

Newer Insulins on the Horizon

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INTRODUCTION

Even with the emergence of numerous pharmacological therapies, insulin therapy has a pivotal role in diabetes treatment and many manipulations of the insulin molecule achieved over the recent years have resulted in newer advanced types, thus allowing for a more individualized therapy. Newer ones such as insulin analogs, including long-acting and rapid-acting insulins serve as promising alternative treatment options to human insulin. Such advancements in insulin formulations and innovations in insulin delivery methods have been able to reduce insulin-associated hypoglycemia, lower intraindividual pharmacokinetic (PK) and pharmacodynamic (PD) variability, and improve imitation of physiological insulin release.¹ The current article outlines some of the newer insulins that are on the near horizon.

NEWER INSULINS ON THE HORIZON (TABLE 1)

Longer-acting Version of Insulin Glargine (Glargine U300, Toujeo®)

Glargine U300 (Toujeo®, Sanofi), an ultralong-acting basal insulin analog, is a higher-strength formulation (300 units/mL) of the original insulin glargine U100 and has differential PK/PD profile

than the latter. Upon subcutaneous injection, U300 forms subcutaneous depot with smaller surface area, creating a prolonged release that results in a flatter PK/PD profile than glargine U100.² It offers PK/PD advantages compared with the glargine U100 and bestows effective glycemic control with less risk of hypoglycemia.³⁻⁵ Glargine U300 is intended especially for these patients and its concentrated formula helps to significantly lower the injection volume. The formulation is also highly useful for those type 1 diabetes (T1D) and type 2 diabetes (T2D) patients who are at high risk of hypoglycemia. Due to its prolonged action that allows once-daily dosing, the formulation will be useful for those who otherwise require twice-daily dosing.⁶

Faster-acting Insulin Aspart (Fiasp®)

An ultrafast-acting insulin with a faster onset and faster offset of action was postulated to reduce postprandial hyperglycemia and frequency of hypoglycemia and ease the severe hypoglycemia anxiety, with more time spent in range. Faster aspart, "Fiasp" is a modified formulation of insulin aspart (IAsp). It is a mealtime insulin with a flexible dosing regimen. It can be administered soon before a meal or within 20 minutes from the start of the meal.⁷ Faster absorption of Fiasp compared to IAsp is even more pronounced in those using continuous subcutaneous insulin infusion (CSII).

TABLE 1: Newer insulins on the horizon.

Type of insulin	Name of insulin formulation	Manufacturer	Product details/characteristics	Status
Longer-acting version of insulin glargine	Glargine U300, Toujeo [®]	Sanofi	Higher-strength formulation (300 units/mL) of insulin glargine U100; flatter pharmacokinetic/pharmacodynamic (PK/PD) profiles; prolonged duration of action (> 24 h)	Received European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approval (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206538Orig1s000TOC.cfm)
Faster-acting insulin aspart	Fiasp [®]	Novo Nordisk	Newer and stable formulation of insulin aspart with faster initial absorption; flexible dosing regimen	Received EMA and the US FDA approval (https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208751Orig1s000TOC.cfm)
Insulins or insulin combos with BioChaperone [®] (BC) technology (https://www.adocia.com/products/biochaperone-ultra-fast-analog-insulin/)	BC Lispro U100—ultra-rapid formulation of insulin lispro	Adocia	Accelerated insulin action profile	Now ready to enter Phase 3
	BC Lispro U200—the first concentrated ultra-rapid prandial insulin (under development)		Concentrated formula decreases injection volumes and number of injections/day	Phase 1 clinical trials completed
	HinsBet U100—rapid insulin		Cost-effective rapid-acting human insulin	Phase I/II completed
	BC Combo—combination of the basal insulin glargine and the rapid insulin lispro		Relative ease-of-use and simplicity of a premixed insulin regimen; physiological control of a basal/bolus regimen	Phase I trials completed
Once-weekly basal insulins	AB101	Rezolute	Sustained and near peakless insulin level	Under first-in-human Phase 1 study (https://www.rezolutebio.com/pipeline/overview)
	LAPS-insulin 115 (HM12470)	Hanmi Pharmaceutical	Substantially prolonged PK/PD profiles	Under Phase 1 clinical trials (https://www.ncbi.nlm.nih.gov/pubmed/28497570)

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Type of insulin	Name of insulin formulation	Manufacturer	Product details/characteristics	Status
	LAI287 (NN1436)	Novo Nordisk	Once-weekly ultralong-acting basal insulin analog	Undergoing Phase 2 clinical trials in type 1 diabetes and type 2 diabetes (T2D) (https://clinicaltrials.gov/ct2/show/NCT03922750)
Liver-preferential mealtime insulin analog	NN1406	Novo Nordisk	Mimics physiology of pancreatic insulin; associated with lesser hypoglycemia and weight gain	Under Phase 1 clinical trials (https://clinicaltrials.gov/ct2/show/NCT02612844)
Oral insulins	Tregopil (formerly IN-105)	Biocon	Clear linear relationship between the administered dose and the decrease in postprandial glucose excursion rates; no drug interactions; diet has no influence on its efficacy	Phase II and III in T2D ongoing (https://www.ncbi.nlm.nih.gov/pubmed/30592549)
	ORMD 0801	Oramed	Physiological insulin delivery system based on Protein Oral Delivery (POD TM) technology; inhibits hepatic glucose production; significantly reduces night-time glucose levels	Completed multiple Phase II clinical trials under an investigational new drug application with the US FDA (https://clinicaltrials.gov/ct2/show/NCT03467932)
Glucose-responsive insulin (smart insulin)	MK-2640	Merck	Automatically respond to changing blood glucose levels	First smart insulin to be tested on humans, results still pending following completion of Phase I of III in July 2016 (https://www.ncbi.nlm.nih.gov/pubmed/30125349) https://www.diabetes.co.uk/insulin/smart-insulin.html)
Inhaled insulin	Dance-501	Dance Pharmaceuticals	Electronic inhaler produces a soft mist of consistently sized insulin particles; efficient and consistent insulin delivery to lungs in a few breaths; intra- and inter-subject variability similar to injections; faster onset and longer duration than Humalog; dose linearity; minimal/no cough	Phase 3 clinical trials ready (https://www.dancebiopharm.com/pipeline)

Moreover, in CSII using T1D subjects, Fiasp was found to be noninferior when compared to IAsp in terms of pump compatibility. In both T1D and T2D subjects, clinical trials have shown superior reduction in postprandial hyperglycemia within 1 hour with Fiasp compared to IAsp, with comparable efficacy at 2 hours.^{7,8}

Insulins or Insulin Combos with BioChaperone® Technology

BioChaperone® (BC) technological platform from Adocia is designed to improve the effectiveness and/or safety of therapeutic proteins while making them easier for patients to use. Many novel insulin formulations are in its clinical pipeline such as two ultrarapid formulations of insulin analogs (BC Lispro U100 and U200), a rapid-acting formulation of human insulin (HinsBet U100), and a combination of basal insulin glargine and rapid-acting insulin lispro (BC Combo). Two combinations of insulin glargine with glucagon-like peptide-1 (GLP-1) (BC Glargine Dulaglutide and BC Glargine Liraglutide), two combinations of insulin lispro with synergistic prandial hormones (BC Lispro Pramlintide and BC Lispro Exenatide), and a concentrated rapid-acting formulation of human insulin (HinsBet U500) are also under preclinical development.⁹

Once-weekly Basal Insulins (AB101, LAPS-Insulin 115, and LAI287)

AB101 (from Rezolute), is a once-weekly injectable basal insulin for T1D and T2D and releases human insulin slowly and uniformly over a period of 1 week. It has comparable activity to regular human insulin *in vitro* and a weekly insulin time-action profile *in vivo*, with no acute or delayed sudden insulin increase. It is postulated to stabilize endogenous insulin-glucose homeostasis and reduce glycemic variability.¹⁰

LAPS-Insulin 115 (HM12470, from Hanmi Pharmaceutical) is a once-weekly insulin analog which has substantially prolonged PK/PD profiles and activates insulin receptor (IR) signalling in all major target tissues. When compared to insulin, LAPS-Insulin 115 has a very slow onset of action, a similar off-rate and a less and reversible IR downregulation under *in vitro* conditions.¹¹

Novo Nordisk is developing a once-weekly ultralong-acting basal insulin analog LAI287 (NN1436), intended for use in T1D and T2D patients.¹²

Liver-preferential Mealtime Insulin Analog (NN1406)

This liver-preferential mealtime insulin from Novo Nordisk intended for T1D and T2D, mimics physiological insulin distribution and is associated with lesser hypoglycemia and weight gain.¹³

Oral Insulins (Tregopil and ORMD 0801)

Oral insulins are a more viable alternative to conventional insulins and can enhance patient compliance to insulin therapy.

Tregopil (formerly IN-105) from Biocon is an oral version of insulin intended for postprandial glycemic control. A clear linear relationship has been noted between the administered dose and the decrease in postprandial glucose excursion rates. No drug interaction has been noted and diet seems to have no influence on the efficacy of tregopil.¹⁴

ORMD 0801 oral insulin capsule from Oramed, intended as a monotherapy for T2D, is based on Protein Oral Delivery (PODTM) technology. The omega-3 fatty acid component protects the insulin from small intestinal proteases and enables direct absorption across the intestinal lumen with the help of an absorption enhancer. This physiological insulin delivery system inhibits hepatic glucose production and reduces night-time glucose levels.¹⁵

Glucose-responsive Insulin (Smart Insulin)

Glucose-responsive insulin (GRI)/“smart” insulin, can automatically respond to changing blood glucose levels. Smart insulin project by SmartCells, Inc., later on acquired by Merck & Co., Inc., initially involved an injectable gel that consisted of lectin and an insulin analog with a sugar moiety attached. During hypoglycemia the lectin binds to insulin inhibiting its action, and during hyperglycemia lectin binds to glucose thereby releasing insulin to stimulate glucose uptake. The technology evolved gradually thus eliminating the need of injecting a

lectin that is toxic and instead the insulin analog binds reversibly to a ubiquitous cell receptor. "Smart" insulin from Merck, MK-2640, is the first smart insulin to be tested on humans.¹⁶

Inhaled Insulin (Dance-501)

Inhaled insulin was launched for the first time by Pfizer (Exubera®). Only one inhaled insulin, MannKind Corporation's rapid-acting inhaled insulin, Alfrezza®, has survived in the market.¹⁷ Inhaled insulin Dance-501 is a recombinant human insulin administered with a small handheld electronic inhaler. It produces a soft mist of consistently sized insulin particles, allowing an efficient and consistent delivery of insulin into the lungs in a few breaths. Intra- and inter-subject variability is similar to injections, has a faster onset and longer duration than Humalog, and shows dose linearity and absence of any adverse events like cough.¹⁸

CONCLUSION

Even with much advancement in diabetes care, treatment of diabetes is still highly unsuccessful across the world and in India, this rate is much lower (only around 4% success rate). The average blood glucose in India, irrespective of the geographical location, remains above 9.4%. The most prominent reason behind this is the clinical inertia to initiate and intensify insulin treatment due to the underlying fear of hypoglycemia and the impending death. With more effective and safer insulin formulations being available, they would be able to extend the promise of a more scientific, safer, and individualized mode of insulin therapy, increase patient compliance and make diabetes management a highly successful one.

REFERENCES

1. Cahn A, Miccoli R, Dardano A, et al. New forms of insulin and insulin therapies for the treatment of type 2 diabetes. *Lancet Diabetes Endocrinol.* 2015;3(8):638-52.
2. Becker RH, Dahmen R, Bergmann K, et al. New insulin glargine 300 units·mL⁻¹ provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 units·mL⁻¹. *Diabetes Care.* 2015;38(4):637-43.
3. Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, Phase 3A, open-label clinical trial (EDITION 4). *Diabetes Care.* 2015;38(12):2217-25.
4. BioSpace. (2017). Switching to Sanofi's Toujeo Showed Significant Reductions in Blood Sugar and Significantly Lower Incidence of Hypoglycemia in a Real-World Observational Study. [online] Available from <https://www.biospace.com/article/releases/switching-to-sanofi-s-toujeo-showed-significant-reductions-in-blood-sugar-and-significantly-lower-incidence-of-hypoglycemia-in-a-real-world-observatio/?s=70> [Last accessed October, 2019].
5. Zhou FL. Lower Risk of Hypoglycemia after Switch to Insulin Glargine 300 U/MI (Gla-300) Vs Other Basal Insulins in Patients with Type 2 Diabetes (T2D) on Basal Insulin in Real-World Clinical Settings (DELIVER 2 study). Orlando, FL, US: Endocrine Society 2017 Annual Meeting [ENDO 2017]; 2017.
6. White JR. Advances in insulin therapy: a review of new insulin glargine 300 Units/mL in the management of diabetes. *Clinical Diabetes.* 2016;34(2):86-91.
7. <https://care.diabetesjournals.org/content/early/2017/04/10/dc16-1771>.
8. Zijlstra E, Demissie M, Graungaard T, et al. Compatibility and safety of faster-acting insulin aspart used in continuous subcutaneous insulin infusion therapy in patients with type 1 diabetes. *Endocrine Society.* 2017;1:697.
9. ADOCIA. (2019). Pipeline. [online] Available from <https://www.adocia.com/products-pipeline/> [Last accessed October, 2019].
10. Marketwired. (2017). AntriaBio Files Investigational New Drug Application for Once-Weekly Basal Insulin AB101. [online] Available from <https://www.rezolutebio.com/news/press-releases/detail/238/antriabio-files-investigational-new-drug-application-for> [Last accessed October, 2019].
11. Wronkowitz N, Hartmann T, Görgens SW, et al. LAPSInsulin115: A novel ultra-long-acting basal insulin with a unique action profile. *Diabetes Obes Metab.* 2017;19(12):1722-31.
12. ClinicalTrials. (2017). A Trial Investigating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Subcutaneously Administered NNC0148-0287 (Insulin 287) in Subjects With Type 2 Diabetes. [online] Available from <https://clinicaltrials.gov/ct2/show/NCT02148861?term=NN1436&rank=2> [Last accessed October, 2019].
13. Novo Nordisk. (2017) R&D Pipeline. [online] Available from <https://www.novonordisk.com/research-and-development/pipeline.html> [Last accessed October, 2019].
14. Biocon. (2017). Active Discovery Programs. [Online] Available from https://www.biocon.com/biocon_research_discovery.asp [Last accessed October, 2019].
15. Oramed. (2016). Oramed Announces Positive Top-line Results from Phase IIb Oral Insulin Study. [online] Available from <http://www.oramed.com/oramed-announces-positive-top-line-results-from-phase-ii-b-oral-insulin-study/> [Last accessed October, 2019].

16. ClinicalTrials. (2019). A Three-part Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of MK-2640 in Healthy Participants (Part I) and Participants With Type 1 Diabetes Mellitus (Parts II and III) (MK-2640-001). [online] Available from <https://clinicaltrials.gov/ct2/show/NCT02269735> [Last accessed October, 2019].
17. Afrezza. (2017). Change the Conversation with inhaled insulin. [online] Available from <https://www.afrezza.com/hcp/> [Last accessed October, 2019].
18. DanceBiopharm. (2017). Dance 501: A Patient-Friendly Approach. [online] Available from <http://www.dancebiopharm.com/dance-501> [Last accessed October, 2019].

SPECIAL POPULATIONS