Equation used for simulation

The final estimate for Cl/F, covariates effect and variance were used for the simulations as follows:

Log (Cl/F)= log (6.22)+ 0.0107*(Clcr-79.08)+ 0.75* (log wt-log 56)+ ETA (5)

(The 6.22 is the typical value of Cl/F in the population, Clcr is the individual creatinine clearances and wt is the individual bodyweights. ETA is the individual random effect and follows and a normal distribution with a mean of 0 and standard deviation of 0.264)

Simulations with R

#First we uploaded the excel design file which contains demographic and dosing information for the 10,000 virtual patients, the file was named LEVO,

file header shown below, wt is weight, clcr is creatinine clearance

```
> head(LEVO)
  ID dose   wt      clcr
1  1 1000 54.0 121.07143
2  2 1000 50.8  96.76190
3  3 1000 54.0 101.78571
4  4 1000 53.2  69.78395
5  5 1000 54.2  99.63552
6  6 1000 46.9  50.62222
```

#The R code used for the simulations is shown below

```
set.seed(1234)

e<-rnorm(10000,0,0.264) # setting the eta distribution for Cl/F

logwt=log(LEVO$wt) # log transforming body weight

A=(LEVO$clcr-79.08)*0.0107 # slope effect of clcr (creatinine clearance) scaled to 79.08 L/hr

B=(logwt-log(57.44))*0.75 # slope effect of log transformed bodyweight scaled to log 55.5 kg


logcli=log(6.22)+A+B+e # setting equation for Cl/F, 6.22 is the typical value of Cl/F in the population

cli=exp(logcli) # returning Cl/F to natural scale

AUC=LEVO$dose/cli # calculating AUC 0-24
```

```
fAUC=0.6*AUC # setting free fraction for LEVO at 0.6

# Target attainment calculated at an MIC = 2 as follows

MIC=2

TA <- fAUC/MIC

100*sum(TA > 53)/10000

100*sum(TA > 100)/10000
```