# \*\*Population PK/PD Analysis Plan: Arimab for Moderate to Severe Asthma\*\*

## \*\*Title Page\*\*

* Study Title: A Pooled Population Pharmacokinetic and Exposure-Response Analysis of Arimab (ARB-401) in Healthy Volunteers and Patients with Moderate to Severe Asthma
* Compound: Arimab (ARB-401, anti-IL-4Rα/IL-13 dual-pathway monoclonal antibody)
* Plan Version: Version 2.0 (Final)
* Date: July 10, 2025
* Author: Dr. Alex Riley, PhD - Quantitative Clinical Pharmacology, InnovatePharma Therapeutics

## \*\*1. Introduction and Background\*\*

Arimab (ARB-401) is a novel humanized monoclonal antibody (mAb) that simultaneously targets the IL-4 receptor alpha (IL-4Rα) and IL-13 pathways, providing dual inhibition of key Type 2 inflammatory mediators. Unlike dupilumab, which blocks the shared IL-4Rα subunit, Arimab's dual-target mechanism is designed for enhanced suppression of Type 2 inflammation. Furthermore, its engineered Fc region provides an extended half-life (projected ~28-35 days), creating the potential for less frequent dosing than the current standard of care.

This analysis plan outlines the population pharmacokinetic (PopPK) and pharmacodynamic (PK/PD) modeling for Arimab, supporting the Phase 2 clinical program. This program includes a head-to-head study (BREATHE-ADVANCE) against dupilumab. As noted by the FDA, a PopPK analysis is crucial for explaining inter-individual variability and establishing exposure-response relationships.

Prior knowledge from preclinical and Phase 1 studies suggests Arimab exhibits typical mAb pharmacokinetics, but the potential for target-mediated drug disposition (TMDD) at lower concentrations, due to binding to high-affinity receptors, will be formally evaluated. The results of this analysis are critical for selecting and justifying the Phase 3 dose regimen, supporting potential labeling claims, and providing a quantitative basis for the drug's differentiated profile.

## \*\*2. Analysis Objectives\*\*

### \*\*Primary Objectives\*\*

* To develop a population PK model that robustly describes the concentration-time profile of Arimab in healthy volunteers and patients with moderate-to-severe asthma.
* To estimate typical population PK parameters (e.g., clearance (CL), volume of distribution (V), absorption rate (Ka)) and their inter-individual variability (IIV).
* To identify and quantify the influence of statistically and clinically significant covariates (e.g., body weight, age, disease characteristics) on Arimab PK.

### \*\*Secondary Objectives\*\*

* To develop exposure-response (E-R) models for key efficacy endpoints (FEV1 improvement, asthma control, annualized exacerbation rates).
* To assess the relationship between Arimab exposure and key PD biomarkers (e.g., fractional exhaled nitric oxide [FeNO], blood eosinophil counts, total IgE).
* To compare Arimab and dupilumab exposure-response relationships for both efficacy and safety endpoints to support comparative effectiveness claims.
* To evaluate the impact of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) on Arimab pharmacokinetics and clinical outcomes.
* To perform simulations using the final validated model to optimize the Phase 3 dosing strategy, including evaluation of extended dosing intervals (e.g., Q6W, Q8W).
* To generate individual exposure metrics (post-hoc estimates) for subsequent integrated safety analyses.

## \*\*3. Data Sources\*\*

### \*\*Clinical Study Data\*\*

Data from the following studies will be pooled for a comprehensive analysis:

* Study ARB-101 (Phase 1): A randomized, SAD/MAD study in healthy volunteers (n=96) with intensive PK sampling.
* Study ARB-201 (BREATHE-ADVANCE, Phase 2): A randomized, double-blind, active-controlled trial (n=420) comparing Arimab (150/300/450 mg Q4W) vs. dupilumab (300 mg Q2W) in patients with moderate-to-severe asthma, utilizing a sparse PK sampling design.
* Study ARB-151 (Phase 1 DDI): A drug-drug interaction study (n=48) with inhaled corticosteroids, including intensive PK sampling.

### \*\*Analysis Dataset Specifications\*\*

* Dataset Structure: A single, NONMEM-ready, CDISC-compliant dataset will be created.
* Handling of BLOQ and Missing Data: Concentrations below the LLOQ will be handled using the M3 method (Beal, 2001). Missing covariate data will be imputed using the population median (continuous) or mode (categorical), with sensitivity analyses for key covariates.
* Outliers and Exclusions: Observations with absolute individual weighted residuals (|IWRES|) > 5 in initial runs will be flagged and investigated. Decisions to exclude data will be scientifically justified and documented.

## \*\*4. Software and Computing Environment\*\*

* Primary Modeling Software:
* NONMEM® (Version 7.5.1) with FOCEI, executed via Perl-speaks-NONMEM (PsN, Version 5.4.0).
* Monolix Suite (2023R1) for exploratory analysis and final model validation (using SAEM).
* Post-processing and Visualization:
* R (Version 4.3 or higher) with packages `tidyverse`, `ggplot2`, `xgxr`, `pmxTools`, `mrgsolve`, and `xpose`.
* Shiny applications for interactive model diagnostics and stakeholder presentations.
* Version Control and Environment:
* Git for version control of all code and scripts.
* Analysis performed on a Linux high-performance cluster within a Docker container to ensure reproducibility.

## \*\*5. Analysis Methods\*\*

### \*\*5.1 Exploratory Data Analysis (EDA)\*\*

Standard EDA will be performed, including spaghetti plots, mean concentration-time profiles by dose, and graphical exploration of relationships between concentrations and potential covariates.

### \*\*5.2 Structural Model Development\*\*

* Base Model Selection: Development will begin with one- and two-compartment models with first-order absorption and linear elimination.
* TMDD Evaluation: A model incorporating target-mediated drug disposition (TMDD) via Michaelis-Menten (non-linear) elimination will be formally tested to account for high-affinity binding to IL-4Rα/IL-13, especially at lower concentrations.
* Model Building Strategy: Model selection will be guided by OFV decrease (p < 0.05), parameter precision (RSE%), diagnostic plots, and physiological plausibility.

### \*\*5.3 Inter-Individual Variability (IIV) Model\*\*

IIV will be modeled using an exponential (log-normal) error model on key parameters (CL, Vc, Ka). A block covariance structure between CL and Vc will be evaluated. ETA-shrinkage will be monitored, and EBEs will not be used for E-R analysis if shrinkage on key parameters exceeds 30%.

### \*\*5.4 Covariate Model Development\*\*

* Covariate Selection: Covariates will include demographics (age, sex, race), body size (weight, BMI), disease characteristics (baseline FEV1, FeNO, eosinophils), organ function, and ADA status.
* Modeling Approach: A hybrid approach will be used:

1. A Priori Inclusion: Body weight will be included first using an allometric scaling relationship on clearance and volume parameters.
2. Screening: Machine learning methods (e.g., LASSO, Random Forest) will be used for initial screening of remaining covariates.
3. Stepwise Modeling: A formal stepwise covariate modeling approach (forward addition p < 0.01; backward elimination p < 0.001) will be applied to the screened covariates.

* Clinical Relevance: A covariate effect will be deemed clinically relevant if it results in a >20% change in key steady-state exposure metrics across its range.

### \*\*5.5 Residual Unexplained Variability Model\*\*

Proportional, additive, and combined (proportional + additive) error models will be evaluated to describe residual variability.

## \*\*6. Model Evaluation and Validation\*\*

### \*\*6.1 Goodness-of-Fit (GOF) Criteria\*\*

Standard graphical diagnostics (DV vs PRED/IPRED, CWRES vs PRED/Time, Q-Q plots) will be generated, stratified by study, dose, and key covariates (e.g., ADA status).

### \*\*6.2 Model Qualification Techniques\*\*

* Visual Predictive Checks (VPC): Prediction-corrected VPCs (pc-VPC) will be generated (n=1000 simulations), stratified by dose and study.
* Normalized Prediction Distribution Errors (NPDE): NPDEs will be calculated to formally assess the predictive performance of the model.
* Bootstrap Analysis: A non-parametric bootstrap (n=1000 replicates) will be performed to assess parameter uncertainty and model stability.
* Cross-Validation: K-fold cross-validation may be used to assess the predictive accuracy of the final model.

## \*\*7. Simulation Plan\*\*

The final validated PopPK model will be used to conduct simulations (n=1000 virtual subjects per scenario) to:

* Support Phase 3 Dose Selection: Predict exposure distributions for proposed Phase 3 regimens.
* Evaluate Alternative Regimens: Assess the viability of extended dosing intervals (e.g., 300 mg Q4W, 450 mg Q6W, 600 mg Q8W) by comparing their simulated trough concentrations to an established efficacy threshold.
* Compare with Active Comparator: Simulate steady-state exposure distributions for Arimab regimens and compare them directly to the dupilumab 300 mg Q2W regimen.
* Assess Special Populations: Predict exposures in populations with specific covariate values (e.g., high body weight, adolescents).

## \*\*8. Reporting and Deliverables\*\*

* Final Report: A comprehensive population PK/PD analysis report detailing the methods, results, and clinical implications, including documentation of any deviations from this plan.
* Model Code and Datasets: Fully commented NONMEM control streams, R scripts, and the final analysis datasets.
* Model Development Log: A detailed log summarizing model building steps, decisions, and associated changes in OFV and diagnostics.
* Regulatory Submission Package: All necessary files (model code, datasets, report, definitions) formatted for regulatory submission (e.g., eCTD Module 2.7.2).
* Presentation Materials: An executive summary presentation for internal and regulatory meetings.

## \*\*9. References\*\*

1. FDA. Guidance for Industry: Population Pharmacokinetics. 2022.
2. EMA. Guideline on Reporting the Results of Population Pharmacokinetic Analyses. 2007.
3. ICH. M15 General Principles on Pharmacokinetics/Pharmacodynamics (PK/PD). (Step 2 version, 2023).
4. Beal, S.L. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn, 28, 481–504 (2001).
5. Wenzel S, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma. N Engl J Med. 2016;375(25):2435-2446.