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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

Background and aims: LY2189102, a humanized neutralizing IL-1β antibody, was studied in type 2 diabetes mellitus (T2DM) patients with C-reactive protein (CRP) ≥ 2 mg/L, who received weekly subcutaneous doses of LY2189102 (0.6, 18 or 180 mg) or placebo over 12 weeks, and were monitored for 12 additional weeks. This report describes the selection of dose level and frequency of LY2189102 treatment using modeling and simulation of LY2189102 PK/PD relationships.

Materials and methods: Data from 106 patients were used in this analysis. A 2-compartment mammillary model with dose-dependent first-order input and bioavailability was fitted to pooled PK data from this study and a previous study conducted in rheumatoid arthritis patients receiving LY2189102 intravenously (IV). Bioavailability (F) was coded as F=1/(1+exp(-(F$_A$+F$_S$/Dose))), and the absorption half-life (T_{ka}) was coded as T_{ka}= α . F, where F$_A$, F$_S$, and α were estimated parameters, and Dose is in mg. Concentrations predicted using the individual Bayesian estimates of PK parameters were used as a forcing function in the PK/PD model, which simultaneously fitted fasting glycemia, insulinemia and HbA$_{1c}$ data. In this model, glucose-dependent insulin secretion capacity (ISC) had a zero-order input and LY2189102-concentration-dependent (inhibitory Emax) first-order output. Glycemia and insulinemia were interdependently related through ISC and fixed insulin sensitivity and liver glucose output parameters. HbA$_{1c}$ was governed by an input rate that is dependent on glycemia and unglycated hemoglobin, and a first order output. Simulations of a wide range of doses and administration frequencies, from once weekly to once every 6 weeks, were conducted.

Results: Data from 5 patients whose PK profiles indicated presumed development of immunogenicity were excluded. The total clearance (CL), distributional clearance (Q), central volume (V$_c$), peripheral volume (V$_p$), F$_A$, F$_S$, and α were (estimate (%SEM)) 9.45 (4.4%) mL/h, 25.1 (16%) mL/h, 3.06 (7.7%) L, 1.91 (7.7%) L, -0.42 (25%), 0.837 (21.1%) and 217 (10.9%) h, respectively. Inter-individual variability (%CV) in CL, V$_c$, V$_p$ and T$_{ka}$ was 44.2%, 51.9%, 69.2%, and 57.9%, respectively. Placebo effect, LY2189102's maximum inhibition of insulin secretion output (I_{max}), the concentration at 50% effect (IC_{50}), and insulin secretion loss rate constant were 6.5% (45%), 10.4% (39%), 342 μg/L (277%), and 4.72 mo^{-1} (37%), respectively. Inter-subject variability in PD parameters was modest. Simulation, conditional on final estimates, showed that while total administered doses saturably determined the magnitude of response, all studied administration schedules were essentially equivalent, probably due to the long half-life of the compound. A dose of 60 mg, administered once every 6 weeks, sustains near maximum glycemic response (-0.9 mM from baseline, -0.55 mM from placebo), while an 18-mg dose sustains 75% of the maximal response. Glycemic response plateaus by 3 months, while the HbA$_{1c}$ response at 6 months was 14% higher than that at 3 months.

Conclusion: Dosing (SC) of LY2189102 can be as infrequent as once every 6 weeks, potentially offering a convenient therapeutic alternative for patients with T2DM.

Background

IL-1β reduces the number of viable pancreatic beta-cells via apoptosis and reduction of proliferation[1,2], and reduces beta-cell insulin secretion and/or sensitivity via pro-inflammatory activity (direct), and induction of pro-inflammatory factors from adipose tissue (indirect)[3,4].

LY2189102 is a humanized IgG4 monoclonal anti-IL1β antibody in development for the treatment of diabetes, with a binding affinity of 2.8 pM, and a half-life and bioavailability of 20.3 days and 55%, respectively, after SC administration to healthy volunteers.

LY2189102 was recently studied in a Phase II study in T2DM patients (CT registry NCT00942188).

This report describes the selection of dose level and frequency of LY2189102 treatment using modeling and simulation of LY2189102 PK/PD relationships.

[1]Diabetes 2004. 53:1706; [2]Diabetes 2001. 50:1683; [3]J. Clin. Invest. 2002.110:851; [4]J. Clin. Invest. 2006.116:1793

Clinical Studies

Study H9C-MC-BBDK (BBDK)

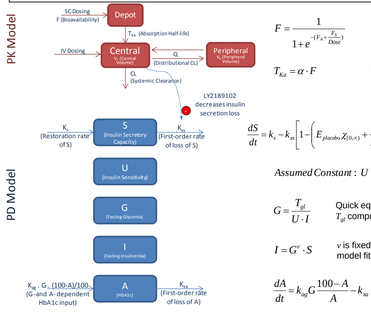
- Phase II, double blind, parallel, multiple dose, placebo-controlled study in 106 T2DM patients on diet and exercise, with or without anti-diabetic medication (excluding TZD and insulin), receiving 0.6, 18, 180 mg LY2189102 (total N = 74) or placebo (N = 32) SC injection every week for a 12-week dosing period
- LY2189102 concentrations obtained at 1, 3, and 4 days, then prior to weekly dosing until end of treatment, and 1, 6 and 12 weeks after last dose
- Fasting glucose, insulin and HbA1c measured for 24 weeks: at baseline , and during 12 weeks of dosing and 12 weeks of follow up
- Analyses herein represent late interim data from all but 1 subject.

Study H9C-MC-BBDE

- Phase Ib/II study in patients with Rheumatoid Arthritis
- Additional PK data (dense sampling) used to augment the PK model (data not shown) obtained in 96 patients receiving 0.02 to 2.5 mg/kg LY2189102 IV injection every week for 5 weeks

The Model

LY2189102, concentration-dependently inhibits the loss of insulin secretory capacity



$$F = \frac{1}{1+e^{-(F_A+\frac{F_S}{Dose})}}$$

Dose-dependent bioavailability and absorption half-life. F_A, F_S and α are estimated parameters.

$$T_{ka} = \alpha \cdot F$$

$$\frac{dS}{dt} = k_{in} - k_{out}\left[1-\left(E_{placebo}\bar{x}_{(0,\infty)} + \frac{E_{max}\cdot C^{LY2189102}}{EC_{50}+C^{LY2189102}}\right)\right]\cdot S, \quad S_0 = S_b$$

$$Assumed\ Constant: U = 5.e^{-5}\ \text{min}^{-1}/(\mu IU/mL)$$

$$G = \frac{T_{gl}}{U \cdot I}$$

Quick equilibration assumed. T_{gl} computed from baseline values

$$I = G' \cdot S$$

v is fixed to ~1, based on early model fits.

$$\frac{dA}{dt} = k_{ag} G \frac{100-A}{A} - k_{xa} \cdot A$$

Model Building Methodology

Non-linear mixed effects modeling and a 2-stage PK/PD approach were utilized, where the PK model was first built using NONMEM® 6.2.0, then, model-predicted individual concentration versus time profiles were used as a forcing function for the PK/PD model implemented in R® 2.10.0 using the nlme package.

At the time of this analysis, immunogenicity data were not available. Five (6.4% of LY2189102-treated) subjects exhibited distinct changes in PK profile (data not shown), and were excluded due to suspicion of immunogenicity. Results herein represent subjects in whom no suspect changes in PK profile were observed. The effect of immunogenicity on LY2189102 PK/PD is yet to be explored.

Pharmacokinetic Model Results

Figure 1 (right). Dose-Normalized Serum LY2189102 Concentrations vs. Time Since Last Dose. Data suggest faster, but less complete absorption as dose increases. Lines are smoothing splines.

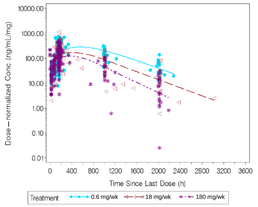


Figure 2 (below). PK Model Goodness of Fit. Population (left) and individual (right) predicted LY2189102 concentrations were congruent with observed values, with no apparent bias, indicating a good fit.

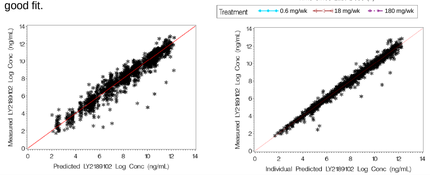


Table 1. Pharmacokinetic Parameter Estimates.

	Final Parameter Estimate		Interindividual Variability (%CV)	
Parameter	**Typical Value**	**%SEM**	**Final Estimate**	**%SEM**
CL (mL/h)	9.45	4.4	44.2	15.3
V_c (L)	3.06	7.7	51.9	18.4
Q (mL/h)	25.1	16	NE	NE
V_p (L)	1.91	7.7	69.2	33.8
α	217	10.9	NE	NE
F_A (-) [a]	-0.42	25	NE	NE
F_S (-) [a]	0.837	21.1	NE	NE
T_{ka} (h) [b]	NE	NE	57.9	19.2
Study BBDK RV (log unit SD)[c]	0.249	13.3	NA	NA

Abbreviations: α, correlation factor between extent of bioavailability and half-life of absorption; CL, elimination clearance; %CV, percent coefficient of variation; F_A, asymptote of the hyperbolic function of dose; F_S, slope of the hyperbolic function of dose; NA, not applicable; NE, not estimated; Q, distribution clearance; RV, residual variability; SD, standard deviation; %SEM, percent standard error of the mean; T_{lag}, half-life of absorption; V_c, central volume of distribution; V_p, peripheral volume of distribution.

[a] SC bioavailability, F, is modeled with the following function of the dose (in mg): $F = 1/\left(1+e^{-(F_A+\frac{F_S}{Dose})}\right)$

[b] The value of T_{ka} was computed as α × F and was modeled with interindividual variability.

[c] The RV value estimated for Study BBDE was 0.459.

Pharmacokinetic/Pharmacodynamic Model Results

Figure 3. PK/PD Model Qualification. The plots of HbA1c, fasting glucose and insulin versus time highlight the time- and dose-dependent decreases in fasting glucose and HbA1c. Minor increases in fasting insulin can also be seen, consistent with the model structure which assumes an improvement of insulin secretion upon LY2189102 treatment. Model predictions (with 95% prediction interval) reproduced well the observed time course of HbA1c, glucose and insulin. A mild skewness could be discerned for insulin predictions, and to much less extent for glucose, but is likely inconsequential. Observed vs. predicted, and weighted residuals vs. time plots showed no clear trend (not shown).

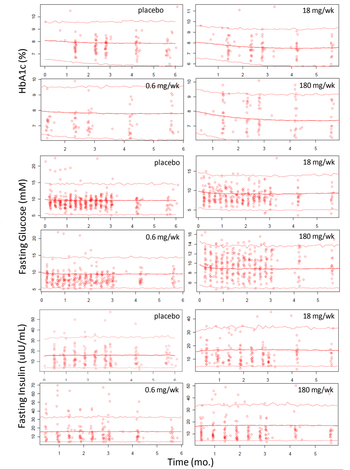


Figure 4 (right). PK/PD Model Predictions for Different LY2189102 Dosing Regimens. Predictions are based on a simulation (n=500 subjects) conditional on the final model parameter estimates. Fasting glucose and HbA1c mean changes from baseline after 3 and 6 months of treatment with dosing regimens of once every half a month (Q 0.5 mo), every month (Q 1 mo) and every 1.5 months (Q 1.5 mo) are displayed. Administered once every 6 weeks, a SC dose of 60 mg sustains near maximum glycemic response (-0.9 mM from baseline, -0.55 mM from placebo), while an 18-mg dose sustains 75% of the maximal response. Infrequent dosing, as little as once every 1.5 months, is adequate to maintain efficacy. Fasting glucose response appears to be near steady-state by 3 months of treatment, while HbA1c response at 3 months is approximately 86% of the response at 6 months.

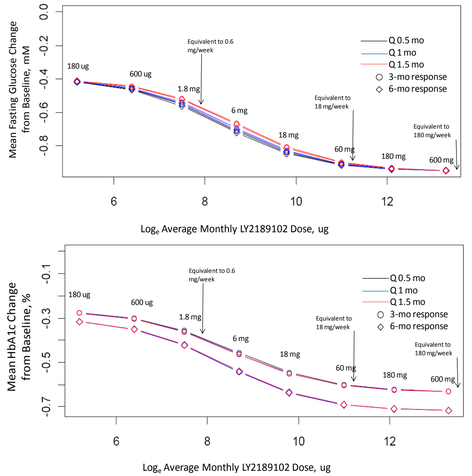


Figure 5. Predicted Time Course of Fasting Glucose (G), Fasting Insulin (I) and HbA1c (A). A dose that continuously achieves near maximum efficacy was simulated (solid lines) or placebo (dashed lines) based on the final model estimates (no added variability, representing a typical subject). G and I reach near steady state within 1-3 month driven by the dynamics of S (half-life of k_{xs} = 0.15 months), while A lags further (half-life of k_{xa} = 0.98 months).

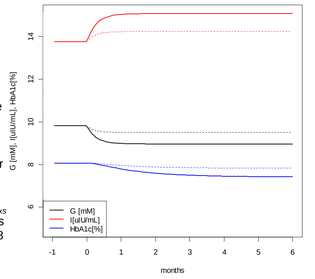


Table 2. Pharmacokinetic/Pharmacodynamic Model Parameter Estimates.

	Final Parameter Estimate		Interindividual
Parameter	**Typical Value**	**%SEM**	**Variability (%CV)[a]**
k_{xs} (mo^{-1})	4.72	37	0.18
$E_{placebo}$ (%)	6.5	45	235
E_{max} (%)[b]	10.4	39	0.57
EC_{50} (ug/L)[b]	342	277	2.0
k_{xa} (mo^{-1})	0.707	18	0.06
HbA1c RV (%CV)[c]	0.045	NA	NA
Glucose RV (%CV)[c]	0.14	NA	NA
Insulin RV (%CV)[c]	0.26	NA	NA

Abbreviations: k_{xs}, rate of loss of insulin secretory capacity at baseline; $E_{placebo}$, placebo effect on k_{xs}; E_{max}, maximum LY2189102 effect; EC_{50}, LY2189102 concentration at 50% of E_{max}; k_{xa}, rate of loss of HbA1c; %CV, percent coefficient of variation; NA, not applicable; RV, residual variability; %SEM, percent standard error of the mean.

[a] Only the diagonal elements of a full dispersion matrix of interindividual variability are reported for brevity. Error of variance terms was not estimated.

[b] While variability of the estimates turned out to be substantial, all parameters except $E_{placebo}$ showed a modest population variability, which could reflect the convergence behavior. Nonetheless, the predictive performance of the model has been qualified (see Fig 3).

[c] A proportional error model was used for each of the variables. The variance of RV was fixed to values estimated from an earlier model fitting step utilizing iteratively reweighted least squares. Fixing RV estimates was done to improve model convergence and model run time.

Conclusions

- LY2189102 bioavailability decreased, while absorption rate increased with increasing SC dose. A linear two-compartment model adequately captured the PK behavior of LY2189102.
- A semi-mechanistic PK/PD model, where LY2189102 effect is modeled as a concentration-dependent inhibition of the loss of insulin secretion capacity, adequately fit the glucodynamic data in T2DM patients.
- LY2189102 effect on fasting glucose nearly reached steady-state after 3 months of treatment.
- LY2189102 achieves near maximum efficacy at 60 mg and can be given as infrequently as once every 6 weeks, potentially offering a convenient therapeutic alternative for patients with T2DM.

Disclosure and Acknowledgement

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