

Health Technology Briefing

May 2023

Canagliflozin for type 2 diabetes mellitus in children and adolescents

Company/Developer

Menarini UK

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 22779

NICE ID: Not available

UKPS ID: 666822

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Canagliflozin is in clinical development for the treatment of type 2 diabetes mellitus (T2DM) in children and adolescents (young people). T2DM causes blood glucose (sugar) to become too high, resulting in symptoms such as urinating more often, tiredness and feeling thirsty. If left untreated, T2DM can have more severe effects on the body leading to heart disease, strokes, nerve damage, foot problems, kidney problems, vision loss and blindness. Most children and young people who have T2DM are overweight or obese, and around half have a high systolic (pressure in the arteries when the heart beats) blood pressure. The most common treatments are metformin and insulin; however, these do not always reduce blood sugar to recommended levels or may lose efficacy over time. As such there is a gap for treatment options that have a different mechanism of action (work differently) to existing therapies.

Canagliflozin inhibits sodium-glucose co-transporter 2 (SGLT2), which is involved in the process whereby glucose is reabsorbed by the kidneys and enters the bloodstream. By inhibiting SGLT2, canagliflozin reduces the amount of glucose absorbed by the body and increases the amount of glucose excreted in urine. Canagliflozin has also been found to also reduce systolic blood pressure in adults and appears to act similarly in children and adolescents in an early-stage clinical trial. Canagliflozin is given by an oral tablet. If licenced, canagliflozin would offer an additional treatment option to children and adolescents with T2DM.

Proposed Indication

For children and adolescents (≥ 10 to < 18 years old) with type 2 diabetes mellitus (T2DM).¹

Technology

Description

Canagliflozin (Invokana) reversibly inhibits sodium-glucose co-transporter 2 (SGLT2) in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion (UGE).^{2,3} Increasing UGE lowers elevated blood plasma glucose concentrations, and canagliflozin's action is independent of insulin. Patients with diabetes have been shown to have elevated renal glucose reabsorption, which may contribute to persistent elevated blood glucose concentrations. Canagliflozin inhibits SGLT2 thereby reducing the reabsorption of glucose, increases UGE and lowers elevated plasma glucose in patients with type 2 diabetes. The increase UGE with SGLT2 inhibition also translates to an osmotic diuresis with the effect leading to a reduction in systolic blood pressure. The increase in UGE also results in a loss of calories and therefore a reduction in body weight, as has been demonstrated in studies of patients with type 2 diabetes.³

Canagliflozin is in clinical development for T2DM in children and adolescents (≥ 10 to < 18 years old). In the phase III clinical trial (NCT03170518) it is administered by oral tablet, once daily, at a dose of 100mg or 300mg canagliflozin.¹

Key Innovation

A phase I, 2-week, open-label, multiple-dose study assessing the pharmacokinetics (PK) and pharmacodynamics (PD) of canagliflozin in paediatric patients with T2DM found that canagliflozin 100mg and 300mg had PK and PD characteristics similar to those observed in adult patients with T2DM.⁴

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY, NCT00081328) has shown that new-onset T2DM in children and adolescents can be well controlled by metformin, however haemoglobin A1c (HbA1c) increases by $> 50\%$ after the first year of treatment. In addition to this, insulin rarely lowers HbA1c levels to $< 7\%$, which is the recommended target by the International Society for Pediatric and Adolescent Diabetes.⁴⁻⁶ At the time of the study design newer glycaemic control medicines such as glucagon-like peptide 1 (GLP-1) receptor agonists and SGLT2 inhibitors were not available.⁷ As such more treatment options like canagliflozin, with an oral administration and mechanism of action that works independent of insulin and β -cell function, could be beneficial for children and adolescents with T2DM.⁴

Regulatory & Development Status

Canagliflozin currently has Marketing Authorisation in the EU/UK for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise:³

- As monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- In addition to other medicinal products for the treatment of diabetes

Canagliflozin is also in phase II/III clinical development for the treatment of:⁸

- Coronary artery disease
- Heart failure
- Diabetic nephropathy

- Obesity
- Diabetes mellitus type 1 (T1DM)
- Renal insufficiency
- Polycystic ovary syndrome
- Breast cancer
- Stroke

Patient Group

Disease Area and Clinical Need

T2DM is a common condition that causes blood glucose (sugar) to become too high.⁹ Insulin, a hormone made by the pancreas, controls the amount of glucose in the blood. In T2DM the pancreas does not produce enough insulin or the body's cells do not react to insulin, this means that glucose stays in the blood and is not used as energy in cells.¹⁰ Symptoms include tiredness, excessive thirst, urinating more than usual, losing weight without trying to, itching around penis or vagina, wounds taking longer to heal, and blurred vision.¹¹ T2DM can lead to heart disease, stroke, nerve damage, foot problems, vision loss and blindness, miscarriage and stillbirth, kidney problems, and sexual problems.¹² People are more at risk of developing T2DM if they have close relatives with diabetes, are overweight or obese, and are of Asian, African-Caribbean or black African descent.¹¹

The number of children and young people with T2DM in the UK is rising.^{13,14} The majority (98.2%) of those with T2DM were overweight or obese, and almost half (46.1%) had a diastolic or systolic blood pressure in the hypertensive range. In England, 2021/22, there were 1,116 children and young people with T2DM receiving care from paediatric diabetes services. 48.3% of those were assessed as requiring additional psychological support. It is estimated that 33.0% of children who live with T2DM (aged 12 and above) receive all six "key" health checks, which are important for living with diabetes.¹⁴ In England, 2021-22, there were 188 young people (aged 10-17 years old) admitted to hospital with a primary diagnosis of T2DM (ICD 10 code E11). This value makes up ~0.34% of all recorded cases, which leads to an estimated 188 finished consultant episodes (FCE) for young people with T2DM, resulting in 11 day cases and 766 FCE bed days.¹⁵

Recommended Treatment Options

The National Institute for Health and Care Excellence currently recommends the following treatment options for children and young people with T2DM:^{16,17}

- Metformin
- Insulin – including long-acting insulin (insulin detemir) and intermediate-acting insulin (neutral protamine Hagedorn insulin)
- Empagliflozin (SGLT2 inhibitor)
- GLP-1 receptor agonists – dulaglutide and liraglutide

The following medicines are also licensed for use in the UK for the treatment of T2DM in children and young people:¹⁷

- Dapagliflozin (SGLT2 inhibitor)
- Exenatide (GLP-1 receptor agonist)

Clinical Trial Information

Trial	<p>NCT03170518; EudraCT 2016-005223-88; A Randomized, Multicenter, Double-Blind, Parallel-Group, Placebo-Controlled Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (≥ 10 to < 18 Years) With Type 2 Diabetes Mellitus</p> <p>Phase III – Active, not recruiting</p> <p>Location(s): 2 EU countries, United States, and other countries</p> <p>Primary completion date: October 2023</p>
Trial Design	Randomised, double-masked (participant and investigator), parallel assignment.
Population	N=171 (actual); aged 10 to 17 years old; with type 2 diabetes mellitus.
Intervention(s)	Canagliflozin 100mg or 300mg tablet administered orally once-daily.
Comparator(s)	Matched placebo.
Outcome(s)	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> • Change in Glycated Hemoglobin (HbA1c) From Baseline at Week 26 [time frame: baseline, up to week 26] • Percentage of Participants with Adverse Events as a Measure of Safety and Tolerability [time frame: up to week 56] <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Canagliflozin (30 tablets) 100mg/300mg has an NHS indicative price of £39.20.¹⁸

Relevant Guidance

NICE Guidance

- NICE guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). Published: August 2015. Updated: May 2023.
- NICE guideline. Diabetic foot problems: prevention and management (NG19). Published: August 2015. Updated: October 2019.
- NICE clinical guideline. Obesity: identification, assessment and management (CG189). Published: November 2014. Updated: September 2022.
- NICE quality standard. Diabetes in children and young people (QS125). July 2016.
- NICE public health guideline (PH47). Weight management: lifestyle services for overweight or obese children and young people. October 2013.

NHS England (Policy/Commissioning) Guidance

- NHS England. Action for Diabetes. January 2014.
- NHS England. 2013/14 NHS Standard Contract Paediatric Medicine: Endocrinology and Diabetes. E03/S/e.

Other Guidance

- Royal College of Paediatrics and Child Health (RCPCH). National Paediatric Diabetes Audit (NPDA) Report on Care and outcomes 2021/22. March 2023.¹⁴
- 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 2019.¹⁶
- International Society for Pediatric and Adolescent Diabetes (ISPAD). ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth. July 2018.⁶
- Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes: A national clinical guideline (SIGN116). Published: March 2010. Updated: November 2017.¹⁹

Additional Information

References

- 1 ClinicalTrials.gov. *A Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (>=10 to <18 Years) With Type 2 Diabetes Mellitus*. Trial ID: NCT03170518. Status: Active, not recruiting. Available from: <https://clinicaltrials.gov/ct2/show/NCT03170518> [Accessed 04 Apr 2023].
- 2 British National Formulary (BNF). *Canagliflozin - Drug action*. Available from: <https://bnf.nice.org.uk/drugs/canagliflozin/#drug-action> [Accessed 17 Apr 2023].
- 3 European Medicines Compendium (emc). *Invokana 100 mg film-coated tablets*. 2021. Available from: <https://www.medicines.org.uk/emc/product/8855/smpc#gref> [Accessed 17 Apr 2023].
- 4 Tamborlane WV, Polidori D, Argenti D, Di Prospero NA. Pharmacokinetics and pharmacodynamics of canagliflozin in pediatric patients with type 2 diabetes. *Pediatr Diabetes*. 2018;19(4):649-55. Available from: <https://doi.org/10.1111/pedi.12626>.
- 5 ClinicalTrials.gov. *Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY)* Trial ID: NCT00081328. Status: Completed. Available from: <https://clinicaltrials.gov/ct2/show/NCT00081328> [Accessed 18 May 2023].
- 6 Zeitler P, Arslanian S, Fu J, Pinhas-Hamiel O, Reinehr T, Tandon N, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth. *Pediatric Diabetes*. 2018;19(S27):28-46. <https://doi.org/10.1111/pedi.12719>.
- 7 Narasimhan S, Weinstock RS. Youth-onset type 2 diabetes mellitus: lessons learned from the TODAY study. *Mayo Clin Proc*. 2014;89(6):806-16. Available from: <https://doi.org/10.1016/j.mayocp.2014.01.009>.
- 8 ClinicalTrials.gov. *Phase II and III clinical trials for canagliflozin*. Available from: https://clinicaltrials.gov/ct2/results?term=Canagliflozin&Search=Apply&age_v=&gndr=&type=&rslt=&phase=1&phase=2 [Accessed 18 Apr 2023].
- 9 NHS. *What is type 2 diabetes?* 2020. Available from: <https://www.nhs.uk/conditions/type-2-diabetes/> [Accessed 18 Apr 2023].
- 10 NHS Inform. *Type 2 diabetes*. 2023. Available from: <https://www.nhsinform.scot/illnesses-and-conditions/diabetes/type-2-diabetes> [Accessed 28 Apr 2023].
- 11 NHS. *Symptoms - Type 2 diabetes*. 2020. Available from: <https://www.nhs.uk/conditions/type-2-diabetes/symptoms/> [Accessed 18 Apr 2023].

- 12 NHS. *Health problems - Type 2 diabetes*. 2020. Available from: <https://www.nhs.uk/conditions/type-2-diabetes/health-problems/> [Accessed 18 Apr 2023].
- 13 Diabetes UK. *Type 2 diabetes in children and young people*. Available from: <https://www.diabetes.org.uk/professionals/position-statements-reports/specialist-care-for-children-and-adults-and-complications/type-2-children> [Accessed 18 Apr 2023].
- 14 Royal College of Paediatrics and Child Health (RCPCH). *National Paediatric Diabetes Audit (NPDA) Report on Care and outcomes 2021/22*. 2023. Available from: <https://www.rcpch.ac.uk/resources/npda-annual-reports> [Accessed 18 Apr 2023].
- 15 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22> [Accessed 28 Apr 2023].
- 16 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*. 2019. Available from: <https://www.england.nhs.uk/midlands/wp-content/uploads/sites/46/2019/09/Diagnosis-and-management-of-Type-2-Diabetes-T2DM-in-Children-and-Young-People-CYP-Clinical-Practice-Guideline.pdf> [Accessed 18 Apr 2023].
- 17 National Institute for Health and Care Excellence (NICE). *Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18)*. Last Update Date: May 2023. Available from: <https://www.nice.org.uk/guidance/ng18/resources/diabetes-type-1-and-type-2-in-children-and-young-people-diagnosis-and-management-pdf-1837278149317> [Accessed 12 May 2023].
- 18 British National Formulary (BNF). *Canagliflozin Tablet Costs*. Available from: <https://bnf.nice.org.uk/drugs/canagliflozin/medicinal-forms/> [Accessed 04 Apr 2023].
- 19 Scottish Intercollegiate Guidelines Network (SIGN). *Management of diabetes: A national clinical guideline (SIGN116)*. Last Update Date: Nov 2017. Available from: <https://www.sign.ac.uk/media/1054/sign116.pdf> [Accessed 28 Apr 2023].

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