

New Medicine Assessment

Insulin degludec plus liraglutide (Xultophy[®]▼)

100 units/mL insulin degludec plus 3.6 mg/mL liraglutide solution for injection in a pre-filled pen

Treatment of adults with type 2 diabetes mellitus (T2DM) to improve glycaemic control, in combination with oral glucose-lowering medicinal products when these alone, or combined with basal insulin, do not provide adequate glycaemic control

Recommendation: **BLACK**

The combination product insulin degludec plus liraglutide (Xultophy[®]▼) is not recommended to treat type 2 diabetes mellitus (T2DM) to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone, or combined with basal insulin, do not adequately provide glycaemic control.

The individual constituents are currently recommended as follows:

- GLP-1 receptor agonists are recommended as an alternative and should only be prescribed as per NICE CG87. Liraglutide is recommended in dual and triple therapy regimens as per [NICE TA203](#)
- Insulin degludec is **not** recommended for use in the treatment of diabetes mellitus; robust evidence of a clear therapeutic advantage to justify the significantly greater acquisition costs compared with existing long-acting insulin analogues is currently lacking. [See LMMG website](#)

Basis for Recommendation:

- Insulin degludec plus liraglutide, with its fixed ratio dosing, offers less flexibility to titrate the individual components and manage interruption of treatment, and at the initiation of treatment does not allow the prescriber to understand how the patient responds to or tolerates each component.
- Liraglutide 1.8 mg daily is not recommended by NICE (TA203), if the maximum recommended liraglutide dose of 1.2 mg is adhered to it would limit the maximum daily dose of insulin degludec to 33 units and therefore the combination preparation would not be suitable for patients requiring higher insulin doses.
- NICE CG87 currently recommends NPH insulin first line in those patients requiring insulin (and remains the recommendation in their **draft** updated guidance).
- NICE CG87 does not recommend adding in a GLP-1 RA (receptor agonist) and insulin at the same time (their draft updated guidance does not recommend this either). Management pathways recommend adding in a single preparation, assessing its benefit and tolerability and intensifying if required.
- Insulin degludec plus liraglutide (Xultophy[®]) does not currently fit into any locally or nationally-defined pathways. Insulin can be prescribed in addition to GLP-1 RAs as per their licences and in line with NICE CG87, but it there is no recommendation to add a GLP-1 RA to insulin.
- The **draft** NICE Guidelines for the management of T2DM state the following, “only offer a glucagon-like peptide-1 (GLP-1) analogue in combination with insulin in a specialist care setting”.
- If a patient is stabilised on insulin and requires intensification, and a GLP-1 RA is deemed suitable

(not currently recommended by NICE), in order to add in liraglutide (in combination with insulin degludec) as a combination product could require the insulin dose being reduced in order to titrate the liraglutide. NB/ patients would start at 16 units of insulin degludec if already taking insulin prior to starting Xultophy[®] - see SPC. The same principle would apply if the patient were already taking liraglutide and wanted to add in insulin.

- If the patient were taking an alternative GLP-1 RA or insulin preparation, and wanted to intensify treatment in the form of Xultophy[®] they would need to discontinue current stabilised therapy in order to initiate the specific combination. If individual constituents were prescribed this would not be necessary (dependent on licensing).
- There are a number of risk management issues with Xultophy[®] (see relevant section below). For example during periods of illness, where higher insulin doses may be required, this will not be possible with the combination preparation, further supporting the prescribing of the individual constituents.
- If a patient suffers from an adverse event it may be difficult to ascertain which preparation has caused this and therefore the patient would need to discontinue both preparations, rather than trialling discontinuation of one then the other, if required.

Summary of Supporting Evidence:

- DUAL I
 - Demonstrated non-inferiority of insulin degludec plus liraglutide (n=834) to insulin degludec (n=414) alone, with a mean decrease in HbA_{1c} of 1.9% and 1.4% respectively (estimated mean treatment difference: -0.47 [-0.58 to - 0.36] p<0.0001).
 - Demonstrated superiority of insulin degludec plus liraglutide compared to liraglutide (n=415), with a mean decrease in HbA_{1c} of 1.9% and 1.3% (estimated mean treatment difference: -0.64 [-0.75 to - 0.53] p<0.0001).
 - Patients who achieved a HbA_{1c} of ≤ 6.5% without weight gain or hypoglycaemia were; 38% for the liraglutide arm, 32% for insulin degludec plus liraglutide arm and 9% for insulin degludec arm (p<0.0001).
 - There was a statistically significant increase in weight for insulin degludec plus liraglutide compared to liraglutide alone 2.44kg (95% CI 2.02 to 2.86, p < 0.0001) and decrease in weight compared to insulin degludec alone -2.22kg (95% CI - 2.74 to - 1.80, p<0.0001)
- DUAL II
 - Demonstrated superiority of insulin degludec plus liraglutide (n=207) over insulin degludec (n= 206), both groups given in addition to metformin, with a mean reduction in HbA_{1c} of 1.9% in comparison to 0.89% for insulin degludec alone (estimated mean treatment difference of -1.1% [95% CI -1.3 to -0.8] p<0.0001).
 - For those who achieved an HbA_{1c} ≤ 6.5% without confirmed hypoglycaemia and weight gain was 29.6% for the combination of insulin degludec plus liraglutide compared to 4.5% for insulin degludec (OR 8.85 [95% CI 4.5-18.89] p<0.001).
 - Mean bodyweight from baseline decreased by 2.7kg for insulin degludec plus liraglutide arm compared with no weight change for insulin degludec arm.
- DUAL IV (unpublished study – results taken from EMA)
 - The study, recruiting 434 patients, found a mean HbA_{1c} reduction of 1.45% to 6.4% in the insulin degludec plus liraglutide group in comparison to a reduction of 0.46% to 7.4% in the placebo group (estimated mean treatment difference: -1.02 [-1.18 to - 0.87] p<0.001).
 - The study participants' weights remained relatively stable in both groups.
- Mathieu C. et al
 - Patients previously treated with insulin degludec, were randomised to either basal insulin degludec in addition to liraglutide (as separate components), or basal insulin degludec in addition to insulin aspart, had mean reduction in HbA_{1c} of 0.73% points in comparison to 0.4% points respectively (estimated mean treatment difference of -0.32% [95% CI -0.53 to - 0.12] p<0.0024).
 - There was no statistically significant difference in between both groups in relation to those achieving an HbA_{1c} <7.0% at end of trial 58% vs. 45%.

- From dose finding studies with liraglutide, it can be concluded that the effect on HbA_{1c} decreases with doses below 0.6 mg but it is not totally absent. The analyses presented support that liraglutide contributes to the effect also at low doses of insulin degludec plus liraglutide. Whether this contribution is of clinical relevance or not remains uncertain.
- The currently published trials do not compare the addition of liraglutide to what would be an alternative at this stage in the management of T2DM e.g. DPP4 inhibitor.
- In DUAL I patients had to be insulin-naïve and treated with 1 to 2 (oral anti-diabetic drugs) OADs. Furthermore the lower HbA_{1c} limit was set at 7.0 %. Thus the included population may not be entirely representative of patients where insulin therapy is considered, since patients may not be considered for insulin therapy unless failing on at least two OADs.
- The EMA concluded that the additive effect of the two components have been adequately shown and although the benefit in terms of additional reduction of HbA_{1c} may be of moderate clinical relevance (about 0.5 %) compared to the mono-components, there are other benefits in terms of insulin dose requirements, weight control and hypoglycaemia risk.

Details of Review

Name of medicine (generic & brand name): Insulin degludec/liraglutide (Xultophy® ▼)
Strength(s) and form(s): 100 units/ml insulin degludec + 3.6 mg/mL liraglutide solution for injection in a pre-filled pen 1 dose step contains 1 unit of insulin degludec and 0.036 mg of liraglutide
Dose and administration: Administered by subcutaneous injection, for adults, <i>as add-on to oral antidiabetics</i> , initially 10 dose-steps once daily (adjusted according to response); <i>when transferring from basal insulin</i> , initially 16 dose-steps once daily (adjusted according to response); max. 50 dose-steps once daily. It is recommended to optimise glycaemic control via dose adjustment based on fasting plasma glucose. It may be administered at any time of day, preferably at the same time of day. Patients who forget a dose are advised to take it upon discovery and then resume their usual once-daily dosing schedule. A minimum of 8 hours between injections should always be ensured. This also applies when administration at the same time of the day is not possible.
BNF therapeutic class / mode of action 6.1.2.3 Other antidiabetic drugs Insulin degludec/Liraglutide; insulin degludec/liraglutide is the first basal insulin (insulin degludec) and GLP-1 receptor agonist (liraglutide) combination in one pen. Insulin degludec is a long-acting human insulin analogue for once daily subcutaneous administration. Liraglutide is a long-acting (24 hours), stable analogue of the natural hormone glucagon-like peptide-1. It increases insulin secretion, suppresses glucagon secretion and slows gastric emptying.
Licensed indication(s): Treatment of adults with type 2 diabetes mellitus to improve glycaemic control in combination with oral glucose-lowering medicinal products when these alone or combined with basal insulin do not provide adequate glycaemic control.
Proposed use (if different from, or in addition to, licensed indication above): The Novo Nordisk proposed positioning of insulin degludec plus liraglutide is for patients with T2DM with a BMI >30kg/m ² who are uncontrolled (HbA _{1c} > 8.5% or 64.4 mmol/l), currently prescribed not more than 40 units of basal insulin; thus, insulin degludec plus liraglutide could be a suitable alternative to the following treatment options: <ul style="list-style-type: none">• Adding a GLP -1 RA (in a loose combination with basal insulin) – <i>note although this is a licensed combination, NICE do not currently recommend adding a GLP-1 RA to insulin</i>• Adding mealtime insulin (basal-bolus therapy)• Changing to biphasic insulin
Course and cost: £159.22; 5 x 3 mL 100 units/mL Novo Nordisk estimate cost per day of £4.47 which includes the product, 1 (self-monitoring blood glucose)

SMBG test and 1 needle. This compares to £5.56 per day for basal insulin (glargine or detemir) + liraglutide, 2 needles and 1 SMBG test per day. Equivalent average annual cost per patient of £1631.55 with a maximum of £1937 annually.

Insulin degludec plus liraglutide has been priced independently of its constituent parts. The price per day is less than the sum of its component parts.

Current standard of care/comparator therapies: (according to Novo Nordisk's proposed use)

- Loose combination of basal insulin + GLP-1RA
- Basal-bolus insulin
- Biphasic insulin

Relevant NICE guidance:

- NICE clinical guideline CG87 Type 2 diabetes: the management of type 2 diabetes 2009
- NICE technology appraisal TA 203 Liraglutide for the treatment of type 2 diabetes. 2010
- NICE Evidence Summary: New Medicines ESNM25: Type 2 diabetes: insulin degludec 2013
- NICE technology appraisal TA53 Guidance on the use of long-acting insulin analogues for the treatment of diabetes - insulin glargine 2002
- NICE key therapeutic topic KTT12 Type 2 diabetes mellitus – summarises the evidence-base on Type 2 diabetes mellitus. It is not NICE guidance. 2015
- *NICE clinical guideline Type 2 diabetes in development – currently in draft publication expected August 2015*

Background and context

The LMMG identified and prioritised the combination product insulin degludec plus liraglutide for review during the annual horizon scanning process. It is a novel combination of a basal insulin (insulin degludec) and GLP-1 receptor agonist (liraglutide) in one pen which constitutes a new treatment paradigm in the management of patients with type 2 diabetes.

NICE recommend that treatment to control blood glucose should be tailored to each person's clinical needs, with safety, paramount.

The evidence base for blood glucose-lowering drugs is particularly complex, with the availability of multiple newer drugs that can be used in varying combinations with older drugs. No randomised controlled trial (RCT) has included all possible combinations for a long enough period, in a large enough number of people at different stages of type 2 diabetes to show which treatment is optimal.¹

Although newer blood glucose-lowering drugs are effective at reducing HbA_{1c} levels, there are limited clinical outcome data, particularly around cardiovascular effects and long-term safety in people with type 2 diabetes. Improvements in surrogate markers (including HbA_{1c} levels) do not automatically confer benefits on mortality or morbidity, and risks may only become apparent over time when these agents have more widespread use in a diverse population.¹

The NICE guideline, CG87², regarding the blood glucose lowering therapy for type 2 diabetes (which is currently being updated; publication expected August 2015) recommends that metformin should be used as the first-line oral hypoglycaemic and a sulfonylurea should usually be used second-line.

NICE currently recommends initiating insulin if the HbA_{1c} continues to be ≥ 58 mmol/mol (7.5%), or other agreed target, following dual therapy with oral hypoglycaemics. If insulin is deemed unacceptable at this stage (because of employment, social, recreational or other personal issues, or obesity), the person may be initiated on triple therapy (see below).

The NICE CG87 recommends that, when insulin therapy is appropriate, human neutral protamine Hagedorn (NPH) (isophane) insulin (for example, Insulatard, Humulin I or Insuman Basal) is the preferred option. This should be administered at bedtime or twice-daily according to need. Metformin and sulphonylurea should be continued (but only if they are licensed to be used with insulin). Long-acting once-daily insulin analogues (insulin detemir, insulin glargine) can be considered if:

- the person needs help from a carer or healthcare professional to administer their insulin and a long-acting insulin analogue would reduce injections from twice to once daily, or
- the person's lifestyle is restricted by recurrent symptomatic hypoglycaemia episodes, or
- the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs or
- the person cannot use the device to inject NPH insulin.

The guideline recommends twice-daily biphasic human insulin (pre-mixed) (particularly if $HbA_{1c} \geq 75$ mmol/mol [9.0%]). A once-daily regimen may be an option.

Consideration can be given to pre-mixed preparations of insulin analogues (including short-acting insulin analogues) rather than pre-mixed human insulin preparations if:

- immediate injection before a meal is preferred, or
- hypoglycaemia is a problem, or
- blood glucose levels rise markedly after meals.

NICE recommends switching to a long-acting insulin analogue (insulin detemir, insulin glargine) from NPH insulin if the person:

- does not reach target HbA_{1c} because of hypoglycaemia, or
- has significant hypoglycaemia with NPH insulin irrespective of HbA_{1c} level, or
- cannot use the delivery device for NPH insulin but could administer a long-acting insulin analogue, or
- needs help to inject insulin and could reduce the number of injections with a long-acting analogue.

In July 2013, LMMG made the following recommendation for insulin degludec: "insulin degludec is not recommended for use in the treatment of diabetes mellitus. Robust evidence of a clear therapeutic advantage to justify the significantly greater acquisition costs compared with existing long-acting insulin analogues is currently lacking."

If triple therapy is considered appropriate, (above), then sitagliptin, pioglitazone, exenatide (twice daily or prolonged release), liraglutide and canagliflozin can all be options (see guidance for exact place in therapy including continuation criteria).

NICE CG87 contains recommendations on the use of liraglutide for Type 2 diabetes, which is taken from NICE TA203³, from 2010 (also due to be updated in 2015). It states the following:

Liraglutide in triple therapy regimens (in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended for the treatment of type 2 diabetes, only when glycaemic control is inadequate, and the patient has:

- a body mass index of 35 kg/m^2 or over and is of European descent (with appropriate adjustment for other ethnic groups) and weight-related psychological or medical problems, or
- a body mass index of less than 35 kg/m^2 , and insulin would be unacceptable for occupational reasons or weight loss would benefit other significant obesity-related comorbidities.

Treatment with liraglutide in a triple therapy regimen should be continued only if HbA_{1c} concentration is reduced by at least 1 percentage point [11 mmol/mol] and a weight loss of at least 3% of initial body weight is achieved within 6 months of starting treatment.

Liraglutide in dual therapy regimens (in combination with metformin or a sulfonylurea) is recommended only if:

- treatment with metformin or a sulfonylurea is contra-indicated or not tolerated, *and*
- treatment with thiazolidinediones and dipeptidylpeptidase-4 inhibitors is contra-indicated or not tolerated.

Liraglutide, in combination with metformin or a sulfonylurea should be continued only if HbA_{1c} concentration is reduced by at least 1 percentage point [11 mmol/mol] within 6 months of starting treatment.

Liraglutide 1.8 mg daily is not recommended. This recommendation is based on the guideline development group concluding that liraglutide 1.8 mg would not be a cost-effective use of NHS resources, and therefore should not be recommended for the treatment of type 2 diabetes. There were no clinical trials which evaluated the effects of dose escalation, and no robust evidence of additional benefits of increasing the dose of liraglutide from 1.2 mg to 1.8 mg.³

To note from current NICE guidance - there are no recommendations on the use of liraglutide in combination with insulin (although liraglutide is licensed to be used in combination with basal insulin). The updated NICE Guidelines for the management of type 2 diabetes, which are only in draft, state the following; “only offer a GLP-1 inhibitor in combination with insulin in a specialist care setting”.²

Summary of evidence

This evidence review draws on the comprehensive overview of key efficacy and safety data included in the EPAR for insulin degludec/liraglutide, published in July 2014.⁴

Summary of efficacy data in proposed use:

The efficacy of the combination product; insulin degludec plus liraglutide was evaluated in two pivotal randomised active-comparator parallel group phase III studies^{5,6} over 26 weeks (see table for summary) with a total of 2058 patients enrolled. These trials evaluated the disease oriented primary outcome of mean reduction in HbA_{1c} from baseline after 26 weeks. Secondary outcome measures included achievement of end of trial HbA_{1c} of less than 7.0% or less than 6.5%, change in bodyweight from baseline, post prandial glycaemic control, daily insulin dose and the safety variable of number of hypoglycaemic episodes (defined as occurrences requiring assistance (severe)) or where self-monitored plasma blood glucose was < 3.1 mmol/L.

Study NCT01336023 (DUAL I)⁵: In this open label study 1663 patients were randomly assigned to 26 weeks of treatment with once daily insulin degludec 100 units/mL (n=414) or liraglutide 6 mg/mL (n=415) or fixed ratio combination of insulin degludec (100 units/mL) plus liraglutide (3.6 mg/mL) (n=834), administered via a 3mL FlexPen[®] injection device at the same time each day. Patients were excluded if they had been treated with GLP-1 RAs, dipeptidyl peptidase or sulphonylurias within 90 days of screening. Patients who were included had been treated with metformin with or without pioglitazone for at least 90 days prior to screening and the dose was maintained at pre-trial doses throughout the study. The insulin degludec group were initiated on a dose of 10 units once daily, with no maximum dose specified. Liraglutide doses were started at 0.6 mg per day and increased by 0.6 mg per week to a maximum of 1.8 mg per day (NB/ NICE TA 203 did not recommend the 1.8 mg dose of liraglutide due to lack of evidence of increased efficacy when increasing the dose from 1.2 to 1.8 mg). The combination preparation of liraglutide plus insulin degludec was initiated at 10 dose steps (10 units of insulin degludec plus 0.36 mg of liraglutide, once daily). The dose was titrated twice weekly to achieve a pre-breakfast plasma glucose of 4-5 mmol/L (taken from an average of the previous 3 consecutive days' readings). The maximum daily dose that could be titrated to was 50 dose steps (50 units of insulin plus 1.8 mg liraglutide).

86.8% of subjects completed the study, which had a 26 week extension. The primary endpoint, (using full analysis set (all randomly assigned patients) last observation carried forward), of mean change in HbA_{1c} from baseline at week 26, demonstrated that the combination preparation of liraglutide plus insulin degludec was non-inferior to insulin degludec and superior to liraglutide p<0.0001 for both. The mean HbA_{1c} had reduced by 1.9% (to 6.4%) for the combination of insulin degludec plus liraglutide, 1.4% (to 6.9%) for insulin degludec and 1.3% (to 7.0%) for liraglutide. There was no significant difference between the combination product of insulin degludec plus liraglutide and insulin degludec alone for reduction in fasting plasma glucose from baseline. However, for the liraglutide group the reduction was significantly less compared to the combination product of insulin degludec plus liraglutide. More patients on liraglutide alone than on the combination of liraglutide plus insulin degludec or insulin degludec alone achieved the HbA_{1c} target of < 7.0% without weight gain or hypoglycaemia; 52%, 36% and 14% respectively. For those achieving an HbA_{1c} of ≤ 6.5% without weight gain or hypoglycaemia the % of patients were; 38% for liraglutide, 32% for insulin degludec plus liraglutide and 9% for insulin degludec. At 26 weeks, significantly lower insulin doses were used in the insulin degludec plus liraglutide group (38 units) compared to the insulin degludec group (53 units) (estimated treatment difference -14.90 units [95% CI -17.4 to -12.66] p<0.0001), while reaching similar mean fasting self-monitored plasma glucose. Notably, in the insulin degludec plus liraglutide group, the mean insulin degludec dose was well below the maximum dose of 50 units. The EMA considered the reduced need for insulin with the combination to be beneficial. From baseline to end of trial, mean body weight decreased by 0.5kg for the combination of insulin degludec plus liraglutide, increased by 1.6kg for with insulin degludec and decreased by 3.0kg with liraglutide alone. This was a statistically significant treatment difference of -2.22kg (95% CI - 2.74 to - 1.80, p<0.0001) for insulin degludec plus liraglutide compared to insulin degludec alone, and a statistically significant treatment

difference of 2.44kg (95% CI 2.02 to 2.86, $p < 0.0001$) for insulin degludec plus liraglutide compared to liraglutide alone.

Study NCT01392573 (DUAL II)⁶: Patients were randomised and blinded to 26 weeks of treatment with the combination preparation of insulin degludec (100 units/mL) plus liraglutide (3.6 mg/mL) administered subcutaneously via a 3mL Flexpen[®] once daily, and metformin at pre-trial dose, ($n=207$) or insulin degludec (100 units/mL) administered subcutaneously via a 3mL Flexpen[®] once daily and metformin, at pre-trial dose, ($n= 206$). Patients were selected who were inadequately controlled (HbA_{1c} 7.5 to 10% inclusive) on basal insulin and metformin with or without sulphonylureas and/or glinides. They had to have a BMI ≥ 27 kg/m² and have been treated with basal insulin for ≥ 90 days at a stable dose (20 – 40 units/day [$\pm 10\%$]). All glucose lowering drugs (with the exception of metformin) were discontinued at allocation and patients were commenced on either insulin degludec (at a dose of 16 units) alone or the combination product of insulin degludec plus liraglutide (at a dose of 16 dose steps; 16 units of insulin degludec and 0.6 mg liraglutide). Doses were adjusted bi-weekly based on self-measured pre-breakfast glucose concentration (mean from previous 3 consecutive days) aiming for 4.0 – 5.0 mmol/L, with a maximum dose of 50 units of insulin degludec and 50 dose steps of the combination of insulin degludec and liraglutide (50 units of insulin degludec and 1.8 mg liraglutide (see note above re liraglutide 1.8 mg dose)).

Completion rates were 85% for the insulin degludec plus liraglutide arm and 83% for insulin degludec arm. The primary endpoint of mean change in HbA_{1c} from baseline at week 26 resulted in a reduction of 1.9% for insulin degludec plus liraglutide and 0.89% for insulin degludec to 6.9% and 8% respectively. The estimated treatment difference was -1.1% [95% CI -1.3% and -0.8%] $P < 0.0001$, confirming superiority of insulin degludec plus liraglutide over insulin degludec. Secondary endpoints included achievement of $HbA_{1c} < 7.0\%$ and $\leq 6.5\%$ with or without confirmed hypoglycaemia or weight gain. At 26 weeks 40% of participants in the insulin degludec plus liraglutide group achieved a $HbA_{1c} < 7.0\%$ without any confirmed hypoglycaemic episodes (during the last 12 weeks of treatment) and without weight gain compared to 8.5% in the insulin degludec group. For those who achieved a $HbA_{1c} \leq 6.5\%$ without confirmed hypoglycaemia and weight gain was 29.6% for the combination of insulin degludec plus liraglutide compared to 4.5% for insulin degludec. Mean bodyweight from baseline decreased by 2.7kg for insulin degludec plus liraglutide arm compared with no weight change for insulin degludec arm, resulting in an estimated treatment difference of 2.5kg [95% CI -3.2, -1.8] $P < 0.0001$. At lower mean HbA_{1c} values the incidence of confirmed hypoglycaemia was comparable for insulin degludec plus liraglutide and insulin degludec of 24% and 25% respectively.

Further to this evidence, data from NCT01618162 (DUAL IV) was submitted during the European Medicines Agency's assessment of insulin degludec plus liraglutide. Please note, neither a full article nor an abstract are available for this. The following information is taken directly from the EPAR:

NCT01618162⁴: A 26 week phase III, double-blinded, parallel, placebo-controlled, treat-to-target RCT in 434 subjects with type 2 diabetes mellitus inadequately controlled (HbA_{1c} 7% - 9%) on their current OAD regimen consisting of sulphonylurea +/- metformin, comparing the efficacy of insulin degludec plus liraglutide once daily with placebo once daily, both added on to current OADs. Mean HbA_{1c} was reduced by 1.45% to 6.4% in the insulin degludec plus liraglutide group in comparison to a reduction of 0.46% to 7.4% in the placebo group (estimated mean treatment difference: -1.02 [-1.18 – 0.87] $p < 0.001$). In both treatment groups the weight remained relatively stable throughout the trial; the mean weight increased in the insulin degludec plus liraglutide group by 0.5 kg whereas it decreased in the placebo group by 1 kg. The estimated mean treatment difference in weight between insulin degludec plus liraglutide and placebo was 1.48 kg, $p < 0.001$; however, this was less than the baseline difference between the groups.

The EMA summarised that “The additive effect of the two components have been adequately shown and although the benefit in terms of additional reduction of HbA_{1c} may be of moderate clinical relevance (about 0.5 %) compared to the mono-components, there are other benefits in terms of insulin dose requirements, weight control and hypoglycaemia risk.”

Other efficacy data:

Supportive data from NCT01388361⁷ Mathieu C. et al. was submitted to the European Medicines Agency. See a full summary of this trial in the Summary of Key RCTs table.

NCT01388361: In this 26 week open-label study, 177 patients with type 2 diabetes mellitus were recruited who had previously completed approximately 104 weeks of treatment with insulin degludec and metformin with an end of treatment HbA_{1c} \geq 7.0% and thereby qualifying for treatment intensification. Patients were randomised to the addition of liraglutide or insulin aspart, with the largest meal, to current insulin degludec and metformin therapy. The mean insulin degludec dose at 26 weeks was 60 units and 65.5% of patients were also taking 1.8 mg daily of liraglutide. This resulted in an estimated mean reduction in HbA_{1c} during the trial of -0.73% points with adding liraglutide in comparison to -0.4% points when adding insulin aspart. The results showed a statistically significant mean difference in HbA_{1c} of -0.32% 95% CI [-0.53 to -0.12] points in favour of insulin degludec plus liraglutide. Of note, this reduction in HbA_{1c} is less than in the DUAL I and DUAL II studies, (however mean baseline HbA_{1c} was lower in this study) and this in the context of the mean insulin degludec dose being 60 units. The observed proportion of subjects achieving HbA_{1c} <7% was 58.0% with insulin degludec and liraglutide and 44.9% with insulin degludec and insulin aspart, which was not statistically significant. The observed proportion of subjects achieving HbA_{1c} <7% without confirmed hypoglycaemia during the last 12 weeks of treatment and without weight gain was 49.4% with insulin degludec and liraglutide and 7.2% with insulin degludec and liraglutide, which was statistically significant.

Summary of safety data:

In the DUAL I study more patients withdrew from the liraglutide group than the insulin degludec or combination liraglutide plus insulin degludec groups; 18%, 12% and 12% respectively. The differences in withdrawals between the treatment groups were driven by higher proportions of subjects treated with liraglutide withdrawing due to adverse events (AE)s. Most of the AEs leading to withdrawal in the liraglutide arm were related to gastrointestinal events (16 out of 24). Withdrawal during the extension period was 5.3% with insulin degludec plus liraglutide, 6.8% with insulin degludec and 6.7% with liraglutide.⁵

In the DUAL II trial the rates of AEs were similar for both treatment arms; insulin degludec plus liraglutide 57.8% and insulin degludec 61.3%. The treatment emergent AEs occurring with a frequency of \geq 5% were; nausea, diarrhoea, headache, nasopharyngitis, lipase increase. A total of 16.2% of the subjects withdrew during the trial. The withdrawal rate was 15.5% in the insulin degludec and liraglutide treatment group and 17.0% in the insulin degludec treatment group. Subjects in both treatment groups withdrew due to withdrawal criteria AEs; ineffective therapy, non-compliance with protocol and for 'other' reasons. The 3 AEs leading to withdrawal in the insulin degludec arm were related to 'acute myocardial infarction', 'cholelithiasis' and 'ischaemic stroke', and the single AE withdrawal in the insulin degludec plus liraglutide arm was related to 'major depression'.⁶

In summary the safety profile for insulin degludec plus liraglutide is in general similar to the two included mono-components with no indications of additive toxicity. Since the actual liraglutide dose in the studies was lower and the up-titration of dose somewhat slower, the prevalence and severity of the well-known gastrointestinal side-effects were lower compared to liraglutide as monotherapy. No new safety issues have been identified for this combination. The incidence of confirmed hypoglycaemia was higher compared to liraglutide, but lower compared to insulin degludec in the active controlled studies. The incidence of hypoglycaemia was highest when insulin degludec plus liraglutide was combined with a sulphonylurea - relevant information has been included in the summary product characteristics (SPC). With regard to the long-term safety, the initial cardiovascular (CV) safety evaluation is acceptable with a potentially beneficial effect on systolic blood pressure in contrast to slight increase in heart rate in the clinical studies. A CV outcome study is ongoing for liraglutide. Otherwise, the long-term safety concerns are the same as for the other GLP-1 RAs and insulin analogues, i.e. identified risk of pancreatitis and potential risks of malignancies e.g. pancreatic and thyroid tumours.^{4,8}

Strengths and limitations of the evidence^{4,5,6,7}:

Strengths:

- The studies were generally well designed and conducted: NCT01336023 (DUAL I) and NCT01392573 (DUAL II) described the method of allocation, suggesting it was concealed; and had adequate power and size as well as adequate follow-up.
- In DUAL I there was no upper limit for the insulin degludec dose instead it was titrated until target glucose levels were met.

Limitations:

- In NCT01336023 (DUAL I), the starting dose of insulin degludec plus liraglutide was 10 dose-steps which provides 10 units of insulin degludec but only 0.36 mg liraglutide. This would be considered sub-therapeutic if liraglutide were to be given as a single agent. The inclusion criteria allowed for patients with an HbA_{1c} >7.0% to take part in the trial. These patients were insulin-naïve and 83% of patients randomised to either insulin degludec plus liraglutide or insulin degludec were taking metformin only and had a mean BMI of 31.2 kg/m². Thus much of the population would not ordinarily be considered for intensification of therapy with either insulin or a GLP-1 RA.
- NCT01392573 (DUAL II) is the key trial which provides evidence for Novo Nordisk's proposed use of this novel drug. It is of note that only 398 patients took part in this trial.
- The placebo-controlled NCT01618162 (DUAL IV) study showed the absolute effect of insulin degludec plus liraglutide when added to sulphonylurea +/- metformin but did not compare to another treatment approach such as those recommended in the current NICE guidelines e.g. addition of insulin alone or a DPP4-inhibitor or pioglitazone. This trial has not been published and an abstract and full text was unobtainable.
- The mean dose of insulin degludec at the end of NCT01388361 (Mathieu et al), in which some participants were given liraglutide in addition to insulin degludec as separate components, was 60 units. The maximum daily dose of insulin degludec plus liraglutide is 50 dose-steps, which gives a maximum of 50 units of insulin degludec. In addition, no formal sample size calculations were made and so this study may have been insufficiently powered to detect true statistical significance.
- In all trials, patients previously treated with GLP-1 RAs were excluded.
- Insulin degludec plus liraglutide has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors, glinides or prandial insulin.
- The primary outcome measured HbA_{1c} which is a disease oriented outcome.

Summary of evidence on cost effectiveness:

No published evidence on the cost-effectiveness of insulin degludec plus liraglutide has been identified in the UK.

Prescribing and risk management issues^{4,8}:

- Insulin degludec plus liraglutide, with its fixed ratio dosing, offers less flexibility to titrate the individual components and manage interruption of treatment, and at the initiation of treatment does not allow the prescriber to understand how the patient responds to or tolerates each component.
- In some insulin-naïve patients who do not obtain adequate glycaemic control on oral therapies, the addition of a single agent will be adequate to achieve glycaemic control, which means that some patients receiving insulin degludec plus liraglutide are exposed to a combination therapy unnecessarily. However, Novo Nordisk has identified its target market as patients currently uncontrolled on basal insulin.
- The maximum dose of insulin degludec is 50 units (giving a concomitant maximum liraglutide dose of 1.8 mg). There is a risk that in order to give higher insulin doses that unlicensed liraglutide doses will be administered.
- The incidences of AEs were similar in patients below and above age 65 years, but the number of subjects ≥ 75 years was very low.
- The clinical experience of insulin degludec plus liraglutide in patients with moderate renal impairment is very limited (n=11) and use is not recommended in line with recommendations for liraglutide.
- No confirmed episodes of pancreatitis were reported with insulin degludec plus liraglutide, but have been reported for other GLP-1 RAs. However, a mean increase of serum lipase and amylase was seen in the insulin degludec plus liraglutide and liraglutide groups compared to patients treated with insulin degludec alone. Acute pancreatitis has previously been identified as a potential safety issue for the GLP-1 RA class and the risk, albeit small, should be taken into account when prescribing these products.
- Although data from the extension period in NCT01336023 (DUAL I) indicate that efficacy is maintained over at least a year without the need for further dose increases the possibility to continue treatment over time will be limited, considering the progressive nature of the disease.
- **Special warnings and precautions for use taken from the SPC⁸:**
 - Xultophy[®] should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.
 - Hypoglycaemia may occur if the dose of Xultophy[®] is higher than required. Omission of a meal or unplanned strenuous physical exercise may lead to hypoglycaemia. In combination with sulphonylurea, the risk of hypoglycaemia may be lowered by a reduction in the dose of sulphonylurea. Concomitant diseases in the kidney, liver or diseases affecting the adrenal, pituitary or thyroid gland may require changes of the Xultophy[®] dose. Patients whose blood-glucose control is greatly improved (e.g. by intensified therapy) may experience a change in their usual warning symptoms of hypoglycaemia, and must be advised accordingly. Usual warning symptoms of hypoglycaemia may disappear in patients with long-standing diabetes. The prolonged effect of Xultophy[®] may delay recovery from hypoglycaemia.
 - Inadequate dosing and/or discontinuation of anti-diabetic treatment may lead to hyperglycaemia and potentially to hyperosmolar coma. In case of discontinuation of Xultophy[®], ensure that instruction for initiation of alternative anti-diabetic medication is followed. Furthermore, concomitant illness, especially infections, may lead to hyperglycaemia and thereby cause an increased requirement for antidiabetic treatment. Usually, the first symptoms of hyperglycaemia develop gradually over a period of hours or days. They include thirst, increased frequency of urination, nausea, vomiting, drowsiness, flushed dry skin, dry mouth, and loss of appetite as well as acetone odour of breath. Administration of rapid-acting insulin

should be considered in situations of severe hyperglycaemia. Untreated hyperglycaemic events eventually lead to hyperosmolar coma/diabetic ketoacidosis, which is potentially lethal.

- Combination of pioglitazone and insulin medicinal products: Cases of cardiac failure have been reported when pioglitazone was used in combination with insulin medicinal products, especially in patients with risk factors for development of cardiac failure. This should be kept in mind if treatment with the combination of pioglitazone and Xultophy[®] is considered. If the combination is used, patients should be observed for signs and symptoms of heart failure, weight gain and oedema. Pioglitazone should be discontinued if any deterioration in cardiac symptoms occurs.
- Eye disorder: Intensification of therapy with insulin with abrupt improvement in glycaemic control may be associated with temporary worsening of diabetic retinopathy, while long-term improved glycaemic control decreases the risk of progression of diabetic retinopathy.
- Antibody formation: Administration of Xultophy[®] may cause formation of antibodies against insulin degludec and/or liraglutide. In rare cases, the presence of such antibodies may necessitate adjustment of the Xultophy[®] dose in order to correct a tendency to hyper- or hypoglycaemia. Very few patients developed insulin degludec specific antibodies, antibodies cross-reacting to human insulin or anti-liraglutide antibodies following treatment with Xultophy[®]. Antibody formation has not been associated with reduced efficacy of Xultophy[®].
- Acute pancreatitis: Use of GLP-1 RAs, including liraglutide, has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute pancreatitis. If pancreatitis is suspected, Xultophy[®] should be discontinued; if acute pancreatitis is confirmed, Xultophy[®] should not be restarted. Caution should be exercised in patients with a history of pancreatitis.
- Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm have been reported in clinical trials with GLP-1 RAs, including liraglutide, in particular in patients with pre-existing thyroid disease, and Xultophy[®] should therefore be used with caution.
- Inflammatory bowel disease and diabetic gastroparesis: There is no experience with Xultophy[®] in this group and is therefore not recommended in these patients.
- Dehydration: Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in clinical trials with GLP-1 RAs including liraglutide. Patients treated with Xultophy[®] should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.
- Avoidance of medication errors: Patients must be instructed to always check the pen label before each injection to avoid accidental mix-ups between Xultophy[®] and other injectable diabetes medicinal products.
- Populations not studied:
 - Transfer to Xultophy[®] from doses of basal insulin > 40 units has not been studied.
 - Transfer from GLP-1 RAs has not been studied.
 - Xultophy[®] has not been studied in combination with dipeptidyl peptidase 4 (DPP-4) inhibitors, glinides or prandial insulin.
 - There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and Xultophy[®] should therefore be used with caution. There is no experience in patients with congestive heart failure NYHA class III-IV and Xultophy[®] is therefore not recommended in these patients.

Commissioning considerations:

Example acquisition costs of basal insulins and Liraglutide:

Product name	5 x 3mL cartridge	5 x 3mL pre-filled pen	3 x 3ml pre-filled pen	2 x 3ml pre-filled pens	Estimated annual cost per patient
Insulin degludec plus liraglutide 100 units/ 3.6mg /ml (Xultophy®)	£159.22				For a maximum dose of 50 dose-steps (50 units of insulin degludec and 1.8mg liraglutide): £1937
Liraglutide (Victoza®)			£117.72	£78.48	For the 1.2mg daily dose recommended by NICE: £952 For the 1.8mg daily dose £1432
Insulin degludec (Tresiba®) 100 units/mL 200 units/mL	£72.00 n/a	£72.00 n/a	n/a £86.40		£526-£1051 (£876 if patient were prescribed 50 units daily)
NPH (isophane) insulin: Insulatard® Humulin I® Insuman Basal®	£22.90 £19.08 £17.50	£20.40 £21.70 £19.80	n/a n/a n/a		£149-£334 £139-£317 £128-£289
Insulin glargine (Lantus®)	£41.50	£41.50	n/a		£303-£606
Insulin detemir (Levemir®)	£42.00	£42.00	n/a		£307-£613
<p>Costs based on cost/unit derived from MIMS list prices as of 12th January 2015 and assumed dosing of 30 to 60 units daily. Costs of needles and disposables excluded. This table does not imply therapeutic equivalence of drugs or doses.</p>					

Associated additional costs or available discounts:

<p>Additional costs: 1 Novofine or Novotwist disposable needle per day = 9p-13p 1 blood glucose monitoring strip and lancet daily = 2p-6p</p> <p>(Costs based on cost/unit derived from MIMS list prices as of 12th January 2015).</p> <p>No available discounts.</p>

Productivity, service delivery, implementation:

- Insulin degludec plus liraglutide would be an additional treatment option.
- Diabetes clinics are already in operation and there should be no requirement for additional services.
- Educational materials and training need to be made available to prospective patients and all clinicians expected to be involved in the treatment and management of patients with T2DM, in addition to all pharmacists who are expected to dispense Xultophy[®]. These should ensure there is an increased awareness of a new fixed-combination insulin degludec and liraglutide (GLP1-based product) as well as a good understanding of the key aspects of the product including, posology of the product, the meaning of “dose-steps” and a reminder of the need to report all medication errors.

Anticipated patient numbers and net budget impact:

The following information is taken from the Novo Nordisk Budget Impact Model for the use of insulin Xultophy[®] in the population in Lancashire.

Estimated population requiring treatment optimisation:

The eligible population is defined as adults (18 years or over) with type 2 diabetes currently uncontrolled on a basal insulin.

Within the total population of Lancashire (1,500,000) the number of adults is 1,179,000 (78.6%). Of this 1,179,000 6% have diabetes, and of this 70,740 population 90% (63,666) have T2DM.

Of these 63,666 3.2% (2037) are treated with basal insulin analogues and of these 69% are uncontrolled defined as an HbA1c of >7.5% which is equal to 1406 patients.

With an estimated average uptake of 5%, 7% and 10% of the eligible populations in years 1, 2 and 3, respectively, in Year 1, 70 new patients would switch to insulin degludec/liraglutide instead of existing options.

Estimated current prescribing costs:

The estimated annual drug expenditures for patients inadequately controlled on basal insulin in the next year are included in Table 1⁹:

Table 1: The proportion of patients and total cost for each current therapeutic option

Treatment	% Patients	Total annual per population cost
Basal-bolus insulin	53.0%	£506,265
Basal insulin + GLP-1RA	9.0%	£172,886
Biphasic insulin	38.0%	£226,361
Self-monitoring and needles	-	£736,855
Total		£1,642,367

The prescribing cost for current treatment intensification is estimated to be £1,642,367. This value includes the direct cost of injectable therapies, self-monitoring and needles. Costs for concurrent oral medications, complications of diabetes (for example hypoglycaemic episodes) and all other supportive treatments are not included.

Prescribing costs for treatment optimisation with Xultophy®

The mean end of trial insulin degludec and liraglutide dose, when used following basal insulin failure (DUAL II clinical study) was 45 units / 1.62 mg (insulin degludec / liraglutide)

The insulin degludec and liraglutide doses used in the model were 38 units and 1.37 mg respectively which have an annual cost of £1,472.

It was estimated by the company that in year 1, 5% of patients would switch to Xultophy® instead of existing treatment intensification strategies, increasing to 10% of patients by year 3. It was assumed that the uptake will be taken from current intensification options proportionally to their market share detailed in Table 1, see Table 2. The estimated annual drug expenditures for new patients requiring treatment intensification (with insulin Xultophy® included as a treatment option) are included in Table 3.

Table 2: The proportion of new patients prescribed each therapeutic option including Xultophy® if made available

	Year 1	Year 2	Year 3
Therapeutic option	% Patients		
Insulin degludec/liraglutide	5.0%	7.0%	10.0%
Basal-bolus insulin	50.4%	49.3%	47.7%
Basal insulin + GLP-1RA	8.6%	8.4%	8.1%
Biphasic insulin	36.1%	35.3%	34.2%

Table 3: Costs of new patients prescribed each therapeutic option including Xultophy® if made available

	Year 1	Year 2	Year 3
New patients intensifying their treatment regimen	1,406	1,406	1,406
Therapeutic option	Costs for new patients each year		
Switching to insulin degludec/liraglutide	£103,486	£144,881	£206,973
Adding bolus insulin	£480,952	£470,827	£455,639
Adding a GLP-1 RA	£164,242	£160,784	£155,597
Switching to biphasic insulin	£215,043	£210,516	£203,725
Self-monitoring and needles	£712,316	£702,501	£687,777

Budget impact results

The estimated annual budget impact for insulin Xultophy® is provided in Table 4. This budget impact is the difference between the estimated current prescribing cost for treatment optimisation and the estimated prescribing costs for new patients undergoing treatment optimisation including insulin Xultophy®.

Table 4: Budget impact new patients intensifying their treatment regimen

	Year 1	Year 2	Year 3
New patients intensifying their treatment regimen	1,406	1,406	1,406
New insulin degludec/liraglutide patients	70	98	141
	Budget impact for new patients each year		
Budget impact	£33,672	£47,141	£67,344

The cumulative budget impact which assumes that patients remain on the chosen escalation therapy is provided in Table 5.

Table 5: Budget impact for cumulative patients intensifying their treatment regimen

	Year 1	Year 2	Year 3
Cumulative patients who underwent treatment intensification	1,406	2,812	4,218
Cumulative insulin degludec/liraglutide patients	70	169	309
	Budget impact for cumulative patients		
Budget impact	£33,672	£80,812	£148,156

Of note, two local diabetologists have indicated they would consider prescribing insulin Xultophy®:

The target population for one consultant would be patients poorly controlled with Type 2 diabetes, overweight and on relatively small doses of basal insulin who also have significant hypoglycaemia risk or in those whom hypoglycaemia would have negative impact on quality of life and work. The estimated number of patients per year in his secondary care setting was 10.

The target population for another consultant diabetologist was Type 2 patients with diabetes who are overweight, poorly controlled and have a fear of hypoglycaemia. This consultant estimated there could be 50 patients who fit these criteria.

Innovation, need, equity:

- Innovation: Xultophy® is a novel fixed-dose combination of long-acting insulin (insulin degludec) with a GLP1 RA (liraglutide), however robust evidence that this novel combination has a clear therapeutic advantage in routine use, over other treatment options is currently lacking.
- Need: According to Novo Nordisk, approximately 69% of patients with T2DM on basal insulin regimens in the UK fail to reach HbA1c <7.5% (58 mmol/mol), putting them at increased risk of developing diabetes-related complications such as diabetic retinopathy, neuropathy, diabetic foot complications, cardiovascular disease and nephropathy. Other treatment strategies are already available to treat such patients such as basal bolus insulin, biphasic insulin or addition of a GLP-1 RA as per NICE guidance.
- Equity: Current feedback indicates that only some local diabetologists will consider prescribing this product.

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Table: Summary of key drug RCTs relevant to use in Xultophy[®] (insulin degludec plus liraglutide)

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
NCT01336023 DUAL I ⁵	Phase III, open-label, parallel, three-arm, treat-to-target RCT with a 26 week main phase, followed by a 26 weeks extension phase to provide evidence of persistence of efficacy and safety during long-term exposure. (n=1660)	<p>Adults with T2DM inadequately controlled on metformin +/- pioglitazone HbA_{1c} of 7.0% - 10.0% (inclusive)</p> <p>Mean age: 55yrs Female: 49.8% White: 62.6% Mean diabetes duration: 6.85 years Mean bodyweight: 87.3kg BMI: ≤ 40kg/m² Mean HbA_{1c} at baseline: 8.3%</p> <p>Subjects on a stable daily dose of 1 or 2 OADs (metformin (≥1500 mg or max tolerated dose) or metformin (≥1500 mg or max tolerated dose) + pioglitazone (≥30 mg) for at least 90 days prior to screening.</p> <p>Able and willing to perform SMBG according to protocol, keep a diabetes diary and use a pre-filled pen or FlexPen[®] device.</p> <p>Exclusion criteria: Previous treatment with insulin (except for short-term treatment due to intercurrent illness at the discretion of the</p>	<p>Previous pre-trial OADs regimen alongside insulin degludec plus liraglutide injected subcutaneously once daily, at any time of day, starting dose of 10 dose-steps and titrated twice weekly to a fasting plasma glucose concentration (FPG) target of 4-5 mmol/L. (n=833; 755 completed study)</p> <p>Previous pre-trial OADs regimen alongside insulin degludec injected once daily, starting dose of 10 units, titrated twice-weekly to achieve a pre-breakfast FPG concentration of 4-5 mmol/L. (n=414; 374 completed study)</p> <p>Previous pre-trial OADs regimen alongside liraglutide 1.8 mg daily. (n=413; 362 completed study)</p>	<p>Primary endpoint:</p> <p>Change in HbA_{1c} after 26 weeks of treatment:</p> <p>Non-inferiority to insulin degludec was demonstrated with a mean decrease in HbA_{1c} for insulin degludec plus liraglutide of 1.9% (to 6.4%) and 1.4% (to 6.9%) for insulin degludec (estimated mean treatment difference (ETD) 0.47 [95% CI -0.58 to -0.36] p<0.0001).</p> <p>Superiority to liraglutide was demonstrated with a mean decrease in HbA_{1c} of 1.3% (to 7.0%) for liraglutide. (ETD -0.64 [95% CI -0.75 to -0.53] p<0.0001).</p>	<p>Key secondary efficacy endpoints were:</p> <p>Achievement of end of trial HbA_{1c} < 7.0%: insulin degludec plus liraglutide 81%, insulin degludec 65% OR 2.38 [95% CI 1.78 – 3.18] p<0.0001, liraglutide 60% OR 3.26 [95% CI 2.45 – 4.33] p<0.0001</p> <p>Achievement of end of trial HbA_{1c} ≤ 6.5%: insulin degludec plus liraglutide 70%, insulin degludec 47% OR 2.82 [95% CI 2.17 – 3.67] p<0.0001, liraglutide 41% OR 3.98 [95% CI 3.05 – 5.18] p<0.0001</p> <p>Changes in body weight: insulin degludec plus liraglutide -0.5 kg, insulin degludec +1.6 kg (ETD -2.22 kg [95% CI -2.64 to -1.80] p<0.0001), liraglutide -3.0 kg (ETD +2.44 kg [95% CI 2.02 to 2.86 p<0.0001).</p> <p>Mean insulin dose: insulin degludec plus liraglutide 38 units, insulin degludec 53 units (ETD -14.90 units [95% CI -17.14 to -12.66] p<0.0001).</p> <p>Hypoglycaemic episodes:</p>	<p>Patient-oriented outcome measure? No - HbA_{1c} is a DOO.</p> <p>Allocation concealment? Yes</p> <p>Blinded if possible? No</p> <p>Intention to treat analysis? Yes</p> <p>Adequate power/size? Yes</p> <p>Adequate follow-up (>80%)? Yes</p> <p>Level 3 evidence based on DOO.</p> <p>Risk of bias unclear based on lack of blinding; however there was</p>

		<p>investigator) Treatment with GLP-1 RA, sulphonylurea or DPP4-inhibitor within 90 days prior to trial Impaired liver function (ALT \geq 2.5 times ULN Impaired renal function (serum creatinine \geq133 μmol/L for males and \geq 125 μmol/L for females) Contraindications to metformin CHF (NYHA class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or MI within the last 12 months and planned coronary, carotid or peripheral artery revascularisation procedures Severe uncontrolled treated or untreated hypertension (systolic BP \geq 180 mmHg or diastolic BP \geq 100 mmHg) History of chronic pancreatitis or idiopathic acute pancreatitis Cancer except for basal cell or squamous cell skin cancer, or cancer during the past 5 years Contraindications or restrictions to use of pioglitazone</p>			<p>insulin degludec plus liraglutide 32%, insulin degludec 39%, (rate ratio 0.68 [95% CI 0.53 to 0.87] $p=0.0023$), liraglutide 7% (rate ratio 7.61 [95% CI 5.17 to 11.21] $p<0.0001$)</p> <p>HbA1c <7.0% without weight gain or hypoglycaemia: (in last 12 weeks of treatment) insulin degludec plus liraglutide 36%, insulin degludec 14% (OR 3.56 [95% CI 2.59 to 4.90] $p<0.0001$) liraglutide 52% (OR 0.49 [95% CI 0.38 to 0.63] $p<0.0001$)</p> <p>HbA1c \leq6.5% without weight gain or hypoglycaemia: (in last 12 weeks of treatment) insulin degludec plus liraglutide 32%, insulin degludec 9% (OR 5.03 [95% CI 3.47 to 7.30] $p<0.0001$) liraglutide 38% (OR 0.79 [95% CI 0.61 to 1.02] $p<0.06$)</p> <p>Reduction in FPG (fasting plasma glucose): decrease from baseline for insulin degludec plus liraglutide 3.6 mmol/L (to 5.6 mmol/L), insulin degludec 3.6 mmol/L (to 5.8 mmol/L), (ETD -0.17 mmol/L [95% CI -0.41 to 0.07] $p=0.16$) liraglutide 1.8 mmol/L (to 7.3 mmol/L) (ETD -1.76 [95% CI -2.00 to -1.53] $p<0.0001$).</p>	<p>allocation concealment, adequate power, follow-up and intention-to-treat analysis.</p>
NCT01392573 DUAL II ⁶	Phase III double-blinded, parallel, two-arm, treat-to-target RCT 26	Adults T2DM inadequately controlled (HbA _{1c} of 7.5% - 10.0% (both inclusive))	Insulin degludec plus liraglutide in combination with pre-trial dose metformin.	Primary endpoint: Change in HbA_{1c} after 26 weeks of treatment to	Secondary endpoints: Achievement of end of trial HbA_{1c} < 7.0%: insulin	Patient-oriented outcome measure?

	<p>weeks duration. n= 398</p>	<p>On 20-40 units of basal insulin and 1 or 2 OADs (metformin or metformin + sulphonylurea or glinides) on stable daily doses for at least 90 days prior to screening of basal insulin BMI ≥ 27 kg/m² Able and willing to perform SMBG according to protocol, keep a diabetes diary and use a FlexPen[®] device.</p> <p>Mean age: 57.5 years Female: 45% White: 78% Mean diabetes duration: 10.5 years Mean BMI: 33.7 kg/m²</p> <p>Exclusion criteria: Treatment with GLP-1 receptor agonists, DPP4 inhibitors and/or thiazolidinediones within 90 days prior to screening Impaired liver function (ALT ≥ 2.5 times ULN Impaired renal function (serum creatinine ≥ 133 μmol/L for males or ≥ 125 μmol/L for females) CHF (NYHA class III-IV), diagnosis of unstable angina pectoris, cerebral stroke and/or MI within the last 12 months and planned coronary, carotid or peripheral artery revascularisation procedures Severe uncontrolled treated or untreated hypertension (systolic BP ≥ 180mmHg or diastolic BP ≥ 100mmHg)</p>	<p>Starting dose of 16 dose-steps of insulin degludec plus liraglutide once daily and titrated twice-weekly to a FPG target of 4-5mmol/L. Maximum dose of 50 dose-steps (n=207; 175 completed study)</p> <p>Insulin degludec in combination with pre-trial dose metformin. Starting dose of 16 units of insulin degludec, dosed once daily and titrated twice-weekly to a FPG target of 4-5 mmol/L. Maximum dose of 50 units.(n=206; 171 completed study)</p>	<p>confirm superiority: Insulin degludec plus liraglutide 1.9% (to 6.9%), insulin degludec 0.89% (to 8%) (ETD -1.05 % [95% CI - 1.25 to -0.84] p < 0.0001).</p>	<p>degludec plus liraglutide 60%, insulin degludec 23% OR 5.44 [95% CI 3.42 – 8.66] p<0.0001</p> <p>HbA1c <7.0% without weight gain or hypoglycaemia: (in last 12 weeks of treatment) insulin degludec plus liraglutide 40%, insulin degludec 8.5% (OR 7.44 [95% CI 4.08 to 13.57] p<0.0001)</p> <p>Achievement of end of trial HbA_{1c} \leq 6.5%: insulin degludec plus liraglutide 45%, insulin degludec 13.1% (OR 5.66 [95% CI 3.37 – 9.51] p<0.0001)</p> <p>HbA1c \leq6.5% without weight gain or hypoglycaemia: (in last 12 weeks of treatment) insulin degludec plus liraglutide 30%, insulin degludec 9% (OR 9% [95% CI 4.15 to 18.89] p<0.0001)</p> <p>Hypoglycaemic episodes: insulin degludec plus liraglutide 24%, insulin degludec 25%, (rate ratio 0.66 [95% CI 0.39 to 1.13] p value reported as not significant.</p> <p>Mean actual daily insulin dose (after 26 weeks of treatment): insulin degludec plus liraglutide 45 units, insulin degludec 45 units. (In insulin degludec plus liraglutide treated subjects 65.3% reached a daily dose of 50 dose steps and 67.3% of</p>	<p>DOO</p> <p>Allocation concealment? Yes</p> <p>Blinded if possible? Yes</p> <p>Intention to treat analysis?</p> <p>Adequate power/size? Yes</p> <p>Adequate follow-up (>80%)? Yes</p> <p>Level 3 evidence based on DOO.</p> <p>Risk of bias low based on allocation concealment, blinding, power and follow-up.</p>
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		H/O chronic pancreatitis or idiopathic acute pancreatitis Cancer except for basal cell or squamous cell skin cancer, or cancer during the past 5 years			the insulin degludec treated subjects reached a daily insulin dose of 50 units). Mean body weight (after 26 weeks of treatment): Insulin degludec plus liraglutide 92.7 kg, insulin degludec 93.5 kg. Change in body weight (from baseline to week 26): Insulin degludec plus liraglutide -2.7 kg, insulin degludec 0.0 kg (ETD -2.51 kg [95% CI -3.21 to -1.82] p < 0.0001) Adverse Events: Insulin degludec plus liraglutide 58% Insulin degludec 61% Reduction in FPG (at 26 weeks from baseline): Insulin degludec plus liraglutide 3.5 mmol/L (to 6.2 mmol/L), insulin degludec 2.6 mmol/L (to 7.0mmol/L) (ETD - 0.73 mmol/L [95% CI -1.19 to -0.27] p=0.0019).	
NCT01388361 Mathieu et al. ⁷	Phase III, open-label, two arm, treat-to-target, RCT n=177 26 weeks.	Adults with T2DM who completed approximately 104 weeks of treatment with insulin degludec + metformin in trial NN1250-3579 and the extension trial NN1250-3643, and with an end-of-treatment HbA _{1c} ≥ 7% Mean age: 61yrs Female: 34% White: 92% Mean diabetes duration: 12.3	Liraglutide once daily as add on to metformin + insulin degludec. Starting dose of liraglutide of 0.6 mg daily, increased to 1.2mg daily after one week, and then maintained at 1.2 mg daily until week 5 whereby the dose could be further increased to 1.8 mg daily if needed, based on FPG.	Primary endpoint: Change in HbA_{1c} after 26 weeks of treatment (for non-inferiority): insulin degludec + liraglutide 0.74 % (to 7.0%) and 0.39 % (to 7.3%) for insulin degludec + insulin aspart (estimated mean treatment difference (ETD) 0.32 [95% CI -0.53 to -0.12] p=0.0024).	Secondary endpoints: Achievement of end of trial HbA_{1c} < 7.0%: insulin degludec + liraglutide 58%, insulin degludec + insulin aspart 44.9% (paper states not statistically significantly different) HbA_{1c} <7.0% without weight gain or hypoglycaemia: insulin degludec + liraglutide 49.4%, insulin degludec +	Patient-oriented outcome measure? DOO Allocation concealment ? Yes Blinded if possible? Not possible to blind the

		<p>years Mean bodyweight: 93.3kg Mean BMI: 32.3 kg/m²</p> <p>Ability and willingness to adhere to the protocol including self-measurement of plasma glucose according to the protocol</p> <p>Exclusion criteria: Previous treatment with GLP-1 RAs (e.g. exenatide, liraglutide) Impaired liver function, ALT 2.5 times ULN Impaired renal function defined as serum-creatinine $\geq 125 \mu\text{mol/l}$ ($\geq 1.4 \text{ mg/dL}$) for males and $\geq 110 \mu\text{mol/l}$ ($\geq 1.3 \text{ mg/dL}$) for females Stroke; NYHA class III or IV MI; unstable angina pectoris; or CABG or angioplasty (within the last 24 weeks prior to "visit 1") Recurrent severe hypoglycaemia (>1 severe hypoglycaemic event during last 12 months) or hypoglycaemic unawareness as judged by the investigator Uncontrolled or untreated severe hypertension defined as systolic blood pressure 180 mmHg and/or diastolic blood pressure $\geq 100 \text{ mmHg}$. Subjects that are diagnosed with acute pancreatitis must be withdrawn from the trial.</p>	<p>Metformin continued at pre-trial dose. Insulin degludec starting dose based on individual end-of-treatment dose in Trial NN1250-3643, hereafter titration of dose according to titration guideline.(n=88 completed study)</p> <p>Insulin aspart once daily, with the main meal of the day, as add on to metformin + insulin degludec. Metformin continued at pre-trial dose. Insulin degludec starting dose based on individual end-of-treatment dose in Trial NN1250-3643, hereafter titration of dose according to titration guideline.(n=89 completed study)</p>		<p>insulin aspart 7.2% (OR 13.79 [95% CI 5.24 to 36.28] $p < 0.0001$)</p> <p>Change in body weight: Insulin degludec + liraglutide - 2.8 kg, insulin degludec + insulin aspart 0.9 kg (ETD - 3.75 kg [95% CI -4.70 to -2.79] $p < 0.0001$)</p> <p>Hypoglycaemic episodes (per patient year of exposure): insulin degludec + liraglutide 1.00, insulin degludec + insulin aspart 8.15, (rate ratio 0.13 [95% CI 0.08 to 0.21] $p < 0.0001$)</p> <p>Mean FPG: Insulin degludec + liraglutide - 0.14 mmol/L (to 6.3 mmol/L), insulin degludec + insulin aspart -0.004 mmol/L (steady at 6.1 mmol/L) (ETD 0.06 mmol/L [95% CI -0.65 to 0.77] $p = 0.0019$).</p>	<p>patients but the investigators were blinded</p> <p>Intention to treat analysis? Yes</p> <p>Adequate power/size? No</p> <p>Adequate follow-up (>80%)?: Yes</p> <p>Level 3 evidence based on inadequate power/size.</p> <p>Risk of bias: High based on inadequate power/ small population and no blinding for patients.</p>
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		Subjects randomized to the liraglutide arm who are unable to tolerate a dose of liraglutide 1.2 mg must be withdrawn.				
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Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: <ul style="list-style-type: none"> • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings 	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: <ul style="list-style-type: none"> • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies 	
Level 3	Disease-oriented evidence, or evidence from: <ul style="list-style-type: none"> • consensus guidelines • expert opinion • case series 	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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