NIHR Innovation Observatory
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Sotagliflozin tablets as an adjuct therapy to insulin for Type 1 diabetes mellitus

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LAY SUMMARY

Type 1 diabetes mellitus is a condition which usually starts early in life where the immune system (blood cells which usually defend the body from infection) attacks an organ called the pancreas. The pancreas usually makes a substance called insulin, which controls the amount of sugar in the blood. However in type 1 diabetes the pancreas, does not produce enough (or sometimes any) insulin. This means that blood sugar levels can become elevated which can damage many organs in the body. This type of diabetes usually runs in families. While type 1 diabetes cannot be cured, having regular, at least daily, injections of insulin can keep blood sugar levels stable. Controlling blood sugar levels is important to prevent related health problems developing later in life. However some people, despite having regular injections of insulin, still do not have stable blood sugar levels.

Sotagliflozin is a drug being developed to lower blood sugar levels in type 1 diabetes by increasing the amount of sugars excreted in the urine. It is taken once a day tablet in conjunction with insulin to prevent large rises and falls in blood sugar levels. This may be especially useful for people who cannot control their blood sugar levels with insulin alone. Sotagliflozin is currently in clinical trials which have shown that sotagliflozin has the potential to reduce and control blood sugar levels when taken with insulin.

TARGET GROUP

Type 1 diabetes mellitus; people with inadequate blood glucose control with insulin or insulin analogues – as an adjunct therapy to insulin

TECHNOLOGY

DESCRIPTION

Sotagliflozin is an oral tablet intended for use alongside insulin in type 1 and type 2 diabetes mellitus. Sotagliflozin works by inhibiting sodium-glucose cotransporter type 2 (SGLT2), responsible for most of the glucose reabsorption in the kidney, and SGLT1, responsible for glucose and galactose absorption in the gastrointestinal tract.[1] It is thought to treat diabetes by increasing urinary glucose excretion, therefore lowering blood glucose levels and mediating the post-prandial-rise in glucose seen after eating.[2]

In the phase III clinical trial, sotagliflozin is administered orally at a dose of 200-400mg once daily fasted (before first meal) for 24 weeks as an adjunct to insulin therapy, these studies have an extended observation period to 52 weeks.[19, 21, 23]

Sotagliflozin does not currently have Marketing Authorisation in the EU for any indication.

Sotagliflozin is currently in phase III trials for type 1 and type 2 diabetes.

INNOVATION and/or ADVANTAGES

As the first oral adjunct therapy for diabetes, if licensed, sotagliflozin will offer an additional treatment option for patients with type 1 diabetes. It has the potential to improve blood glucose control (HbA1c) in people with type 1 diabetes who have not achieved blood glucose control with insulin or insulin analogue therapies.

DEVELOPER

Lexicon Pharmaceuticals Inc. (Licensor) and Sanofi (Licensee).

AVAILABILITY, LAUNCH or MARKETING

A PIP (Paediatric Investigation Plan) (EMEA-001517-PIP02-14) was approved by the EMA (P/0150/2015) for Sotagliflozin for the treatment of type 1 diabetes mellitus in July 2015.[3]

PATIENT GROUP

BACKGROUND

Diabetes mellitus is a lifelong condition where the body's glucose (blood sugar) levels are not adequately controlled by insulin. There are two types of diabetes; type 1 diabetes where the pancreas does not produce insulin, and type 2 diabetes where the pancreas does not produce enough insulin and/or the body's cells do not respond to insulin.[4] Type 1 diabetes in less common than type 2, accounting for approximately 10% of all diabetes cases.[5]

Type 1 diabetes mellitus is an autoimmune condition where the immune system attacks the pancreas which is then unable to produce insulin.[4] Type 1 diabetes can occur at any age but usually develops before 40 years, most commonly in childhood.[5] Type 1 diabetes usually develops rapidly in young people (over days or weeks) or slightly longer in adults (over a few months). Symptoms develop as a result of the bodies attempt to reduce high glucose levels in the blood stream. Insulin deficiency leads to fats being used by the body and can generate a condition called diabetic ketoasidosis which, before the discovery of insulin, was the inevitable cause of death in patients with type 1 diabetes. As type 1 diabetes develops, the lack of insulin and rise in glucose leads to symptoms such as feeling very thirsty, passing urine more often than usual (especially at night), feeling tired, weight loss and loss of muscle mass (due to the lack of insulin) by excreting excess glucose in the urine.[4]

As a chronic condition, type 1 diabetes can impact everyday life in a variety of ways. Diabetes can also lead to a variety of physical complications due to blood vessel, nerve and organ damage due to raised glucose levels, including peripheral neuropathy, diabetic retinopathy, kidney disease, foot ulcers and sexual dysfunction. Type 1 diabetes also increases risk of heart disease and stroke by up to five times and of miscarriage and still birth.[6] Apart from managing physical symptoms of diabetes, there is also an established link between diabetes and depression.[7] Anxiety regarding hypoglycaemic attacks are also common, affecting 25% people with diabetes.[8] Dealing with a chronic condition can also be very stressful and tiring and 'diabetes burnout' can occur where people become overwhelmed or angry about managing their diabetes.[9] As the management of diabetes can include monitoring and changing diet, psychological changes around food and diet may occur. The eating disorder, diabulimia (where people deliberately and regularly reduce the amount of insulin they take in order to lose weight), is specific to those with diabetes and can cause hyperglycaemia and contribute towards future physical complications.[10]

CLINICAL NEED and BURDEN OF DISEASE

Type 1 diabetes is less common than type 2 diabetes, accounting for less than 10% of all diabetes cases in the UK and affecting over 370,000 adults in the UK.[17, 11] Hospital admissions data for England in 2015-2016 recorded 26,766 admissions and 39, 289 finished consultant episodes for type 1 diabetes.[12]

Poor glycaemic control is common in type 1 diabetes, with only 13-15% patients achieving the target of less than 7% (53nmol/mole) which is recommended. More than 57% of people with the disease have HbA1c levels above 8% and 32% have levels above 9%. Improvement of glycaemic control has clearly been demonstrated to reduce the risk of microvascular complications. Risk of mortality from any cause has been seen to increase with poor glycaemic control, with type 1 diabetic patients at a 2 times increase risk of death compared to the general population and type 1 diabetic patients with poor glycaemic control at 8 to 10 time increased risk of death compare to the general population.[13,14]

Diabetes can cause a significant amount of disability, distress and increases the risk of developing several severe complications. These can include short term complications, such as hypoglycaemia diabetic ketoacidosis and hyperosmolar hyperglycaemia state, and long term complications such as renal disease (the major complication in Type 1 Diabetes), retinopathy (a common cause of blindness), cardiovascular disease (including heart disease and stroke), kidney disease, neuropathy (which can lead to pain, loss of feeling and muscle wasting) and foot complications (including foot ulcers and infections with the potential to lead to amputations).[15] The direct cost (regarding diagnosis, lifestyle interventions, ongoing treatment, management and complications) and indirect cost (regarding

mortality, sickness, loss of productivity and informal care) for type 1 diabetes is high at an estimated £1 bn and £0.9 bn respectively in the UK in 2010/2011.[16]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance under development. Diabetes – buccal insulin (ID311). Expected publication date TBC.
- NICE Technology appraisal guidance. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (TA151). July 2008.
- NICE Guideline. Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NG18). November 2016.
- NICE clinical guideline. Type 1 diabetes: diagnosis and management (NG17). July 2016.
- NICE Diagnostics Guidelines. Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) (DG21). February 2016.
- NICE Interventional Procedures Guidance. Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus (IPG257). April 2008.
- NICE Quality Standard. Diabetes in adults (QS6). August 2016.
- NICE Quality Standard. Diabetes in children and young people (QS125). July 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Islet Transplantation Service. A03/S/c.
- NHS England. 2013/14 NHS Standard Contract for Pancreas transplantation service (adult). A03/S/a.

OTHER GUIDANCE

- American Diabetes Association. Type 1 Diabetes through the life span: a position statement of the American diabetes association. Diabetes Care. 2014 Jul; 37(7): 2034-2054.

CURRENT TREATMENT OPTIONS

NICE recommends the following in the management and treatment of type 1 diabetes in adults:[17]

Education and Management

- Annually reviewed individual care plan including:
    - insulin dose adjustments
    - avoiding and awareness of hypoglycaemia
    - contraception and family planning (to women of childbearing potential)
    - Discussion of frequency of follow up consultations including review of HbA1c levels, hypoglycaemia and next annual review.
- Education and information:

- o Offer of an evidence based structured education programme, e.g. DAFNE (dose adjustment for normal eating programme) for 6-12 months after diagnosis.
  - o Provide information about type 1 diabetes and its management to patients.
  - o Consider Blood Glucose Awareness Training (BGAT) for those who have recurrent episodes of hypoglycaemia.
- Education and training on recognising, managing and preventing hypoglycaemia
- Ketone monitoring and management of diabetic ketoacidosis (DKA)
- Monitoring and management of potential associated illnesses and diabetes complications e.g. cardiovascular events, eye disease, diabetic kidney disease, diabetic and autonomic neuropathy, gastroparesis, diabetic foot problems, erectile dysfunction, thyroid disease, psychological problems and eating disorders.

Lifestyle based treatments

- Dietary management:
  - o Carbohydrate counting training
  - o Provide nutritional information for issues other than blood glucose control such as for weight control and cardiovascular risk management.
  - o Discuss the hyperglycaemic effects of different foods in the context of insulin preparations chosen to match those food choices.
  - o Agree the choice, timing and amount of snacks between meals.
- Physical Activity:
  - o Advise physical activity as a way of reducing cardiovascular risk.
  - o Provide physical activity advice, including; appropriate intensity and frequency of activity, effect of activity on blood glucose levels and the appropriate adjustments of insulin dosage for exercise and post exercise periods.
- Blood glucose management:
  - o Measurement of HbA1c levels every 3-6 months with a target of 48nmol/L/mol (6.5%) or lower.
  - o Routine blood glucose self-monitoring (at least 4 times a day before each meal and before bed) with a target blood glucose level of 5-7nmol/L fasted, 4-7nmol/L before meals and 5-9nmol/L at least 90mins after eating.

Pharmacological and surgical treatments

- Insulin therapy: administered by injection using an insulin pen
  - o Long acting insulin – work up to a day and the first line therapy for those with Type 1 diabetes. E.g. twice daily insulin detemir or once daily insulin glargine.
  - o Subcutaneous insulin infusion (CS11 or insulin pump) therapy – a pump which injects insulin connected by a long thing tubing with a needle at the end which is inserted into the body (usually stomach) an alternative to injecting insulin.
  - o Rapid acting insulin – injected before meals, not advised for regular use.
- Islet/Pancreas Transplantation:
  - o Recommended for people who have recurrent hypoglycaemia or have not responded to other treatments.

Trial	inTandem1, NCT02384941; adults above 18 years; high dose sotagliflozin vs low dose Sotagliflozin vs placebo, as adjunct to insulin or insulin analogue; phase III	inTandem2, NCT02421510; adults above 18 years; high dose sotagliflozin vs low dose Sotagliflozin vs placebo, as adjunct to insulin or insulin analogue; phase III
Sponsor	Lexicon Pharmaceuticals and Sanofi	Lexicon Pharmaceuticals and Sanofi
Status	Published in abstract	Published in abstract
Source of Information	Abstract[18], trial registry[19]	Abstract,[20] trial registry[21]
Location	USA and Canada	13 EU countries including the UK
Design	Randomised, placebo-controlled, parallel arm	Randomised, placebo-controlled, parallel arm
Participants	n=750; aged above 18 years; diagnosed with Type 1 diabetes; inadequate glycaemic control achieved with insulin therapy	N=782; aged above 18 years; diagnosed with Type 1 diabetes; inadequate glycaemic control achieved with insulin therapy
Schedule	400 or 200mg tablet of sotagliflozin or placebo once a day before the first meal of the day.	400 or 200mg tablet of sotagliflozin or placebo once a day before the first meal of the day.
Follow-up	Active treatment for 24 weeks	Active treatment for 24 weeks
Primary Outcomes	Change from baseline to 24 weeks of either sotagliflozin versus placebo of HbA1c.	Change from baseline to 24 weeks of either sotagliflozin versus placebo of HbA1c.
Secondary Outcomes	Change in body weight (baseline to 24 weeks), change in bolus insulin dose (baseline to 24 weeks), change in fasting plasma glucose (baseline to 24 weeks) No quality of life measurement included in trial outcomes	Change in proportion of patients with HbA1c <7% (baseline to 24 weeks), change in body weight (baseline to 24 weeks), change in bolus insulin dose (baseline to 24 weeks), change in fasting plasma glucose (baseline to 24 weeks) No quality of life measurement included in trial outcomes
Key Results	Trial results concluded it met the primary outcome. Treatment with sotagliflozin 200mg, sotagliflozin 400mg and placebo resulted in 0.43%, 0.49% and 0.08% mean reduction in HbA1c respectively. Treatment with 200mg and 400mg sotagliflozin significantly reduced mean HbA1c compared to placebo (p=<0.001).	Trial results concluded it met the primary outcome. Treatment with sotagliflozin 200mg, sotagliflozin 400mg and placebo resulted in 0.39%, 0.37% and 0.03% mean reduction in HbA1c respectively. Treatment with 200mg and 400mg sotagliflozin significantly reduced mean HbA1c compared to placebo (p=<0.001).
Adverse effects (AEs)	Incidence of treatment emergent adverse events in the sotagliflozin	Incidence of treatment emergent adverse events in the sotagliflozin

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<td>200mg, 400mg and placebo was 67.3%, 71.0% and 67.5% respectively, incidence of serious adverse events in the sotagliflozin 200mg, 400mg and placebo was 3.8%, 6.9% and 3.4% respectively. The number of participants with severe hypoglycaemic events and diabetic ketoacidosis events during the study was 11 (4.2%) and 3 (1.1%) respectively in the sotagliflozin 200mg group, 12 (4.6%) and 8 (3.1%) respectively in the sotagliflozin 400mg group and 18 (6.7%) and 0 (0%) respectively in the placebo group. The most common adverse events in the placebo group was severe hypoglycaemic event (18%), severe hypoglycaemia (6.7%) and diarrhoea (5.6%). The most common adverse events in the sotagliflozin 200mg group were severe hypoglycaemic event (11%), diarrhoea (7.2%) and genital mycocytic infection (6.1%). The most common adverse events in the sotagliflozin 400mg group were severe hypoglycaemic event (12%), genital mycocytic infection (10.3%) and diarrhoea (9.9%)</td>
<td>200mg, 400mg and placebo was 51.4%, 55.9% and 54.4% respectively, incidence of serious adverse events in the sotagliflozin 200mg, 400mg and placebo was 3.5%, 4.2% and 4.2% respectively. The mean number of participants with severe hypoglycaemic events and diabetic ketoacidosis events during the study was 7 (2.7%) and 0 respectively in the sotagliflozin 200mg group, 10 (3.8%) and 0.4 respectively in the sotagliflozin 400mg group and 6 (2.3%) and 1.1 respectively in the placebo group. The most common adverse events in the placebo group was severe hypoglycaemic event (7%), diarrhoea (3.9%) and severe hypoglycaemia (2.7%). The most common adverse events in the sotagliflozin 200mg group were severe hypoglycaemic event (10%), genital mycocytic infection (7.3%) and diarrhoea (5.4%). The most common adverse events in the sotagliflozin 400mg group were genital mycocytic infection (8.4%), diarrhoea (7.2%) and severe hypoglycaemic effect (6%).</td>
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Trial	**InTandem3, NCT02531035; adults above 18 years; Sotagliflozin vs placebo, both as adjunct to insulin or insulin analogue; phase III**
Sponsor	Lexicon Pharmaceuticals and Sanofi
Status	Ongoing
Source of Information	Publication[22], trial registry[23]
Location	EU (including UK), USA, Canada and countries in Africa and Oceania.
Design	Randomised, placebo-controlled, parallel arm
Participants	n=1400; aged above 18 years; diagnosed with Type 1 diabetes; inadequate glycaemic control achieved with insulin therapy
Schedule	400mg tablet of sotagliflozin or placebo once a day before the first meal of the day.
Follow-up	Active treatment for 24 weeks
Primary Outcomes	Proportion of patients with HbA1c below 7% and no episode of severe hypoglycemia or diabetic ketoacidosis from baseline to week 24.

Secondary Outcomes	Change in body weight (baseline to 24 weeks), change in HbAc1 (baseline to 24 weeks), change in systolic blood pressure(baseline to 24 weeks) No quality of life measurement included in trial outcomes
Key Results	A significantly larger proportion of patients in the sotagliflozin group than in the placebo group achieved the primary end point (200 of 699 patients [28.6%] vs. 107 of 703 [15.2%], P<0.001). The least-squares mean change from baseline was significantly greater in the sotagliflozin group than in the placebo group for glycated hemoglobin (difference, −0.46 percentage points), weight (−2.98 kg), systolic blood pressure (−3.5 mm Hg), and mean daily bolus dose of insulin (−2.8 units per day) (P≤0.002 for all comparisons)
Adverse effects (AEs)	The rate of severe hypoglycemia was similar in the sotagliflozin group and the placebo group (3.0% [21 patients] and 2.4% [17], respectively). The rate of documented hypoglycemia with a blood glucose level of 55 mg per deciliter (3.1 mmol per liter) or below was significantly lower in the sotagliflozin group than in the placebo group. The rate of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group (3.0% [21 patients] and 0.6% [4], respectively)
Expected reporting date	September 2017

ESTIMATED COST and IMPACT

COST

The cost of sotagliflozin is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: greater control of symptoms and potential complications of type 1 diabetes, wider societal benefits through increased control of symptoms.

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☒ Other: potentially reduced need for additional service if diabetic symptoms and complications are better controlled.   ☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs   ☐ Reduced drug treatment costs

☐ Other increase in costs   ☒ Other reduction in costs: potential reduced use of secondary care/specialist services, reduced need for interventional procedures for complications.

☒ Other: uncertain unit cost compared to existing treatments   ☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified   ☒ None identified

INFORMATION FROM

UK PharmaScan ID number 646050.

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