**Toxicity and safety study of D-PLEX100 in** **a sternal surgical defect in New Zealand white rabbits**

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Supplementary Table 1. Group Mean Hematology and Coagulation Results (1-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 6.35 | 6.69 | 6.70 | 7.01 | 6.40 | 6.47 | 6.13 | 6.40 |
| Hematocrit | % | 42.6 | 44.6 | 44.3 | 46.3 | 42.8 | 42.9 | 40.8 | 42.6 |
| Hemoglobin | g/dL | 13.3 | 14.1 | 13.8 | 14.4 | 13.9 | 14.0 | 12.7 a | 13.5 |
| MCV | fL | 67.3 | 66.7 | 66.1 | 66.2 | 66.9 | 66.4 | 66.6 | 66.5 |
| MCH | pg | 21.0 | 21.0 | 20.6 | 20.5 | 21.8 | 21.7 | 20.8 | 21.1 |
| MCHC | g/dL | 31.2 | 31.6 | 31.1 | 31.0 | 32.5 | 32.8 | 31.2 | 31.7 |
| CHCM | g/dL | 31.1 | 31.2 | 31.1 | 30.8 | 31.5 | 31.5 | 31.2 | 31.5 |
| CH | pg | 20.9 | 20.8 | 20.5 | 20.4 | 21.1 | 20.9 | 20.7 | 20.9 |
| Reticulocytes | ×10⁹/L | 86.1 | 88.9 | 118.1 | 96.2 | 80.9 | 104.4 | 108.7 | 83.1 |
| % | 1.36 | 1.33 | 1.76 | 1.40 | 1.25 | 1.59 | 1.78 | 1.31 |
| White Cell Count | ×10³/µL | 4.83 | 6.73 | 6.04 | 7.58 | 6.32 | 5.46 | 6.09 | 5.24 |
| Neutrophils | ×10³/µL | 0.92 | 1.64 | 1.78 | 1.62 | 1.61 | 1.03 | 1.19 | 1.63 |
| % | 18.7 | 24.5 | 29.3a | 20.2 | 25.8 | 19.0 | 19.5 | 31.3 |
| Lymphocytes | ×10³/µL | 3.57 | 4.51 | 3.75 | 5.39 | 4.20 | 4.01 | 4.45 | 3.13 |
| % | 74.2 | 66.8 | 62.3 | 72.2 | 66.0 | 73.6 | 72.8 | 59.8 |
| Monocytes | ×10³/µL | 0.03 | 0.05 | 0.05 | 0.07 | 0.05 | 0.05 | 0.03 | 0.04 |
| % | 0.6 | 0.7 | 0.9 | 0.8 | 0.8 | 1.0 | 0.5 | 0.8 |
| Eosinophils | ×10³/µL | 0.06 | 0.13 | 0.08 | 0.12 | 0.11 | 0.11 | 0.09 | 0.10 |
| % | 1.3 | 1.9 | 1.3 | 1.5 | 1.7 | 1.9 | 1.7 | 1.9 |
| Basophils | ×10³/µL | 0.25 | 0.40 | 0.37 | 0.38 | 0.35 | 0.44 | 0.32 | 0.34 |
| % | 5.1 | 6.0 | 6.1 | 5.3 | 5.6 | 7.7 | 5.6 | 6.1 |
| Large Unstained Cells | ×10³/µL | 0.00 | 0.00 | 0.01 | 0.01 | 0.01 | 0.00 | 0.01 | 0.01 |
| % | 0.1 | 0.0 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 |
| PT | sec | 8.7 | 8.8 | 8.7 | 8.7 | 8.9 | 8.9 | 8.8 | 9.0 |
| APTT | sec | 13.1 | 13.8 | 13.1 | 13.3 | 13.6 | 14.0 | 15.0 | 13.7 |
| Platelets | ×10³/µL | 329 | 318 | 340 | 366 | 301 | 376 | 335 | 335 |

a statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 2. Group Mean Hematology and Coagulation Results (1-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 6.02 | 6.49 | 6.42 | 6.61 | 6.20 | 5.89 | 5.89 | 6.34 |
| Hematocrit | % | 40.6 | 43.3 | 43.0 | 44.2 | 41.6 | 38.4 | 39.4 | 43.0 |
| Hemoglobin | g/dL | 12.5 | 13.4 | 13.0 | 13.5 | 12.9 | 12.3 | 12.0 | 13.2 |
| MCV | fL | 67.6 | 66.8 | 66.9 | 66.9 | 67.1 | 65.4 | 67.0 | 67.8 |
| MCH | pg | 20.8 | 20.6 | 20.2 | 20.4 | 20.7 | 20.8 | 20.4 | 20.8 |
| MCHC | g/dL | 30.8 | 30.9 | 30.3 | 30.6 | 30.9 | 31.9 | 30.6 | 30.7 |
| CHCM | g/dL | 30.3 | 30.6 | 30.0 | 29.9 | 30.7 | 31.5 | 30.3 | 30.4 |
| CH | pg | 20.5 | 20.4 | 20.0 | 20.0 | 20.5 | 20.5 | 20.2 | 20.5 |
| Reticulocytes | ×10⁹/L | 71.5 | 97.8 | 82.5 | 78.7 | 149.7 | 123.0 | 129.2 | 97.0 |
| % | 1.19 | 1.52 | 1.29 | 1.18 | 2.46 | 2.11 | 2.21 | 1.53 |
| White Cell Count | ×10³/µL | 7.37 | 7.25 | 7.68 | 8.23 | 6.51 | 6.29 | 6.28 | 5.58 |
| Neutrophils | ×10³/µL | 1.88 | 1.70 | 2.36 | 1.95 | 1.89 | 1.87 | 1.67 | 1.97 |
| % | 25.0 | 23.3 | 30.2 | 23.7 | 28.9 | 29.1 | 26.6 | 35.1 |
| Lymphocytes | ×10³/µL | 4.93 | 4.99 | 4.76 | 5.72 | 4.13 | 3.77 | 3.94 | 3.08 |
| % | 67.4 | 69.1 | 62.7 | 69.5 | 63.7 | 60.6 | 62.2 | 55.4 |
| Monocytes | ×10³/µL | 0.05 | 0.05 | 0.07 | 0.06 | 0.05 | 0.09 | 0.05 | 0.05 |
| % | 0.7 | 0.6 | 0.9 | 0.7 | 0.7 | 1.3 | 0.7 | 0.9 |
| Eosinophils | ×10³/µL | 0.11 | 0.10 | 0.09 | 0.08 | 0.12 | 0.12 | 0.27 | 0.10 |
| % | 1.6 | 1.3 | 1.1 | 1.0 | 1.9 | 1.9 | 4.6 | 1.7 |
| Basophils | ×10³/µL | 0.39 | 0.42 | 0.40 | 0.43 | 0.31 | 0.45 | 0.36 | 0.38 |
| % | 5.3 | 5.7 | 5.1 | 5.1 | 4.9 | 7.0 | 5.8 | 6.8 |
| Large Unstained Cells | ×10³/µL | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.00 |
| % | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| PT | sec | 8.8 | 8.8 | 8.6 | 8.6 | 9.1 | 8.9 | 8.6 | 8.6 |
| APTT | sec | 12.6 | 13.8 | 11.6 | 12.3 | 12.7 | 12.8 | 12.3 | 11.2 |
| Platelets | ×10³/µL | 351 | 360 | 372 | 472 | 378 | 371 | 456 | 470 |

Supplementary Table 3. Group Mean Hematology and Coagulation Results (3-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 6.63 | 6.71 | 6.60 | 6.27 | 6.49 | 6.16 | 6.68 | 6.24 |
| Hematocrit | % | 45.2 | 45.3 | 43.5 | 43.6 | 44.3 | 41.5 | 43.5 | 40.9 |
| Hemoglobin | g/dL | 14.2 | 14.2 | 13.5 | 13.8 | 14.0 | 13.1 | 13.9 | 13.4 |
| MCV | fL | 68.2 | 67.7 | 66.0 | 69.5 | 68.6 | 67.3 | 65.2 | 65.7 |
| MCH | pg | 21.4 | 21.2 | 20.5 | 22.0 | 21.7 | 21.3 | 20.7 | 21.6 |
| MCHC | g/dL | 31.4 | 31.3 | 31.0 | 31.6 | 31.6 | 31.5 | 31.8 | 32.9 |
| CHCM | g/dL | 31.2 | 31.0 | 31.0 | 31.3 | 30.1 | 31.2 | 32.0 a | 31.9 a |
| CH | pg | 21.3 | 20.9 | 20.4 | 21.7 | 20.6 | 21.0 | 20.8 | 20.9 |
| Reticulocytes | ×10⁹/L | 107.1 | 105.9 | 73.9 | 116.2 | 118.6 | 110.4 | 96.4 | 118.6 |
| % | 1.61 | 1.58 | 1.13 | 1.85 | 1.92 | 1.80 | 1.43 | 1.93 |
| White Cell Count | ×10³/µL | 6.66 | 6.25 | 6.35 | 6.03 | 5.28 | 5.42 | 6.96 | 4.90 |
| Neutrophils | ×10³/µL | 1.11 | 1.19 | 1.17 | 1.62 | 1.04 | 1.14 | 1.65 | 1.09 |
| % | 17.1 | 18.8 | 18.7 | 26.9 | 19.6 | 20.7 | 23.7 | 22.5 |
| Lymphocytes | ×10³/µL | 5.07 | 4.59 | 4.72 | 3.87 | 3.86 | 3.74 | 4.69 | 3.40 |
| % | 75.7 | 73.9 | 74.1 | 64.3 | 73.2 | 69.4 | 67.3 | 69.3 |
| Monocytes | ×10³/µL | 0.05 | 0.05 | 0.07 | 0.05 | 0.04 | 0.03 | 0.08a | 0.03 |
| % | 0.8 | 0.9 | 1.1 | 0.8 | 0.7 | 0.6 | 1.1 | 0.6 |
| Eosinophils | ×10³/µL | 0.07 | 0.11 | 0.10 | 0.10 | 0.07 | 0.10 | 0.10 | 0.08 |
| % | 1.1 | 1.8 | 1.7 | 1.6 | 1.3 | 1.9 | 1.3 | 1.6 |
| Basophils | ×10³/µL | 0.34 | 0.30 | 0.28 | 0.39 | 0.27 | 0.40 | 0.44 | 0.30 |
| % | 5.4 | 4.7 | 4.4 | 6.4 | 5.2 | 7.4 | 6.6 | 6.0 |
| Large Unstained Cells | ×10³/µL | 0.00 | 0.01 | 0.01 | 0.00 | 0.01 | 0.01 | 0.01 | 0.00 |
| % | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 | 0.1 | 0.1 |
| PT | sec | 8.5 | 13.3 | 8.6 | 8.9 | 8.7 | 8.8 | 9.0 | 8.7 |
| APTT | sec | 13.6 | 13.5 | 14.3 | 13.5 | 14.3 | 15.0 | 13.9 | 14.6 |
| Platelets | ×10³/µL | 343 | 363 | 338 | 341 | 348 | 391 | 325 | 313 |

a statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 4. Group Mean Hematology and Coagulation Results (3-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 6.44 | 6.41 | 6.19 | 6.11 | 6.31 | 5.96 | 6.61 | 6.38 |
| Hematocrit | % | 44.4 | 45.0 | 41.5 | 43.0 | 43.7 | 40.7 | 45.2 | 43.3 |
| Hemoglobin | g/dL | 14.2 | 14.1 | 13.1 | 13.9 | 13.6 | 13.0 | 14.4 | 13.8 |
| MCV | fL | 69.0 | 70.2 | 67.1 | 70.3 | 69.2 | 68.4 | 68.5 | 67.9 |
| MCH | pg | 22.0 | 22.1 | 21.1 | 22.7 | 21.7 | 21.8 | 21.9 | 21.6 |
| MCHC | g/dL | 31.9 | 31.5 | 31.6 | 32.3 | 31.3 | 31.9 | 31.9 | 31.8 |
| CHCM | g/dL | 31.6 | 30.8 | 31.0 | 31.8 | 30.6 | 31.2 | 31.0 | 30.9 |
| CH | pg | 21.8 | 21.6 | 20.7 | 22.3 | 21.1 | 21.3 | 21.2 | 21.0 |
| Reticulocytes | ×10⁹/L | 117.3 | 124.1 | 107.0 | 113.5 | 138.4 | 119.2 | 119.6 | 122.8 |
| % | 1.82 | 1.96 | 1.75 | 1.86 | 2.19 | 2.01 | 1.82 | 1.93 |
| White Cell Count | ×10³/µL | 8.38 | 7.81 | 7.83 | 7.15 | 6.01 | 6.03 | 7.31 | 6.19 |
| Neutrophils | ×10³/µL | 1.39 | 1.45 | 1.53 | 1.52 | 1.15 | 1.34 | 1.32 | 1.48 |
| % | 16.8 | 18.5 | 19.7 | 22.2 | 19.3 | 21.6 | 18.1 | 23.9 |
| Lymphocytes | ×10³/µL | 6.37 | 5.83 | 5.78 | 5.08 | 4.25 | 4.08 | 5.38 | 4.03 |
| % | 75.7 | 74.7 | 73.5 | 69.9 | 70.6 | 68.5 | 73.4 | 65.4 |
| Monocytes | ×10³/µL | 0.06 | 0.07 | 0.06 | 0.06 | 0.04 | 0.06 | 0.06 | 0.06 |
| % | 0.7 | 0.9 | 0.8 | 0.8 | 0.7 | 0.9 | 0.9 | 0.9 |
| Eosinophils | ×10³/µL | 0.09 | 0.11 | 0.15 | 0.11 | 0.10 | 0.10 | 0.09 | 0.12 |
| % | 1.1 | 1.4 | 1.9 | 1.6 | 1.7 | 1.6 | 1.2 | 2.0 |
| Basophils | ×10³/µL | 0.46 | 0.34 | 0.32 | 0.38 | 0.47 | 0.45 | 0.45 | 0.49 |
| % | 5.6 | 4.4 | 4.1 | 5.5 | 7.6 | 7.2 | 6.4 | 7.8 |
| Large Unstained Cells | ×10³/µL | 0.01 | 0.00 | 0.01 | 0.00 | 0.01 | 0.01 | 0.01 | 0.01 |
| % | 0.1 | 0.0 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| PT | sec | 9.0 | 8.9 | 8.9 | 9.5 | 9.0 | 9.1 | 8.9 | 8.8 |
| APTT | sec | 15.1 | 14.1 | 13.8 | 15.6 | 14.8 | 13.8 | 14.2 | 14.1 |
| Platelets | ×10³/µL | 307 | 342 | 327 | 290 | 198 | 295 | 261 | 284 |

Supplementary Table 5. Group Mean Hematology and Coagulation Results (6-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 6.64 | 7.07 | 6.77 | 6.70 | 6.61 | 6.36 | 6.57 | 6.89 |
| Hematocrit | % | 45.0 | 48.8 | 46.9 | 45.9 | 44.5 | 44.0 | 45.1 | 47.0 |
| Hemoglobin | g/dL | 14.0 | 14.9 | 14.4 | 14.3 | 13.8 | 13.7 | 13.9 | 14.4 |
| MCV | fL | 67.7 | 69.1 | 69.3 | 68.6 | 67.3 | 69.3 | 68.7 | 68.2 |
| MCH | pg | 21.1 | 21.1 | 21.4 | 21.4 | 20.9 | 21.5 | 21.1 | 21.0 |
| MCHC | g/dL | 31.1 | 30.6 | 30.8 | 31.2 | 31.1 | 31.0 | 30.7 | 30.8 |
| CHCM | g/dL | 30.8 | 30.2 | 30.3 | 30.9 | 30.2 | 30.8 | 30.0 | 30.2 |
| CH | pg | 20.8 | 20.8 | 21.0 | 21.2 | 20.3 | 21.3 | 20.6 | 20.6 |
| Reticulocytes | ×10⁹/L | 113.0 | 122.9 | 112.5 | 107.2 | 80.6 | 142.4 | 93.8 | 100.5 |
| % | 1.69 | 1.75 | 1.65 | 1.62 | 1.22 | 2.29 | 1.44 | 1.45 |
| White Cell Count | ×10³/µL | 7.22 | 7.58 | 6.98 | 5.98 | 7.07 | 6.51 | 6.96 | 7.12 |
| Neutrophils | ×10³/µL | 1.47 | 1.77 | 1.50 | 1.27 | 1.44 | 1.22 | 1.36 | 1.19 |
| % | 20.4 | 22.7 | 21.6 | 20.9 | 20.9 | 18.6 | 19.5 | 16.8 |
| Lymphocytes | ×10³/µL | 5.26 | 5.34 | 4.91 | 4.27 | 5.08 | 4.81 | 5.20 | 5.50 |
| % | 72.8 | 71.1 | 70.2 | 71.7 | 71.3 | 74.0 | 74.4 | 77.1 |
| Monocytes | ×10³/µL | 0.04 | 0.04 | 0.05 | 0.04 | 0.06 | 0.04 | 0.03 | 0.03 |
| % | 0.5 | 0.5 | 0.6 | 0.6 | 0.8 | 0.6 | 0.4 | 0.4 |
| Eosinophils | ×10³/µL | 0.10 | 0.09 | 0.16 | 0.10 | 0.12 | 0.14 | 0.09 | 0.10 |
| % | 1.4 | 1.2 | 2.2 | 1.6 | 1.7 | 2.1 | 1.4 | 1.4 |
| Basophils | ×10³/µL | 0.35 | 0.34 | 0.37 | 0.31 | 0.36 | 0.30 | 0.28 | 0.31 |
| % | 4.8 | 4.6 | 5.4 | 5.2 | 5.3 | 4.6 | 4.3 | 4.3 |
| Large Unstained Cells | ×10³/µL | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.00 | 0.00 |
| % | 0.0 | 0.0 | 0.0 | 0.0 | 0.2 | 0.1 | 0.1 | 0.1 |
| PT | sec | 8.9 | 8.6 | 8.6 | 8.8 | 8.8 | 8.9 | 8.8 | 8.9 |
| APTT | sec | 14.0 | 13.4 | 13.0 | 14.0 | 12.5 | 14.5 | 13.5 | 13.2 |
| Platelets | ×10³/µL | 351 | 331 | 282 | 291 | 307 | 344 | 307 | 326 |

Supplementary Table 6. Group Mean Hematology and Coagulation Results (6-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 6.18 | 6.54 | 6.34 | 6.22 | 6.08 | 6.02 | 6.00 | 6.09 |
| Hematocrit | % | 42.5 | 45.7 | 43.7 | 43.5 | 41.5 | 42.3 | 41.7 | 42.5 |
| Hemoglobin | g/dL | 14.4 | 14.9 | 14.5 | 14.4 | 13.5 | 13.7 | 13.4 | 13.8 |
| MCV | fL | 69.0 | 69.8 | 69.1 | 70.0 | 68.2 | 70.3 | 69.5 | 69.9 |
| MCH | pg | 23.5 | 22.8 | 23.0 | 23.2 | 22.3 | 22.7 | 22.4 | 22.6 |
| MCHC | g/dL | 34.1 | 32.7 | 33.2 | 33.0 | 32.7 | 32.3 | 32.2 | 32.4 |
| CHCM | g/dL | 31.6 | 31.6 | 32.1 | 32.0 | 31.5 | 31.2 | 31.0 | 31.0 |
| CH | pg | 21.7 | 22.0 | 22.1 | 22.4 | 21.4 | 21.9 | 21.5 | 21.6 |
| Reticulocytes | ×10⁹/L | 107.9 | 106.4 | 82.7 | 93.0 | 114.5 | 120.7 | 108.8 | 119.8 |
| % | 1.78 | 1.63 | 1.31 | 1.50 | 1.87 | 2.01 | 1.83 | 1.97 |
| White Cell Count | ×10³/µL | 7.90 | 7.64 | 7.46 | 7.13 | 7.67 | 6.13 | 6.82 | 6.08 |
| Neutrophils | ×10³/µL | 1.66 | 1.35 | 1.71 | 1.76 | 1.73 | 1.57 | 1.41 | 1.13 |
| % | 20.8 | 17.5 | 23.0 | 24.5 | 22.8 | 25.6 | 21.5 | 19.5 |
| Lymphocytes | ×10³/µL | 5.72 | 5.69 | 5.19 | 4.78 | 5.39 | 4.07 | 4.93 | 4.49 |
| % | 72.6 | 74.7 | 69.5 | 67.2 | 69.7 | 66.5 | 71.0 | 73.0 |
| Monocytes | ×10³/µL | 0.08 | 0.07 | 0.11 | 0.12 | 0.10 | 0.12 | 0.06 | 0.10 |
| % | 1.0 | 0.8 | 1.5 | 1.6 | 1.4 | 2.0 | 0.9 | 1.6 |
| Eosinophils | ×10³/µL | 0.10 | 0.10 | 0.07 | 0.12 | 0.10 | 0.09 | 0.09 | 0.08 |
| % | 1.3 | 1.3 | 1.0 | 1.6 | 1.4 | 1.5 | 1.5 | 1.4 |
| Basophils | ×10³/µL | 0.34 | 0.42 | 0.36 | 0.36 | 0.34 | 0.26 | 0.33 | 0.26 |
| % | 4.3 | 5.6 | 4.8 | 5.1 | 4.6 | 4.3 | 5.0 | 4.3 |
| Large Unstained Cells | ×10³/µL | 0.01 | 0.01 | 0.02 | 0.01 | 0.02 | 0.01 | 0.01 | 0.02 |
| % | 0.1 | 0.1 | 0.2 | 0.1 | 0.2 | 0.2 | 0.1 | 0.3 |
| PT | sec | 8.9 | 8.9 | 8.7 | 9.2 | 9.0 | 8.9 | 8.9 | 8.6 |
| APTT | sec | 12.8 | 13.7 | 13.0 | 14.6 | 12.7 | 12.4 | 12.7 | 12.4 |
| Platelets | ×10³/µL | 249 | 270 | 303 | 202 | 225 | 240 | 255 | 274 |

Supplementary Table 7. Group Mean Hematology and Coagulation Results (9-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 6.65 | 7.06 | 7.17 | 7.29a | 6.46 | 6.70 | 6.45 | 6.72 |
| Hematocrit | % | 45.1 | 45.5 | 47.0 | 47.2 | 42.7 | 42.8 | 42.0 | 43.7 |
| Hemoglobin | g/dL | 14.3 | 14.3 | 14.9 | 14.9 | 13.6 | 13.3 | 13.5 | 14.0 |
| MCV | fL | 67.8 | 64.5 a | 65.7 | 64.8 a | 66.3 | 63.9 | 65.2 | 65.1 |
| MCH | pg | 21.4 | 20.2 | 20.7 | 20.5 | 21.0 | 19.9 | 21.0 | 20.9 |
| MCHC | g/dL | 31.6 | 31.4 | 31.6 | 31.6 | 31.7 | 31.2 | 32.2 | 32.1 |
| CHCM | g/dL | 31.8 | 31.6 | 31.6 | 31.6 | 31.8 | 31.0 | 32.0 | 32.1 |
| CH | pg | 21.5 | 20.3 a | 20.7 | 20.4 a | 21.0 | 19.7 | 20.8 | 20.9 |
| Reticulocytes | ×10⁹/L | 117.9 | 111.1 | 111.5 | 157.0 | 101.5 | 99.2 | 135.1 | 95.3 |
| % | 1.77 | 1.57 | 1.55 | 2.16 | 1.63 | 1.50 | 2.16 | 1.42 |
| White Cell Count | ×10³/µL | 6.00 | 5.81 | 6.23 | 6.50 | 6.06 | 5.85 | 5.26 | 6.50 |
| Neutrophils | ×10³/µL | 1.04 | 1.32 | 1.43 | 1.65 | 1.17 | 1.22 | 1.18 | 1.68 |
| % | 17.3 | 22.4 | 22.6 | 25.5 | 19.1 | 20.9 | 21.9 | 25.9 |
| Lymphocytes | ×10³/µL | 4.42 | 3.88 | 4.05 | 4.18 | 4.36 | 3.98 | 3.46 | 4.07 |
| % | 73.6 | 66.9 | 65.2 | 64.2 | 71.9 | 67.4 | 66.1 | 62.6 |
| Monocytes | ×10³/µL | 0.12 | 0.11 | 0.21 | 0.15 | 0.14 | 0.16 | 0.15 | 0.17 |
| % | 2.0 | 2.0 | 3.4 | 2.2 | 2.4 | 2.9 | 2.8 | 2.6 |
| Eosinophils | ×10³/µL | 0.07 | 0.10 | 0.09 | 0.10 | 0.11 | 0.19 | 0.18 | 0.14 |
| % | 1.2 | 1.7 | 1.4 | 1.6 | 1.9 | 3.6 | 3.5 | 2.3 |
| Basophils | ×10³/µL | 0.34 | 0.38 | 0.44 | 0.40 | 0.27 | 0.29 | 0.27 | 0.41 |
| % | 5.8 | 6.7 | 7.2 | 6.3 | 4.5 | 5.0 | 5.2 | 6.3 |
| Large Unstained Cells | ×10³/µL | 0.01 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.03 |
| % | 0.2 | 0.4 | 0.2 | 0.3 | 0.3 | 0.3 | 0.5 | 0.3 |
| PT | sec | 8.7 | 8.7 | 8.7 | 8.8 | 9.0 | 8.9 | 8.8 | 8.9 |
| APTT | sec | 13.5 | 14.1 | 13.3 | 13.2 | 15.2 | 14.8 | 15.9 | 14.9 |
| Platelets | ×10³/µL | 330 | 259 | 360 | 262 | 273 | 303 | 157 | 264 |

a Statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 8. Group Mean Hematology and Coagulation Results (9-Month Cohort) - Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 5.99 | 5.69 | 6.13 | 6.03 | 5.60 | 5.58 | 5.88 | 5.83 |
| Hematocrit | % | 42.9 | 39.3 | 43.3 | 41.3 | 39.6 | 37.8 | 41.1 | 40.7 |
| Hemoglobin | g/dL | 14.0 | 13.3 | 14.2 | 13.6 | 12.8 | 12.0 | 13.3 | 13.2 |
| MCV | fL | 71.7 | 69.0 | 70.7 | 68.4 a | 70.7 | 67.7 | 70.1 | 70.0 |
| MCH | pg | 23.3 | 23.4 | 23.3 | 22.5 | 22.9 | 21.5 | 22.7 | 22.7 |
| MCHC | g/dL | 32.5 | 33.9 | 32.9 | 32.8 | 32.3 | 31.7 | 32.4 | 32.5 |
| CHCM | g/dL | 31.7 | 31.4 | 31.5 | 31.6 | 31.2 | 30.5 | 31.1 | 31.4 |
| CH | pg | 22.7 | 21.6 | 22.2 | 21.6a | 21.9 | 20.6 | 21.7 | 21.9 |
| Reticulocytes | ×10⁹/L | 125.8 | 125.5 | 108.9 | 147.9 | 111.1 | 119.8 | 127.1 | 103.5 |
| % | 2.11 | 2.22 | 1.79 | 2.43 | 1.98 | 2.15 | 2.18 | 1.77 |
| White Cell Count | ×10³/µL | 5.12 | 5.59 | 5.59 | 5.76 | 5.31 | 5.44 | 5.13 | 5.88 |
| Neutrophils | ×10³/µL | 1.03 | 1.26 | 1.30 | 1.42 | 1.12 | 1.12 | 1.10 | 1.36 |
| % | 20.5 | 22.1 | 23.6 | 25.0 | 20.9 | 20.9 | 21.9 | 23.8 |
| Lymphocytes | ×10³/µL | 3.70 | 3.82 | 3.82 | 3.91 | 3.82 | 3.97 | 3.61 | 4.02 |
| % | 71.7 | 68.5 | 67.9 | 67.4 | 72.5 | 72.4 | 69.9 | 67.5 |
| Monocytes | ×10³/µL | 0.03 | 0.04 | 0.05 | 0.04 | 0.03 | 0.03 | 0.03 | 0.04 |
| % | 0.6 | 0.7 | 0.8 | 0.7 | 0.5 | 0.6 | 0.5 | 0.6 |
| Eosinophils | ×10³/µL | 0.10 | 0.14 | 0.11 | 0.12 | 0.08 | 0.08 | 0.10 | 0.12 |
| % | 1.9 | 2.6 | 2.0 | 2.0 | 1.4 | 1.6 | 1.9 | 2.2 |
| Basophils | ×10³/µL | 0.27 | 0.34 | 0.31 | 0.28 | 0.26 | 0.24 | 0.29 | 0.33 |
| % | 5.3 | 6.0 | 5.7 | 5.0 | 4.8 | 4.6 | 5.8 | 5.9 |
| Large Unstained Cells | ×10³/µL | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| % | 0.0 | 0.0 | 0.1 | 0.0 | 0.0 | 0.1 | 0.1 | 0.1 |
| PT | sec | 8.7 | 8.8 | 8.6 | 8.7 | 9.6 | 8.7 | 8.6 | 9.0 |
| APTT | sec | 14.5 | 15.0 | 14.2 | 14.6 | 14.4 | 14.3 | 15.3 | 14.9 |
| Platelets | ×10³/µL | 286 | 265 | 339 | 236 | 309 | 341 | 212 | 276 |

a Statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 9. Group Mean Hematology and Coagulation Results (15-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Red Cell Count | ×10⁶/µL | 7.09 | 6.56 | 6.50 | 6.88 | 6.92 | 6.39 | 6.76 | 6.16 |
| Hematocrit | % | 49.1 | 45.5 | 45.6 | 47.0 | 47.1 | 44.0 | 46.1 | 43.3 |
| Hemoglobin | g/dL | 15.4 | 14.1 | 14.8 | 14.2 | 14.7 | 13.6 | 14.2 | 13.1 |
| MCV | fL | 69.3 | 69.4 | 70.1 | 68.4 | 68.2 | 68.8 | 68.3 | 70.6 |
| MCH | pg | 22.0 | 21.5 | 22.8 | 20.7 | 21.3 | 21.3 | 21.0 | 21.5 |
| MCHC | g/dL | 31.6 | 31.1 | 32.4 | 30.3 | 31.2 | 31.0 | 30.7 | 30.5 |
| CHCM | g/dL | 30.4 | 30.6 | 30.7 | 29.8 | 30.7 | 30.3 | 29.9 | 30.2 |
| CH | pg | 21.0 | 21.1 | 21.5 | 20.3 | 20.8 | 20.9 | 20.4 | 21.3 |
| Reticulocytes | ×10⁹/L | 110.5 | 132.3 | 117.3 | 93.8 | 102.4 | 85.1 | 75.0 | 92.2 |
| % | 1.58 | 2.00 | 1.76 | 1.37 | 1.51 | 1.34 | 1.15 | 1.48 |
| White Cell Count | ×10³/µL | 6.41 | 6.01 | 5.97 | 5.29 | 6.85 | 6.14 | 7.36 | 7.21 |
| Neutrophils | ×10³/µL | 1.28 | 1.28 | 1.47 | 1.24 | 1.14 | 1.38 | 1.65 | 1.29 |
| % | 20.1 | 21.6 | 24.9 | 23.0 | 16.6 | 22.4 | 23.5 | 19.1 |
| Lymphocytes | ×10³/µL | 4.59 | 4.35 | 4.01 | 3.67 | 5.23 | 4.44 | 5.18 | 5.46 |
| % | 71.5 | 72.0 | 66.8 | 69.6 | 76.4 | 72.2 | 69.2 | 74.4 |
| Monocytes | ×10³/µL | 0.04 | 0.03 | 0.03 | 0.02 | 0.02 | 0.03 | 0.03 | 0.04 |
| % | 0.6 | 0.5 | 0.5 | 0.4 | 0.3 | 0.4 | 0.4 | 0.6 |
| Eosinophils | ×10³/µL | 0.12 | 0.09 | 0.12 | 0.09 | 0.17 | 0.09 | 0.11 | 0.11 |
| % | 1.9 | 1.4 | 2.0 | 1.9 | 2.4 | 1.6 | 1.5 | 1.5 |
| Basophils | ×10³/µL | 0.38 | 0.27 | 0.34 | 0.28 | 0.30 | 0.20 | 0.39 | 0.30 |
| % | 5.9 | 4.6 | 5.7 | 5.1 | 4.3 | 3.4 | 5.4 | 4.4 |
| Large Unstained Cells | ×10³/µL | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 | 0.01 |
| % | 0.0 | 0.0 | 0.1 | 0.0 | 0.1 | 0.0 | 0.0 | 0.1 |
| PT | sec | 8.9 | 8.8 | 8.8 | 8.7 | 9.0 | 8.9 | 8.7 | 8.9 |
| APTT | sec | 13.5 | 13.9 | 12.9 | 14.2 | 13.1 | 14.2 | 13.1 | 12.5 |
| Platelets | ×10³/µL | 306 | 370 | 363 | 331 | 265 | 351 | 362 | 313 |

Supplementary Table 10. Group Mean Hematology and Coagulation Results (15-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 3/4 a | 4 |
| Red Cell Count | ×10⁶/µL | 6.41 | 6.10 | 6.35 | 6.04 | 6.41 | 5.97 | 5.82 | 5.86 |
| Hematocrit | % | 45.4 | 42.2 | 44.7 | 42.0 | 43.9 | 41.2 | 38.8 | 39.9 |
| Hemoglobin | g/dL | 15.0 | 14.1 | 15.0 | 13.8 | 14.3 | 13.4 | 12.8 | 13.3 |
| MCV | fL | 70.9 | 69.3 | 70.5 | 69.5 | 68.4 | 69.1 | 66.6 | 68.1 |
| MCH | pg | 23.5 | 23.1 | 23.7 | 22.8 | 22.4 | 22.4 | 22.0 | 22.7 |
| MCHC | g/dL | 33.1 | 33.4 | 33.6 | 32.8 | 32.7 | 32.5 | 33.0 | 33.4 |
| CHCM | g/dL | 31.2 | 31.7 | 31.7 | 30.3 | 31.0 | 31.1 | 31.3 | 31.7 |
| CH | pg | 22.1 | 21.9 | 22.3 | 21.1 | 21.2 | 21.4 | 20.7 | 21.5 |
| Reticulocytes | ×10⁹/L | 154.6 | 188.2 | 176.8 | 110.1 | 168.9 | 169.3 | 157.8 | 138.3 |
| % | 2.42 | 3.12 | 2.79 | 1.83 | 2.57 | 2.86 | 2.72 | 2.38 |
| White Cell Count | ×10³/µL | 6.71 | 6.14 | 5.23 | 5.18 | 5.82 | 6.11 | 5.77 | 6.67 |
| Neutrophils | ×10³/µL | 1.23 | 1.39 | 1.09 | 1.19 | 1.42 | 1.41 | 1.30 | 1.18 |
| % | 17.9 | 22.7 | 20.9 | 22.0 | 24.4 | 23.2 | 22.7 | 18.8 |
| Lymphocytes | ×10³/µL | 5.04 | 4.37 | 3.77 | 3.63 | 3.99 | 4.35 | 3.90 | 4.99 |
| % | 75.7 | 71.0 | 71.9 | 71.0 | 68.8 | 71.1 | 67.4 | 73.2 |
| Monocytes | ×10³/µL | 0.05 | 0.04 | 0.03 | 0.04 | 0.04 | 0.05 | 0.11 | 0.11 |
| % | 0.7 | 0.7 | 0.6 | 0.7 | 0.7 | 0.8 | 1.7 | 1.7 |
| Eosinophils | ×10³/µL | 0.08 | 0.08 | 0.08 | 0.09 | 0.09 | 0.07 | 0.14 | 0.09 |
| % | 1.2 | 1.3 | 1.6 | 1.7 | 1.6 | 1.1 | 2.4 b, c | 1.4 |
| Basophils | ×10³/µL | 0.29 | 0.26 | 0.27 | 0.24 | 0.26 | 0.23 | 0.33 | 0.30 |
| % | 4.5 | 4.4 | 5.2 | 4.7 | 4.5 | 3.9 | 5.8 | 4.8 |
| Large Unstained Cells | ×10³/µL | 0.01 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 | 0.00 |
| % | 0.1 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 | 0.1 | 0.1 |
| PT | sec | 8.6 | 8.6 | 8.7 | 8.7 | 8.6 | 8.6 | 11.1 | 8.7 |
| APTT | sec | 14.4 | 14.0 | 12.8 | 14.2 | 13.6 | 14.9 | 22.1 | 14.9 |
| Platelets | ×10³/µL | 279 | 323 | 261 | 275 | 280 | 309 | 273 | 289 |

a N = 3 for hematology parameters; N = 4 for coagulation parameters

b Statistically significant at p < 0.05 vs. Group 1 controls.

c Log transformation for group pairwise comparisons = 0.37% (Eosinophils for Group 1 Females = 0.19%)

Supplementary Table 11. Group Mean Serum Chemistry Results (1-Month Cohort) - Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 141 | 142 | 141 | 142 | 142 | 141 | 142 | 140 |
| Potassium | mEq/L | 4.4 | 4.7 | 4.8 | 4.6 | 4.6 | 4.4 | 4.8 | 4.3 |
| Chloride | mEq/L | 108 | 105 | 105 | 107 | 108 | 108 | 106 | 108 |
| Calcium | mg/dL | 13.2 | 13.5 | 13.4 | 13.5 | 13.3 | 13.3 | 13.5 | 13.2 |
| Phosphorus | mg/dL | 4.7 | 4.6 | 4.6 | 5.2 | 4.9 | 4.8 | 4.3 | 4.4 |
| Glucose | mg/dL | 137 | 134 | 134 | 129 | 123 | 124 | 128 | 125 |
| ALT | U/L | 56 | 36 | 35 | 35 | 39 | 39 | 31 | 36 |
| AST | U/L | 21 | 17 | 17 | 16 | 20 | 22 | 16 | 18 |
| ALP | U/L | 44 | 52 | 43 | 41 | 46 | 40 | 57 | 44 |
| T. Bilirubin | mg/dL | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Creatinine | mg/dL | 0.96 | 1.03 | 1.11 | 1.02 | 1.19 | 1.20 | 1.19 | 1.16 |
| BUN | mg/dL | 12 | 16 | 14 | 13 | 15 | 17 | 18 | 18 |
| T. Protein | g/dL | 6.0 | 6.1 | 6.1 | 6.1 | 6.0 | 5.8 | 5.8 | 5.9 |
| Albumin | g/dL | 4.5 | 4.6 | 4.4 | 4.5 | 4.4 | 4.4 | 4.3 | 4.4 |
| Globulin | g/dL | 1.6 | 1.6 | 1.7 | 1.6 | 1.6 | 1.5 | 1.6 | 1.5 |
| A/G | ratio | 2.9 | 2.9 | 2.6 | 2.8 | 2.8 | 3.0 | 2.8 | 3.0 |
| Cholesterol | mg/dL | 27 | 25 | 28 | 28 | 49 | 42 | 48 | 39 |
| Triglycerides | mg/dL | 32 | 43 | 35 | 47 | 28 | 31 | 44 | 43 |

Supplementary Table 12. Group Mean Serum Chemistry Results (1-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 140 | 140 | 141 | 141 | 141 | 142 | 142 | 141 |
| Potassium | mEq/L | 5.2 | 5.3 | 5.8 | 5.0 | 4.6 | 4.8 | 5.0 | 5.3 |
| Chloride | mEq/L | 106 | 106 | 108 | 107 | 108 | 106 | 109 | 109 |
| Calcium | mg/dL | 13.9 | 13.5 | 13.9 | 13.8 | 13.4 | 13.8 | 13.3 | 13.7 |
| Phosphorus | mg/dL | 4.3 | 3.9 | 3.7 | 4.1 | 3.3 | 3.6 | 4.0 | 3.8 |
| Glucose | mg/dL | 133 | 134 | 130 | 129 | 128 | 135 | 139 | 133 |
| ALT | U/L | 33 | 29 | 26 | 28 | 30 | 27 | 22 | 29 |
| AST | U/L | 14 | 21 | 16 | 16 | 13 | 18 | 11 | 13 |
| ALP | U/L | 39 | 44 | 40 | 36 | 50 | 40 | 58 | 47 |
| T. Bilirubin | mg/dL | 0.1 | 0.2 | 0.1 | 0.2 | 0.1 | 0.2 | 0.1 | 0.1 |
| Creatinine | mg/dL | 1.12 | 1.13 | 1.22 | 1.09 | 1.12 | 1.12 | 1.21 | 1.23 |
| BUN | mg/dL | 13 | 12 | 14 | 11 | 12 | 12 | 15a | 11 |
| T. Protein | g/dL | 5.5 | 5.6 | 5.8 | 5.7 | 5.6 | 5.7 | 5.5 | 5.8 |
| Albumin | g/dL | 4.0 | 4.2 | 4.2 | 4.1 | 4.0 | 4.3 | 4.1 | 4.3 |
| Globulin | g/dL | 1.5 | 1.4 | 1.7 | 1.6 | 1.6 | 1.5 | 1.4 | 1.6 |
| A/G | ratio | 2.8 | 3.0 | 2.5 | 2.6 | 2.6 | 3.0 | 3.0 | 2.8 |
| Cholesterol | mg/dL | 25 | 26 | 27 | 28 | 28 | 32 | 31 | 32 |
| Triglycerides | mg/dL | 77 | 62 | 69 | 87 | 59 | 55 | 63 | 69 |

a Statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 13. Group Mean Serum Chemistry Results (3-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 142 | 143 | 139 | 141 | 144 | 141 | 141 | 140 |
| Potassium | mEq/L | 4.9 | 4.5 | 4.3a | 4.8 | 4.8 | 4.8 | 4.5 | 4.2 |
| Chloride | mEq/L | 105 | 106 | 106 | 105 | 108 | 107 | 106 | 107 |
| Calcium | mg/dL | 13.2 | 13.4 | 13.1 | 13.4 | 13.7 | 13.4 | 13.3 | 13.3 |
| Phosphorus | mg/dL | 4.6 | 4.9 | 5.1 | 4.7 | 5.1 | 5.1 | 4.3 | 5.0 |
| Glucose | mg/dL | 140 | 134 | 133 | 129 | 138 | 132 | 128 | 122 |
| ALT | U/L | 34 | 37 | 41 | 24 | 45 | 27 | 35 | 32 |
| AST | U/L | 16 | 17 | 19 | 15 | 20 | 15 | 16 | 15 |
| ALP | U/L | 60 | 29a | 53 | 45 | 47 | 54 | 43 | 40 |
| T. Bilirubin | mg/dL | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Creatinine | mg/dL | 1.00 | 1.17 | 1.15 | 1.03 | 1.34 | 1.34 | 1.26 | 1.32 |
| BUN | mg/dL | 12 | 15 | 12 | 13 | 17 | 18 | 17 | 17 |
| T. Protein | g/dL | 5.9 | 6.0 | 5.7 | 6.0 | 6.0 | 5.9 | 5.8 | 5.8 |
| Albumin | g/dL | 4.4 | 4.4 | 4.3 | 4.4 | 4.4 | 4.4 | 4.2 | 4.2 |
| Globulin | g/dL | 1.5 | 1.6 | 1.5 | 1.6 | 1.6 | 1.5 | 1.6 | 1.6 |
| A/G | ratio | 2.9 | 2.8 | 3.0 | 2.8 | 2.7 | 2.9 | 2.6 | 2.7 |
| Cholesterol | mg/dL | 25 | 25 | 33a | 26 | 38 | 48 | 59 | 48 |
| Triglycerides | mg/dL | 35 | 35 | 37 | 45 | 40 | 34 | 32 | 31 |

a Statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 14. Group Mean Serum Chemistry Results (3-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 142 | 144 | 141 | 142 | 142 | 143 | 144 | 143 |
| Potassium | mEq/L | 5.3 | 5.6 | 4.6 | 5.0 | 5.3 | 5.3 | 5.5 | 5.5 |
| Chloride | mEq/L | 103 | 106 | 106 | 105 | 107 | 105 | 106 | 107 |
| Calcium | mg/dL | 14.2 | 14.2 | 13.7 | 14.0 | 14.2 | 14.5 | 14.5 | 14.1 |
| Phosphorus | mg/dL | 4.5 | 4.9 | 4.6 | 4.3 | 4.6 | 4.4 | 4.6 | 5.2 |
| Glucose | mg/dL | 135 | 138 | 123 a | 133 | 124 | 132 | 122 | 131 |
| ALT | U/L | 29 | 28 | 25 | 22 | 32 | 28 | 32 | 28 |
| AST | U/L | 13 | 14 | 12 | 11 | 13 | 17 | 13 | 12 |
| ALP | U/L | 39 | 30 | 38 | 51 | 41 | 52 | 37 | 37 |
| T. Bilirubin | mg/dL | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Creatinine | mg/dL | 1.03 | 1.25a | 1.12 | 1.03 | 1.26 | 1.23 | 1.20 | 1.34 |
| BUN | mg/dL | 17 | 19 | 18 | 18 | 22 | 23 | 23 | 23 |
| T. Protein | g/dL | 5.8 | 6.0 | 5.7 | 6.0 | 5.9 | 6.1 | 6.1 | 5.9 |
| Albumin | g/dL | 4.3 | 4.4 | 4.3 | 4.5 | 4.3 | 4.5 | 4.5 | 4.3 |
| Globulin | g/dL | 1.5 | 1.6 | 1.5 | 1.5 | 1.6 | 1.6 | 1.7 | 1.6 |
| A/G | ratio | 3.0 | 2.8 | 2.9 | 3.1 | 2.8 | 2.8 | 2.7 | 2.7 |
| Cholesterol | mg/dL | 25 | 25 | 27 | 25 | 41 | 47 | 45 | 59 |
| Triglycerides | mg/dL | 94 | 50 | 50 | 65 | 58 | 49 | 55 | 39 |

a Statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 15. Group Mean Serum Chemistry Results (6-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 147 | 148 | 147 | 147 | 147 | 146 | 146 | 147 |
| Potassium | mEq/L | 4.9 | 5.4 | 5.3 | 5.2 | 4.8 | 4.9 | 4.8 | 5.3 |
| Chloride | mEq/L | 107 | 108 | 106 | 110 | 107 | 108 | 107 | 105 |
| Calcium | mg/dL | 14.6 | 15.2 | 15.5 | 14.9 | 14.3 | 14.4 | 14.3 | 14.7 |
| Phosphorus | mg/dL | 3.3 | 3.3 | 3.3 | 3.3 | 4.0 | 4.1 | 3.5 | 3.9 |
| Glucose | mg/dL | 128 | 125 | 126 | 126 | 134 | 129 | 143 | 115 |
| ALT | U/L | 33 | 42 | 41 | 39 | 26 | 30 | 38 | 31 |
| AST | U/L | 15 | 17 | 21 | 15 | 16 | 14 | 19 | 19 |
| ALP | U/L | 47 | 37 | 38 | 48 | 52 | 52 | 52 | 55 |
| T. Bilirubin | mg/dL | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Creatinine | mg/dL | 0.95 | 0.88 | 1.01 | 0.93 | 1.26 | 1.07 | 1.13 | 1.14 |
| BUN | mg/dL | 17 | 15 | 17 | 17 | 16 | 18 | 19 | 16 |
| T. Protein | g/dL | 6.0 | 6.2 | 6.2 | 6.0 | 5.9 | 5.8 | 5.7 | 5.9 |
| Albumin | g/dL | 4.5 | 4.6 | 4.7 | 4.5 | 4.3 | 4.3 | 4.2 | 4.4 |
| Globulin | g/dL | 1.5 | 1.6 | 1.5 | 1.5 | 1.6 | 1.6 | 1.5 | 1.6 |
| A/G | ratio | 3.0 | 2.9 | 3.1 | 3.1 | 2.8 | 2.7 | 2.9 | 2.8 |
| Cholesterol | mg/dL | 29 | 28 | 33 | 26 | 73 | 49 | 53 | 44 |
| Triglycerides | mg/dL | 72 | 52 | 76 | 40 | 42 | 50 | 53 | 47 |

Supplementary Table 16. Group Mean Serum Chemistry Results (6-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 143 | 141 | 142 | 142 | 141 | 143 | 143 | 144 |
| Potassium | mEq/L | 5.3 | 5.3 | 5.1 | 5.2 | 5.1 | 5.3 | 5.1 | 6.1 |
| Chloride | mEq/L | 104 | 104 | 106 | 106 | 104 | 105 | 104 | 106 |
| Calcium | mg/dL | 14.4 | 14.3 | 14.1 | 14.0 | 14.6 | 14.4 | 14.2 | 14.2 |
| Phosphorus | mg/dL | 4.2 | 4.0 | 4.2 | 4.0 | 4.0 | 4.4 | 4.0 | 4.3 |
| Glucose | mg/dL | 143 | 139 | 135 | 130 | 132 | 134 | 149 | 135 |
| ALT | U/L | 32 | 32 | 26 | 30 | 25 | 38 | 35 | 36 |
| AST | U/L | 16 | 14 | 15 | 16 | 15 | 15 | 14 | 24 |
| ALP | U/L | 29 | 25 | 25 | 31 | 29 | 38 | 32 | 28 |
| T. Bilirubin | mg/dL | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 | 0.2 | 0.1 | 0.2 |
| Creatinine | mg/dL | 1.06 | 1.05 | 1.16 | 1.10 | 1.09 | 1.22 | 1.25 | 1.22 |
| BUN | mg/dL | 18 | 17 | 18 | 18 | 19 | 25 | 24 | 20 |
| T. Protein | g/dL | 6.1 | 5.9 | 6.0 | 5.9 | 6.1 | 6.2 | 5.9 | 6.2 |
| Albumin | g/dL | 4.7 | 4.6 | 4.6 | 4.5 | 4.5 | 4.6 | 4.4 | 4.7 |
| Globulin | g/dL | 1.4 | 1.4 | 1.4 | 1.4 | 1.6 | 1.6 | 1.5 | 1.5 |
| A/G | ratio | 3.3 | 3.3 | 3.3 | 3.2 | 2.8 | 2.9 | 3.1 | 3.1 |
| Cholesterol | mg/dL | 30 | 25 | 25 | 25 | 47 | 45 | 46 | 40 |
| Triglycerides | mg/dL | 88 | 52 | 52 | 51 | 101 | 74 | 66 | 72 |

Supplementary Table 17. Group Mean Serum Chemistry Results (9-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 143 | 142 | 142 | 143 | 141 | 141 | 141 | 143 |
| Potassium | mEq/L | 5.1 | 5.4 | 5.0 | 5.1 | 4.8 | 4.9 | 4.8 | 4.9 |
| Chloride | mEq/L | 108 | 107 | 105 | 106 | 106 | 106 | 107 | 107 |
| Calcium | mg/dL | 14.2 | 14.0 | 13.8 | 14.2 | 14.0 | 14.1 | 13.6 | 14.3 |
| Phosphorus | mg/dL | 5.8 | 5.6 | 5.7 | 5.8 | 5.6 | 5.7 | 5.0 | 4.7 |
| Glucose | mg/dL | 128 | 135 | 132 | 134 | 135 | 128 | 141 | 132 |
| ALT | U/L | 30 | 25 | 36 | 34 | 47 | 36 | 42 | 44 |
| AST | U/L | 14 | 19 | 17 | 15 | 18 | 13 | 16 | 18 |
| ALP | U/L | 91 | 75 | 63 | 77 | 60 | 66 | 73 | 44 |
| T. Bilirubin | mg/dL | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.1 | 0.2 |
| Creatinine | mg/dL | 0.95 | 0.88 | 1.00 | 1.02 | 1.43 | 1.29 | 1.27 | 1.11 a |
| BUN | mg/dL | 17 | 15 | 16 | 16 | 21 | 21 | 18 | 18 |
| T. Protein | g/dL | 6.4 | 6.4 | 6.3 | 6.5 | 6.2 | 6.1 | 6.1 | 6.0 |
| Albumin | g/dL | 4.7 | 4.8 | 4.7 | 4.8 | 4.6 | 4.5 | 4.4 | 4.4 |
| Globulin | g/dL | 1.7 | 1.7 | 1.7 | 1.7 | 1.7 | 1.6 | 1.6 | 1.6 |
| A/G | ratio | 2.8 | 3.0 | 2.9 | 2.8 | 2.7 | 2.9 | 2.7 | 2.8 |
| Cholesterol | mg/dL | 29 | 30 | 29 | 26 | 54 | 51 | 60 | 66 |
| Triglycerides | mg/dL | 78 | 71 | 35 | 43 | 40 | 47 | 34 | 33 |

a Statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 18. Group Mean Serum Chemistry Results (9-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 145 | 145 | 145 | 146 | 143 | 144 | 145 | 145 |
| Potassium | mEq/L | 5.5 | 5.4 | 5.5 | 5.5 | 4.9 | 5.5 | 5.5 | 5.5 |
| Chloride | mEq/L | 108 | 108 | 107 | 109 | 106 | 110 | 109 | 110 |
| Calcium | mg/dL | 14.4 | 14.1 | 14.4 | 14.4 | 14.2 | 14.4 | 14.2 | 14.0 |
| Phosphorus | mg/dL | 2.8 | 3.0 | 3.2 | 3.1 | 3.3 | 3.4 | 3.4 | 3.3 |
| Glucose | mg/dL | 122 | 126 | 117 | 120 | 123 | 122 | 122 | 124 |
| ALT | U/L | 31 | 21 | 28 | 28 | 35 | 30 | 50 | 43 |
| AST | U/L | 13 | 14 | 12 | 15 | 14 | 10 | 20 | 13 |
| ALP | U/L | 45 | 31 | 24 | 28 | 26 | 41 | 32 | 20 |
| T. Bilirubin | mg/dL | 0.2 | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.1 |
| Creatinine | mg/dL | 0.90 | 0.81 | 0.88 | 0.94 | 1.13 | 1.02 | 1.22 | 0.99 |
| BUN | mg/dL | 20 | 18 | 20 | 21 | 23 | 26 | 23 | 23 |
| T. Protein | g/dL | 6.0 | 5.8 | 6.1 | 5.8 | 6.3 | 6.1 | 6.1 | 6.0 |
| Albumin | g/dL | 4.4 | 4.2 | 4.4 | 4.3 | 4.4 | 4.4 | 4.4 | 4.3 |
| Globulin | g/dL | 1.6 | 1.6 | 1.7 | 1.6 | 1.8 | 1.7 | 1.8 | 1.8 |
| A/G | ratio | 2.8 | 2.6 | 2.7 | 2.8 | 2.5 | 2.6 | 2.5 | 2.4 |
| Cholesterol | mg/dL | 25 | 25 | 25 | 25 | 39 | 31 | 43 | 38 |
| Triglycerides | mg/dL | 69 | 94 | 75 | 51 | 86 | 88 | 54 | 47 |

Supplementary Table 19. Group Mean Serum Chemistry Results (15-Month Cohort) – Predose

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Sodium | mEq/L | 148 | 147 | 148 | 148 | 147 | 147 | 149 | 147 |
| Potassium | mEq/L | 5.2 | 5.2 | 5.4 | 5.1 | 4.4 | 4.7 | 5.2 | 5.0 |
| Chloride | mEq/L | 108 | 107 | 108 | 108 | 103 | 106 | 109 | 108 |
| Calcium | mg/dL | 15.3 | 14.9 | 14.9 | 15.4 | 14.1 | 14.2 | 14.6 | 15.0 |
| Phosphorus | mg/dL | 3.5 | 3.7 | 2.9 | 3.1 | 4.1 | 4.0 | 3.7 | 3.5 |
| Glucose | mg/dL | 124 | 131 | 127 | 132 | 135 | 133 | 137 | 135 |
| ALT | U/L | 27 | 31 | 29 | 44 | 32 | 31 | 24 | 32 |
| AST | U/L | 16 | 15 | 11 | 24 | 20 | 18 | 14 | 14 |
| ALP | U/L | 46 | 55 | 57 | 52 | 57 | 54 | 55 | 56 |
| T. Bilirubin | mg/dL | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.1 |
| Creatinine | mg/dL | 0.87 | 0.93 | 0.92 | 0.92 | 1.33 | 1.10 | 1.23 | 1.11 |
| BUN | mg/dL | 16 | 17 | 18 | 19 | 15 | 16 | 15 | 16 |
| T. Protein | g/dL | 6.2 | 6.1 | 6.0 | 6.2 | 6.0 | 5.8 | 6.0 | 6.2 |
| Albumin | g/dL | 4.6 | 4.5 | 4.5 | 4.5 | 4.4 | 4.3 | 4.4 | 4.5 |
| Globulin | g/dL | 1.5 | 1.5 | 1.5 | 1.7 | 1.6 | 1.5 | 1.6 | 1.7 |
| A/G | ratio | 3.1 | 3.0 | 2.9 | 2.7 | 2.8 | 2.9 | 2.7 | 2.7 |
| Cholesterol | mg/dL | 25 | 27 | 25 | 37 | 58 | 57 | 55 | 55 |
| Triglycerides | mg/dL | 56 | 108 | 48 | 53 | 55 | 41 | 36 | 65 |

Supplementary Table 20. Group Mean Serum Chemistry Results (15-Month Cohort) – Termination

|  |  |  |
| --- | --- | --- |
| Gender | Males | Females |
| Group | 1 | 2 | 3 | 4 | 1 | 2 | 3 | 4 |
| Treatment(mg/kg) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) | Sham(N/A) | Low(0.72) | Mid(1.2) | High(4.8) |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 3 | 4 |
| Sodium | mEq/L | 143 | 143 | 143 | 143 | 143 | 142 | 142 | 143 |
| Potassium | mEq/L | 4.7 | 4.7 | 4.8 | 5.1 | 5.1 | 5.1 | 5.1 | 4.8 |
| Chloride | mEq/L | 105 | 105 | 104 | 106 | 104 | 104 | 105 | 106 |
| Calcium | mg/dL | 14.0 | 14.0 | 13.8 | 13.7 | 14.0 | 13.8 | 14.0 | 13.7 |
| Phosphorus | mg/dL | 3.8 | 3.7 | 3.7 | 4.1 | 4.5 | 3.5 | 3.4 | 3.7 |
| Glucose | mg/dL | 130 | 129 | 132 | 138 | 127 | 128 | 132 | 131 |
| ALT | U/L | 20 | 24 | 27 | 27 | 31 | 32 | 26 | 31 |
| AST | U/L | 15 | 10 | 16 | 17 | 17 | 16 | 19 | 14 |
| ALP | U/L | 29 | 43 | 32 | 30 | 30 | 30 | 18 | 27 |
| T. Bilirubin | mg/dL | 0.1 | 0.2 | 0.2 | 0.2 | 0.2 | 0.1 | 0.2 | 0.2 |
| Creatinine | mg/dL | 1.17 | 1.10 | 1.15 | 1.24 | 1.25 | 1.19 | 1.11 | 1.12 |
| BUN | mg/dL | 19 | 18 | 22 | 21 | 21 | 23 | 21 | 19 |
| T. Protein | g/dL | 6.2 | 6.1 | 6.0 | 6.0 | 6.0 | 5.7 | 6.0 | 5.9 |
| Albumin | g/dL | 4.6 | 4.5 | 4.5 | 4.3 | 4.3 | 4.1 | 4.3 | 4.4 |
| Globulin | g/dL | 1.7 | 1.6 | 1.5 | 1.6 | 1.7 | 1.6 | 1.7 | 1.5 |
| A/G | ratio | 2.8 | 2.8 | 3.0 | 2.7 | 2.5 | 2.6 | 2.6 | 3.0 |
| Cholesterol | mg/dL | 25 | 25 | 25 | 28a | 37 | 36 | 33 | 34 |
| Triglycerides | mg/dL | 58 | 94 | 52 | 45 | 80 | 69 | 111 | 58 |

a Statistically significant at p < 0.05 vs. Group 1 controls.

Supplementary Table 21. Individual Animal Ophthalmic Examination Findings by Exception

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID (Cohort) | AnimalID | StudyDay | Eye | Finding(s) |
| 1F6:306 (1-Month) | 306 | 22 | Right | +1 dischargea |
| 3F6:371 (1-Month) | 371 | 22 | Right | +1 dischargea |
| 4M5:338 (1-Month) | 338 | -16 | Left | Fibrous hyaloid remnant |
| 4F5:343 (1-Month) | 343 | 22 | Left | +2 dischargea |
| 2M18:588 (15-Month) | 588 | 448 | Both | 1 corneal edemab, 1 buphthalmos,optic disc cupping |
| 3M18:578 (15-Month) | 578 | 448 | Both | 1 ocular discharge |

a+1 = Mild: Discharge is above normal and present on the inner portion of the eye but not on the lids or hairs of the eyelids. +2 = Moderate: Discharge is abundant, easily observed, and has collected on the lids and around the hairs of the eyelids.