

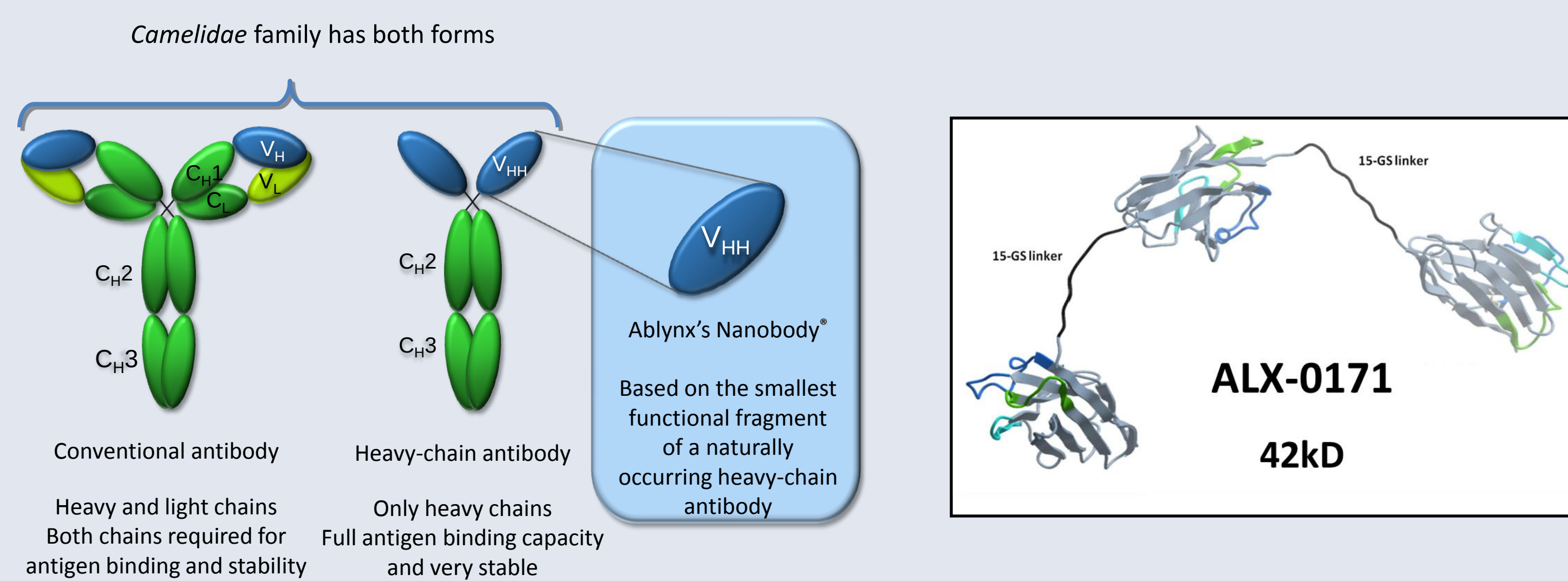
Ingrid Ottevaere, Massimiliano Germani, Eline Vanheule, Laura Sargentini
Ablynx nv, Technologiepark 21, B-9052 Zwijnaarde, Belgium

INTRODUCTION

ALX-0171 is a **Nanobody®** (therapeutic protein based on the smallest functional fragments of naturally occurring heavy-chain antibodies, see fig below) targeting the F-protein of the Respiratory Syncytial Virus (RSV). ALX-0171 is being developed for treatment of RSV infection.

RSV infection is a recurrent cause of human lower respiratory tract infections during the winter months and can lead to severe respiratory infections such as pneumonia and bronchiolitis, especially in very young children.

ALX-0171 has a specific high affinity for RSV and inhibits RSV fusion to the target cells. It is composed of 3 heavy chain variable region (VHH) domains and due to this trivalent interaction has an avid binding to RSV. Due to absence of Fc fragment, ALX-0171 does not induce antibody-dependent or cell-dependent cytotoxicity.

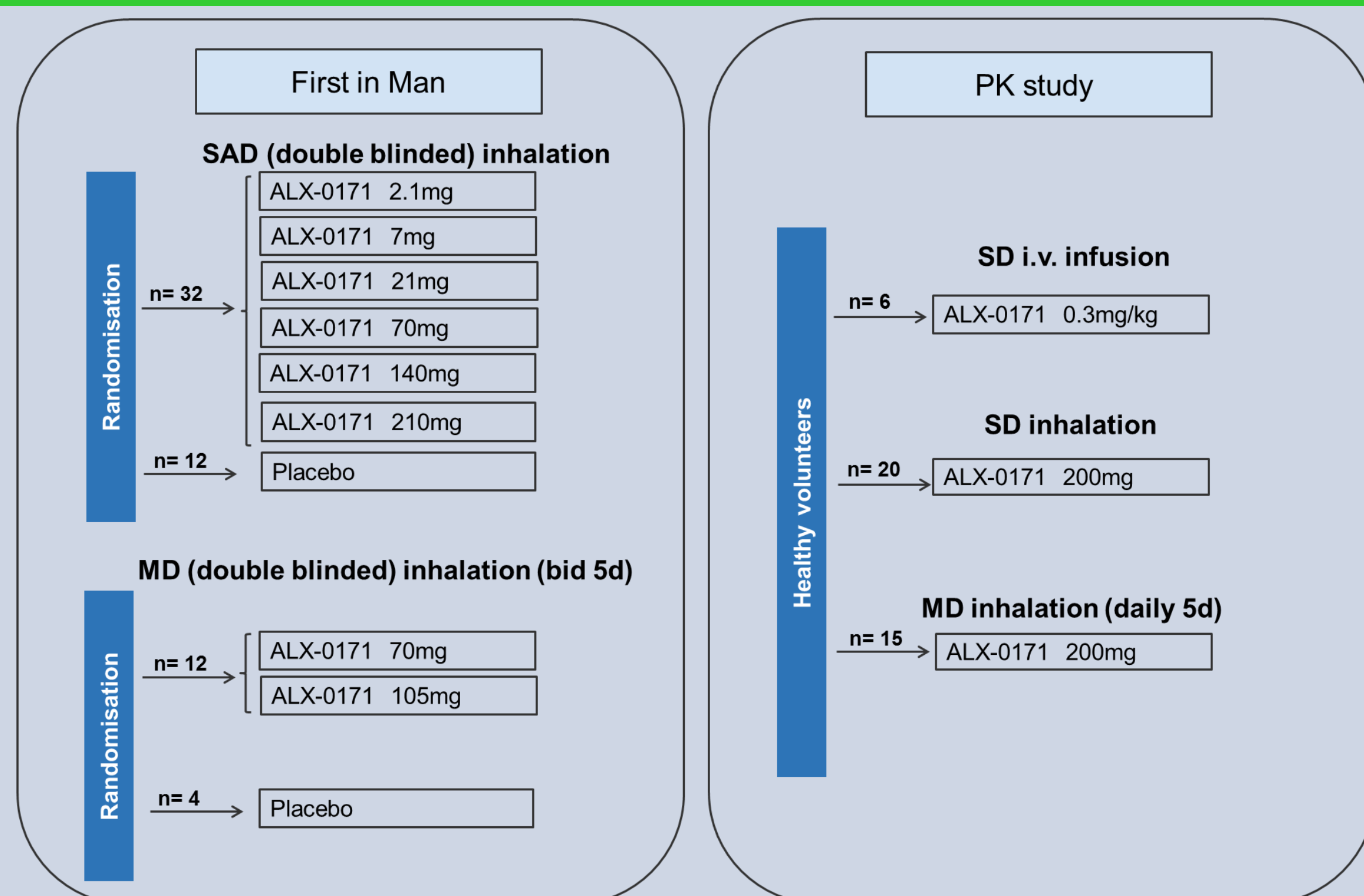


OBJECTIVES AND METHODS

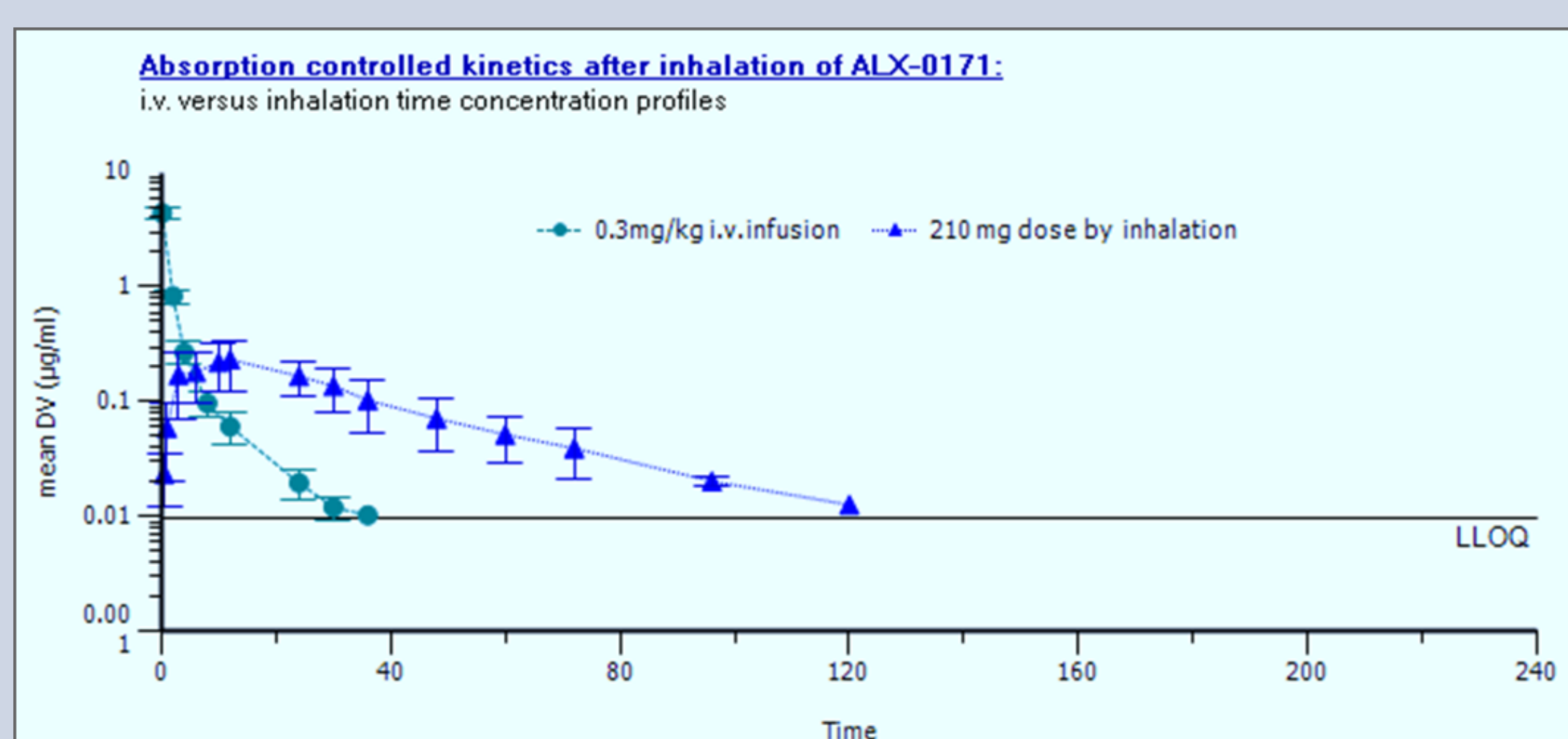
Objectives: The anti-RSV Nanobody ALX-0171 is developed as a **nebulizer solution** to enable direct treatment at the site of **RSV infection**. The aim of the study was to characterize the pharmacokinetics (PK) of ALX-0171 in a healthy adult population after oral inhalation or intravenous (i.v.) administration.

Methods: Population PK analyses were performed on data from 2 clinical studies (85 healthy volunteers) via nonlinear mixed-effects modeling with the NONMEM software, Version VII. Plasma concentration data obtained after i.v. and inhalation were modeled simultaneously. Covariate analysis was performed by stepwise regression modelling with a forward univariate additive step (p-value < 0.05) and a backward elimination step (p-value < 0.01).

CLINICAL STUDIES

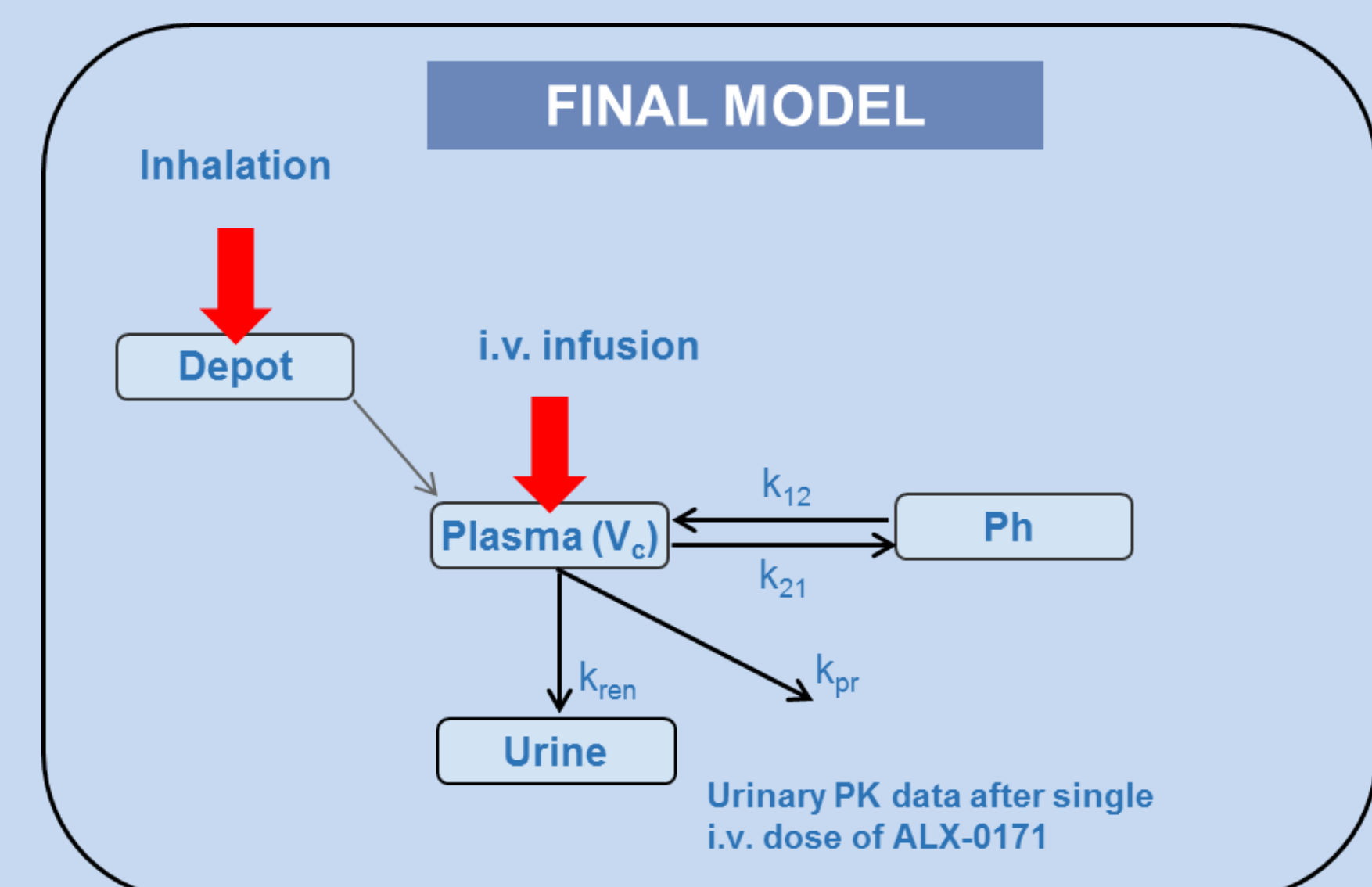


Demographic characteristics	Race	Age (min-max)	Weight (min-max)	Height (min-max)	BSA (min-max)	BMI (min-max)	CRCL (min-max)
First in Man	Caucasian:44 Other: 0	24 y (18-54)	81.5 kg (70.0-107)	185 cm (173-198)	2.06 m ² (1.85-2.34)	25.0 kg/m ² (20.6-29.7)	154 mL/min (109-217)
PK study	Caucasian:39 Other:2	37 y (18-55)	84.0 kg (61.6-96.0)	180 cm (170-188)	2.01 m ² (1.80-2.21)	26.4 kg/m ² (18.2-30.0)	129 mL/min (88.4-185)
Overall	Caucasian:83 Other: 2	31 y (18-55)	83 kg (61.6-107)	182 cm (170-198)	2.11 m ² (1.80-2.34)	25.5 kg/m ² (18.2-30.0)	141 mL/min (88.4-217)



STEPWISE MODELING APPROACH

- Analysis of i.v. plasma data to define model structure.
- Addition of urine data to estimate renal clearance.
- Inter-compartmental rate constants were fixed to the i.v. estimates to enable fitting of the combined i.v. and inhalation data via a bicompartamental model. Similar clearance was assumed after i.v. and inhalation.
- No improvement of goodness of fit of inhalation data by additional transit compartments [1] or different absorption rate constant [2] models.



- Demographic covariates were tested on central V_c, K_a and F₁

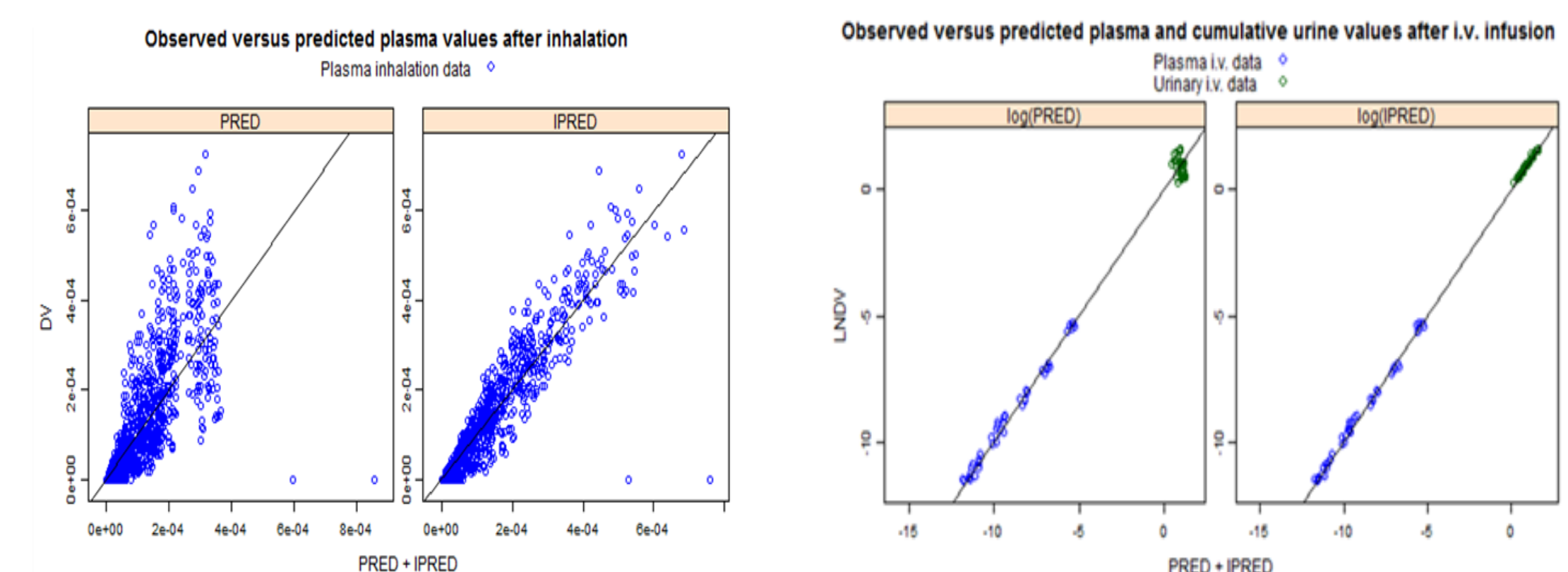
RESULTS

- Final model estimates of population fixed and random effect parameters

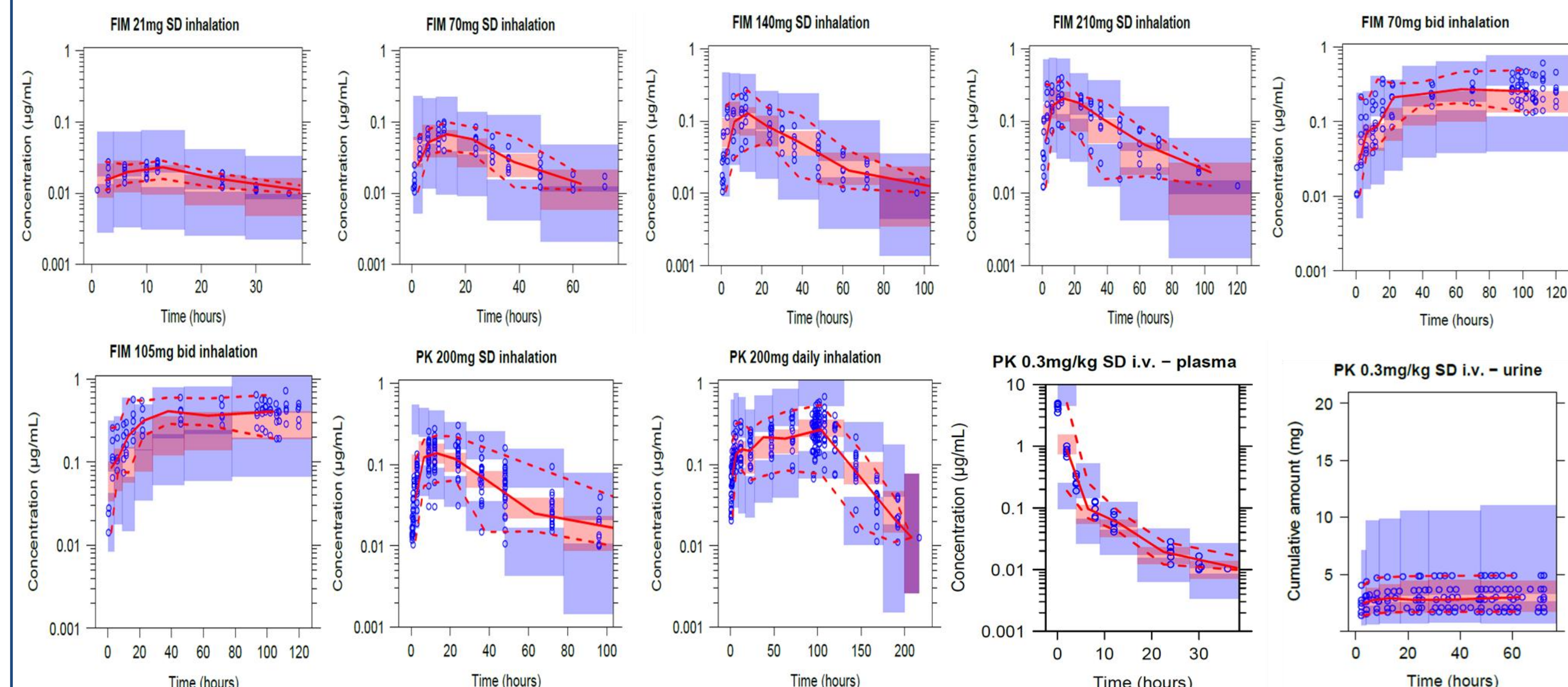
Residual variability	Estimate (RSE %)
RE plasma (σ exp)	0.109 (3%)
RE Urine (σ prop)	0.002 (10%)

Parameter	Estimate (RSE %)	Exponential IIV (RSE%)
Vc (L)	5.44 (8%)	0.015 (39%)
Kren (/h)	0.08 (19%)	0.603 (17%)
K12 (/h)	0.14 FIX	
K21 (/h)	0.11FIX	
Ka (/h)	0.03 (4%)	0.0686 (18%)
F1 (%)	12.3 (10%)	0.183 (10%)
Age effect on Ka	-0.322 (41%)	

- Goodness of fit plots



- Visual predictive check



Red lines: observed median (solid line) with 5th and 95th percentiles of observations (striped line)
Areas: model predicted confidence interval (95%) for the median (red) and for the 5th and 95th percentile (blue)

CONCLUSIONS

- The PK of ALX-0171 in healthy volunteers was consistent with a **bicompartamental** model with **first-order absorption** and **linear clearance** from the central compartment, with limited **inter-individual variability**.
- Covariate analysis showed that **age** had a significant effect on the **absorption** rate constant.
- The PK of the inhaled Nanobody ALX-0171 is consistent with prolonged lung exposure and is in line with the expected PK properties, warranting further **clinical development** of inhaled ALX-0171 for treatment of RSV infection in infants.