Supplementary material S1. **Development of the pharmacokinetic models** (Monolix®)

The main steps of the model selection workflow are presented here with the results. Several intermediate steps and additional model calculations, which did not lead to model improvement, are not presented here to reduce the amount of information presented. Also, Plots of concentration time course were observed as well as residual distributions but are not fully reported here.

In this appendix, the original parameters (names) are presented as generated by Monolix®. To compare to the article, use the following equivalence:

| Name in the Appendix | Name in the article / Tables |
|---|---|
| V1 | $V_{(S/R)-1}$ |
| Cl | $Cl_{(S/R)e}$ |
| Q | $Cl_{(S/R)-12}$ |
| V2 | $V_{(S/R)-2}$ |
| Clm | $Cl_{(S/R)-1N}$ |
| Kpm | $Cl_{(S/R)Ne}$ |

# Index

# 1. Modelling for S-Ketamine:

## 1.1. Noncompartmental analysis (NCA):

Model applied: Intravascular administration, “linear up log down” method for integral of AUC calculation, 3 last points for lambda_z, BLQ=LOQ/2.

**TableS1_1.1.1** Median/Mean adjusted $R^2$ with different weighting.

| *Weighting* | Uniform | 1/Y | $1/Y^2$ |
|---|---|---|---|
| Median adjusted $R^2$ | 0.91/0.87 | 0.91/0.88 | 0.94/0.89 |

Conclusion: The weighting $1/Y^2$ was retained.

**Table S1_1.1.2** Final NCA estimates for S-Ketamine.

| | Q1 | median | Q3 | mean | SD | SE | CV (%) | GeoMean |
|---|---|---|---|---|---|---|---|---|
| $C_{max}$ ($mg \cdot L^{-1}$) | 0.15 | 0.16 | 0.25 | 0.21 | 0.12 | 0.042 | 55.3 | 0.19 |
| $V_d$ ($L \cdot kg^{-1}$) | 3.25 | 5.19 | 6.33 | 5.35 | 3.13 | 1.11 | 58.5 | 4.57 |
| CL ($L \cdot min^{-1} \cdot kg^{-1}$) | 0.21 | 0.25 | 0.28 | 0.26 | 0.082 | 0.029 | 31.25 | 0.25 |
| $T_{1/2}$ (min) | 9.09 | 11.15 | 17.87 | 14.45 | 8.84 | 3.13 | 61.17 | 12.59 |
| $k_{el}$ ($min^{-1}$) | 0.039 | 0.063 | 0.077 | 0.062 | 0.03 | 0.011 | 49.06 | 0.055 |
| $AUC_{0\text{-}inf}$ ($min \cdot mg \cdot L^{-1}$) | 1.79 | 2.01 | 2.36 | 2.05 | 0.55 | 0.19 | 26.68 | 1.99 |
| $AUMC_{0\text{-}inf}$ ($min^2 \cdot mg \cdot L^{-1}$) | 23.78 | 31.44 | 46.29 | 36.88 | 20.76 | 7.34 | 56.28 | 32.34 |
| $MRT_{0\text{-}inf}$ (min) | 10.19 | 14.61 | 21.67 | 17.3 | 10.01 | 3.54 | 57.84 | 15.16 |

## 1.2. Individual compartmental analysis:

Model applied: Intravenous infusion administration, no delay, mammillary 1-to-3 compartments, linear elimination, BLQ=LOQ/2.

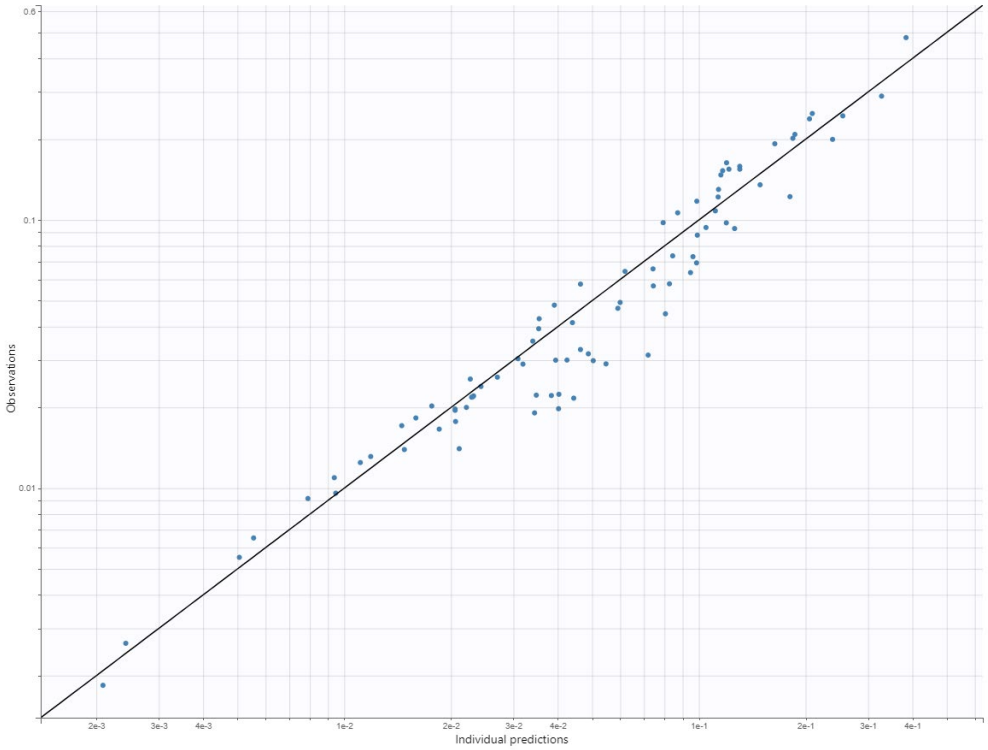
First run with **Optimization Cost function**: $(Y_{pred}-Y_{obs})^2 / Y_{pred}^2$

**TableS1_1.2.1** Diagnostic values with different compartment models.

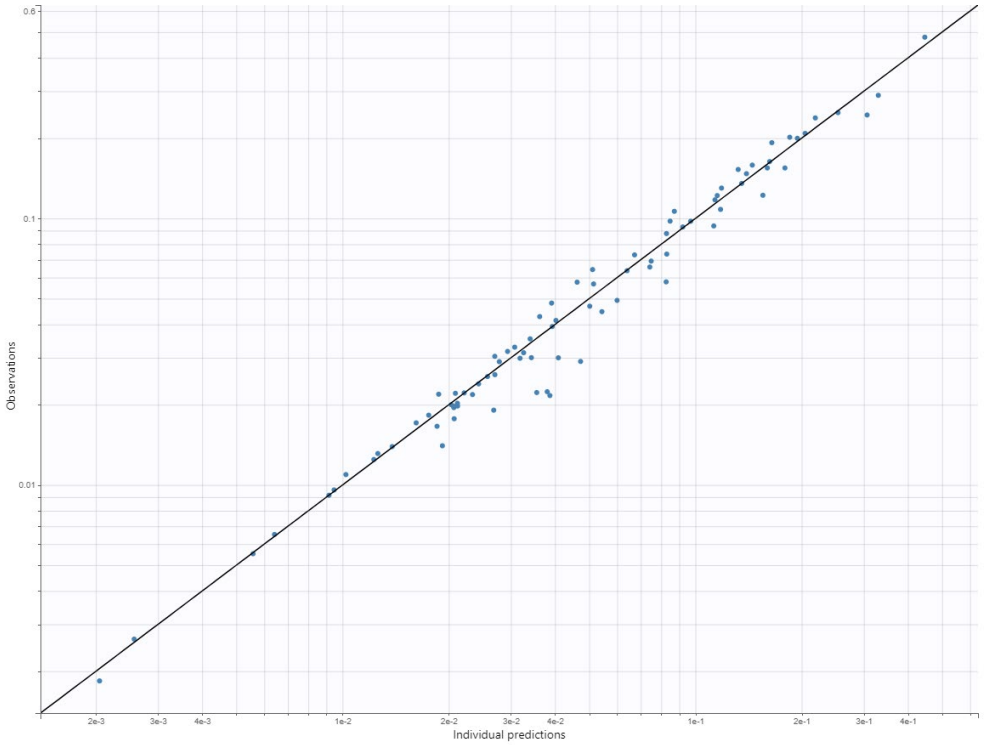
| *Model* | 1-Comp | 2-Comp | 3-Comp |
|---|---|---|---|
| -2LL (OFV) | -521 | -608 | -556 |
| AIC | -455 | -478 | -362 |
| BIC | -464 | -498 | -394 |

**Figure S1_1.2.1** Observed vs. predicted concentrations with different compartment models

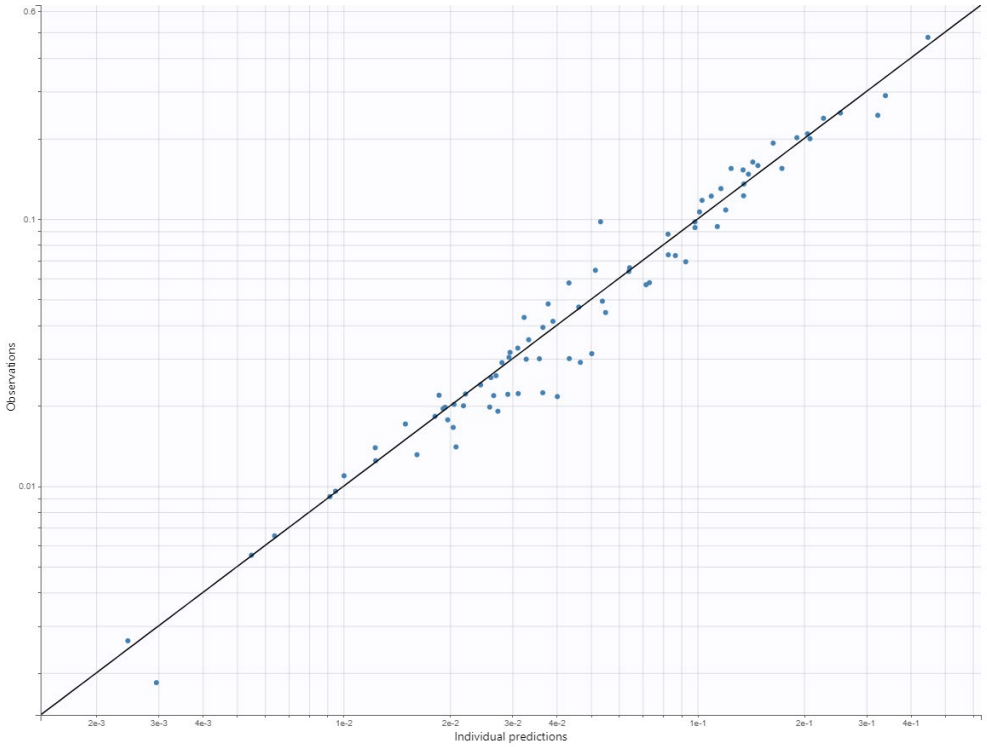
S1_1.2.1.a One-compartment model



S1_1.2.1.b Two-compartments model




S1_1.2.1.c Three-compartments model




Conclusion: The two-compartments model was retained.

Definition: $Y = (Y_{pred}-Y_{obs})$

**TableS1_1.2.2** Diagnostic values with different cost function used for approximation.

| *Cost function* | $Y^2$ | $Y^2 / Y_{obs}$ | $Y^2 / Y_{pred}$ | $Y^2 / Y_{obs}^2$ | $Y^2 / Y_{pred}^2$ | $Y^2 / \lvert Y_{pred} . Y_{obs} \rvert$ |
|---|---|---|---|---|---|---|
| Cost | 0.01 | 0.1 | 0.08 | 1.8 | 1.76 | 1.85 |
| -2LL (OFV) | -562 | -594 | -604 | -610 | -606 | -608 |
| AIC | -432 | -464 | -474 | -480 | -476 | -478 |
| BIC | -452 | -484 | -494 | -500 | -496 | -498 |

Conclusion: The Cost function $\mathbf{Y^2 / Y_{obs}^2}$ is retained.

**TableS1_1.2.3** Confirmation of the most appropriate compartment model.

| *Model* | 1-Comp | 2-Comp | 3-Comp |
|---|---|---|---|
| -2LL (OFV) | -526 | -610 | -600 |
| AIC | -460 | -480 | -405 |
| BIC | -468 | -500 | -437 |

Conclusion: The Two-compartmental model is further retained.

**Figure S1_1.2.2** Observed vs. predicted concentrations.

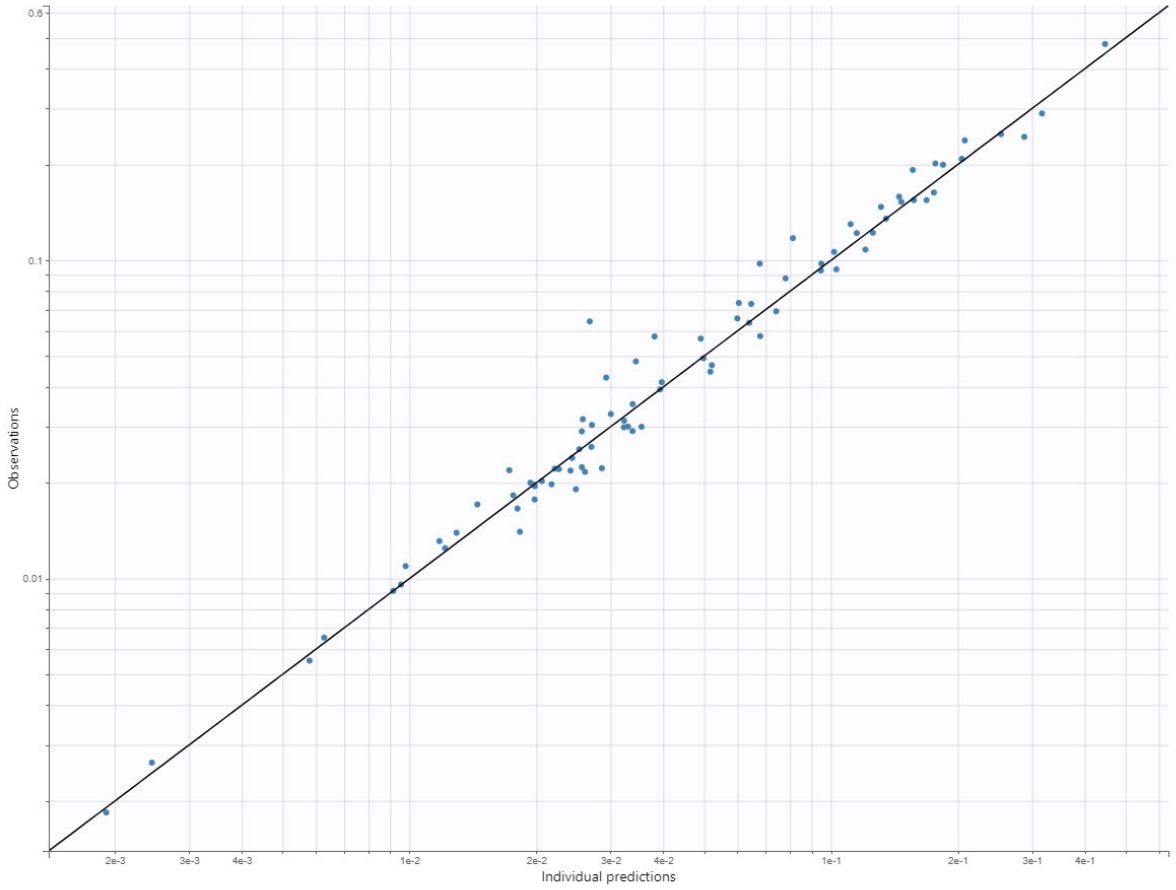


**Table S1_1.2.4** Final estimates of the two-compartmental model for S-Ketamine.

| | Q1 | median | Q3 | mean | SD | SE | CV (%) | GeoMean |
|---|---|---|---|---|---|---|---|---|
| Cl ($L \cdot min^{-1} \cdot kg^{-1}$) | 0.16 | 0.2 | 0.24 | 0.21 | 0.065 | 0.016 | 31.59 | 0.2 |
| V1 ($L \cdot kg^{-1}$) | 0.55 | 1.27 | 1.65 | 1.3 | 1.02 | 0.25 | 78.09 | 0.93 |
| Q ($L \cdot min^{-1} \cdot kg^{-1}$) | 0.1 | 0.3 | 0.48 | 0.38 | 0.34 | 0.084 | 87.72 | 0.24 |
| V2 ($L \cdot kg^{-1}$) | 0.98 | 2.59 | 4.45 | 3.62 | 3.47 | 0.87 | 96.04 | 2.05 |

## 1.3. Population compartmental analysis

Model applied: Intravenous infusion administration, no delay, mammillary 2-compartments model, linear elimination, BLQ=LOQ/2. Concentrations are modeled with a lognormal distribution. Parameters are modeled by Stochastic Approximation Expectation-Maximization (SAEM) algorithm (Monolix©).

Main settings: Burn-in phase with 50 iterations. Exploratory phase with 250-5000 iterations (auto-stop criteria), stepsize exponent=0, enabled simulated annealing with a decreasing rate of 0.95. Smoothing phase with 100-1000 iterations (auto-stop criteria), stepsize exponent=0.7. Conditional mode with maximal 1000 iterations, tolerance at 0.000001. Stochastic approximation with 100-500 iterations. Monte Carlo size of 10000, with optimized degrees of freedom (1 to 15).
Initial estimates are adjusted, and a final run is repeated using the last final estimates.

**Table S1_1.3.1** Diagnostic results with a *combined_1* error model on predicted concentration ( Cp = Cc + (a + b.Cc).e ), and a random effect for inter-individual variability (IIV).

| Cl | V1 | Q | V2 | -2LL (OFV) | AIC | BIC |
|---|---|---|---|---|---|---|
| X | | | | -413 | -399 | -394 |
| X | X | | | -433 | -417 | -411 |
| X | | X | | -437 | -421 | -415 |
| X | | | X | -425 | -409 | -403 |
| X | X | X | | -437 | -419 | -412 |
| X | | X | X | -437 | -419 | -412 |

Conclusion: An IIV random effect is included for Cl and Q.

**TableS1_1.3.2** Diagnostic results with a IIV random effect on Cl and Q:

| *Error Model* | | -2LL (OFV) | AIC | BIC |
|---|---|---|---|---|
| Constant | Cc + a . e | -434 | -420 | -415 |
| Proportional | Cc + b . Cc . e | -431 | -417 | -411 |
| Combined_1 | Cc + (a + b . Cc ) . e | -437 | -421 | -415 |
| Combined_2 | $Cc + \sqrt{(a^2 + (b \,.\, cC)^2}$ . e | -438 | -422 | -416 |

**TableS1_1.3.3** Diagnostic results with a covariate effect (Body Weight of the individuals).

| *Criteria* | No covariate | Weight |
|---|---|---|
| Cl | -2.8 | -4.1 |
| Q | 28.5 | 30.4 |

**Table S1_1.3.4** Diagnostic results with a Combined_2 error model on predicted concentration ( $\bar{C}c + \sqrt{(a^{\ 2} + (b\ \ .\ \ \ \ )^2}$ . e ) and a random effect for inter-occasion variability (IOV), including IIV for Cl and Q, as well as Covariate effect of weight on Cl.

| Cl | V1 | Q | V2 | -2LL (OFV) | AIC | BIC |
|---|---|---|---|---|---|---|
| | | | | -442 | -424 | -417 |
| X | | | | -444 | -424 | -317 |
| | X | | | -441 | -421 | -413 |
| | | X | | -454 | -434 | -427 |
| | | | X | -443 | -423 | -415 |
| X | | X | | -458 | -436 | -428 |
| | X | X | | -446 | -424 | -416 |
| | | X | X | -453 | -432 | -423 |
| X | X | X | | -459 | -435 | -426 |
| X | | X | X | -459 | -435 | -426 |
| X | X | X | X | -459 | -433 | -423 |

**TableS1_1.3.5** Best final estimates for the 2-compartments model for S-ketamine including IIV and IOV for Cl and Q, a Weight-covariate effect on Cl, and a combined_2 error model.

| | VALUE | STOCH. APPROX. | |
|---|---|---|---|
| | | S.E. | R.S.E.(%) |
| **Fixed Effects** | | | |
| Cl_pop | 0.32 | 0.14 | 44.8 |
| beta_Cl_Weight_kg_ | -0.056 | 0.047 | 84.1 |
| V1_pop | 1.3 | 0.12 | 9.09 |
| Q_pop | 0.11 | 0.042 | 37.3 |
| V2_pop | 3.64 | 1.02 | 28.0 |
| **Standard Deviation of the Random Effects** | | | |
| | Value | C.V.(%) | |
| omega_Cl | 0.0099 | 0.99 | 0.15 | 1.50e+3 |
| omega_Q | 0.21 | 21.14 | 0.76 | 365 |

| | VALUE | | STOCH. APPROX. | |
|---|---|---|---|---|
| | | | S.E. | R.S.E.(%) |
| **gamma_Cl** | 0.23 | 23.81 | 0.057 | 24.2 |
| **gamma_Q** | 1.26 | 197.64 | 0.34 | 27.0 |
| **Error Model Parameters** | | | | |
| **a** | | 0.18 | 0.046 | 25.1 |
| **b** | | 0.059 | 0.018 | 30.1 |

Due to observed correlations and several inappropriate RSE%, IIV is then removed stepwise.

**TableS1_1.3.6** Diagnostic values for models including different IIV contributions.

| Cl | V1 | Q | V2 | Weight | -2LL (OFV) | AIC | BIC | R.S.E.(%) > 50 |
|---|---|---|---|---|---|---|---|---|
| | | | | Cl | -458 | -440 | -434 | $\beta_{Cl\_Weight}$ |
| | | | | | -457 | -441 | -435 | |
| X | | | | Cl | -459 | -439 | -431 | $\beta_{Cl\_Weight}$ , $\omega Cl$ |
| X | | | | | -457 | -439 | -432 | $\omega Cl$ |
| | | X | | Cl | -458 | -438 | -431 | $\beta_{Cl\_Weight}$ , $\omega Q$ |
| | | X | | | -457 | -439 | -432 | $\omega Q$ |

**TableS1_1.3.7** Diagnostic results with a covariate effect (Body Weight of the individuals).

| *Criteria* | No covariate | Weight |
|---|---|---|
| Cl | 4.7 | 5.3 |
| Q | 53.8 | 56.4 |

In the final best model no IIV remains to explain parameters variability, only IOV for Cl and Q, including no covariate (Weight) effect.

**TableS1_1.3.8** Validation of the error model for the final model.

| *Error Model* | | OFV | AIC | BIC | Comment |
|---|---|---|---|---|---|
| Constant | Cc + a . e | -454 | -440 | -435 | |
| Proportional | Cc + b . Cc . e | -447 | -433 | -428 | $b_{R.S.E.}$ < 10% |
| Combined_1 | Cc + (a + b . Cc ) . e | -457 | -441 | -434 | $b_{R.S.E.}$ > 50% |
| Combined_2 | $Cc + \sqrt{(a^2 + (b\,.\,cC)^2}\,.\,e$ | -457 | -441 | -435 | |

**TableS1_1.3.9** Shapiro Wilk tests for normal distribution of random effects for the final model.

| | STATISTICS | P-VALUE |
|---|---|---|
| eta_Cl | 0.96 | 6.87e-1 |
| eta_Q | 0.96 | 9.18e-1 |

**TableS1_1.3.10** Shapiro Wilk tests for normal distribution of individual parameters for the final model.

| | DISTRIBUTION | STATISTICS | P-VALUE |
|---|---|---|---|
| Cl | lognormal | 0.96 | 6.87e-1 |
| Q | lognormal | 0.96 | 9.18e-1 |

**TableS1_1.3.11** Shapiro Wilk tests for normal distribution of residuals for the final model.

| | STATISTICS | P-VALUE |
|---|---|---|
| IWRES | 0.98 | 5.43e-2 |
| PWRES | 0.99 | 8.57e-1 |
| NPDE | 0.99 | 5.73e-1 |

**TableS1_1.3.12** Symmetry test around 0 for residuals for the final model

| | STATISTICS | P-VALUE |
|---|---|---|
| IWRES | 1.18 | 2.39e-1 |
| PWRES | -0.13 | 8.94e-1 |
| NPDE | 0.47 | 6.39e-1 |

The model does not detect correlations between random effects, which may improve the model.

**TableS1_1.3.13** Best final estimates of the pharmacokinetic parameters of S-Ketamine with the final model including no IIV, no covariate effect (weight), and IOV for Cl and Q.

| | VALUE | STOCH. APPROX. | |
|---|---|---|---|
| | | S.E. | R.S.E.(%) |
| **Fixed Effects** | | | |
| Cl_pop | 0.19 | 0.018 | 9.56 |
| V1_pop | 1.32 | 0.12 | 8.80 |
| Q_pop | 0.11 | 0.042 | 37.1 |
| V2_pop | 3.9 | 1.16 | 29.8 |
| **Standard Deviation of the Random Effects** | | | |
| | Value C.V.(%) | | |
| gamma_Cl | 0.25 25.36 | 0.06 | 24.0 |
| gamma_Q | 1.29 206.94 | 0.34 | 26.0 |
| **Error Model Parameters** | | | |
| a | 0.18 | 0.045 | 24.7 |
| b | 0.059 | 0.017 | 28.5 |

**Figure S1_1.3.1** Observed vs. predicted concentrations for S-Ketamine.

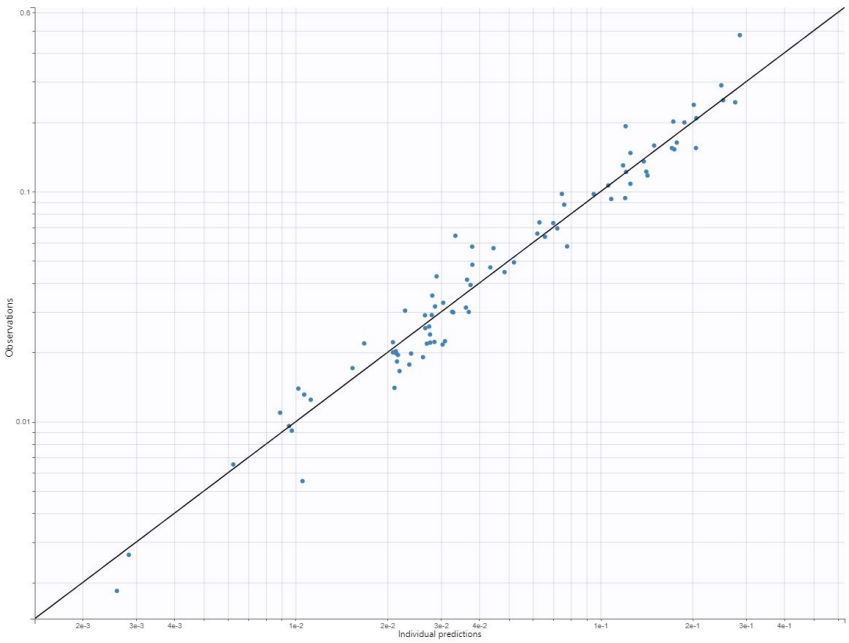


**Figure S1_1.3.2** Distribution of the residuals.

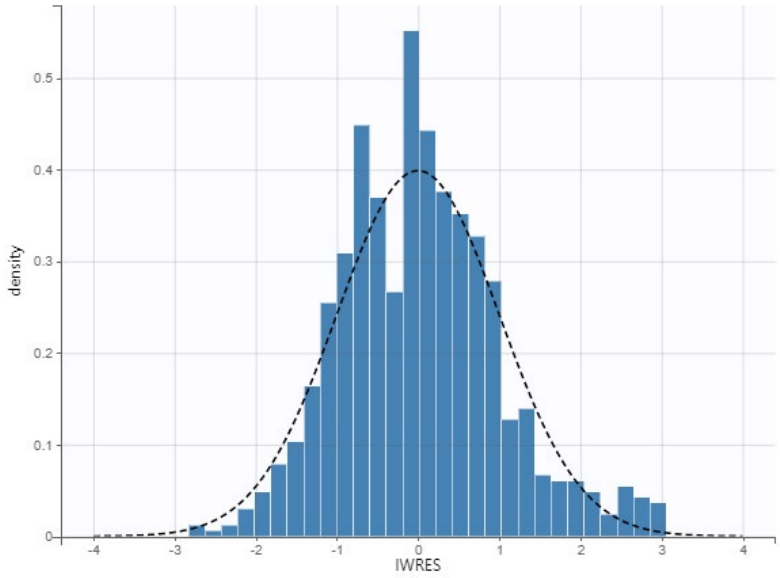
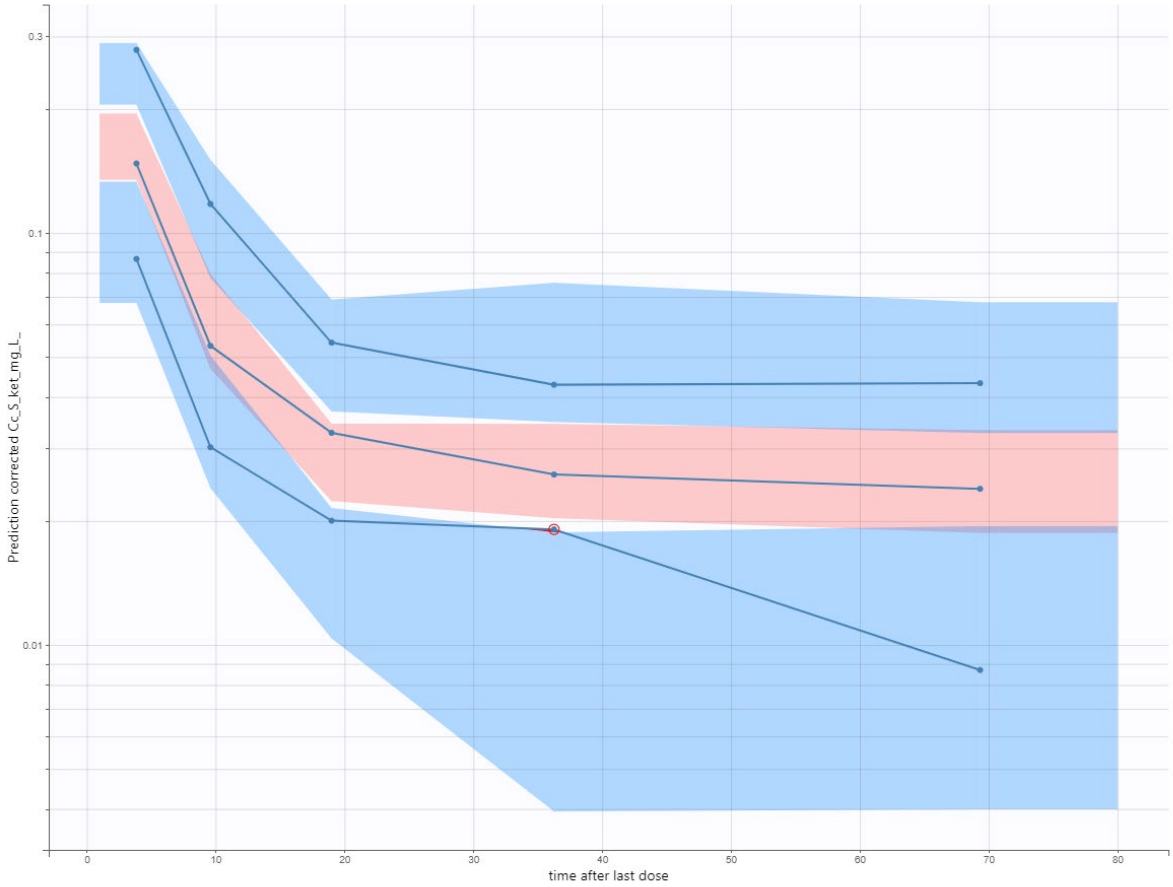



**Figure S1_1.3.3** Visual predictive check of the final model.



# 2. Modelling for S-Ketamine and S-Norketamine:

## 2.1. Individual compartmental analysis:

Model applied: Intravenous infusion administration, no delay, no first pass effect, unidirectional Parent-metabolite conversion, mammillary 2 compartments model with linear elimination for S-Ketamine (Parent), Linear elimination for S-Norketamine, BLQ=LOQ/2.

First run with **Optimization Cost function**: $\mathbf{(Y_{pred}-Y_{obs})^2 / Y_{pred}^2}$

**TableS1_2.1.1** Diagnostic values with different compartment models.

| | Metabolite from Parent Comp 1 | | | Metabolite from Parent Comp 2 | |
|---|---|---|---|---|---|
| *Model* | **1-Comp** | **2-Comp** | **3-Comp** | **1-Comp** | **2-Comp** |
| -2LL (OFV) | -1130 | -1146 | -1120 | -1084 | -1065 |
| AIC | -936 | -888 | -798 | -890 | -807 |
| BIC | -900 | -842 | -741 | -854 | -761 |

Conclusion: The One-compartment-metabolite model issued from the first Parent-compartment was retained.

Definition: $Y = (Y_{pred}-Y_{obs})$

**TableS1_2.1.2** Total cost and diagnostic values with different cost functions.

| *Cost function* | $\mathbf{Y^2}$ | $\mathbf{Y^2 / Y_{obs}}$ | $\mathbf{Y^2 / Y_{pred}}$ | $\mathbf{Y^2 / Y_{obs}^2}$ | $\mathbf{Y^2 / Y_{pred}^2}$ | $\mathbf{Y^2 / \lvert Y_{pred} . Y_{obs} \rvert}$ |
|---|---|---|---|---|---|---|
| Cost | 0.02 | 0.26 | 0.24 | 7.34 | 4.78 | 7.16 |
| -2LL (OFV) | -1080 | -1156 | -1164 | -1151 | -1205 | -1155 |
| AIC | -886 | -962 | -970 | -957 | -1011 | -961 |
| BIC | -851 | -926 | -935 | -922 | -976 | -925 |

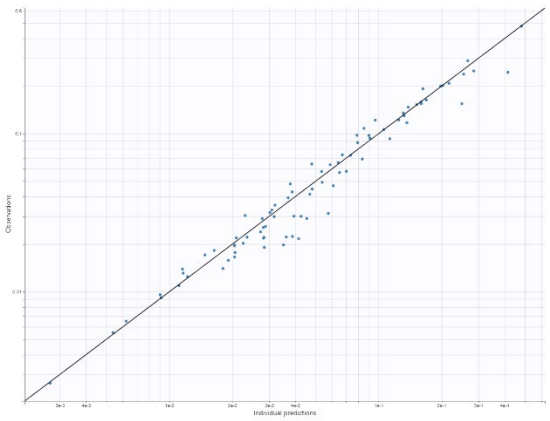
Conclusion: The Cost function $\mathbf{Y^2 / Y_{pred}^2}$ is retained.

**TableS1_2.1.3** Confirmation of the best compartment model for S-Norketamine.

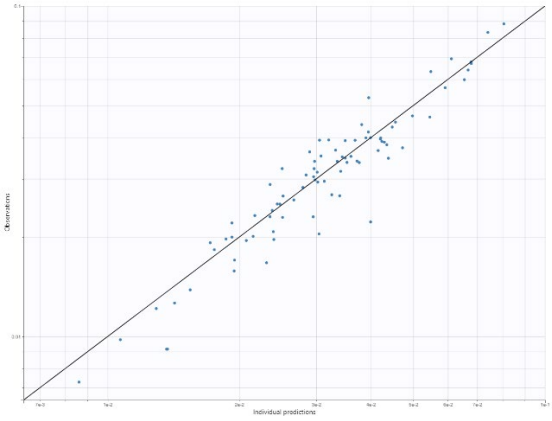
| *Model* | **1-Comp** | **2-Comp** | **3-Comp** |
|---|---|---|---|
| -2LL (OFV) | -1216 | -1195 | -1191 |
| AIC | -1022 | -937 | -869 |
| BIC | -986 | -891 | -812 |

Conclusion: The One-compartmental model is further retained.

**Figure S1_2.1.1** Observed vs. predicted concentrations with the final model (Two-compartment for S-Ketamine, One compartment issued from the central parent compartment for S-Norketamine.



S-Ketamine (Parent)



S-Norketamine (Metabolite)

**Table S1_2.1.4** Best final estimates of the Parent-Metabolite model: Standard mammillary 2-Compartments model for S-Ketamine (Parent), and a standard mammillary 1-Compartment model for S-Norketamine (Metabolite), issued from the first Parent compartment.

| | Q1 | median | Q3 | mean | SD | SE | CV (%) | GeoMean |
|---|---|---|---|---|---|---|---|---|
| V1 | 0.026 | 0.34 | 0.87 | 0.46 | 0.4 | 0.1 | 87.26 | 0.17 |
| Cl | 0.089 | 0.12 | 0.17 | 0.13 | 0.061 | 0.015 | 48.02 | 0.11 |
| Q | 0.039 | 0.22 | 0.32 | 0.25 | 0.26 | 0.066 | 107.01 | 0.11 |
| V2 | 0.28 | 1.19 | 1.85 | 1.47 | 1.42 | 0.35 | 96.52 | 0.58 |
| Clm | 0.00065 | 0.018 | 0.047 | 0.028 | 0.028 | 0.007 | 98.26 | 0.0071 |
| Kpm | 0.014 | 0.041 | 0.069 | 0.045 | 0.034 | 0.0085 | 75.04 | 0.028 |

## 2.2. Population compartmental analysis:

Model applied: Intravenous infusion administration, no delay, no first pass effect, Parent-Metabolite mammillary compartments model, Parent (S-Ketamine) is modeled as a 2-compartment model, linear elimination, Metabolite (S-Norketamine) ) is modeled as a 1-compartment model issued from the main parent compartment, linear elimination. BLQ=LOQ/2. Concentrations are modeled with a lognormal distribution. Parameters are modeled by Stochastic Approximation Expectation-Maximization (SAEM) algorithm (Monolix©).

Main settings: Burn-in phase with 50 iterations. Exploratory phase with 250-5000 iterations (auto-stop criteria), stepsize exponent=0, enabled simulated annealing with a decreasing rate of 0.95. Smoothing phase with 100-1000 iterations (auto-stop criteria) ), stepsize exponent=0.7. Conditional mode with maximal 1000 iterations, tolerance at 0.000001. Stochastic approximation with 100-500 iterations. Monte Carlo size of 10000, with optimized degrees of freedom (1 to 15). Initial estimates are adjusted, and a final run is repeated using the last final estimates.

**Table S1_2.2.1** Diagnostic results with a combined_1 error model on predicted concentration ( Cp = Cc + (a + b.Cc).e ) for both parent and metabolite concentrations. Based on the preliminary results, the model includes first IOV for Cl and Q for the parent model.

| IIV | | IOV | | | | |
|---|---|---|---|---|---|---|
| Clm | Kpm | Clm | Kpm | -2LL (OFV) | AIC | BIC |
| | | | | -963 | -939 | -930 |
| X | | | | -965 | -939 | -929 |
| | X | | | -972 | -946 | -936 |
| | X | | X | -1000 | -972 | -961 |
| | X | X | | -980 | -952 | -942 |
| | | | X | -1000 | -974 | -964 |

Conclusion: The model with IOV on Kpm is retained

**TableS1_2.2.2** Diagnostic results with different error models (OFV / AIC / BIC, all values are negatives).

| Parent/Metabolite | Constant | Proportional | Combined_1 | Combined_2 |
|---|---|---|---|---|
| Constant | 998/976/967 | 1000/978/970 | 1000/976/967 | 1000/976/967 |
| Proportional | 987/965/957 | 989/967/958 | 988/964/955 | 989/965/955 |
| Combined_1 | 998/974/965 | 1000/976/967 | 1001/975/965 | 1000/974/964 |
| Combined_2 | 998/974/965 | 1001/977/967 | 1001/975/965 | 1001/975/965 |

**Table S1_1_2.2.3** Diagnostic values to compare the use of Covariate Body weight (kg) on the model parameters (OFV / AIC / BIC, all values are negatives).

| | - | Q | Kpm |
|---|---|---|---|
| - | 1000/978/970 | | |
| Cl | 1004/980/971 | 1005/979/969 | 1005/979/969 |
| Q | 1000/976/967 | | |
| Kpm | 1000/976/967 | | |

The model detects a **correlation between IOV random effects for Cl and Q.**

| **-2LL (OFV)** | **AIC** | **BIC** |
|---|---|---|
| -1012 | -986 | -976 |

**Final model equations:**

log(V1) = log(V1_pop)

$\log(Cl) = \log(Cl\_pop) + \beta_{Cl\_Weight} * Weight + \gamma_{Cl}$

$\log(Q) = \log(Q\_pop) + \gamma_{Q}$

log(V2) = log(V2_pop)

log(Clm) = log(Clm_pop)

$\log(Kpm) = \log(Kpm\_pop) + \gamma_{Kpm}$

**TableS1_2.2.4** Best estimates for the Parent-metabolite model for S-Ketamine and S-Norketamine with Constant and Proportional error models on S-Ketamine (Parent) and S-Norketamine (metabolite), respectively, no IIV, IOV on Cl, Q, and Kpm, and a covariate effect of Weight on Cl, and a correlation between IOV random effects for Cl and Q.

| | VALUE | STOCH. APPROX. | |
|---|---|---|---|
| | | S.E. | R.S.E.(%) |
| **Fixed Effects** | | | |
| V1_pop | 1.05 | 0.12 | 11.5 |
| Cl_pop | 0.42 | 0.23 | 53.7 |
| beta_Cl_Weight_kg_ | -0.13 | 0.061 | 45.8 |
| Q_pop | 0.18 | 0.05 | 27.6 |
| V2_pop | 2.82 | 0.36 | 12.9 |
| Clm_pop | 0.079 | 0.014 | 17.6 |
| Kpm_pop | 0.062 | 0.0078 | 12.6 |
| **Standard Deviation of the Random Effects** | | | |
| | Value | C.V.(%) | |
| gamma_Cl | 0.4 | 41.82 | 0.098 | 24.4 |
| gamma_Q | 0.88 | 108.84 | 0.22 | 24.5 |
| gamma_Kpm | 0.36 | 36.82 | 0.074 | 20.6 |
| **Correlations** | | | |
| corr2_Q_Cl | 0.77 | 0.16 | 21.2 |
| **Error Model Parameters** | | | |
| a1 | 0.26 | 0.025 | 9.64 |
| b2 | 0.066 | 0.006 | 9.17 |

**Figure S1_2.2.1** Observed versus predicted concentrations of S-Ketamine.

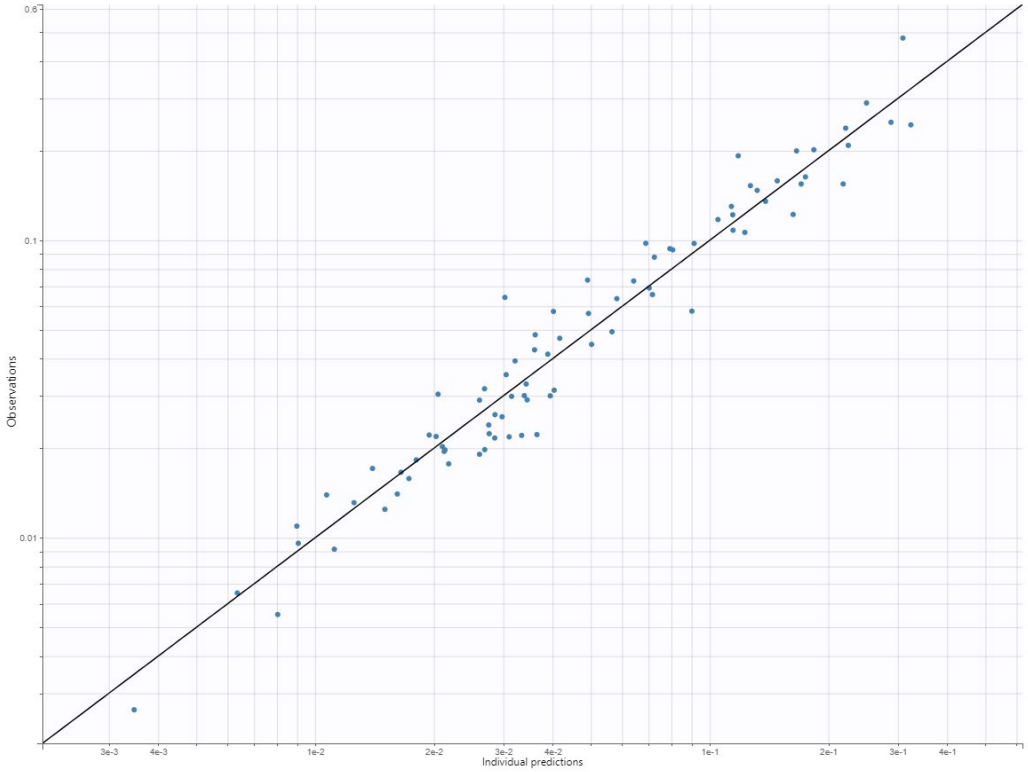



**Figure S1_2.2.2** Residual distribution for S-Ketamine.

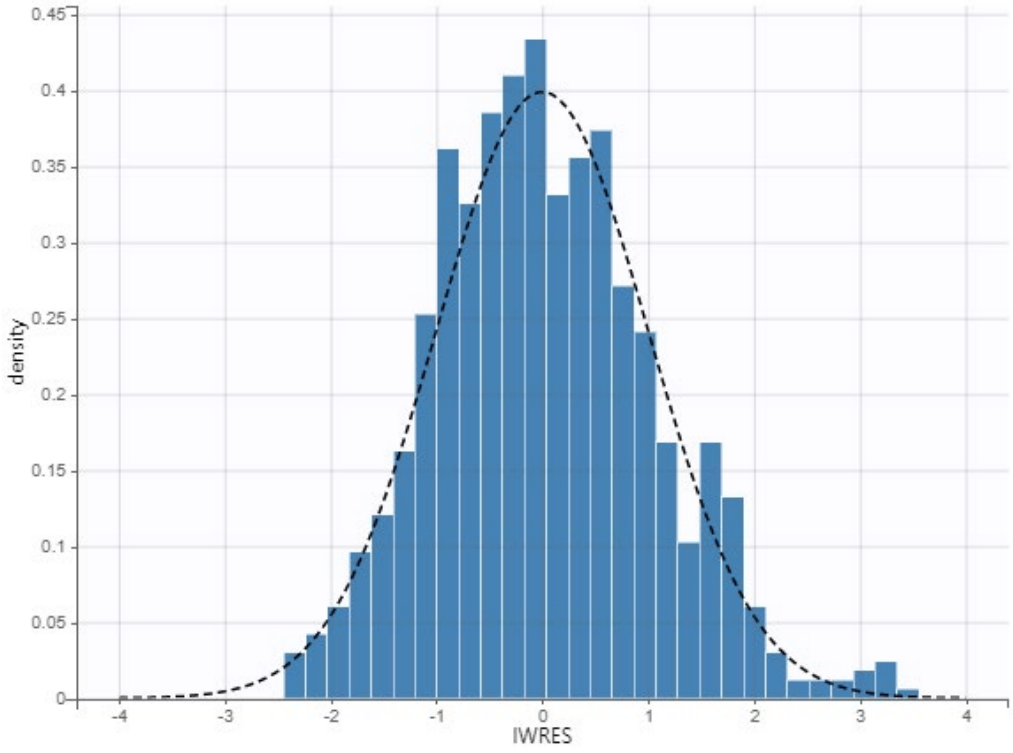


**Figure S1_2.2.3** Visual predictive check for S-Ketamine.

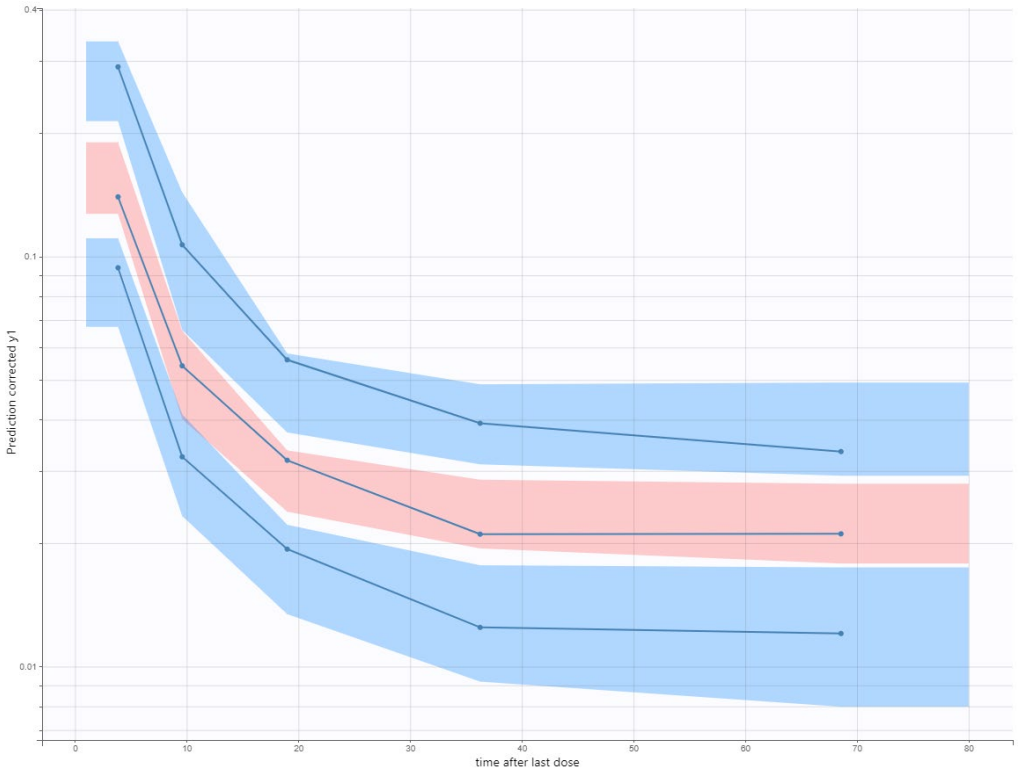



**Figure S1_2.2.4** Observed versus predicted concentrations of S-Norketamine.

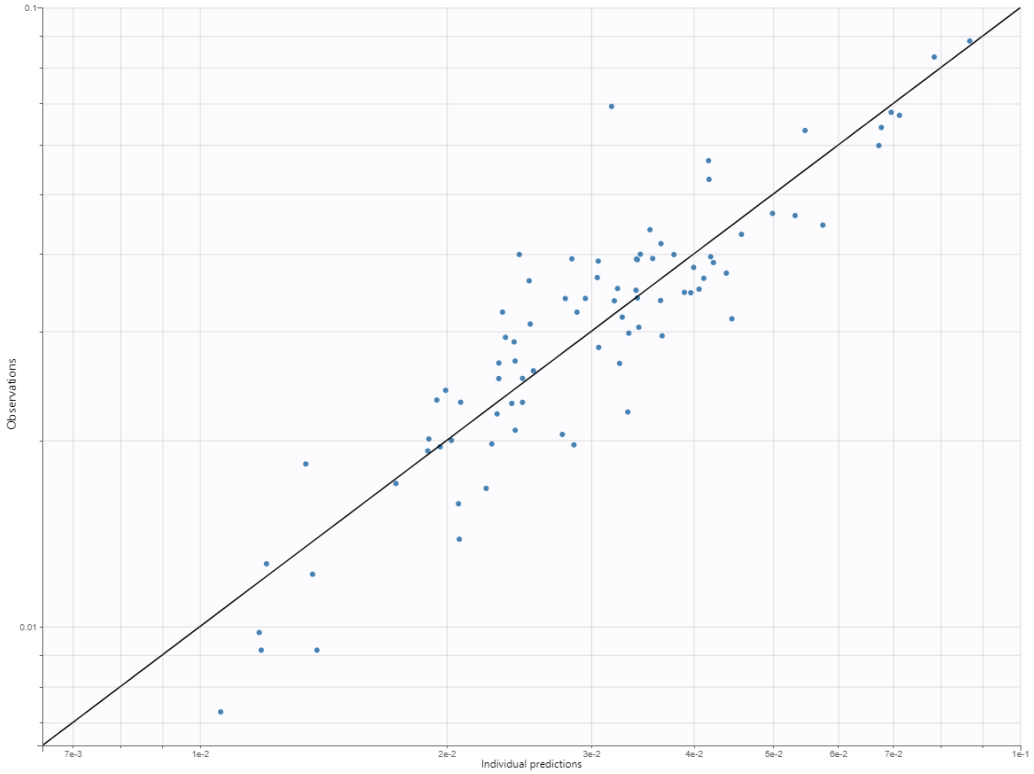


**Figure S1_2.2.5** Residual distribution for S-Norketamine

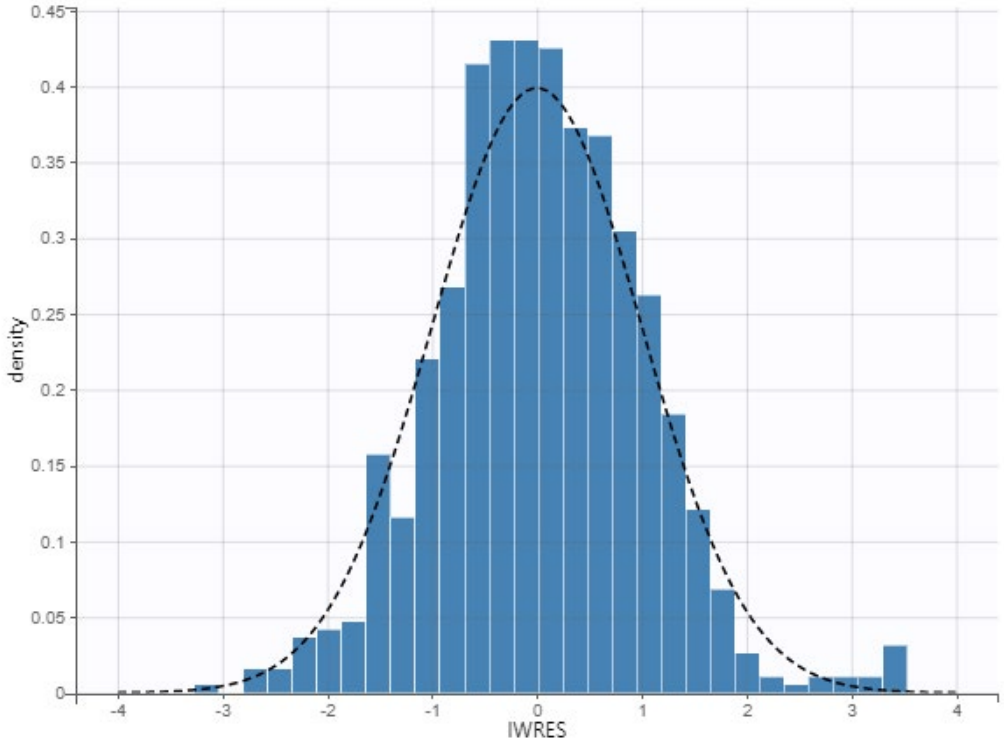
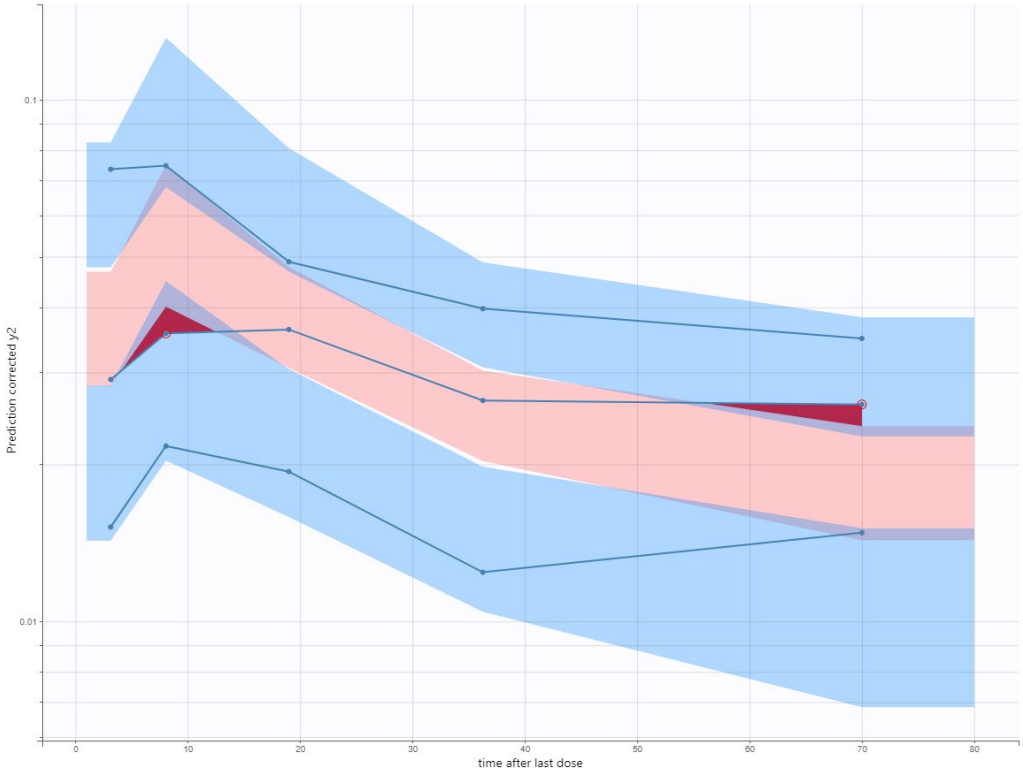



**Figure S1_2.2.6** Visual predictive check for S-Norketamine.



# 3. Modelling for R-Ketamine:

## 3.1. Noncompartmental analysis (NCA):

Model applied: Intravascular administration, “linear up log down” method for integral of AUC calculation, 3 last points for lambda_z, BLQ=LOQ/2.

**TableS1_3.1.1** Mean and Median adjusted $R^2$ with different weighting.

| *Weighting* | Uniform | 1/Y | $1/Y^2$ |
|---|---|---|---|
| Median adjusted $R^2$ | 0.89 ; 0.86 | 0.9 ; 0.86 | 0.93 ; 0.86 |

Conclusion: The weighting $1/Y^2$ was retained.

**Table S1_3.1.2** Final NCA estimates for R-Ketamine.

| | Q1 | median | Q3 | mean | SD | SE | CV (%) | GeoMean |
|---|---|---|---|---|---|---|---|---|
| $C_{max}$ ($mg \cdot L^{-1}$) | 0.14 | 0.15 | 0.22 | 0.19 | 0.096 | 0.034 | 50.4 | 0.17 |
| $V_d$ ($L \cdot kg^{-1}$) | 3.6 | 6.23 | 7.23 | 6.17 | 3.62 | 1.28 | 58.74 | 5.25 |
| CL ($L \cdot min^{-1} \cdot kg^{-1}$) | 0.22 | 0.24 | 0.27 | 0.26 | 0.078 | 0.028 | 29.91 | 0.25 |
| $T_{1/2}$ (min) | 10.99 | 13.6 | 19.82 | 16.44 | 9.5 | 3.36 | 57.76 | 14.42 |
| $k_{el}$ ($min^{-1}$) | 0.035 | 0.052 | 0.063 | 0.054 | 0.03 | 0.01 | 54.41 | 0.048 |
| $AUC_{0\text{-}inf}$ ($min \cdot mg \cdot L^{-1}$) | 1.89 | 2.07 | 2.28 | 2.03 | 0.45 | 0.16 | 22.05 | 1.98 |
| $AUMC_{0\text{-}inf}$ ($min^2 \cdot mg \cdot L^{-1}$) | 24.32 | 38.09 | 53.76 | 41.58 | 22.13 | 7.82 | 53.21 | 36.76 |
| $MRT_{0\text{-}inf}$ (min) | 11.9 | 17.92 | 24.38 | 19.81 | 11.04 | 3.9 | 55.73 | 17.43 |

## 3.2. Individual compartmental analysis:

Model applied: Intravenous infusion administration, no delay, mammillary 1-to-3 compartments, linear elimination, BLQ=LOQ/2.

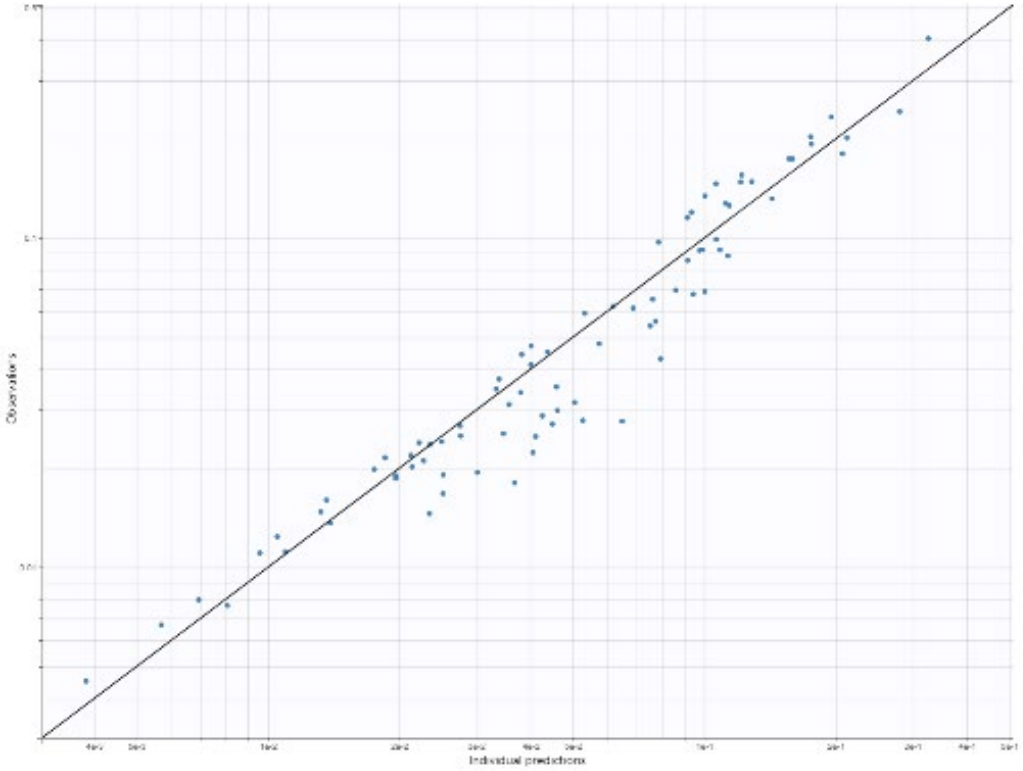
First run with **Optimization Cost function**: $(Y_{pred}-Y_{obs})^2 / Y_{pred}^2$

**TableS1_3.2.1** Diagnostic values with different compartment models.

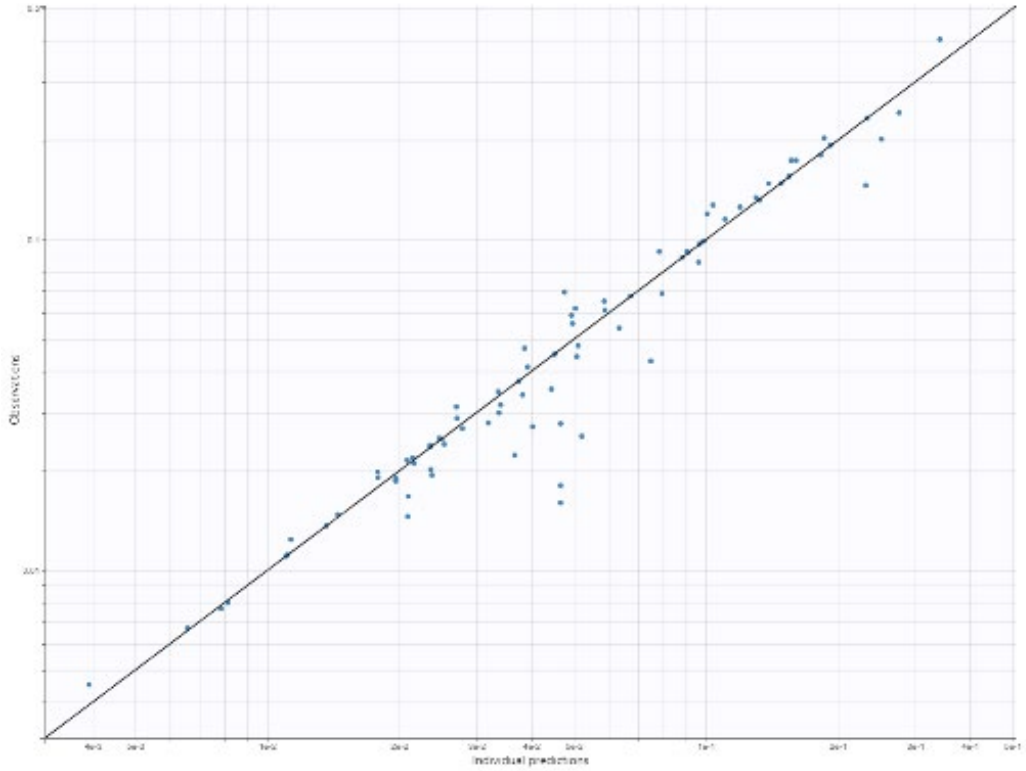
| *Model* | 1-Comp | 2-Comp | 3-Comp |
|---|---|---|---|
| -2LL (OFV) | -527 | -562 | -548 |
| AIC | -461 | -432 | -354 |
| BIC | -470 | -453 | -387 |

**Figure S1_3.2.1** Observed vs. predicted concentrations with different compartment models

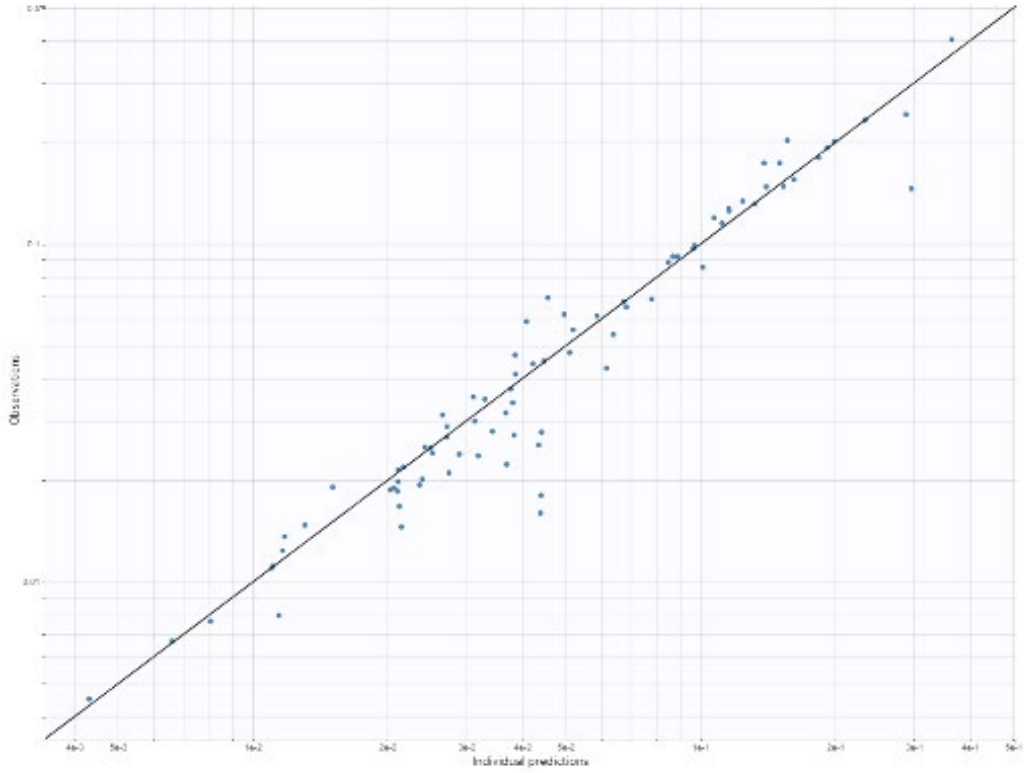
S1_3.2.1.a One-compartment model



S1_3.2.1.a Two-compartment model



S1_3.2.1.a Three-compartment model



Conclusion: The two-compartment model was retained.

Definition: $Y = (Y_{pred}-Y_{obs})$

**TableS1_3.2.2** Diagnostic values with different cost function used for approximation.

| *Cost function* | $Y^2$ | $Y^2 / Y_{obs}$ | $Y^2 / Y_{pred}$ | $Y^2 / Y_{obs}^2$ | $Y^2 / Y_{pred}^2$ | $Y^2 / \lvert Y_{pred} . Y_{obs} \rvert$ |
|---|---|---|---|---|---|---|
| Cost | 0.01 | 0.12 | 0.08 | 1.42 | 2.59 | 1.63 |
| -2LL (OFV) | -539 | -569 | -598 | -621 | -562 | -610 |
| AIC | -409 | -439 | -468 | -491 | -432 | -480 |
| BIC | -430 | -460 | -489 | -512 | -453 | -501 |

Conclusion: The Cost function $\mathbf{Y^2 / Y_{obs}^2}$ is retained.

**TableS1_3.2.3** Confirmation of the most appropriate compartment model.

| *Model* | 1-Comp | 2-Comp | 3-Comp |
|---|---|---|---|
| -2LL (OFV) | -530 | -621 | -593 |
| AIC | -464 | -491 | -399 |
| BIC | -473 | -512 | -431 |

Conclusion: The Two-compartmental model is further retained.

**Figure S1_3.2.2** Observed vs. predicted concentrations.

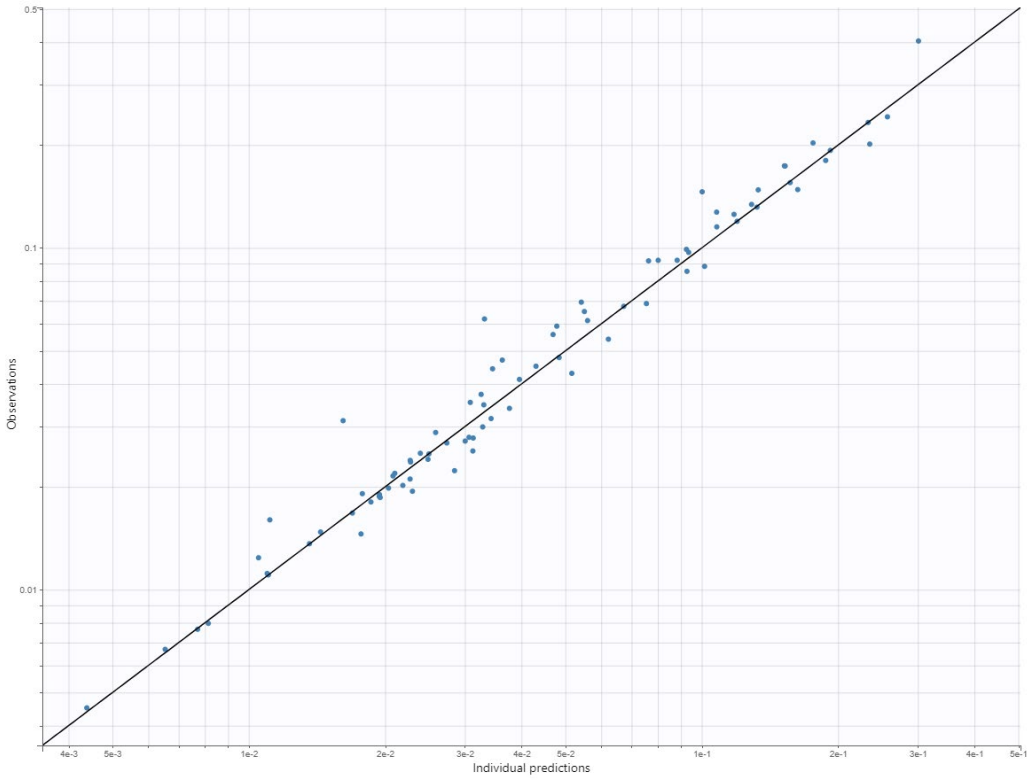


**Table S1_3.2.4** Final estimates of the two-compartmental model for R-Ketamine.

| | Q1 | median | Q3 | mean | SD | SE | CV (%) | GeoMean |
|---|---|---|---|---|---|---|---|---|
| Cl ($L \cdot min^{-1} \cdot kg^{-1}$) | 0.12 | 0.2 | 0.22 | 0.21 | 0.18 | 0.045 | 84.25 | 0.13 |
| V1 ($L \cdot kg^{-1}$) | 0.7 | 1.6 | 3.13 | 2.11 | 1.87 | 0.47 | 88.73 | 1.34 |
| Q ($L \cdot min^{-1} \cdot kg^{-1}$) | 0.24 | 0.35 | 0.76 | 1.13 | 2.44 | 0.61 | 215.99 | 0.42 |
| V2 ($L \cdot kg^{-1}$) | 3.01 | 5.01 | 31.29 | 19.66 | 27.3 | 6.82 | 138.85 | 4.24 |

## 3.3. Population compartmental analysis

Model applied: Intravenous infusion administration, no delay, mammillary 2-compartments model, linear elimination, BLQ=LOQ/2. Concentrations are modeled with a lognormal distribution. Parameters are modeled by Stochastic Approximation Expectation-Maximization (SAEM) algorithm (Monolix©).

Main settings: Burn-in phase with 50 iterations. Exploratory phase with 250-5000 iterations (auto-stop criteria), stepsize exponent=0, enabled simulated annealing with a decreasing rate of 0.95. Smoothing phase with 100-1000 iterations (auto-stop criteria), stepsize exponent=0.7. Conditional mode with maximal 1000 iterations, tolerance at 0.000001. Stochastic approximation with 100-500 iterations. Monte Carlo size of 10000, with optimized degrees of freedom (1 to 15).
Initial estimates are adjusted, and a final run is repeated using the last final estimates.

**Table S1_3.3.1** Diagnostic results with a *combined_1* error model on predicted concentration ( Cp = Cc + (a + b.Cc).e ), and a random effect for inter-individual variability (IIV).

| Cl | V1 | Q | V2 | -2LL (OFV) | AIC | BIC |
|---|---|---|---|---|---|---|
| X | | | | -398 | -384 | -379 |
| X | X | | | -416 | -400 | -394 |
| X | | X | | -412 | -396 | -390 |
| X | | | X | -406 | -390 | -384 |
| X | X | X | | -416 | -398 | -391 |
| X | X | | X | -415 | -397 | -391 |

Conclusion: An IIV random effect is included for Cl and V1.

**TableS1_3.3.2** Diagnostic results with a IIV random effect on Cl and Q:

| *Error Model* | | -2LL (OFV) | AIC | BIC |
|---|---|---|---|---|
| Constant | Cc + a . e | -416 | -402 | -396 |
| Proportional | Cc + b . Cc . e | -407 | -393 | -387 |
| Combined_1 | Cc + (a + b . Cc ) . e | -416 | -400 | -394 |
| Combined_2 | $Cc + \sqrt{(a^2 + (b \,.\, cC)^2}$ . e | -416 | -400 | -394 |

**TableS1_3.3.3** Diagnostic results with a covariate effect (Body Weight of the individuals).

| *Criteria* | No covariate | Weight |
|---|---|---|
| Cl | -25 | -23 |
| V1 | 31 | 32 |

**Table S1_3.3.4** Diagnostic results with a Constant error model on predicted concentration ( Cc + a . e ) and a random effect for inter-occasion variability (IOV), including IIV for Cl and V1, without a Covariate effect (Body weight).

| Cl | V1 | Q | V2 | -2LL (OFV) | AIC | BIC |
|---|---|---|---|---|---|---|
| | | | | -416 | -402 | -396 |
| X | | | | -436 | -420 | -414 |
| | X | | | -429 | -413 | -406 |
| | | X | | -426 | -410 | -404 |
| | | | X | -429 | -413 | -407 |
| X | X | | | -440 | -422 | -415 |
| X | | X | | -452 | -434 | -427 |
| X | | | X | -437 | -419 | -412 |
| X | X | X | | -452 | -433 | -425 |
| X | | X | X | -452 | -432 | -424 |

**TableS1_3.3.5** Best final estimates for the 2-compartments model for R-ketamine including IIV for Cl and V1, and IOV for Cl and Q, without covariate effect, and a constant error model.

| | VALUE | STOCH. APPROX. | |
|---|---|---|---|
| | | S.E. | R.S.E.(%) |
| **Fixed Effects** | | | |
| Cl_pop | 0.2 | 0.024 | 11.6 |
| V1_pop | 1.58 | 0.19 | 11.7 |
| Q_pop | 0.19 | 0.065 | 34.4 |
| V2_pop | 4.91 | 0.74 | 15.1 |

| **Standard Deviation of the Random Effects** | | | | |
|---|---|---|---|---|
| | Value | C.V.(%) | | |
| omega_Cl | 0.011 | 1.15 | 0.15 | 1.35e+3 |
| omega_V1 | 0.064 | 6.42 | 0.26 | 412 |
| gamma_Cl | 0.41 | 43.03 | 0.08 | 19.5 |
| gamma_Q | 1.14 | 164.52 | 0.32 | 27.8 |

| | VALUE | STOCH. APPROX. | |
|---|---|---|---|
| | | S.E. | R.S.E.(%) |
| **Error Model Parameters** | | | |
| **a** | 0.23 | 0.023 | 9.83 |

Due to observed correlations and several inappropriate RSE%, IIV is then removed stepwise.

**TableS1_3.3.6** Diagnostic values for models including different IIV contributions.

| Cl | V1 | Q | V2 | -2LL (OFV) | AIC | BIC | R.S.E.(%) > 50 |
|---|---|---|---|---|---|---|---|
| | | | | -452 | -438 | -433 | |
| X | | | | -452 | -436 | -430 | ωCl |
| | X | | | -452 | -436 | -430 | ωV1 |
| | | X | | -452 | -436 | -430 | ωQ |
| X | X | | | -452 | -434 | -427 | ωCl, ωV1 |

The model detects a correlation between Cl and Q for IOV:

| -2LL (OFV) | AIC | BIC | R.S.E.(%) > 50 |
|---|---|---|---|
| -458 | -442 | -436 | |

**TableS1_3.3.7** Diagnostic results with a covariate effect (Body Weight of the individuals).

| *Criteria* | No covariate | Weight |
|---|---|---|
| Cl | 21.16 | 22.68 |
| Q | 49.11 | 51.86 |

In the final best model no IIV remains to explain parameters variability, only IOV for Cl and Q, including no covariate (Weight) effect, and a correlation between Cl and Q IOV.

**TableS1_3.3.8** Validation of the error model for the final model.

| *Error Model* | | OFV | AIC | BIC | Comment |
|---|---|---|---|---|---|
| Constant | Cc + a . e | -458 | -442 | -436 | |
| Proportional | Cc + b . Cc . e | -448 | -432 | -426 | $b_{R.S.E.}$ < 10% |
| Combined_1 | Cc + (a + b . Cc ) . e | -458 | -440 | -433 | $b_{R.S.E.}$ > 50% |
| Combined_2 | $Cc + \sqrt{(a^2 + (b \,.\, cC)^2}$ . e | -458 | -440 | -433 | $a_{R.S.E}$ & $b_{R.S.E.}$ > 50% |

**TableS1_3.3.9** Shapiro Wilk tests for normal distribution of random effects for the final model.

| | STATISTICS | P-VALUE |
|---|---|---|
| eta_Cl | 0.95 | 6.89e-1 |
| eta_Q | 0.94 | 7.3e-1 |

**TableS1_3.3.10** Shapiro Wilk tests for normal distribution of individual parameters for the final model.

| | DISTRIBUTION | STATISTICS | P-VALUE |
|---|---|---|---|
| Cl | lognormal | 0.95 | 6.89e-1 |
| Q | lognormal | 0.94 | 7.3e-1 |

**TableS1_3.3.11** Shapiro Wilk tests for normal distribution of residuals for the final model.

| | STATISTICS | P-VALUE |
|---|---|---|
| IWRES | 0.98 | 3.53e-1 |
| PWRES | 0.98 | 2.66e-1 |
| NPDE | 0.99 | 6.3e-1 |

**TableS1_3.3.12** Symmetry test around 0 for residuals for the final model

| | STATISTICS | P-VALUE |
|---|---|---|
| IWRES | 0.62 | 5.34e-1 |
| PWRES | -1.14 | 2.56e-1 |
| NPDE | -1.32 | 1.88e-1 |

**TableS1_3.3.13** Best final estimates of the pharmacokinetic parameters of R-Ketamine with the final model including a constant error model, no IIV, no covariate effect (weight), and IOV for Cl and Q including correlation.

| | VALUE | STOCH. APPROX. | |
|---|---|---|---|
| | | S.E. | R.S.E.(%) |
| **Fixed Effects** | | | |
| Cl_pop | 0.2 | 0.024 | 11.6 |
| V1_pop | 1.52 | 0.15 | 10.2 |
| Q_pop | 0.19 | 0.059 | 30.9 |
| V2_pop | 4.67 | 0.64 | 13.7 |
| **Standard Deviation of the Random Effects** | | | |
| | Value | C.V.(%) | |
| gamma_Cl | 0.43 | 44.82 | 0.082 | 19.2 |
| gamma_Q | 1.05 | 142.83 | 0.25 | 23.4 |
| **Correlations** | | | |
| corr2_Q_Cl | 0.64 | 0.19 | 29.9 |
| **Error Model Parameters** | | | |
| a | 0.24 | 0.023 | 9.69 |

**Figure S1_3.3.1** Observed vs. predicted concentrations for R-Ketamine.

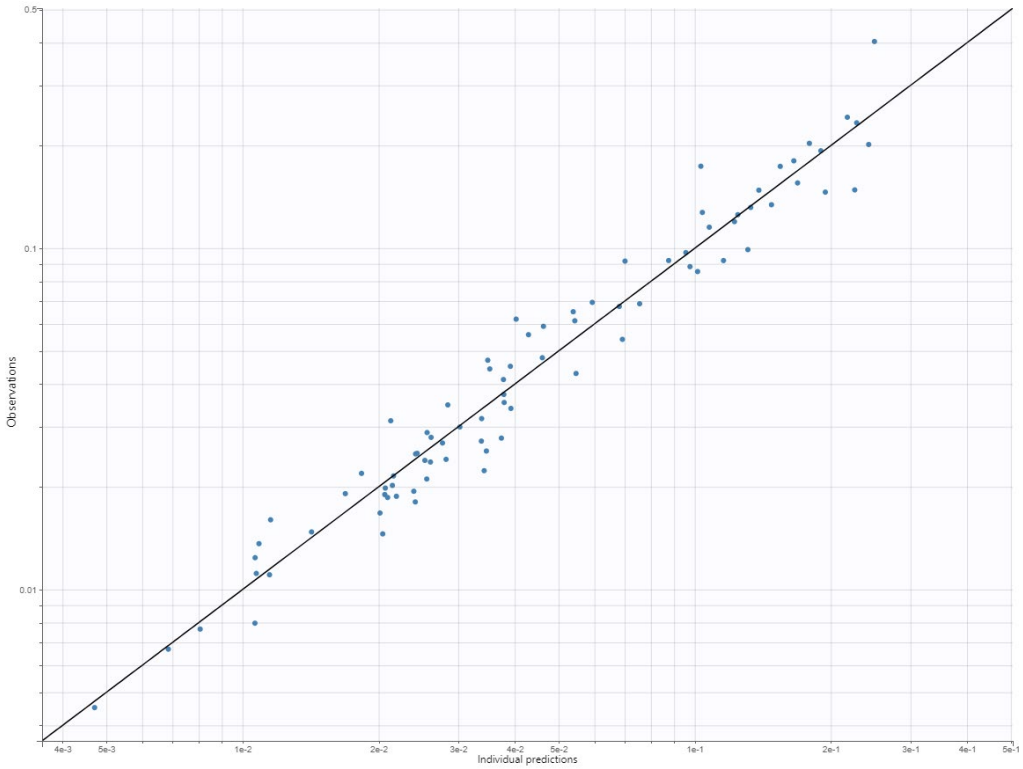



**Figure S1_3.3.2** Distribution of the residuals.

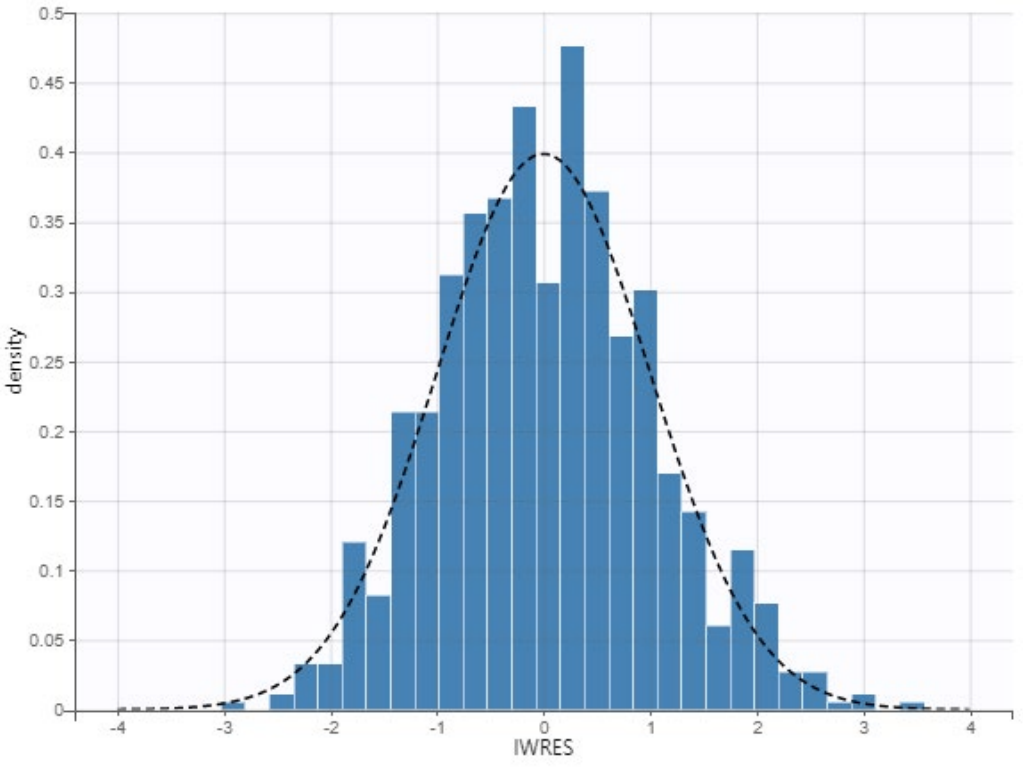
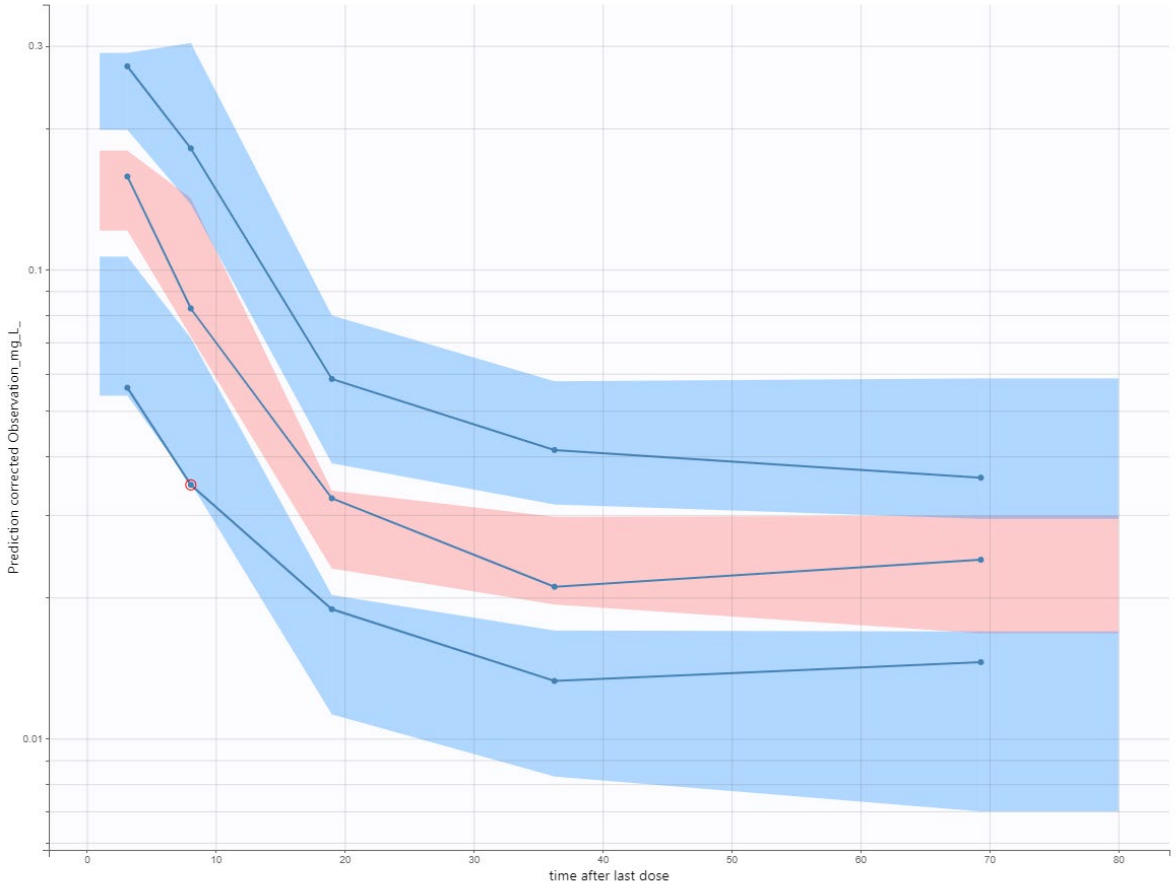


**Figure S1_3.3.3** Visual predictive check of the final model.



# 4. Modelling for R-Ketamine and R-Norketamine:

## 4.1. Individual compartmental analysis:

Model applied: Intravenous infusion administration, no delay, no first pass effect, unidirectional Parent-metabolite conversion, mammillary 2 compartments model with linear elimination for S-Ketamine (Parent), Linear elimination for S-Norketamine, BLQ=LOQ/2.

First run with **Optimization Cost function**: $\mathbf{(Y_{pred}-Y_{obs})^2 / Y_{pred}^2}$

**TableS1_4.1.1** Diagnostic values with different compartment models.

| | Metabolite from Parent Comp 1 | | | Metabolite from Parent Comp 2 | |
|---|---|---|---|---|---|
| *Model* | **1-Comp** | **2-Comp** | **3-Comp** | **1-Comp** | **2-Comp** |
| -2LL (OFV) | -1206 | -1184 | -1178 | -1143 | -1192 |
| AIC | -1012 | -926 | -856 | -949 | -934 |
| BIC | -977 | -880 | -799 | -913 | -888 |

Conclusion: The One-compartment-metabolite model issued from the first Parent-compartment was retained.

Definition: $Y = (Y_{pred}-Y_{obs})$

**TableS1_4.1.2** Total cost and diagnostic values with different cost functions.

| *Cost function* | $\mathbf{Y^2}$ | $\mathbf{Y^2 / Y_{obs}}$ | $\mathbf{Y^2 / Y_{pred}}$ | $\mathbf{Y^2 / Y_{obs}^2}$ | $\mathbf{Y^2 / Y_{pred}^2}$ | $\mathbf{Y^2 / \lvert Y_{pred} . Y_{obs} \rvert}$ |
|---|---|---|---|---|---|---|
| Cost | 0.01 | 0.18 | 0.18 | 6.73 | 6.31 | 6.93 |
| -2LL (OFV) | -1196 | -1241 | -1239 | -1217 | -1206 | -1211 |
| AIC | -1002 | -1047 | -1045 | -1023 | -1012 | -1017 |
| BIC | -966 | -1012 | -1010 | -988 | -977 | -982 |

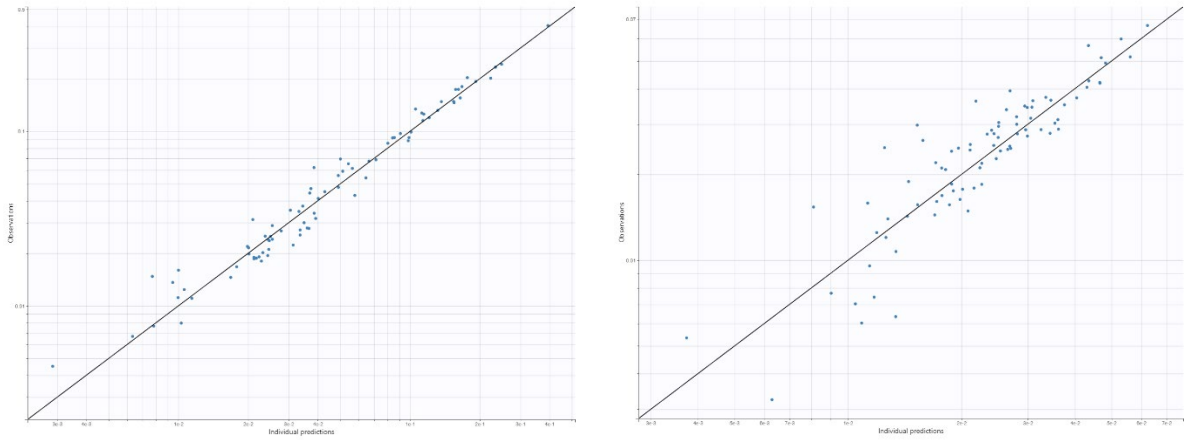
Conclusion: The Cost function $\mathbf{Y^2 / Y_{obs}}$ is retained.

**TableS1_4.1.3** Confirmation of the best compartment model for S-Norketamine.

| *Model* | **1-Comp** | **2-Comp** | **3-Comp** |
|---|---|---|---|
| -2LL (OFV) | -1261 | -1200 | -1160 |
| AIC | -1067 | -942 | -838 |
| BIC | -1032 | -896 | -781 |

Conclusion: The One-compartmental model is further retained.

**Figure S1_4.1.1** Observed vs. predicted concentrations with the final model (Two-compartment for S-Ketamine, One compartment issued from the central parent compartment for S-Norketamine.



S-Ketamine (Parent) S-Norketamine (Metabolite)

**TableS1_4.1.4** Best final estimates of the Parent-Metabolite model: Standard mammillary 2-Compartments model for S-Ketamine (Parent), and a standard mammillary 1-Compartment model for S-Norketamine (Metabolite), issued from the first Parent compartment.

| | Q1 | median | Q3 | mean | SD | SE | CV (%) | GeoMean |
|---|---|---|---|---|---|---|---|---|
| V1 | 0.12 | 0.7 | 1.18 | 0.83 | 0.76 | 0.19 | 91.08 | 0.22 |
| Cl | 0.13 | 0.19 | 0.22 | 0.17 | 0.063 | 0.016 | 36.88 | 0.16 |
| Q | 0.17 | 0.32 | 0.95 | 0.83 | 1.32 | 0.33 | 158.88 | 0.27 |
| V2 | 1.82 | 3 | 4.5 | 3.14 | 1.6 | 0.4 | 51.03 | 2.67 |
| Clm | 0.00092 | 0.04 | 0.1 | 0.074 | 0.11 | 0.028 | 151.23 | 0.012 |
| Kpm | 0.03 | 0.048 | 0.086 | 0.056 | 0.034 | 0.0084 | 60.15 | 0.047 |

## 4.2. Population compartmental analysis:

Model applied: Intravenous infusion administration, no delay, no first pass effect, Parent-Metabolite mammillary compartments model, Parent (S-Ketamine) is modeled as a 2-compartment model, linear elimination, Metabolite (S-Norketamine) ) is modeled as a 1-compartment model issued from the main parent compartment, linear elimination. BLQ=LOQ/2. Concentrations are modeled with a lognormal distribution. Parameters are modeled by Stochastic Approximation Expectation-Maximization (SAEM) algorithm (Monolix©).

Main settings: Burn-in phase with 50 iterations. Exploratory phase with 250-5000 iterations (auto-stop criteria), stepsize exponent=0, enabled simulated annealing with a decreasing rate of 0.95. Smoothing phase with 100-1000 iterations (auto-stop criteria), stepsize exponent=0.7. Conditional mode with maximal 1000 iterations, tolerance at 0.000001. Stochastic approximation with 100-500 iterations. Monte Carlo size of 10000, with optimized degrees of freedom (1 to 15). Initial estimates are adjusted, and a final run is repeated using the last final estimates.

**Table S1_4.2.1** Diagnostic results with a constant error model on predicted concentration ( Cp = Cc + a.e ) for both parent and metabolite concentrations. Based on the preliminary results, the model includes first IOV for Cl and Q for the parent model.

| IIV | | IOV | | | | |
|---|---|---|---|---|---|---|
| Clm | Kpm | Clm | Kpm | -2LL (OFV) | AIC | BIC |
| | | | | -993 | -971 | -963 |
| X | | | | -995 | -971 | -962 |
| | X | | | -1004 | -980 | -971 |
| | | X | | -997 | -973 | -963 |
| | | | X | -1006 | -982 | -973 |
| | X | | X | -1007 | -981 | -971 |
| | | X | X | -1007 | -981 | -971 |

Conclusion: The model with IOV on Kpm is retained

**TableS1_4.2.2** Diagnostic results with different error models (OFV / AIC / BIC, all values are negatives).

| Parent/Metabolite | Constant | Proportional | Combined_1 | Combined_2 |
|---|---|---|---|---|
| Constant | 1006/982/973 | 1018/994/984 | 1017/991/981 | 1017/991/981 |

**Table S1_4.2.3** Diagnostic values to compare the use of Covariate Body weight (kg) on the model parameters (OFV / AIC / BIC, all values are negatives).

| | |
|---|---|
| - | 1006/982/973 |
| Kpm | 1020/995/985 |

**Final model equations:**

$\log(V1) = \log(V1\_pop)$

$\log(Cl) = \log(Cl\_pop) + \gamma_{Cl}$

$\log(Q) = \log(Q\_pop) + \gamma_{Q}$

$\log(V2) = \log(V2\_pop)$

$\log(Clm) = \log(Clm\_pop)$

$\log(Kpm) = \log(Kpm\_pop) + \beta_{Kpm\_Weight} * Weight + \gamma_{Kpm}$

**TableS1_4.2.4** Best estimates for the Parent-metabolite model for R-Ketamine and R-Norketamine with Constant and Proportional error models on R-Ketamine (Parent) and R-Norketamine (metabolite), respectively, no IIV, IOV on Cl, Q, and Kpm, and a covariate effect of Weight on Kpm, correlation between Cl and Q.

| | VALUE | STOCH. APPROX. | |
|---|---|---|---|
| | | S.E. | R.S.E.(%) |
| **Fixed Effects** | | | |
| V1_pop | 1.52 | 0.13 | 8.31 |
| Cl_pop | 0.11 | 0.019 | 16.8 |
| Q_pop | 0.16 | 0.043 | 26.4 |
| V2_pop | 4.14 | 0.69 | 16.8 |
| Clm_pop | 0.091 | 0.014 | 15.4 |
| Kpm_pop | 0.016 | 0.0083 | 50.4 |
| beta_Kpm_Weight_kg_ | 0.11 | 0.053 | 49.6 |
| **Standard Deviation of the Random Effects** | | | |
| | Value | C.V.(%) | |
| gamma_Cl | 0.46 | 49.11 | 0.1 | 22.4 |
| gamma_Q | 0.92 | 114.92 | 0.21 | 23.3 |
| gamma_Kpm | 0.25 | 25.67 | 0.084 | 33.3 |
| **Correlations** | | | |
| corr2_Q_Cl | 0.61 | 0.21 | 35.0 |
| **Error Model Parameters** | | | |
| a1 | 0.22 | 0.022 | 10.2 |
| b2 | 0.097 | 0.0089 | 9.15 |

**Figure S1_4.2.1** Observed versus predicted concentrations of R-Ketamine.

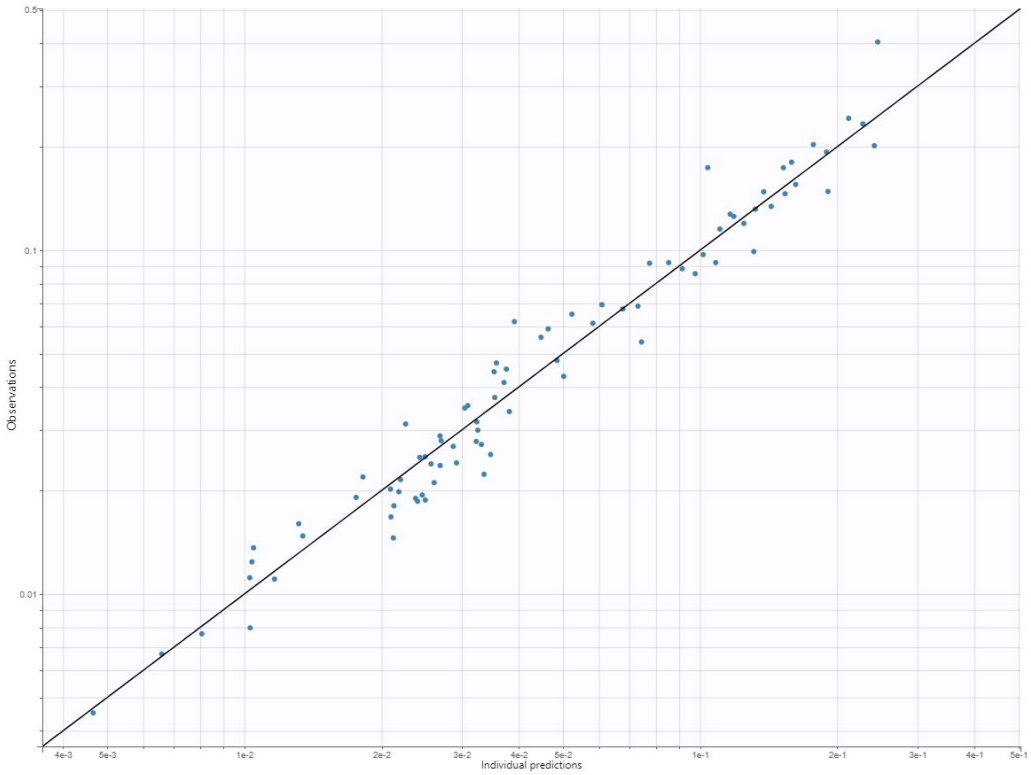



**Figure S1_4.2.2** Residual distribution for R-Ketamine.

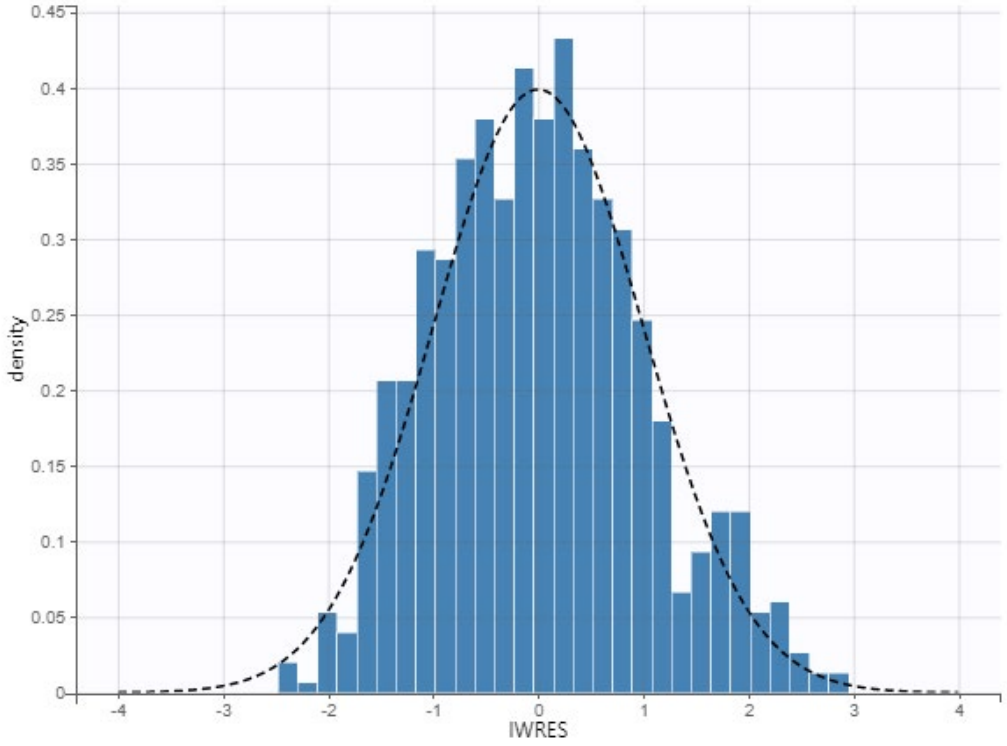


**Figure S1_4.2.3** Visual predictive check for S-Ketamine.

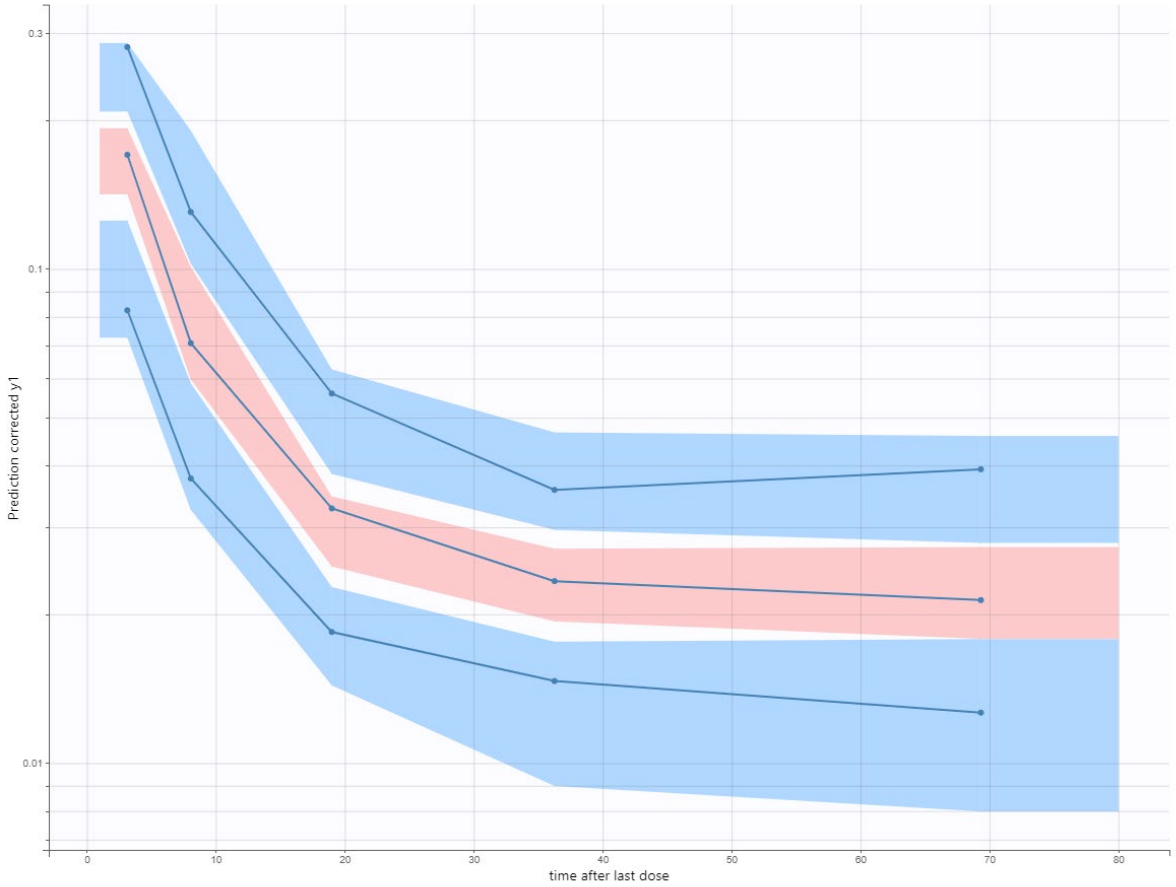


**Figure S1_4.2.4** Observed versus predicted concentrations of R-Norketamine.

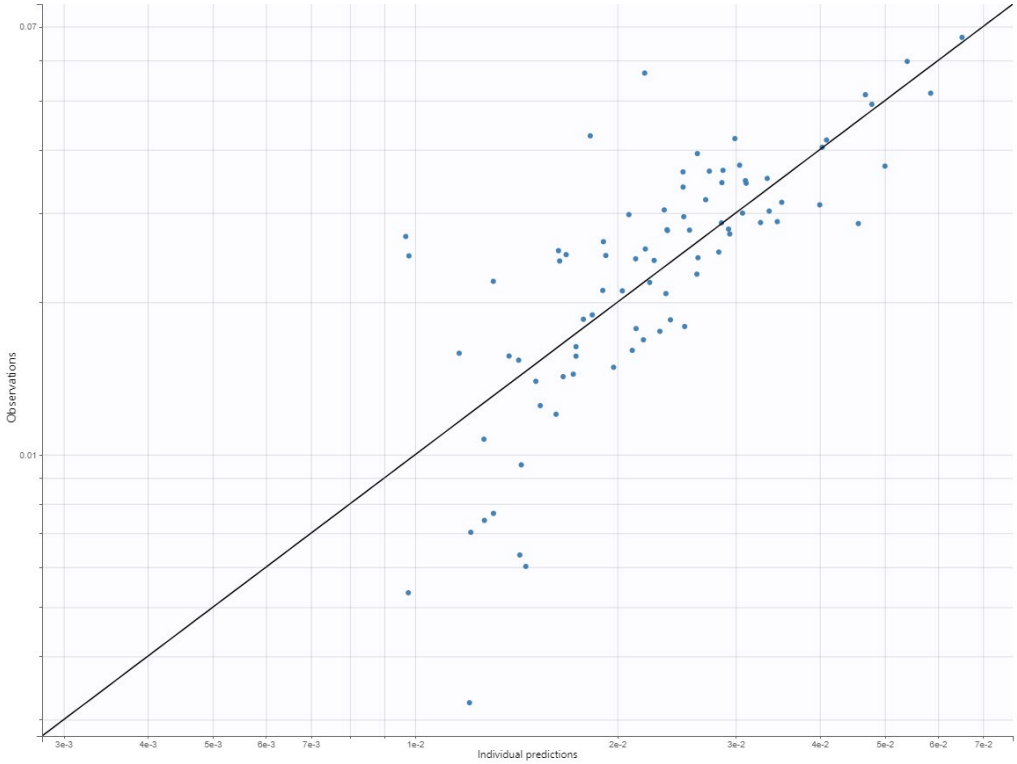



**Figure S1_4.2.5** Residual distribution for R-Norketamine

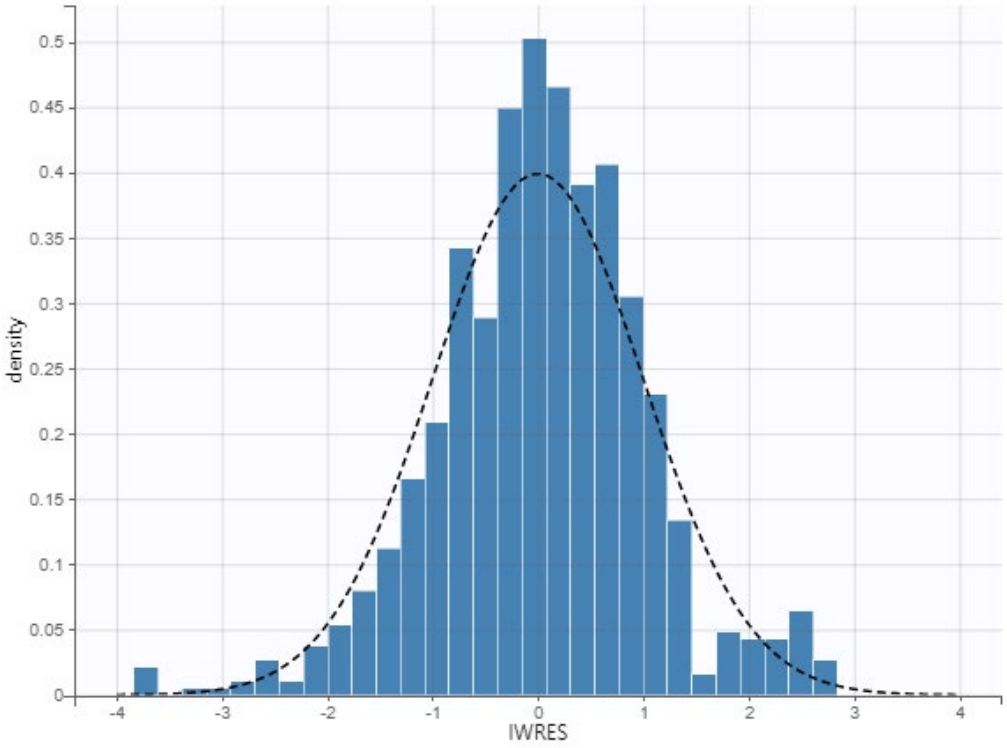
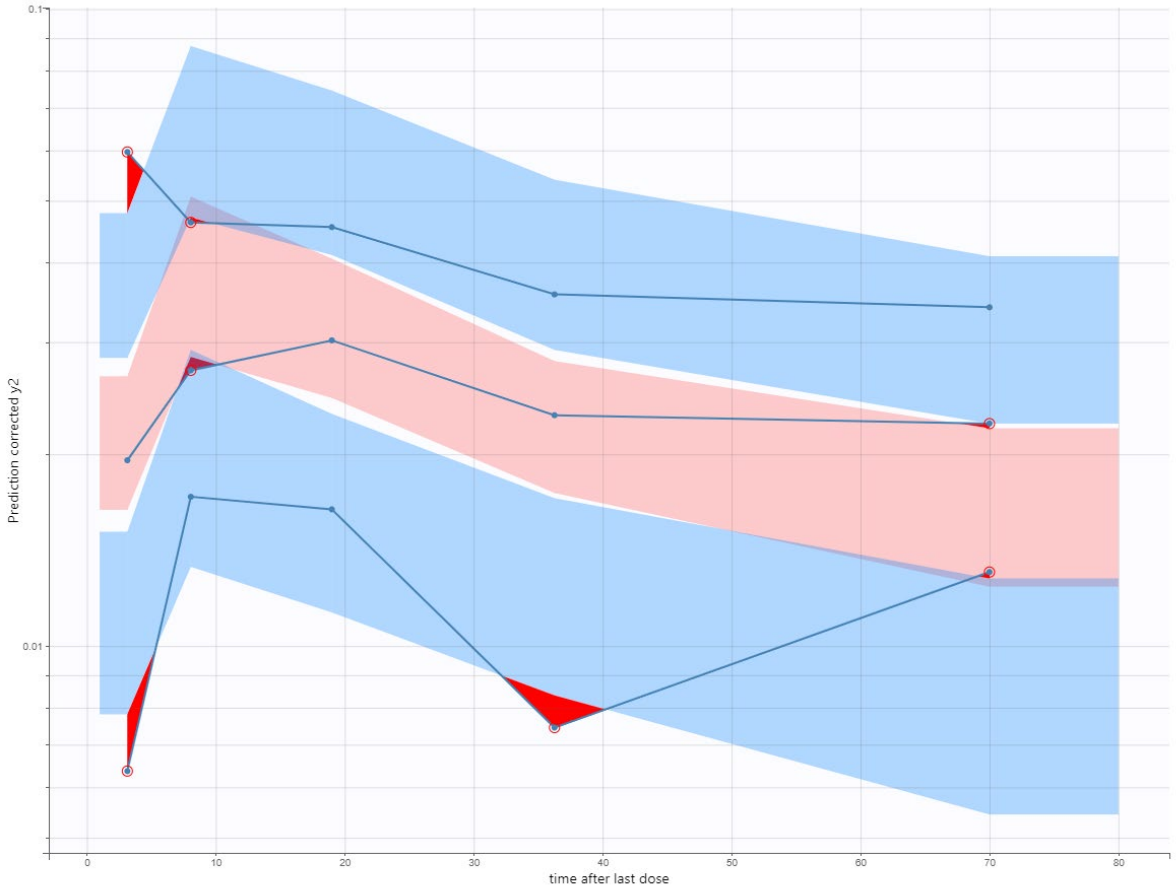


**Figure S1_4.2.6** Visual predictive check for R-Norketamine.



## 5. Prediction S-ketamine:

Based on the final Population Parent-metabolite model obtained for S-ketamine, a prediction is performed with administration of 0.5 mg/kg IV racemic ketamine over 1 minute, followed by 2 mg/kg/h for 60 minutes, reduced to 1.8 mg/kg/h for further 60 minutes.

**Figure S1_5.1** Prediction for S-Ketamine plasma concentration over time (minute) showing median and 5-95% confidence interval divided in 6 areas (5-20%, 20-35%, 35-50%, 50-65%, 65-80%, 80-95%).

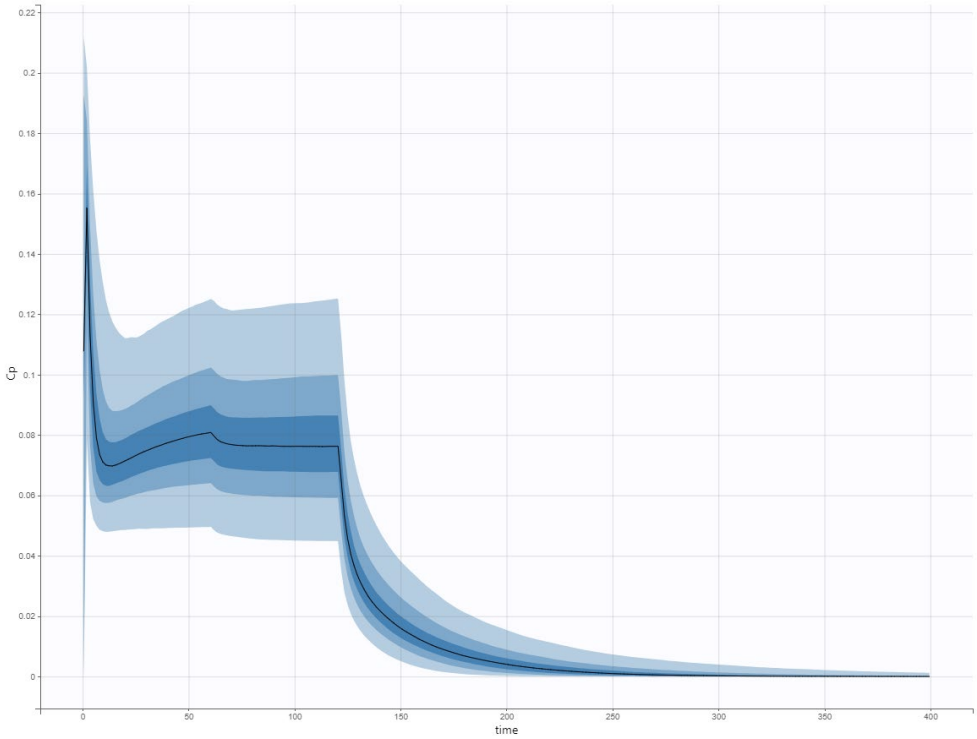



**Figure S1_5.1** Prediction for S-Norketamine plasma concentration over time showing median and 5-95% confidence interval divided in 6 areas (5-20%, 20-35%, 35-50%, 50-65%, 65-80%, 80-95%).