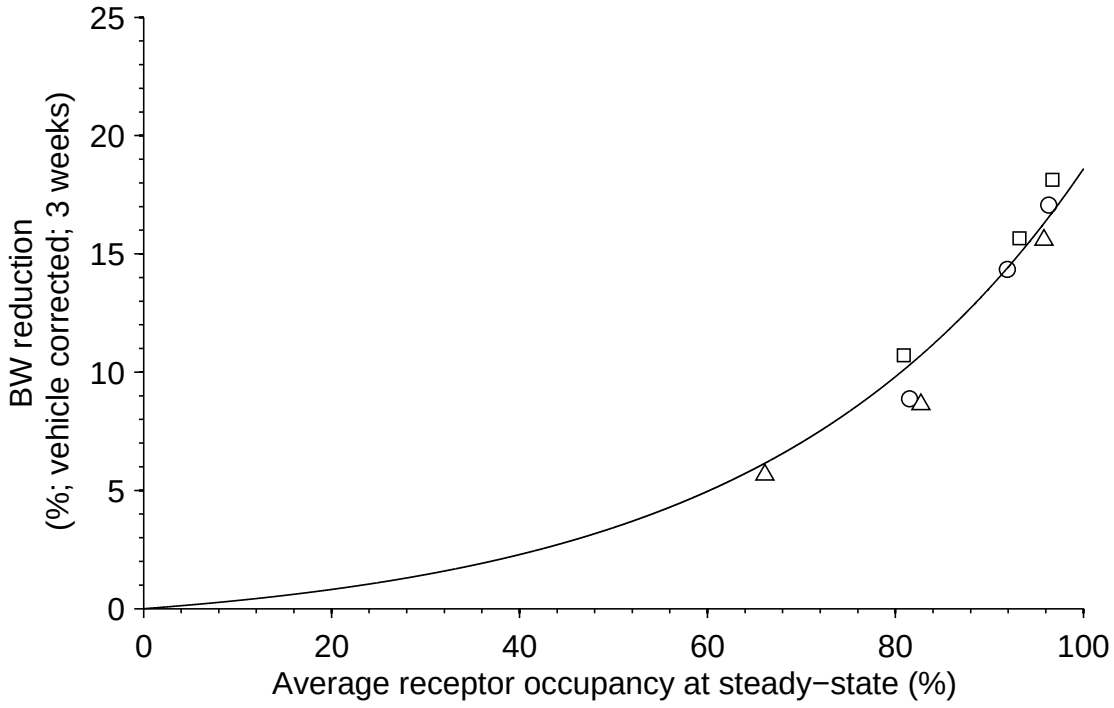

Supplementary Figure 4. Model selection for body-weight (BW) reduction to receptor occupancy (RO) in the mouse (Step 2). The main assumption was that RO at 24 h drives the BW reduction in animals. An alternative model is that average RO drives BW reduction. Time-series data on RO are relatively sparse since every time-point requires one mouse to be sacrificed. Therefore, samples in the in vivo studies have been focused on the 24 h time-point. We can, however, model plasma concentration and RO, and predict average RO at steady state in the same way as described in Ploj et al. (2016). Data from several compounds of the chemical series indicate an exponential relationship between BW reduction and average RO at steady state in the mouse (circles represent AZD1979, squares represent Compound 99, and triangles represent Compound 88). Because of the additional modelling step, and because of the non-linear relationship, we argue that observed RO at 24 h is a more robust measure, and we have therefore used it in the interspecies translation.