RESPONSE TO COMMENT ON KAZDA ET AL.

Evaluation of Efficacy and Safety of the Glucagon Receptor Antagonist LY2409021 in Patients With Type 2 Diabetes: 12- and 24-Week Phase 2 Studies. Diabetes Care 2016;39:1241–1249

Christof M. Kazda,[1] Ying Ding,[2] Ronan P. Kelly,[3] Parag Garhyan,[2] Chunxue Shi,[4] Chay Ngee Lim,[2] Haoda Fu,[2] David E. Watson,[2] Andrew J. Lewin,[5§] William H. Landschulz,[2] Mark A. Deeg,[2] David E. Moller,[2] and Thomas A. Hardy[2]

Diabetes Care 2016;39:e199–e200 | DOI: 10.2337/dci16-0030

We appreciate the thoughtful comments raised by Agrawal and Gupta (1) on our recent article (2) on the efficacy and safety of the glucagon receptor antagonist LY2409021 in patients with type 2 diabetes. We are pleased that they acknowledge that this study has provided further proof of efficacy of glucagon antagonism as a treatment for type 2 diabetes with acceptable adverse effects at a dose of 30 mg (1). Agrawal and Gupta queried how we arrived at the unequal allocation to the treatment groups with the ratio of 1.5:2.1:1:1 (for 60 mg, 30 mg, 10 mg, and placebo, respectively). Our randomization was probability based and computer generated with the goal to optimize the number of patients allocated to the 30 mg dose, selected on the basis of the results of the phase 1 studies (3). Agrawal and Gupta also inquired about the reason for fasting triglycerides >400 mg/dL as an exclusion criterion and wanted to understand the basis for this exclusion since no significant change in triglyceride concentration was noted in the phase 1 study of this molecule (3). The rationale to exclude patients with uncontrolled hypertriglyceridemia in the reported clinical studies was not based on expected side effects of LY2409021, as suspected by Agrawal and Gupta, but rather to exclude a bias of hypertriglyceridemia-induced insulin resistance on the primary efficacy objective. In addition, it is considered ethically inappropriate to include patients with severe hypertriglyceridemia in placebo-controlled studies because of the potential risk of worsening during placebo treatment including secondary adverse effects. The authors also noted that we used weekly change in HbA_{1c} as a secondary outcome measure and were of the opinion that the clinical implications of a weekly change in HbA_{1c} is difficult to comprehend because of the fact that HbA_{1c} levels change gradually over a 3-month period. Although change in HbA_{1c} from baseline to end was used to assess the primary end point in each study, we did not in fact use weekly change in HbA_{1c} as a secondary outcome measure. In both studies, HbA_{1c} was not determined weekly but every other week, and depicting the course of HbA_{1c} in a graphical manner as done in Fig. 1*A* and *B* of the article (2) is a common way of reporting the data for diabetes studies. Agrawal and Gupta further pointed out that the efficacy of the treatment is reported to be dose dependent but the least squares mean change in HbA_{1c} from baseline is highest in the 10-mg group and lower in the 30- and 60-mg groups, which was unexplained. We agree that in the phase 2a study, a dose-dependent difference between the 10-mg dose and higher doses (30 and 60 mg) was not apparent, indicating that the higher doses were on the upper end of dose-response curve; this result is consistent with the previously reported exposure-response data for LY2409021 (3). However, there is an obvious dose-dependent change in HbA_{1c} in the phase 2b study between the 2.5-mg and 20-mg dose levels, thus confirming that the 30-mg and 60-mg doses used in the phase 2a study were on the upper end of dose-response curve.

Duality of Interest. The study was sponsored by Eli Lilly and Company and/or one of its subsidiaries. C.M.K., R.P.K., P.G., H.F., D.E.W., W.H.L., M.A.D., D.E.M., and T.A.H. are employees and stockholders of Eli Lilly and Company and/or one of its subsidiaries. Y.D. and C.N.L. were employees of Eli Lilly and Company and/or one of its subsidiaries. A.J.L. was an employee of the National Research Institute, Los Angeles, CA, at the time of the study and is currently retired. No other potential

[1]*Eli Lilly and Company, Suresnes, France*
[2]*Eli Lilly and Company, Indianapolis, IN*
[3]*Lilly-NUS Centre for Clinical Pharmacology, Singapore*
[4]*inVentiv Health Clinical, Clarksville, MD*
[5]*National Research Institute, Los Angeles, CA*

Corresponding author: Christof M. Kazda, kazda_christof@lilly.com.

Y.D. is currently affiliated with the Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, and C.N.L. is currently affiliated with the Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN.

[§]*Retired.*

conflicts of interest relevant to this article were reported.

References

1. Agrawal S, Gupta Y. Comment on Kazda et al. Evaluation of efficacy and safety of the glucagon receptor antagonist LY2409021 in patients with type 2 diabetes: 12- and 24-week phase 2 studies. Diabetes Care 2016;39:1241–1249 (Letter). Diabetes Care 2016;39:e198. DOI: 10.2337/dc16-1340
2. Kazda CM, Ding Y, Kelly RP, et al. Evaluation of efficacy and safety of the glucagon receptor antagonist LY2409021 in patients with type 2 diabetes: 12- and 24-week phase 2 studies. Diabetes Care 2016;39:1241–1249
3. Kelly RP, Garhyan P, Raddad E, et al. Short-term administration of the glucagon receptor antagonist LY2409021 lowers blood glucose in healthy people and in those with type 2 diabetes. Diabetes Obes Metab 2015;17:414–422