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Health Technology Briefing
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Insulin icodec for treating Type 1 and Type 2 diabetes

Company/Developer	Novo Nordisk Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 33362	NICE ID: 11770	UKPS ID: 663426

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Insulin icodec is currently in clinical development for the treatment of Type 1 (T1D) and Type 2 (T2D) diabetes mellitus. Diabetes mellitus is a condition where blood glucose levels are too high due to an issue with either insulin production (T1D) or insulin resistance (T2D). Insulin is a hormone that controls blood glucose levels. T1D occurs due to an autoimmune response against pancreatic cells that produce insulin whilst T2D occurs when cells no longer react to insulin in the correct way – both result in high glucose levels which can cause severe dehydration, diabetic comas, vision problems and permanent damage to nerves, kidneys, and blood vessels. Current treatment requires daily insulin injections which can hinder adherence to treatment and be a burden to individuals.

Insulin icodec is a basal insulin analogue meaning it is given to individuals to maintain their insulin levels. Insulin icodec is advantageous over other basal insulin analogues as it can last for up to one week at high concentrations, meaning it is suitable for once weekly subcutaneous injections (under the skin). If licensed, insulin icodec, administered weekly by SC injection, will provide an additional treatment option for adult patients with T1D or T2D.

Proposed Indication

Treatment of type 1 (T1D) and 2 (T2D) diabetes mellitus in adult patients.[1-6]

Technology

Description

Insulin icodec (LAI287, Insulin 287) is a basal insulin analogue administered once weekly that is in development for the treatment of patients with diabetes. With a time to maximum concentration of 16 hours and a half-life of approximately one week, insulin icodec has a pharmacokinetic and pharmacodynamic profile suitable for once-weekly injection.[7] The long half-life of icodec can be attributed to its strong, reversible albumin binding, reduced enzymatic degradation, and slow receptor-mediated clearance. After subcutaneous (SC) injection and absorption into the circulation, icodec monomers bind to albumin to form an essentially inactive depot, from which icodec molecules slowly reach insulin receptors at target tissues to stimulate glucose lowering. With each weekly injection, the pool of albumin-bound icodec gradually increases, until steady state is reached after 3–4 weeks when the full glucose-lowering effect is achieved, and insulin clearance matches administered insulin dose. At steady state, a slow, continuous release of icodec from the inactive albumin-bound depot provides effective glucose lowering throughout the week, which was shown to be near evenly distributed across a 1-week dosing interval.[8]

In phase III clinical trials (NCT04460885, NCT04770532, NCT04795531, NCT04880850, NCT04760626, NCT04848480), insulin icodec is given once weekly as a SC injection.[1-6]

Key Innovation

Insulin icodec has the advantage over other insulin analogues by only needing to be administered once a week, in comparison to once or twice a day, which has the potential to increase adherence.[9] Previous data have indicated that patients with type 2 diabetes would generally prefer fewer injections and greater flexibility than is typical of the current once-daily treatment options. Therefore, reducing the number of injections could potentially increase acceptance of and adherence to insulin treatment among patients with type 2 diabetes, thereby potentially improving glycaemic control.[10] As well as this, insulin treatment is particularly burdensome for those who have to administer it frequently and fewer injections may increase the quality of life of patients.[11]

If licensed, insulin icodec will offer an additional basal insulin analogue for the treatment of T1D and T2D in adult patients that can be administered once weekly.

Regulatory & Development Status

Insulin icodec does not currently have Marketing Authorisation in the EU/UK for any indication.

Insulin icodec is not currently in clinical trials for any other indication.

Patient Group

Disease Area and Clinical Need

Diabetes is a condition where blood glucose levels are too high. High blood glucose levels can lead to life-threatening complications such as diabetic ketoacidosis and hyperosmolar hyperglycaemic state, as well as permanent damage to the eyes, nerves, kidneys and blood vessels.[12] There are two main types of diabetes: T1D and T2D. T1D is a condition where blood glucose levels are too high due to pancreatic cells being unable to make sufficient insulin which results from an autoimmune reaction. Symptoms of T1D

include thirst, weight loss and frequent need to use the toilet. There are currently no cures for T1D. Risk factors for T1D are family history of the disease and age, with T1D usually developing in younger individuals.[13] T2D is caused by cells not responding normally to insulin i.e., insulin resistance. The pancreas tries to produce more insulin to overcome the resistance but this can only occur for so long before this does not work and blood glucose levels begin to rise.[14] There is an increased risk of T2D if an individual is obese, is of an older age, has a close relative with T2D or are of Asian, African Caribbean or black African origin.[15] Basal-bolus insulin treatments are common in diabetes treatment with long-acting insulin (basal) given daily alongside short-acting insulin (bolus) before meals.[16,17]

In the UK, more than 4.9 million people have diabetes with 13.6 million more at an increased risk of T2D. Of those with diabetes, around 90% have T2D and 8% have T1D.[18] In 2019, 3,319,266 individuals in England had diabetes.[19] Using the estimation that 98% of individuals have either T1D or T2D, around 3.25 million people would be eligible for this treatment in England. In 2020-21, in England, there were 39,563 finished consultant episodes (FCE) for T1D (ICD code E10), 24,961 admissions and 89,913 FCE bed days. In 2020-21, in England, there were 52,036 finished consultant episodes (FCE) for T2D (ICD code E11), 29,858 admissions and 180,826 FCE bed days.[20]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends SC insulin injection for treatment of T1D.[21] Basal-bolus insulin treatment regimens are common.[16,22,23]

NICE recommended treatment options for T2D are:[24]

- Metformin
- SGLT2 inhibitors
- DPP-4 inhibitors
- Pioglitazone
- Sulfonylureas
- GLP-1 receptor agonists
- Insulin (glargine, detemir, degludec, neutral protamine Hagedorn)

Clinical Trial Information

Trial	**ONWARDS 1;** NCT04460885, 2020-000442-34; A 78-week Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Glargine 100 Units/mL, Both in Combination With Non-insulin Anti-diabetic Treatment, in Insulin naïve Subjects With Type 2 Diabetes **Phase III –** Active, not recruiting **Location(s):** 5 EU countries, UK, USA and other countries **Primary completion date:** April 2022
Trial Design	Randomised, parallel assignment, open-label, active comparator
Population	N=984; aged 18 years and older; diagnosed with T2D 180 days or more prior to the day of screening; insulin naive
Intervention(s)	Insulin icodec (+ non-insulin anti-diabetic drug) SC injection once weekly for 78 weeks
Comparator(s)	Insulin glargine (+ non-insulin anti-diabetic drug) SC injection once daily for 78 weeks

Outcome(s)	Change in glycated haemoglobin (HbA1c) [Time frame: From baseline week 0 to week 52] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**ONWARDS 2; NCT04770532, 2020-000454-10;** A 26-week Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Degludec, Both With or Without Non-insulin Anti-diabetic Drugs, in Subjects With Type 2 Diabetes Treated With Basal Insulin **Phase III –** Completed **Location(s):** 4 EU countries, USA and other countries **Study completion date:** March 2022
Trial Design	Randomised, parallel assignment, open-label, active comparator
Population	N=526; aged 18 years and older; diagnosed with T2D greater than or equal to 180 days prior to the day of screening.
Intervention(s)	Insulin icodec (+ non-insulin anti-diabetic drugs) SC injection once weekly for 26 weeks
Comparator(s)	Insulin degludec (+ non-insulin anti-diabetic drugs) SC injection once daily for 26 weeks
Outcome(s)	Change in HbA1c [Time frame: from baseline week 0 to week 26] See trial record for full list of other outcomes
Results (efficacy)	• Trial achieved its primary endpoint of demonstrating non-inferiority in reducing HbA1c at week 26 with insulin icodec compared to insulin degludec • From an overall baseline HbA1c of 8.13%, once-weekly insulin icodec achieved a superior reduction in estimated HbA1c of 0.93% compared to 0.71% for insulin degludec • There was no statistical difference in estimated hypoglycaemia rates, and no severe hypoglycaemia events were observed for people treated with insulin icodec. The rates of severe or clinically significant hypoglycaemia (blood glucose below 3 mmol/L) were 0.73 events per patient year exposed to once-weekly insulin icodec and 0.27 events per patient-year exposed to insulin degludec.[25]
Results (safety)	• Once-weekly insulin icodec appeared to have a safe and well-tolerated profile.[25]

Clinical Trial Information	
Trial	**ONWARDS 3:** NCT04795531, 2020-000472-37; A 26-week Double Blinded, Multiregional, Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Degludec 100 Units/mL, Both in Combination With Non-insulin Anti-diabetic Drugs, in Insulin naïve Subjects With Type 2 Diabetes. **Phase III –** Active, not recruiting **Location(s):** 4 EU countries, USA, Canada and other countries **Primary completion date:** May 2022
Trial Design	Randomised, parallel assignment, quadruple blinded, placebo controlled
Population	N=574; aged 18 years and older; diagnosed with T2D greater than or equal to 180 days prior to the day of screening; insulin naive
Intervention(s)	• 700 units/ml insulin icodec once weekly SC injection • 100 units/ml insulin degludec once daily SC injection
Comparator(s)	Matched placebos
Outcome(s)	Change in HbA1c [Time frame: From baseline week 0 to week 26] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**ONWARDS 4;** NCT04880850, 2020-000474-16; A 26-week Trial Comparing the Effect and Safety of Once Weekly Insulin Icodec and Once Daily Insulin Glargine 100 Units/mL, Both in Combination With Bolus Insulin With or Without Non-insulin Anti-diabetic Drugs, in Subjects With Type 2 Diabetes on a Basal-bolus Regimen **Phase III –** Active, not recruiting **Location(s):** 4 EU countries, USA and other countries **Primary completion date:** June 2022
Trial Design	Randomised, parallel assignment, open-label, active comparator
Population	N=578; aged 18 years and older; diagnosed with T2D greater than or equal to 180 days prior to the day of screening; HbA1c from 7.0-10.0%
Intervention(s)	Insulin icodec once weekly by SC injection for 26 weeks in combination with insulin aspart by SC injection 2-4 times daily
Comparator(s)	Insulin glargine once weekly by SC injection for 26 weeks in combination with insulin aspart by SC injection 2-4 times daily
Outcome(s)	Change in HbA1c [Time frame: From baseline week 0 to week 26]

	See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**ONWARDS 5**; NCT04760626, 2020-000476-38; Effectiveness and Safety of Once Weekly Insulin Icodec Used With DoseGuide Versus Once Daily Basal Insulin Analogues in an Insulin naïve Type 2 Diabetes Population in a Clinical Practice Setting **Phase III –** Active, not recruiting **Location(s):** 4 EU countries, USA, Canada, Puerto Rico, Turkey and Serbia **Primary completion date:** June 2022
Trial Design	Randomised, parallel assignment, open label, active comparator
Population	N=1,085; aged 18 years and older; diagnosed with T2D greater than or equal to 180 days prior to the day of screening; insulin naive
Intervention(s)	Insulin icodec once weekly for 52 weeks by SC injection in combination with the DoseGuide App
Comparator(s)	Insulin analogues (glargine (100U/ml or 300U/ml) or degludec) by SC injection once daily for 52 weeks
Outcome(s)	Change in HbA1c [Time frame: From baseline week 0 to week 26] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	**ONWARDS 6**; NCT04848480, 2020-002374-27; Efficacy and Safety of Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec 100 Units/mL, Both in Combination With Insulin Aspart, in Adults With Type 1 Diabetes. A 26-week, Randomised, Multicentre, Open-label, Active-controlled, Parallel Group, Two Armed, Treat-to-target Trial Investigating the Effect on Glycaemic Control and Safety of Treatment With Once Weekly Insulin Icodec Compared to Once Daily Insulin Degludec, Both in Combination With Insulin Aspart in Adults With Type 1 Diabetes, With a 26-week Extension Investigating Long Term Safety **Phase III –** Active, not recruiting **Location(s):** 5 EU countries, UK, USA, Canada and other countries. **Primary completion date:** May 2022
Trial Design	Randomised, parallel assignment, open label, active comparator

Population	N=580; aged 18 years and older; diagnosed with T1D; HbA1c below 10% at screening
Intervention(s)	Insulin icodec (700 units/ml) SC injection once weekly in combination with 2-4 times daily SC injections of insulin aspart (100 units/ml) at mealtimes
Comparator(s)	Insulin degludec (100 units/ml) SC injection once weekly in combination with 2-4 times daily SC injections of insulin aspart (100 units/ml) at mealtimes
Outcome(s)	Change in HbA1c [Time frame: From baseline week 0 to week 26] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of insulin icodec is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Sotagliflozin for treating type 2 diabetes. (GID-TA10665). Expected date of issue to be confirmed.
- NICE technology appraisal. Sotagliflozin with insulin for treating type 1 diabetes. (TA622). February 2020.
- NICE technology appraisal. Ertugliflozin with metformin and a dipeptidyl peptidase-4 inhibitor for treating type 2 diabetes. (TA583). June 2019
- NICE technology appraisal. Ertugliflozin as monotherapy or with metformin for treating type 2 diabetes (TA572). March 2019.
- NICE technology appraisal. Dapagliflozin in combination therapy for treating type 2 diabetes (TA288). November 2016.
- NICE technology appraisal. Dapagliflozin in triple therapy for treating type 2 diabetes (TA418). November 2016.
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- NICE technology appraisal. Empagliflozin in combination therapy for treating type 2 diabetes (TA336). March 2015.
- NICE technology appraisal. Canagliflozin in combination therapy for treating type 2 diabetes (TA315). June 2014
- NICE technology appraisal. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (TA151). July 2008.
- NICE clinical guideline. Type 2 diabetes in adults: management. (NG28). March 2022.
- NICE clinical guideline. Type 1 diabetes in adults: diagnosis and management. (NG17). July 2021.
- NICE quality standard. Diabetes in adults (QS6). August 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. Action for Diabetes. January 2014.

- NHS England. 2013/14 NHS Standard Contract for specialised endocrinology services (Adult) A03/S/a.

Other Guidance

- Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of glycaemic control in people with type 2 diabetes. 2017.[26]
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