### Male Clinical Chemistry Summary

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Endpoint** | 0.0 mg/kg N = 9-10 | 0.15 mg/kg N = 4-5 | 0.5 mg/kg N = 5 | 1.4 mg/kg N = 5 | 4.0 mg/kg N = 4 | 12.0 mg/kg N = 5 | 37.0 mg/kg N = 5 | 111.0 mg/kg N = 5 | 333.0 mg/kg N = 5 | 1000.0 mg/kg N = 1 | BMD1Std (mg/kg) | BMDL1Std (mg/kg) |
| Creatinine (mg/dL) | 0.41 ± 0.01\*\* | 0.42 ± 0.02 | 0.42 ± 0.02 | 0.42 ± 0.02 | 0.43 ± 0.03 | 0.38 ± 0.02 | 0.44 ± 0.02 | 0.46 ± 0.02 | 0.50 ± 0.03\*\* | 0.50 | 97.38 | 32.365 |
| Globulin (measured) (g/dL) | 1.95 ± 0.03\*\* | 1.96 ± 0.05 | 2.10 ± 0.06 | 2.28 ± 0.16 | 2.03 ± 0.09 | 1.70 ± 0.03\* | 1.76 ± 0.05\* | 1.40 ± 0.10\*\* | 1.34 ± 0.14\*\* | 1.20 | 0.322 | 0.188 |
| A/G Ratio (g/dL) | 2.29 ± 0.06\*\* | 2.28 ± 0.06 | 2.13 ± 0.04 | 2.03 ± 0.13 | 2.27 ± 0.08 | 2.69 ± 0.07\* | 2.71 ± 0.06\* | 3.50 ± 0.31\*\* | 3.75 ± 0.31\*\* | 3.92 | 0.456 | 0.237 |
| Albumin (g/dL) | 4.46 ± 0.06\*\* | 4.46 ± 0.07 | 4.46 ± 0.08 | 4.54 ± 0.06 | 4.58 ± 0.05 | 4.56 ± 0.05 | 4.76 ± 0.07\*\* | 4.78 ± 0.07\*\* | 4.86 ± 0.11\*\* | 4.70 | 13.365 | 4.084 |
| Cholesterol (mg/dL) | 106.6 ± 3.8\*\* | 107.6 ± 1.8 | 103.2 ± 2.2 | 114.0 ± 15.8 | 92.8 ± 5.4 | 89.6 ± 6.9 | 84.8 ± 4.2\*\* | 75.6 ± 2.8\*\* | 69.2 ± 4.9\*\* | 50.0 | NVM | NVM |
| Triglycerides (mg/dL) | 99.9 ± 9.9\*\* | 85.6 ± 9.9 | 107.4 ± 19.0 | 118.4 ± 35.2 | 82.0 ± 3.0 | 48.8 ± 8.3\*\* | 66.8 ± 14.0\* | 53.0 ± 2.9\*\* | 58.6 ± 14.8\* | 111.0 | NVM | NVM |
| Alanine aminotransferase (IU/L) | 61.2 ± 3.6\*\* | 64.0 ± 5.2 | 55.0 ± 2.6 | 58.8 ± 3.2 | 70.5 ± 4.3 | 57.4 ± 3.7 | 72.2 ± 3.1\* | 110.2 ± 19.6\* | 209.2 ± 67.2\*\* | 134.0 | 36.116 | 21.468 |
| Alkaline phosphatase (IU/L) | 302.2 ± 19.9\*\* | 315.8 ± 18.4 | 277.2 ± 11.1 | 322.8 ± 18.7 | 346.0 ± 15.5 | 325.0 ± 16.9 | 335.8 ± 23.5 | 357.2 ± 18.3 | 527.8 ± 34.1\*\* | 466.0 | 89.383 | 74.114 |
| Aspartate Aminotransferase (U/L) | 80.10 ± 4.72\*\* | 83.40 ± 4.86 | 72.20 ± 3.09 | 78.40 ± 3.36 | 82.50 ± 4.56 | 74.20 ± 3.73 | 91.00 ± 4.71 | 128.40 ± 17.32\*\* | 195.00 ± 54.03\*\* | 154.00 | 28.117 | 19.352 |
| Sorbitol dehydrogenase (IU/L) | 14.8 ± 1.7\* | 20.5 ± 4.9 | 11.6 ± 1.6 | 14.6 ± 3.1 | 10.1 ± 1.6 | 10.5 ± 0.6 | 19.6 ± 3.5 | 46.1 ± 17.1 | 56.3 ± 21.9 | 12.6 | 48.424 | 31.861 |

### Female Clinical Chemistry Summary

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Endpoint** | 0.0 mg/kg N = 10 | 0.15 mg/kg N = 5 | 0.5 mg/kg N = 5 | 1.4 mg/kg N = 5 | 4.0 mg/kg N = 5 | 12.0 mg/kg N = 5 | 37.0 mg/kg N = 5 | 111.0 mg/kg N = 5 | 333.0 mg/kg N = 5 | 1000.0 mg/kg N = 5 | BMD1Std (mg/kg) | BMDL1Std (mg/kg) |
| Creatinine (mg/dL) | 0.41 ± 0.02\* | 0.40 ± 0.00 | 0.44 ± 0.02 | 0.42 ± 0.02 | 0.44 ± 0.02 | 0.42 ± 0.02 | 0.48 ± 0.02 | 0.40 ± 0.00 | 0.46 ± 0.02 | 0.46 ± 0.02 | NVM | NVM |
| Cholesterol (mg/dL) | 95.6 ± 4.9\*\* | 100.6 ± 7.7 | 104.8 ± 8.0 | 93.6 ± 11.9 | 82.2 ± 3.8 | 84.8 ± 2.2 | 90.4 ± 2.7 | 92.8 ± 3.1 | 38.0 ± 4.5\*\* | 54.0 ± 6.8\*\* | 1.591 | 0.58 |
| Triglycerides (mg/dL) | 70.9 ± 10.4\* | 68.6 ± 18.8 | 45.4 ± 6.3 | 40.6 ± 7.7 | 34.6 ± 9.3 | 39.4 ± 5.2 | 47.0 ± 10.5 | 53.0 ± 7.7 | 111.0 ± 7.1 | 143.2 ± 25.2 | 1.518 | 0.255 |
| Aspartate Aminotransferase (U/L) | 72.80 ± 1.78\*\* | 73.60 ± 2.44 | 71.80 ± 2.03 | 76.40 ± 3.53 | 77.00 ± 2.59 | 75.60 ± 2.48 | 79.20 ± 2.97 | 74.00 ± 3.70 | 76.00 ± 2.74 | 103.60 ± 19.79\*\* | 497.046 | 340.458 |
| Bile salts/acids (umol/L) | 15.7 ± 1.6\* | 26.2 ± 3.5 | 16.4 ± 2.4 | 21.2 ± 4.9 | 19.8 ± 3.6 | 17.6 ± 3.8 | 27.0 ± 6.4 | 21.8 ± 4.9 | 30.0 ± 5.5 | 24.8 ± 7.3 | 257.017 | 21.486 |

Values given as mean ± SEM (N) of animals that survived to study termination.

Statistical analysis were performed by Jonckheere (trend) and Shirley or Dunn (pairwise) tests.

Statistical significance for the control group indicates a significant trend test

Statistical significance for a treatment group indicates a significant pairwise test compared to the vehicle control group

\* Statistically significant at p ≤ 0.05

\*\* Statistically significant at p ≤ 0.01

Only one animal in the male highest dose group so it was excluded from stats and BMD calculation.

One value for Alkaline Phosphatase in the male 0 mg/kg group and one value for Alkaline Phosphatase in the male 0.15 mg/kg group were excluded due to sample and/or analysis problems.

BMD1Std and BMDL1Std: Benchmark response (BMR) set at 1 standard deviation from the mean.

NVM = no viable model