**SUPPLEMENTAL MATERIAL**

**OUTLIER ANALYSIS**

Data analysis revealed that 1 animal in the control group and 3 animals in the high dose lixivaptan group had ratios of organ weight over total body weight that were greater than 1.5 to 2 standard deviations above the mean. In particular, the organ to body weight ratios for kidney, heart and spleen were concomitantly elevated in these animals. The significance of this finding remains unknown, however it indicates an underlying process that may confound the experimental results. Supplemental Table 1 shows the organ to body weight ratios for these animals relative to the group mean value.

**Supplemental Table 1. Organ to body weight ratios for 4 outlier animals**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Kidney weight to body weight ratio** | **Spleen weight to body weight ratio** | **Heart weight to body weight ratio** |
| **Control group** |  |  |  |
| Animal 469 | 3.59 | 1.37 | 1.60 |
| Group mean\* | 1.67 | 0.42 | 0.52 |
| Group standard deviation\* | 0.58 | 0.28 | 0.32 |
| **High Dose Lixivaptan group** |  |  |  |
| Animal 459 | 3.92 | 2.41 | 1.42 |
| Animal 477 | 3.26 | 0.66 | 1.44 |
| Animal 453 | 2.66 | 1.30 | 1.29 |
| Group mean\* | 1.61 | 0.51 | 0.56 |
| Group standard deviation\* | 0.78 | 0.51 | 0.37 |

\* Group mean and SD include all animals.

Analysis of the efficacy parameters for the high dose group with and without the 3 outliers is shown in Supplemental Table 2. Note that the outlier in the Control group was removed as well. Note: the results for the low dose of lixivaptan remained unchanged as no outliers were identified in this group. Removing these three outliers from the high dose group and one similar outlier from the control group resulted in a significant difference between high dose and control for the % kidney weight/body weight (1.3% vs. 1.6%, respectively; p=0.007).

**Supplemental Table 2. Effects of high dose lixivaptan after correcting for outliers**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameters** | **Control†** | **Lixivaptan high dose,**  **outliers included** | | **Lixivaptan high dose,**  **outliers excluded** | |
|  | Mean ± SD | Mean ± SD | p-value vs. control\* | Mean ± SD | p-value vs. control\* |
| Kidney weight/body weight ratio, % | 1.57 ± 0.37 | 1.61 ± 0.78 | 0.81 | 1.30 ± 0.11 | **0.007** |
| Cystic index, % | 16.2 ± 5.4 | 11.9 ± 3.3 | **0.011** | 12.3 ± 3.2 | **0.015** |
| Kidney fibrosis score | 2.81 ± 2.08 | 2.5 ± 1.1 | 0.61 | 2.58 ± 1.13 | 0.68 |
| Plasma Creatinine, mg/dL | 0.73 ± 0.06 | 0.68 ± 0.05 | **0.006** | 0.67 ± 0.05 | **0.006** |
| Liver cyst index, % | 5.7 ± 2.1 | 6.5 ± 1.0 | 0.67 | 5.9 ± 2.1 | 0.75 |
| Renal cAMP, pmol/mg protein | 20.3 ± 6.5 | 23.8 ± 9.8 | 0.23 | 22.1 ± 6.2 | 0.42 |

**†** Data in the control group exclude 1 outlier (animal 469).

\* P-values were calculated using a Student t-test comparison vs. control.

In bold: statistically significant p-values.