New insulins for diabetes

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Abstract

Diabetes treatments have come a long way, but continual efforts are needed to make the disease easier to manage and more affordable. Nearly half a million patients in the UK are prescribed insulin; however, despite insulin’s increasing use, current licensed insulin products incur significant barriers, which have fuelled the need to develop novel insulins and drug delivery methods.

This review will critically consider the role of new insulin preparations and delivery methods, such as Technosphere insulin, buccal spray insulin, very-long acting insulins, new insulin combinations, and ultra-fast acting insulin that aim to surmount these hurdles. Copyright © 2015 John Wiley & Sons.

Key words
Technosphere insulin; buccal spray insulin; peglispro; IDeG Lira; ultra-fast acting insulin

Introduction

The IDF (International Diabetes Federation) diabetes atlas estimated that in 2011 there were 366 million people worldwide with diabetes and this is expected to rise to 552 million by 2030. More locally, in 2010 there was an estimated 3.1 million people aged 16 years and older with diabetes in England, and this number is projected to rise to 4.6 million by 2030. Leading on from this, the most comprehensive analysis to date concluded that in 2010/11 the direct costs of diabetes to the NHS were £9.8bn with £1bn spent on type 1 diabetes mellitus (T1DM) and £8.8bn spent on type 2 diabetes mellitus (T2DM); approximately 80% of this was spent on complications. Diabetes care accounts for 10% of the NHS budget, which is projected to grow to 17% of the entire NHS budget within the next 20 years. Accordingly, diabetes is a major threat to health with a prevalence increasing in epidemic proportions. Inevitably, diabetes and its complications will strain public health resources.

Insulin therapy is the most physiological treatment for T1DM and, notwithstanding the significance of insulin sensitisation and weight reduction, is an effective glucose-lowering treatment in progressive T2DM when non-insulin therapies have failed. Leading on from this, the crude prevalence rate of insulin use in the UK increased from 2.43 (95% CI 2.38–2.49) per 1000 population in 1991 to 6.71 (6.64–6.77) per 1000 in 2010, and the absolute number of patients using insulin increased from 137 000 (121 000–155 000) in 1991 to 421 000 (400 000–444 000) in 2010. However, despite its increasing use, current licensed insulin products incur significant barriers – namely needle phobia, psychological insulin resistance, hypoglycaemia, poor compliance, weight gain, and fear of reduced quality of life – all of which add to the challenges of initiating and intensifying therapy to achieve euglycaemia and negate vascular risk. Current rapid and long-acting analogues only partially solve problems linked to insulin therapy such as flexibility and quality of life, but hypoglycaemia still represents an important cause of hospitalisation, increased health expenditure, morbidity and mortality. This has fuelled the need to develop novel insulins and drug delivery methods that surmount these hurdles.

This review will critically consider the role of new insulin preparations and delivery methods – such as Technosphere® insulin, buccal spray insulin, very-long acting insulins, new insulin combinations, and ultra-fast acting insulin – in the treatment of diabetes.

Technosphere insulin (Afrezza)

A dry powder formulation of recombinant human insulin, marketed under the trade name Afrezza, has recently been approved by the United States Food and Drug Administration (FDA).

Afrezza consists of Technosphere insulin (TI) particles that, following inhalation, reach the lung and...
dissolve on contact. The device to administer TI is well designed, small, and easy to use.\textsuperscript{7} TI’s kinetics makes it an ultra- rapid acting insulin; its onset of action is 12–15 minutes with a peak at 60 minutes and a duration of action of 150–180 minutes.

TI is targeted towards patients with needle phobia and psychological insulin resistance, and is indicated as a prandial insulin in adults with T1DM or T2DM, representing an alternative to bolus injections. TI is associated with acute bronchospasm and is therefore contraindicated in patients with obstructive Airways disease. It should be used with caution in patients who smoke. Leading on from this, regular monitoring of the forced expiratory volume in 1 second (FEV\textsubscript{1}) is recommended at baseline, 6 months, 12 months and then annually. If the FEV\textsubscript{1} drops by $\geq 20\%$ from baseline, TI should be discontinued.

In an open-label, 52-week randomised controlled trial, 677 patients with T2DM with a mean baseline HbA\textsubscript{1c} of 8.7% were randomly assigned to receive either prandial TI plus glargine or twice-daily premixed aspart 70/30. Patients randomised to TI/glargine had a lower reduction in mean HbA\textsubscript{1c} compared to patients randomised to premixed aspart 70/30 (-0.59% vs -0.71%). However, patients in the TI/glargine group experienced greater reductions in fasting plasma glucose (FPG) relative to patients in the premixed aspart 70/30 group (-1.78mmol/L vs -1.08mmol/L).

While the TI/glargine group experienced a significant reduction in 1-hour postprandial glucose, it took ~6 hours for postprandial glucose to reach preprandial levels. In contrast, postprandial glucose concentrations in the premixed aspart 70/30 group reached preprandial levels much more quickly in ~4 hours. Patients randomised to TI/glargine reported a mean weight gain of +0.9kg, which was significantly less than the average weight gain of +2.5kg in patients randomised to premixed aspart 70/30. A non-productive cough was reported by 35% of subjects receiving TI/glargine and tended to occur during the first 10 minutes of inhalation in the first week of therapy. Cough was the main reason for patient withdrawal, being greater in patients receiving TI/glargine compared to those receiving premixed aspart 70/30 (9% vs 4%, respectively). Hypoglycaemia of any severity was most likely to occur with premixed aspart 70/30 vs TI/glargine (odds ratio 0.417; 95\% CI 0.303–0.573), and the occurrence of severe hypoglycaemic events was higher with premixed aspart 70/30.\textsuperscript{8}

Further corroboratory evidence on the efficacy and tolerability of TI was provided by a 52-week study of patients with T1DM, with a baseline HbA\textsubscript{1c} of 7.0–11.0\%, who were randomly assigned to receive glargine plus prandial TI (n=301) or prandial rapid-acting analogue insulin (n=288). Patients receiving TI/glargine had a lower mean HbA\textsubscript{1c} reduction compared to those receiving rapid-acting analogue insulin/glargine (-0.17% vs -0.47%).

Similar to the previous study, there was a statistically significant reduction in FPG in patients receiving TI compared with rapid-acting analogue insulin (-2.5mmol/L vs -1.3mmol/L, p=0.0052). Furthermore, patients randomised to TI/glargine had a statistically significant reduction in weight relative to those on rapid-acting analogue insulin who reported an overall weight gain (-0.5kg vs +1.4kg, p=0.0001). Postprandial glucose at 1 hour was significantly lower in the TI group compared to patients receiving rapid-acting analogue insulin (9.2mmol/L vs 11.2mmol/L, p=0.0203). Mild to moderate hypoglycaemia occurred less frequently in those receiving TI relative to rapid-acting analogue insulin (85.67% vs 92.65%, respectively; p=0.0091), but severe hypoglycaemia occurred similarly between the groups (32.76% vs 37.50%, respectively).\textsuperscript{9}

In summary, TI is inferior to premixed and rapid-acting analogue insulin in lowering HbA\textsubscript{1c}, but demonstrates superiority in reducing postprandial glucose excursions, aiding weight loss, and is also associated with a lower occurrence of hypoglycaemia. As TI must be used alongside basal insulin, it does not completely alleviate fear and anxiety in patients with needle phobia and psychological insulin resistance.

**Buccal spray insulin (Oral-lyn)**

Insulin delivery via the buccal mucosa has a number of advantages that include: easy accessibility; a large physico-chemical and mechanically robust surface area for absorption; direct contact with the buccal mucosa, establishing a drug concentration gradient favouring diffusion into highly vascularised underlying tissue; low enzymatic activity; bypassing pre-systemic hepatic metabolism; and improved patient compliance due to the elimination of pain and fear associated with injections. Accordingly, the only buccal spray insulin, marketed under the trade name Oral-lyn, is a liquid formulation of recombinant human regular insulin.

Oral-lyn is indicated as prandial insulin alongside basal insulin in T1DM and T2DM. Oral-lyn encompasses an advanced buccal drug-delivery technology consisting of a surfactant, solubiliser, micelle-creating agent and emulsifying agent. The formulation results in an aerosol with relatively large micelles that is sprayed into the mouth at high speed by use of a propeller. Peak insulin levels are achieved at 40–60 minutes and are effective for 120 minutes after administration, which allows repeated application of prandial insulin during a meal with a long duration without running into the risk of adding-up the metabolic effect of multiple insulin injections. Each 28ml canister contains 400 units of recombinant human regular insulin and each puff delivers a metered dose of ~10 units insulin with a bioavailability of 10%.

Oral-lyn has been approved by the US FDA for patients with T1DM and T2DM as part of its Treatment Investigational New Drug (IND) programme. Oral-lyn is available in Ecuador, India and parts of Canada. Evidence from a randomised, double-blind, placebo-controlled trial of 26 patients with T2DM on glargine and metformin who either received Oral-lyn thrice daily or placebo revealed at 12 weeks’ follow up that: there was no change in FPG between the groups; there was a 15.4% decrease in postprandial glucose in the group treated with Oral-lyn (from 211.2mg to 178.5mg).
compared to a 3.5% increase in the placebo group (from 202.7mg to 210.1mg); and a ~50% improvement in HbA1c in the Oral-lyn treated group relative to placebo.10

Additional evidence on the efficacy of Oral-lyn in reducing post-prandial hyperglycaemia was provided by an open-label, randomised, cross-over study of 23 patients with T2DM who received 100 units Oral-lyn on one study day and an injection of 0.1 IU/kg insulin lispro on the other study day 10 minutes prior to a standardised meal. The +30 and +60 minutes postprandial blood glucose levels were lower in the Oral-lyn arm of the study.11

Further corroboratory evidence on the utility of Oral-lyn was provided by an open-label study of 25 patients with T1DM. The control group consisted of 11 patients on twice-daily isophane insulin; the treatment group consisted of 14 patients on twice-daily isophane insulin and three times daily prandial split doses of Oral-lyn. At 99 days follow up, there was a significantly greater reduction (p<0.035) in HbA1c in patients receiving Oral-lyn (from 6.8% to 6.1%, i.e. -0.7%) compared to the control group (from 7.3% to 6.8%, i.e. -0.5%). The number of hypoglycaemic events was comparable between both groups and no severe hypoglycaemic episodes were reported.12

Oral-lyn appears to have a desirable tolerability and safety profile; in a phase III clinical trial involving 400 patients, Oral-lyn was associated with a reduction in BMI and fewer hypoglycaemic episodes at six months’ follow up.13

However, there are a number of limitations with Oral-lyn: the buccal mucosa is not an absorptive organ and, accordingly, buccal absorption of insulin is highly variable with negligible–low absorption through the palate and cheek respectively, with higher absorption in the sublingual region; the low bioavailability translates to 10 puffs being required to deliver 10 units of insulin, which is time-consuming and not user friendly; data on the efficacy, safety and tolerability of Oral-lyn are confined to poorly-designed and performed phase II and III clinical trials involving a small number of patients, which limits the reliability of the data; and the reproducibility of the glucose-lowering effect and associated intra-individual variability with Oral-lyn has not been reliably determined. Furthermore, as Oral-lyn must be used alongside basal insulin, it does not completely alleviate fear and anxiety in patients with needle phobia and psychological insulin resistance.

Very-long acting insulin: peglispro

The basal insulin products currently licensed do not optimally mimic endogenous insulin secretion. This unmet clinical need has fuelled the development of novel basal insulin analogues with an improved pharmacological profile. Accordingly, peglispro is a new long-acting basal insulin currently in phase III clinical trials; it is comprised of modified insulin lispro conjugated to a polyethylene glycol (PEG) group. This enables each monomer to bind three molecules of water thus increasing its hydrodynamic diameter; the resultant large functional molecular size reduces renal clearance, slows absorption from subcutaneous tissues, and alters its tissue distribution with preferential peripheral action, thus prolonging its half-life. Accordingly, peglispro has a duration of action of ~56 hours and exhibits a flat serum concentration for ~48 hours.

Data from a phase II clinical trial in patients with T2DM revealed peglispro showed non-inferiority in reducing serum glucose relative to glargine; at 12 weeks, fasting blood glucose and HbA1c were similar between patients treated with peglispro and glargine (6.57mmol/L and 7% vs 6.49mmol/L and 7.2%,

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aim</th>
<th>Duration</th>
<th>Sample size</th>
<th>Study group</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>IMAGINE-1</td>
<td>Peglispro vs glargine in combination with prandial insulin (unblinded)</td>
<td>78 weeks</td>
<td>Peglispro n=295;</td>
<td>T1DM</td>
<td>Formal release of results expected 2015</td>
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<tr>
<td>IMAGINE-2</td>
<td>Peglispro vs glargine in insulin naïve patients</td>
<td>52 weeks</td>
<td>Peglispro n=1003;</td>
<td>T2DM</td>
<td>Formal release of results expected 2015</td>
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<tr>
<td>IMAGINE-3</td>
<td>Peglispro vs glargine in combination with prandial insulin (blinded)</td>
<td>52 weeks</td>
<td>Peglispro n=664;</td>
<td>T1DM</td>
<td>Formal release of results expected 2015</td>
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<tr>
<td>IMAGINE-4</td>
<td>Peglispro vs glargine in combination with prandial insulin</td>
<td>26 weeks</td>
<td>Peglispro n=691;</td>
<td>T2DM</td>
<td>Formal release of results expected 2015</td>
</tr>
<tr>
<td>IMAGINE-5</td>
<td>Peglispro vs glargine in patients already taking a basal insulin</td>
<td>52 weeks</td>
<td>Peglispro n=307;</td>
<td>T2DM</td>
<td>Formal release of results expected 2015</td>
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<tr>
<td>IMAGINE-6</td>
<td>Peglispro vs NPH insulin in insulin naïve patients</td>
<td>26 weeks</td>
<td>Peglispro n=428;</td>
<td>T2DM</td>
<td>Formal release of results expected 2015</td>
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<tr>
<td>IMAGINE-7</td>
<td>Peglispro once daily at a fixed time vs variable time peglispro (cross-over study)</td>
<td>36 weeks</td>
<td>n=182</td>
<td>T1DM</td>
<td>Formal release of results expected 2015</td>
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Table 1. Details of the IMAGINE 1–7 phase III clinical trials on peglispro

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respectively). However, daily blood glucose variability was reduced and nocturnal hypoglycaemia was 48% lower in patients treated with peglispro compared to glargine, although there was no significant difference in the incidence and rate of total hypoglycaemia. Furthermore, patients in the peglispro group achieved statistically significant weight loss (-0.6kg, p=0.007) independent of BMI and not related to gastrointestinal adverse effects or hypoglycaemia. However, peglispro was associated with an adverse lipid profile characterised by increased LDL and reduced HDL cholesterol concentrations. There was also a transient increase in hepatic aminotransferases in patients treated with peglispro. Similarly, results that met non-inferiority criteria and additionally superiority criteria were reported in a phase II randomised, cross-over study in patients with T1DM treated with peglispro compared to glargine. Peglispro was associated with significant reductions in daily mean blood glucose (8.01mmol/L vs 8.43mmol/L, p<0.001), fasting blood glucose variability and HbA1c (p<0.001), and weight loss (-1.2kg vs +0.7kg, p<0.001). The nocturnal hypoglycaemia rate was lower for peglispro, but the total hypoglycaemia rate was higher (p=0.04). Peglispro was associated with increased hepatic aminotransferases, triglycerides, and LDL cholesterol and lower HDL cholesterol.15

Leading on from phase II trials, data from the seven recently completed, but as yet unpublished, phase III IMAGINE clinical trials evaluating the efficacy of peglispro are summarised in Table 1.

Preliminary unpublished results from the IMAGINE 1–5 trials reported the primary efficacy endpoint of non-inferior reduction in HbA1c compared to glargine was met and, additionally, peglispro showed a statistically superior reduction in HbA1c. Furthermore, data from the unblinded IMAGINE-1 and blinded IMAGINE-3 phase III clinical trials demonstrated that peglispro, relative to glargine, was associated with lower rates of nocturnal hypoglycaemia and weight loss. However, compared to glargine, peglispro was also associated with an increased frequency of daytime hypoglycaemia, including severe hypoglycaemic events; injection site reactions; hypertension; statistically significant increases in liver fat content and aminotransferase enzyme levels; and a significant increase in triglyceride and LDL levels. IMAGINE-6 met its primary efficacy endpoint at 26 weeks of non-inferior reductions in HbA1c compared with NPH insulin and also demonstrated superiority in this regard. IMAGINE-7 showed there was no statistically significant difference in HbA1c between peglispro dosed at the same time every day versus peglispro dosed at variable times. Across all trials the rates of major adverse cardiovascular events were similar between patients treated with peglispro, insulin glargine or NPH insulin. Detailed results from all phase III IMAGINE trials are expected to be published in 2015.16,17

**New insulin combinations: IDEgLira**

Current licensed basal insulin preparations are limited in their application by hypoglycaemia and weight gain, while glucagon-like peptide-1 (GLP-1) analogues are limited by issues of efficacy when used as monotherapy. However, in combination, they show a complementarity of action in terms of reducing the incidence of hypoglycaemia while providing sufficient glycaemic control, thus counterbalancing their individual weaknesses. Accordingly, IDEgLira is a novel fixed-ratio combination of the GLP-1 analogue liraglutide and the basal insulin analogue degludec, which has been developed as a once-daily injection for the treatment of T2DM.

In the randomised, open-label, phase III DUAL-I trial of 1665 insulin-naive patients with T2DM comparing IDEgLira (n=834) with degludec (n=414) and liraglutide (n=415), at 26 weeks IDEgLira was associated with an HbA1C reduction of 1.9%, which contrasted favourably with 1.4% for degludec and 1.3% with liraglutide. IDEgLira was non-inferior to degludec with a treatment difference of -0.45% (p<0.0001) and superior to liraglutide with a treatment difference of -0.64% (p<0.0001). IDEgLira was well tolerated with fewer patients reporting nausea relative to liraglutide (8.8% vs 19.7%), although the lowest rates were observed in patients treated with degludec (3.6%). The number of hypoglycaemic episodes per patient year was 1.8 for IDEgLira, 0.2 for liraglutide, and 2.6 for degludec. Serious adverse events, defined as hypoglycaemic requiring third-party assistance, occurred in 2% of patients treated with IDEgLira, 2% treated with degludec and 3% in those treated with liraglutide.18

Further evidence has been revealed from the 26-week, double-blind, randomised controlled DUAL II trial of 413 patients with T2DM that aimed to assess the distinct liraglutide component of IDEgLira on efficacy and safety indices. It was shown that IDEgLira achieved superior glycaemic control relative to degludec (-1.9% vs -0.9%, p<0.0001); IDEgLira achieved superior weight loss compared to degludec (-2.7kg vs no weight change, p<0.0001); hypoglycaemic incidence was comparable between the two groups (24% vs 25%); and the incidence of nausea was higher in those treated with IDEgLira (6.5% vs 3.5%).19

Based on desirable efficacy and safety profile data, in September 2014 IDEgLira was approved in the EU for treatment of adults with T2DM in combination with oral glucose-lowering drugs when these alone or combined with basal insulin do not provide adequate glycaemic control. Accordingly, IDEgLira was launched in the UK in November 2014.

**Ultra-fast acting insulin and co-use of rHuPH20 hyaluronidase**

Rapid-acting insulin analogues were designed to improve the treatment of diabetes by: shortening the optimum time delay between injections and meals; decreasing postprandial hyperglycaemia; and reducing the risk of hypoglycaemia.

However, the endogenous insulin response to a meal is very fast and currently available rapid-acting analogues are unable to replicate this profile. Accordingly, recombinant human hyaluronidase (rHuPH20) has been used to increase the absorption and dispersion of rapid-acting insulin analogues thus...
conferring both ultra-fast absorption and action profiles.

Hyaluronan functions to confer a gel-like consistency to the subcutaneous tissues, which impedes the absorption of injected insulin by limiting its dispersion from the injection site. rHuPH20 depolymerises hyaluronan thus transiently and reversibly breaking down this barrier, allowing bulk fluid flow of the injected insulin to occur. Thus the effects of rHuPH20 on insulin absorption are due to two synergistic actions: the spreading of the injected insulin results in access to a greater capillary surface area thus increasing access to the vasculature; and the increased dispersion reduces the local concentration of the injected insulin, which aids the dissociation of non-absorbable insulin multimers into smaller capillary permeable monomers and dimers. This results in a faster, shorter time-action profile that more closely mimics normal physiology.20

The accelerated pharmacokinetics and glucodynamics of rapid-acting analogue insulin co-injected

<table>
<thead>
<tr>
<th>Trial</th>
<th>Aim</th>
<th>Duration</th>
<th>Sample size</th>
<th>Study group</th>
<th>Main outcome(s)</th>
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<tr>
<td>Rosenstock, et al.8</td>
<td>Technosphere insulin (TI) + glargine vs twice-daily aspart 70/30</td>
<td>52 weeks</td>
<td>677 patients</td>
<td>T2DM</td>
<td>• Lower mean HbA1c reduction for TI compared to aspart (-0.59 vs -0.71%)</td>
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<td></td>
<td>• Greater reduction in fasting plasma glucose for TI compared to aspart (-1.78 vs -1.08mmol/L)</td>
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<td></td>
<td>• Less weight gain for TI compared to aspart (+0.9 vs +2.5kg)</td>
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<tr>
<td>Kapsner, et al.9</td>
<td>Glargine + prandial TI vs prandial rapid-acting analogue (RAA) insulin</td>
<td>52 weeks</td>
<td>589 patients</td>
<td>T1DM</td>
<td>• Lower mean HbA1c reduction for TI compared to RAA insulin (-0.17 vs -0.47%)</td>
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<td></td>
<td>• Greater reduction in fasting plasma glucose for TI compared to RAA insulin (-2.5 vs -1.3mmol/L)</td>
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<td>• Less weight gain for TI compared to RAA insulin (-0.5 vs +1.4kg)</td>
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<tr>
<td>Raz, et al.10</td>
<td>Glargine &amp; metformin + Oral-lyn vs glargine &amp; metformin + placebo</td>
<td>26 weeks</td>
<td>26 patients</td>
<td>T2DM</td>
<td>• No change in fasting plasma glucose</td>
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<td></td>
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<td>• 15.4% decrease in postprandial plasma glucose for Oral-lyn vs 3.5% increase in placebo</td>
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<td>• ~50% improvement in HbA1c for Oral-lyn compared to placebo</td>
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<tr>
<td>Guevara-Aguirre, et al.11</td>
<td>Cross-over study: 100 units Oral-lyn on one study day and 0.1 IU/kg insulin lispro on the other study day</td>
<td>2-day cross-over study</td>
<td>23 patients</td>
<td>T2DM</td>
<td>• +30 and +60 minutes postprandial blood glucose levels were lower in the Oral-lyn arm of the study</td>
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<td>Guevara-Aguirre, et al.12</td>
<td>Twice-daily isophane insulin and thrice-daily prandial Oral-lyn vs twice-daily isophane insulin and thrice-daily regular insulin</td>
<td>99 days</td>
<td>25 patients</td>
<td>T1DM</td>
<td>• Greater reduction in HbA1c for Oral-lyn compared to regular insulin (-0.7 vs -0.5%)</td>
</tr>
<tr>
<td>Gough, et al. (DUAL I)18</td>
<td>lDegLira vs degludec and liraglutide separately</td>
<td>26 weeks</td>
<td>1663 patients</td>
<td>T2DM</td>
<td>• Significant HbA1c reduction of -1.9% for lDegLira vs -1.4% for degludec vs -1.3% for liraglutide</td>
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<tr>
<td>Buse, et al. (DUAL II)19</td>
<td>To assess the distinct liraglutide component of lDegLira on efficacy and safety</td>
<td>26 weeks</td>
<td>413 patients</td>
<td>T2DM</td>
<td>• lDegLira achieved superior glycaemic control relative to degludec (-1.9 vs -0.9%)</td>
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<td>• lDegLira achieved superior weight loss compared to degludec (-2.7kg vs no weight change)</td>
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<td>• Hypoglycaemic incidence was comparable between the 2 groups (24 vs 25%)</td>
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<td>• Incidence of nausea was higher in those treated with lDegLira (6.5 vs 3.5%)</td>
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<tr>
<td>Hompesch, et al.25</td>
<td>To assess the efficacy of rHuPH20 on postprandial glucose control in test meal settings</td>
<td>8 hours of postprandial observation</td>
<td>43 patients</td>
<td>T1DM and T2DM</td>
<td>• The addition of rHuPH20 to RAA insulin significantly reduced 4-hour peak postprandial glucose from 9.67 to 8.22mmol/L</td>
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</tbody>
</table>

Table 2. A summary of the main clinical trials discussed in this review
with recombinant human hyaluronidase has been illustrated in a proof-of-concept study in healthy volunteers. During the first hour following injection, the addition of rHuPH20 resulted in a doubling of insulin exposure with a corresponding halving of insulin exposure after 2 hours.\textsuperscript{21} The reliability of these findings is corroborated by replication of similar results in another study.\textsuperscript{22} Furthermore, the addition of rHuPH20 to insulin lispro shifted the time–exposure profile as a function of insulin dosage – the time to 50% of total insulin exposure for 2, 6 and 20 units of insulin lispro was reduced from 75, 96 and 113 minutes to 52, 62 and 83 minutes respectively, when the same doses of insulin lispro were co-injected with rHuPH20 (p<0.0006).\textsuperscript{23} In a separate study, the addition of rHuPH20 has been shown to reduce intra-patient variability of exposure to, and action of, insulin.\textsuperscript{24} Efficacy studies on rHuPH20 have shown improved postprandial glucose control in test meal settings. In a study of 22 patients with T1DM and 21 patients with T2DM, the addition of rHuPH20 to rapid-acting analogue insulin reduced 4-hour peak postprandial glucose from 9.67 to 8.22 mmol/L (p=0.002) without affecting minimum postprandial glucose levels or hypoglycaemia risk during 8 hours of postprandial observation.\textsuperscript{25} Furthermore, rHuPH20 appears to be safe and well tolerated with no local or systemic adverse events reported; however, long-term safety data are lacking.

**Summary**

A quick reference guide to the main clinical trial data presented in this review is provided in Table 2 (data from the peglispro trials are cited in Table 1).

**Conclusion**

Diabetes treatments have come a long way, but continual efforts are needed to make the disease easier to manage and more affordable. New insulin products under development with improved pharmacological profiles that closely mimic physiological insulin secretion and activity, coupled with non-invasive methods of insulin delivery, offer hope that these limitations may be surmountable.

**Declaration of interests**

There are no conflicts of interest declared. Funding source: none.

**Key points**

- Current licensed insulin products incur significant barriers – namely needle phobia, psychological insulin resistance, hypoglycaemia, poor compliance, weight gain, and fear of reduced quality of life – all of which add to the challenges of initiating and intensifying therapy to achieve euglycaemia and negate vascular risk.
- New insulin products under development with improved pharmacological profiles that closely mimic physiological insulin secretion and activity, coupled with non-invasive methods of insulin delivery, offer hope that these limitations may be surmountable.
- New insulin products showing promise include: Technosphere insulin; buccal spray insulin; peglispro; IDegLira; and ultra-fast-acting insulin.

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