



**Figure S7:** The simulation for the PK profiles of unbound vismodegib in the plasma and effect compartment and the proportion of grade  $\geq 1$  muscle spasm was based on 150mg daily dose for 12-weeks with 24-weeks washout using the PO model. The actual age and body weight (from the 74 patients in the dataset), and the typical value of AAG ( $30 \mu\text{M}$ ) were used in the simulation as PK covariate. 500 simulations with 200 patients for each simulation (sampling with replacement from the 74 patients) were conducted. The shaded areas are the 95% prediction intervals. The observed proportion of grade  $\geq 1$  muscle spasm over time (red cycle) was from the cohort 2.