**Supplementary Information**

*Clinical Pharmacokinetics*

# Population Pharmacokinetics and Pharmacodynamics of Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

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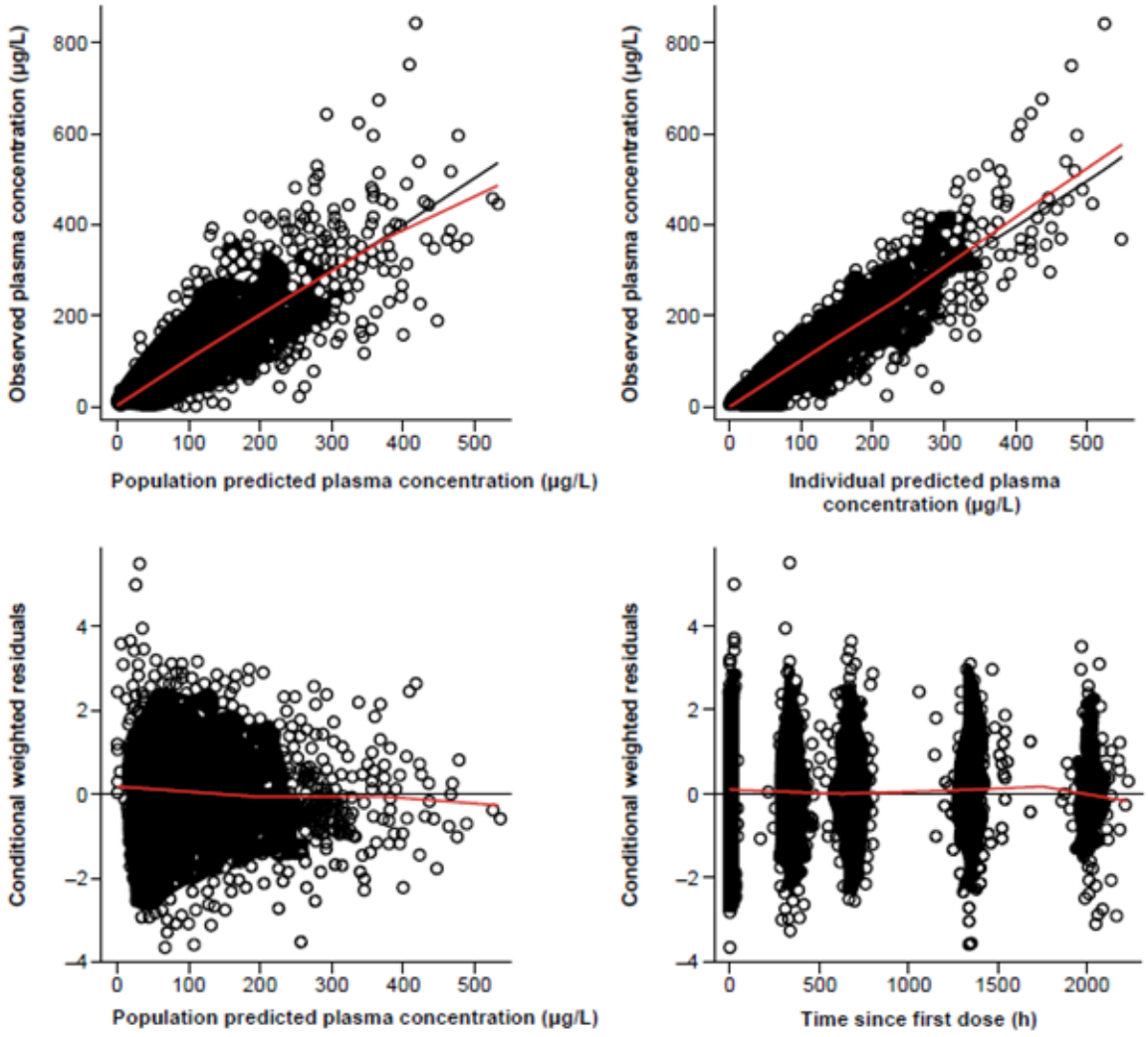
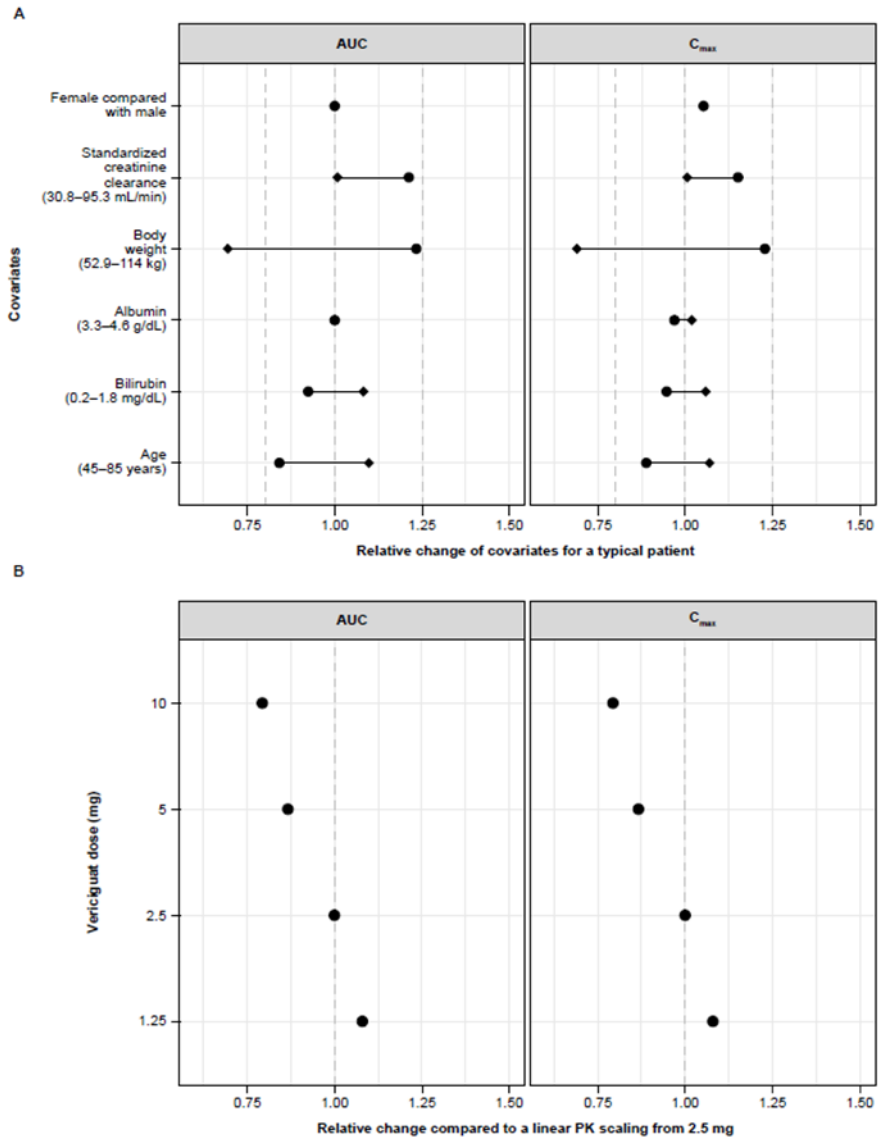
**Supplementary Fig. 1** Goodness-of-fit plots for the final population PK model



**Supplementary Fig. 2** Forest plots of deterministic simulations visualizing covariate influence on PK exposure (AUC and $C_{max}$ at steady-state)




A) Relative change in PK exposure (AUC and $C_{max}$ at steady state) compared to a typical patient with a daily 2.5 mg vericiguat administration. In the case of continuous covariates, the diamonds indicate the change corresponding to the 95$^{th}$ percentile of the covariate and the circles indicate the change corresponding to the 5$^{th}$ percentile of the covariate. B) Relative change in PK exposure (AUC and $C_{max}$) from popPK model with dose-dependence of bioavailability compared with a linear PK scaling from 2.5 mg. Dashed lines indicate the 0.8 and 1.25-fold change.

**Supplementary Table 1** Pharmacokinetic sampling scheme for the population PK analysis

| **Measurement** | **Sampling scheme** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Visit** | **Screening** | **1** | **2** | **3** | **4** | **5[c]** | **Follow-up** |
| Day/Window | −28–0[a] | 0 | 14±2[b] | 28±2[b] | 56±2[b] | 84±2[b] | +30±5[d] |
| PK[e] | | x | x | x | x | x | |
| Blood[f] | | x | x | x | x | x | x |
| BP/HR[g] | x | x | x | x | x | x | x |

*BP* blood pressure, *HR* heart rate

[a]Can start from hospitalization (or equivalent) up to 4 weeks after discharge (or after clinical stabilization upon hospitalization equivalent) and no more than 4 weeks before randomization

[b]Allows for timeframes of 5 days, e.g. visit 2 can take place on days 12–16

[c]Completion or premature discontinuation visit (in case of premature stop of study drug, the same measurements and procedures should be performed as at visit 5)

[d] After last intake of study drug

[e]Blood samples were taken at baseline/trough at Visits 2–4 (prior to study drug) and at Visit 5; at Visits 1 and 3, 1–3 hours and 4–6 hours post-study drug dosing; and at Visits 2 and 4, 1–3 hours post-study drug dosing. Optional additional pre-dose sample on Day 1 (trough 24 hours after first study drug) for hospitalized patients

[f]NT-proBNP, clinical chemistry, hematology, coagulation (prior to drug intake or on visit 5 ~24 hours after last drug intake)

[g]Three measurements, 2 min apart; measurements are taken prior to and at 2h post study-drug dosing

**Supplementary Table 2** Run record of key runs in base model development

| Run name | Parent run | OFV | ΔOFV | Comments |
|---|---|---|---|---|
| 0 | – | 26,194.906 | n/a | One-compartment model with first-order absorption, proportional error model, no lag-time |
| 1 | 0 | 26,131.062 | −63.844 | Test of residual error model |
| 2 | 0 | 26,050.443 | −144.463 | Combined error model |
| 3 | 2 | 26,048.332 | −2.111 | Lag-time |
| 4 | 2 | 25,940.152 | −110.291 | Correlation between CL/F and V/F included |
| 5 | 2 | 26,047.805 | −2.638 | Two-compartment model |
| 6 | 4 | 25,985.740 | 45.588 | Variability on $k_a$ removed |

*CL/F* apparent clearance, $k_a$ absorption rate constant, *OFV* objective function value, *V/F* apparent volume of distribution.

**Supplementary Table 3** Stepwise covariate modeling results

| Run[a] | Covariates included[a] | Covariate relationship included/eliminated[b] | ΔOFV | IIV of | | | Change in IIV of (%)[c]: | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | $k_a$ | CL/F | V/F | $k_a$ | CL/F | V/F |
| 0 | – | – | | 0.696 | 0.1300 | 0.0732 | | | |
| 1 | – | WGHT on CL/F, exponent fixed: 0.75, WGHT on V/F, exponent fixed: 1.0 | −160.836 | 0.923 | 0.0909 | 0.0504 | 32.60 | −30.10 | −31.10 |
| 2 | on CL/F: WGHT<br>on V/F: WGHT | AGE on CL/F | −46.887 | 0.951 | 0.0775 | 0.0491 | 3.00 | −14.70 | −2.60 |
| 3 | on CL/F: WGHT, AGE<br>on V/F: WGHT | BILI on CL/F | −18.098 | 0.949 | 0.0731 | 0.0485 | −0.20 | −5.70 | −1.20 |
| 4 | on CL/F: WGHT, AGE, BILI<br>on V/F: WGHT | ALB on $k_a$ | −19.199 | 0.856 | 0.0724 | 0.0485 | −9.80 | −1.00 | 0.00 |
| 5 | on CL/F: WGHT, AGE, BILI<br>on V/F: WGHT<br>on $k_a$: ALB | CRCL on CL/F | −16.064 | 0.856 | 0.0685 | 0.0485 | 0.00 | −5.40 | 0.00 |
| 6 | on CL/F: WGHT, AGE, BILI, CRCLST<br>on V/F: WGHT<br>on $k_a$: ALB | SEX on V/F | −15.219 | 0.861 | 0.0686 | 0.0437 | 0.60 | 0.10 | −9.90 |
| 7 | on CL/F: WGHT, AGE, BILI, CRCLST<br>on V/F: WGHT, SEX<br>on $k_a$: ALB | WGHT on $k_a$ | −15.198 | 0.795 | 0.0683 | 0.0400 | −7.70 | −0.40 | −8.50 |
| 8 | on CL/F: WGHT, AGE, BILI, CRCLST<br>on V/F: WGHT, SEX<br>on $k_a$: ALB, WGHT | RACE on V/F | −10.806 | 0.817 | 0.0679 | 0.0366 | 2.8 | −0.6 | −8.5 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 9 | on CL/F: WGHT, AGE, BILI, CRCLST<br>on V/F: WGHT, SEX, RACE<br>on $k_a$: ALB, WGHT | RACE on V/F<br>(eliminated) | +10.806 | 0.795 | 0.0683 | 0.04 | −2.7 | 0.6 | 9.3 |
| 10 | on CL/F: WGHT, AGE, BILI, CRCLST<br>on V/F: WGHT, SEX, RACE<br>on $k_a$: ALB, WGHT<br>on F: DOSE | DOSE on F | −126.699 | 0.867 | 0.061 | 0.043 | 9.1 | −10.3 | 7.5 |

*ALB* albumin, *BILI* bilirubin, *CL/F* apparent clearance, *CRCLST* standardized creatinine clearance, *IIV* inter-individual variability, $k_a$ absorption rate constant, *RSE* relative standard error, *V/F* apparent volume of distribution, *WGHT* weight.

[a]Covariate parameter relationships previously included.

[b]Covariate parameter relationships included in the current step, additionally to the previously included relationship or relationships eliminated in the current step, of the relationship included.

[c]Change vs. result of the previous run from the stepwise covariate model development, i.e. as documented in column “IIV of …”

**Supplementary Table 4** Descriptive statistics of PK estimates of vericiguat (including dose dependency)

| PK parameter | Vericiguat dose | n | Arithmetric mean | Arithmetric std | Geometric mean | Geometric std | Min | Median | Max | 5th percentile | 95th percentile |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $AUC_{\tau,ss}$ (µg*h/L) | 1.25 | 68 | 1142.328 | 440.881 | 1069.344 | 1.433 | 507.558 | 1000.559 | 2646.634 | 611.949 | 1850.920 |
| | 2.5 | 71 | 2156.314 | 701.038 | 2053.981 | 1.366 | 1015.985 | 1998.008 | 4251.011 | 1215.585 | 3465.766 |
| | 5 | 64 | 3703.806 | 1220.686 | 3513.932 | 1.39 | 1878.42 | 3668.427 | 7934.754 | 2063.794 | 5908.759 |
| | 10 | 40 | 6588.793 | 2136.623 | 6247.014 | 1.398 | 3375.199 | 6327.505 | 11018.953 | 3471.135 | 10049.354 |
| $C_{max,ss}$ (µg/L) | 1.25 | 68 | 63.373 | 21.741 | 60.140 | 1.378 | 28.398 | 55.732 | 137.769 | 37.046 | 100.703 |
| | 2.5 | 71 | 119.732 | 33.872 | 115.505 | 1.305 | 64.948 | 114.708 | 212.901 | 71.921 | 198.263 |
| | 5 | 64 | 203.337 | 58.024 | 195.378 | 1.331 | 112.302 | 205.521 | 374.067 | 126.212 | 307.057 |
| | 10 | 40 | 370.173 | 103.866 | 355.809 | 1.334 | 194.387 | 348.508 | 611.790 | 212.723 | 532.722 |
| $C_{trough,ss}$ (µg/L) | 1.25 | 68 | 32.313 | 14.797 | 29.437 | 1.535 | 12.662 | 27.838 | 81.906 | 15.769 | 59.820 |
| | 2.5 | 71 | 61.27 | 24.997 | 56.706 | 1.488 | 22.932 | 55.82 | 142.389 | 26.658 | 110.379 |
| | 5 | 64 | 107.225 | 45.007 | 98.428 | 1.529 | 40.522 | 105.169 | 280.943 | 48.310 | 185.855 |
| | 10 | 40 | 180.993 | 73.705 | 166.055 | 1.538 | 69.933 | 176.512 | 343.245 | 78.348 | 314.342 |
| $PTR_{ss}$ | 1.25 | 68 | 2.078 | 0.391 | 2.043 | 1.202 | 1.258 | 2.027 | 3.404 | 1.521 | 2.823 |
| | 2.5 | 71 | 2.082 | 0.458 | 2.037 | 1.233 | 1.300 | 2.022 | 3.784 | 1.457 | 2.818 |
| | 5 | 64 | 2.036 | 0.490 | 1.985 | 1.250 | 1.331 | 1.948 | 3.885 | 1.388 | 2.993 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 10 | 40 | 2.190 | 0.483 | 2.143 | 1.233 | 1.444 | 2.110 | 3.453 | 1.519 | 3.241 |
| $t_{1/2}$ (h) | 1.25 | 98 | 21.787 | 5.695 | 21.085 | 1.293 | 10.857 | 21.457 | 41.205 | 13.939 | 32.158 |
| | 2.5 | 114 | 21.606 | 5.633 | 20.912 | 1.293 | 11.809 | 21.365 | 40.253 | 12.278 | 32.175 |
| | 5 | 87 | 22.049 | 7.679 | 20.955 | 1.366 | 11.462 | 20.702 | 49.550 | 12.700 | 40.002 |
| | 10 | 58 | 20.181 | 5.609 | 19.483 | 1.302 | 11.138 | 18.616 | 35.020 | 12.913 | 32.841 |

*AUC* $_{\tau,ss}$ area under the plasma concentration–time curve at steady state, $C_{max,ss}$ maximum plasma drug concentration at steady state, $C_{trough,ss}$ trough plasma concentration at steady state, *PTR* peak-to-trough ratio, $t_{1/2}$ elimination half-life.

**Supplementary Table 5** Linear regression parameter table

| | Visit 1 | Visit 4 |
|---|---|---|
| Intercept (SBP change from pre- to post-dose [mmHg]) | −5.857 ($p < 0.001$) | −5.124 ($p < 0.001$) |
| Slope (vericiguat $C_{max}$ [µg/L]) | −0.039 ($p = 0.047$) | – |
| Slope (vericiguat $C_{max,ss}$ [µg/L]) | – | −0.003 ($p = 0.528$) |

*$C_{max}$* maximum plasma drug concentration, *$C_{max,ss}$*, maximum plasma drug concentration at steady state, *SBP* systolic blood pressure.