

## ORIGINAL ARTICLE

# Basal insulin peglispro versus insulin glargine in insulin-naïve type 2 diabetes: IMAGINE 2 randomized trial

M. J. Davies MD<sup>1</sup> | D. Russell-Jones MD<sup>2</sup> | J.-L. Selam MD<sup>3</sup> | T. S. Bailey MD<sup>4</sup> |  
 Z. Kerényi MD<sup>5</sup> | J. Luo PhD<sup>6</sup> | J. Bue-Valleskey MS<sup>6</sup> | T. Iványi MD<sup>7</sup> |  
 M. L. Hartman MD<sup>6</sup> | J. G. Jacobson PhD<sup>6</sup> | S. J. Jacober DO<sup>6</sup> | for the IMAGINE 2 Study  
 Investigators

<sup>1</sup>Department of Health Sciences, Diabetes Research Centre, University of Leicester, Leicester, UK

<sup>2</sup>Department of Endocrinology and Diabetes, Royal Surrey County Hospital, Guildford, UK

<sup>3</sup>Diabetes Research Center, Tustin, California

<sup>4</sup>AMCR Institute, Escondido, California

<sup>5</sup>Csepel Health Service, Budapest, Hungary

<sup>6</sup>Eli Lilly and Company, Indianapolis, Indiana

<sup>7</sup>Eli Lilly and Company, Budapest, Hungary

**Conflict of Interests:** M.J.D. has served on Advisory Panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis, has had Board Membership of AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis, has acted as a consultant for AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Novo Nordisk and Sanofi-Aventis. D.R.-J. has served on Advisory Panels for Eli Lilly and Company, Novo Nordisk and Sanofi-Aventis, and as a consultant for Eli Lilly and Company, Novo Nordisk and Sanofi-Aventis, and has received research support for Lilly, Novo Nordisk, Sanofi-Aventis and Sandoz. J.-L.S. has served as a speaker for Novo Nordisk and as a consultant for Sanofi-Aventis, and has received research support from Eli Lilly and Company. T.S.B. has acted as a consultant for Astra Zeneca, Bayer, Becton-Dickinson, Eli Lilly and Company, Medtronic, Novo Nordisk and Sanofi-Aventis, has received research support from Abbott, ACON, Bayer, Bristol Myers Squibb, Dexcom, GlaxoSmithKline, Halozyme, Insulet, Janssen, Lexicon, Lifescan, Eli Lilly and Company,

**Aims:** To compare, in a double-blind, randomized, multi-national study, 52- or 78-week treatment with basal insulin peglispro or insulin glargine, added to pre-study oral antihyperglycaemic medications, in insulin-naïve adults with type 2 diabetes.

**Material and methods:** The primary outcome was non-inferiority of peglispro to glargine with regard to glycated haemoglobin (HbA1c) reduction (margin = 0.4%). Six gated secondary objectives with statistical multiplicity adjustments focused on other measures of glycaemic control and safety. Liver fat content was measured using MRI, in a subset of patients.

**Results:** Peglispro was non-inferior to glargine in HbA1c reduction [least-squares (LS) mean difference: -0.29%, 95% confidence interval (CI) -0.40, -0.19], and had a lower nocturnal hypoglycaemia rate [relative rate 0.74 (95% CI 0.60, 0.91);  $p = .005$ ], more patients achieving HbA1c <7.0% without nocturnal hypoglycaemia [odds ratio (OR) 2.15 (95% CI 1.60, 2.89);  $p < .001$ ], greater HbA1c reduction ( $p < .001$ ), and more patients achieving HbA1c <7.0% [OR 1.97 (95% CI 1.57, 2.47);  $p < .001$ ]. Total hypoglycaemia rate and fasting serum glucose did not achieve statistical superiority. At 52 weeks, peglispro-treated patients had higher triglyceride (1.9 vs 1.7 mmol/L), alanine transaminase (34 vs 27 IU/L), and aspartate transaminase levels (27 vs 24 IU/L). LS mean liver fat content was unchanged with peglispro at 52 weeks but decreased 3.1% with glargine [difference: 2.6% (0.9, 4.2);  $p = .002$ ]. More peglispro-treated patients experienced adverse injection site reactions (3.5% vs 0.6%,  $p < .001$ ).

**Conclusions:** Compared with glargine at 52 weeks, peglispro resulted in a statistically superior reduction in HbA1c, more patients achieving HbA1c targets, less nocturnal hypoglycaemia, no improvement in total hypoglycaemia, higher triglyceride levels, higher aminotransferase levels, and more injection site reactions.

## KEYWORDS

basal insulin peglispro, BIL, insulin-naïve, insulin therapy, type 2 diabetes

Medtronic, Merck, Novo Nordisk, Orexigen, and Sanofi-Aventis, and has served on the Speaker's Bureau for Abbott, Insulet, Novo Nordisk and Sanofi-Aventis. J.L., J.B.-V., T.I., M.L.H., J.G.J., and S.J.J. are employees of and minor stock holders in Eli Lilly and Company. Z.K. reports no conflicts of interest.

**Corresponding Author:** Dr Scott J. Jacober, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN USA 46285 (sjacober@lilly.com).

## 1 | INTRODUCTION

Initiation of insulin treatment for type 2 diabetes is generally recommended to be basal insulin in combination with oral antihyperglycaemic medications.<sup>1-3</sup> Basal analogue insulins, such as insulin glargine, offer advantages over exogenous human basal insulin such as NPH,<sup>4</sup> but many patients have difficulty attaining recommended glycated haemoglobin (HbA1c) targets without weight gain and nocturnal hypoglycaemia.<sup>2</sup> In treat-to-target, comparative insulin trials, insulin dose is progressively increased until a prespecified glycaemic target is achieved or unacceptable hypoglycaemia occurs. In these trials, comparators routinely have similar HbA1c results, with other outcomes providing differentiation.<sup>5-7</sup> It is reasonable, therefore, to design an insulin comparator study by testing non-inferiority in HbA1c change as the primary objective and superiority in HbA1c change as a key secondary objective adjusted for multiplicity.

Endogenous insulin is secreted into the portal circulation, passing first to the liver where much of it is extracted. This results in higher levels in the liver than in peripheral target tissues (muscle and adipose). In contrast, subcutaneous administration of glargine and other conventional insulins results in similar portal and peripheral insulin levels. Compared with conventional insulins, a hepato-preferential insulin with reduced peripheral activity might manifest lower peripheral glucose uptake and lipogenesis and therefore may reduce hypoglycaemia and weight gain.<sup>8</sup>

Basal insulin peglispro is a PEGylated molecule<sup>9</sup> with a flat pharmacokinetic and glycodynamic profile;<sup>10</sup> recent research has shown it has a hepato-preferential action which is attributable to reduced peripheral effects.<sup>11,12 (fig.2), 13</sup> High molecular weight molecules (e.g. lipoproteins) pass readily through the fenestrations of the hepatic sinusoidal endothelium, but are restricted by the continuous endothelium of the systemic circulation.<sup>14,15</sup> The reduced peripheral action of peglispro may be related to reduced availability to muscle and adipose tissue.

In the present phase III, double-blind study, we compared peglispro with insulin glargine, a conventional basal insulin, in insulin-naïve patients with type 2 diabetes.

## 2 | METHODS

This phase III, double-blind, randomized trial was approved by local Ethical Review Boards, and was conducted in accordance with Good Clinical Practice guidelines of the International Conference on Harmonisation. Investigators at 197 sites in 23 countries participated (Appendix S1, File S1, Supporting Information). All patients provided

written informed consent. Race/ethnicity was self-reported by patients with fixed categories to demonstrate inclusivity of minorities according to sponsor policy. The trial was registered at ClinicalTrials.gov: number NCT01435616. Data were analysed according to the predefined statistical analysis plan.

Adults with type 2 diabetes (World Health Organization criteria)<sup>16</sup> were eligible if their duration of diabetes was  $\geq 1$  year, they had received stable doses of  $\geq 2$  oral antihyperglycaemic medications, had HbA1c levels of 7.0%-11.0%, and had a body mass index  $\leq 45.0$  kg/m<sup>2</sup> (additional criteria, Appendix S2, File S1). Patients were randomized 2:1 to treatment with peglispro or glargine using a computer-generated random sequence. The study design is shown in Figure S1, File S1. Per protocol, the first 920 patients randomized were enrolled for 78-week treatment, to gain safety data during longer exposure to peglispro. All subsequently randomized patients were enrolled for 52-week treatment. The primary study endpoint was 52 weeks (Figure S1, File S1). Randomization was completed at the country level, with a block size of six and was stratified on baseline HbA1c ( $\leq 8.5\%$  or  $>8.5\%$ ), LDL cholesterol ( $<$  or  $\geq 2.6$  mmol/L [100 mg/dL]), and baseline sulphonylurea or meglitinide use.

Study insulin was blinded using vials that allowed visual inspection of the insulin but hid all differentiating vial features. Unblinded analyses were periodically performed for safety monitoring purposes by an independent Data Monitoring Committee, which was external to the sponsor, the investigators and the manuscript authors. The initial basal insulin dose was 10 units, which was increased according to a treat-to-target algorithm (Table S1, File S1).<sup>17</sup> Glycaemic goals were attained solely by insulin adjustment; oral antihyperglycaemic medication doses were altered only for non-glycaemic side effects and safety.

Patients were encouraged to perform self-monitored blood glucose (SMBG) tests, using a study-provided glucose meter, daily before breakfast and whenever hypoglycaemia (defined in Appendix S3, File S1) was suspected. Two six-point SMBG profiles (fasting, pre-midday meal, pre-evening meal, bedtime, ~03:00 hours, and next-day fasting) were performed on two non-consecutive days during the week before prespecified visits.

From randomization to week 12, investigators were blinded to lipid values, and adjustments in lipid-lowering therapy/dose were prohibited. Adjustments were permitted after week 12, when new lipid-lowering therapy (except for bile acid sequestrants and niacin preparations) could be initiated. Patients could be discontinued from study insulin if their triglycerides or hepatic laboratory values reached predetermined levels, or for other reasons (Appendix S4, File S1).

We used MRI to assess liver fat content and abdominal visceral to subcutaneous fat ratios at baseline, week 26 and week 52 in a

patient subgroup from preselected investigator sites in the USA and Puerto Rico with nearby availability of MRI facilities. Free fatty acids were measured in this and another substudy. Participation in the substudies was optional for patients at those sites and required additional informed consent.

## 2.1 | Statistical analyses

The primary objective was to test for non-inferiority of peglispro to glargine for HbA1c change from baseline to week 52. The recommended non-inferiority margin of 0.4%<sup>18</sup> was used. To control overall Type 1 error at  $\alpha = .05$ , a sequential gatekeeping strategy<sup>19,20</sup> was used to adjust for multiplicity for the primary and six key (gated) secondary outcomes. While most traditional methods control the overall type 1 error by splitting the  $\alpha$  value, the gatekeeping strategy controls the overall type 1 error by fixing the order of testing with the same  $\alpha$  level. If a prior test fails ( $p > .05$ ), all subsequent tests will be deemed non-significant regardless of the nominal  $p$  values. When prespecified secondary outcomes are powered appropriately and adjusted for multiple comparisons, these outcomes carry the same validity as a primary outcome. The six gated secondary objectives (in order of hypothesis testing) were to demonstrate peglispro was statistically superior at, or during, the first 52 weeks for: nocturnal hypoglycaemia rate; patients with HbA1c < 7.0% without nocturnal hypoglycaemia; HbA1c reduction; patients with HbA1c < 7.0%; total hypoglycaemia rate; and fasting serum glucose (central laboratory). The gated objective was met if all preceding objectives were met and the gated objective reached statistical significance at  $\alpha = .05$ . No multiplicity adjustments were conducted for non-gated hypothesis tests, or for values collected at week 78. These tests may therefore only be interpreted as exploratory.

A total of 1516 randomized patients provided  $\geq 99\%$  statistical power to demonstrate non-inferiority of BIL to glargine for HbA1c change from baseline to week 52 with the assumption of no difference between treatments, 84% power to demonstrate superiority in HbA1c reduction, and 88% power to demonstrate superiority in nocturnal hypoglycaemia rate.

The primary objective of the substudy on liver fat was to compare peglispro and glargine treatment for change in percent liver fat content from baseline to week 52. A sample size of 195 randomized patients, with 156 completing 52 weeks of treatment, was calculated to provide 80% statistical power to detect a 3.3% difference between the two treatment groups.

Analyses (conducted using SAS 9.2, Cary, North Carolina) were based on all randomized patients who took  $\geq 1$  dose of study drug. A mixed-model repeated measures approach was used to analyse HbA1c, other continuous variables of glycaemic measures, and weight. HbA1c < 7.0%, and HbA1c < 7.0% with no nocturnal hypoglycaemia were compared between treatments using a logistic regression (for data at week 52 with last observation carried forward) as the primary analysis and a longitudinal logistic regression as a sensitivity analysis. The number of hypoglycaemic events during a specific period was compared between treatments using a negative binomial regression<sup>21–23</sup> by adjusting for baseline sulphonylurea/meglitinide use and pre-randomization (baseline) hypoglycaemia rate. In addition,

**TABLE 1** Baseline demographics

	Glargine (N = 535)	Peglispro (N = 1003)
Men, n (%)	308 (57.6)	550 (54.8)
Race, n (%)		
American-Indian or Alaskan Native	15 (2.8)	24 (2.4)
Asian	12 (2.2)	25 (2.5)
Black or African-American	34 (6.4)	68 (6.8)
Multiple	3 (0.6)	8 (0.8)
Native Hawaiian or Other Pacific Islander	2 (0.4)	3 (0.3)
White	469 (87.7)	875 (87.2)
Hispanic or Latino ethnicity, n (%)	96 (17.9)	201 (20.0)
Age, years, mean (s.d.)	59.4 (9.8)	58.8 (9.9)
Weight, kg, mean (s.d.)	90.9 (18.7)	91.0 (18.4)
Body mass index, kg/m <sup>2</sup> , mean (s.d.)	32.0 (5.2)	32.2 (5.3)
Duration of diabetes, years, mean (s.d.)	11.0 (6.6)	10.6 (6.1)
Hypertension, n (%)	440 (82.2)	803 (80.1)
Patients using lipid-lowering medications at baseline, n (%)		
Lipid-lowering medication	332 (62.1)	608 (60.6)
Statins	305 (57.0)	552 (55.0)
Non-statin lipid-lowering medications <sup>1</sup>	88 (16.4)	151 (15.1)
Pre-study oral antihyperglycaemic medications, n (%)		
Biguanides	517 (96.6)	969 (96.6)
Pioglitazone	51 (9.5)	100 (10.0)
Sulphonylureas	448 (83.7)	839 (83.6)
Oral antihyperglycaemic medication use during treatment, n (%)		
None	2 (0.4)	4 (0.4)
One	12 (2.2)	26 (2.6)
Two	420 (78.5)	779 (77.7)
Three	95 (17.8)	188 (18.7)
Four or more	6 (1.1)	6 (0.6)

s.d., standard deviation.

<sup>1</sup> Some patients were receiving treatment with both statin and non-statin lipid-lowering medications.

a statistical joint modelling on HbA1c and basal insulin dose was conducted to evaluate the HbA1c reduction per 10 units of basal insulin (peglispro vs glargine) from baseline and week 52. Major adverse cardiac events (MACE) and MACE plus unstable angina with hospitalization (MACE+) were analysed using a Cox proportional hazard model and log-rank test.

Between-group differences are presented as least-squares (LS) mean differences with 95% confidence intervals (CIs). Baseline and endpoint values are presented as LS mean with 95% CIs unless otherwise indicated.

## 2.2 | Role of the funding source

Eli Lilly and Company was involved in the study design and protocol development, provided logistical support, and played a role in the conduct of the study and collection of the data. Data were evaluated jointly by the authors and the sponsor. All authors participated in

TABLE 2 Assessments at baseline, and after 52 and 78 weeks of treatment<sup>1</sup>

	Baseline			52 weeks			78 weeks			
	Glargine (N = 535)	Peglispro (N = 1003)	Glargine (N = 535)	Peglispro (N = 1003)	Glargine (N = 535)	Peglispro (N = 1003)	Glargine (N = 315)	Peglispro (N = 605)	LS meanΔ/RR/PR (95%CI)	p value
<b>Primary outcome</b>										
HbA1c <sup>2</sup> , %	8.5	8.5	7.2	6.9	6.9	7.2	7.1	7.1	-0.13 <sup>3</sup> (-0.27, 0)	.049
HbA1c <sup>2</sup> , mmol/mol	69	69	55	52	52	55	54	54	-1.47 <sup>3</sup> (-2.93, -0.01)	
<b>Gated secondary outcomes</b>										
Nocturnal hypoglycaemia rate <sup>4</sup> , events/patient/30 days	0.06	0.06	0.40	0.30	0.30	0.40	0.37	0.20	0.55 <sup>5</sup> (0.37, 0.82)	.004
Patients with HbA1c <7.0% and no nocturnal hypoglycaemia, n (%)	13 (2.5)	29 (2.9)	80 (15.3)	259 (26.2)	259 (26.2)	80 (15.3)	38 (12.3)	131 (22.1)	2.30 <sup>6</sup> (1.53, 3.46)	<.001
Patients with HbA1c <7.0%, n (%)	13 (2.5)	30 (3.0)	224 (42.8)	570 (57.6)	570 (57.6)	224 (42.8)	130 (42.1)	303 (51.0)	1.51 <sup>6</sup> (1.13, 2.03)	.006
Total hypoglycaemia rate <sup>4</sup> , events/patient/30 days	0.26	0.31	1.21	1.16	1.16	1.21	0.99	0.69	0.70 <sup>5</sup> (0.53, 0.91)	.008
Fasting serum glucose <sup>2,7</sup> , mg/dL	176	178	120	115	115	120	126	119	-6.81 <sup>3</sup> (-12.65, -0.96)	.023
<b>Non-gated outcomes</b>										
Fasting blood glucose (SMBG) <sup>2</sup> , mg/dL	169	170	112	113	112	112	110	114	4.00 <sup>3</sup> (0.58, 7.42)	.022
Within-day glycaemic variability <sup>2,8</sup> , mg/dL	36	36	34	31	31	34	33	30	-2.89 <sup>3</sup> (-5.03, -0.76)	.008
Between-day glycaemic variability <sup>2,9</sup> , mg/dL	21	22	17	16	16	17	16	15	-1.01 <sup>3</sup> (-2.85, 0.83)	.28
Weight <sup>2</sup> , kg	90.9	91.1	93.8	93.3	93.8	93.8	93.7	93.3	-0.35 <sup>3</sup> (-0.98, 0.28)	.28
Total hypoglycaemia incidence <sup>10</sup> , n (%)	28 (5.2)	53 (5.3)	427 (79.8)	771 (77.0)	771 (77.0)	427 (79.8)	155 (59.6)	258 (52.1)	0.72 <sup>6</sup> (0.53, 0.97)	.03
Documented symptomatic total hypoglycaemia rate <sup>4</sup> , events/patient/30 days	0.06	0.13	0.50	0.51	0.51	0.50	0.46	0.31	0.69 <sup>5</sup> (0.47, 1.01)	.053
Documented symptomatic total hypoglycaemia incidence <sup>10</sup> , n (%)	8 (1.5)	22 (2.2)	313 (58.5)	579 (57.8)	579 (57.8)	313 (58.5)	94 (36.2)	167 (33.7)	0.86 <sup>6</sup> (0.62, 1.19)	.36
Documented nocturnal hypoglycaemia rate <sup>4</sup> , events/patient/30 days			0.20	0.12	0.12	0.20	0.21	0.07	0.32 <sup>5</sup> (0.19, 0.54)	<.001
Nocturnal hypoglycaemia incidence <sup>10</sup> , n (%)	8 (1.5)	12 (1.2)	320 (59.8)	489 (48.9)	489 (48.9)	320 (59.8)	96 (36.9)	131 (26.5)	0.60 <sup>6</sup> (0.44, 0.83)	.002
Documented symptomatic nocturnal hypoglycaemia incidence <sup>10</sup> , n (%)	1 (0.2)	5 (0.5)	213 (39.8)	309 (30.9)	309 (30.9)	213 (39.8)	55 (21.2)	74 (14.9)	0.64 <sup>6</sup> (0.43, 0.95)	.027
Non-nocturnal hypoglycaemia rate <sup>4</sup> , events/patient/30 days	0.20	0.24	0.81	0.86	0.86	0.81	0.63	0.48	0.76 <sup>5</sup> (0.55, 1.05)	.101
Non-nocturnal hypoglycaemia incidence <sup>10</sup> , n (%)	22 (4.1)	47 (4.7)	382 (71.4)	772 (72.1)	772 (72.1)	382 (71.4)	125 (48.1)	224 (45.3)	0.87 <sup>6</sup> (0.64, 1.18)	.37
Severe hypoglycaemia rate <sup>11</sup> , events/100 patient years	0	0	3.34	0.40	0.40	3.34	0	0	-	-
Severe hypoglycaemia incidence <sup>10</sup> , n (%)	0	0	3 (0.6)	4 (0.4)	4 (0.4)	3 (0.6)	0	0	-	-
ALT <sup>2</sup> , IU/L	29	30	27	34	34	27	27	33	5.22 <sup>3</sup> (3.50, 6.94)	<.001
AST <sup>2</sup> , IU/L	24	24	24	27	27	24	23	27	3.51 <sup>3</sup> (2.30, 4.72)	<.001

TABLE 2 Continued

	Baseline		52 weeks			78 weeks				
	Glargine (N = 535)	Peglispro (N = 1003)	Glargine (N = 535)	Peglispro (N = 1003)	LS mean $\Delta$ /RR/OR (95%CI)	p value	Glargine (N = 315)	Peglispro (N = 605)	LS mean $\Delta$ /RR/OR (95%CI)	p value
LDL cholesterol <sup>2,7</sup> , mg/dL	96	98	99	99	-0.32 <sup>3</sup> (-3.08, 2.43)	.82	98	97	-0.99 <sup>3</sup> (-4.64, 2.66)	.59
HDL cholesterol <sup>2,7</sup> , mg/dL	48	47	46	46	-0.09 <sup>3</sup> (-0.79, 0.61)	.81	45	44	-0.61 <sup>3</sup> (-1.50, 0.28)	.181
Triglycerides <sup>2,7</sup> , mmol/L	1.80	1.81	1.70	1.90	0.20 <sup>3</sup> (0.11, 0.29)	<.001	1.73	1.96	0.23 <sup>3</sup> (0.11, 0.35)	<.001
Patients with anti-pegalispro antibodies <sup>12</sup> , n (%)	82 (15.9)	158 (16.0)	116 (26.4)	267 (31.9)		.046	68 (28.2)	144 (32.6)		.26
Patients with treatment-emergent antibody response <sup>12</sup>			87 (19.8%)	230 (27.5)	1.56 <sup>6</sup> (1.18, 2.08)	.002	53 (22.0)	117 (26.5)	1.27 <sup>6</sup> (0.90, 1.81)	.177
Liver fat content <sup>2,13</sup> , %	12.73	13.25	9.97	12.55	2.58 <sup>3</sup> (0.94, 4.21)	.002				
Free fatty acids <sup>2,14</sup> , mmol/L	0.59	0.64	0.46	0.55	0.09 <sup>3</sup> (0.02, 0.16)	.011				

LS mean $\Delta$ , difference in LS means, RR, relative risk.

<sup>1</sup> Primary objectives and all gated objectives specified 52-week time point; continuous variables were analyzed using mixed model repeated measures. Hypoglycaemia rate was analysed using negative binomial regression. Hypoglycaemia incidence was analysed using logistic regression.

<sup>2</sup> LS mean.

<sup>3</sup> LS mean difference.

<sup>4</sup> Group mean; values shown are for baseline, baseline to week 52, and weeks 52-78. For definitions of hypoglycaemia, see Appendix S3, File S1, Supporting Information.

<sup>5</sup> Relative rate.

<sup>6</sup> OR.

<sup>7</sup> From central laboratory.

<sup>8</sup> Within-day glycaemic variability is based on the standard deviation (s.d.) of SMBG measures over 24 hours.

<sup>9</sup> Between-day glycaemic variability is based on the s.d. of fasting blood glucose for the preceding 7 days.

<sup>10</sup> Number of patients (%), values shown are for baseline, baseline to week 52, and weeks 52-78. For definitions of hypoglycaemia, see Appendix S3, File S1, Supporting Information.

<sup>11</sup> Mean, values shown are for baseline, baseline to week 52, and weeks 52-78.

<sup>12</sup> Number of patients (%). Patients with treatment-emergent anti-pegalispro antibody response are patients with change from baseline to post-baseline in the anti-pegalispro antibody level either from undetectable to detectable, or from detectable to a value with at least 130% relative increase from baseline.

<sup>13</sup> For liver fat content, N = 56 for glargine, N = 112 for peglispro. Not measured after week 52.

<sup>14</sup> For free fatty acids, N = 56 for glargine, N = 115 for peglispro at baseline. Not measured after week 52.

writing the manuscript, which was drafted primarily by two of the sponsor-employed authors. The sponsor participated in review and approval of the manuscript. The sponsor had no veto rights regarding the decision to submit the manuscript for publication.

### 3 | RESULTS

A total of 1538 patients were enrolled in the trial: 920 were enrolled to receive 78-week treatment, and 618 to receive 52-week treatment. A subset of patients ( $n = 168$ ) also agreed to participate in the MRI substudy. Patient disposition (Figure S2, File S1) and baseline characteristics (Table 1) were similar for peglispro-treated ( $n = 1003$ ) and glargine-treated ( $n = 535$ ) patients. Over the course of the study, patients had 667 patient-years exposure to glargine, and 1248 patient-years exposure to peglispro. Two patients were unblinded because of tampered vials and discontinued study drug.

#### 3.1 | Primary outcome

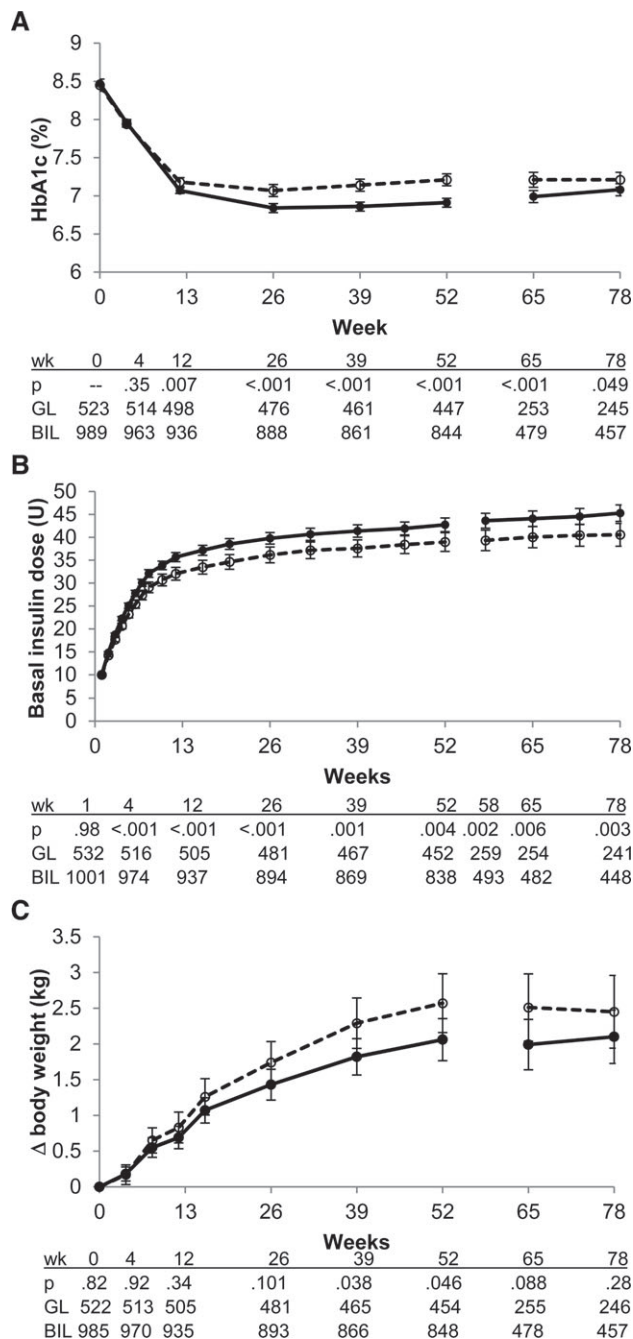
From baseline to week 52, HbA1c decreased by 1.6% to an LS mean of 6.9% in peglispro-treated patients and by 1.3% to an LS mean of 7.2% in glargine-treated patients ( $p < .001$ ; Figure 1A). The LS mean difference was  $-0.29\%$  (95% CI  $-0.40, -0.19$ ). The upper limit of the 95% CI was less than the prespecified non-inferiority margin of 0.4%, therefore the primary study objective, non-inferiority of peglispro compared with glargine for HbA1c change at week 52, was achieved.

#### 3.2 | Gated secondary outcomes

For the interval from baseline to week 52, nocturnal hypoglycaemia rate was lower with peglispro than glargine with multiplicity adjustment (0.30 vs 0.40 events/patient/30 days); relative rate 0.74 (95% CI 0.60, 0.91);  $p = .005$  (Table 2). At 52 weeks, peglispro treatment reduced HbA1c more than glargine (1.6% vs 1.3%;  $p < .001$ ), because the 95% CI upper limit was  $<0$  and the  $p$  value  $<.05$ ; therefore, the multiplicity adjustment<sup>19</sup> for this gated objective was met. Additionally, more peglispro-treated than glargine-treated patients achieved the HbA1c  $<7\%$  target without nocturnal hypoglycaemia [26% vs 15%; odds ratio (OR) 2.15 (95% CI 1.60, 2.89);  $p < .001$ ] and achieved HbA1c  $<7\%$  [58% vs 43%; OR 1.97 (95% CI 1.57, 2.47);  $p < .001$ ]. Total hypoglycaemia during the first 52 weeks was not statistically different between treatments and therefore, due to the gating strategy, the difference in fasting serum glucose between peglispro and glargine at week 52 [115 vs 120 mg/dL, LS mean difference  $-5$  (95% CI  $-9, -1$ ); Table 2] should be considered non-significant.

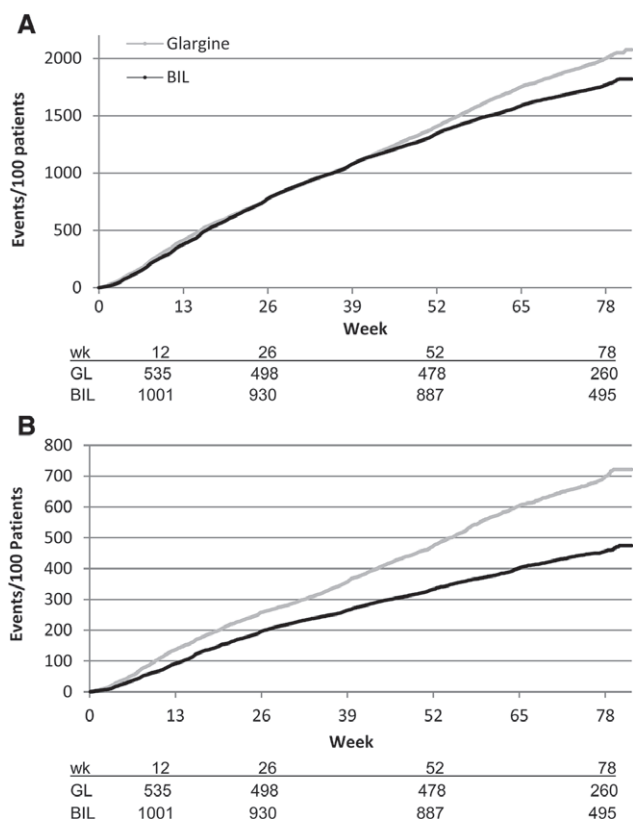
#### 3.3 | Non-gated secondary outcomes

The non-gated secondary outcomes were not adjusted for multiplicity and are considered exploratory. SMBG profiles were similar between treatments at week 52 except blood glucose was lower for peglispro at pre-midday and pre-evening meals (Figure S3, File S1). Within-day glycaemic variability was lower with peglispro [1.7 vs 1.9 mmol/L (31 vs 34 mg/dL); LS mean difference:  $-0.15$  mmol/L (95% CI  $-0.25, -0.05$ );



**FIGURE 1** HbA1c, insulin dose and weight. Graphs show values for basal insulin peglispro (BIL; solid line, black circles) and insulin glargine (GL; dashed line, white circles). Week 0 was the randomization time point. The gap between values for weeks 52 and 65 indicates that these values were derived from different populations. Data up to week 52 are for the entire population ( $N = 1538$ ); data thereafter are for the 78-week cohort ( $N = 920$ ). Data were analysed using mixed-model repeated measures. LS mean values are shown. Error bars indicate 95% CIs;  $p$ -values for between-group differences and the number of patients assessed in each treatment group are shown at key time points below each graph. HbA1c (%; panel A), insulin dose (U; panel B), change in weight from baseline (kg; panel C).

$p = .003$ ], as was between-day fasting glycaemic variability [0.9 vs 1.0 mmol/L (16 vs 17 mg/dL); LS mean difference:  $-0.08$  mmol/L (95% CI  $-0.15, -0.01$ );  $p = .02$ ; Table 2]. Fasting blood glucose from SMBG at week 52 was similar in the two treatment groups [peglispro:



**FIGURE 2** Cumulative rates of hypoglycaemia. (A) Total hypoglycaemia. (B) Nocturnal hypoglycaemia. For both panels, “lines” are continuous data points indicating rates of hypoglycaemia throughout the study. Black lines indicate basal insulin peglispro (BIL). Grey lines indicate insulin glargine (GL). The number of episodes of hypoglycaemia per 100 patients was calculated and plotted against actual time, rather than visit dates. Because variability was allowed in the timing of study visits, hypoglycaemia was recorded up to 82 weeks. No inferential statistical analyses were conducted. The number of patients assessed in each treatment group is shown at key time points below each graph.

6.3 mmol/L (113 mg/dL); glargine: 6.2 mmol/L (112 mg/dL); LS mean difference: 0.03 mmol/L (95% CI -0.12, 0.18);  $p = .07$ ; Table 2].

At week 52, insulin dose was greater for peglispro than glargine [0.45 vs 0.42 U/kg, difference: 0.03 U/kg (95% CI 0, 0.06);  $p = .02$ ; Figure 1B]. At week 52, weight increase was significantly less with peglispro than glargine [2.06 vs 2.57 kg; LS mean difference: -0.51 kg (95% CI -1.01, -0.01);  $p = .046$ ; Figure 1C]. Additionally, with statistical joint modelling on HbA1c and basal insulin dose, HbA1c reduction per 10 units of basal insulin from baseline to week 52 was 0.36% for peglispro and 0.33% for glargine, and HbA1c reduction per unit/kg of basal insulin from baseline to week 52 was 3.39% for peglispro and 3.03% for glargine, suggesting that peglispro may be at least as potent as glargine on a unit basis.

Total, non-nocturnal, severe, and documented symptomatic total hypoglycaemia were similar between treatments during 52-week treatment (Table 2). For the 78-week cohort, total hypoglycaemia rate and incidence from weeks 52 to 78 were significantly lower for peglispro. Nocturnal hypoglycaemia was lower with peglispro throughout the study (Table 2). The numbers of cumulative total and nocturnal hypoglycaemia events per 100 patients over time are shown in Figure 2.

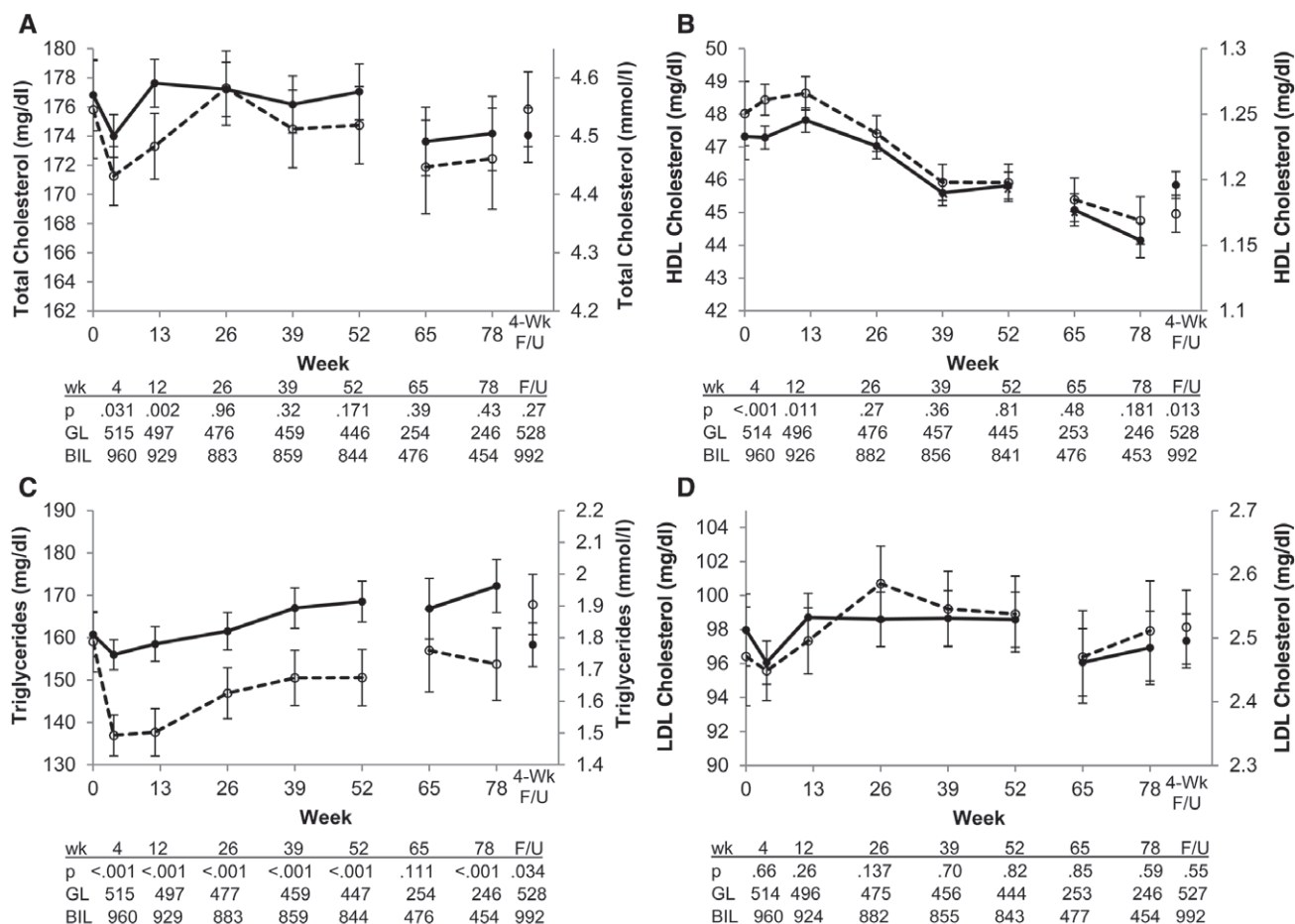
### 3.4 | Adverse events and other safety assessments

Treatment-emergent serious and non-serious adverse events with peglispro and glargine were mostly similar (Table S2, File S1). More peglispro-treated patients experienced injection site reactions (3.5% vs 0.6%;  $p < .001$ ), mostly lipohypertrophy (2.1% vs 0.4%;  $p = .007$ ). Fewer peglispro-treated patients reported neoplasms (2.5% vs 4.7%;  $p = .02$ ); no single neoplasm type had clinically meaningful between-group differences. There were no significant differences between treatments for vital signs (Table S3, File S1). Adjudicated cardiovascular events were similar between peglispro- and glargine-treated patients [MACE (death due to cardiovascular cause, non-fatal myocardial infarction and non-fatal stroke): 1.9% vs 1.5%, hazard ratio 1.23 (95% CI 0.54, 2.79); MACE+: 2.0% vs 2.1%, hazard ratio 0.95 (95% CI 0.46, 1.99); Table S4, File S1].

At week 52, there was no statistically significant difference between peglispro and glargine for total cholesterol, LDL cholesterol or HDL cholesterol (Figure 3). For glargine-treated patients, triglycerides decreased sharply at week 4, and then increased gradually (Figure 3C). For peglispro-treated patients, triglycerides did not change from baseline to week 26, and were above baseline at weeks 52 and 78. In addition, triglyceride levels were higher with peglispro than with glargine at week 4 and beyond. At week 52, the difference was 0.2 mmol/L (95% CI 0.11, 0.29) [18 mg/dL (95% CI 9.7, 26.2); Table 2].

No change in lipid-lowering medications was permitted by the protocol during the first 12 weeks of the study although six (1.1%) glargine-treated patients and 12 (1.2%) peglispro-treated patients had changes in their medications or alterations of the dose. During the first 52 weeks, 42 (7.9%) glargine-treated patients and 74 (7.4%) peglispro-treated patients had changes made to their lipid-lowering medications. Time to first change of lipid-lowering medication was similar in the two groups [hazard ratio 1.05 (95% CI 0.72, 1.51);  $p = .77$ ]. Comparisons of lipids between the two treatments are consistent whether or not the data collected after change for lipid-lowering medication are included.

Serum alanine transaminase (ALT) increased from baseline to week 52 in peglispro-treated patients ( $p < .001$ ), with no further increase at week 78, whereas ALT decreased from baseline in glargine-treated patients ( $p < .001$ ; Table 2; Figure S4, File S1). Differences in ALT between peglispro and glargine were 6 IU/L (95% CI 4.8, 7.5) and 5 IU/L (95% CI 3.5, 6.9) at weeks 52 and 78, respectively. Aspartate transaminase (AST) did not change with glargine, but with peglispro it was higher than baseline at 12 weeks and beyond. At weeks 52 and 78, differences in AST between peglispro and glargine were 3 IU/L (95% CI 2.5, 4.4) and 4 IU/L (95% CI 2.3, 4.7), respectively. Twenty-three (2.3%) peglispro-treated and three (0.6%) glargine-treated patients ( $p = .01$ ) had increases in ALT to  $\geq 3\times$  the upper limit of normal (ULN); one of these peglispro-treated patients also had a corresponding total bilirubin elevation  $>2\times$  ULN associated with an adverse event of biliary colic that was considered unrelated to study drug. By Hy's law (ALT or AST  $>3\times$  ULN and total bilirubin  $>2\times$  ULN without findings of cholestasis and without any other apparent cause),<sup>24</sup> there was no evidence of acute, severe drug-induced liver injury.



**FIGURE 3** Change in lipids over time. A. Total Cholesterol, B. HDL Cholesterol, C. Triglycerides, 4. LDL Cholesterol Graphs show values for basal insulin peglispro (BIL; solid line, black circles) and insulin glargine (GL; dashed line, white circles). The gap between values for weeks 52 and 65 indicates these values are derived from different populations. Data up to week 52 are for the entire population (N = 1538); data for weeks 65 and 78 are for the 78-week cohort (N = 920). Data were analysed using mixed-model repeated measures. LS mean values are shown. Error bars indicate 95% CIs; p values for between-group differences and the number of patients assessed in each treatment group are shown at key time points below each graph.

Liver fat content measured by MRI (Table 2) did not change significantly from baseline to week 52 for peglispro-treated patients (n = 94, -0.6%; p = 0.23); however, in glargine-treated patients (n = 47), liver fat content decreased by 3.1% (p < .001) at week 52, resulting in a difference from peglispro of 2.6% (95% CI 0.9, 4.2). LS mean (standard error) abdominal visceral to subcutaneous fat ratios were similar [peglispro: 0.66 (0.01); glargine: 0.65 (0.02); LS mean difference: 0.01 (95% CI -0.03, 0.05); p = 0.61]. Free fatty acid levels decreased significantly from baseline to 52 weeks in both groups [peglispro (n = 115): -0.08 mmol/l, p < .001; glargine (n = 56): -0.17 mmol/L; p < .001] and were higher in the peglispro group [LS mean difference 0.09 mmol/L (95% CI 0.02, 0.16); p = .011].

More peglispro-treated patients had detectable anti-peglispro antibodies at week 52; more had treatment-emergent antibody response with peglispro than glargine at week 52 (Table 2); however, treatment-emergent antibody status (positive or negative) did not appear to affect HbA1c, total hypoglycaemia, insulin dose or immune-related adverse events.

## 4 | DISCUSSION

This double-blind, phase III, treat-to-target trial in insulin-naïve patients with type 2 diabetes showed that peglispro treatment was non-inferior to glargine in reducing HbA1c (primary objective). In addition, prespecified, secondary gated outcomes showed statistically greater reduction in HbA1c, with more peglispro-treated patients achieving HbA1c < 7.0%. Although the between-group difference in HbA1c was clinically modest, it was associated with less nocturnal hypoglycaemia, and potentially, no increase in total hypoglycaemia. In previous studies, different insulin regimens have shown similar HbA1c-lowering effects when titrated to similar fasting SMBG levels in similarly-designed treat-to-target studies.<sup>17,25-28</sup> These differences may be related to the reduced peripheral glucose disposal rates,<sup>11,12</sup>(fig. 2),<sup>13</sup> flat pharmacokinetic profile,<sup>10</sup> and/or reduced glucose variability associated with peglispro, which may allow titration to a higher dose without hypoglycaemia. Despite receiving ~10% more basal insulin than glargine-treated patients, peglispro-treated patients had similar total hypoglycaemia, less nocturnal hypoglycaemia, and potentially less weight gain



and glycaemic variability; more peglispro-treated patients achieved HbA1c < 7.0% without hypoglycaemia.

Differences in triglycerides may reflect the decrease in peripheral insulin action observed with peglispro.<sup>11,12(fig. 2),13</sup> When insulin was administered intraperitoneally to restore a hepato-preferential effect in type 1 diabetes, triglyceride levels increased compared with peripherally administered insulin;<sup>29</sup> however, this was not observed in type 2 diabetes.<sup>30</sup> Conventional insulins lower triglycerides by both decreasing secretion of very low-density lipoproteins from the liver and by suppressing adipose tissue lipolysis.<sup>31</sup> Recently, a study in rats showed hepatic triglyceride synthesis was driven mainly by esterification of fatty acids and was dependent on fatty acid availability rather than insulin-mediated hepatic *de novo* lipogenesis.<sup>32</sup> Peglispro has less of a suppressive effect on lipolysis than glargine;<sup>11</sup> this may explain why decreases in triglycerides and liver fat are seen with glargine but not with peglispro treatment.

The aetiology and significance of ALT and AST increases with peglispro treatment are unknown. No patient in this study met Hy's law criteria,<sup>24</sup> suggesting that these increases were not attributable to significant acute hepatotoxicity. Although some PEGylated proteins, such as pegvisomant,<sup>33</sup> are associated with increased aminotransferases, this is not true of all PEGylated proteins. Mean increases in aminotransferases could reflect an increase in liver fat content, although peglispro did not increase mean liver fat content in this study. Glargine slightly reduced both mean ALT and liver fat content. This is consistent with an earlier, smaller study,<sup>34</sup> showing similar reductions in liver fat content with basal insulin. By contrast, in patients with type 2 diabetes previously treated with basal insulin, a significant increase in liver fat content was observed with peglispro.<sup>35</sup> The clinical significance of the 3% liver fat content reduction in glargine-treated patients in that study is unknown.

Increased lipohypertrophy frequency with peglispro may reflect prolonged absorption from the injection site along with infrequent injection site rotation. As peglispro is predominantly absorbed via the lymphatic system,<sup>36</sup> reduced local lymphatic drainage may be a contributing factor.

The present study's primary outcomes were limited to 52 weeks' duration, as defined by the primary objective. A cohort of patients did complete 78 weeks of treatment, but these findings are limited by the smaller patient population and lack of multiplicity adjustment. Patients with liver disease other than non-alcoholic fatty liver disease, serum creatinine 177 micromol/L, and triglycerides >4.5 mmol/L were excluded, which limits the safety interpretation in such patients. The study was conducted globally but had limited participation of patients of Asian or black ethnicity. Some glucose-lowering drugs were excluded. Although the MRI substudy was large, participants were not selected randomly from the overall study population, but were limited to patients from certain pre-selected sites; however, participants in the MRI substudy were randomly assigned to treatment groups. MRI was not performed after withdrawal of study insulins.

Observations of higher triglyceride levels, lower nocturnal hypoglycaemia, and potentially less weight gain in the present study may reflect the hepato-preferential action of peglispro resulting from reduced peripheral action. HbA1c reductions associated with reduced nocturnal hypoglycaemia and reduced glycaemic variability may have

benefits for patients with diabetes beyond those demonstrable in a 52- to 78-week study.

On December 4, 2015, Lilly formally announced that they will cease the development of basal insulin peglispro based on discussions with regulatory authorities and other external experts, particularly concerning the liver fat changes that were observed in the IMAGINE trials. Based on the information gleaned from these discussions, the company concluded that further studies to address the safety findings would have required a significant amount of time and investment, and stated it was unclear whether any such study would produce conclusive answers on the liver data. The present study was the largest of all of the six phase III programmes and the difference in liver fat compared with the comparator was thought to be associated with the hepato-preferential action of this insulin. The data from this randomized clinical trial are highly relevant to clinicians as the hepato-preferential action is thought to offer potential clinical advantages, as was observed in the present study and the other IMAGINE trials. The liver fat differences may result from the more physiological action of this hepato-preferential insulin and may not be pathological.

In conclusion, among insulin-naïve patients with type 2 diabetes, the use of basal insulin peglispro compared with glargine resulted in primarily, non-inferior glycaemic control and secondarily, greater reduction in HbA1c, more patients achieving HbA1c targets, and less nocturnal hypoglycaemia without improvement in total hypoglycaemia. Higher triglyceride and aminotransferase levels, and more injection site reactions were observed with peglispro.

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## Author contributions

S.J.J. and J.L. participated in design of the trial. M.J.D., D.R.J., J.L.S., T.S.B. and Z.K. were trial investigators. J.L. conducted the statistical analyses. S.J.J., M.L.H., T.I. and J.B.V. participated in the conduct of the study. S.J.J. wrote the first draft of the manuscript. J.G.J. wrote subsequent drafts. All authors contributed to discussion and interpretation of the data, and provided critical revisions of the manuscript. All authors approved the final manuscript for publication.

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## SUPPORTING INFORMATION

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