NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Basal Insulin-Fc for type 2 diabetes mellitus

Company/Developer	Eli Lilly and Company Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27970	NICE TSID: 11837	UKPS ID: Not available

Licensing and Market Availability Plans

Currently in phase II/III clinical trials.

Summary

Basal Insulin-Fc (BIF) is currently in clinical development for type 2 diabetes mellitus (T2DM). 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 that enables sugar to enter body cells. Signs and symptoms of T2DM often develop slowly. When signs and symptoms are present, they may include increased thirst, frequent urination, increased hunger, unintended weight loss etc. Current treatment options require daily insulin injections which can hinder adherence to treatment and be a burden to individuals.

BIF is a slow acting type of insulin meaning it is given to individuals to maintain their insulin levels. BIF is advantageous over other types of basal insulin as it can last for up to one week at high concentrations, meaning it is suitable for once weekly subcutaneous injections (under the skin). An insulin with this flat profile could reduce occurrence of low blood sugar. If licensed, BIF administered weekly by SC injection, will provide an additional treatment option for adult patients with T2DM.

Proposed Indication

Treatment for adults with type 2 diabetes mellitus (T2DM).[1]

Technology

Description

Basal insulin Fc (BIF) (LY3209590) is comprised of a novel single-chain variant of insulin fused to a human Immunoglobulin G2 (IgG2) fragment crystallisable region of an antibody domain using a peptide linker. The *in vitro* binding affinity of BIF for the human insulin receptor (IR) was two orders of magnitude weaker relative to human insulin. BIF stimulated IR phosphorylation in cells with reduced potency, yet full agonism, and exhibited a significantly faster dephosphorylation kinetic profile than human insulin or AspB10 insulin. BIF stimulated de novo lipogenesis in 3T3-L1 adipocytes and cell proliferation in SAOS-2 and H4IIE cells with ≥70-fold reduction in *in vitro* potency compared with human insulin.[2]

BIF is currently in clinical development for adults with T2DM that have already been treated with basal insulin and at least 2 injections per day of prandial insulin. In a phase III clinical trial (NCT05275400), BIF is administered subcutaneously (SC), once weekly.[3,4]

Key Innovation

A phase II study (NCT03736785) showed that BIF, when administered weekly according to either dosing algorithm (to maintain fasting blood glucose of <140 milligram per decilitre (mg/dL) and of <120 mg/dL), was non-inferior to insulin degludec for glycaemic control as measured by change in haemoglobin A1C (HbA1c) after 32 weeks with a lower rate of documented and nocturnal hypoglycaemia ≤70 mg/dL and less weight gain. Additionally, no safety signals were detected.[5]

Furthermore, a once-weekly option means fewer injections for people with diabetes, which could improve the likelihood that people adhere to their medication regimen. Prior research on once-weekly medications has suggested that people with diabetes may be more likely to take their medications as scheduled with once-weekly injections compared with once-daily. Also, many people reported that taking an injection once daily was inconvenient.[6,7] If licensed, BIF will offer an additional treatment option for adults with T2DM.

Regulatory & Development Status

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

BIF is currently not in clinical development for any other indications.[8]

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.[10] Signs and symptoms of T2DM often develop slowly. When signs and symptoms are present, they may include: increased thirst, frequent urination, increased hunger, unintended weight loss, fatigue, blurred vision, slow-healing sores, frequent infections, numbness or tingling in the hands or feet, areas of darkened skin, usually in the armpits and neck.[11] T2DM 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] Type 2 diabetes is more common in people of African, African-Caribbean and South Asian family background. It can occur in all age groups and is increasingly being diagnosed in adolescents and young adults.[14]

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 T2DM.[14,15] In 2019, 3,319,266 individuals in England had diabetes.[16] Using the estimation that 90% of individuals have T2DM, almost 3 million people would be eligible for this treatment in England. In 2021-22, in England, there were 55,440 finished consultant episodes (FCE) for T2DM (ICD code E11), 30,973 admissions and 225,263 FCE bed days.[17]

Recommended Treatment Options

National institute for Health and Care Excellence (NICE) recommended treatment options for T2DM are:[14]

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

Clinical Trial Information

Trial	**QWINT-4;** NCT05462756; EudraCT 2021-005878-25; A Phase 3, Parallel-Design, Open-Label, Randomized Controlled Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Glargine in Adults With Type 2 Diabetes on Multiple Daily Injections **Phase III –** Recruiting **Location(s):** 3 EU countries, USA and other countries **Primary completion date:** October 2023
Trial Design	Randomised, parallel assignment, open-label
Population	N= 670 (estimated); adults with T2D currently treated with basal insulin and at least 2 injections of prandial insulin per day
Intervention(s)	• SC BIF • SC Insulin Lispro
Comparator(s)	• SC Insulin Glargine • SC Insulin Lispro
Outcome(s)	**Primary outcome measure:** Change from Baseline in HbA1c [time frame: Baseline, Week 26] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**QWINT-3;** NCT05275400; EudraCT 2021-002569-16; A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Trial to Evaluate the Efficacy and Safety of LY3209590 Compared With Insulin Degludec in Participants With Type 2 Diabetes Currently Treated With Basal Insulin (QWINT-3) **Phase III –** Active, not recruiting **Location(s):** 4 EU countries, USA and other countries **Primary completion date:** April 2024
Trial Design	Randomised, parallel assignment, open-label
Population	N= 1228 (actual); adults with type 2 diabetes mellitus
Intervention(s)	SC BIF
Comparator(s)	SC Insulin Degludec
Outcome(s)	**Primary outcome measure:** Change from Baseline in Hemoglobin A1c (HbA1c) [time frame: Baseline, Week 26]
Results (efficacy)	-
Results (safety)	-

Trial	**QWINT-2;** NCT05362058; EudraCT 2021-005891-21; A Phase 3, Parallel-Design, Open-Label, Randomized Control Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Degludec in Insulin Naïve Adults With Type 2 Diabetes **Phase III –** Recruiting **Location(s):** 3 EU countries, USA, Canada and other countries **Primary completion date:** April 2024
Trial Design	Randomised, parallel assignment, open-label
Population	N=912 (estimated); adults with T2D
Intervention(s)	SC BIF
Comparator(s)	SC Insulin Degludec
Outcome(s)	**Primary outcome measure:** Change from Baseline in Haemoglobin A1c (HbA1c) [time frame: Baseline, Week 52] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT03736785; A Phase 2, Randomized, Open-Label Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants With Type 2 Diabetes Mellitus Previously Treated With Basal Insulin **Phase II** – Completed

	Location(s): USA, Mexico, Puerto Rico **Study completion date:** February 2020
Trial Design	Randomised, parallel-assignment, open-label
Population	N=399 (actual); adults with type 2 diabetes mellitus
Intervention(s)	• SC BIF (dose titration was done to maintain fasting blood glucose of <140 milligram per decilitre (mg/dL)) • SC BIF (dose titration was done to maintain fasting blood glucose of <120 mg/dL.)
Comparator(s)	• Insulin Degludec
Outcome(s)	**Primary outcome measure:** Change From Baseline in HbA1c [time frame: Baseline, Week 32] See trial record for full list of other outcomes.
Results (efficacy)	See trial record.
Results (safety)	See trial record.
Trial	NCT04450394; EudraCT 2019-003339-53; A Phase 2, Parallel, Comparator-Controlled Trial to Evaluate the Safety and Efficacy of LY3209590 in Insulin-Naïve Patients With Type 2 Diabetes Mellitus **Phase II** – Completed **Location(s):** 2 EU countries, USA, Argentina and Puerto Rico **Study completion date:** October 2021
Trial Design	Randomised, parallel assignment, open-label, comparator-controlled
Population	N=278 (actual); adults with type 2 diabetes mellitus
Intervention(s)	20mg SC BIF
Comparator(s)	SC Insulin Degludec
Outcome(s)	**Primary outcome measure:** Change From Baseline in Haemoglobin A1c (HbA1c) [time frame: Baseline, Week 26] See trial record for full list of other outcomes.
Results (efficacy)	See trial record.
Results (safety)	See trial record.

Estimated Cost

The cost of BIF 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. 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). June 2013. Last updated: November 2016.
- NICE technology appraisal. Canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes. (TA390). May 2016
- NICE technology appraisal. Dapagliflozin in triple therapy for treating type 2 diabetes (TA418). November 2016.
- 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 clinical guideline. Type 2 diabetes in adults: management (NG28). December 2015. Last updated: June 2022.

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.[18]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of diabetes. 2017.[19]

Additional Information

Eli Lilly and Company Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 ClinicalTrials.gov. *A Study of LY3209590 as a Weekly Basal Insulin Compared to Insulin Glargine in Adult Participants With Type 2 Diabetes on Multiple Daily Injections (QWINT-4).* 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT05462756 [Accessed 28 November 2022].

2 Moyers JS, Hansen RJ, Day JW, Dickinson CD, Zhang C, Ruan X, et al. Preclinical Characterization of LY3209590, a Novel Weekly Basal Insulin Fc-Fusion Protein. *Journal of*

Pharmacology and Experimental Therapeutics. 2022;382(3):346-55. Available from: https://doi.org/10.1124/jpet.122.001105.

3 Heise T, Chien J, Beals J, Benson C, Klein O, Moyers JS, et al. Basal Insulin Fc (BIF), A Novel Insulin Suited For Once Weekly Dosing For The Treatment of Patients With Diabetes Mellitus. *Journal of the Endocrine Society*. 2021;5(Supplement_1):A329-A. Available from: https://doi.org/10.1210/jendso/bvab048.672.

4 ClinicalTrials.gov. *A Study of LY3209590 Compared With Insulin Degludec in Participants With Type 2 Diabetes Currently Treated With Basal Insulin.* 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT05275400 [Accessed 10 January 2023].

5 Frias JP, Chien J, Zhang Q, Chigutsa E, Landschulz W, Wullenweber P, et al. Once Weekly Basal Insulin Fc (BIF) is Safe and Efficacious in Patients with Type 2 Diabetes Mellitus (T2DM) Previously Treated With Basal Insulin. *Journal of the Endocrine Society*. 2021;5(Supplement_1):A448-A9. Available from: https://doi.org/10.1210/jendso/bvab048.916.

6 DiaTribe Learn. *Once-Weekly Insulin for Type 1 Diabetes.* 2022. Available from: https://diatribe.org/once-weekly-insulin-type-1-diabetes [Accessed 29 November 2022].

7 DiaTribe Learn. *Once-Weekly Insulins: One Step Closer.* 2022. Available from: https://diatribe.org/once-weekly-insulins-one-step-closer [Accessed 29 Novemeber 2022].

8 ClinicalTrials.gov. *LY3209590 | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Phase 2, 3.* Available from: https://clinicaltrials.gov/ct2/results?cond=&term=LY3209590&type=&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort= [Accessed 29 November 2022].

9 NHS Inform. *Type 2 diabetes.* 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/diabetes/type-2-diabetes [Accessed 13 October 2022].

10 Diabetes UK. *Type 2 diabetes.* Available from: https://www.diabetes.org.uk/diabetes-the-basics/types-of-diabetes/type-2 [Accessed 29 September 2022].

11 Mayoclinic. *Type 2 diabetes.* 2022. Available from: https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/symptoms-causes/syc-20351193 [Accessed 29 November 2022].

12 National Institute of Diabetes and Digestive and Kidney Diseases. *Type 2 Diabetes.* Available from: https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-2-diabetes [Accessed 29 September 2022].

13 Trikkalinou A, Papazafiropoulou AK, Melidonis A. Type 2 diabetes and quality of life. *World J Diabetes*. 2017;8(4):120-9. Available from: https://doi.org/10.4239/wjd.v8.i4.120.

14 National Institute for Health and Care Excellence (NICE). *Type 2 diabetes in adults: management.* 2022. Available from: https://www.nice.org.uk/guidance/ng28 [Accessed 29 November 2022].

15 Diabetes UK. *Diabetes Statistics, .* Available from: https://www.diabetes.org.uk/professionals/position-statements-reports/statistics [Accessed 29 November 2022].

16 Diabetes UK. *Diabetes prevalence 2019.* 2019. Available from: https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2019 [Accessed 29 November 2022].

17 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22: Diagnosis.* 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 29 November 2022].

18 Scottish Intercollegiate Guidelines Network (SIGN). *Pharmacological management of glycaemic control in people with type 2 diabetes (SIGN154).* 2017. Available from: https://www.sign.ac.uk/media/1090/sign154.pdf [Accessed 29 November 2022].

19 Scottish Intercollegiate Guidelines Network (SIGN). *Management of diabetes.* 2017. Available from: https://www.sign.ac.uk/assets/sign116.pdf [Accessed 29 November 2022].

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