ONLINE RESOURCE

Clinical Pharmacokinetics

Title: Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase 2 and Phase 3 Trials

Authors: Aksana K. Jones¹, Eliford Ngaimisi², Mathangi Gopalakrishnan², Malcolm A Young¹, Celine M. Laffont¹

Authors’ Affiliations:

1. Indivior Inc., Richmond, VA
2. Center for Translational Medicine, University of Maryland Baltimore

Aksana K. Jones and Eliford Ngaimisi contributed equally

*Corresponding author: Celine M Laffont (celine.laffont@indivior.com)
Table S1  Genotype Distribution in Phase 3 Efficacy Study (Study 2) for CYP450 and UGT enzymes

| Characteristics | Level | 300/100 mg | 300/300 mg | Placebo |
|-----------------|-------|------------|------------|---------|
| CYP2C8*3 (rs10509681) (N(%)) | CC    | 1 (0.5)    | 2 (1.0)    | 0 (0.0) |
|                 | TC    | 23 (11.9)  | 33 (16.8)  | 14 (14.1)|
|                 | TT    | 160 (82.5) | 147 (75.0) | 81 (81.8)|
|                 | Missing | 10 (5.2)   | 14 (7.1)   | 4 (4.0)  |
|                 |       | 2 (1.0)    | 14 (7.1)   | 4 (4.0)  |
| CYP3A4*22 (rs35599367) (N(%)) | AA    | 0 (0.0)    | 1 (0.5)    | 0 (0.0)  |
|                 | GA    | 9 (4.6)    | 13 (6.6)   | 6 (6.1)  |
|                 | GG    | 175 (90.2) | 169 (86.2) | 89 (89.9)|
|                 | Missing | 10 (5.2)   | 13 (6.6)   | 4 (4.0)  |
| CYP3A4*2 (rs55785340) (N(%)) | AA    | 0 (0.0)    | 183 (94.3) | 95 (96.0)|
|                 | GA    | 1 (0.5)    | 183 (94.3) | 0 (0.0)  |
|                 | Missing | 10 (5.2)   | 13 (6.6)   | 4 (4.0)  |
| CYP3A4*1B (rs2740574) (N(%)) | CC    | 25 (12.9)  | 26 (13.3)  | 6 (6.1)  |
|                 | TC    | 36 (18.6)  | 32 (16.3)  | 12 (12.1)|
|                 | TT    | 122 (62.9) | 124 (63.3) | 76 (76.8)|
|                 | Missing | 11 (5.7)   | 14 (7.1)   | 5 (5.1)  |
| UGT2B7*3 (rs12233719) (N(%)) | GG    | 184 (94.8) | 183 (93.4) | 95 (96.0)|
|                 | Missing | 10 (5.2)   | 13 (6.6)   | 4 (4.0)  |
| UGT1A1 (rs8175347) (N(%)) | TA5TA5 | 0 (0.0)    | 1 (0.5)    | 0 (0.0)  |
|                 | TA5TA6 | 1 (0.5)    | 3 (1.5)    | 3 (3.0)  |
|                 | TA5TA7 | 2 (1.0)    | 0 (0.0)    | 1 (1.0)  |
|                 | TA5TA8 | 1 (0.5)    | 1 (0.5)    | 0 (0.0)  |
|                 | TA6TA6 | 73 (37.6)  | 77 (39.3)  | 42 (42.4)|
|                 | TA6TA7 | 79 (40.7)  | 70 (35.7)  | 39 (39.4)|
|                 | TA6TA8 | 2 (1.0)    | 2 (1.0)    | 1 (1.0)  |
|                 | TA7TA7 | 24 (12.4)  | 24 (12.2)  | 10 (10.1)|
|                 | TA7TA8 | 1 (0.5)    | 4 (2.0)    | 0 (0.0)  |
|                 | Missing | 11 (5.7)   | 14 (7.1)   | 3 (3.0)  |
## Table S2  Parameter Estimates of Population Pharmacokinetic Model at Each Step of Model Development

| Parameter | Description | Step 1 (Study 1) | Step 2 (Studies 1+2) | Step 3 (Studies 1+2+3) |
|-----------|-------------|-----------------|---------------------|-----------------------|
| CL/F      | BUP-XR apparent elimination clearance (L/hr) | 51.7 (1.4) | 49.8 (2.8) | 52.0 (1.5) |
| V4/F      | BUP-XR apparent volume of central compartment (L) | 362 (1.3) | 462 (7.4) | 433 (27) |
| Q/F       | BUP-XR apparent distribution clearance (L/hr) | 79.5 (1.6) | 79.5 (FIXED) | 79.5 (FIXED) |
| V5 (L)    | BUP-XR apparent volume of peripheral compartment (L) | 1110 (1.6) | 1110 (FIXED) | 1110 (FIXED) |
| k14       | SL absorption rate constant (1/hr) | 1.17 (33) | 1.17 (FIXED) | 1.17 (FIXED) |
| k24       | Fast absorption rate constant from SC depot (1/hr) | 0.0181 (1.6) | 0.0294 (9.9) | 0.0276 (5.1) |
| k36       | Slow absorption rate constant from SC depot (1/hr) | 0.00333 (1.9) | 0.00370 (8.3) | 0.00362 (3.7) |
| k64       | Rate constant from Transit to Central compartments (1/hr) | 0.000433 (1.1) | 0.000483 (5.4) | 0.0000510 (3.7) |
| F1        | Relative bioavailability for SL buprenorphine tablets vs. BUP-XR | 0.185 (4.3) | 0.185 (FIXED) | 0.185 (FIXED) |
| F2        | Fraction of SC dose absorbed by fast process | 0.0612 (2.1) | 0.0661 (2.8) | 0.0679 (2.2) |
| FRK14     | Relative change in k14 for film vs tablet formulation | NA | 0.898 (28) | 0.650 (11) |
| FRF1      | Relative change in F1 for film | NA | 1.37 (9.1) | 1.47 (3.5) |
| Parameter | Description | Step 1 (Study 1) | Step 2 (Studies 1+2) | Step 3 (Studies 1+2+3) |
|-----------|-------------|-----------------|---------------------|------------------------|
|           |             | Estimate (%RSE) | Variance (%RSE) | %CV | Estimate (%RSE) | Variance (%RSE) | %CV | Estimate (%RSE) | Variance (%RSE) | %CV |
| F1DOSE    | vs tablet formulation | 0.674 (41) | NA | NA | 0.765 (36) | NA | NA | 0.765 (FIXED\(^b\)) | NA | NA |
| θ\(_{BMI}\) (CL) | Relative change in F1 for dose ≥16mg compared to <16mg | NA | NA | NA | -0.408 (21) | NA | NA | -0.364 (21) | NA | NA |
| θ\(_{BMI}\) (k24) | Power coefficient for BMI on CL/F | NA | NA | NA | -1.29 (15) | NA | NA | -1.32 (14) | NA | NA |
| θ\(_{SEX}\) (k36) | Power coefficient for BMI on k24 | NA | NA | NA | 0.0759 (140) | NA | NA | 0.0313 (282) | NA | NA |
| PROP      | Fractional increase in k36 for females | NA | NA | NA | 0.0759 (140) | NA | NA | 0.0313 (282) | NA | NA |
| ADD       | Proportional residual error | 0.179 (0.52) | 0.190 (0.97) | 0.190 (0.66) | 0.190 (0.97) | 0.190 (0.66) |
|           | Additive residual error (ng/mL) | 0.01 (FIXED) | 0.0378 (14) | 0.0373 (14) | 0.0378 (14) | 0.0373 (14) |

\(^a\) logit-normal distribution

\(^b\) fixed, given extremely sparse SL data in Study 3 (1 sample taken prior to BUP-XR Injection 1)

BMI=body mass index; CV=coefficient of variation for log-normal distribution calculated as 100 × \(\sqrt{\exp(\omega^2)} - 1\), where \(\omega^2\) is the variance of the random effect; NA=not applicable; RSE=relative standard error; SC=subcutaneous; SL=sublingual
Figure S1  Effect of Body Mass Index (BMI) on Buprenorphine Plasma Exposure Following BUP-XR Administration in the Phase 3 Efficacy Study (Study 2)

Dots: observed data; Black bold dotted curve: observed medians; Black dotted curves: observed 5th and 95th percentiles
Red curve: medians of the simulated data; Shaded blue area: 90% prediction intervals of the simulated data;
Figure S2  Standard Diagnostic Plots for Final Population Pharmacokinetic Model

Upper panels: the blue dashed line represents the line of unity. Lower panels: grey and blue dashed lines are reference lines. Red lines are tendency curves through the data.