Table 1: **Studies Included in the Population Pharmacokinetic Analysis of NNZ-2566**

| Protocol No. | Study Description | Study Population | Dose (mg/kg) | Regimen | Number of Evaluable Subjects | PK Sampling Scheme |
|---|---|---|---|---|---|---|
| Neu-2566-HV-001 | Neu-2566-HV-001: A Phase 1a, Single Dose, Double-Blind, Randomized, Dose Escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of NNZ-2566 | Healthy volunteers (male) | 0.1 mg/kg<br>1 mg/kg<br>10 mg/kg<br>20 mg/kg<br>30 mg/kg | 10 min i.v. infusion | 20 (5 per cohort) | Pre-dose (approximately 15 min prior to start of infusion), at end of infusion (10 min) and at 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 120, 150 and 180 min post-start of infusion. |
| Neu-2566-HV-004 | Neu-2566-HV-004: A Phase I, double-blind, randomized, dose escalation study to assess the safety, tolerability and pharmacokinetics of NNZ-2566 | Healthy volunteers (female) | 10 min i.v. bolus of 6 mg/kg<br>10 min i.v. bolus of 20 mg/kg<br>20 mg/kg i.v. bolus over 10 min followed by 1 mg/kg/h for 72 hours<br>20 mg/kg i.v. bolus over 10 min followed by 3 mg/kg/h for 72 hours<br>20 mg/kg i.v. bolus over 10 min followed by 6 mg/kg/h for 72 hours | 10 min i.v. infusion followed by long infusion | 31 | |

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|---|---|---|---|---|---|---|
| Neu-2566-HV-005 | A Phase I, Double-Blind, Randomized, Dose Escalation Study to Assess the Safety, Tolerability, and<br>Pharmacokinetics of NNZ-2566 in Healthy Subjects,<br>following Oral Administration | Healthy volunteers<br>(male and female) | 6 | Single oral dose | 6 | Pre-dose (within -60 to -5 min from dosing), 15 min post dose (±2 min), 30 min post dose (±2 min), and 1, 1.5, 2 (all fasted), 3, 4, 5, 6 and 8 hr post dose (all ±5 min). |
| | | | 30 | Single oral dose | 6 | Pre-dose (-60 to -5 min of dosing) and 1hr (fasted), at 2, 4, 6, 8 10, 12, 18, 24 and 32 hr post dose. |
| | | | 100 | 100 mg/kg b.i.d. oral dose on Day 1 followed by 100 mg/kg b.i.d. oral dose for 5 days commencing on Day 5 | 6 | Pre-dose (-60 to -5 min of dosing) and 1hr (fasted), at 2, 3, 4, 8 and 12 hr post the first dose, and at 1, 2, 3, 4, 8, 12, 18, 24 and 36 hr post the second dose.<br>Pre-dose on Day 5 (-60 to -5 min of dosing) and 1hr (fasted), at 2, 3, 4, 8 and 12 hr post the first dose, at 2, 4, 8 and 12 hr post the second dose, at 2, 4, 8 and 12 hr post the first dose on Day 6, at 2, 4 and 12 hr post the first doses on Days 7-9 (all 12 hr were taken prior to the following scheduled dose), and at 1, 2, 3, 4, 8, 12, 24 and 36 hr post the last dose. |

Table 2: **Overall summary of demographic characteristics and per study**

| Covariate | Summary Statistics or Category | Neu-2566-HV-001 (n=20) | Neu-2566-HV-004 (n=29) | Neu-2566-HV-005 (n=12) | Overall (n=61) |
|---|---|---|---|---|---|
| Weight (kg) | Median (range) | 74.5 (59-95) | 61.8 (52.2-88.2) | 70.1 (53.4-83.8) | 66.5 (52.2-95) |
| Age (y) | Median (range) | 21 (19-28) | 23 (19-30) | 23 (19-38) | 23 (19-38) |
| Height (cm) | Median (range) | 181.5 (162-199) | 166 (156-174) | 169.7 (161-183.6) | 169 (156-199) |
| BMI | Median (range) | 22.2 (18.3-27.6) | 22.2 (20-29.1) | 24.9 (20.2-27.5) | 22.8 (18.3-29.1) |
| Sex | Female [N (%)] | 0 (0%) | 29 (100%) | 6 (50%) | 37 (59%) |
| | Male [N (%)] | 20 (100%) | 0 (0%) | 6 (50%) | 26 (41%) |

Table 3: **Population Pharmacokinetic Parameter Estimates after Administration of NNZ-2566 to Healthy Subjects**

| Parameter (unit)[a] | Notation | Population Estimate | RSE (%) | Bootstrap Mean (95% CI) |
|---|---|---|---|---|
| Absorption rate constant, Ka (1/h) | $\theta 1$ | 0.28 | 15.19 | 0.29 (0.20-0.39) |
| Systemic clearance, CL (L/h) | $\theta 2$ | 10.35 | 2.34 | 10.36 (9.89-10.86) |
| Intercompartmental clearance, Q (L/h) | $\theta 3$ | 1.04 | 15.02 | 1.06 (0.79-1.41) |
| Central volume of distribution, V2 (L) | $\theta 4$ | 20.23 | 2.32 | 20.22 (19.29-21.24) |
| Peripheral compartment volume of distribution, V3 (L) | $\theta 5$ | 41.47 | 8.96 | 41.43 (33.07-49.24) |
| Bioavailability morning dose, $F1_{AM}$ | $\theta 6$ | 0.63 | 4.88 | 0.63 (0.57-0.69) |
| Bioavailability afternoon dose, $F1_{PM}$ | $\theta 7$ | 0.50 | 5.15 | 0.50 (0.45-0.55) |
| Inter-individual variability | | Population Estimate (CV%)[b] | RSE (%) | Bootstrap Mean (95% CI) |
| $\eta$CL variance | $\Omega 1$ | 0.02 (12.25%) | 9.12 | 0.01 (0.01-0.02) |
| $\eta$V2 variance | $\Omega 2$ | 0.02 (12.92%) | 11.39 | 0.02 (0.01-0.02) |
| $\eta$KA variance | $\Omega 3$ | 0.26 (50.89%) | 10.89 | 0.24 (0.11-0.38) |
| $\eta$Q variance | $\Omega 4$ | 0.71 (84.26%) | 7.31 | 0.70 (0.48-0.94) |
| $\eta$V3 variance | $\Omega 5$ | 0.08 (27.98%) | 10.65 | 0.08 (0.02-0.14) |
| Residual error | | Population Estimate (CV%) | RSE (%) | Bootstrap Mean (95% CI) |
| Exponential error (µg/mL) | $\sigma 1$ | 0.03 (17.06%) | 7.42 | 0.03 (0.02-0.04) |

Abbreviations: CI = confidence interval; CV = coefficient of variation, RSE = percent relative standard error, WT = body weight, $\theta$ = PK parameter estimation; $\eta$ = inter-individual variability; $\Omega$, = inter-individual in population PK parameter; $\sigma$= Residual population variance

a. Population parameter point-estimates for the full two compartment model and 95% CI and %CV from a non-parametric bootstrap are presented
b. Value in parentheses represents the inter-individual variability of the PK parameters calculated as the square root of Ω x 100%

Table 4: **Overview of secondary pharmacokinetic parameters**.

Numbers reported are the geometric mean and 95% confidence interval. AUC is the area under the curve for the total study. Normalized AUC is the AUC divided by the total drug taken.

| Study | Infusion rate (mg/kg/hr) | Bolus (mg/kg) | AUC | Normalized AUC | $C_{max}$ | $t_{half}$ |
|---|---|---|---|---|---|---|
| HV-001 | 0 | 0.1 | 0.6 (0.5-0.7) | 6.2 (5.4-7.2) | 0.4 (0.3-0.5) | 1.2 (0.9-1.5) |
| HV-001 | 0 | 1 | 6.3 (5.3-7.5) | 6.3 (5.3-7.5) | 3.6 (2.8-4.7) | 1.2 (1-1.6) |
| HV-001 | 0 | 10 | 55.7 (41.6-74.6) | 5.6 (4.2-7.5) | 32.3 (27.8-37.5) | 1.3 (1-1.7) |
| HV-001 | 0 | 20 | 123 (84.3-179.3) | 6.1 (4.2-9) | 57.4 (46.8-70.3) | 1.5 (1.2-1.8) |
| HV-004 | 0 | 6 | 34.6 (26.2-45.7) | 5.8 (4.4-7.6) | 17.6 (13.3-23.3) | 1.4 (1.3-1.6) |
| HV-004 | 0 | 20 | 102.8 (74.6-141.8) | 5.1 (3.7-7.1) | 55.2 (46.1-66.1) | 1.3 (1.2-1.4) |
| HV-004 | 1 | 20 | 461.9 (247.8-860.9) | 5.6 (4.4-7.2) | 61.9 (53.4-71.7) | 1.6 (1.2-2) |
| HV-004 | 3 | 20 | 1502.2 (1103.2-2045.4) | 6.4 (4.7-8.7) | 64.7 (55.6-75.4) | 1.4 (1.1-1.8) |
| HV-004 | 6 | 20 | 2493.9 (1964.5-3166) | 5.5 (4.3-7) | 59.9 (49.1-73) | 1.3 (1.1-1.6) |
| HV-005 | 0 | 30* | 118.9 (96.4-146.7) | 4 (3.2-4.9) | 10.8 (7-16.8) | 5.5 (3.8-8) |
| HV-005 | 0 | 100* | 4808.7 (3854.2-5999.7) | 4 (3.2-5) | 74.7 (62.8-88.8) | 2.6 (2.5-2.7) |
| *Study HV-005 received NNZ-2566 orally | | | | | | |