Development of new basal insulin peglispro (LY2605541) ends in a disappointing result

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On 4 December 2015, Eli Lilly and Company (Indianapolis, IN, USA) announced that they made the decision to end the basal insulin peglispro (BIL) development program, which was on its way to phase III trials. Stable and prolonged pharmacokinetic (PK) and pharmacodynamic (PD) profiles are very important for basal insulin, and several analog insulins for basal supplement have been developed in this decade [1]. More efficient and safer glycemic control has been realized with subsequent new basal insulins. Established long-acting basal insulins available in Japan include insulin glargine 100 U/ml [2], insulin detemir [3], insulin degludec [4], and insulin glargine 300 U/ml [5, 6].

LY2605541 is a novel PEGylated basal insulin known as BIL. Insulin lispro is a 5.8-kDa peptide hormone; 20-kDa polyethylene glycol (PEG) is a neutral linear conjugated to insulin lispro to give rise to the basal analog LY2605541. It is able to bind three molecules of water, allowing it to become highly hydrated, thereby increasing the hydrodynamic size of the molecule, which delays absorption and reduces renal filtration, resulting in a protracted half-life of LY2605541. The PEGylation process also protects against proteolytic degradation. PEGylation is novel in the context of insulin but is a well-established strategy to improve therapeutic properties of proteins, as shown for interferon. In the phase I study, LY2605541 showed flat PK and PD profiles accompanied by glucose normalization, prandial insulin

dose reduction, and no severe hypoglycemia [7]. In addition to the long and flat PK/PD profile, LY2605541 demonstrates preferential hepatic versus peripheral action relative to insulin glargine in healthy individuals [8]. In this euglycemic clamps study, insulin glargine resulted in increased glucose disposal rate (GDR) at insulin concentrations where endogenous glucose production (EGP) was significantly suppressed. In contrast, at comparable EGP suppression, LY2605541 had minimal effect on GDR at lower doses and substantially less effect on GDR than insulin glargine at higher doses. This hepatospecific characteristic of LY2605541 may mimic physiological endogenous insulin, which is directly secreted into the portal system.

The IMAGINE phase III studies investigated LY2605541 in several patient populations [9–15]. Over all in those studies, LY2605541 led to a significantly greater reduction in HbA_{1c} compared with insulin glargine 100 U/ml, although other recently launched basal insulins reduced HbA_{1c} no less effectively in the treat-to-target studies [16]. In the IMAGINE 1 and 3 studies, there was a greater rate of total hypoglycemia, but lower nocturnal hypoglycemia, compared with insulin glargine 100 U/ml. The increased rate of daytime hypoglycemia may be due to bolus insulin overdose after covering with strong basal insulin LY2605541. All these studies reported elevated alanine transaminases, and some studies also reported increased fat content in the liver [9–13]. Although Nippon Eli Lilly accomplished phase 3 studies in Japan, Eli Lilly and Company announced in February 2015 that regulatory submission for approval by the US Food and Drug Administration (FDA) had been delayed so that additional clinical data could be gathered to further understand and characterize the potential effects on changes in liver fat induced by LY2605541 [16].

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Finally, on the date stated in the beginning of this report, the company announced that they made the decision to end the BIL development program, which was on its way to phase III trials. The company explained that the reason for this decision was that the investment of time and money needed to assess potential development plans addressing liver data observations in IMAGINE trials. Although liver data may not show LY2605541 to be hepatotoxic, the authors speculate that it induces liver steatosis and the probability that it induces nonalcoholic steatohepatitis ((NASH)-like status cannot be excluded. In conclusion, whereas the company's decision is disappointing, it is discerning, as it may take much time to attain liver-safety approval of LY2605541. However, the author believes that the massive amounts of data regarding liver-specific basal insulin is useful and contributes greatly to the development of future insulin therapy.

Compliance with ethical standards

Conflict of interest statement Total clinical research grant: Sanofi, Eli Lilly, Novo Nordisk, Kissei, Boehringer Ingelheim, Ono, AstraZeneca. Honoraria for lectures: Sanofi, Eli Lilly, Novo Nordisk, Merck (MSD), Dainippon-Sumitomo, Novartis, Kissei, Boehringer Ingelheim, Ono, Kissei, AstraZeneca.

Ethics policy All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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