Both subcutaneous (SC) and intravenous (IV) abatacept, a selective T-cell co-stimulation modulator, are approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) and pediatric patients with rheumatoid arthritis, juvenile idiopathic arthritis (JIA), and psoriatic arthritis (PsA).

Abatacept has a mechanism of action that is fundamentally different from that of other biologic disease-modifying antirheumatic drugs (DMARDs), and has proven efficacy and a good safety profile in rheumatoid arthritis (RA).

The exposure-response (E-R) relationship established in 8A and 8B has demonstrated a steady-state trough concentration (Cminss) of 10 µg/mL, providing a near-maximal efficacy response.

For RA, abatacept is approved as either weight-based (10-15 mg/kg monthly) or fixed-dose SC (15 mg/kg) treatment. In the UK, the treatment for adults with active disease in the EU is the SC option at a dose of 10 mg/kg (MTX) for the treatment of active PA in adult patients when response to previous DMARD therapy has been inadequate, and for whom additional systemic therapy for psoriatic skin lesions is not required.

Objectives
- Evaluate the safety and efficacy of IV and SC abatacept in adults with moderately to severely active RA.
- Determine whether the proposed IV and SC dosing regimens provided near-maximal efficacy and were therapeutically equivalent in patients with RA.

Methods
- Combined data from studies with IV abatacept were analyzed to assess clinically relevant exposure outcome measures applicable to both formulations.
- The E-R model was developed with data from 13 Phase III trials in RA (31 studies [90%/10%] and EU studies [90%/15%]).
- The E-R of 20% improvement in American College of Rheumatology response criteria (ACH20) at Day 169 was characterized with data from two PAH/SC studies by a logistic regression model (n = 82).

Results
- The PK model for abatacept was developed and evaluated using abatacept concentration data from 273 patients, 493 with IV and 2444 with SC.
- Prior to the study, the IV formulation was administered in a Phase I clinical trial with another co-variator (IV infusion in fasted or SC). Absorption and first-order elimination (Clr). The PK of abatacept was similar in IV and PAH patients.
- Baseline body weight was the only significant covariate considered to have a clinically relevant effect on abatacept exposure (Figure 1).
- All other covariates were contained within the 80-125% range and therefore not considered clinically relevant.
- Model evaluation, performed by prediction-corrected VPC, showed that most of the observed abatacept exposure concentrations fell within the 80-125% predicted interval, indicating that the final PK model adequately described abatacept concentration-time profiles (Table 2).
- E-R analysis
  - As in RA, the C1 and C2 model (maximum response in logit for C1 and C2 adequately described the E-R relationship for ACH20 in PAH.
  - The final IV-ECH20 model parameter estimates are shown in Table 2. When comparing across regimens of responses, C1 and C2 were considered to be the best predictor of ACH20 response compared to C1 and C2. The probability of ACH20 response at Day 169 increased with increasing levels of C1 and C2. The concentrations of greater or equal to 10 µg/mL were associated with near-maximal ACH20 responses.
  - There was good agreement between the model-predicted probability of ACH20 response and observed ACH20 response rates across the range of C1 and C2 (Figure 3).
  - MTX use was a statistically significant predictor of ACH20.
  - The probability of ACH20 response on Day 169 increased with an upper limit of 50% to 55% in all C1 and C2 associated with the 10 mg/kg/ wk IV regimen. However, use of ACH20 expression related to placebo use were compared, MTX did not affect the ACH20 E-R relationship. The improvement in ACH20 response was similar regardless of MTX use.

Conclusions
- The PK and E-R analyses demonstrate that the abatacept dosing regimens for IV (10 mg/kg/ monthly) and SC (15 mg/kg/ monthly) are therapeutically equivalent for the treatment of RA.

Stochastic simulations
- While the IV and SC courses of administration have different PK profiles, C12 was similar following administration of weight-based IV abatacept (10 mg/kg/ monthly) and fixed-dose 15 mg SC weekly abatacept regimens. For both regimens, Cminss exceeded 10 µg/mL in 95% of patients with RA at body weight.

The simulated probability of ACH20 showed that 125 µg SC weekly dosing provided a similar response to 10 µg/kg IV once-monthly dosing (both dosing regimens showed improvements over the 3 mg/kg IV once-monthly dosing (Figure 4).

References