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# Population pharmacokinetics of brodalumab in patients with moderate to severe plaque psoriasis

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At the time the clinical trials were conducted, Brodalumab was being codeveloped by Amgen and AstraZeneca

**Abstract**

Brodalumab is a fully human monoclonal antibody targeting the IL-17 receptor A leading to an inhibition of the biological effect of IL-17A, IL-17F, IL-17A/F heterodimer, IL-17C and IL-17E isoforms. It has shown to be efficacious in the treatment of moderate to severe plaque psoriasis (210 mg administered subcutaneously at weeks 0, 1 and 2 followed by 210 mg every 2 weeks [Q2W+1]). A population pharmacokinetic model based on psoriasis patients only from six clinical trials was developed to describe the pharmacokinetics and identify sources of variability. In patients with psoriasis, Brodalumab exhibits non-linear pharmacokinetics due to target-mediated drug disposition resulting in concentration-dependent clearance. The pharmacokinetics was best described by a two-compartment model with linear absorption and combined linear and Michaelis-Menten elimination. The subcutaneous bioavailability of Brodalumab was 55%, absorption rate was 0.30 $day^{-1}$, and body-weight was found to affect the volume of distribution and clearance. For a reference patient with plaque psoriasis (body-weight of 90 kg), the estimates were 0.16 L/d for linear serum clearance, 6.1 mg/d for the maximum non-linear clearance rate, and 4.7 and 2.4 L for central and peripheral volume of distribution, respectively. For the approved dosing regimen, time to maximum concentration was 4 days and 90% of steady-state was achieved after 10 weeks for a reference patient. Following last dose at steady-state, 90% of the population of reference patients will reach serum concentrations below lower limit of quantification after 45 days.

**KEYWORDS**

Brodalumab, IL-17RA, population pharmacokinetics, psoriasis, target-mediated drug disposition

## 1 | INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory disorder that is estimated to affect 1%-3% of the population worldwide although the prevalence is lower in Asia. Plaque psoriasis is the most common form and is clinically characterized by well-defined, raised, red and scaly plaques. In addition, a significant psychological burden, social stigmatization and increased risk of comorbidities may also be associated with the disease resulting in huge impact on patient well-being.[1,2] Treatment options for moderate to severe plaque psoriasis patients have expanded in recent

*Kyntheum® is sold in Europe by LEO Pharma, as Siliq® in the United States by Bausch Health and as LUMICEF® in Japan by Kyowa Hakko Kirin.

years and now include systemic immune modulators for effective control. Recently, a new generation of monoclonal antibodies (mABs) (Taltz® and Cosentyx®) that targets and neutralizes the effect of interleukin-17A (IL-17A) has become available on the market demonstrating good effect on primary clinical endpoints.[3,4]

Brodalumab is a fully human monoclonal immunoglobulin G2 (IgG2) which binds with high affinity (Kd = 239 pM) to the human IL-17 receptor A (IL-17RA) and hence blocks the biological effect of not only IL-17A but also IL-17C, IL-17F, IL-17A/F heterodimer and IL-17E (IL-25). The first clinical trial of Brodalumab indicated that single doses up to 700 mg IV had an acceptable safety profile and provided evidence that factors signalling through IL-17RA, including IL-17A, IL-17C and IL-17F, are proximal and central drivers of psoriasis pathology. Indeed, IL-17A, IL-17C and IL-17F are present at high levels in psoriatic skin, and IL-17RA is highly expressed on the cell surface of keratinocytes and in psoriasis lesions.[5-8]

During the clinical development of Brodalumab, efficacy and safety have been assessed in more than 4200 adult plaque psoriasis patients across 3 (AMAGINE-1 [NCT01708590], AMAGINE-2 [NCT01708603] and AMAGINE-3 [NCT01708629]) phase III clinical trials as part of the approval process.[9,10] Brodalumab is indicated for moderate to severe plaque psoriasis in adult patients who are candidates for systemic treatment and launched in Europe under the trade name Kyntheum®, in the USA and Canada as Siliq® and in Japan as LUMICEF®. The recommended dose of Kyntheum® is 210 mg administered by subcutaneous (SC) injections at weeks 0, 1, 2 followed by 210 mg every 2 weeks (Q2W+1).

The pharmacokinetic fate of Brodalumab has previously been described in healthy individuals as well as in patients with moderate to severe plaque psoriasis following single and multiple doses.[11,12] It is clear from these initial phase I and II trials that Brodalumab displays non-linear kinetics and other hallmark features of a monoclonal IgG2 antibody interacting with a cell surface receptor such as half-life in the duration of days and low systemic clearance.[13,14] Serum concentrations of Brodalumab could be described by a two-compartment model with parallel linear and non-linear elimination, and it was also established that body-weight has a significant impact on the distribution and clearance of Brodalumab, which will influence steady-state systemic exposure ($AUC_{ss}$ and $C_{max}$) and that the systemic clearance of Brodalumab is lower in healthy compared to patients with plaque psoriasis.[11,12] Since these publications, the phase III program has been completed. With the availability of pharmacokinetic data from the phase III trials, it has become possible to investigate the pharmacokinetics in the target population only and to re-evaluate the impact of previously identified covariates on a larger data set.

The objectives of this analysis were to investigate and describe the population pharmacokinetics of Brodalumab in plaque psoriasis patients only and to identify sources of variability.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients and trial designs

This analysis exclusively contained data from plaque psoriasis patients. Data from six clinical trials (2 phase I, 1 phase II and 3 phase III) were included (Table 1). Except for the open-label extension part of the phase II trial (NCT01101100) and a phase I drug-drug interaction (DDI) trial (NCT01937260), trial design details have been presented elsewhere.[9-12] For the DDI trial, briefly, the trial objective was to characterize the effect of Brodalumab on the pharmacokinetics of midazolam. Twenty-one psoriasis patients received a single oral dose of midazolam on day 1 and again on day 9. On day 2, a single SC dose of 210 mg Brodalumab was administered. In addition, 10 patients received 140 mg Brodalumab as a single SC dose. The pharmacokinetic profile of midazolam on day 1 and day 9 was compared, and any difference was deemed related to the Brodalumab exposure. The Brodalumab pharmacokinetics was not expected to change as a result of midazolam dosing which justifies the inclusion of both the 210 mg and the 140 mg dose in the population pharmacokinetic analysis. In the open-label extension part of the phase II trial, patients completing the week 16 visit in the phase II trial received either 140 or 210 mg Q2W Brodalumab (140 mg for patients with body-weight ≤100 kg and 210 mg for patients with a body-weight >100 kg or inadequate response following 140 mg treatment) for up to 264 weeks. All clinical trials were conducted in accordance with the BCPT policy for experimental and clinical trials.[15] In all clinical trials, unbound Brodalumab serum concentrations were measured by a validated enzyme-linked immunosorbent assay method with a range of quantification of 50-2000 ng/mL. During all clinical trials, serum samples were tested for binding anti-drug antibodies (ADAs) using an electrochemiluminescent bridging immunoassay. If positive, serum samples were then tested for neutralizing ADAs using a validated cell-based assay.

Psoriasis Area and Severity Index (PASI) is one way to assess and describe disease severity of psoriasis. PASI is a composite score of four categories (redness, thickness, scaling and involved skin area) and ranges from 0 to 72. In order to be eligible for the phase III trials, a baseline PASI score of minimum 12 was required.

### 2.2 | Dataset for population pharmacokinetic analysis

A full data set was compiled from the six clinical trials and included patients with at least one quantifiable Brodalumab serum concentration. For population pharmacokinetic model development, a population pharmacokinetic analysis set (PK data set) was defined as those patients from the full data set who had rich blood sampling (at least one quantifiable non-trough serum concentration). This data set consisted of

622 psoriasis patients and included intravenous or subcutaneous administration following single or multiple doses of 70-700 mg from 1 up to 2015 days (Table 1). PASI score at baseline and relevant demographic characteristics of the full data set and the PK data set are listed in Table 2.

## 2.3 | Population pharmacokinetic model development

As described above, the population pharmacokinetics of Brodalumab has previously been investigated, and the present analysis is based on the assumption that the pharmacokinetics is well characterized by a two-compartment model with first-order absorption (subcutaneous administration) and combined linear and Michaelis-Menten elimination. The initial structural model was parameterized by central and intercompartmental clearances (CL and Q), central and peripheral volumes of distribution (V1 and V2), maximum rate of elimination ($V_{max}$), Michaelis-Menten constant (Km) and rate of absorption (Ka) for subcutaneous administration. Bioavailability of the subcutaneous administration (F) was implemented using the logit function to restrict the final parameter value to the interval [0,1]. Due to a relatively short duration of infusion of the intravenous doses, this route of administration was modelled as a bolus dose. The initial structural model also included a random effect

**TABLE 1** Clinical trials included in population pharmacokinetic analysis

| Trial | No of randomized patients receiving at least one dose of Brodalumab | Treatment | PK sampling (non-trough time-points) | No of patients included in the PK analysis set |
|---|---|---|---|---|
| Phase I<br>First-in-Man<br>NCT00867100 | 20 PSO subjects<br>(20 with at least one quantifiable PK sample) | Single IV or SC dose<br>SC: 140 or 350 mg<br>IV: 700 mg | 0.5, 2, 4, 8 h post-dose and 2, 7, 14, 28, 42, 63 and 85 d | Total 20<br>4 on 140 mg SC<br>8 on 350 mg SC<br>8 on 700 mg IV |
| Phase I<br>Drug-drug interaction trial<br>NCT01937260 | 31 PSO patients<br>(29 with at least one quantifiable PK sample) | Single SC dose<br>Midazolam on day 1 and 9.<br>Brodalumab, 210 mg day 2<br>140 mg SC Brodalumab | For Brodalumab:<br>4 h post-Brodalumab dose and 2, 3, 4, 5, 8, 12, 15, 18, 22, 25 and 29 d post-Brodalumab dose | Total 28<br>9 on 140 mg<br>19 on 210 mg |
| Phase IIb<br>NCT00975637 with long-term extension trial<br>NCT01101100 | 158 PSO patients<br>(157 with at least one quantifiable PK sample) | Multiple SC dose<br>70, 140, 210 mg on day 1 and on weeks 1, 2, 4, 6, 8 and 10 followed by 140 or 210 mg Q2W or<br>280 mg on day 1 and wk 4 and 8 | Week 1 +3 d<br>Week 8 +3, +7 d | Total 33<br>9 on 70 mg<br>10 on 140 mg<br>7 on 210 mg<br>7 on 280 mg |
| Phase III<br>AMAGINE-1<br>NCT01708590 | 648 PSO patients<br>(637 with at least one quantifiable PK sample) | Multiple SC dose<br>140 and/or 210 mg Q2W+1 | Week 2 +3 d<br>Week 10 +3, +7, +10 d<br>Week 16 +3, +7, +10 d | Total 102<br>Week 10: 67<br>Week 16: 85 |
| Phase III<br>AMAGINE-2<br>NCT01708603 | 1790 PSO patients<br>(1739 with at least one quantifiable PK sample) | Multiple SC dose<br>140 and/or 210 mg Q2W+1/Q4W/Q8W | Week 2 +3 d<br>Week 10 +3, +7, +10 d<br>Week 20 +3, +7, +10 d | Total 254<br>Week 10: 205<br>Week 20: 238 |
| Phase III<br>AMAGINE-3<br>NCT01708629 | 1835 PSO patients<br>(1723 with at least one quantifiable PK sample) | Multiple SC dose<br>140 and/or 210 mg Q2W+1/Q4W/Q8W | Week 2 +3 d<br>Week 10 +3, +7, +10 d<br>Week 20 +3, +7, +10 d | Total 185<br>Week 10: 154<br>Week 20: 178 |
| Total no of individuals | 4487 patients<br>(4305 patients with at least one quantifiable PK sample) | | | 622 patients |

IV, intravenous dosing; PSO, psoriasis patients; Q2W, dosing every 2 wk; Q2W+1, dosing at weeks 0, 1, 2 followed by dosing every 2 wk; Q4W, every 4th week; Q8W, every 8th week; SC, subcutaneous dosing.

**TABLE 2** Relevant demographic characteristics of the patients included in the analysis

| | PK data set (622 individuals) | | Full data set (4305 individuals with at least one quantifiable PK sample) | |
|---|---|---|---|---|
| | **Median** | **Range** | **Median** | **Range** |
| Age (yr) | 46 | 18-75 | 45 | 18-76 |
| Weight (kg) | 87.8 | 43-186 | 87.2 | 39.3-236 |
| BMI (kg/m$^2$) | 29.6 | 16.7-66.1 | 29.1 | 15.5-78.4 |
| PASI at baseline | 17.7 | 8.8-60.6 | 17.3 | 8.8-72 |
| | **Number of patients** | **Percentage** | **Number of patients** | **Percentage** |
| Males | 417 | 67 | 2989 | 69 |
| Caucasians | 576 | 93 | 3899 | 91 |

model (as multiplicative exponential terms) and a combined additive/multiplicative residual error model to account for the between-subject variability in the fixed effect parameters and the remaining unexplained variability, respectively. An off-diagonal term was included in the covariance matrix to account for the correlation between CL and V1.

The mixed effect analysis was performed using Phoenix NLME 8.0, Certara USA, Inc., 100 Overlook Center, Suite 101, Princeton, NJ 08540 USA. The Quasi-Random Parametric Expectation Maximization (QRPEM) method was used for parameter estimation. Model simulations were performed within Phoenix NLME, and graphical presentation of results was done using Phoenix and R (version 3.4.2)/RStudio (version 1.1.383, 250 Northern Ave, Boston, MA 02210, USA).

The Michaelis-Menten constant was in previous analysis[12] fixed to a value below the lower limit of quantification (LLOQ) based on a sensitivity analysis. In the present analysis, pharmacokinetic data from the phase III trials have been added. The addition of the phase III data would not provide new information regarding the estimation of Km since the bioanalytical method and LLOQ was the same across all clinical trials. Thus, Km was fixed to the value used in the previous analysis (Km = 0.02 μg/mL). Even though the addition of phase III data would not provide new information to support the estimation of the bioavailability of the subcutaneous administration, the parameter was estimated in the initial model run using the logit function and then fixed before moving to the covariate analysis. Concentration values below LLOQ were included in the analysis and treated as censored data in the parameter estimation (the M3 method[16]).

The model development consisted of the following steps:

*Development of structural model*. The initial structural model was run on the PK data set to identify an appropriate error model and provide parameter estimate of *F*. In the final structural model used for covariate analysis, *F* was fixed to enhance stability.

*Covariate model.* The relationships between model parameter estimates from the final structural model and covariates were exploratorily analysed to support the identification of covariates to include and test in the model. The covariates considered for investigation included body-weight, sex, age and PASI baseline score. The impact of binding ADAs was not tested due to the low number of patients tested positive for ADAs and the transient nature of the positive ADA samples.[10] Race was not tested since 93% of the patients were Caucasian. Continuous covariates were included using a normalized power function (normalized by a value close to the median of the covariate), and categorical covariates were included as a fraction of the typical value. To maintain a covariate in the model, a drop in objective function value (OFV) larger than 6.63 points ($P < 0.01$) should be obtained.

*Model evaluation*. Decision criteria during model development included judgement of model robustness and plausibility, inspection of goodness-of-fit plots and evaluation of precision of parameter estimates. The predictability of the final model was assessed through a visual predictive check (VPC) plot using the PK data set.[17] To construct the VPC, patients receiving only 210 mg dosages were extracted from the PK data set. 1000 replicates of the extracted data set were produced, and 95% confidence intervals (CIs) for the 5th, 50th and 95th percentiles of the simulated serum concentrations were calculated and plotted together with the 5th, 50th and 95th percentiles of the observed serum concentrations. Observed and simulated concentration values below LLOQ were set to LLOQ.

*Model-based simulations*. Brodalumab population pharmacokinetic characteristics such as area under the concentration-time curve ($AUC_{ss}$) in a dosing interval at steady-state, time to steady-state, time to complete washout following last dose at steady-state and accumulation ratio for a Q2W dosing schedule were derived using model-based simulations with the final model.

## 3 | RESULTS

The population pharmacokinetic model was developed based on the PK data set which included 7725 quantifiable Brodalumab serum concentrations and 2508 concentrations below LLOQ from 622 patients with moderate to severe plaque psoriasis. The PK data set constitutes 14.4% of the population in the full data set, and the PK data set provides a demographically good representation of the total data set (Table 2). A typical person included in the full data set was a male Caucasian, 45 years of age, weighing 87 kg and with a PASI score at baseline of 17.3.

During model development, diagnostic and VPC plots from the structural model were used to evaluate the ability of the model to describe and predict the data. No trends were observed in individual and population predictions vs observed data or the weighted residual vs time and VPCs were supportive of the model (data not shown). In contrast to earlier analyses,[11,12] random effects were included on intercompartmental clearance (Q). A model without random effects on $Q$ was tested but rejected since it resulted in worsening of the model fit upon graphical inspection of the individual model fits and diagnostic plots (data not shown).

The graphical inspection of the inter-individual variability (IIV) values vs the covariates to be investigated showed a large correlation between body-weight and CL, V1 and $V_{max}$. Body-weight was included as a covariate on all three parameters simultaneously, and a statistically significant drop in OFV was observed ($P < 0.001$) together with a decrease in IIV associated with each of the three parameters. Subsequently, body-weight was also included on V2 and $Q$ in parallel. This resulted in a change in the estimate of the power associated with body-weight on CL (from 0.767 to 0.12), and the power estimate for V2 was above 4. Additionally, no model improvement was observed so body-weight was only kept on CL, $V_{max}$ and V1.

Baseline PASI score appeared to have a minor impact on $V_{max}$ and CL from graphical inspection. However, including the covariate resulted in an increase of OFV and was thus not kept in the final model. Likewise, the inclusion of age on CL and $V_{max}$ did not improve the model fit. Sex did not show to have an impact on any parameter from graphical inspection. When including sex on V1, CL and $V_{max}$, the power associated with body-weight on CL dropped to 0.35, probably due to the correlation between sex and body-weight. For this reason, sex was not included in the model. The final model parameters are listed in Table 3. Eta-shrinkage above 20%-30% was observed for all parameters (V1, 40%; CL, 32%; V2, 38%; $Q$, 63%), except for $V_{max}$ (20%), indicating that diagnostic plots based on individual parameter estimates should be treated with caution.[18] Epsilon-shrinkage was low (8%) indicating that the goodness-of-fit plots based on the individual predictions could be used to evaluate model performance. Goodness-of-fit plots are shown in Figure 1.

**TABLE 3** Population parameter estimates of the final pharmacokinetic model

| Parameter | Value (RSE%) | IIV %CV |
|---|---|---|
| Ka ($d^{-1}$) | 0.300 (2.8) | 62.6 |
| V1 (L) | 4.68 (0.99) | 25.5 |
| CL (L/d) | 0.155 (0.20) | 57.5 |
| $V_{max}$ (mg/d) | 6.07 (0.53) | 24.7 |
| Km (μg/mL) | 0.02 (fixed) | NA |
| Q (L/d) | 0.328 (5.34) | 91 |
| V2 (L) | 2.41 (3.08) | 189 |
| F (%) | 54.8 (fixed) | NA |
| Power of weight on V1 | 0.938 (1.1) | NA |
| Power of weight on CL | 0.767 (1.02) | NA |
| Power of weight on $V_{max}$ | 0.769 (0.91) | NA |
| Correlation between CL and V1 | 0.75 | NA |
| Proportional residual error (CV%) | 35.5 (1.08) | NA |
| Additive residual error (μg/mL) | 3.00 (0.54) | NA |

CL, V1 and $V_{max}$ are given for patients with a body-weight of 90 kg. Proportional and additive errors are given as %CV and standard deviation.
CL, clearance; CV, coefficient of variation; F, bioavailability; IIV, inter-individual variability; Ka, first-order absorption rate constant; Km, Michaelis-Menten constant; NA, not applicable; Q, intercompartmental clearance; RSE, relative standard error; V1, central volume of distribution; V2, peripheral volume of distribution; $V_{max}$, maximum non-linear elimination rate.

To evaluate the predictive capability of the final model, a VPC plot was made for patients in the phase III trials who only received 210 mg Brodalumab. Patients on placebo for the first 12 weeks and then randomized to 210 mg Brodalumab were included in the VPC plot. Figure 2 shows VPC plots from first dose to 1000 days after first dose with a zoom in on the first 24 weeks of treatment where non-trough data are available.

The VPC plot provides a good description of the data and shows that the model is capable of capturing the large variability seen in the serum concentration data. A tendency to overpredict data is seen, however, as the 95th percentile of the data lies close to the lower limit of the 95% CI of the 95th percentile of the simulations.

### 3.1 | Simulation with the final model

In the covariate analysis, body-weight was found to have a significant impact on clearance (CL and $V_{max}$) and on the central volume of distribution. To illustrate the relationship between body-weight and systemic exposure

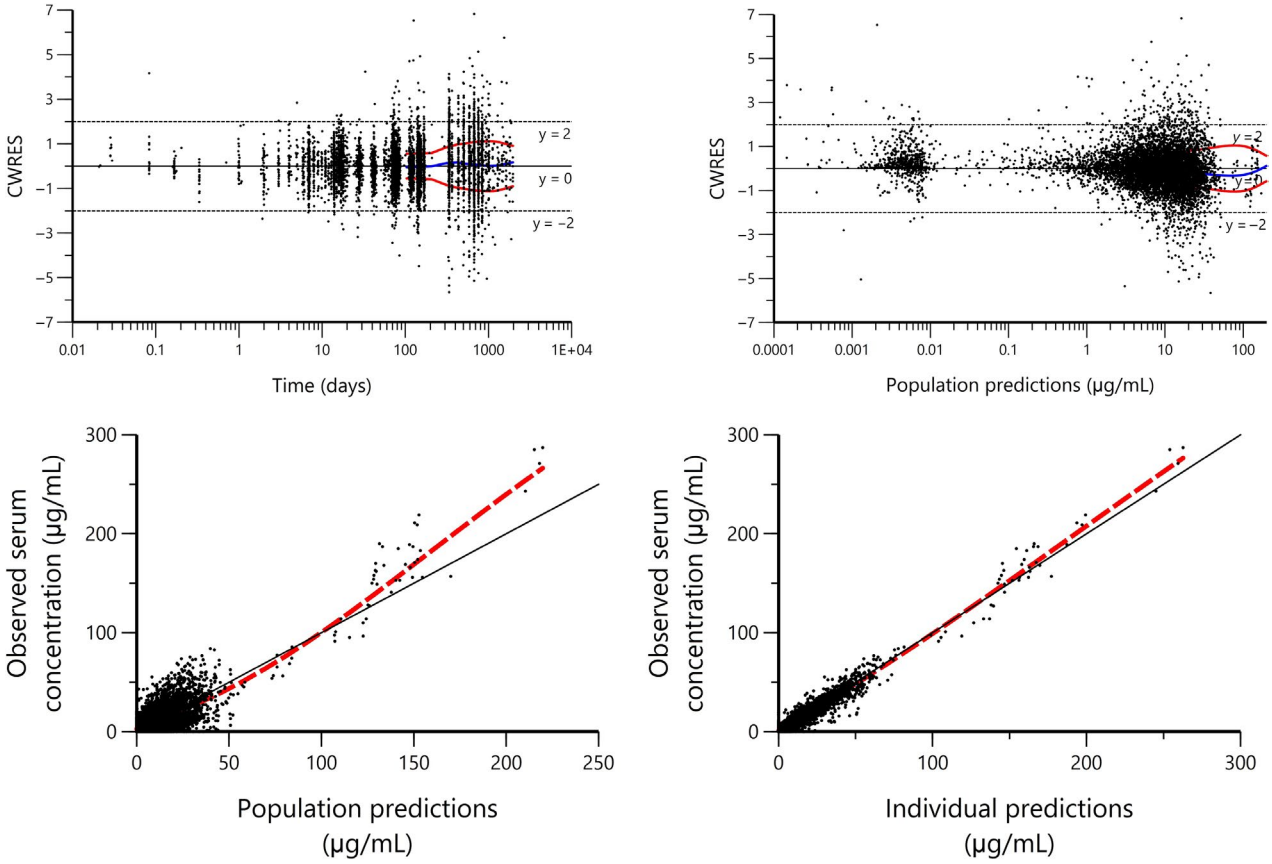


**FIGURE 1** Goodness-of-fit plots for the final model. For conditional weighted residuals (CWRES) vs time and vs population predictions plots, the black solid line is the line of unity and the dashed lines are $y = 2$. Since values of CWRES should be approximately normally distributed with mean zero and variance 1, the CWRES values should be concentrated within the interval [−2,2]. The blue solid line is a trendline, and the red lines are the loess for the absolute values mirrored around $y = 0$. For the observed concentrations vs the individual and vs population predictions plots, the black solid line is the line of unity and the red dashed line is a trendline

at steady-state, simulations to steady-state with the final model for body-weights of 60, 80, 90, 100 and 120 kg were performed. The simulation results showed that 60-kg and 120-kg patients with plague psoriasis are predicted to have a more than twofold increase and a more than 50% reduction in systemic exposure at steady-state when dosing 210 mg every second week compared to patients weighing 90 kg (Figure 3).

Concentration-time profiles following first dose (0-7 days) and at steady-state when dosing 210 mg Q2W+1 were simulated for 1000 patients with a body-weight of 90 kg, and pharmacokinetic parameters have been calculated (Table 4). Furthermore, additional simulations show that for a reference patient (body-weight of 90 kg), the average time to 90% of steady-state following 210 mg Q2W+1 is 10 weeks (Figure 4).

The mean $C_{max}$ at steady-state was estimated to 20 µg/mL and the $AUC_{ss}$ to 225 µg day/mL. Based on the mean AUC in the interval 0-14 days after a single dose of 210 mg, the accumulation ratio ($AUC_{ss}/AUC_{0\text{-}14\ days}$) was determined to 2.7. It takes 45 days for 90% of patients to achieve serum levels below LLOQ (0.05 µg/mL) after termination of treatment at steady-state.

## 4 | DISCUSSION AND CONCLUSION

Brodalumab is a highly efficacious drug in the treatment of plaque psoriasis with 42%, 44% and 37%, respectively, achieving complete skin clearance in the phase III trials after 12 weeks of dosing.[9,10] For drugs with non-linear pharmacokinetics, like Brodalumab which exhibits target-mediated drug disposition (TMDD), it may be difficult to determine the concentration-effect relationship and optimizing the dosage regimen.[19] Thus, it is important to accurately describe the population pharmacokinetics of such drugs. In the present publication, a population pharmacokinetic model based on all available pharmacokinetic data from psoriasis patients was developed and sources of variability were investigated.

In contrast to previous publications,[11,12,20] the present analysis only included patient data. The population

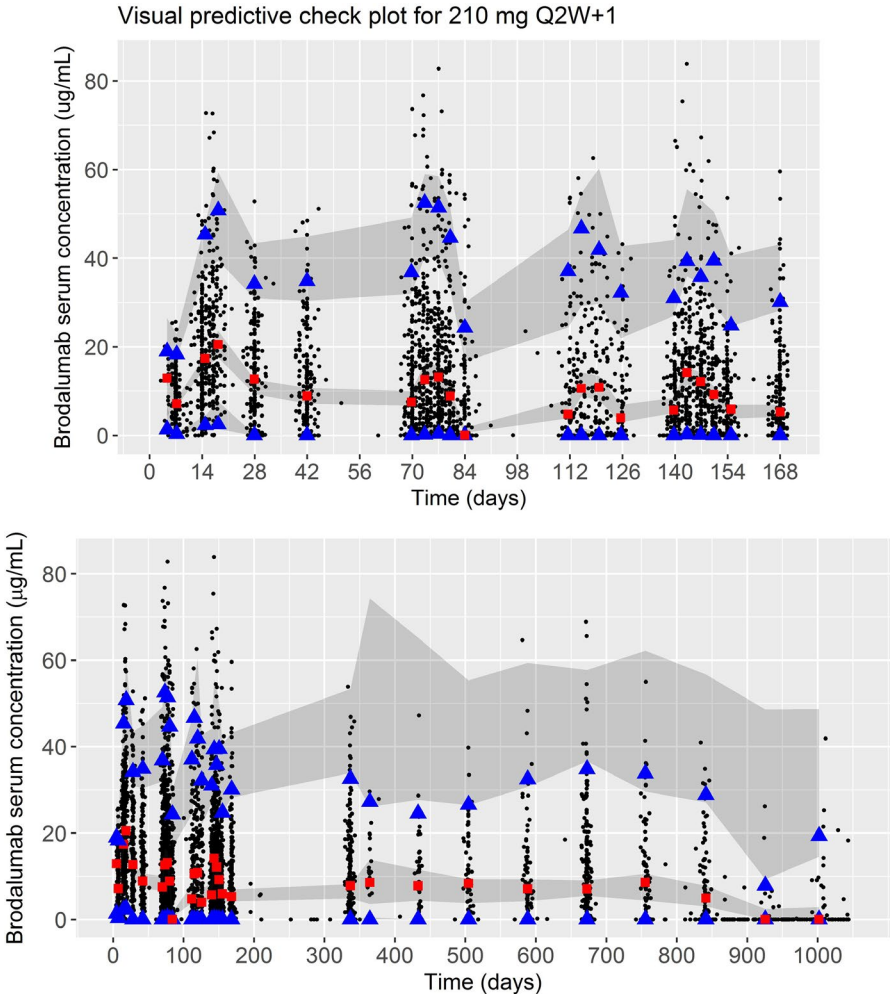


**FIGURE 2** Visual predictive check plot for the final model for the 210 mg dose (Phase 3 data only). Observed vs simulated Brodalumab serum concentration-time profiles for patients receiving only 210 mg dosages. Black dots are observations. Red squares and blue triangles are median and the 5th/95th percentiles of the observations, respectively. Grey shaded areas are the 95% CIs around the median and the 5th/95th percentiles of the simulations. At most time-points, the CI around the 5th percentile is not visible because the lower and upper limits of the CI are both zero

pharmacokinetic model was based on 622 moderate to severe psoriasis patients with rich blood sampling. The rationale for excluding healthy individuals was based on the observations made by Endres *et al*[12] suggesting a difference in systemic clearance. Based on the disease insight that the IL-17RA, the target for Brodalumab, is very differently expressed in the diseased and healthy population[8] and the suspected high impact of TMDD, this difference needs to be considered. This could have been done by including more parameters in the model but to reduce model complexity and data variability, healthy individuals were excluded from the analysis. The obvious advantage of this is that the model parameters derived are associated with the intended to treat population only. One disadvantage is that the absorption phase is often best described in initial dose escalation trials performed in healthy individuals. The decision to only include patients with non-trough concentrations in the analysis was based on the observation that a substantial amount of pre-dose samples were below LLOQ. Initially, the structural model was run on the full data set (patients with at least one quantifiable concentration) which resulted in run times around 2 days assumably due to the non-linearity in the pharmacokinetics and the large amount of concentrations below LLOQ also at the 210 mg dose level. Furthermore, the fact that the majority of patients in the full data set only had trough concentrations and that a large proportion of the trough concentrations was below LLOQ might lead to numerical unidentifiability estimating the non-linear and linear clearance parameters,[21] leading to unreliable model development (structural model and covariate analysis). The final model was run on the full data set with resulting parameter estimates similar to the parameter estimates for the PK data set ($Ka = 0.264\ day^{-1}$, $CL = 0.151$ L/d, $V1 = 4.54$ L and $V_{max} = 5.99$ mg/d).

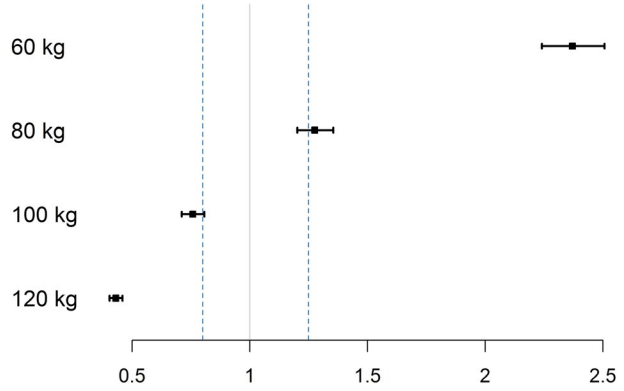


**FIGURE 3** Fold change in AUC at steady-state dosing 210 mg Q2W+1 due to change in body-weight. For each fixed body-weight value, the steady-state profiles of 1000 individuals dosed 210 mg Q2W+1 were simulated. AUC in a dosing interval (14 d) at steady-state was calculated using standard non-compartmental analysis. Black squares represent the geometric mean relative to the geometric mean of steady-state AUC for a standard patient with a body-weight of 90 kg. The vertical lines represent the 90% CI of the change (two-sided *t* test of the log-transformed AUCs). The blue dotted lines indicate the 0.8-1.25 range

**TABLE 4** Model-derived secondary pharmacokinetic parameters for a reference patient (body-weight of 90 kg) receiving 210 mg Q2W+1

| Pharmacokinetic parameter | Mean | Median | CV% |
|---|---|---|---|
| $C_{max}$ at week 1 dosing 210 mg Q2W+1 (µg/mL) | 9.95 | 9.57 | 50.7 |
| $C_{max}$ at steady-state dosing 210 mg Q2W+1 (µg/mL) | 20.2 | 16.1 | 76.8 |
| $t_{max}$ at steady-state dosing 210 mg Q2W+1 (d) | NR | 4 | 1-6 |
| $AUC_{ss}$ dosing 210 mg Q2W+1 (µg d/mL) | 225 | 160 | 92.8 |

$AUC_{ss}$, area under the concentration-time curve in a dosing interval at steady-state; $C_{max}$, maximum concentration; CV%, coefficient of variation (range is provided for $t_{max}$); NR, not reported; Q2W+1, dosing at weeks 0, 1, 2 followed by dosing every 2 wk; $t_{max}$, time to reach $C_{max}$ after last dose.

Following 210 mg of Brodalumab subcutaneously administered at weeks 0, 1, 2 followed by 210 mg every 2 weeks, observed serum concentrations were well described by a two-compartment model with combined linear and non-linear elimination (Figure 2). Body-weight proved to impact clearance (CL and $V_{max}$) and central volume of distribution, whereas neither sex, age nor baseline disease severity had significant impact on the exposure.

Due to the non-linear behaviour, the elimination half-life decreases as the concentration decreases. This means that the half-life cannot be used to provide estimates such as time to steady-state or time to clear the body. Instead, model-derived predictions (Table 4 and Figure 4) are useful to describe the pharmacokinetic fate of Brodalumab. Simulations showed that 90% of patients would reach a serum level below LLOQ 45 days after last dose at steady-state. Compared to most mABs (IgG subtypes except IgG3) with linear kinetics and a typical elimination half-life of 20-21 days,[22] this is a much shorter time period until complete washout.

The Michaelis-Menten constant was fixed in the model to a value below LLOQ. This means that the non-linear clearance term will at relatively small concentration values (around 1 µg/mL) reach its maximum value. In practice, this means that the non-linear elimination term could be replaced by a zero-order elimination term which would simplify the model. However, a model with combined zero- and first-order elimination can predict negative concentrations which are not desirable. Thus, Km is in that respect artificial and pharmacological interpretation of the estimated value should be cautioned.

In comparison with previous characterization of the Brodalumab pharmacokinetics, the most noteworthy differences are found in the parameter estimates of CL and Q. In our model, CL and Q were 25% (0.207-0.155 L/d) and 53% (0.70-0.33 L/d) lower, respectively, compared to the results from the initial analysis based on the phase I and II data.[12] $V_{max}$ increased slightly (8%). The intercompartmental clearance is often difficult to estimate which is why models often do not include random effects on $Q$.[12,23] One possibility is that only patients were considered in this analysis, whereas

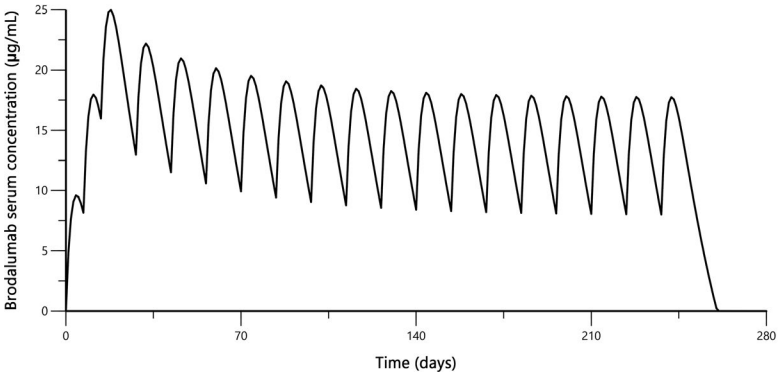


**FIGURE 4** Model-predicted concentration-time profile for a reference patient (body-weight of 90 kg) receiving 210 mg Q2W+1. Model-predicted concentration-time profile for a reference patient (body-weight of 90 kg) receiving 210 mg Brodalumab at weeks 0, 1, 2 followed by 210 mg every 2 wk

also healthy individuals were included in the previous analysis. The previous analysis showed that healthy individuals had a slightly higher CL and a lower $V_{max}$ than patients. A second explanation for the difference in CL (and $V_{max}$) could be the mere size of the populations included in the two different analyses. Thirdly, an explanation could be linked to the sampling strategies. Due to the nature of phase III trial set-up, blood sampling time-points are often taken just prior to the next dose, at trough. One limitation in the present analysis is the many serum concentrations that are at or below LLOQ. LLOQ in all of the included clinical trials has been 0.05 μg/mL or 400 times lower than the model-predicted average $C_{max}$. Still, 24% of all observations included in the analysis were below LLOQ (Figure 2). The large proportion of observations below LLOQ is believed to be associated with the increased elimination rate at low concentrations, which increases the variability. In order for the model to capture this large proportion of observations below LLOQ, the model has a tendency to overpredict high concentrations. The difficulties highlighted here suggest that trough concentrations might not be enough to perform population pharmacokinetic analyses of mABs exhibiting TMDD.

In relation to previous identified covariates,[12,20] bodyweight was also in our analysis found to have a significant impact on the exposure of Brodalumab. The simulation results predict a several-fold difference in exposure between a 60-kg and a 120-kg patient (Figure 3). Inter-individual variability (IIV) seen for clearance was high (Table 3), and body-weight only explained part of the variability. However, the IIV observed was within the range of other mAbs.[14] To further investigate the impact of body-weight on the pharmacokinetics and efficacy of Brodalumab, a post-approval trial is planned to address the benefits of a dose increase in patients with high body-weight and sub-optimal response to the standard treatment of Brodalumab.

No other covariates were identified as significant, which is in contrast to the analysis by Endres *et al*[12] where also age and diagnosis (healthy/patient) were identified as significant covariates on CL and $V_{max}$. In the review by Galluzzo *et al*,[20] age, sex and race were listed as non-significant covariates which is in line with our results.

In conclusion, Brodalumab serum concentrations in patients with plaque psoriasis were accurately described by a two-compartment model with parallel linear and non-linear elimination, and it was also established that body-weight has a significant impact on clearance and volume of distribution that in turn will influence the steady-state systemic exposure. No other covariates were identified as having significant impact on the exposure of Brodalumab. This population pharmacokinetic model will pave the way for further analyses regarding the investigation of the exposure-effect relationship and impact of body-weight.

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## CONFLICT OF INTEREST

Stine Timmermann and Anders Hall are both full-time employees of LEO Pharma A/S.

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