

Review Article**Insulin Icodec: A Silver Lining to the Diabetic Cloud**Meenu Thomas¹, Prithpal Singh Matreja¹, Jedidiah Solomon Prakash², Naveen Kumar Singh³**Abstract**

Adequate glycaemic control is the sole way to circumvent the microvascular and macrovascular complications of diabetes mellitus. Currently, available treatment options include oral hypoglycaemic agents and insulin. Oral antidiabetic drugs are often limited in their efficacy to reduce HbA1c beyond 1-2%. It is insulin alone that can reduce HbA1c exceptionally and keep it near normal. The benchmark route of insulin administration is subcutaneous injections. However, subcutaneous insulin administration accompanies issues like pain at injection site, needle phobia, lipodystrophy, peripheral hyperinsulinemia and consequently medication non-adherence. To overcome this hurdle there has been ongoing research for basal longer acting insulins. However, these basal insulins necessitate at least one daily injection. If somehow, a basal insulin could be injected just once a week, it is logical to anticipate that this would augment medication compliance, enhance patients' quality of life, granted that it involves minimal risk of hypoglycaemia. Insulin icodec is a novel once-a week, subcutaneously administered insulin for the treatment of diabetes mellitus. Pre-clinical as well as clinical data from all six ONWARDS trials have met their primary endpoints. If approved, insulin icodec would be the first and only once-weekly basal insulin option for individuals with diabetes, filling the lacunae created by currently available basal insulins.

Keywords: Diabetes mellitus, Insulin, Icodec, weekly, injection

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Introduction

Diabetes mellitus (DM) is chronic, lasting progressive metabolic disorder characterized by hyperglycaemia due to absolute or relative insulinopaenia.¹ The origin of diabetes mellitus finds its place in antiquity through Egyptian parchments dating back to 1500 B.C. Due to its enticing property ancient Indians called it 'madhumeha' (honey urine). Worldwide diabetes prevalence in 2019 was estimated to be 9.3% (463 million people), projected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045.² Indian Scenario suggests

that in 2019 around 77 million individuals had diabetes, which is predicted to rise to over 134 million by 2045.³ Solitarily, adequate glycaemic control is the way to minimise microvascular and macrovascular complications of DM, which can be attained by effective pharmacotherapeutic agents.⁴ Currently, available treatment options include oral hypoglycaemic agents and insulin. Oral antidiabetic drugs are often limited in their efficacy to shrink HbA1c beyond 1-2%. Exclusively, Insulin is the drug that can reduce HbA1c to exceptionally lower range and keep it near normal.⁵

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Numerous researchers made efforts to isolate the glucose lowering factor produced by the pancreas, but Banting, Best, Macleod, and Collip could extricate and purify “isletin” to manage human diabetes in 1921. From that moment forward, the process of insulin development, purification has evolved immensely.⁶

Insulin continues to be inestimably precious for therapy in diabetics, but its availability in injectable form alone adversely affects patient adherence and compliance. For the maintenance of serum glucose in the optimum range, a great deal of type 2 diabetes mellitus (T2DM) patients with advanced disease and all patients with type 1 diabetes mellitus (T1DM) require insulin. The archetypal route of insulin administration is subcutaneous injections.⁷ In spite of being the customary route of insulin administration, subcutaneous insulin administration accompanies issues like pain at injection site, needle phobia, lipodystrophy, medication non-adherence and peripheral hyperinsulinemia. The exact timing of insulin administration along with optimal titration supplements its convolutedness making it even more testing.⁸ Therefore, the demand arose for insulin delivery in a minimally invasive or non-invasive and in most physiological manner.

Insulin delivery by inhalational route was the introductory approved non-invasive and alternative technique for insulin delivery, but it has been withdrawn from the market. Innovative research is being explored to make the dream of non-invasive delivery of insulin a reality. Meagre success has been achieved with non-invasive methodologies of insulin delivery such as oral, buccal, nasal, peritoneal and transdermal and research in this arena is continuing.⁹

Protracting the sunshine

Insubstantial triumph in developing surrogate routes of administration for insulin has shifted the focus to develop longer acting insulins and consequently curbing the frequency of injections and augmenting adherence. Minimising the injection frequency may mitigate both provider and recipient disinclination to insulin initiation, decrease treatment cargo, conclusively leading to enhanced glycaemic control and overall quality of life.¹⁰

Basal insulin (Longer acting insulins) is the cornerstone of insulin therapy in type 1 diabetes and continues to be vitally important for controlling

blood glucose right through nocturnal fasting and intra-prandial periods in type 2 diabetes.¹¹ Over the century, insulin therapy has unfolded adjacent to technological advances in drug administration.

Preliminary attempts to make it a sunny day

Initial victory in the protraction of insulin duration of action were accomplished by altering its composition by adding agents like protamine and zinc, providing leading to production of what we know today as “intermediate-acting” neutral protamine Hagedorn (NPH) insulin and the lente household of insulins in the 1940s and 1950s respectively. Nevertheless, these intermediate-acting insulins still accompanied numerous drawbacks such as significant arbitrariness of effect as well as a conspicuous peak in their time-action profile.¹²

Moving forward post development of intermediate-acting insulins and realising their limitations, the 1980s with the development of genetic and protein engineering witnessed a shift in the focus of research to the alteration of insulin molecule targeting the production of “long-acting” insulin that could better gratify the basal insulin requirements throughout the day. Hence, came the first generation of long-acting basal insulin analogs, insulin glargine U100 and insulin detemir, depicting plasma half-lives of around 12 h and 5–7 h, respectively, and consequently a duration of action of up to 24 h. Nonetheless, their half-lives, mainly that of insulin detemir have been found out to be inadequate to facilitate once-daily dosing in all patients.¹³ The second generation of basal insulin analogs, insulin degludec and insulin glargine U300, portray competent, augmented (>24 h) and almost peak less activity profiles making them dependable once-daily basal insulin doses for numerous patients. When combined with other treatments for diabetes these second-generation basal insulin analogs are associated with a reduced risk of hypoglycaemia than the previously available longer-acting insulins. Additionally, these analogs have an upper edge over “intermediate-acting” insulins in terms of risk of hypoglycaemia both at day time as well as night time and reduced day-to-day glucose variability, facilitating a preferable fasting and overall glycaemic command.¹⁴

However, it is required that these basal insulins be injected at least once a day. Supposing, that a basal insulin could be injected just once a week, it is logically predictable that this would

reduce clinical dormancy, augment compliance, enhancing patients' quality of life, granted that it involves minimal risk of hypoglycaemia.¹⁵

Few studies of other glucose-lowering agents, namely glucagon-like peptide 1 (GLP-1) agonists, suggest that once a week treatment schedule enhances optimal glucose control and medication compliance as compared to a once-daily schedule.

Weekly basal Insulin Analogs – a beam of light

Research on numerous once a week to be administered insulin analogs is unfolding. Contenders such as AstraZeneca had presented a group of recombinant native single chain insulin molecules, consisting of B chain to A chain linker variants fused to Fc. However, the current status of this molecule remains obscure. In addition, Antria/Rezolute's PEGylated presented with insulin AB101 that depicted activity of duration more than a week in a phase 1 trial and was well tolerated by the subjects. Nonetheless, with the incremental doses, the variance in time to onset and drug volume was more than anticipated, and further research on AB101 has been discontinued. Also, Hanmi Pharmaceutical Co. Ltd. Has come up with data for two Fc-fusion insulins, HM12460A and HM12470. Although, both these candidates continue to be on the company's pipeline webpage, yet, over several years, their current status of development seems somewhat shrouded.¹⁷

Insulin Icodec

Insulin icodec is a novel in-development insulin analog which is actually a re-engineered version of the investigational oral basal insulin OI338. Insulin icodec is a once-a week, subcutaneously administered insulin for the treatment of diabetes mellitus. It was elected post-screening in dogs for prolonged plasma half-life intra-venously whilst guaranteeing glucose-reducing potency succeeding subcutaneous administration in rodents. It demonstrates a stable pharmacokinetic and pharmacodynamic profile, with a plasma half-life of 7 days, reinforcing once-a week administration.¹⁸ The lengthy plasma half-life of icodec might be accounted to its strong and reversible binding to albumin, minimal vulnerability to enzymatic degradation, and sluggish receptor-mediated clearance. It is the Addition of a C20 fatty diacid-containing side chain which lends a strong, reversible albumin binding, whilst three amino acid substitutions (A14E, B16H and B25H) boosts the stability of the molecule and mitigate insulin

receptor (IR) binding and clearance, further augmenting the plasma half-life. Same dose-dependent IR-mediated signalling and metabolic responses as vernacular human insulin (HI) as per some in vitro cell-based research. However, in vitro mitogenic effect of insulin icodec in various human cells is less in comparison to HI. Clinical pharmacological trial in type 2 diabetics depict that insulin icodec is quite well tolerated and portrays a pharmacokinetic/pharmacodynamic profile that is suitable for once-a week dosing schedule, with an average half-life of around 196 hours and almost an even distribution of glucose-lowering effect throughout the dosing interval of a week.¹⁹

Supporting Research

Phase 1 and 2 studies: Insulin icodec demonstrated a robust long duration of action portraying a plasma half-life of 60 hours in dogs. Phase 1 study depicted insulin icodec possessing a half-life of 196 h (>1 week) while suggesting that a plasma steady state concentration shall be attained in 3-4 weeks' time. In phase 2 trials, comparing insulin icodec and once-daily insulin glargine U 100, the initiation and weekly titration of both was found to be equally efficacious and safe in insulin-naïve subjects with type 2 diabetes mellitus. Moreover, the transitioning to once-weekly icodec from daily basal insulins enabled effective blood glucose control without any additional risk of hypoglycaemia.²⁰

Using a one-time supplemental icodec dose while moving from daily basal insulin dose avoided transient elevations in fasting glucose concentrations during the transfer without increasing the risk of hypoglycaemia. Titrating once-weekly icodec to the American Diabetes Association's suggested pre-breakfast self-measured blood glucose target of 80-130 mg/dL (44-672 mmol/L) ensures adequate glycaemic control with a low risk of hypoglycemia.²¹

Phase 3 studies – Onwards to a brighter future for Diabetics - the onwards trials: The phase 2 icodec research programme outcomes bolstered up the advancement of icodec into phase 3a development stages, and gave inputs concerning goals for glycaemia, titration of dose, and the insulin switch approach for the subsequent phase 3a clinical trials.

ONWARDS is a clinical research project for once-weekly insulin icodec that currently includes six phase 3a worldwide clinical trials, including one

with real-world aspects, involving over 4,000 persons with type 1 or type 2 diabetes.

Six randomised controlled studies in individuals with type 2 diabetes (T2D) (insulin-naïve: ONWARDS 1, 3, and 5; previously insulin-treated: ONWARDS 2 and 4) and type 1 diabetes (T1D) (ONWARDS 6) have begun. Each trial examines icodec use in a specific clinical context, taking into account long-term safety and a variety of comparator treatments (insulin glargine U100 or U300 or insulin degludec).²²

ONWARDS 1: It has been a 78-week randomised, open-label, treat-to-target phase 3a trial including persons with type 2 diabetes who had not previously received insulin (containing a 52-week main phase and a 26-week extension phase, as well as a 5-week follow-up period). 492 people were randomly assigned to either once-weekly insulin icodec or once-daily insulin glargine U100. Each group had 492 people in it. The two groups had identical baseline characteristics. At 52 weeks, the mean reduction in glycated haemoglobin level was larger with icodec than with glargine U100, confirming both non-inferiority and superiority of Insulin Icodec. Furthermore, the percentage of time spent in the glycaemic zone of 70 to 180 mg per decilitre with icodec was considerably higher than with glargine U100, confirming superiority in weeks 48 to 52. Glycaemic control was significantly improved with once-weekly insulin icodec compared to once-daily insulin glargine U100, with no new safety signals discovered and adverse event rates comparable in both groups.²³

ONWARDS 2: A phase 3a, open-label, active-controlled, 26-week effectiveness and safety treat-to-target trial comparing once-weekly insulin icodec against insulin degludec in 526 persons with type 2 diabetes transitioning from once-daily insulin was carried out in 71 sites across nine countries. The results were announced on April 28, 2022. Eligible participants were assigned at random (1:1) to either once-weekly icodec or once-daily degludec. At week 26, HbA1c was reduced to a higher extent with icodec than with degludec, indicating an estimated treatment difference (ETD) that demonstrated non-inferiority and superiority. The projected mean change in bodyweight from baseline to week 26 reflected a slight weight gain. In this trial, no additional safety problems were discovered when icodec was compared to degludec. Overall, hypoglycaemia rates were minimal, with icodec having numerically but not statistically

substantially higher occurrence rates of level 2 or level 3 hypoglycaemia than degludec.²⁴

ONWARDS 3: ONWARDS 3 is a 26-week randomised, double-masked, noninferiority, treat-to-target phase 3a trial in adults with type 2 diabetes treated with any noninsulin glucose-lowering agent with HbA1c of 7%-11% (53-97 mmol/mol) from March 2021 to June 2022 at 92 sites in 11 countries. Participants were randomly randomised to receive either once-weekly icodec and once-daily placebo or once-weekly degludec and once-weekly placebo in a 1:1 ratio. The decrease in mean HbA1c levels from baseline to 26 weeks supported Insulin Icodec's noninferiority and superiority. There were no significant differences in fasting plasma glucose change from baseline to week 26, mean weekly insulin dose during the last two weeks of treatment, or body weight change from baseline to week 26 between the icodec and degludec groups. After 26 weeks of treatment, once-weekly icodec outperformed once-daily degludec in terms of HbA1c reduction, with no difference in weight change and a higher rate of combined level 2 or 3 hypoglycaemic events in the context of less than 1 event per patient-year exposure in both groups.²⁵

ONWARDS 4: ONWARDS 4 is a 26-week, phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial in which adults from 80 sites (outpatient clinics and hospital departments) across nine countries were compared to once-daily insulin glargine U100 (glargine U100) in individuals with long-standing type 2 diabetes on a basal-bolus regimen. Once-weekly icodec exhibited equivalent gains in glycaemic control to once-daily glargine U100 in persons with long-standing type 2 diabetes on a basal-bolus regimen, with fewer basal insulin injections, lower bolus insulin dose, and no increase in hypoglycaemic rates.²⁶

ONWARDS 5: ONWARDS 5 is a 52-week study that compares once-weekly insulin icodec to daily basal insulin (insulin degludec or glargine U 100/ U300). The goal of this randomised open-label efficacy and safety treat-to-target experiment was to evaluate the efficacy and safety of insulin icodec in 1085 insulin-naïve adults with type 2 diabetes in a clinical practise context, with an app providing dose recommendations. It began in March 2021. The trial lasted 52 weeks, with a 5-week follow-up period. The trial included a comparison arm that included once daily basal insulin analogues

(degludec, glargine U100 or U300) with noninsulin glucose lowering medications and an Icodec arm that included once weekly icodec (with digital titration solution) plus noninsulin glucose lowering drugs. At week 52, the ONWARDS 5 trial met its primary goal, demonstrating non-inferiority in lowering HbA1c. The once-weekly insulin icodec achieved a greater reduction in estimated HbA1c of -1.68% points from a baseline HbA1c of 8.9%, compared to -1.31% points for once-daily basal insulins.²⁷

ONWARDS 6: ONWARDS 6 is a Phase IIIa, 52-week efficacy and safety treat-to-target trial investigating once-weekly insulin icodec vs insulin degludec, both in combination with three daily mealtime insulin injections, in 582 people with type 1 diabetes. The completion of the main phase of the trial is followed by a 26-week extension phase investigating long term safety. The trial achieved its primary endpoint of demonstrating non-inferiority in reducing HbA1c at week 26 with insulin icodec compared to insulin degludec.²⁸

Is the ICODEC sunshine enough?

This lovely rose of Insulin Icodec does, indeed, have thorns. Once insulin icodec is approved for usage, some practical challenges and concerns about clinical application will arise. According to the ONWARDS initiative, patients with type 2 diabetes who are candidates for insulin icodec will include insulin-naïve patients as well as basal insulin-treated patients who are not meeting glycaemic objectives, especially where adherence to daily injections is an issue. More research may be needed before insulin icodec may be suggested for type 1 diabetes. Other ONWARDS programme findings that are keenly sought include participant satisfaction and/or adherence scores in ONWARDS 5 and 6.^{27,28} Future studies should look into the effect of exercise frequency and intensity on hypoglycaemia in icodec-treated participants. Furthermore, clinical situations where hypoglycaemia is more likely, particularly when oral intake is reduced due to acute illness or a medical procedure/surgery, may present challenges for icodec dosing, both in terms of maintaining icodec doses and temporarily switching back to daily basal insulin, perhaps during hospitalisation.

Because insulin icodec will very certainly be used with other non-insulin antihyperglycemic medications, a background-medication-specific study of ONWARDS effectiveness and safety

data will aid in elucidating the effects of icodec when paired with different agents. There is also the exciting possibility of combining a weekly GLP-1 receptor agonist with a weekly insulin injection in persons with type 2 diabetes. Icosema (Novo Nordisk, Bagsvaerd, Denmark), a fixed ratio combination of icodec and semaglutide, has recently begun a phase IIIa clinical trial. This combination has the potential to reduce injection burden from two to one injection per week, while also enhancing acceptability, gastrointestinal tolerance, and adherence, with the possibility of weight loss and a lower risk of hypoglycemia.²⁹

Insulin icodec has equivalent or greater glycaemic performance than daily basal insulin in type 2 diabetes, with good tolerability and encouraging hypoglycaemic safety findings. Although serious clinical problems remain, cutting the number of basal insulin injections from 365 to 52 each year may be the most significant improvement in insulin therapy since its discovery more than a century ago.²⁷

With weekly insulin administration, it is necessary to address potential concerns about hypoglycaemia, particularly related to unintentional mismatches between insulin requirement and dose administered, for example in the case of a miscalculated dose. Novel insulin products should not be associated with a further deterioration of hypoglycaemia awareness and counter-regulation.³⁰

Basal Insulin Fc (BIF): A new entrant?

Eli Lilly's once-weekly Basal insulin-FC, which is currently in Phase III, is the only potential serious competitor for Insulin Icodec. LY3209590 basal insulin Fc (BIF), BIF is a fusion protein developed for once-weekly subcutaneous delivery that combines a new single-chain insulin variation with a human IgG2 Fc domain. Previous phase 1 studies showed that BIF had a low peak-to-trough ratio (1.14, or 15% variance in insulin concentration) and a half-life of 17 days, with a sustained drop in fasting glucose over a week. Because of the low peak-to-trough ratio, glucose levels may be more consistent both within and between days. In a phase 2 study of persons with T2D who had previously been treated with basal insulin, BIF also demonstrated good glycaemic control.³¹

Future prospects

All six ONWARDS trials have met their primary endpoints. Novo Nordisk submitted a biologics

licence application (BLA) to the US Food & Drug Administration (FDA) in April 2023 for once-weekly insulin icodec for the treatment of diabetes based on findings from the ONWARDS clinical trial programme. The agency's conclusion is expected in April 2024. If approved, insulin icodec will be the first and only once-weekly basal insulin option for individuals with diabetes, filling a treatment gap left by the daily basal insulin

option.^{23,25}

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References

1. Tanase DM, Gosav EM, Costea CF, Ciocoiu M, Lacatusu CM, Maranduca MA, et al. The Intricate Relationship between Type 2 Diabetes Mellitus (T2DM), Insulin Resistance (IR), and Nonalcoholic Fatty Liver Disease (NAFLD). *J Diabetes Res.* 2020;2020:3920196.
2. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract.* 2019;157:107843.
3. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. *Indian J Ophthalmol.* 2021;69(11):2932-8.
4. YimamAhmed M, Hambisa Ejigu S, Zewudie Zeleke A, Yimam Hassen M. Glycemic Control, Diabetes Complications and Their Determinants Among Ambulatory Diabetes Mellitus Patients in Southwest Ethiopia: A Prospective Cross-Sectional Study. *Diabetes Metab Syndr Obes.* 2020;13:1089-95.
5. Kim K, Unni S, Brixner DI, Thomas SM, Olsen CJ, Sterling KL, et al. Longitudinal changes in glycated haemoglobin following treatment intensification after inadequate response to two oral antidiabetic agents in patients with type 2 diabetes. *Diabetes Obes Metab.* 2019;21(7):1725-33.
6. March CA, Libman IM, Becker DJ, Levitsky LL. From Antiquity to Modern Times: A History of Diabetes Mellitus and Its Treatments. *Horm Res Paediatr.* 2022;95(6):593-607.
7. Janež A, Guja C, Mitrakou A, Lalic N, Tankova T, Czupryniak L, et al. Insulin Therapy in Adults with Type 1 Diabetes Mellitus: a Narrative Review. *Diabetes Ther.* 2020;11(2):387-409.
8. Mirahmadizadeh A, Delam H, Seif M, Banihashemi SA, Tabatabaee H. Factors Affecting Insulin Compliance in Patients with Type 2 Diabetes in South Iran, 2017: We Are Faced with Insulin Phobia. *Iran J Med Sci.* 2019;44(3):204-13.
9. Cheng R, Taleb N, Stainforth-Dubois M, Rabasa-Lhoret R. The promising future of insulin therapy in diabetes mellitus. *Am J Physiol Endocrinol Metab.* 2021;320(5):E886-90.
10. Guerci B, Chanan N, Kaur S, Jasso-Mosqueda JG, Lew E. Lack of Treatment Persistence and Treatment Nonadherence as Barriers to Glycaemic Control in Patients with Type 2 Diabetes. *Diabetes Ther.* 2019;10(2):437-49.
11. Tien KJ, Hung YJ, Chen JF, Chen CC, Wang CY, Hwu CM, et al. Basal insulin therapy: Unmet medical needs in Asia and the new insulin glargine in diabetes treatment. *J Diabetes Investig.* 2019;10(3):560-70.
12. Lau E, Salem A, Chan JCN, So WY, Kong A, Lamotte

- M, et al. Insulin glargine compared to neutral protamine Hagedorn (NPH) insulin in patients with type-2 diabetes uncontrolled with oral anti-diabetic agents alone in Hong Kong: a cost-effectiveness analysis. *Cost Eff Resour Alloc*. 2019;17:13.
13. Meneghini L, Blonde L, Gill J, Dauchy A, Bacevicius A, Strong J, et al. Insulin glargine 300 U/mL versus first-generation basal insulin analogues in insulin-naïve adults with type 2 diabetes: 12-month outcomes of ACHIEVE Control, a prospective, randomized, pragmatic real-life clinical trial. *Diabetes Obes Metab*. 2020;22(11):1995-2003.
 14. Ivers NM, Jiang M, Alloo J, Singer A, Ngui D, Casey CG, et al. Diabetes Canada 2018 clinical practice guidelines: Key messages for family physicians caring for patients living with type 2 diabetes. *Can Fam Physician*. 2019;65(1):14-24.
 15. Polonsky WH, Fisher L, Hessler D, Bruhn D, Best JH. Patient perspectives on once-weekly medications for diabetes. *Diabetes Obes Metab*. 2011;13(2):144-9.
 16. Qiao Q, Ouwens MJ, Grandy S, Johnsson K, Kostev K. Adherence to GLP-1 receptor agonist therapy administered by once-daily or once-weekly injection in patients with type 2 diabetes in Germany. *Diabetes Metab Syndr Obes* 2016;9:201-5.
 17. Rosenstock J, Del Prato S. Basal weekly insulins: the way of the future! *Metabolism*. 2022;126:154924.
 18. Kjeldsen TB, Hubálek F, Hjörtinggaard CU, Tagmose TM, Nishimura E, Stidsen CE, et al. Molecular Engineering of Insulin Icodec, the First Acylated Insulin Analog for Once-Weekly Administration in Humans. *J Med Chem*. 2021;64(13):8942-50.
 19. Nishimura E, Pridal L, Glendörff T, Hansen BF, Hubálek F, Kjeldsen T, et al. Molecular and pharmacological characterization of insulin icodec: a new basal insulin analog designed for once-weekly dosing. *BMJ Open Diabetes Res Care*. 2021;9(1):e002301.
 20. Bajaj HS, Bergenstal RM, Christoffersen A, Davies MJ, Gowda A, Isendahl J, et al. Switching to Once-Weekly Insulin Icodec Versus Once-Daily Insulin Glargine U100 in Type 2 Diabetes Inadequately Controlled on Daily Basal Insulin: A Phase 2 Randomized Controlled Trial. *Diabetes Care*. 2021;44(7):1586-94.
 21. Lingvay I, Buse JB, Franek E, Hansen MV, Koefoed MM, Mathieu C, et al. A Randomized, Open-Label Comparison of Once-Weekly Insulin Icodec Titration Strategies Versus Once-Daily Insulin Glargine U100. *Diabetes Care*. 2021;44(7):1595-1603.
 22. Singh AK, Singh A, Singh R, Misra A. Once-weekly basal insulin icodec: Looking ONWARDS from pharmacology to clinical trials. *Diabetes Metab Syndr*. 2022;16(9):102615.
 23. Rosenstock J, Bain SC, Gowda A, Jódar E, Liang B, Lingvay I, et al; ONWARDS 1 Trial Investigators. Weekly Icodec versus Daily Glargine U100 in Type 2 Diabetes without Previous Insulin. *N Engl J Med*. 2023;389(4):297-308.
 24. Philis-Tsimikas A, Asong M, Franek E, Jia T, Rosenstock J, Stachlewska K, et al. Switching to once-weekly insulin icodec versus once-daily insulin degludec in individuals with basal insulin-treated type 2 diabetes (ONWARDS 2): a phase 3a, randomised, open label, multicentre, treat-to-target trial. *Lancet Diabetes Endocrinol*. 2023;11(6):414-25.
 25. Lingvay I, Asong M, Desouza C, Gourdy P, Kar S, Vianna A, et al. Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naïve Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial. *JAMA*. 2023;330(3):228-37.
 26. Mathieu C, Ásbjörnsdóttir B, Bajaj HS, Lane W, Matos ALSA, Murthy S, et al. Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial. *Lancet*. 2023;401(10392):1929-40.
 27. Bajaj HS, Goldenberg RM. Insulin Icodec Weekly: A Basal Insulin Analogue for Type 2 Diabetes. *touchREV Endocrinol*. 2023;19(1):4-6.
 28. Philis-Tsimikas A, Bajaj HS, Begtrup K, Cailleateau R, Gowda A, Lingvay I, et al. Rationale and design of the phase 3a development programme (ONWARDS 1-6 trials) investigating once-weekly insulin icodec in diabetes. *Diabetes Obes Metab*. 2023;25(2):331-41.
 29. Kalra S, Bhattacharya S, Kapoor N. Contemporary Classification of Glucagon-Like Peptide 1 Receptor Agonists (GLP1RAs). *Diabetes Ther*. 2021;12(8):2133-47.
 30. Rosenstock J, Bajaj HS, Janež A, Silver R, Begtrup K, Hansen MV, et al ; NN1436-4383 Investigators. Once-Weekly Insulin for Type 2 Diabetes without Previous Insulin Treatment. *N Engl J Med*. 2020;383(22):2107-16.
 31. Frias J, Chien J, Zhang Q, Chigutsa E, Landschulz W, Syring K, et al. Safety and efficacy of once-weekly basal insulin fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study. *Lancet Diabetes Endocrinol*. 2023;11:158-68.