO. | % |
| Eosinophils | EOS. | % |
| Basophils | BASO. | % |
| Absolute neutrophils | ANEU. | 10E9/L |
| Absolute lymphocytes | ALYM. | 10E9/L |
| Absolute monocytes | AMON. | 10E9/L |
| Absolute eosinophils | AEOS. | 10E9/L |
| Absolute basophils | ABAS. | 10E9/L |
| **Platelets** |  |  |
| Platelet count | PLT. | 10E9/L |
| **Coagulation** |  |  |
| Prothrombin time | PT. | s |
| Activated partial thromboplastin time | APTT. | s |
| Fibrinogen | FIB. | g/L |

Table 2. Clinical chemistry parameters

| **Clinical parameter** | **Abbreviation** | **Units** |
| --- | --- | --- |
| Alanine aminotransferase | ALT. | U/L |
| Albumin | ALB. | g/L |
| Albumin/globulin ratio | A:G. |  |
| Alpha-amylase | AAMY. | U/L |
| Alkaline phosphatase | ALP. | U/L |
| Aspartate aminotransferase | AST. | U/L |
| Blood urea | BU. | mmol/L |
| Calcium | CA. | mmol/L |
| Chloride | CL. | mmol/L |
| Creatinine | CREA. | μmol/L |
| Gamma glutamyl transferase | GGT. | U/L |
| Globulin | GLOB. | g/L |
| Glucose | GLU. | mmol/L |
| Glutamate dehydrogenase | GLDH. | U/L |
| Inorganic phosphorus | PHOS. | mmol/L |
| Lipase | LIP. | U/L |
| Potassium | K. | mmol/L |
| Sodium | NA. | mmol/L |
| Total bilirubin | TBIL. | μmol/L |
| Total cholesterol | CHOL. | mmol/L |
| Total immunoglobulin G | G | IGG. |
| Total immunoglobulin M | M | IGM. |

Table 3. Urinalysis parameters

| **Urine parameter** | **Abbreviation** | **Units** |
| --- | --- | --- |
| **Quantitative** |  |  |
| Urine volume | UVOL. | mL |
| Urine specific gravity by UG-1 | USGR. | - |
| **Qualitative** |  |  |
| Urine pH | UPH. | - |
| Urine leucocytes | ULEU. | Leuco/μL |
| Urine nitrite | UNIT. | - |
| Urine qualitative protein | UPRO. | g/L |
| Urine qualitative glucose | URGL. | mmol/L |
| Urine ketone | UKET. | mmol/L |
| Urine urobilinogen | UUBG. | μmol/L |
| Urine bilirubin | UBIL. | μmol/L |
| Urine occult blood | UOBL. | Ery/μL |
| Urine color by Urisys 1800 | UCOL. | - |
| Urine clarity | UCLA. | - |

Table 4. Immunophenotyping parameters

| **Antibodies** | **Units** |
| --- | --- |
| CD16+ NK cells | 10E9/L |
| CD20+ B cells | 10E9/L |
| CD3+ T cells | 10E9/L |
| CD3+CD4+ T helper-cells | 10E9/L |
| CD3+CD8+ cytotoxic T cells | 10E9/L |
| CD20low / CD21+ B cells | 10E9/L |
| CD20high / CD21- B cells | 10E9/L |
| CD20+ CD21+ CD27+ memory B cells | 10E9/L |
| CD20+ CD21+ CD27- naïve B cells | 10E9/L |

**Results**

*Clinical pathology*

Table 5. Summary of hematology data. Bolded values were statistically significant from the respective control group (P ≤ 0.05).

|  |  | Predose | Dosing | | | | | | | | | | | | | | | | Recovery |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Parameter Treatment | Sex (No animal)\* | D1 | D1 | D8 | D15 | D22 | D29 | D36 | D43 | D48 | D50 | D57 | D64 | D71 | D78 | D85 | D86 | D92 | D204 |
| **Red blood cell (1012/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 5.87 ± 0.45 | 5.65 ± 0.42 | 5.58 ± 0.21 | 5.76 ± 0.25 | 5.92 ± 0.50 | 5.91 ± 0.39 | 5.94 ± 0.43 | 5.90 ± 0.36 | 5.81 ± 0.27 | 5.85 ± 0.31 | 5.75 ± 0.38 | 5.70 ± 0.37 | 5.77 ± 0.33 | 5.81 ± 0.43 | 5.77 ± 0.42 | 5.54 ± 0.37 | 5.65 ± 0.56 | 5.79 |
|  | Female (3+2) | 5.43 ± 0.28 | 5.43 ± 0.28 | 5.33 ± 0.23 | 5.32 ± 0.32 | 5.34 ± 0.39 | 5.53 ± 0.32 | 5.49 ± 0.35 | 5.55 ± 0.28 | 5.59 ± 0.28 | 5.52 ± 0.40 | 5.40 ± 0.21 | 5.62 ± 0.25 | 5.37 ± 0.29 | 5.37 ± 0.28 | 5.48 ± 0.21 | 5.19 ± 0.33 | 5.26 ± 0.29 | 5.21 |
| 10 mg/kg/week SC | Male (3) | 5.65 ± 0.75 | 4.93 ± 0.50 | 5.24 ± 0.63 | 5.43 ± 0.48 | 5.61 ± 0.52 | 5.6 ± 0.37 | 5.75 ± 0.54 | 5.71 ± 0.67 | 5.61 ± 0.25 | 5.54 ± 0.30 | 5.67 ± 0.29 | 5.73 ± 0.25 | 5.52 ± 0.27 | 5.73 ± 0.16 | 5.72 ± 0.31 | 5.37 ± 0.30 | 5.51 ± 0.37 |  |
|  | Female (3) | 5.16 ± 0.33 | 5.16 ± 0.25 | 4.96 ± 0.24 | 5.18 ± 0.25 | 5.10 ± 0.30 | 5.08 ± 0.14 | 5.09 ± 0.24 | 5.33 ± 0.35 | 5.39 ± 0.34 | 5.25 ± 0.42 | 5.08 ± 0.33 | 5.2 ± 0.26 | 5.12 ± 0.28 | 5.03 ± 0.39 | 5.05 ± 0.47 | 4.86 ± 0.526 | 5.02 ± 0.24 |  |
| 50 mg/kg/week SC | Male (3) | 5.35 ± 0.21 | 5.23 ± 0.19 | 5.21 ± 0.10 | 5.24 ± 0.17 | 5.29 ± 0.13 | 5.35 ± 0.17 | 5.3 ± 0.28 | 5.49 ± 0.26 | 5.33 ± 0.31 | 5.22 ± 0.23 | 5.34 ± 0.35 | 5.33 ± 0.45 | 5.18 ± 0.47 | 4.88 ± 0.42 | 5.01 ± 0.30 | **4.86 ± 0.33** | 4.90 ± 0.23 |  |
|  | Female (3) | 5.48 ± 0.15 | 5.45 ± 0.17 | 5.35 ± 0.11 | 5.35 ± 0.10 | 5.57 ± 0.21 | 5.57 ± 0.07 | 5.48 ± 0.14 | 5.66 ± 0.34 | 5.68 ± 0.23 | 5.69 ± 0.39 | 5.47 ± 0.03 | 5.73 ± 0.05 | 5.28 ± 0.22 | 5.5 ± 0.16 | 5.35 ± 0.061 | 5.12 ± 0.06 | 5.14 ± 0.06 |  |
| 150 mg/kg/week SC | Male (3+2) | 5.85 ± 0.37 | 5.75 ± 0.54 | 5.63 ± 0.46 | 5.75 ± 0.52 | 5.82 ± 0.50 | 5.82 ± 0.48 | 5.79 ± 0.56 | 5.79 ± 0.30 | 5.70 ± 0.33 | 5.85 ± 0.46 | 5.74 ± 0.56 | 5.71 ± 0.54 | 5.41 ± 0.44 | 5.7 ± 0.48 | 5.67 ± 0.34 | 5.43 ± 0.13 | 5.46 ± 0.24 | 5.67 |
|  | Female (3+2) | 5.59 ± 0.12 | 5.64 ± 0.29 | 5.63 ± 0.42 | 5.57 ± 0.16 | 5.69 ± 0.41 | 5.65 ± 0.25 | 5.76 ± 0.27 | 5.86 ± 0.26 | 5.97 ± 0.29 | 5.74 ± 0.25 | 5.59 ± 0.19 | 5.86 ± 0.17 | 5.65 ± 0.25 | 5.58 ± 0.24 | 5.55 ± 0.24 | 5.37 ± 0.26 | 5.38 ± 0.28 | 5.78 |
| 150 mg/kg/week IV | Male (3+2) | 5.96 ± 0.27 | 5.98 ± 0.37 | 5.81 ± 0.45 | 5.84 ± 0.36 | 5.92 ± 0.20 | 5.99 ± 0.29 | 5.97 ± 0.39 | 6.12 ± 0.36 | 5.89 ± 0.28 | 6.03 ± 0.39 | 5.96 ± 0.40 | 5.83 ± 0.39 | 5.78 ± 0.46 | 5.88 ± 0.55 | 5.73 ± 0.29 | 5.52 ± 0.24 | 5.62 ± 0.28 | 5.68 |
|  | Female (3+2) | 5.28 ± 0.15 | 5.15 ± 0.19 | 4.97 ± 0.28 | 5.14 ± 0.16 | 5.19 ± 0.21 | 5.24 ± 0.19 | 5.26 ± 0.25 | 5.36 ± 0.17 | 5.41 ± 0.21 | 5.32 ± 0.14 | 5.16 ± 0.37 | 5.42 ± 0.25 | 5.32 ± 0.20 | 5.32 ± 0.35 | 5.17 ± 0.31 | 4.72 ± 0.29 | **4.82 ± 0.12** | 5.13 |
| **Reticulocyte (1012/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.0631 ± 0.0133 | 0.0653 ± 0.022 | 0.0867 ± 0.021 | 0.0719 ± 0.025 | 0.0736 ± 0.011 | 0.0564 ± 0.016 | 0.0651 ± 0.017 | 0.0764 ± 0.006 | 0.0757 ± 0.015 | 0.0758 ± 0.012 | 0.0732 ± 0.017 | 0.0421 ± 0.011 | 0.0827 ± 0.016 | 0.0643 ± 0.017 | 0.065 ± 0.008 | 0.0599 ± 0.005 | 0.0986 ± 0.018 | 0.0355 |
|  | Female (3+2) | 0.0507 ± 0.0204 | 0.0404 ± 0.022 | 0.0728 ± 0.021 | 0.0654 ± 0.038 | 0.0754 ± 0.013 | 0.0524 ± 0.020 | 0.0643 ± 0.017 | 0.0508 ± 0.015 | 0.0382 ± 0.015 | 0.0452 ± 0.015 | 0.0563 ± 0.024 | 0.0327 ± 0.016 | 0.067 ± 0.015 | 0.0718 ± 0.016 | 0.0568 ± 0.024 | 0.0684 ± 0.019 | 0.0763 ± 0.011 | 0.0488 |
| 10 mg/kg/week SC | Male (3) | 0.0576 ± 0.0624 | 0.0462 ± 0.036 | 0.0747 ± 0.029 | 0.056 ± 0.020 | 0.0656 ± 0.026 | 0.0565 ± 0.012 | 0.0442 ± 0.007 | **0.0256 ± 0.015** | **0.0375 ± 0.008** | **0.023 ± 0.006** | 0.0344 ± 0.009 | 0.0201 ± 0.014 | 0.0522 ± 0.006 | 0.0538 ± 0.010 | 0.0501 ± 0.005 | 0.0513 ± 0.004 | 0.0594 ± 0.019 |  |
|  | Female (3) | 0.0519 ± 0.0197 | 0.0644 ± 0.033 | 0.0692 ± 0.028 | 0.0551 ± 0.020 | 0.1039 ± 0.042 | 0.0876 ± 0.042 | 0.0862 ± 0.030 | 0.0746 ± 0.031 | 0.0464 ± 0.016 | 0.0626 ± 0.016 | 0.0705 ± 0.006 | 0.0372 ± 0.008 | 0.0865 ± 0.038 | 0.103 ± 0.035 | 0.0875 ± 0.017 | 0.0811 ± 0.020 | 0.0983 ± 0.004 |  |
| 50 mg/kg/week SC | Male (3) | 0.0755 ± 0.0340 | 0.0398 ± 0.017 | 0.070 ± 0.027 | 0.0713 ± 0.023 | 0.080 ± 0.029 | 0.0705 ± 0.031 | 0.0741 ± 0.041 | 0.0526 ± 0.027 | 0.0549 ± 0.024 | **0.0452 ± 0.015** | 0.0509 ± 0.024 | 0.042 ± 0.016 | 0.1006 ± 0.061 | 0.134 ± 0.117 | 0.1431 ± 0.108 | 0.138 ± 0.084 | 0.1584 ± 0.080 |  |
|  | Female (3) | 0.0736 ± 0.0515 | 0.0378 ± 0.006 | 0.0664 ± 0.024 | 0.056 ± 0.019 | 0.0888 ± 0.023 | 0.0682 ± 0.029 | 0.061 ± 0.018 | 0.0696 ± 0.028 | 0.0467 ± 0.015 | 0.050 ± 0.020 | 0.0549 ± 0.023 | 0.0345 ± 0.013 | 0.0677 ± 0.007 | 0.0781 ± 0.030 | 0.0851 ± 0.030 | 0.0908 ± 0.041 | 0.1124 ± 0.050 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.0479 ± 0.0165 | 0.0396 ± 0.014 | 0.0554 ± 0.013 | 0.048 ± 0.017 | 0.0516 ± 0.012 | 0.0481 ± 0.015 | 0.0478 ± 0.013 | **0.0444 ± 0.010** | **0.0447 ± 0.011** | **0.0425 ± 0.014** | 0.0548 ± 0.015 | 0.0343 ± 0.011 | 0.072 ± 0.031 | 0.0568 ± 0.016 | 0.0617 ± 0.017 | 0.0581 ± 0.017 | 0.0628 ± 0.017 | 0.0393 |
|  | Female (3+2) | 0.0645 ± 0.0348 | 0.0381 ± 0.014 | 0.0621 ± 0.012 | 0.0481 ± 0.008 | 0.0689 ± 0.015 | 0.0602 ± 0.017 | 0.0522 ± 0.012 | 0.0421 ± 0.017 | 0.035 ± 0.007 | 0.0448 ± 0.017 | 0.0507 ± 0.020 | 0.0378 ± 0.015 | 0.0597 ± 0.020 | 0.0676 ± 0.012 | 0.0625 ± 0.022 | 0.068 ± 0.024 | 0.0653 ± 0.025 | 0.051 |
| 150 mg/kg/week IV | Male (3+2) | 0.0591 ± 0.0324 | 0.0452 ± 0.015 | 0.0705 ± 0.023 | 0.0747 ± 0.016 | 0.0715 ± 0.020 | 0.0565 ± 0.020 | 0.0617 ± 0.024 | 0.0518 ± 0.014 | **0.047 ± 0.019** | **0.0459 ± 0.015** | 0.0527 ± 0.019 | 0.0294 ± 0.014 | 0.0671 ± 0.032 | 0.0619 ± 0.033 | 0.0627 ± 0.029 | 0.0561 ± 0.030 | 0.0968 ± 0.066 | 0.0221 |
|  | Female (3+2) | 0.0545 ± 0.0218 | 0.0434 ± 0.022 | 0.0824 ± 0.038 | 0.0817 ± 0.031 | 0.0778 ± 0.022 | 0.0527 ± 0.012 | 0.0592 ± 0.020 | 0.0504 ± 0.019 | 0.0427 ± 0.011 | 0.0471 ± 0.009 | 0.0533 ± 0.017 | 0.0303 ± 0.010 | 0.0622 ± 0.026 | 0.058 ± 0.029 | 0.0666 ± 0.036 | 0.0703 ± 0.028 | 0.0907 ± 0.029 | 0.0669 |
| **Platelet (109/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 381 ± 66.0 | 434 ± 68.4 | 427 ± 63.6 | 402 ± 35.9 | 337 ± 21.2 | 351 ± 41.5 | 374 ± 55.6 | 355 ± 42.4 | 356 ± 20.0 | 352 ± 31.8 | 367 ± 28.2 | 365 ± 30.6 | 383 ± 52.2 | 368 ± 60.9 | 348 ± 17.4 | 316 ± 22.2 | 378 ± 8.1 | 298 |
|  | Female (3+2) | 349 ± 51.7 | 351 ± 40.9 | 355 ± 53.2 | 370 ± 42.7 | 353 ± 29.7 | 327 ± 33.8 | 336 ± 43.0 | 320 ± 52.1 | 333 ± 51.6 | 331 ± 44.0 | 329 ± 56.8 | 305 ± 54.6 | 338 ± 43.3 | 330 ± 58.6 | 331 ± 38.7 | 307 ± 24.9 | 352 ± 42.2 | 342 |
| 10 mg/kg/week SC | Male (3) | 408 ± 49.1 | 400 ± 12.7 | 389 ± 26.2 | 357 ± 52.4 | 322 ± 10.6 | 306 ± 17.1 | 332 ± 2.1 | 314 ± 15.4 | 352 ± 28.9 | 360 ± 37.3 | 348 ± 35.4 | 289 ± 30.3 | 341 ± 7.9 | 313 ± 18.7 | 318 ± 22.6 | 292 ± 11.4 | 357 ± 17.6 |  |
|  | Female (3) | 313 ± 10.2 | 323 ± 22.9 | 315 ± 10.0 | 330 ± 26.6 | 342 ± 24.8 | 309 ± 35.0 | 331 ± 24.7 | 316 ± 20.5 | 323 ± 39.7 | 322 ± 37.8 | 315 ± 29.0 | 310 ± 35.5 | 343 ± 52.4 | 320 ± 19.5 | 309 ± 41.0 | 302 ± 40.1 | 327 ± 35.6 |  |
| 50 mg/kg/week SC | Male (3) | 345 ± 12.9 | 343 ± 30.8 | 338 ± 12.7 | 326 ± 16.3 | 294 ± 14.7 | 288 ± 5.2 | 305 ± 23.7 | 310 ± 3.8 | 293 ± 9.0 | 284 ± 15.5 | 302 ± 29.0 | 296 ± 33.6 | 318 ± 27.9 | 352 ± 69.7 | 334 ± 47.4 | 321 ± 51.4 | 375 ± 60.5 |  |
|  | Female (3) | 395 ± 41.1 | 361 ± 42.4 | 374 ± 35.3 | 379 ± 46.9 | 398 ± 52.3 | 329 ± 34.8 | 338 ± 50.8 | 346 ± 51.4 | 362 ± 44.4 | 333 ± 26.3 | 323 ± 34.6 | 311 ± 55.2 | 368 ± 82.5 | 348 ± 34.0 | 335 ± 29.7 | 316 ± 46.7 | 354 ± 28.9 |  |
| 150 mg/kg/week SC | Male (3+2) | 388 ± 27.4 | 377 ± 55.7 | 385 ± 51.6 | 378 ± 31.0 | 320 ± 39.8 | 313 ± 40.8 | 327 ± 44.9 | 316 ± 36.7 | 318 ± 47.4 | 337 ± 45.4 | 341 ± 50.1 | 339 ± 61.2 | 344 ± 51.2 | 348 ± 46.9 | 344 ± 51.8 | 316 ± 43.7 | 338 ± 48.2 | 367 |
|  | Female (3+2) | 374 ± 80.8 | 402 ± 74.4 | 390 ± 68.7 | 411 ± 64.3 | 425 ± 96.6 | 353 ± 68.1 | 389 ± 67.9 | 369 ± 64.1 | 365 ± 43.0 | 353 ± 43.8 | 376 ± 59.0 | 345 ± 38.2 | 379 ± 56.3 | 366 ± 57.1 | 359 ± 46.3 | 357 ± 50.4 | 392 ± 57.5 | 389 |
| 150 mg/kg/week IV | Male (3+2) | 425 ± 93.2 | 409 ± 77.1 | 418 ± 82.1 | 412 ± 68.1 | 391 ± 102.6 | 349 ± 72.0 | 387 ± 88.6 | 373 ± 88.3 | 349 ± 88.6 | 344 ± 86.8 | 341 ± 95.9 | 335 ± 92.5 | 349 ± 67.3 | 361 ± 59.4 | 300 ± 33.1 | 299 ± 49.8 | 359 ± 67.9 | 405 |
|  | Female (3+2) | 422 ± 94.2 | 469 ± 149.2 | 419 ± 119.9 | 441 ± 133.9 | 429 ± 95.2 | 369 ± 73.3 | 386 ± 81.4 | 387 ± 80.1 | 387 ± 84.6 | 377 ± 77.6 | 373 ± 85.8 | 377 ± 80.2 | 403 ± 97.5 | 388 ± 90.0 | 399 ± 90.5 | 383 ± 95.9 | 433 ± 106.2 | 350 |
| **White blood cell (109/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 12.46 ± 4.06 | 9.69 ± 3.50 | 11.04 ± 4.60 | 12.93 ± 5.60 | 10.39 ± 3.46 | 10.54 ± 2.86 | 11.52 ± 4.13 | 11.59 ± 3.40 | 9.79 ± 4.423 | 11.06 ± 4.27 | 11.63 ± 3.63 | 12.47 ± 3.13 | 11.43 ± 4.19 | 10.58 ± 3.49 | 11.3 ± 3.935 | 9.31 ± 4.64 | 9.67 ± 4.268 | 16.01 |
|  | Female (3+2) | 7.72 ± 3.36 | 9.82 ± 3.46 | 8.73 ± 2.67 | 9.28 ± 2.28 | 12.88 ± 7.58 | 8.87 ± 2.57 | 9.72 ± 2.94 | 10.07 ± 3.28 | 9.02 ± 2.64 | 9.48 ± 2.39 | 11.66 ± 2.25 | 10.01 ± 3.27 | 10.68 ± 2.07 | 11.04 ± 3.63 | 9.95 ± 3.03 | 9.43 ± 3.06 | 9.71 ± 4.06 | 9.95 |
| 10 mg/kg/week SC | Male (3) | 11.4 ± 6.23 | 9.47 ± 6.99 | 12.18 ± 3.41 | 10.51 ± 3.12 | 10.43 ± 3.27 | 9.67 ± 3.54 | 11.39 ± 2.58 | 8.63 ± 2.66 | 6.4 ± 2.73 | 9.66 ± 3.47 | 11.5 ± 3.49 | 9.66 ± 2.81 | 11.26 ± 4.54 | 11.84 ± 1.84 | 11.08 ± 3.73 | 12.62 ± 3.38 | 9.04 ± 3.11 |  |
|  | Female (3) | 10.99 ± 4.29 | 10.66 ± 4.19 | 10.98 ± 4.2 | 9.88 ± 2.31 | 11.49 ± 0.67 | 12.76 ± 4.12 | 9.62 ± 1.93 | 10.76 ± 3.05 | 11.12 ± 2.73 | 12.54 ± 2.98 | 13.99 ± 2.07 | 12.2 ± 0.85 | 10.37 ± 2.27 | 12.35 ± 2.05 | 11.53 ± 3.76 | 10.99 ± 4.74 | 11.22 ± 4.82 |  |
| 50 mg/kg/week SC | Male (3) | 12.5 ± 0.85 | 8.12 ± 2.44 | 10.71 ± 2.28 | 10.21 ± 2.37 | 11.88 ± 2.35 | 8.83 ± 2.14 | 9.63 ± 1.93 | 7.64 ± 2.48 | 5.68 ± 1.95 | 9.01 ± 1.77 | 9.7 ± 2.09 | 9.82 ± 0.59 | 9.02 ± 0.82 | 12.45 ± 4.20 | 9.45 ± 0.91 | 8.57 ± 0.80 | 10.29 ± 2.06 |  |
|  | Female (3) | 13.22 ± 1.91 | 12.23 ± 2.95 | 12.64 ± 6.24 | 9.43 ± 0.85 | 13.07 ± 1.88 | 10.66 ± 3.98 | 9.9 ± 1.13 | 9.27 ± 1.17 | 10.97 ± 2.67 | 9.59 ± 1.91 | 13.06 ± 3.32 | 9.51 ± 1.69 | 9.71 ± 1.36 | 8.91 ± 1.81 | 9.41 ± 1.75 | 8.53 ± 2.16 | 6.36 ± 0.82 |  |
| 150 mg/kg/week SC | Male (3+2) | 12.63 ± 2.15 | 10.49 ± 2.12 | 11.32 ± 2.35 | 10.87 ± 1.30 | 9.43 ± 1.65 | 9.13 ± 0.81 | 10.27 ± 1.57 | 10.65 ± 2.13 | 8.04 ± 1.66 | 10.21 ± 0.97 | 10.35 ± 2.16 | 10.79 ± 2.70 | 9.54 ± 2.52 | 10.3 ± 2.74 | 11.72 ± 3.59 | 11.22 ± 4.81 | 8.41 ± 2.39 | 14.21 |
|  | Female (3+2) | 10.65 ± 3.48 | 10.25 ± 3.95 | 10.96 ± 3.67 | 9.98 ± 3.30 | 11.88 ± 2.28 | 10.84 ± 4.22 | 10.7 ± 4.61 | 9.37 ± 1.72 | 11.7 ± 5.36 | 9.31 ± 2.78 | 10.55 ± 3.28 | 9.44 ± 3.38 | 8.14 ± 1.40 | 10.34 ± 3.52 | 8.87 ± 2.02 | 9.31 ± 1.65 | 7.66 ± 3.23 | 14.12 |
| 150 mg/kg/week IV | Male (3+2) | 12.55 ± 3.14 | 12.4 ± 5.09 | 11.66 ± 2.78 | 11.51 ± 3.72 | 11.49 ± 5.2 | 9.77 ± 3.59 | 8.56 ± 3.39 | 8.32 ± 3.32 | 7.44 ± 3.72 | 9.86 ± 2.42 | 9.47 ± 3.16 | 10.05 ± 3.44 | 9.39 ± 3.08 | 8.65 ± 3.29 | 10.1 ± 3.69 | 7.71 ± 1.74 | 7.6 ± 2.60 | 15.62 |
|  | Female (3+2) | 7.94 ± 1.56 | 10.01 ± 2.07 | 10.82 ± 3.46 | 9.37 ± 1.83 | 8.86 ± 1.38 | 7.63 ± 1.49 | 7.4 ± 1.69 | 8.5 ± 1.14 | 7.37 ± 1.68 | 9.61 ± 1.22 | 10.51 ± 0.96 | 8.92 ± 2.87 | 8.75 ± 1.42 | 9.9 ± 0.60 | 8.28 ± 1.95 | 8.46 ± 3.52 | 6.65 ± 1.16 | 8.61 |
| **Lymphocyte (109/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 4.92 ± 1.51 | 3.81 ± 1.24 | 4.83 ± 1.37 | 5.21 ± 1.24 | 5.63 ± 1.35 | 5.74 ± 1.58 | 6.44 ± 2.01 | 5.65 ± 1.62 | 4.07 ± 1.39 | 5.57 ± 1.91 | 6.24 ± 1.87 | 6.14 ± 1.52 | 6.36 ± 2.07 | 6.07 ± 2.14 | 5.83 ± 2.13 | 3.92 ± 1.57 | 4.92 ± 1.33 | 5.47 |
|  | Female (3+2) | 3.37 ± 0.89 | 4.74 ± 0.84 | 4.97 ± 1.08 | 5.28 ± 1.71 | 5.51 ± 1.16 | 5.14 ± 1.80 | 6.12 ± 2.41 | 6.2 ± 1.94 | 4.16 ± 1.27 | 5.96 ± 1.35 | 6.59 ± 2.32 | 5.18 ± 1.68 | 6.3 ± 2.17 | 6.61 ± 2.60 | 6.01 ± 2.87 | 4.68 ± 2.21 | 5.36 ± 1.41 | 4.07 |
| 10 mg/kg/week SC | Male (3) | 5.69 ± 3.69 | 4.66 ± 3.84 | 6.55 ± 3.11 | 5.83 ± 2.49 | 6.29 ± 2.35 | 5.47 ± 1.93 | 6.14 ± 1.89 | 5.16 ± 2.52 | 2.53 ± 0.64 | 5.78 ± 2.26 | 7.25 ± 2.07 | 5.64 ± 1.85 | 6.76 ± 2.26 | 6.86 ± 0.53 | 5.83 ± 1.25 | 3.05 ± 1.23 | 4.19 ± 1.52 |  |
|  | Female (3) | 4.52 ± 1.82 | 4.64 ± 1.83 | 4.83 ± 1.74 | 5.1 ± 1.89 | 5.89 ± 1.54 | 4.87 ± 1.05 | 5.25 ± 1.54 | 5.27 ± 1.62 | 4.11 ± 2.43 | 6.31 ± 1.29 | 6.71 ± 0.71 | 5.46 ± 1.85 | 5.78 ± 1.92 | 5.98 ± 2.13 | 5.28 ± 2.34 | 3.76 ± 1.69 | 4.43 ± 1.35 |  |
| 50 mg/kg/week SC | Male (3) | 4.79 ± 0.87 | 3.56 ± 0.62 | 6.19 ± 1.17 | 6.34 ± 1.58 | 6.19 ± 1.58 | 5.09 ± 1.59 | 5.93 ± 2.10 | 4.23 ± 1.28 | 2.58 ± 0.22 | 5.34 ± 1.07 | 6.39 ± 2.06 | 6.03 ± 0.95 | 6.19 ± 1.19 | 6.61 ± 1.26 | 5.8 ± 0.61 | 5.03 ± 0.87 | 6.17 ± 0.94 |  |
|  | Female (3) | 3.91 ± 0.13 | 3.14 ± 0.20 | 4.68 ± 1.02 | 4.05 ± 0.64 | 4.21 ± 0.52 | 3.57 ± 0.76 | 4.36 ± 1.07 | 4.34 ± 0.74 | 2.78 ± 0.93 | 4.53 ± 0.92 | 4.16 ± 0.87 | 3.37 ± 0.53 | 4.33 ± 0.90 | 4.3 ± 0.14 | 3.89 ± 1.08 | 3.00 ± 0.87 | 3.41 ± 0.54 |  |
| 150 mg/kg/week SC | Male (3+2) | 4.47 ± 0.32 | 4.33 ± 0.90 | 5.55 ± 0.79 | 6.04 ± 0.83 | 5.47 ± 1.54 | 4.85 ± 0.96 | 5.26 ± 1.07 | 4.91 ± 1.11 | 2.47 ± 0.62 | 4.85 ± 1.04 | 5.33 ± 1.51 | 4.63 ± 1.64 | 5.7 ± 1.81 | 5.17 ± 1.50 | 4.01 ± 0.68 | 2.79 ± 0.90 | 3.94 ± 0.98 | 6.22 |
|  | Female (3+2) | 4.20 ± 2.14 | 4.79 ± 2.16 | 5.35 ± 2.01 | 5.08 ± 1.89 | 5.40 ± 1.04 | 4.45 ± 1.66 | 4.69 ± 1.01 | 5.28 ± 0.96 | 3.36 ± 1.05 | 4.85 ± 1.25 | 4.88 ± 0.85 | 4.3 ± 0.79 | 4.32 ± 0.28 | 5.11 ± 1.03 | 4.25 ± 0.64 | 3.92 ± 1.27 | 3.92 ± 1.31 | 8.07 |
| 150 mg/kg/week IV | Male (3+2) | 4.11 ± 0.73 | 3.74 ± 1.02 | 5.17 ± 1.60 | 5.78 ± 1.67 | 5.54 ± 1.89 | 4.69 ± 1.50 | 4.12 ± 1.23 | 4.11 ± 1.47 | 2.39 ± 0.58 | 4.28 ± 1.07 | 4.68 ± 1.19 | 4.26 ± 0.97 | 4.98 ± 1.96 | 4.41 ± 1.28 | **3.3 ± 1.16** | 2.7 ± 0.43 | 3.16 ± 0.73 | 4.05 |
|  | Female (3+2) | 3.59 ± 1.30 | 5.17 ± 2.27 | 5.25 ± 2.15 | 5.00 ± 1.50 | 5.08 ± 1.94 | 4.17 ± 1.56 | 4.07 ± 1.59 | 4.68 ± 1.66 | 3.01 ± 1.24 | 5.84 ± 1.67 | 5.57 ± 1.34 | 4.24 ± 0.91 | 4.44 ± 0.89 | 4.72 ± 1.19 | 3.12 ± 0.72 | 3.42 ± 1.02 | 3.64 ± 1.06 | 3.88 |
| **Monocyte (109/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.57 ± 0.167 | 0.43 ± 0.113 | 0.54 ± 0.079 | 0.78 ± 0.31 | 0.21 ± 0.073 | 0.21 ± 0.070 | 0.21 ± 0.072 | 0.26 ± 0.099 | 0.14 ± 0.041 | 0.21 ± 0.031 | 0.22 ± 0.066 | 0.24 ± 0.08 | 0.2 ± 0.048 | 0.24 ± 0.081 | 0.2 ± 0.026 | 0.14 ± 0.078 | 0.21 ± 0.083 | 0.2 |
|  | Female (3+2) | 0.32 ± 0.084 | 0.48 ± 0.128 | 0.45 ± 0.184 | 0.56 ± 0.247 | 0.81 ± 0.392 | 0.14 ± 0.068 | 0.18 ± 0.111 | 0.19 ± 0.072 | 0.14 ± 0.056 | 0.18 ± 0.062 | 0.19 ± 0.09 | 0.18 ± 0.062 | 0.18 ± 0.06 | 0.21 ± 0.086 | 0.19 ± 0.086 | 0.15 ± 0.06 | 0.19 ± 0.087 | 0.15 |
| 10 mg/kg/week SC | Male (3) | 0.79 ± 0.438 | 0.49 ± 0.29 | 0.59 ± 0.045 | 0.62 ± 0.188 | 0.14 ± 0.021 | 0.16 ± 0.078 | 0.17 ± 0.029 | 0.21 ± 0.061 | 0.16 ± 0.053 | 0.26 ± 0.068 | 0.21 ± 0.036 | 0.19 ± 0.021 | 0.26 ± 0.076 | 0.27 ± 0.058 | 0.23 ± 0.078 | 0.23 ± 0.095 | 0.19 ± 0.085 |  |
|  | Female (3) | 0.76 ± 0.506 | 0.51 ± 0.276 | 0.46 ± 0.252 | 0.58 ± 0.207 | 0.62 ± 0.192 | 0.16 ± 0.049 | 0.17 ± 0.059 | 0.19 ± 0.055 | 0.14 ± 0.067 | 0.23 ± 0.049 | 0.24 ± 0.036 | 0.18 ± 0.091 | 0.21 ± 0.093 | 0.3 ± 0.114 | 0.25 ± 0.164 | 0.18 ± 0.076 | 0.22 ± 0.106 |  |
| 50 mg/kg/week SC | Male (3) | 0.54 ± 0.087 | 0.28 ± 0.091 | 0.39 ± 0.075 | 0.56 ± 0.221 | **0.1 ± 0.031** | 0.1 ± 0.015 | 0.1 ± 0.012 | 0.13 ± 0.025 | 0.12 ± 0.031 | 0.21 ± 0.032 | 0.2 ± 0.13 | 0.21 ± 0.085 | 0.28 ± 0.163 | 0.36 ± 0.229 | 0.21 ± 0.086 | 0.26 ± 0.186 | 0.26 ± 0.055 |  |
|  | Female (3) | 0.4 ± 0.029 | 0.37 ± 0.087 | 0.38 ± 0.304 | 0.45 ± 0.125 | 0.4 ± 0.083 | 0.08 ± 0.006 | 0.13 ± 0.04 | 0.12 ± 0.047 | 0.12 ± 0.076 | 0.12 ± 0.031 | 0.16 ± 0.042 | 0.15 ± 0.015 | 0.18 ± 0.046 | 0.2 ± 0.023 | 0.16 ± 0.031 | 0.12 ± 0.015 | 0.16 ± 0.032 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.48 ± 0.075 | 0.35 ± 0.126 | 0.49 ± 0.123 | 0.5 ± 0.236 | **0.1 ± 0.025** | 0.12 ± 0.044 | 0.13 ± 0.066 | 0.18 ± 0.081 | 0.16 ± 0.151 | 0.23 ± 0.2 | 0.21 ± 0.144 | 0.2 ± 0.15 | 0.24 ± 0.108 | 0.23 ± 0.119 | 0.18 ± 0.09 | 0.15 ± 0.055 | 0.17 ± 0.059 | 0.12 |
|  | Female (3+2) | 0.45 ± 0.1 | 0.45 ± 0.196 | 0.53 ± 0.178 | 0.57 ± 0.218 | 0.63 ± 0.213 | 0.13 ± 0.085 | 0.16 ± 0.099 | 0.15 ± 0.046 | 0.14 ± 0.081 | 0.15 ± 0.051 | 0.18 ± 0.093 | 0.16 ± 0.04 | 0.15 ± 0.058 | 0.2 ± 0.057 | 0.19 ± 0.077 | 0.18 ± 0.058 | 0.16 ± 0.054 | 0.18 |
| 150 mg/kg/week IV | Male (3+2) | 0.6 ± 0.104 | 0.49 ± 0.154 | 0.62 ± 0.244 | 0.85 ± 0.575 | 0.14 ± 0.073 | 0.16 ± 0.085 | 0.16 ± 0.075 | 0.13 ± 0.071 | 0.13 ± 0.059 | 0.21 ± 0.045 | 0.17 ± 0.078 | 0.17 ± 0.112 | 0.19 ± 0.079 | 0.21 ± 0.058 | 0.19 ± 0.131 | 0.17 ± 0.077 | 0.15 ± 0.036 | 0.22 |
|  | Female (3+2) | 0.39 ± 0.059 | 0.58 ± 0.422 | 0.47 ± 0.068 | 0.59 ± 0.182 | 0.58 ± 0.085 | 0.13 ± 0.037 | 0.15 ± 0.086 | 0.16 ± 0.077 | 0.12 ± 0.036 | 0.17 ± 0.058 | 0.18 ± 0.034 | 0.17 ± 0.078 | 0.19 ± 0.078 | 0.27 ± 0.125 | 0.16 ± 0.021 | 0.14 ± 0.044 | 0.16 ± 0.057 | 0.15 |
| **Neutrophil (109/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 6.86 ± 2.79 | 5.4 ± 2.27 | 5.58 ± 3.29 | 6.85 ± 4.31 | 4.35 ± 2.24 | 4.37 ± 2.18 | 4.64 ± 2.34 | 5.39 ± 2.62 | 5.48 ± 3.41 | 5.06 ± 3.42 | 4.95 ± 1.99 | 5.87 ± 2.12 | 4.65 ± 3.31 | 4.1 ± 1.76 | 5.13 ± 3.02 | 5.2 ± 3.35 | 4.36 ± 3.32 | 10.3 |
|  | Female (3+2) | 3.97 ± 2.63 | 4.36 ± 2.78 | 3.07 ± 1.97 | 3.23 ± 1.43 | 6.36 ± 7.37 | 3.45 ± 1.72 | 3.23 ± 1.53 | 3.46 ± 2.66 | 4.62 ± 1.88 | 3.11 ± 2.23 | 4.61 ± 1.68 | 4.41 ± 3.03 | 4 ± 1.66 | 3.94 ± 2.56 | 3.45 ± 1.36 | 4.44 ± 2.04 | 3.91 ± 2.91 | 5.65 |
| 10 mg/kg/week SC | Male (3) | 4.85 ± 2.22 | 4.29 ± 2.88 | 4.85 ± 1.54 | 3.93 ± 0.62 | 3.82 ± 0.95 | 3.85 ± 1.70 | 4.88 ± 1.95 | 3.15 ± 0.49 | 3.67 ± 2.07 | 3.46 ± 2.00 | 3.72 ± 1.92 | 3.55 ± 1.78 | 3.95 ± 2.56 | 4.48 ± 1.87 | 4.87 ± 2.80 | 9.29 ± 2.99 | 4.56 ± 1.88 |  |
|  | Female (3) | 5.66 ± 2.58 | 5.33 ± 4.13 | 5.52 ± 3.95 | 4.04 ± 2.50 | 4.75 ± 1.55 | 7.57 ± 4.31 | 4.01 ± 1.58 | 5.17 ± 3.77 | 6.72 ± 4.28 | 5.82 ± 3.60 | 6.8 ± 2.80 | 6.3 ± 2.61 | 4.2 ± 2.33 | 5.81 ± 1.88 | 5.88 ± 4.31 | 6.94 ± 5.74 | 6.44 ± 5.22 |  |
| 50 mg/kg/week SC | Male (3) | 7.09 ± 0.80 | 4.22 ± 1.79 | 3.88 ± 1.34 | 2.99 ± 0.90 | 5.24 ± 0.89 | 3.45 ± 1.14 | 3.42 ± 0.85 | 3.11 ± 1.40 | 2.88 ± 1.81 | 3.2 ± 1.69 | 2.78 ± 1.10 | 3.16 ± 0.87 | 2.25 ± 0.92 | 5.13 ± 4.39 | 3.16 ± 1.45 | 3.04 ± 1.49 | 3.52 ± 3.06 |  |
|  | Female (3) | 8.88 ± 1.93 | 8.65 ± 2.78 | 7.46 ± 5.23 | 4.82 ± 1.43 | 8.2 ± 1.42 | 6.95 ± 3.49 | 5.31 ± 0.45 | 4.73 ± 1.47 | 8 ± 2.00 | 4.81 ± 0.93 | 8.52 ± 2.19 | 5.88 ± 1.48 | 5.08 ± 0.49 | 4.33 ± 1.89 | 5.28 ± 1.36 | 5.36 ± 1.94 | 2.67 ± 0.65 |  |
| 150 mg/kg/week SC | Male (3+2) | 7.65 ± 2.15 | 5.78 ± 1.40 | 5.14 ± 2.12 | 4.19 ± 1.37 | 3.65 ± 1.24 | 3.99 ± 1.08 | 4.7 ± 2.03 | 5.31 ± 1.93 | 5.29 ± 1.70 | 4.81 ± 0.87 | 4.4 ± 0.61 | 5.65 ± 2.23 | 3.36 ± 0.66 | 4.68 ± 1.53 | 7.35 ± 3.15 | 8.2 ± 4.65 | 4.15 ± 1.53 | 7.81 |
|  | Female (3+2) | 5.93 ± 3.08 | 4.9 ± 2.10 | 4.93 ± 2.27 | 4.2 ± 1.33 | 5.66 ± 2.46 | 6.12 ± 3.39 | 5.65 ± 3.85 | 3.76 ± 1.20 | 8.11 ± 5.53 | 4.12 ± 1.99 | 5.27 ± 2.49 | 4.81 ± 3.31 | 3.45 ± 1.06 | 4.76 ± 2.82 | 4.21 ± 1.57 | 5.08 ± 1.34 | 3.43 ± 2.32 | 5.74 |
| 150 mg/kg/week IV | Male (3+2) | 7.79 ± 2.59 | 8.06 ± 4.21 | 5.64 ± 2.32 | 4.72 ± 2.68 | 5.43 ± 4.20 | 4.72 ± 2.58 | 4.17 ± 2.92 | 3.97 ± 2.26 | 4.89 ± 3.32 | 5.19 ± 1.93 | 4.45 ± 2.13 | 5.38 ± 2.92 | 4.08 ± 2.30 | 3.92 ± 2.56 | 6.51 ± 2.90 | 4.81 ± 1.67 | 4.19 ± 2.51 | 11.27 |
|  | Female (3+2) | 3.9 ± 0.91 | 4.13 ± 2.00 | 4.77 ± 2.89 | 3.44 ± 0.97 | 2.81 ± 0.89 | 3.18 ± 0.74 | 3.05 ± 0.32 | 3.45 ± 0.90 | 4.15 ± 1.51 | 3.26 ± 1.48 | 4.39 ± 1.33 | 4.24 ± 2.22 | 3.94 ± 1.59 | 4.64 ± 1.85 | 4.87 ± 1.81 | 4.8 ± 3.89 | 2.65 ± 1.37 | 4.44 |
| **Eosinophil (109/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.07 ± 0.051 | 0.03 ± 0.032 | 0.06 ± 0.047 | 0.06 ± 0.06 | 0.15 ± 0.084 | 0.17 ± 0.088 | 0.19 ± 0.112 | 0.24 ± 0.069 | 0.07 ± 0.041 | 0.18 ± 0.076 | 0.16 ± 0.110 | 0.19 ± 0.153 | 0.19 ± 0.125 | 0.13 ± 0.079 | 0.11 ± 0.066 | 0.03 ± 0.024 | 0.14 ± 0.140 | 0.02 |
|  | Female (3+2) | 0.04 ± 0.039 | 0.22 ± 0.167 | 0.21 ± 0.133 | 0.19 ± 0.142 | 0.17 ± 0.119 | 0.11 ± 0.052 | 0.16 ± 0.098 | 0.17 ± 0.108 | 0.07 ± 0.065 | 0.19 ± 0.123 | 0.23 ± 0.161 | 0.21 ± 0.138 | 0.17 ± 0.106 | 0.25 ± 0.171 | 0.26 ± 0.266 | 0.13 ± 0.092 | 0.22 ± 0.218 | 0.07 |
| 10 mg/kg/week SC | Male (3) | 0.04 ± 0.023 | 0.02 ± 0.028 | 0.18 ± 0.216 | 0.12 ± 0.081 | 0.16 ± 0.199 | 0.17 ± 0.201 | 0.18 ± 0.22 | 0.10 ± 0.106 | 0.02 ± 0.035 | 0.14 ± 0.105 | 0.29 ± 0.355 | 0.26 ± 0.150 | 0.27 ± 0.234 | 0.20 ± 0.100 | 0.13 ± 0.131 | 0.04 ± 0.032 | 0.09 ± 0.050 |  |
|  | Female (3) | 0.03 ± 0.044 | 0.16 ± 0.217 | 0.15 ± 0.146 | 0.16 ± 0.178 | 0.23 ± 0.204 | 0.14 ± 0.125 | 0.17 ± 0.197 | 0.11 ± 0.061 | 0.13 ± 0.165 | 0.17 ± 0.142 | 0.21 ± 0.140 | 0.23 ± 0.164 | 0.16 ± 0.095 | 0.25 ± 0.240 | 0.10 ± 0.123 | 0.10 ± 0.085 | 0.10 ± 0.031 |  |
| 50 mg/kg/week SC | Male (3) | 0.06 ± 0.098 | 0.04 ± 0.075 | 0.24 ± 0.306 | 0.31 ± 0.453 | 0.32 ± 0.401 | 0.18 ± 0.197 | 0.17 ± 0.184 | 0.14 ± 0.155 | 0.08 ± 0.121 | 0.25 ± 0.236 | 0.31 ± 0.353 | 0.40 ± 0.279 | 0.26 ± 0.174 | 0.32 ± 0.170 | 0.25 ± 0.217 | 0.21 ± 0.275 | 0.31 ± 0.399 |  |
|  | Female (3) | 0.01 ± 0.012 | 0.06 ± 0.017 | 0.11 ± 0.079 | 0.09 ± 0.012 | 0.26 ± 0.053 | 0.05 ± 0.012 | 0.08 ± 0.025 | 0.06 ± 0.032 | 0.06 ± 0.064 | 0.11 ± 0.110 | 0.21 ± 0.289 | 0.11 ± 0.055 | 0.11 ± 0.081 | 0.07 ± 0.04 | 0.07 ± 0.025 | 0.05 ± 0.026 | 0.12 ± 0.047 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.02 ± 0.023 | 0.03 ± 0.035 | 0.12 ± 0.128 | 0.13 ± 0.074 | 0.19 ± 0.118 | 0.14 ± 0.074 | 0.16 ± 0.174 | 0.22 ± 0.267 | 0.10 ± 0.181 | 0.28 ± 0.339 | 0.36 ± 0.496 | 0.28 ± 0.317 | 0.21 ± 0.151 | 0.2 ± 0.113 | 0.15 ± 0.093 | 0.05 ± 0.051 | 0.13 ± 0.071 | 0.03 |
|  | Female (3+2) | 0.05 ± 0.048 | 0.10 ± 0.100 | 0.12 ± 0.101 | 0.12 ± 0.073 | 0.18 ± 0.066 | 0.11 ± 0.076 | 0.19 ± 0.125 | 0.16 ± 0.079 | 0.07 ± 0.041 | 0.17 ± 0.078 | 0.20 ± 0.087 | 0.14 ± 0.051 | 0.20 ± 0.140 | 0.23 ± 0.133 | 0.20 ± 0.160 | 0.12 ± 0.101 | 0.13 ± 0.124 | 0.09 |
| 150 mg/kg/week IV | Male (3+2) | 0.04 ± 0.036 | 0.09 ± 0.150 | 0.21 ± 0.122 | 0.14 ± 0.151 | 0.36 ± 0.315 | 0.18 ± 0.157 | 0.09 ± 0.074 | 0.09 ± 0.064 | 0.02 ± 0.013 | 0.16 ± 0.126 | 0.15 ± 0.122 | 0.22 ± 0.196 | 0.11 ± 0.046 | 0.09 ± 0.078 | 0.08 ± 0.034 | 0.02 ± 0.016 | 0.09 ± 0.047 | 0.05 |
|  | Female (3+2) | 0.04 ± 0.045 | 0.12 ± 0.078 | 0.30 ± 0.325 | 0.33 ± 0.294 | 0.38 ± 0.302 | 0.13 ± 0.073 | 0.12 ± 0.085 | 0.18 ± 0.119 | 0.08 ± 0.047 | 0.30 ± 0.216 | 0.35 ± 0.278 | 0.25 ± 0.136 | 0.15 ± 0.091 | 0.25 ± 0.156 | 0.11 ± 0.129 | 0.09 ± 0.07 | 0.17 ± 0.130 | 0.11 |
| **Basophil (109/L)** | | | | | | | | | | | | | | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.04 ± 0.041 | 0.02 ± 0.004 | 0.03 ± 0.010 | 0.03 ± 0.009 | 0.06 ± 0.023 | 0.04 ± 0.011 | 0.05 ± 0.019 | 0.05 ± 0.016 | 0.03 ± 0.013 | 0.04 ± 0.009 | 0.05 ± 0.013 | 0.03 ± 0.007 | 0.04 ± 0.020 | 0.04 ± 0.022 | 0.03 ± 0.011 | 0.03 ± 0.007 | 0.04 ± 0.011 | 0.03 |
|  | Female (3+2) | 0.01 ± 0.005 | 0.02 ± 0.013 | 0.03 ± 0.008 | 0.02 ± 0.008 | 0.02 ± 0.011 | 0.03 ± 0.023 | 0.04 ± 0.011 | 0.03 ± 0.011 | 0.03 ± 0.005 | 0.04 ± 0.022 | 0.04 ± 0.015 | 0.03 ± 0.019 | 0.04 ± 0.016 | 0.04 ± 0.016 | 0.04 ± 0.028 | 0.03 ± 0.011 | 0.03 ± 0.008 | 0.03 |
| 10 mg/kg/week SC | Male (3) | 0.02 ± 0.010 | 0.02 ± 0.007 | 0.01 ± 0.000 | 0.01 ± 0.006 | **0.02 ± 0.010** | **0.01 ± 0.012** | 0.02 ± 0.015 | 0.02 ± 0.010 | 0.01 ± 0.010 | 0.02 ± 0.010 | 0.02 ± 0.006 | 0.01 ± 0.006 | 0.03 ± 0.000 | 0.03 ± 0.006 | 0.02 ± 0.006 | 0.01 ± 0.006 | 0.02 ± 0.006 |  |
|  | Female (3) | 0.02 ± 0.012 | 0.02 ± 0.006 | 0.01 ± 0.006 | 0.01 ± 0.000 | 0.01 ± 0.000 | 0.02 ± 0.006 | 0.02 ± 0.006 | 0.01 ± 0.000 | 0.01 ± 0.006 | 0.02 ± 0.006 | 0.03 ± 0.006 | 0.02 ± 0.000 | 0.02 ± 0.010 | 0.01 ± 0.012 | 0.02 ± 0.010 | 0.01 ± 0.006 | 0.02 ± 0.010 |  |
| 50 mg/kg/week SC | Male (3) | 0.02 ± 0.006 | 0.01 ± 0.006 | 0.01 ± 0.000 | 0.01 ± 0.006 | **0.02 ± 0.015** | **0.02 ± 0**.**000** | **0.02 ± 0**.**000** | 0.02 ± 0.000 | 0.01 ± 0.006 | 0.02 ± 0.006 | 0.02 ± 0.015 | 0.02 ± 0.015 | 0.03 ± 0.015 | 0.03 ± 0.015 | 0.03 ± 0.010 | 0.03 ± 0.015 | 0.03 ± 0.012 |  |
|  | Female (3) | 0.02 ± 0.010 | 0.01 ± 0.006 | 0.01 ± 0.006 | 0.01 ± 0.006 | 0.01 ± 0.006 | 0.01 ± 0.006 | 0.02 ± 0.012 | 0.02 ± 0.006 | 0.02 ± 0.006 | 0.02 ± 0.006 | 0.02 ± 0.006 | 0.01 ± 0.000 | 0.02 ± 0.006 | 0.02 ± 0.006 | 0.01 ± 0.006 | 0.01 ± 0.006 | **0.01 ± 0.000** |  |
| 150 mg/kg/week SC | Male (3+2) | 0.02 ± 0.009 | 0.01 ± 0.004 | 0.01 ± 0.005 | 0.01 ± 0.008 | **0.02 ± 0.007** | **0.02 ± 0.013** | 0.03 ± 0.011 | 0.03 ± 0.025 | 0.02 ± 0.023 | 0.04 ± 0.032 | 0.05 ± 0.068 | 0.03 ± 0.028 | 0.03 ± 0.019 | 0.03 ± 0.02 | 0.03 ± 0.016 | 0.02 ± 0.009 | 0.02 ± 0.01 | 0.03 |
|  | Female (3+2) | 0.03 ± 0.007 | 0.02 ± 0.005 | 0.03 ± 0.018 | 0.01 ± 0.005 | 0.02 ± 0.005 | 0.02 ± 0.004 | 0.02 ± 0.008 | 0.02 ± 0.007 | 0.02 ± 0.009 | 0.02 ± 0.007 | 0.02 ± 0.009 | 0.03 ± 0.000 | 0.03 ± 0.008 | 0.04 ± 0.021 | 0.03 ± 0.013 | 0.02 ± 0.011 | 0.03 ± 0.012 | 0.05 |
| 150 mg/kg/week IV | Male (3+2) | 0.02 ± 0.005 | 0.02 ± 0.005 | 0.01 ± 0.004 | 0.02 ± 0.012 | **0.02 ± 0.009** | **0.02 ± 0.008** | **0.02 ± 0.014** | **0.02 ± 0.008** | 0.01 ± 0.004 | 0.02 ± 0.008 | 0.02 ± 0.015 | 0.01 ± 0.005 | 0.02 ± 0.019 | 0.02 ± 0.008 | 0.02 ± 0.004 | **0.01 ± 0.005** | **0.02 ± 0.009** | 0.04 |
|  | Female (3+2) | 0.02 ± 0.008 | 0.01 ± 0.005 | 0.02 ± 0.008 | 0.01 ± 0.004 | 0.02 ± 0.011 | 0.01 ± 0.009 | **0.02 ± 0.015** | 0.03 ± 0.021 | **0.01 ± 0.008** | 0.03 ± 0.015 | 0.02 ± 0.011 | 0.02 ± 0.004 | 0.02 ± 0.009 | 0.03 ± 0.009 | 0.02 ± 0.008 | 0.02 ± 0.008 | 0.01 ± 0.005 | 0.03 |

Standard deviation not calculated for less than three values

\* Number of animals at 0 mg/kg/week SC, 150 mg/kg/week SC and 150 mg/kg/week IV is a total of 5 (3+2) per sex in predose and dosing phase and of 2 per sex in recovery

Table 6. Summary of coagulation data. Bolded values were statistically significant from the respective control group (P ≤ 0.05).

|  |  | Predose | Dosing | | Recovery |
| --- | --- | --- | --- | --- | --- |
| Parameter Treatment | Sex (No animal)\* | D1 | D48 | D86 | D204 |
| **Fibrinogen (g/L)** |  |  |  |  |  |
| 0 mg/kg/week SC | Male (3+2) | 2.42 ± 0.502 | 2.00 ± 0.265 | 2.02 ± 0.268 | 1.50 |
|  | Female (3+2) | 2.02 ± 0.259 | 1.88 ± 0.327 | 1.88 ± 0.148 | 1.50 |
| 10 mg/kg/week SC | Male (3) | 2.23 ± 0.058 | 1.87 ± 0.058 | 1.97 ± 0.153 |  |
|  | Female (3) | 2.10 ± 0.781 | 1.70 ± 0 | 1.70 ± 0 |  |
| 50 mg/kg/week SC | Male (3) | 2.20 ± 0.265 | 1.77 ± 0.306 | 2.93 ± 1.137 |  |
|  | Female (3) | 2.10 ± 0.200 | 1.77 ± 0.252 | 1.87 ± 0.208 |  |
| 150 mg/kg/week SC | Male (3+2) | 1.90 ± 0.430 | 1.82 ± 0.045 | 1.88 ± 0.249 | 1.50 |
|  | Female (3+2) | 1.98 ± 0.192 | 2.08 ± 0.249 | 1.88 ± 0.228 | 1.40 |
| 150 mg/kg/week IV | Male (3+2) | 2.14 ± 0.207 | 1.92 ± 0.179 | 2.00 ± 0.212 | 1.90 |
|  | Female (3+2) | 1.96 ± 0.089 | 1.98 ± 0.11 | 2.08 ± 0.192 | 1.50 |
| **Prothrombin time (s)** |  |  |  |  |  |
| 0 mg/kg/week SC | Male (3+2) | 16.6 ± 1.76 | 16.7 ± 0.64 | 16.4 ± 0.15 | 15.9 |
|  | Female (3+2) | 17.0 ± 1.98 | 17.4 ± 1.95 | 16.4 ± 1.04 | 16.0 |
| 10 mg/kg/week SC | Male (3) | 16.2 ± 0.61 | 17.2 ± 0.66 | 16.2 ± 0.10 |  |
|  | Female (3) | 15.5 ± 0.66 | 15.6 ± 0.95 | 16.7 ± 0.25 |  |
| 50 mg/kg/week SC | Male (3) | 16.5 ± 1.86 | 15.9 ± 1.33 | 14.0 ± 1.19 |  |
|  | Female (3) | 15.1 ± 0.44 | 16.4 ± 2.48 | 15.9 ± 1.80 |  |
| 150 mg/kg/week SC | Male (3+2) | 15.3 ± 1.87 | 16.0 ± 1.09 | 16.0 ± 0.89 | 16.6 |
|  | Female (3+2) | 16.0 ± 2.26 | 17.1 ± 1.63 | 16.5 ± 0.99 | 17.0 |
| 150 mg/kg/week IV | Male (3+2) | 18.0 ± 4.29 | 17.6 ± 3.53 | 17.1 ± 2.93 | 18.6 |
|  | Female (3+2) | 16.2 ± 1.25 | 16.9 ± 2.13 | 16.7 ± 1.31 | 16.6 |
| **Activated partial thromboplastin time (s)** |  |  |  |  |  |
| 0 mg/kg/week SC | Male (3+2) | 20.0 ± 2.23 | 19.4 ± 1.36 | 18.6 ± 1.56 | 17.9 |
|  | Female (3+2) | 19.7 ± 1.42 | 19.4 ± 2.56 | 19.4 ± 1.23 | 18.4 |
| 10 mg/kg/week SC | Male (3) | 19.6 ± 1.82 | 18.5 ± 1.85 | 18.8 ± 2.49 |  |
|  | Female (3) | 19.3 ± 1.35 | 18.6 ± 1.11 | 19.8 ± 1.33 |  |
| 50 mg/kg/week SC | Male (3) | 20 ± 1.33 | 18.0 ± 1.7 | 18.8 ± 2.19 |  |
|  | Female (3) | 19.5 ± 0.72 | 18.6 ± 2.14 | 18.4 ± 1.86 |  |
| 150 mg/kg/week SC | Male (3+2) | 18.4 ± 1.97 | 18.2 ± 1.18 | 18.3 ± 1.56 | 18 |
|  | Female (3+2) | 21.4 ± 1.8 | 19.9 ± 1.57 | 20.3 ± 1.19 | 20.6 |
| 150 mg/kg/week IV | Male (3+2) | 20.4 ± 1.45 | 19.4 ± 0.91 | 18.6 ± 1.05 | 19.7 |
|  | Female (3+2) | 19.5 ± 0.62 | 18.3 ± 1.26 | 18.0 ± 0.94 | 18 |

Standard deviation not calculated for less than three values

\* Number of animals at 0 mg/kg/week SC, 150 mg/kg/week SC and 150 mg/kg/week IV is a total of 5 (3+2) per sex in predose and dosing phase and of 2 per sex in recovery

Table 7. Summary of clinical chemistry data. Bolded values were statistically significant from the respective control group (P ≤ 0.05).

|  |  | Predose | Dosing |  | Recovery |
| --- | --- | --- | --- | --- | --- |
| Parameter Treatment | Sex (No animal)\* | D1 | D48 | D86 | D204 |
| **Total bilirubin (μmol/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 5.13 ± 1.12 | 4.67 ± 1.47 | 6.00 ± 1.18 | 5.09 |
|  | Female (3+2) | 5.09 ± 1.38 | 4.44 ± 1.05 | 4.05 ± 0.46 | 4.97 |
| 10 mg/kg/week SC | Male (3) | 4.93 ± 0.49 | 4.82 ± 1.18 | 5.83 ± 0.31 |  |
|  | Female (3) | 4.19 ± 0.49 | 4.28 ± 0.27 | 4.00 ± 0.07 |  |
| 50 mg/kg/week SC | Male (3) | 4.62 ± 0.57 | 5.32 ± 0.91 | 5.99 ± 1.10 |  |
|  | Female (3) | 4.29 ± 0.43 | 4.49 ± 0.27 | 4.02 ± 0.25 |  |
| 150 mg/kg/week SC | Male (3+2) | 4.85 ± 0.65 | 4.38 ± 0.65 | 6.67 ± 1.52 | 5.87 |
|  | Female (3+2) | 4.40 ± 0.39 | 4.13 ± 0.31 | 3.74 ± 0.44 | 4.62 |
| 150 mg/kg/week IV | Male (3+2) | 6.01 ± 1.25 | 5.36 ± 0.63 | 7.01 ± 2.04 | 5.63 |
|  | Female (3+2) | 4.66 ± 1.10 | 4.96 ± 1.33 | 4.61 ± 1.38 | 7.03 |
| **Creatinine (μmol/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 73.55 ± 4.54 | 72.92 ± 5.31 | 75.59 ± 6.40 | 73.82 |
|  | Female (3+2) | 77.73 ± 4.08 | 68.64 ± 7.85 | 60.99 ± 3.96 | 64.03 |
| 10 mg/kg/week SC | Male (3) | 66.73 ± 1.65 | 67.71 ± 3.85 | 62.21 ± 1.81 |  |
|  | Female (3) | 73.53 ± 4.36 | 68.24 ± 5.08 | 61.84 ± 3.15 |  |
| 50 mg/kg/week SC | Male (3) | 68.71 ± 6.55 | 70.74 ± 11.06 | 63.29 ± 7.96 |  |
|  | Female (3) | 68.73 ± 2.70 | 70.53 ± 4.94 | 61.81 ± 2.61 |  |
| 150 mg/kg/week SC | Male (3+2) | 76.50 ± 8.93 | 75.76 ± 8.88 | 77.10 ± 8.65 | 75.09 |
|  | Female (3+2) | 74.13 ± 6.64 | 72.79 ± 6.73 | 64.13 ± 3.86 | 63.94 |
| 150 mg/kg/week IV | Male (3+2) | 77.13 ± 8.04 | 79.23 ± 8.52 | 81.21 ± 6.04 | 88.03 |
|  | Female (3+2) | 69.28 ± 6.31 | 66.64 ± 5.52 | 61.90 ± 5.29 | 64.80 |
| **Blood urea (mmol/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 6.30 ± 1.00 | 5.96 ± 0.23 | 5.56 ± 0.79 | 5.72 |
|  | Female (3+2) | 7.07 ± 1.32 | 7.24 ± 1.76 | 5.57 ± 0.82 | 6.98 |
| 10 mg/kg/week SC | Male (3) | 6.42 ± 0.493 | 7.75 ± 1.07 | 6.52 ± 0.64 |  |
|  | Female (3) | 8.41 ± 0.51 | 7.47 ± 0.78 | 6.67 ± 1.07 |  |
| 50 mg/kg/week SC | Male (3) | 6.47 ± 0.55 | **8.10 ± 0.92** | 6.95 ± 0.53 |  |
|  | Female (3) | 6.79 ± 0.88 | 6.70 ± 1.19 | 5.05 ± 1.26 |  |
| 150 mg/kg/week SC | Male (3+2) | 6.05 ± 0.74 | 6.77 ± 1.36 | 6.56 ± 0.79 | 6.97 |
|  | Female (3+2) | 6.44 ± 1.24 | 6.18 ± 1.29 | 4.75 ± 1.21 | 6.71 |
| 150 mg/kg/week IV | Male (3+2) | 7.30 ± 1.68 | **7.85 ± 1.16** | 7.32 ± 1.19 | 8.52 |
|  | Female (3+2) | 6.57 ± 1.21 | 6.34 ± 0.79 | 5.94 ± 1.47 | 6.28 |
| **Glutamate dehydrogenase (U/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 14.28 ± 3.88 | 15.63 ± 2.15 | 17.23 ± 5.99 | 24.00 |
|  | Female (3+2) | 13.16 ± 3.85 | 12.37 ± 2.41 | 15.36 ± 3.55 | 68.39 |
| 10 mg/kg/week SC | Male (3) | 15.59 ± 9.97 | 13.85 ± 3.78 | 14.98 ± 4.60 |  |
|  | Female (3) | 12.8 ± 2.72 | 13.27 ± 8.39 | 14.74 ± 4.44 |  |
| 50 mg/kg/week SC | Male (3) | 12.51 ± 0.81 | 16.24 ± 1.20 | 14.37 ± 3.34 |  |
|  | Female (3) | 14.50 ± 5.55 | 10.70 ± 4.32 | 16.18 ± 6.30 |  |
| 150 mg/kg/week SC | Male (3+2) | 11.92 ± 2.17 | 39.26 ± 35.39 | 21.03 ± 10.31 | 18.15 |
|  | Female (3+2) | 13.34 ± 3.35 | 11.29 ± 2.09 | 13.59 ± 1.64 | 14.53 |
| 150 mg/kg/week IV | Male (3+2) | 15.75 ± 7.47 | 26.54 ± 25.59 | 21.68 ± 14.29 | 12.26 |
|  | Female (3+2) | 18.24 ± 11.42 | 13.55 ± 6.28 | 19.45 ± 14.60 | 13.74 |
| **Aspartate aminotransferase (U/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 45.60 ± 12.27 | 41.92 ± 8.40 | 56.45 ± 11.98 | 46.12 |
|  | Female (3+2) | 32.48 ± 4.42 | 31.10 ± 1.97 | 42.69 ± 9.04 | 36.74 |
| 10 mg/kg/week SC | Male (3) | 35.90 ± 8.09 | 33.75 ± 1.51 | 41.41 ± 4.27 |  |
|  | Female (3) | **24.13 ± 3.68** | 22.31 ± 2.03 | 37.92 ± 10.98 |  |
| 50 mg/kg/week SC | Male (3) | 33.92 ± 3.79 | 31.21 ± 7.04 | 42.32 ± 15.71 |  |
|  | Female (3) | 48.81 ± 10.10 | 31.02 ± 6.15 | 60.51 ± 18.42 |  |
| 150 mg/kg/week SC | Male (3+2) | 43.70 ± 12.92 | 57.34 ± 39.05 | 85.65 ± 38.78 | 46.7 |
|  | Female (3+2) | 29.44 ± 0.99 | 28.13 ± 4.51 | 36.17 ± 7.33 | 38.52 |
| 150 mg/kg/week IV | Male (3+2) | 49.96 ± 16.09 | 48.30 ± 10.56 | 124.91 ± 145.03 | 36.53 |
|  | Female (3+2) | 37.98 ± 8.62 | 34.16 ± 15.81 | 54.73 ± 39.59 | 28.81 |
| **Alanine aminotransferase (U/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 36.51 ± 8.44 | 34.88 ± 6.07 | 48.07 ± 7.95 | 55.91 |
|  | Female (3+2) | 35.24 ± 14.07 | 29.86 ± 4.90 | 34.81 ± 8.45 | 85.18 |
| 10 mg/kg/week SC | Male (3) | 34.43 ± 12.08 | 31.93 ± 6.50 | 34.46 ± 7.76 |  |
|  | Female (3) | 25.77 ± 5.66 | 31.56 ± 17.21 | 39.57 ± 9.62 |  |
| 50 mg/kg/week SC | Male (3) | 35.16 ± 2.99 | 37.06 ± 2.07 | 38.08 ± 12.28 |  |
|  | Female (3) | 39.01 ± 19.09 | 33.05 ± 11.36 | 50.53 ± 23.51 |  |
| 150 mg/kg/week SC | Male (3+2) | 47.07 ± 14.58 | 87.64 ± 60.56 | 93.55 ± 40.80 | 50.05 |
|  | Female (3+2) | 33.14 ± 5.31 | 36.63 ± 9.66 | 40.83 ± 11.62 | 41.70 |
| 150 mg/kg/week IV | Male (3+2) | 39.96 ± 12.51 | 51.75 ± 33.05 | 71.39 ± 31.01 | 39.42 |
|  | Female (3+2) | 46.49 ± 16.97 | 34.17 ± 11.00 | 46.42 ± 30.47 | 30.65 |
| **Alkaline phosphatase (U/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 381.51 ± 115.74 | 450.05 ± 98.08 | 505.66 ± 86.14 | 443.42 |
|  | Female (3+2) | 393.46 ± 93.13 | 380.85 ± 104.02 | 412.56 ± 142.67 | 277.87 |
| 10 mg/kg/week SC | Male (3) | **715.61 ± 170.16** | 697.88 ± 127.65 | 784.53 ± 320.83 |  |
|  | Female (3) | 401.67 ± 26.78 | 421.13 ± 59.53 | 378.70 ± 41.42 |  |
| 50 mg/kg/week SC | Male (3) | 424.02 ± 78.54 | 385.53 ± 78.87 | 472.71 ± 178.83 |  |
|  | Female (3) | 433.54 ± 132.11 | 386.33 ± 144.72 | 389.48 ± 101.65 |  |
| 150 mg/kg/week SC | Male (3+2) | 316.86 ± 80.17 | 391.06 ± 167.17 | 426.71 ± 192.58 | 536.26 |
|  | Female (3+2) | 394.41 ± 42.90 | 441.86 ± 84.40 | 434.39 ± 74.70 | 468.36 |
| 150 mg/kg/week IV | Male (3+2) | 426.95 ± 107.48 | 485.3 ± 121.92 | 440.17 ± 155.76 | 434.31 |
|  | Female (3+2) | 509.19 ± 172.08 | 497.43 ± 124.49 | 442.32 ± 127.93 | 366.65 |
| **Gamma glutamyl transferase (U/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 56.93 ± 10.42 | 59.70 ± 12.13 | 52.78 ± 7.78 | 59.76 |
|  | Female (3+2) | 60.33 ± 15.19 | 55.48 ± 12.56 | 47.94 ± 11.71 | 47.58 |
| 10 mg/kg/week SC | Male (3) | 71.75 ± 9.49 | 68.44 ± 6.92 | 60.37 ± 4.73 |  |
|  | Female (3) | 71.88 ± 7.86 | 65.60 ± 2.22 | 49.52 ± 1.93 |  |
| 50 mg/kg/week SC | Male (3) | 73.00 ± 12.80 | 71.37 ± 10.14 | 39.06 ± 9.80 |  |
|  | Female (3) | 65.60 ± 8.13 | 60.42 ± 10.99 | 50.93 ± 4.86 |  |
| 150 mg/kg/week SC | Male (3+2) | 57.24 ± 15.09 | 62.06 ± 23.31 | 52.18 ± 17.98 | 76.35 |
|  | Female (3+2) | 72.22 ± 18.70 | 66.58 ± 19.74 | 54.01 ± 10.50 | 67.55 |
| 150 mg/kg/week IV | Male (3+2) | 66.99 ± 10.61 | 74.73 ± 13.27 | 57.14 ± 13.11 | 67.13 |
|  | Female (3+2) | 79.40 ± 11.74 | 76.86 ± 6.50 | 55.18 ± 9.96 | 75.20 |
| **Glucose (mmol/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 5.01 ± 0.52 | 4.03 ± 0.39 | 4.42 ± 0.58 | 3.92 |
|  | Female (3+2) | 4.56 ± 0.66 | 5.22 ± 0.66 | 4.45 ± 0.32 | 3.39 |
| 10 mg/kg/week SC | Male (3) | 4.40 ± 0.88 | 3.67 ± 0.65 | **2.91 ± 0.43** |  |
|  | Female (3) | 5.33 ± 0.43 | 5.26 ± 0.85 | 4.39 ± 0.44 |  |
| 50 mg/kg/week SC | Male (3) | 5.09 ± 0.45 | 3.74 ± 0.57 | 3.76 ± 0.61 |  |
|  | Female (3) | 4.47 ± 0.56 | 5.92 ± 0.74 | 5.07 ± 0.92 |  |
| 150 mg/kg/week SC | Male (3+2) | 4.34 ± 0.30 | 3.80 ± 0.39 | **3.38 ± 0.42** | 3.82 |
|  | Female (3+2) | 4.69 ± 0.84 | 5.35 ± 0.71 | 5.26 ± 1.28 | 3.82 |
| 150 mg/kg/week IV | Male (3+2) | 4.30 ± 0.74 | 3.76 ± 0.47 | 3.86 ± 0.29 | 4.13 |
|  | Female (3+2) | 4.87 ± 0.92 | 4.76 ± 0.35 | 4.45 ± 0.71 | 4.02 |
| **Cholesterol (mmol/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 4.13 ± 0.74 | 4.48 ± 0.37 | 4.12 ± 0.62 | 4.16 |
|  | Female (3+2) | 3.60 ± 0.74 | 3.55 ± 0.50 | 3.30 ± 0.47 | 2.86 |
| 10 mg/kg/week SC | Male (3) | 3.81 ± 0.57 | 3.84 ± 0.48 | 3.81 ± 0.77 |  |
|  | Female (3) | 3.17 ± 0.11 | 3.49 ± 0.27 | 3.12 ± 0.52 |  |
| 50 mg/kg/week SC | Male (3) | 3.40 ± 0.26 | 3.93 ± 0.40 | 2.94 ± 0.47 |  |
|  | Female (3) | 4.35 ± 1.11 | 4.26 ± 0.75 | 4.10 ± 0.37 |  |
| 150 mg/kg/week SC | Male (3+2) | 4.23 ± 1.06 | 4.55 ± 0.88 | 3.95 ± 0.77 | 3.26 |
|  | Female (3+2) | 3.86 ± 0.50 | 3.95 ± 0.87 | 3.60 ± 0.52 | 3.89 |
| 150 mg/kg/week IV | Male (3+2) | 4.74 ± 0.97 | 4.53 ± 0.52 | 4.28 ± 0.98 | 4.98 |
|  | Female (3+2) | 3.39 ± 0.50 | 3.54 ± 0.50 | 3.00 ± 0.54 | 3.58 |
| **Triglyceride (mmol/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.55 ± 0.16 | 0.6 ± 0.22 | 0.49 ± 0.10 | 0.50 |
|  | Female (3+2) | 0.40 ± 0.13 | 0.72 ± 0.45 | 0.87 ± 0.43 | 1.03 |
| 10 mg/kg/week SC | Male (3) | 0.43 ± 0.07 | 0.77 ± 0.04 | 0.69 ± 0.17 |  |
|  | Female (3) | 0.37 ± 0.02 | 0.85 ± 0.55 | 0.95 ± 0.40 |  |
| 50 mg/kg/week SC | Male (3) | 0.43 ± 0.10 | 0.57 ± 0.04 | 2.10 ± 1.49 |  |
|  | Female (3) | 0.40 ± 0.14 | 0.74 ± 0.11 | 0.75 ± 0.19 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.47 ± 0.10 | 0.62 ± 0.09 | 0.53 ± 0.10 | 0.46 |
|  | Female (3+2) | 0.34 ± 0.09 | 0.55 ± 0.18 | 0.69 ± 0.20 | 0.48 |
| 150 mg/kg/week IV | Male (3+2) | 0.51 ± 0.25 | 0.57 ± 0.06 | 0.41 ± 0.11 | 0.61 |
|  | Female (3+2) | 0.34 ± 0.112 | 0.45 ± 0.113 | 0.74 ± 0.316 | 0.53 |
| **Total protein (g/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 82.28 ± 3.73 | 81.86 ± 2.59 | 77.62 ± 4.40 | 81.66 |
|  | Female (3+2) | 71.68 ± 3.13 | 74.06 ± 3.41 | 68.94 ± 2.05 | 66.06 |
| 10 mg/kg/week SC | Male (3) | 81.60 ± 4.52 | **76.00 ± 2.16** | **71.19 ± 1.13** |  |
|  | Female (3) | 71.45 ± 2.56 | 73.07 ± 6.07 | 67.68 ± 4.67 |  |
| 50 mg/kg/week SC | Male (3) | 77.34 ± 4.39 | **75.49 ± 2.35** | **63.56 ± 6.51** |  |
|  | Female (3) | 80.18 ± 5.34 | 75.58 ± 1.25 | 71.35 ± 3.77 |  |
| 150 mg/kg/week SC | Male (3+2) | 79.13 ± 2.11 | 80.99 ± 3.02 | 75.05 ± 1.57 | 74.28 |
|  | Female (3+2) | 77.32 ± 3.55 | 77.48 ± 5.43 | 73.03 ± 5.39 | 76.80 |
| 150 mg/kg/week IV | Male (3+2) | 79.42 ± 2.50 | 81.24 ± 2.12 | 79.56 ± 1.22 | 78.89 |
|  | Female (3+2) | 75.33 ± 5.64 | 75.99 ± 4.45 | 69.46 ± 3.94 | 71.25 |
| **Albumin (g/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 47.60 ± 4.77 | 46.05 ± 4.72 | 42.36 ± 1.55 | 42.49 |
|  | Female (3+2) | 46.55 ± 5.28 | 47.27 ± 4.32 | 41.64 ± 2.20 | 39.98 |
| 10 mg/kg/week SC | Male (3) | 50.92 ± 5.48 | 48.60 ± 4.59 | 42.09 ± 0.81 |  |
|  | Female (3) | 45.31 ± 5.90 | 48.59 ± 5.32 | 42.76 ± 2.36 |  |
| 50 mg/kg/week SC | Male (3) | 50.18 ± 5.02 | 48.40 ± 4.37 | 34.90 ± 6.84 |  |
|  | Female (3) | 46.87 ± 7.25 | 45.87 ± 3.83 | 41.38 ± 2.24 |  |
| 150 mg/kg/week SC | Male (3+2) | 49.19 ± 5.72 | 47.98 ± 5.39 | 41.96 ± 2.08 | 42.32 |
|  | Female (3+2) | 48.32 ± 5.96 | 49.86 ± 6.00 | 42.49 ± 2.19 | 47.24 |
| 150 mg/kg/week IV | Male (3+2) | 51.85 ± 4.98 | 51.50 ± 0.89 | 44.27 ± 2.37 | 47.52 |
|  | Female (3+2) | 52.90 ± 5.49 | 50.29 ± 5.07 | 41.14 ± 2.01 | 45.27 |
| **Globulin (g/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 34.67 ± 4.67 | 35.81 ± 3.49 | 35.25 ± 3.59 | 39.18 |
|  | Female (3+2) | 25.12 ± 6.50 | 26.79 ± 6.07 | 27.30 ± 2.67 | 26.09 |
| 10 mg/kg/week SC | Male (3) | 30.67 ± 3.46 | **27.40 ± 2.90** | **29.10 ± 1.73** |  |
|  | Female (3) | 26.14 ± 5.02 | 24.49 ± 1.02 | 24.92 ± 2.31 |  |
| 50 mg/kg/week SC | Male (3) | 27.16 ± 1.35 | **27.09 ± 2.34** | **28.66 ± 0.44** |  |
|  | Female (3) | 33.31 ± 4.06 | 29.71 ± 2.74 | 29.97 ± 2.68 |  |
| 150 mg/kg/week SC | Male (3+2) | 29.94 ± 7.11 | 33.01 ± 4.68 | 33.09 ± 2.19 | 31.96 |
|  | Female (3+2) | 29.01 ± 6.44 | 27.62 ± 2.35 | 30.54 ± 3.82 | 29.56 |
| 150 mg/kg/week IV | Male (3+2) | 27.57 ± 5.05 | **29.74 ± 2.32** | 35.28 ± 2.81 | 31.37 |
|  | Female (3+2) | 22.43 ± 2.14 | 25.70 ± 2.63 | 28.32 ± 2.17 | 25.98 |
| **Albumin/Globulin ratio** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 1.40 ± 0.30 | 1.30 ± 0.25 | 1.21 ± 0.10 | 1.09 |
|  | Female (3+2) | 2.02 ± 0.83 | 1.87 ± 0.62 | 1.54 ± 0.20 | 1.53 |
| 10 mg/kg/week SC | Male (3) | 1.68 ± 0.34 | 1.80 ± 0.37 | 1.45 ± 0.11 |  |
|  | Female (3) | 1.81 ± 0.63 | 1.98 ± 0.17 | 1.72 ± 0.07 |  |
| 50 mg/kg/week SC | Male (3) | 1.85 ± 0.25 | 1.80 ± 0.30 | 1.22 ± 0.26 |  |
|  | Female (3) | 1.43 ± 0.38 | 1.56 ± 0.29 | 1.39 ± 0.14 |  |
| 150 mg/kg/week SC | Male (3+2) | 1.75 ± 0.56 | 1.49 ± 0.37 | 1.28 ± 0.14 | 1.35 |
|  | Female (3+2) | 1.77 ± 0.61 | 1.82 ± 0.31 | 1.40 ± 0.136 | 1.68 |
| 150 mg/kg/week IV | Male (3+2) | 1.96 ± 0.53 | 1.74 ± 0.15 | 1.27 ± 0.18 | 1.51 |
|  | Female (3+2) | 2.38 ± 0.36 | 1.98 ± 0.34 | 1.46 ± 0.07 | 1.77 |
| **Total immunoglobulin G (g/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 13.04 ± 1.34 | 12.12 ± 1.26 | 11.52 ± 1.51 | 12.86 |
|  | Female (3+2) | 8.33 ± 1.40 | 9.29 ± 1.96 | 8.76 ± 2.06 | 9.00 |
| 10 mg/kg/week SC | Male (3) | 12.74 ± 3.09 | **9.00 ± 1.80** | **8.29 ± 2.05** |  |
|  | Female (3) | 8.54 ± 0.41 | 7.76 ± 1.26 | 7.21 ± 0.92 |  |
| 50 mg/kg/week SC | Male (3) | **9.30 ± 1.10** | 9.45 ± 1.03 | **8.46 ± 0.95** |  |
|  | Female (3) | 10.51 ± 1.00 | 9.99 ± 1.81 | 10.05 ± 1.74 |  |
| 150 mg/kg/week SC | Male (3+2) | **9.79 ± 1.58** | 13.43 ± 1.26 | 13.43 ± 1.09 | 10.91 |
|  | Female (3+2) | 9.12 ± 1.53 | **12.17 ± 1.16** | **13.26 ± 1.65** | 10.73 |
| 150 mg/kg/week IV | Male (3+2) | 10.51 ± 1.61 | 13.91 ± 1.57 | **15.93 ± 1.26** | 10.59 |
|  | Female (3+2) | 8.07 ± 1.15 | 11.63 ± 0.57 | **12.17 ± 0.51** | 8.58 |
| **Total immunoglobulin M (g/L)** | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 1.21 ± 0.34 | 0.95 ± 0.29 | 0.86 ± 0.19 | 0.74 |
|  | Female (3+2) | 0.73 ± 0.24 | 0.69 ± 0.23 | 0.62 ± 0.23 | 0.85 |
| 10 mg/kg/week SC | Male (3) | 0.98 ± 0.45 | 0.59 ± 0.24 | 0.61 ± 0.18 |  |
|  | Female (3) | 0.72 ± 0.26 | 0.79 ± 0.40 | 0.70 ± 0.38 |  |
| 50 mg/kg/week SC | Male (3) | 1.01 ± 0.16 | 0.76 ± 0.26 | 0.62 ± 0.15 |  |
|  | Female (3) | 1.14 ± 0.80 | 0.99 ± 0.79 | 0.94 ± 0.81 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.89 ± 0.23 | 0.74 ± 0.24 | 0.72 ± 0.16 | 0.57 |
|  | Female (3+2) | 0.92 ± 0.16 | 0.76 ± 0.13 | 0.68 ± 0.15 | 0.82 |
| 150 mg/kg/week IV | Male (3+2) | 0.90 ± 0.26 | 0.86 ± 0.28 | 0.80 ± 0.25 | 0.89 |
|  | Female (3+2) | 1.02 ± 0.32 | 0.92 ± 0.38 | 0.74 ± 0.33 | 1.02 |

Standard deviation not calculated for less than three values

\* Number of animals at 0 mg/kg/week SC, 150 mg/kg/week SC and 150 mg/kg/week IV is a total of 5 (3+2) per sex in predose and dosing phase and of 2 per sex in recovery

*Blood immunophenotyping*

Table 8. Summary of blood immunophenotyping data at the end of dosing phase

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Predose | Dosing | | | Recovery |
| Antibodies/cells Treatment | Sex (No animal)\* | D1 | D2 | D48 | D86 | D204 |
| **CD16+ NK cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.85 ± 0.63 | 0.50 ± 0.34 | 0.68 ± 0.38 | 0.44 ± 0.38 | 0.37 |
|  | Female (3+2) | 0.33 ± 0.20 | 0.23 ± 0.10 | 0.34 ± 0.13 | 0.30 ± 0.09 | 0.17 |
| 10 mg/kg/week SC | Male (3) | 0.68 ± 0.10 | 0.50 ± 0.12 | 0.36 ± 0.06 | 0.47 ± 0.14 |  |
|  | Female (3) | 0.89 ± 0.32 | 0.51 ± 0.03 | 0.79 ± 0.08 | 0.69 ± 0.09 |  |
| 50 mg/kg/week SC | Male (3) | 0.62 ± 0.23 | 0.49 ± 0.16 | 0.42 ± 0.07 | 0.76 ± 0.32 |  |
|  | Female (3) | 0.38 ± 0.13 | 0.18 ± 0.07 | 0.23 ± 0.13 | 0.25 ± 0.08 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.35 ± 0.20 | 0.29 ± 0.26 | 0.28 ± 0.16 | 0.27 ± 0.16 | 0.33 |
|  | Female (3+2) | 0.48 ± 0.33 | 0.45 ± 0.37 | 0.52 ± 0.28 | 0.79 ± 0.69 | 0.21 |
| 150 mg/kg/week IV | Male (3+2) | 0.40 ± 0.14 | 0.45 ± 0.31 | 0.31 ± 0.18 | 0.32 ± 0.20 | 0.33 |
|  | Female (3+2) | 0.32 ± 0.14 | 0.32 ± 0.30 | 0.41 ± 0.32 | 0.43 ± 0.33 | 0.20 |
| **CD20+ B cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 1.87 ± 0.88 | 1.87 ± 0.91 | 1.66 ± 0.91 | 1.73 ± 0.96 | 2.33 |
|  | Female (3+2) | 1.25 ± 0.59 | 1.86 ± 0.67 | 1.61 ± 0.82 | 1.72 ± 0.89 | 1.44 |
| 10 mg/kg/week SC | Male (3) | 3.11 ± 3.05 | 3.19 ± 2.51 | 0.86 ± 0.56 | 0.86 ± 0.83 |  |
|  | Female (3) | 1.51 ± 0.68 | 1.99 ± 0.79 | 0.99 ± 0.6 | 0.83 ± 0.41 |  |
| 50 mg/kg/week SC | Male (3) | 2.06 ± 0.32 | 2.69 ± 0.08 | 0.64 ± 0.10 | 1.08 ± 0.18 |  |
|  | Female (3) | 1.20 ± 0.66 | 1.33 ± 0.44 | 0.58 ± 0.26 | 0.57 ± 0.12 |  |
| 150 mg/kg/week SC | Male (3+2) | 2.35 ± 0.40 | 2.70 ± 0.77 | 0.85 ± 0.29 | 0.94 ± 0.45 | 3.71 |
|  | Female (3+2) | 1.86 ± 1.71 | 2.40 ± 1.92 | 0.97 ± 0.77 | 0.88 ± 0.57 | 5.26 |
| 150 mg/kg/week IV | Male (3+2) | 1.99 ± 0.72 | 2.28 ± 0.89 | 0.70 ± 0.24 | 0.70 ± 0.20 | 1.92 |
|  | Female (3+2) | 1.58 ± 0.74 | 2.31 ± 0.92 | 0.84 ± 0.48 | 0.81 ± 0.40 | 1.99 |
| **CD3+ T cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 2.19 ± 0.66 | 2.30 ± 0.87 | 1.78 ± 0.65 | 1.73 ± 0.81 | 2.75 |
|  | Female (3+2) | 1.77 ± 0.41 | 3.41 ± 0.66 | 2.24 ± 0.64 | 2.67 ± 1.36 | 2.33 |
| 10 mg/kg/week SC | Male (3) | 1.85 ± 0.51 | 2.47 ± 0.78 | 1.32 ± 0.47 | 1.68 ± 0.37 |  |
|  | Female (3) | 2.16 ± 1.18 | 3.01 ± 1.07 | 2.33 ± 1.74 | 2.26 ± 1.24 |  |
| 50 mg/kg/week SC | Male (3) | 2.16 ± 0.51 | 3.13 ± 1.06 | 1.55 ± 0.25 | 3.23 ± 0.55 |  |
|  | Female (3) | 2.29 ± 0.58 | 3.27 ± 1.22 | 1.96 ± 0.8 | 2.17 ± 0.79 |  |
| 150 mg/kg/week SC | Male (3+2) | 1.78 ± 0.31 | 2.32 ± 0.46 | 1.34 ± 0.42 | 1.58 ± 0.54 | 2.07 |
|  | Female (3+2) | 1.88 ± 0.66 | 3.76 ± 1.51 | 1.91 ± 0.43 | 2.25 ± 0.59 | 2.58 |
| 150 mg/kg/week IV | Male (3+2) | 1.68 ± 0.32 | 2.15 ± 0.55 | 1.39 ± 0.33 | 1.65 ± 0.20 | 1.7 |
|  | Female (3+2) | 1.71 ± 0.52 | 3.41 ± 0.46 | 1.74 ± 0.48 | 2.19 ± 0.38 | 1.61 |
| **CD3+CD4+ T helper-cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 1.19 ± 0.27 | 1.33 ± 0.39 | 1.04 ± 0.29 | 0.97 ± 0.29 | 1.37 |
|  | Female (3+2) | 1.03 ± 0.25 | 1.26 ± 0.58 | 1.33 ± 0.38 | 1.62 ± 0.88 | 1.39 |
| 10 mg/kg/week SC | Male (3) | 1.04 ± 0.46 | 1.46 ± 0.41 | 0.85 ± 0.33 | 1.06 ± 0.33 |  |
|  | Female (3) | 1.32 ± 0.77 | 0.85 ± 0.30 | 1.60 ± 1.29 | 1.56 ± 0.93 |  |
| 50 mg/kg/week SC | Male (3) | 1.27 ± 0.31 | 1.97 ± 0.72 | 0.96 ± 0.31 | 1.92 ± 0.40 |  |
|  | Female (3) | 1.00 ± 0.18 | 0.69 ± 0.12 | 1.00 ± 0.2 | 1.08 ± 0.17 |  |
| 150 mg/kg/week SC | Male (3+2) | 1.05 ± 0.23 | 1.40 ± 0.29 | 0.85 ± 0.28 | 1.05 ± 0.41 | 1.23 |
|  | Female (3+2) | 1.07 ± 0.33 | 1.56 ± 1.22 | 1.15 ± 0.14 | 1.32 ± 0.28 | 1.57 |
| 150 mg/kg/week IV | Male (3+2) | 1.01 ± 0.23 | 1.28 ± 0.38 | 0.94 ± 0.29 | 1.04 ± 0.16 | 1.1 |
|  | Female (3+2) | 1.05 ± 0.29 | 1.39 ± 0.68 | 1.12 ± 0.32 | 1.32 ± 0.38 | 1.05 |
| **CD3+CD8+ cytotoxic T cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.50 ± 0.30 | 0.61 ± 0.55 | 0.41 ± 0.36 | 0.49 ± 0.49 | 0.62 |
|  | Female (3+2) | 0.56 ± 0.13 | 0.95 ± 0.15 | 0.65 ± 0.19 | 0.74 ± 0.39 | 0.57 |
| 10 mg/kg/week SC | Male (3) | 0.41 ± 0.19 | 0.61 ± 0.39 | 0.28 ± 0.19 | 0.34 ± 0.18 |  |
|  | Female (3) | 0.67 ± 0.34 | 0.79 ± 0.23 | 0.58 ± 0.37 | 0.52 ± 0.24 |  |
| 50 mg/kg/week SC | Male (3) | 0.70 ± 0.27 | 0.89 ± 0.35 | 0.43 ± 0.18 | 0.84 ± 0.25 |  |
|  | Female (3) | 1.13 ± 0.71 | 1.21 ± 0.82 | 0.81 ± 0.51 | 0.81 ± 0.48 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.53 ± 0.25 | 0.68 ± 0.25 | 0.31 ± 0.11 | 0.38 ± 0.13 | 0.59 |
|  | Female (3+2) | 0.66 ± 0.43 | 1.26 ± 0.93 | 0.60 ± 0.32 | 0.67 ± 0.47 | 0.67 |
| 150 mg/kg/week IV | Male (3+2) | 0.42 ± 0.11 | 0.55 ± 0.15 | 0.28 ± 0.04 | 0.39 ± 0.11 | 0.3 |
|  | Female (3+2) | 0.45 ± 0.19 | 0.94 ± 0.26 | 0.44 ± 0.16 | 0.56 ± 0.19 | 0.30 |
| **CD20low / CD21+ B cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.36 ± 0.23 | 0.48 ± 0.37 | 0.28 ± 0.15 | 0.41 ± 0.28 | 0.38 |
|  | Female (3+2) | 0.37 ± 0.17 | 0.78 ± 0.23 | 0.50 ± 0.24 | 0.62 ± 0.56 | 0.31 |
| 10 mg/kg/week SC | Male (3) | 1.11 ± 0.97 | 1.12 ± 0.77 | 0.37 ± 0.13 | 0.60 ± 0.62 |  |
|  | Female (3) | 0.53 ± 0.15 | 0.77 ± 0.21 | 0.54 ± 0.37 | 0.51 ± 0.23 |  |
| 50 mg/kg/week SC | Male (3) | 0.67 ± 0.24 | 1.10 ± 0.32 | 0.34 ± 0.11 | 0.70 ± 0.21 |  |
|  | Female (3) | 0.31 ± 0.10 | 0.42 ± 0.08 | 0.24 ± 0.06 | 0.34 ± 0.05 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.60 ± 0.17 | 0.89 ± 0.16 | 0.34 ± 0.12 | 0.57 ± 0.24 | 0.82 |
|  | Female (3+2) | 0.39 ± 0.12 | 0.76 ± 0.35 | 0.35 ± 0.1 | 0.48 ± 0.18 | 0.75 |
| 150 mg/kg/week IV | Male (3+2) | 0.34 ± 0.11 | 0.63 ± 0.34 | 0.23 ± 0.12 | 0.33 ± 0.14 | 0.39 |
|  | Female (3+2) | 0.36 ± 0.19 | 0.85 ± 0.41 | 0.43 ± 0.24 | 0.54 ± 0.26 | 0.30 |
| **CD20high / CD21- B cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 1.45 ± 0.74 | 1.35 ± 0.71 | 1.26 ± 0.84 | 1.37 ± 0.86 | 1.98 |
|  | Female (3+2) | 0.86 ± 0.46 | 1.08 ± 0.51 | 1.03 ± 0.74 | 1.10 ± 0.56 | 1.14 |
| 10 mg/kg/week SC | Male (3) | 1.94 ± 1.95 | 2.05 ± 1.70 | 0.43 ± 0.41 | 0.27 ± 0.25 |  |
|  | Female (3) | 0.95 ± 0.62 | 1.21 ± 0.67 | 0.41 ± 0.28 | 0.29 ± 0.11 |  |
| 50 mg/kg/week SC | Male (3) | 1.32 ± 0.35 | 1.56 ± 0.25 | 0.28 ± 0.12 | 0.37 ± 0.26 |  |
|  | Female (3) | 0.89 ± 0.56 | 0.84 ± 0.37 | 0.30 ± 0.21 | 0.24 ± 0.12 |  |
| 150 mg/kg/week SC | Male (3+2) | 1.73 ± 0.48 | 1.80 ± 0.68 | 0.48 ± 0.19 | 0.37 ± 0.26 | 2.95 |
|  | Female (3+2) | 1.46 ± 1.63 | 1.59 ± 1.57 | 0.57 ± 0.76 | 0.42 ± 0.44 | 4.62 |
| 150 mg/kg/week IV | Male (3+2) | 1.63 ± 0.66 | 1.59 ± 0.61 | 0.43 ± 0.17 | 0.38 ± 0.11 | 1.54 |
|  | Female (3+2) | 1.19 ± 0.58 | 1.43 ± 0.57 | 0.37 ± 0.30 | 0.27 ± 0.15 | 1.74 |
| **CD20+ CD21+ CD27+ memory B cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.01 ± 0.01 | 0.02 ± 0.02 | 0.12 ± 0.07 | 0.08 ± 0.06 | 0.02 |
|  | Female (3+2) | 0.01 ± 0.01 | 0 ± 0 | 0.13 ± 0.09 | 0.09 ± 0.07 | 0.04 |
| 10 mg/kg/week SC | Male (3) | 0.02 ± 0.01 | 0.03 ± 0.03 | 0.08 ± 0.05 | 0.05 ± 0.06 |  |
|  | Female (3) | 0.01 ± 0.01 | 0 ± 0 | 0.17 ± 0.07 | 0.08 ± 0.01 |  |
| 50 mg/kg/week SC | Male (3) | 0.02 ± 0.01 | 0.04 ± 0.03 | 0.06 ± 0.03 | 0.06 ± 0.03 |  |
|  | Female (3) | 0.01 ± 0.01 | 0 ± 0 | 0.06 ± 0.03 | 0.04 ± 0.02 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.02 ± 0.01 | 0.04 ± 0.01 | 0.12 ± 0.04 | 0.07 ± 0.02 | 0.07 |
|  | Female (3+2) | 0.02 ± 0.01 | 0.02 ± 0.03 | 0.10 ± 0.05 | 0.06 ± 0.03 | 0.12 |
| 150 mg/kg/week IV | Male (3+2) | 0.01 ± 0.01 | 0.03 ± 0.03 | 0.08 ± 0.03 | 0.05 ± 0.02 | 0.05 |
|  | Female (3+2) | 0.01 ± 0 | 0.01 ± 0.02 | 0.08 ± 0.04 | 0.05 ± 0.02 | 0.06 |
| **CD20+ CD21+ CD27- naïve B cells** | | | | | | |
| 0 mg/kg/week SC | Male (3+2) | 0.35 ± 0.22 | 0.45 ± 0.35 | 0.15 ± 0.09 | 0.32 ± 0.22 | 0.35 |
|  | Female (3+2) | 0.36 ± 0.16 | 0.77 ± 0.23 | 0.35 ± 0.16 | 0.53 ± 0.51 | 0.27 |
| 10 mg/kg/week SC | Male (3) | 1.09 ± 0.96 | 1.09 ± 0.75 | 0.28 ± 0.07 | 0.54 ± 0.55 |  |
|  | Female (3) | 0.51 ± 0.14 | 0.77 ± 0.21 | 0.35 ± 0.28 | 0.42 ± 0.23 |  |
| 50 mg/kg/week SC | Male (3) | 0.65 ± 0.23 | 1.06 ± 0.29 | 0.26 ± 0.08 | 0.63 ± 0.19 |  |
|  | Female (3) | 0.30 ± 0.10 | 0.42 ± 0.08 | 0.18 ± 0.04 | 0.29 ± 0.06 |  |
| 150 mg/kg/week SC | Male (3+2) | 0.58 ± 0.16 | 0.84 ± 0.15 | 0.21 ± 0.13 | 0.49 ± 0.23 | 0.74 |
|  | Female (3+2) | 0.37 ± 0.11 | 0.73 ± 0.33 | 0.24 ± 0.07 | 0.41 ± 0.15 | 0.61 |
| 150 mg/kg/week IV | Male (3+2) | 0.33 ± 0.10 | 0.59 ± 0.31 | 0.14 ± 0.09 | 0.27 ± 0.13 | 0.33 |
|  | Female (3+2) | 0.35 ± 0.18 | 0.84 ± 0.39 | 0.34 ± 0.20 | 0.49 ± 0.25 | 0.23 |

Standard deviation not calculated for less than three values  
\* Number of animals at 0 mg/kg/week SC, 150 mg/kg/week SC and 150 mg/kg/week IV is a total of 5 (3+2) per sex in predose and dosing phase and of 2 per sex in recovery.

### Anatomic pathology

Table 9. Summary of relevant histopathological changes in CFZ533 dosed animal at the end of the dosing phase.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Sex | | Male | | | | | Female | | | | |
| Dose of CFZ533 (mg/kg/week) | | 0 SC | 10 SC | 50 SC | 150 SC | 150 IV | 0 SC | 10 SC | 50 SC | 150 SC | 150 IV |
| **Eye** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Inflammation subacute* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Mild | - | - | 1 | - | - | - | - | - | - | - |
| **Heart** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Inflammatory cell infiltrate* | No. affected | 3 | 0 | 1 | 0 | 0 | 2 | 0 | 0 | 2 | 0 |
|  | Minimal | 3 | - | - | - | - | 2 | - | - | 2 | - |
|  | Mild | - | - | 1 | - | - | - | - | - | - | - |
| **Kidney** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Atrophy tubule* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Moderate | - | - | 1 | - | - | - | - | - | - | - |
| *Cast, hyaline* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Mild | - | - | 1 | - | - | - | - | - | - | - |
| *Degeneration/regeneration, tubular* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
|  | Minimal | - | - | - | - | - | - | - | - | 1 | - |
|  | Moderate | - | - | 1 | - | - | - | - | - | - | - |
| *Inflammatory cell infiltrate* | No. affected | 1 | 2 | 2 | 3 | 3 | 2 | 2 | 2 | 2 | 3 |
|  | Minimal | 1 | 1 | 1 | 3 | 3 | 2 | 2 | 2 | 2 | 3 |
|  | Mild | - | 1 | 1 | - | - | - | - | - | - | - |
| *Inflammation, chronic* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Moderate | - | - | 1 | - | - | - | - | - | - | - |
| **Lung** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Hyperplasia, BALT* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Minimal | - | - | 1 | - | - | - | - | - | - | - |
| *Inflammation, chronic* | No. affected | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Moderate | - | - | 2 | - | - | - | - | - | - | - |
| **Lymph node, axillary** | No. examined | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 3 | 3 | 0 |
| *Increased lymphocytes, T-cell region* | No. affected | 0 | 0 | 2 | 0 | - | 0 | 0 | 0 | 0 | - |
|  | Moderate | - | - | 1 | - | - | - | - | - | - | - |
|  | Marked | - | - | 1 | - | - | - | - | - | - | - |
| *Germinal center, absent* | No. affected | 0 | 2 | 3 | 3 | - | 0 | 3 | 3 | 3 | - |
|  | Present | 0 | 2 | 3 | 3 | - | 0 | 3 | 3 | 3 | - |
| **Lymph node, inguinal** | No. examined | 0 | 0 | 2 | 0 | 3 | 0 | 0 | 0 | 0 | 3 |
| *Increased lymphocytes, T-cell region* | No. affected | - | - | 2 | - | 0 | - | - | - | - | 0 |
|  | Moderate | - | - | 1 | - | - | - | - | - | - | - |
|  | Marked | - | - | 1 | - | - | - | - | - | - | - |
| *Germinal center, absent* | No. affected | - | - | 2 | - | 0 | - | - | - | - | 1 |
|  | Present | - | - | 2 | - | - | - | - | - | - | 1 |
| **Lymph node, mandibular** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Increased lymphocytes, T-cell region* | No. affected | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Minimal | - | - | 1 | - | - | - | - | - | - | - |
|  | Mild | - | - | 1 | - | - | - | - | - | - | - |
| *Germinal center, absent* | No. affected | 0 | 2 | 3 | 3 | 3 | 0 | 3 | 3 | 2 | 3 |
|  | Present | 0 | 2 | 3 | 3 | 3 | 0 | 3 | 3 | 2 | 3 |
| **Lymph node, mesenteric** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Increased lymphocytes, T-cell region* | No. affected | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 1 | 0 |
|  | Mild | 1 | - | - | 1 | - | - | - | - | - | - |
|  | Moderate | - | - | - | - | - | - | 1 | - | 1 | - |
| *Germinal center, absent* | No. affected | 0 | 3 | 3 | 2 | 2 | 0 | 3 | 2 | 3 | 3 |
|  | Present | 0 | 3 | 3 | 2 | 2 | 0 | 3 | 2 | 3 | 3 |
| **Salivary gland, parotid** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Inflammatory cell infiltrate* | No. affected | 1 | 1 | 2 | 0 | 1 | 2 | 3 | 0 | 1 | 1 |
|  | Minimal | 1 | 1 | 1 | - | 1 | 2 | 3 | 0 | 1 | 1 |
|  | Moderate | - | - | 1 | - | - | - | - | - | - | - |
| **Skeletal muscle** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Inflammatory cell infiltrate* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Minimal | - | - | 1 | - | - | - | - | - | - | - |
| **Thymus** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Increased cellularity lymphocytes* | No. affected | 0 | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
|  | Minimal | - | - | - | - | - | - | - | - | 1 | - |
|  | Mild | - | 1 | 2 | - | - | - | - | - | - | - |
| **Trachea** | No. examined | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| *Inflammation, acute* | No. affected | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  | Minimal | - | - | 1 | - | - | - | - | - | - | - |

### Figure 1. Representative photomicrographs of CD20 staining (B) in enlarged mesenteric lymph node of infected animal M7 (CFZ533 at 50 mg/kg) and CD40 staining (D) in enlarged axillary lymph node of infected animal M8 (CFZ533 at 50 mg/kg) showing absence of staining difference (with exception of absent germinal center in CFZ533 dosed) compared to control animal M2 (A: CD20 and C: CD40) (Original scan 2x).

Figure 2. Kidney absolute weight (A) and relative to body weight (B) and liver absolute weight (A) and relative to body weight (B) in male and female animal dosed with CFZ533 showing higher kidney and liver weights of animal M8. Data are reported as individual values and mean.

Figure 3. Histopathological changes in kidney with chronic inflammation, tubular degeneration/regeneration and hyaline cast (A) and lung with chronic inflammation and BALT hyperplasia (B) in animal M8 dosed for 13 weeks with CFZ533 at 50 mg/kg. All sections stained with hematoxylin and eosin. (Original scan 2x).