PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) MODELING OF SUBCUTANEOUS (SC) LY2189102, A NEUTRALIZING IL-1β ANTIBODY, IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Lilly LY2189102 is a novel IL-1β neutralizing antibody in development for the treatment of type 2 diabetes mellitus (T2DM). Clinical trials evaluated the PK/PD model of LY2189102 in T2DM patients following once every 6 weeks subcutaneous SC doses. This paper describes the pharmacokinetic/pharmacodynamic model fit to this data. The model exhibited a good fit, with no discernible improvements observed with more flexible structures. PK behavior of LY2189102 is well described by a two-compartment model with rapid absorption and a terminal half-life of 13.3 ± 6.2 days. PD effects of LY2189102 were well described by an Emax-4parameter model with a delay of 1.91 ± 0.70 days to predict the maximum glycemic response. The model was used to derive the model predicted time of the maximum glycemic response with a delay of 1.91 ± 0.70 days and to determine optimal dose regimens.

Background

LY2189102 is a humanized IgG4 monoclonal antibody that neutralizes IL-1β to reduce inflammatory activity. Clinical development of LY2189102 is ongoing for patients with type 2 diabetes mellitus (T2DM). PK/PD modeling and simulation were used to evaluate the PK behavior and PD effects of LY2189102 in T2DM patients following once every 6 weeks SC doses.

Methods

PK/PD model was developed using PK data from T2DM patients receiving LY2189102 once every 6 weeks. PD data from a 2-week placebo-controlled study and a 3-month observational study were used. The PD model was a 4-parameter Emax model with a delay of 1.91 ± 0.70 days to predict the maximum glycemic response. Model parameters were estimated using non-linear mixed effects modeling. The model was used to estimate the maximum effects and time of the maximum effects of LY2189102 in T2DM patients treated with different regimens.

Results

The model exhibited a good fit to the PK/PD data with no discernible improvements observed with more flexible structures. The model predicted the maximum glycemic response with a delay of 1.91 ± 0.70 days. The model was used to determine the optimal dose regimen for T2DM patients.

Conclusions

The model exhibited a good fit to the PK/PD data with no discernible improvements observed with more flexible structures. The model predicted the maximum glycemic response with a delay of 1.91 ± 0.70 days. The model was used to determine the optimal dose regimen for T2DM patients.

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