Pharmacometric Analysis Report

|  |  |
| --- | --- |
| **Title:** | **Population Pharmacokinetic Analysis Report for Drug X** |
| **Study number(s):** | *ISoP-101, ISoP-102* |
| **Development Phase:** | **Phase II** |
| **Investigational Medicinal Product(s):** | **Drug X** |
| **Indication:** | **Disease Y** |
| **Sponsor:** | **ISoP** |
| **Author:** | **Report Template Working Group** |
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| Confidential |

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**List of Abbreviations and Definition of Terms**

| Term | Definition |
| --- | --- |
| %CV | coefficient of variation expressed as a percentage |
| Cavg1 | time-averaged concentration over the first dosing interval |
| CI | confidence interval |
| CL | clearance |
| Cmax | peak concentration |
| Cmin | trough concentration |
| COV | covariance |
| CV | coefficient of variation |
| CWRES | conditional weighted residuals |
| Diff | difference |
| IIV | interindividual variability |
| LLOQ | lower limit of quantitation |
| NONMEM | nonlinear mixed effects modeling |
| OFV | objective function value |
| pcVPC | prediction-corrected visual predictive check |
| PI | prediction interval |
| PK | pharmacokinetic(s) |
| PPK | population pharmacokinetic(s) |
| PsN | Perl-speaks-NONMEM |
| QC | quality control |
| RSE | relative standard error |
| SD | standard deviation |
| V/F | Apparent volume of distribution |
| VPC | visual predictive check |
| WT | baseline body weight |

# Executive Summary

Drug X, an oral tablet which is being developed by company A and is used to treat Disease Y, has undergone N number of completed studies. A population PK analysis was performed to characterize the PK and identify sources of variability in the PK based on rich and sparse samples collected in Phase 1 and Phase 3 studies. As part of the population PK analysis, data from NN subjects was utilized where the doses were ranging from 5 mg- 100 mg Q3W.

The data was adequately described using a 1-compartment model with a first-order absorption rate constant (Ka) with lag time (Tlag). A bootstrap method resulted in model reduction compared to reducing the full model with the additional of all the covariates like (age, sex, baseline body weight, race, baseline GFR, drug product) by removing covariates for which the 95% PIs included the null value relative to the reference compared stepwise covariate modeling using forward addition and backward elimination. Both continuous and categorical variables were evaluated and. The final population estimates of CL/F and V/F for drug X were 19.49 L/h and 198.72 L, respectively, and are for a male patient who is 92.5 kg, has a CRCL of 116.5 mL/min, and is taking a dose of 150 mg. Based on the population PK model, the half-life of drug X was 7.07 The effect of creatinine clearance was added on CL/F since the drug was previously demonstrated as important as Drug X is expected to undergo renal excretion. Baseline body weight of each subjects was modeled as covariate on the CL, VC using a power function and the the estimates are respectively. Sex was a significant covariate on CL and VC (Figure 6), with male subjects having a higher CL and higher Vc than female subjects.

Final Model-based simulations were performed to evaluate drug X CL under various conditions, estimate effective half-life, predict exposure metrics for 60 mg Q4W vs 30 mg Q2W dose regimens, and assess the clinical relevance of covariates of interest such as sex, hepatic function, renal function, race, manufacture process, and shorter infusion time in the final PPK model. Results suggest that exposures were higher in female subjects than males for subjects who received 60 mg Q4W. The predicted geometric means of drug X exposure (Cmin1, Cmax1, Cavg1, Cavd28, Cminss, Cmaxss, and Cavgss) at 60 mg Q4W and 30 mg Q2W are summarized in Table 5. As expected, Cavgss was similar across the two different regimens (difference < 5%). The exposures were higher with drug X 30 mg Q2W relative to 60 mg Q4W by approximately 51% for Cmind28 and 42% for Cminss. The exposures were lower with drug X 30 mg Q2W relative to 60 mg Q4W by approximately 50% for Cmax1 and 31% for Cmaxss, which were also expected.

# Introduction

Drug X, an oral tablet which is being developed by company A and is used to treat Disease Y. Disease Y is a chronic brain disorder for which no cure has been identified. The symptoms includes change in mood, memory, blood pressure, sleep, fatigue and sensation.

# Objectives

* To characterize the PK of drug X, including effects of key intrinsic and extrinsic covariates on PK parameters, in subjects with disease Y.
* To compare key measures of drug X exposures for subjects with different body weight.

# Data

# Description of Studies

The PPK analysis was performed using data from 4 clinical studies conducted in subjects with disease Y (Table 3.1-1). These studies were selected to represent the intended patient population, and provided intense PK data. Study ISoP-102 was conducted in subjects with disease Y. Data from Studies ISoP-101 provided drug X intense PK profile over time.

# Bioanalytical Methods

The PK samples collected in the studies listed in Table 3.1-1 were analyzed for drug X concentration by mass spectrum assay. The bioanalytical report is included in Appendix 2.

# Analysis Datasets

#### Analysis Population

The drug X PPK analysis dataset included all subjects from studies listed in Table 3.1-1 for whom drug X plasma concentration data were available (Table 3.3.1.1-1). Subjects for whom no plasma concentrations were available or had PK samples that could not be associated with clinical data were excluded. The PPK analysis dataset is representative of the studies included in the only ~1% of subjects were excluded from the analysis.

| Table 3.3.1.1-1: Subjects Included in the Drug X Population Pharmacokinetic Analysis Dataset by Study | | | | |
| --- | --- | --- | --- | --- |
| Study | Number of Subjects | | | |
| Drug X Treated | PK Database | Flagged | Included (% of subjects in PK Database) |
| **ISoP-101** | 25 | 335 | 3 | 332 (99.1) |
| **ISoP-102** | 175 | 1398 | 17 | 1381 (98.8) |
| **Total** | **200** | **1733** | **20** | **1713 (98.8)** |

Source:

#### Handling of Unquantifiable or Missing Data

Drug X plasma concentration values below the LLOQ were flagged in the PPK analysis dataset and excluded from the analysis. Dataset records of missing plasma concentrations corresponding to collected PK samples were retained in the analysis dataset but were flagged and excluded from the analysis.

Missing dose data (dose amount, infusion duration, dosing time, or dosing date) were imputed as described below to enable inclusion of PK samples associated with subsequent doses. However, Drug X plasma concentrations in the PPK analysis dataset were flagged and excluded from the analysis if the PK sample date/time was missing. Dose data with missing dates were not included in the analysis.

Baseline subject covariates were determined from the baseline/randomization visit. If a subject covariate was missing at the baseline/randomization visit, then the covariate value was taken either from the pre-study (screening) visit or from the earliest post-randomization visit, whichever was closest to the baseline visit. Baseline covariates that were missing after the above procedure were imputed as the median value (continuous) or mode (categorical) in the study population if < 10% of covariate values were missing.

# Methods

# Model Development

**Figure 1: Schematic Overview of Population Pharmacokinetic Model Development**

|  |
| --- |
| **Base Model**   * Determine structural model (linear vs non-linear CL, one-compartment vs two-compartment) * Determine residual error model (additive, proportional and combined) * Determine IIV model * Evaluated extreme values (|CWRES > 6|) and excluded the outliers from the dataset used |
|  |
| **Full Model**  The following pre-specified covariates are included in the Full model to assess their impact on PK parameters:   * CL/F: baseline body weight * V/F: baseline body weight |
|  |
| **Final Model**   * Final model was developed by removing all non-significant covariates from the full model. |

# Results

## Exploratory Data Analysis

Concentration-time profiles of drug X following oral administration of the first dose on Day 1 in healthy subjects are presented in **Figure 2**. Additional concentration-time profiles of drug X are presented in Appendix 2. A list of samples excluded from the analysis is presented in Appendix 2. Drug X was rapidly absorbed following oral administration and declined in an exponential manner.

## Model Development

### Base Model

A population PK analysis was performed based on rich and sparse samples collected in Phase 1 and Phase 3 studies in order to identify the structural model. Highlights of the base population PK analysis are presented below and in Appendix 2.

* 1- and 2-compartment models with linear elimination were tested. The 1-compartment model resulted in the lowest OFV. A first-order absorption rate constant (Ka) was used to characterize the rapid absorption of drug X. A proportional error model resulted in a substantially lower OFV relative to combined (additive and proportional) or additive error models.
* Additional model refinements are presented below.
  + An allometric function accounting for body weight effect on clearance (CL/F) and volume of distribution (V/F) was included in the model.
  + An allometric function accounting for body weight effect on volume of distribution (V/F) was included in the model as well.

### Covariate Model

Potential relationships between PK parameters (random effects) of drug X and continuous covariates from the base PK model (run2) are presented in Appendix 2. A stepwise covariate analysis was performed to identify sources of variability in PK parameters of drug X.

Results for covariate analysis are presented in Appendix 2.

Covariates were evaluated using a forward inclusion approach with p<0.01 (ΔOFV>6.6349). The effect of body weight on CL/F resulted in the most important decrease in OFV as part of the first step of the analysis (ΔOVF = -322.051). In the second step, the effect of body weight on V/F resulted in the most important decrease in OFV (ΔOVF = -161.224).

During the backward testing, none of the covariate were removed. Additional information is available in Appendix 2.

### Final Model

Typical population PK parameters of drug X derived with the final model (run1) are presented in Table 7. The continuous covariate (body weight) was centered to a reference value in the population PK analysis (92.5 kg). The reference value is <1% different than the median value in the Phase 3 studies.

The population estimates of CL/F and V/F for drug X were 10 L/h and 109 L, respectively, and for a male patient who is 92.5 kg. Based on the population PK model, the half-life of drug X was 7.07 h.

**Table 3: Parameter Estimates of the Final Drug X Population Pharmacokinetic Model**

| **Parameter [Units]a** | **Symbol** | **Estimate** | **Standard Error, RSE%d** | **95% CIc** |
| --- | --- | --- | --- | --- |
| **Fixed Effects** | | | | |
| *CLREF* [L/h] | θ**1** | 10.00 | 0.379 (3.79) | 6.48 - 7.46 |
| *VCREF* [L] | θ2 | 109.0 | 4.55 (4.17) | 4.04 - 4.21 |
| *KA REF* | θ3 | 0.938 | 0.0456 (4.86) | 0.598 - 0.846 |
| **Random Effects** |  |  |  |  |
| *ZCL* | ω1,1 | 0.279 | 0.0271 (9.71) | 0.126 - 0.162 |
| *ZV* | ω2,2 | 0.325 | 0.00321 (9.88) | 0.0578 - 0.0689 |
| *ZKA* | ω3,3 | 0.412 | 0.0223 (5.41) | 0.150 - 0.190 |
| *ZCL:ZV* | ω1,2 | 0.172 | 0.00595 (34.6) | 0.0376 - 0.0547 |
| **Residual Error** |  |  |  |  |
| Proportional Error [-] | θ4 | 0.204 | 0.00107 (0.523) | 0.202 - 0.207 |

Source: Analysis-Directory/

**Note 1:** *CLREF* is the typical value of clearance in a reference subject, weighing 75 kg,. *VCREF* *KAREF* are typical values in a reference subject weighing 75 kg.

**Note 2:** Eta shrinkage (%): ETA\_CL: 21.1; ETA\_VC: 19.8; ETA\_V2: 41.8; EPS shrinkage (%): 15.7

**Note 3:** Condition no: 58

Abbreviations: CI = confidence interval; RSE = relative standard error.

a Random Effects and Residual Error parameter names containing a colon (:) denote correlated parameters.

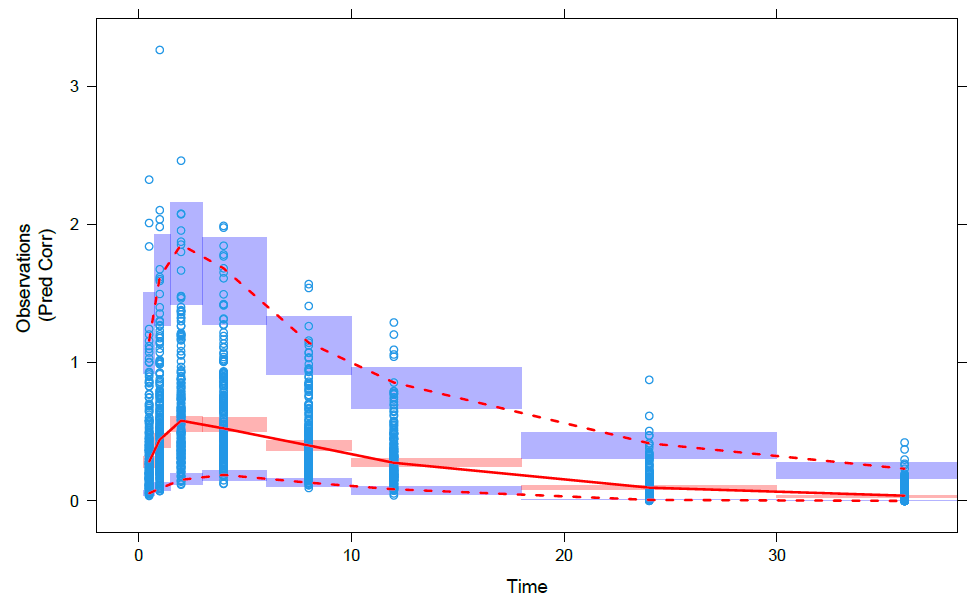
b RSE% is the relative standard error (Standard Error as a percentage of Estimate).

c Confidence intervals of Random Effects and Residual Error parameters are for *Variance* or *Covariance.*

## Model Evaluation

Visual predictive checks were performed for the final PPK model s, and the results are in Figure 5. Overall, the pcVPC results indicate that the model adequately characterized the data and predicted concentrations to be used for E-R efficacy and safety analyses. The observed 5th, 50th (median), and 95th percentiles generally fall within the 90% PI (the shaded band) up to 36 hours after dose.

**Figure 5: Prediction-Corrected Visual Predictive Check of Drug X Concentrations versus Actual Time (Final Population Pharmacokinetic Model)**



Source:

## Model Application

Model-based simulations were performed to evaluate drug X CL under various conditions, estimate effective half-life, predict exposure metrics for 60 mg Q4W vs 30 mg Q2W dose regimens, and assess the clinical relevance of covariates of interest such as sex, hepatic function, renal function, race, manufacture process, and shorter infusion time in the final PPK model. The final model was used in these simulations.

### Covariate Model Evaluation of Effect of Body Weight

Body weight was a significant covariate on CL/F and V/F (Figure 6), with CL/F and V/F increase when body weigh increases. Comparisons of model predicted drug exposure at 100 mg QD by body weight are presented in Figure 6. In general, exposures were lower in subjects with higher body weight.

**Figure 6: Distribution of Model Predicted Drug X Exposures (Cavg1 and Cavgss) at 100 mg by Body Weight**

Source:

# Discussion

PPK analyses were performed to assess the PK of drug X and to support dosing of drug X based on PK data from 2 clinical studies (ISoP-101 and ISoP-102).The PK of drug X was described by a 1-compartment, first-order oral absorption PK model with linear CL. A visual predictive check demonstrated that the model adequately characterized the central tendency as well as the variability in drug X concentrations with time after dosing 100 mg in subjects with disease Y. The typical baseline CL of drug X was 10.00 L/h for a reference mal subject body weight of 75 kg.

Baseline body weight was found to be the statistically significant covariates on drug X PK parameters. The analysis showed that CL/F, and V/F increase with increasing body weight. Relative to 75 kg (selected reference body weight value), the effect of body weight at the 95th percentile on CL was 34% (95% CI: 27% - 40%) and on VC was 13%, which was not considered to be clinically relevant. In addition, The exposures at steady state were less than 30% higher in subjects with lower body weight (at 5th percentile) and were less than 45% lower in subjects with higher body weight (at 95th percentile) relative to the exposure in typical subjects at a body weight of 75 kg.

# Conclusions

* Drug X PK is well described by a 1-compartment, first-order absorption PK model with linear CL.
* CL/F and V/F of drug X were higher in subjects with higher baseline body weight.
* The effect of body weight at the 95th percentile on CL was 34% (95% CI: 27% - 40%) and on VC was 13%, which was not considered to be clinically relevant

# References

Interim Clinical Study Report for Study ISoP-101. A Phase 1 Dose Escalation Study of the Safety, Tolerability of Drug X; Company A; 2021. Document Control No. 9035.

2 Drug X Investigator Brochure. Company A. Document Control No. 7620.

# Appendices

## Pharmacometric Modeling Analysis Plan

*Insert a link to the Pharmacometric Modeling Analysis Plan.*

## Define.doc

*List all variables or insert a link to the Define.pdf.*

**Table 6 Stepwise Covariate Analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Steps** | **Covariates** | **Base OFV** | **New OFV** | **ΔOFV** |
| 1 | Body weight on CL/F | -6187 | -6262 | -75 |

CL/F: apparent oral clearance, OFV: Objective Function Value; V/F: apparent central volume of distribution

## Overview of Files

### Files used in Analysis

### Modifications and Excluded Observations

*Insert an overview with all used NIFs and the differences between them, if several NIFs are used during the course of analysis.*

*List all excluded observations and reasons for exclusion.*

## Population PK Model

*Adapt numbering as appropriate.*

### Design Optimization

*This section is optional, as the selection of sampling points may have been empirical}*

### Exploratory Data Analysis Output

*Additional analysis output, not given in the body text.*

### Base Model NONMEM Control

*If not submitted electronically.*

### Base Model NONMEM Output

*If not submitted electronically.*

### Final Model NONMEM Control

*If not submitted electronically.*

### Final Model NONMEM Output

*If not submitted electronically.*

### Final Model Goodness of Fit and Validation

*Additional analysis output, not given in the body text.*

### Additional Analysis

*Additional analysis output or simulations, not given in the body text.*

*Additional subsections (continue numbering), for further (PD, clinical endpoints) models.*