

Health Technology Briefing November 2022

Empagliflozin with linagliptin for treating type 2 diabetes mellitus in children and adolescents

Company/Developer

Boehringer Ingelheim Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 23983

NICE TSID: 11818

UKPS ID: 666339

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Empagliflozin and linagliptin are currently in clinical development for type 2 diabetes mellitus (T2DM) in children and adolescents. T2DM is a lifelong condition that develops when the body becomes resistant to, or does not produce enough, insulin – a hormone produced in the pancreas. Insulin is needed for controlling the amount of sugar in the blood. A lack of insulin in T2DM patients causes blood sugar levels to become too high. If blood sugar remains high over a long period of time this can result in serious complications. However, medicinal options for children and adolescents with T2DM are limited at this time.

Empagliflozin is a type of inhibitor which works by blocking a protein in the kidneys called sodium-glucose co-transporter 2 (SGLT2). As blood is filtered by the kidneys, SGLT2 stops glucose in the bloodstream from being passed out into the urine. By blocking the action of SGLT2, empagliflozin causes more glucose to be removed via the kidney, through the urine, thereby reducing the levels of glucose in the blood. Linagliptin is a type of inhibitor which works by blocking the breakdown of ‘incretin’ hormones, which are released after a meal and stimulate the pancreas to produce insulin in the body. By prolonging the action of incretin hormones in the blood, linagliptin stimulates the pancreas to produce more insulin when blood glucose levels are high. If licensed, empagliflozin and linagliptin, administered orally, will offer an additional treatment option for children and adolescents with T2DM.

Proposed Indication

Treatment of type 2 diabetes mellitus (T2DM) in children and adolescents aged between 10 years and 17 years.¹

Technology

Description

Empagliflozin (DINAMO; Jardiance) is a reversible, highly potent and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT2). Empagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is 5,000 times more selective for SGLT2 versus SGLT1, the major transporter responsible for glucose absorption in the gut. SGLT2 is highly expressed in the kidney, whereas expression in other tissues is absent or very low. It is responsible, as the predominant transporter, for the reabsorption of glucose from the glomerular filtrate back into the circulation. In patients with T2DM and hyperglycaemia a higher amount of glucose is filtered and reabsorbed. Empagliflozin improves glycaemic control in patients with T2DM by reducing renal glucose reabsorption. By blocking the action of SGLT2, empagliflozin causes more glucose to be removed via the kidney, through the urine, thereby reducing the levels of glucose in the blood.²

Linagliptin (Trajenta) is an inhibitor of the enzyme DPP-4 (dipeptidyl peptidase 4, EC 3.4.14.5) an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore, GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binds very effectively to DPP-4 in a reversible manner and thus leads to a sustained increase and a prolongation of active incretin levels. Linagliptin glucose-dependently increases insulin secretion and lowers glucagon secretion thus resulting in an overall improvement in glucose homeostasis.³

Empagliflozin with linagliptin are currently in clinical development for treatment of T2DM in children and adolescents. In the phase III trial (DINAMO; NCT03429543), empagliflozin and linagliptin are administered orally, as 10mg or 25mg (empagliflozin) and 5 mg (linagliptin) doses.¹

Key Innovation

Currently, only metformin and insulin are approved for treating T2DM in patients under the age of 18 years. This is a much smaller number of pharmacological treatment options compared to the many drug classes approved for adults with T2DM. There is an increasing need for new medicinal products for treating type 2 diabetes in younger age groups as more children and adolescents are being diagnosed with this condition.^{4,5}

A systematic review on the effectiveness and tolerability of empagliflozin plus linagliptin for type T2DM has concluded that the combination is effective, safe, tolerable and cost effective compared to placebo and either drug alone, for the management of T2DM.⁶ If licensed, empagliflozin and linagliptin will offer an additional treatment option for children and adolescents with T2DM.

Regulatory & Development Status

Empagliflozin is already licensed in the EU/UK for the following indications: ²

- For the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise:
 - as monotherapy when metformin is considered inappropriate due to intolerance
 - in addition to other medicinal products for the treatment of diabetes
- For the treatment of adults with symptomatic chronic heart failure

Linagliptin is already licensed in the EU/UK in adults with T2DM as an adjunct to diet and exercise to improve glycaemic control:³

- As monotherapy when metformin is inappropriate due to intolerance, or contraindicated due to renal impairment
- In combination with other medicinal products for the treatment of diabetes, including insulin, when these do not provide adequate glycaemic control

Empagliflozin is in phase II/III clinical development for a number of indications, including:⁷

- Ascites hepatic
- Chronic renal insufficiency
- Cardiotoxicity
- Heart failure
- Kidney stones

Linagliptin is in phase II/III clinical development for:⁸

- Glucose metabolism disorders
- Gastric adenocarcinoma or gastroesophageal junction adenocarcinoma or oesophageal carcinoma
- Non-small-cell lung cancer

Patient Group

Disease Area and Clinical Need

T2DM is a lifelong condition that develops when the body becomes resistant to, or does not produce enough insulin – a hormone produced in the pancreas.⁹ When someone has T2DM, their body still breaks down carbohydrate from food and drink and turns it into glucose. The pancreas then responds to this by releasing insulin. However, because this insulin cannot work properly, the blood sugar levels keep rising. This means more insulin is released.¹⁰ Type 2 diabetes in children may develop so gradually that there are no noticeable symptoms. Some children might experience these signs and symptoms as a result of too much sugar in their bloodstream: increased thirst, frequent urination, increased hunger, fatigue, blurry vision, darkened areas of skin, most often around the neck or in the armpits and groin, unintended weight loss, and frequent infections.¹¹ Type 2 diabetes is caused by several factors, including being overweight and having obesity, not being physically active, insulin resistance and genes.¹² Comorbidities that tend to coexist with type 2 diabetes include: obesity, hypertension, dyslipidaemia, depression and arthritis.¹³

There were around 1,560 children and young adults (under the age of 19 years) with a diagnosis of type 2 diabetes in 2019-20 in England and Wales.¹⁴ A study found that the estimated UK population aged <17 years in mid-2015 was 13,008,432, resulting in a national UK incidence of type 2 diabetes in children aged 0–16 years of 0.72 per 100,000 (95% CI 0.58–0.88). When compared with white children [0.44 per 100,000 (95% CI 0.31–0.60)], there was strong evidence that Asian [2.92 per 100,000 (95% CI 2.00–4.12); P <0.001] and black/African/Caribbean/black British [1.67 per 100,000 (95% CI 0.77–3.18); P <0.001] children had a higher incidence of type 2 diabetes.¹⁵

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the use of standard-release metformin for the treatment of T2DM in children and young people.⁵

Clinical Trial Information

Trial	<p>DINAMO; NCT03429543; EudraCT 2016-000669-21; A Double-blind, Randomised, Placebo-controlled, Parallel Group Trial to Evaluate the Efficacy and Safety of Empagliflozin and Linagliptin Over 26 Weeks, With a Double-blind Active Treatment Safety Extension Period up to 52 Weeks, in Children and Adolescents</p> <p>Phase III – Active, not recruiting</p> <p>Location(s): One EU country, UK, USA, Canada and other countries</p> <p>Primary completion date: November 2022</p>
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=175 (actual); children and adolescents aged 10-17 years who have a documented diagnosis of T2DM
Intervention(s)	<ul style="list-style-type: none"> • Oral linagliptin • Oral empagliflozin
Comparator(s)	Matched placebo
Outcome(s)	<p>Primary outcome measures:</p> <ul style="list-style-type: none"> • DINAMO TM: Change from baseline in HbA1c (%) [Time Frame: 26 Weeks] • DINAMO TM Mono: Occurrence of treatment failure up to or at Week 26 [Time Frame: Up to 26 Weeks] <p>See trial record for full list of other outcomes</p>
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Empagliflozin is already marketed in the UK; 10mg and 25mg packs of 28 tablets cost £36.59.¹⁶
Linagliptin is already marketed in the UK; a 5mg pack of 28 tablets cost £33.26.¹⁷

Relevant Guidance

NICE Guidance

- NICE clinical guideline in development. Diabetes (type 1 and type 2) in children and young people: diagnosis and management - medicines for type 2 diabetes (update) (NG10286). Expected April 2023.
- NICE guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). August 2015 (Updated June 2022).

- NICE quality standard. Diabetes in children and young people (QS125). July 2016.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Endocrinology and Diabetes. E03/S/e.

Other Guidance

- NICE Clinical Knowledge Summary. Diabetes – type 2. 2021.¹⁸
- Children and Young People's West Midlands Diabetes Network. Diagnosis and management of Type 2 Diabetes (T2DM) in Children and Young People (CYP): Clinical Practice Guideline. June 2019.¹⁹
- International society for paediatric and adolescent diabetes (ISPAD). ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth. July 2018.²⁰

Additional Information

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