1. EXECUTIVE SUMMARY

Title of Study:

Population Pharmacokinetic Analysis of Intramuscular Administration of IMMUNORHO in the Prevention of RhD Isoimmunisation in Rh(D) Negative Women Pregnant with Rh(D) Positive Foetuses

Study Objective(s):

• To develop a population pharmacokinetic (popPK) model to characterize the pharmacokinetics (PK) of anti-D immunoglobulin in Rh(D) negative women pregnant with a Rh(D) positive foetus following intramuscular (IM) administration at week 28 of gestation.

• To identify significant covariates affecting anti-D immunoglobulin PK, and to quantify the magnitude of the effects of covariates.

• To perform PK simulations to generate subject-specific estimates of anti-D immunoglobulin exposure (maximum serum concentrations [C_{max}], time to reach C_{max} [t_{max}], area under the curve from zero to infinite [$AUC_{0\text{-}inf}$], elimination half-life [$t_{1/2}$], apparent clearance [CL/F], apparent total volume of distribution [V/F]).

Data:

The data for the popPK analysis was obtained from study KB065: "A phase III, open-label, uncontrolled, multicentre study to assess efficacy, PK, and safety of IMMUNORHO in the prevention of RhD isoimmunisation in Rh(D) negative women pregnant with Rh(D) positive foetuses". IMMUNORHO 300 µg (1500 IU) solution for injection for IM use was administered at week 28 (Antenatal prophylaxis) and within 72 hours after delivery. Blood samples were collected to measure serum concentrations of anti-D immunoglobulin between week 28 to week 38 of pregnancy (before delivery). Sixty-three subjects were included in the PK population of study KB065.

PK Methodology:

A graphical analysis of the serum concentration-time data for anti-D immunoglobulin serum concentrations was conducted prior to fitting any models to the data. The popPK models were developed following an iterative model building process using a non-linear mixed effects approach. The first-order conditional estimation with η-ε interaction (FOCE-INT) in the nonlinear mixed effects modelling software (NONMEM®, version 7.3) was employed for all model runs. Covariate analysis including the effect of baseline body weight (BW), baseline body mass index (BMI), and white blood cell (WBC) count was conducted as part of the popPK analysis to explain the variability in anti-D immunoglobulin serum concentrations.

The final popPK model for anti-D immunoglobulin was determined based on a range of statistical

and graphical assessments of each of the models evaluated. Prediction-corrected visual predictive checks (pcVPCs) were created to evaluate if the final model adequately described the median trend and between subject variability (BSV) in time profiles. Once the final popPK model was validated, this was used to simulate individual PK-profiles for each subject evaluable within the popPK analysis dataset and to calculate individual anti-D immunoglobulin PK parameters (C_{max}, t_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$, CL/F, V/F) using non-compartmental analysis (NCA) methods.

Results:

A total of 208 serum concentrations from 62 Rh(D) negative women pregnant with Rh(D) positive foetuses, after receiving a single dose of IMMUNORHO at week 28 of pregnancy, were available for model development. Anti-D immunoglobulin serum concentrations were best described by a one-compartment linear PK model with first-order absorption and first-order elimination. Random effects to describe the BSV in the first-order absorption rate constant (k_a), CL/F and V/F, and a proportional residual error model to describe the residual unexplained variability (RUV) of anti-D immunoglobulin serum concentrations were integrated into the model. CL/F, V/F and k_a were allometric scaled by BMI. Dependence between CL/F and V/F random effects was identified and introduced into the model. The pcVPC of the final popPK model demonstrate that the median, 10^{th} and 90^{th} percentiles of the prediction-corrected observed data are contained within the 95% confidence intervals of the corresponding simulations, confirming the predictive performance of the model.

Based on simulation results and using a noncompartmental approach an arithmetic mean CL/F of 0.48 L/day and an arithmetic mean V/F of 17 L were calculated following a single IM dose administration of 300 µg immunoglobulin at week 28 of gestation in Rh(D) negative women pregnant with Rh(D) positive foetuses. These parameters exhibited moderate variability, ranging from 47% to 58%. The arithmetic mean $t_{1/2}$ was approximately 24 days, with a range of 17 to 35 days. The C_{max} was 18.08 ng/mL (coefficient of variation [CV] 47.37%), occurring at a median t_{max} of 7 days (range: 4 to 14 days). The overall exposure, measured as $AUC_{0\text{-}inf}$, was 755.64 ng*day/mL (CV 40.38%).

Conclusions:

- IMMUNORHO serum-concentration time-course in Rh(D) negative women pregnant with a Rh(D) positive foetus, after single IM administration of IMMUNORHO, was adequately described with a 1-compartment model with first-order absorption and elimination.

- Body mass index influences the key parameters of the structural model: CL/F, V/F and ka, where parameters CL/F and V/F increase non-linearly and k_a decreases non-linearly with BMI.
    - BMI inclusion on CL/F explains ~25% of the BSV in the final model
    - BMI inclusion on V/F explains ~41% of the BSV in the final model
    - BMI inclusion on k_a explains ~11% of the BSV in the final model

- IMMUNORHO (300 µg/2 mL), administered intramuscularly, showed slow absorption with a mean peak concentration of 18.08 ng/mL (CV: 47.4%) and a median t_{max} of 7 days post-dose. Serum concentrations declined monophasically with a mean $t_{1/2}$ of 24.15 days (CV: 14.0%). Mean CL/F was 0.48 L/days (CV: 47.3%) and mean V/F was 17.19 L (CV: 58.0%).