NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
January 2023

Basal Insulin-Fc for treating type 1 diabetes

Company/Developer	Eli Lilly and Company Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 30044	NICE TSID: 11836	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 adults with type 1 diabetes (T1D). T1D is a chronic condition where the pancreas makes little or no insulin. Insulin is a hormone the body uses to allow sugar (glucose) to enter cells to produce energy. Symptoms of T1D include thirst, weight loss and frequent need to use the toilet. There are currently no cures for T1D, and the treatment options are limited to 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 insulin therapy 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, will provide an additional treatment option for adult patients with T1D.

Proposed Indication

Treatment for adults with type 1 diabetes (T1D) treated with multiple daily injection therapy.[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 T1D that have already been treated with multiple daily injection therapy. In a phase III clinical trial (NCT05463744), BIF is administered subcutaneously (SC).[1,3]

Key Innovation

There are currently no once-weekly insulin treatment options available to T1D patients. There are several potential benefits to a once-weekly insulin option for people with T1D. 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.[4,5] If licensed, BIF will offer an additional treatment option for adults with T1D.

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.[6]

Patient Group

Disease Area and Clinical Need

Diabetes is a chronic 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.[7,8] 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, before the age of 40.[9,10]

In the UK, more than 4.9 million people have diabetes. Of those with diabetes, around 8% have T1D.[11] In 2019-20, there were 218,670 people with T1D.[12] In 2021-22, in England, there were 44,704 finished consultant episodes (FCE) for T1D (ICD code E10), 28,368 admissions and 108,048 FCE bed days.[13]

Recommended Treatment Options
The National Institute for Health and Care Excellence (NICE) recommends SC insulin injection for treatment of T1D.[14] Basal-bolus insulin treatment regimens are common.[15,16] NICE recommends twice-daily insulin detemir as basal insulin therapy for adults with T1D. Alternatives to twice-daily insulin detemir include:[14] • Once-daily insulin glargine (100 units/ml) if insulin detemir is not tolerated or the person has a strong preference for once-daily basal injections • Once-daily insulin degludec (100 units/ml) if there is a particular concern about nocturnal hypoglycaemia • Once-daily ultra-long-acting insulin such as degludec (100 units/ml) for people who need help from a carer or healthcare professional to administer injections

Clinical Trial Information	
Trial	**QWINT-5; NCT05463744; EudraCT 2021-005892-38;** A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared With Insulin Degludec in Participants With Type 1 Diabetes Treated With Multiple Daily Injection Therapy **Phase III –** Recruiting **Location(s):** 2 EU countries, USA and other countries **Primary completion date:** September 2023
Trial Design	Randomised, parallel-assignment, open-label
Population	N=670 (estimated); adults (18 years and older) who have a diagnosis of TID mellitus for at least 1 year
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 26] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Clinical Trial Information	
Trial	NCT04450407; EudraCT 2019-003589-41; A Phase 2, Randomized, Parallel, Open-Label Comparator-Controlled Trial to Evaluate the Safety and Efficacy of

	LY3209590 in Study Participants With Type 1 Diabetes Mellitus Previously Treated With Multiple Daily Injection Therapy **Phase II –** Completed **Location(s):** 3 EU countries, USA and Puerto Rico **Study completion date:** October 2021
Trial Design	Randomised, parallel assignment, open-label, comparator-controlled
Population	N=266 (actual); adults (18 years and older) who have a diagnosis of TID mellitus for at least 1 year; using multiple daily injections for at least 3 months
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 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. Sotagliflozin with insulin for treating type 1 diabetes (TA622). February 2020.
- NICE technology appraisal. Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (TA151). July 2008.
- NICE clinical guideline. Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes (GID-TA10845). Expected date of issue to be confirmed.
- NICE clinical guideline. Type 1 diabetes in adults: diagnosis and management (NG17). July 2008. Last updated: August 2022.
- NICE quality standard. Diabetes in adults (QS6). March 2011. Last updated: 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). Management of diabetes. 2017.[17]
- American Diabetes Association. Type 1 Diabetes through the life span: a position statement of the American Diabetes Association. 2014.[18]

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 Compared With Insulin Degludec in Participants With Type 1 Diabetes Treated With Multiple Daily Injection Therapy (QWINT-5).* 2022. Available from: https://clinicaltrials.gov/ct2/show/NCT05463744 [Accessed 29 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 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].

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

6 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].

7 National Health Service (NHS). *High blood sugar (hyperglycaemia).* 2022. Available from: https://www.nhs.uk/conditions/high-blood-sugar-hyperglycaemia/ [Accessed 29 November 2022].

8 Mayoclinic. *Type 1 diabetes.* 2022. Available from: https://www.mayoclinic.org/diseases-conditions/type-1-diabetes/symptoms-causes/syc-20353011 [Accessed 29 November 2022].

9 Diabetes UK. *Type 1 Diabetes.* Available from: https://www.diabetes.org.uk/diabetes-the-basics/types-of-diabetes/type-1 [Accessed 29 November 2022].

10 NHS Inform. *Type 1 diabetes.* 2021. Available from: https://www.nhsinform.scot/illnesses-and-conditions/diabetes/type-1-diabetes [Accessed 29 November 2022].

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

12 NHS Digital. *National Diabetes Audit, 2019-20: Type 1 Diabetes.* 2021. Available from: https://files.digital.nhs.uk/1C/9A4484/NDA%202019-20%20Type%201%20Diabetes%20Report.pdf [Accessed 14 December 2022].

13 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].

14 National Institute for Health and Care Excellence (NICE). *Type 1 diabetes in adults: diagnosis and management.* 2022. Available from: https://www.nice.org.uk/guidance/ng17 [Accessed 29 November 2022].

15 National Institute for Health and Care Excellence (NICE). *Type 1 diabetes.* Available from: https://bnf.nice.org.uk/treatment-summaries/type-1-diabetes/ [Accessed 30 November 2022].

16 National Institute for Health and Care Excellence (NICE). *Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus.* 2008. Available from: https://www.nice.org.uk/guidance/ta151 [Accessed 30 November 2022].

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

18 Chiang JL, Kirkman MS, Laffel LMB, Peters AL, Authors obotTDS. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. *Diabetes Care*. 2014;37(7):2034-54. Available from: https://doi.org/10.2337/dc14-1140.

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