

REVIEW

How Can a Good Idea Fail? Basal Insulin Peglispro [LY2605541] for the Treatment of Type 2 Diabetes

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ABSTRACT

Introduction: Lack of control in diabetic patients has stimulated the development of new insulin analogues. One of these was basal insulin peglispro (BIL) or LY2605541; it had a large hydrodynamic size, flat pharmacokinetic profile, half life of 2–3 days and acted preferably in the liver.

Methods: We reviewed the recent literature examining the pharmacokinetics, pharmacodynamics, efficacy and safety of BIL treatment in type 2 diabetes patients.

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Results: The pharmacodynamic and pharmacokinetic outline of BIL seemed to have an advantage over neutral protamine Hagedorn and glargine insulins. Recently, phase 3 studies suggested BIL was superior to glargine in reducing glucose levels in type 1 and type 2 diabetes patients in addition to causing less weight gain. It showed a different hypoglycaemia rate profile depending on the study population, with less nocturnal hypoglycaemia compared to glargine. Unfortunately, it caused higher transaminase and triglyceride levels, which led the company to discontinue development. The decision came after it had been analysed by the regulatory authorities and other external experts concerning the worse liver profile data from the IMAGINE trials.

Conclusions: BIL was an adequate basal insulin analogue with interesting specific properties. Unfortunately the disadvantages as shown in the lipid values and liver function tests led to its failure.

Keywords: Basal insulin peglispro; Pharmacokinetics; Pharmacodynamics; Type 2 diabetes; Efficacy; Hypoglycemia

INTRODUCTION

Insulin is increasingly used in type 2 diabetes (T2D), in large part because of its rising prevalence worldwide and a focus on intensifying glycaemic control. Unfortunately, even with first-generation basal insulin on the market, less than one third of the people with T2D on basal-bolus therapy reach the ambitious HbA1c target of <6.5%. In an ideal setting, insulin treatment is intended to simulate the functioning of a healthy pancreas, with a peak secretion of more insulin at mealtimes and maintenance baseline throughout the day.

When we initiate an insulin therapy it has an anabolic effect, and it is accompanied by a risk of hypoglycaemia. Unfortunately, it usually results in weight gain although this effect will vary depending on the insulin characteristics and regimens used [1, 2].

A high percentage of our patients treated with insulin experience inadequate glycaemic control and this can be explained, in part, by the fact that the basal insulins available right now do not properly simulate physiological insulin secretion. The intention of these new insulin analogues and the changes in insulin regimens is to meet the clinical needs and improve the pharmacokinetic/pharmacodynamic (PK/PD) profile.

New insulin analogues are being developed to improve metabolic control and reduce side effects. Now we can use insulin degludec in our clinics and PEGylated insulin lispro (BIL) was in development until recently. They demonstrated long-lasting action profiles using different mechanisms. They were designed to be used once a day, with a stable PK/PD profile at steady state, and showed lower hypoglycaemia rates. Another study is being developed with enhanced strength formulations of insulin glargine (IG).

This is interesting for patients using high insulin doses and appears to reduce the number of injections and volume used with a better profile [3].

METHODS

Overview of the Market

To control type 2 diabetes glucose levels the most effective and powerful treatment is insulin. Since its development in 1946, the neutral protamine Hagedorn (NPH) has been the most used basal insulin. Unfortunately, it has some disadvantages: it needs re-suspension to be absorbed and has peak activity between 4 and 6 h after subcutaneous administration, which can produce higher between-meal and nocturnal hypoglycaemia. Afterwards, in the 1980s, the insulin molecule was modified with recombinant DNA technology, which enabled the first soluble long-acting insulin analogues: IG and detemir. They seem to reduce the risk of hypoglycaemia compared to NPH because of their enhanced time-action profile and less glucose variability from day to day [4]. IG has an earlier onset and longer duration of action (median 24 h). Insulin detemir has a longer duration than NPH, but this is less than 24 h. It produces less variability than IG, possibly related to its protraction mechanism, which does not precipitate.

New basal analogues have been designed with an ultra-long-acting profile and high-strength formulations to reduce glycaemic variability, cause less (nocturnal) hypoglycaemia and offer a weight-loss advantage. However, these new basal insulin analogues need to be monitored closely for adverse effects. Degludec is now on the market. It forms long, subcutaneous multi-hexamers that delay its absorption.

Recent phase 3 trials in type 1 and type 2 diabetes have shown its non-inferiority to comparators (predominantly IG) with an advantage in reducing overall hypoglycaemia and a small but significant difference in nocturnal hypoglycaemia.

IG's modified formulation (U300) results in a flatter and more long-lasting profile than the first IG. The mechanism of protraction is essentially the same as that of the U100 formulation, but forms post-injection precipitates. Nevertheless the PK/PD profile of this high-strength formulation will be different because the higher concentration presents a smaller depot surface area from which a given dose can be absorbed. This may amplify the T_{max} , resulting in a higher steady-state profile and reduced peak-to-trough ratio [3, 5].

Finally, BIL is designed with insulin lispro combined with polyethylene glycol to increase its hydrodynamic size and retard absorption from the subcutaneous tissue. The active component of BIL is covalently coupled to a single 20-kDa polyethylene glycol moiety via a urethane bound to lysine B28. It implies a large hydrodynamic size of the molecule, delaying the absorption rate of insulin lispro by slowing the diffusion rate and reducing renal filtration. With the molecular pegylation it also prolongs the half-life by increasing the stability against proteolysis.

The large size appears to alter the tissue distribution of this insulin. Hypothetically, the hepatic sinusoidal endothelium with its wide fenestration may allow greater transport of the molecule to the liver than to muscles and fat, ensuring a preferential hepatic action.

BIL, subcutaneously administered, presents as long-acting insulin with an apparent half-life of 2–3 days, enabling use of once daily basal insulin [6–8].

Chemistry

Polyethylene glycol is a branched or linear neutral polyether with the chemical formula $HO-(CH_2-CH_2O)_n-H$. It is non-toxic and can be conjugated to proteins; each monomer is able to bind three molecules of water, allowing it to become highly hydrated. In aqueous solution, polyethylene glycol is effective at excluding other polymers from its presence through the formation of two-phase systems [9, 10].

As explained by Caparrotta et al., pegylation of proteins serves to increase the hydrodynamic size of the molecule to which it is appended. Hydrodynamic size is the effective size of a molecule in solution and includes the molecules of a solvent interacting with the solute. Variations in hydrodynamic size affect the behaviour of molecules in solution with particles of a larger size being subject to a greater drag. When administered subcutaneously, the bigger hydrodynamic size serves to delay the absorption of pegylated proteins by slowing their diffusion rate. Additionally, renal filtration of such proteins is also reduced because the increase in molecular size exceeds the glomerular ultra-filtration cutoff. These new characteristics are important considerations with respect to extending the half-life of pegylated proteins [10].

PK/PD and Metabolism

The large hydrodynamic size of BIL protected its duration of action and caused a delay in subcutaneous insulin absorption and decreased clearance. Hexameric formulated human insulin is reported to be absorbed by the capillary system and to a lesser degree by the lymphatic system. Administering large globular proteins subcutaneously, they are absorbed

more via the lymphatic than the vascular system because of differences in the capillary structures. The large hydrodynamic size of BIL may allow slow absorption of monomers predominantly via the lymphatic system.

Initial studies in sheep demonstrated absorption of human insulin via the lymphatic system of 17.3% while the absorption of BIL was 88%. There appeared to be a good correlation between both the molecular weight and hydrodynamic size, and it influenced the percentage of the dose absorbed via the lymphatic system [11]. Furthermore, when using BIL, the hepato-preferential action shown by a greater transport into the liver relative to peripheral tissues (through the fenestrated hepatic sinusoidal) potentially provided a closer to normal physiology.

The mechanism of insulin receptor (IR) activation by BIL was demonstrated with the use of a model of IR binding, which was compared to that of biosynthetic human insulin. The investigation concluded that the IR activation by BIL was similar to that of human insulin based on the preservation of a bell-shaped dose response for negative cooperativity showing that, despite a large hydrodynamic size in comparison to human insulin, up to three molecules could bind to IR at the same time in a concentration-dependent manner. Upon BIL binding to the receptor, the subsequent process of binding site crosslinking, which was thought to be a critical step in IR activation, appeared to be unaffected as evidenced by the preservation of the crosslinking constant [12].

Beals et al. [13] evaluated the effect of the hydrodynamic size of the molecule. Dynamic light scattering studies showed that BIL was four times larger than insulin lispro protamine. This suggests BIL should have delayed absorption and less renal filtration. The authors reported a

dose-ranging study of BIL in a streptozotocin rat model, indicating significantly delayed subcutaneous absorption.

The bioavailability of BIL after subcutaneous administration is >70%, which is similar to that of human insulin. Furthermore pegylation of proteins serves to reduce enzymatic breakdown and elimination through steric hindrance. Consequently, degradation is slower than that of the original non-pegylated protein, breaking down into smaller molecules able to experience endocytosis or renal ultrafiltration [9].

To explain the effect of reduced renal function on the clearance of BIL, Linnebjerg et al. used a nephrectomised rat model. They administered intravenous BIL and lispro protamine to remove subcutaneous absorption as a potential variable. It showed that clearance of lispro protamine was significantly reduced in renal impairment, but with no effect on the clearance of BIL keeping its glucose-lowering properties. This observation occurred because of BIL's increased hydrodynamic size, which reduced renal ultrafiltration [14].

Preparing a euglycaemic clamp study in dogs, Moore et al. [15] described their pre-clinical findings on the hepatic glucose uptake and output of BIL. Compared to regular human insulin (RHI), BIL produced greater suppression of the glucose appearance rate. Conversely, non-hepatic glucose uptake in subjects exposed to BIL increased less than in subjects exposed to RHI. These data support BIL's hepato-preferential effect, similar to that of endogenous insulin and different from exogenously administered RHI.

Clinical Efficacy

Phase 1 and Phase 2 Studies

Pharmacokinetic and glucodynamic studies were undertaken in healthy volunteers

followed by euglycaemic glucose clamps [16]. In the first, 33 subjects received a single subcutaneous ascending dose of BIL or IG. A second study assessed the absolute bioavailability of BIL after an intravenous dose. These studies proposed that BIL's duration was sustained for at least 36 h compared to IG, which showed a peak effect at 12–14 h and reduced action at 24 h.

The intra-subject coefficient of variability for BIL (%) was calculated using data from previous studies; it was <18% for PK and <32% for GD. This is an interesting consideration because part of the insulin is degraded locally after subcutaneous administration or distributed to other compartments where it has fewer glucose-lowering effects. The results proposed that BIL could be administered once a day and had low intra-subject variability. Additionally, when compared with IG, the duration of action of BIL was significantly sustained [17, 18].

Sinha et al. affirmed that after using BIL as basal insulin, there was a reduction of prandial insulin requirements and fasting blood glucose without increasing the rate of nocturnal hypoglycaemia and with no severe or long-lasting hypoglycaemia [18].

Studies performed with insulin degludec indicated a similar profile without a peak and with 26-h duration of action [19]. These works cannot be directly compared, but on the basis of the indirect comparison from phase 1 studies, degludec and BIL showed similar PK profiles but with different GD profiles due to degludec binding to albumin.

The Linnebjerg study analysed the influence of renal function. The authors proved that the half-life or apparent clearance was not significantly affected and that there were no significant relationships between the apparent clearance and estimated creatinine clearance. However, dose-normalised C_{max} (C_{max}/dose)

was reduced in patients with moderate to severe renal impairment. In patients undergoing dialysis, BIL did not appear to be significantly eliminated, less than 25%. They concluded BIL was well tolerated in patients with different degrees of renal function and with no need to reduce the dose [14].

Further simulations based on data from euglycaemic clamp showed hepatic glucose output and muscle glucose uptake [20]. This work used a validated model Metabolism Physioblab platform derived from the transit rate of both IG and BIL through the capillaries and lymphatics. When administered once in healthy volunteers, the model predicted how IG concentrations were likely to be similar in the plasma, muscles and liver, while the BIL concentration was higher in the liver than in the muscles. This could be explained by its slower transit across the capillary bed relative to lymph flow, prompting lymphatic absorption of BIL [9]. This work suggested that BIL exerted its glucose-lowering effects during fasting because it reduced hepatic glucose output, whereas IG stimulated muscle glucose uptake and inhibited hepatic action.

Henry et al. compared endogenous glucose production and the glucose disposal rate over a range of doses of BIL and IG in healthy subjects. Suppression of endogenous glucose production and stimulation of the glucose disposal rate were observed with increasing concentrations of both insulins. IG resulted in an increased glucose disposal rate. In contrast, BIL had a minimal effect on the glucose disposal rate at lower doses and had a substantially lesser effect than IG at higher doses, demonstrating its relative hepato-preferential action [21].

Results of a phase 2 trial comparing BIL with IG in a short time period reported non-inferiority of BIL. Bergenstal et al. [22] conducted a 12-week, randomised, open label,

two-arm, multinational parallel-group study comparing once-daily BIL to once-daily IG in basal-insulin treated patients with T2D. All BIL patients were changed from NPH or IG. After 12 weeks, fasting blood glucose was similar in the combined BIL group vs. the IG group [118.2 ± 2.0 mg/dl (6.6 ± 0.1 mmol/dl) vs. 116.9 ± 2.7 mg/dl (6.5 ± 0.2 mmol/dl)]. An eight-point self-measured blood glucose profile showed no difference between BIL and IG in HbA1c. Furthermore, there were no differences between the groups in the incidence of total and nocturnal hypoglycaemia. During the run-in phase, after adjusting for the incidence of hypoglycaemia, BIL showed a reduction of the hypoglycaemia rate. In addition, at the end of the study, patients treated with BIL evidenced a significant mean weight loss compared to those treated with IG, who gained weight (-0.6 to $+0.3$ kg). The bodyweight difference between subjects was 0.8 kg. A possible explanation for these findings could be the liver preferential effect of BIL suggested in the preclinical and phase 1 studies. Unfortunately, serum transaminases were higher but in the normal range in the BIL group. It was higher for males than females and remained elevated at 16 weeks [alanine transaminase (ALT) = 5.9 vs. 3.7 units/l, respectively] [22].

Another randomised control study using continuous glucose monitoring with BIL versus IG reported similar findings to Bergenstal et al. in T2D [23]. After 12 weeks using BIL there was less time with interstitial glucose <70 mg/dl (3.9 mmol/l) during the night and the whole 24-h period compared to those using IG. Finally, they concluded that both treatments presented similar mean glucose values, but the intra-day glucose deviation was lower for BIL vs. IG (1.00 ± 0.07 vs.

1.35 ± 0.16 mmol/l nocturnally and 2.03 ± 0.10 vs. 2.50 ± 0.18 mmol/l diurnally).

Phase 3 Studies

The most recent studies were intended to be an advance in the management of BIL. The IMAGINE studies were phase 3, randomised clinical trials designed to assess the efficacy of BIL compared with IG or NPH for control of HbA1c and blood glucose. These trials compared BIL and IG in three common T2D patient populations: insulin naive (IMAGINE-2), basal bolus (IMAGINE-4) and basal insulin alone or plus oral antihyperglycaemic medications (IMAGINE-5).

In all three T2D trials, BIL was superior to IG reducing HbA1c levels from baseline to the primary endpoint: IMAGINE-2 (reductions of 1.6% vs. 1.3% at 52 weeks), IMAGINE-4 (reductions of 1.7% vs. 1.5% at 26 weeks) and IMAGINE-5 (reductions of 0.82% vs. 0.29% at 26 weeks) [24–26]. In addition, a higher percentage of patients taking BIL reached the recommended target HbA1C of less than 7% compared to those taking IG at the primary endpoint: 58% vs. 43% in IMAGINE-2, 63% vs. 53% in IMAGINE-4 and 73% vs. 52% in IMAGINE-5 (see Fig. 1).

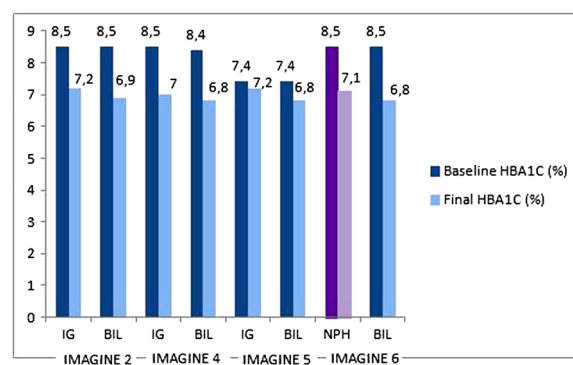


Fig. 1 Changes in HbA1C (%) in IMAGINE trials in type 2 diabetes patients. IG insulin glargine, BIL basal insulin lispro

In an additional phase 3 study (IMAGINE-6), patients taking BIL were compared with those taking NPH and experienced greater reductions in HbA1c (−1.7% vs. −1.4%). More BIL patients reached the ADA goals of less than 7% (63.1% vs. 43.4%) [27].

Important data from IMAGINE-2, IMAGINE-4 and IMAGINE-5 showed that patients taking BIL had a lower risk of nocturnal hypoglycaemia and lower glucose variability.

It is important to notice that this is the first phase 3 insulin development programme, where three of the six comparator trials were double-blinded (IMAGINE-2, IMAGINE-3, in type 1 diabetes patients, and IMAGINE-4) and powered to detect differences in nocturnal hypoglycaemia.

In IMAGINE-2 total hypoglycaemia rates were similar, BIL vs. IG: 1.16 vs. 1.21 events/patient per 30 days. Nocturnal hypoglycaemia rates were lower, BIL vs. IG: 0.3 vs. 0.4 events/patients per 30 days ($P < 0.001$). More patients had HbA1c $< 7.0\%$ without nocturnal hypoglycaemia with BIL, 27 vs. 16% ($P < 0.001$). Severe hypoglycaemia incidence was similar: BIL: 4%, IG: 6%. At the end of the study, the BIL insulin dose was higher, 45 vs. 41 U/kg ($P = 0.003$). IMAGINE-4 was conducted with electronic diaries, which collected daily insulin doses, hypoglycaemic events and self-monitored blood glucose results directly from the glucose metres. Less nocturnal hypoglycaemia (45% rate reduction) but higher daytime hypoglycaemia and no difference in severe events were reported. The BIL insulin dose was 11% higher. IMAGINE-5 had similar results with lower nocturnal and total hypoglycaemia rates and lower glucose variability.

Pooled analyses of four randomised controlled trials in T2D patients treated with

BIL compared to IG found no statistically significant difference in total hypoglycaemia rates between groups. Treatment with this novel basal insulin resulted in less nocturnal hypoglycaemia despite greater reductions in HbA1c and higher basal insulin doses [28]. The results of IMAGINE-6 also showed a significant reduction in nocturnal hypoglycaemia compared to NPH [27].

We have to point out that the higher doses of BIL compared to other basal insulins did not reflect a lack of potency of a unit of BIL and were consistent with improved glycaemic control with less nocturnal hypoglycaemia.

An analysis of weight loss observed in the phase 2 studies was conducted by Jacober et al. [29]. The weight loss reported in the randomised studies of BIL vs. IG in T2D [22] and type 1 diabetes was compared [30]. In the T2D study, a treatment difference of -0.84 kg was found with BIL compared to IG with a weight change of -0.6 kg and $+0.3$, respectively; weight loss was more common with BIL than IG (57% vs. 40%) and loss of $\geq 5\%$ of body weight was more frequent with BIL (5% vs. 0%). They did not find a correlation between the baseline body mass index and mean weight change. Frequency of hypoglycaemia events was not related with weight change using BIL; however, high insulin doses were associated with less weight loss with BIL and more weight gain with IG. Changes in body weight reported with BIL are similar to those seen with insulin detemir [31]. The weight-sparing mechanisms of insulin detemir may be related to the potential hepatoselectivity coupled with satiety signalling upon central nervous system insulin penetration. In case of BIL it was speculative and appeared most likely a function of the hepatoselective nature of the molecule; large hydrodynamics limit central nervous system penetration.

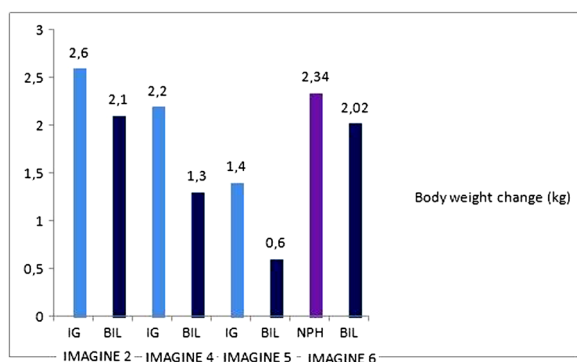


Fig. 2 Changes in body weight (kg) in IMAGINE trials in type 2 diabetes patients. *IG* insulin glargine, *BIL* basal insulin lispro

Further analysis from the IMAGINE trials reported less weight gain with BIL; the IMAGINE-2 weight increase was less with BIL than IG (2.1 vs. 2.6 kg, $P = 0.046$); the IMAGINE-4 mean treatment difference was -1.0 kg; IG gain was 2.2 kg vs. BIL 1.3 kg, and IMAGINE-5 mean treatment difference was -0.6 kg (CI 1.4–0.1). In IMAGINE-6, weight increase from baseline to week 26 was similar in the BIL group (2.0 kg) and the NPH group (2.3 kg). The mean treatment difference was -0.32 (see Fig. 2).

Safety and Tolerability

Primarily safety assessments compared BIL to IG. The proportions of T2D patients with serious adverse events (SAEs) were balanced between both basal insulins (10.4% BIL vs. 10.9% glargine). Severe hypoglycaemia was the most commonly reported SAE between T2D (BIL: 1.2%; glargine: 1.2%; $P = 0.604$).

Type 2 diabetes patients also reported treatment-emergent adverse events (TEAEs) in a similar proportion between the BIL and glargine groups (68.1% vs. 66.6%, $P = 0.829$). The most commonly reported events included nasopharyngitis, upper respiratory tract infection, back pain and headache. There were no differences in patients leaving the study

because of AEs or other safety-related reasons among these patients.

There was just a tendency to higher potential hypersensitivity events considered to be related to the study drug for BIL patients and this manifested as local allergic reactions and lipohypertrophy (1.46% and 0.14%; $P < 0.001$).

Hepatic findings have been analysed integrating analyses of T2D clinical trials comparing BIL to IG [32]. More patients taking BIL had a mean ALT increase from baseline at 52 weeks (mean difference between treatment groups: 7.4 IU/l).

A greater proportion of BIL patients had ALT levels higher than or equal to three times the upper limit of the normal range ($ALT \geq 3 \times ULN$) compared to IG (2.03% vs. 0.62%). These findings did not cause any severe drug-induced liver injury.

IMAGINE-2 reported ALT changes from 4.1 IU/l with BIL vs. -2.0 IU/l with IG, with $ALT \geq 3 \times ULN$: 2.3% vs. 0.6%. IMAGINE-4 reported ALT change from 7.6 IU/l vs. -0.6 IU/l and $ALT \geq 3 \times ULN$: 1.9% vs. 0.9%. IMAGINE-5 reported ALT change from baseline at 52 weeks: 8.3 IU/l vs. 0.4 IU/l with $ALT \geq 3 \times ULN$: 2.3% vs. 0.0%.

In IMAGINE-6, BIL showed ALT levels increasing from baseline while for NPH ALT decreased at 26 weeks (mean difference between treatment groups: 7.4 IU/l). However, the proportion of BIL patients who had ALT levels greater than or equal to three times the upper limit of the normal range ($ALT \geq 3 \times ULN$) was similar to that of patients treated with NPH insulin. ALT decreased after discontinuation of BIL and trended towards baseline in 91% of T2D patients during the studies.

These results demonstrated that insulin-naïve patients experienced slightly smaller increases in ALT (difference at 52 weeks: 6 IU/l, $P < 0.001$) compared to

patients who were previously treated with insulin (difference at 52 weeks: 8 IU/l, $P < 0.001$). There was a slight decrease in ALT among insulin-naive patients treated with IG (-2 IU/l); this was not seen in those T2D patients previously treated with insulin (Table 1).

Liver fat was measured in the IMAGINE-2 and IMAGINE-5 trials using magnetic resonance imaging in a subset of patients. Results in IMAGINE-2, with insulin-naive patients, showed liver fat was the same in patients treated with BIL, while patients taking IG decreased their liver fat from 12.7% at baseline to 10.0% at 52 weeks.

In IMAGINE-5, where patients were treated with basal insulin prior to entering the study, those patients taking BIL increased liver fat from 10.4% at baseline to 14.9% at 52 weeks, while it did not change significantly in patients taking IG. The mean difference between treatment groups at 52 weeks was 5.3% [32].

One possible explanation for the differences in liver fat content (LFC) in T2D patients who were insulin-naive vs. those who had been previously treated with insulin is that the increased LFC observed with BIL treatment may have been the result of withdrawal of conventionally acting insulin. The mechanism behind the LFC findings may also be related to the reduced peripheral insulin action of BIL treatment compared to IG [15, 21]. Changing from an IG that potently suppresses lipolysis to BIL, which has a weaker effect on lipolysis, may result in increased flux of free fatty acids (FFAs) to the liver. FFAs are known to be the main source of hepatic LFC, especially in patients with non-alcoholic fatty liver disease, but their implications remain unclear and need more investigation.

An analysis of six studies (phase 2 and phase 3 IMAGINE trials) of between 12- and 78-week duration concluded that BIL treatment had little effect on HDL-c and LDL-c in all patients with no significant difference with IG. Similar results were observed for systolic and diastolic blood pressure. Triglyceride levels between patients treated with BIL or IG were also examined and the differences found depended on whether patients had been previously treated with insulin (triglyceride levels remained the same with IG and increased 15% to 25% with BIL) [33, 34] (see Fig. 3).

It is interesting to note that these levels decreased to pre-study levels when the drug was discontinued [33, 34]. Between insulin-naive patients and those previously treated with insulin the decrease only occurred in the T2D patients previously treated with insulin. Insulin-naive patients showed a decrease in these parameters with IG and an increase in triglyceride levels in patients treated with BIL [33, 34].

Rates of major adverse cardiac events (cardiovascular death, non-fatal stroke, non-fatal myocardial infarction and hospitalisation due to unstable angina) were similar in the meta-analysis from six phase 2 and 3 studies. An analysis across all trials, including type 1 diabetes, showed that the rates of major adverse cardiovascular events among patients taking BIL and those taking IG or NPH were similar, with an observed hazard ratio below 1 and the upper limit of the 95% confidence interval below 1.4 [35].

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Table 1 Overview of IMAGINE studies and liver enzyme analysis

Study	N	Blinding	Prior therapy	Insulin therapy during trial	Duration	Cohort with MRI for liver fat content, N
<i>Type 1 diabetes (T1D)</i> —integrated for liver enzyme analysis						
Rosenstock J et al. (Phase 2)	IG: 68 BIL: 89	Open label	Insulin	Basal bolus	8 weeks	
IMAGINE-1 (Phase 3)	IG: 159 BIL:294	Open label	Insulin	Basal bolus	78 weeks	T1D integrated, IG: 64 BIL: 118
IMAGINE-3 (Phase 3)	IG: 449 BIL:663	Double blind	Insulin	Basal bolus	52 weeks	
<i>Type 2 Diabetes (T2D)</i> —integrated for liver enzyme analysis						
Bergental RM et al. (Phase 2)	IG: 93 BIL:195	Open label	OAMs, insulin	Basal only	12 weeks	
IMAGINE-4 (Phase 3)	IG: 677 BIL:691	Double blind	OAMs, Insulin	Basal bolus	26 weeks	
IMAGINE-2 (Phase 3)	IG: 535 BIL:1003	Double blind	OAMs,	Basal only	52 or 78 weeks	T2D insulin-naïve, IG: 56 BIL: 112
IMAGINE-5 (Phase 3)	IG: 159 BIL:305	Open label	OAMs, insulin	Basal only	52 weeks	T2D previously treated with insulin, IG: 50 BIL: 110

IG insulin glargine, BIL basal insulin lispro, OAMs oral antidiabetic medications

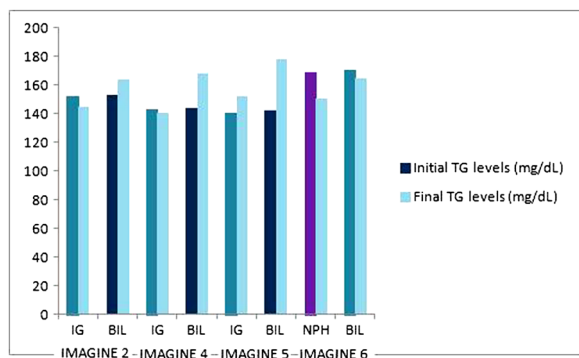


Fig. 3 Changes in triglyceride levels (mg/dl) in the IMAGINE trials in type 2 diabetes patients. *IG* insulin glargine, *BIL* basal insulin lispro, *NPH* neutral protamine Hagedorn, *TG* triglyceride levels

DISCUSSION

BIL's development demonstrated greater reduction in HbA1c, less nocturnal hypoglycaemia and less weight gain, but higher triglyceride levels compared to IG. This was explained by its reduced peripheral action and the hepato-preferential effect of BIL. Liver fat content stayed the same as baseline with BIL but decreased with IG.

The PD/PK profiles of BIL offered an advantage over human insulin and over other basal insulin analogues [13, 22, 26, 33, 34]. The potential hepatoselectivity of BIL resulted in reduced peripheral exogenous insulin delivery, a relatively greater suppression of hepatic glucose output and subsequent lower prandial insulin dose requirements. This could finally show an improvement in overall glucose control with an associated weight reduction effect.

BIL patients experienced weight loss, whereas IG and NPH patients gained. This can be explained by the lower peripheral action of BIL; patients changing from prior insulin therapy to BIL may experience transiently greater lipolysis, less lipogenesis, increased lipid oxidation and ultimately weight loss.

Overall, recent studies comparing BIL with IG found no differences with regard to the incidence of total hypoglycaemia. In each IMAGINE study analysed, BIL treatment met the key secondary objective of superiority to IG in the nocturnal hypoglycaemia rate (with multiplicity adjustment) [28].

For combined BIL versus IG, the mean rates of total hypoglycaemia and nocturnal hypoglycaemia were similar. When adjusted for baseline, the combined BIL group had a 48% rate reduction in nocturnal hypoglycaemia ($P = 0.021$). No patient experienced a severe hypoglycaemia event in any of the treatment groups [23, 27, 28]. Although major adverse events were similar across treatments, the ALT and AST level findings increased above the normal range with BIL ($P < 0.001$) [22, 23, 30] and the higher liver fat levels seen in patients previously treated with basal insulin led the company to cease production. This problem did not appear in insulin-naive patients.

In short, this insulin analogue showed PD properties superior to those of IG, currently the most widely used basal insulin, as it had less peak effect, a longer duration of action, less intra-subject variability and a hepatoselective action (fewer peripheral effects in subcutaneous tissue and muscle with comparable action in the liver). Clinical results showed superior efficacy with lower HbA1c values and a reduction in hypoglycaemia, in particular nocturnal hypoglycaemia. However, some safety findings warranted further investigation including a small but significant increase in triglycerides and transaminases. In addition, a number of patients experienced local reactions at the injection site. Eli Lilly, the developer of BIL, announced that further development of BIL will be abandoned because of the considerable time and investment that would be needed to clarify these issues.

CONCLUSION

BIL was an adequate basal insulin analogue with specific PK and PD properties. The bigger hydrodynamic size of BIL delayed absorption and reduced clearance, producing slower onset and longer duration of action so BIL was created to be once-daily dosing.

The results of the randomised controlled trial in T2D suggested that BIL was non-inferior to IG. After adjustment for baseline, BIL offered an advantage in terms of hypoglycaemia. Patient source data also suggested that BIL was associated with reduced fear of hypoglycaemia. BIL also held an advantage with regard to weight loss, but with increased circulating triglycerides possibly due to its preferential hepatic effect. Mean increases within normal range for serum ALT and AST levels were seen, possibly reflecting a hepatic adaptation reaction to the pegylated insulin that only occurs in patients previously treated with insulin but not in insulin naive-patients. Another explanation could be that pegylation had adverse effects on the liver. The reason for this increase was unknown and was the main reason for discontinuing its development.

BIL was the first and only basal insulin to demonstrate superior glycaemic benefits to IG, providing patients with T2D a lower risk of nocturnal hypoglycaemia and reduced glycaemic variability. Unfortunately, BIL's disadvantages concerning lipid values and liver function tests caused its failure as a product.

Since 1945 we have been treating patients via the peripheral route far from the mainly hepatic effect of exogenous hyperinsulinism. This practice has become a habit. The introduction of new insulins that better mimic the effect of endogenous insulin will not be easy, especially in patients who switch from insulins that necessarily have an

increased hepatic affinity and that have an impact on the liver physiology. More time is needed to determine whether it is better or worse to mimic the effect of endogenous insulin or to continue hyperinsulinisation of peripheral tissue. In our opinion, the discontinuation of pegylated insulin was a missed opportunity to examine this issue, yet there is still room for further refinements of basal insulin analogues.

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Data Availability. Data sharing is not applicable to this article as no data sets were generated or analysed during the current study.

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REFERENCES

- Vaag A, Lund SS. Insulin initiation in patients with type 2 diabetes mellitus: treatment guidelines, clinical evidence and patterns of use of basal vs premixed insulin analogues. *Eur J Endocrinol.* 2012;166:159–70.
- Chan JC, Gagliardino JJ, Baik SH, et al. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). *Diabetes Care.* 2009;32:227–33.
- Esposito K, Giugliano D. Current insulin analogues in the treatment of diabetes: emphasis on type 2 diabetes. *Expert Opin Biol Ther.* 2012;12:209–21.
- Owens David R, Matfin Glenn, Monnier Louis. “Basal insulin analogues in the management of diabetes mellitus: what progress have we made? *Diabetes Metab Res Rev.* 2014;30(2):104–19.
- Garber AJ. Will the next generation of basal insulins offer clinical advantages? *Diabetes Obes Metab.* 2014;16(6):483–91.
- Beals JM, Cutler GB, Doyle B, et al. Pegylated insulin lispro compounds. U.S. patent 20090312236 A1.
- Hansen RJ, Cutler GB, Vick A, et al. LY260541: leveraging hydrodynamic size to develop a novel basal insulin. *Diabetes.* 2012;61(Suppl. 1):A228.
- Madsbad S. LY2605541—a preferential hepato-specific insulin analogue. *Diabetes.* 2014;63(2):390–2.
- Hinds KD, Kim SW. Effects of PEG conjugation on insulin properties. *Adv Drug Deliv Rev.* 2002;54:505–30.
- Caparrotta1 TM, Evans M. PEGylated insulin Lispro, (LY2605541)—a new basal insulin analogue. *Diabetes Obesity Metab.* 2014. 16: 388–95.
- Knadler MP, Nguyen T-H, Campanale KM, De Veer MJ, Beals JM, Porter CJH. Lymphatic absorption of basal insulin peglispro (BIL) in sheep. *Diabetes.* 2015;64:A262.
- Kiselyov VV, Ding L, Wu GY, Moyers J. Analysis of basal insulin peglispro (BIL) binding kinetics with the use of a harmonic oscillator insulin receptor binding model. *Diabetes.* 2015;64:A264–5.
- Beals JM, Cutler GB, Vick A, et al. LY2605541: leveraging hydrodynamic size to develop a novel basal insulin. *Diabetologia.* 2012;55(Suppl. 1):S23.
- Linnebjerg H, Choi SL, Lam ECQ, Mace KF, Hodgson TS, Sinha VP. Pharmacokinetics (PK) of the novel, long-acting basal insulin LY2605541 in subjects with varying degrees of renal function. *Diabetologia.* 2012;55(Suppl. 1):S379.
- Moore MC, Smith MS, Mace KF, et al. Novel PEGylated basal insulin LY2605541 has a preferential hepatic effect on glucose metabolism. *Diabetes.* 2014;63(2):494–504.
- Sinha VP, Howey DC, Kwang Wei Soon D, et al. Single-dose pharmacokinetics and glucodynamics of the novel long-acting basal insulin LY2605541 in healthy subjects. *J Clin Pharmacol.* 2014;54:792–9.
- Garhyan P, Choi SL, Smith LaBell E, Knadler MP, Prince MJ. Clinical pharmacokinetics (PK) and renal elimination of basal insulin peglispro (BIL) and its polyethylene glycol (PEG)-containing products. *Diabetes.* 2015;64:LB22.
- Sinha VP, Heise T, Howey DC, Choi SL, Mace KF. Steady-state pharmacokinetics (PK) and glucodynamics (GD) of the novel, long-acting basal insulin LY2605541 dosed once-daily (QD) in patients with type 2 diabetes mellitus (T2DM). *Diabetes Obes Metab.* 2014;16:344–50.
- Kiss I, Arnold G, Böttcher S, Thrane M, Haahr H. Insulin degludec has similar pharmacokinetic properties in subjects with renal impairment and subjects with normal renal function. *Diabetes.* 2012;61(Suppl. 1):A296–7.
- Topp BG, Geiser JS, Soon DKW, et al. Effects of a novel PEGylated basal insulin, LY2605541, on hepatic glucose output and muscle glucose uptake: simulations based on data from

- euglycaemic clamp studies. *Diabetologia*. 2012;55(Suppl. 1):S376.
21. Henry RR, Mudaliar S, Ciaraldi TP, Armstrong DA, Burke P, Pettus J, Garhyan P, Choi SL, Jacober SJ, Knadler MP, Lam EC, Prince MJ, Bose N, Porksen N, Sinha VP, Linnebjerg H. Basal insulin peglispro demonstrates preferential hepatic versus peripheral action relative to insulin glargine in healthy subjects. *Diabetes Care*. 2014;37(9):2609–15.
 22. Bergenstal RM, Rosenstock J, Arakaki RF, et al. A randomized, controlled study of once-daily LY2605541, a novel long-acting basal insulin, vs. insulin glargine in basal insulin-treated patients with type 2 diabetes. *Diabetes Care*. 2012;35:2140–7.
 23. Bastyr EJ, Bergenstal RM, Rosenstock J, Prince MJ, Qu Y, Jacober SJ. Lower glucose variability and hypoglycaemia measured by continuous glucose monitoring with novel long-acting insulin LY2605541 versus insulin glargine. *Diabetologia*. 2012;55(Suppl. 1):S378.
 24. Davies MJ, Russell-Jones D, Selam J-L, Bailey TS, Kerényi Z, Luo J, Bue-Valleskey J, Iványi T, Hartman ML, Jacobson JG, Jacober SJ. Basal insulin peglispro vs insulin glargine in insulin-naïve type 2 diabetes: IMAGINE 2 randomized trial. *Diabetes Obes Metab*. 2016;18(11):1055–64.
 25. Blevins T, Pieber TR, Colón Vega G, Zhang S, Bastyr EJ III, Chang AM. Randomized double-blind clinical trial comparing basal insulin peglispro and insulin glargine, in combination with prandial insulin lispro, in patients with type 2 diabetes: IMAGINE 4. *Diabetes Obes Metab*. 2016;18(11):1072–80.
 26. Buse JB, Rodbard HW, Trescoli Serrano C, et al. A randomized clinical trial comparing basal insulin peglispro and insulin glargine in patients with type 2 diabetes mellitus previously treated with basal insulin: IMAGINE 5. *Diabetes Care*. 2016;39(92):100.
 27. Grunberger G, Chen L, Rodriguez A, Tinahones FJ, Jacober SJ, Bue-Valleskey J, On behalf of the IMAGINE 6 Investigators. A randomized clinical trial of basal insulin peglispro vs NPH in insulin-naïve patients with type 2 diabetes: the IMAGINE 6 trial. *Diabetes Obes Metab*. 2016;18(11):1034–42.
 28. Rosenstock J, Marre M, Qu Y, Zhang S, Bastyr EJ III, Prince MJ, Chang AM. Reduced Nocturnal Hypoglycemia with Basal Insulin Peglispro Compared to Insulin Glargine: Pooled Analyses of 5 Randomized Controlled Trials. *Diabetes Obes Metab*. 2016;18(11):1093–7.
 29. Jacober SJ, Rosenstock J, Bergenstal RM, Prince MJ, Qu Y, Beals JM. Contrasting weight changes with LY2605541, a novel long-acting insulin, and insulin glargine despite similar improved glycaemic control in type 1 diabetes and type 2 diabetes. *Diabetologia*. 2012;55(Suppl. 1):S377.
 30. Rosenstock J, Bergenstal RM, Blevins TC, et al. Better glycemic control and weight loss with the novel long-acting basal insulin LY2605541 compared with insulin glargine in type 1 diabetes: a randomized, crossover study. *Diabetes Care*. 2012;36:522–8.
 31. Dornhorst A, Luddeke H-J, Sreenan S, et al. Insulin detemir improves glycaemic control without weight gain in insulin-naive patients with type diabetes: subgroup analysis from the PREDICTIVE study. *Int J Clin Pract*. 2008;62:659–65.
 32. Cusi K, Sanyal AJ, Zhang S, Hoogwerf BJ, Chang AM, Jacober SJ, Bue-Valleskey JM, Higdon AN, Bastyr EJ III, Haupt A, Hartman ML. Different effects of basal insulin peglispro and insulin glargine on liver enzymes and liver fat content in patients with type 1 and type 2 diabetes. *Diabetes Obes Metab*. 2016;18(11):1050–8.
 33. Ginsberg H, Cariou B, Orchard T, Chen L, Luo J, Bastyr EJ III, Bue-Valleskey J, Chang AM, Ivanyi T, Jacober SJ, Jacobson JG, Hoogwerf BJ. Lipid changes during basal insulin peglispro, insulin glargine, or NPH treatment in six IMAGINE trials. *Diabetes Obes Metab*. 2016;18(11):1089–92.
 34. Ginsberg H, Cariou B, Orchard TJ, et al. Lipid changes during 26-wk treatment with the novel basal insulin peglispro (BIL) vs. insulin glargine (GL) or insulin NPH in 6 IMAGINE trials. *Diabetes*. 2015;64:A251.
 35. Hoogwerf BJ, Lincoff AM, Rodriguez A, Chen L, Qu Y. Major adverse cardiovascular events with basal insulin peglispro versus comparator insulins in patients with type 1 or type 2 diabetes: a meta-analysis. *Cardiovasc Diabetol*. 2016;15:78.