Drugs
https://doi.org/10.1007/s40265-023-01925-1

LEADING ARTICLE

Insulin Tregopil: An Ultra-Fast Oral Recombinant Human Insulin Analog: Preclinical and Clinical Development in Diabetes Mellitus

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Accepted: 24 July 2023

Abstract
Insulin therapy is indispensable for achieving glycemic control in all patients with type 1 diabetes mellitus and many patients with type 2 diabetes mellitus. Insulin injections are associated with negative connotations in patients owing to administration discomfort and adverse effects such as hypoglycemia and weight gain. Insulin administered orally can overcome these limitations by providing a convenient and effective mode of delivery with a potentially lower risk of hypoglycemia. Oral insulin mimics the physiologic process of insulin secretion, absorption into the portal circulation, and subsequent peripheral delivery, unlike the subcutaneous route that results in peripheral hyperinsulinemia. Insulin tregopil (IN-105), a new generation human recombinant insulin, methoxy (polyethylene glycol) hexanoyl human recombinant insulin, is developed by Biocon as an ultra-fast onset short-acting oral insulin analog. This recombinant oral insulin is a single short-chain amphiphilic oligomer modified with the covalent attachment of methoxy-triethylene-glycol-propionyl moiety at Lys-β_{29}-amino group of the B-chain via an amide linkage. Sodium caprate, an excipient in the insulin tregopil formulation, is a permeation enhancer that increases its absorption through the gastrointestinal tract. Also, meal composition has been shown to non-significantly affect its absorption. Several global randomized, controlled clinical trials have been conducted in type 1 and type 2 diabetes patients towards the clinical development of insulin tregopil. The formulation shows post-prandial glucose control that is more effective than placebo throughout the meal period; however, compared with an active comparator insulin aspart, the post-prandial control is more effective mainly in the early post-meal period. It shows a good safety profile with a lower incidence of clinically significant hypoglycemia. This review covers the overall clinical development of insulin tregopil establishing it as an ultra-fast onset, short-acting oral insulin analog for optimizing post-prandial glucose.

1 Introduction

Insulin therapy is indispensable to achieve glycemic control in all patients with type 1 diabetes mellitus (T1DM) and patients with type 2 diabetes mellitus (T2DM) with uncontrolled hyperglycemia despite treatment with oral antidiabetics. Generally, insulin can be administered through the peripheral (subcutaneous [SC], inhalational, buccal) and portal (oral) routes, with the peripheral (mainly SC) route being the most widely utilized. However, this non-physiological insulin delivery method is often associated with patient non-adherence due to apprehension and distress caused by needle phobia, resulting in inadequate glucose control and in turn, poor quality of life (QoL) [1, 2]. Other challenges in initiating and maintaining insulin therapy include fear of disease progression, burdensome regimens, pain/discomfort, severe psychological disturbances, poor communication between health care providers and patients, and concerns about hypoglycemia [3, 4]. In patients with T2DM who use oral hypoglycemics as monotherapy and yet have uncontrolled blood glucose levels, oral insulin administration might be an effective way to overcome therapeutic inertia [5].

Several investigations on oral insulin delivery are underway [6]. However, physiological barriers like proteolytic degradation, the presence of tightly bound layers of mucus cells in the stomach and small intestine as well as large molecular size of peptides are major hindrances for the optimal bioavailability of oral insulins and other peptides [7]. Nobex Corporation, one of the pioneers in oral insulin discoveries, developed an orally active amphiphilic human insulin analog, methoxy (polyethylene glycol) hexanoyl human recombinant insulin (HIM2). Data from randomized controlled Phase I/II clinical trials suggested that

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Published online: 14 August 2023

Key Points

Insulin tregopil (IN-105) is an ultra-fast onset, short-acting oral insulin analog for managing diabetes mellitus.

Insulin tregopil is absorbed through the gastrointestinal tract with the first pass into the portal vein, i.e., the liver, before reaching the systemic circulation, thereby minimizing the adverse effects of peripheral hyperinsulinemia.

Tregopil provides improved post-prandial glucose control and lowers hypoglycemia risk. Patients with confirmed needle phobia and/or inadequate adherence to injectable insulin therapy are especially expected to benefit from oral insulin therapy.

oral doses of HIM2 were safe, well tolerated, and effectively controlled post-prandial glucose (PPG) in patients with diabetes mellitus (DM). The reported adverse events were predominantly mild with no serious concerns. Additionally, HIM2 was found to be safe when administered as an adjunct to basal insulin regimen [8–10].

Biocon developed HIM2 into an advanced generation, novel, ultra-fast onset, short-acting oral prandial insulin for PPG control, called insulin tregopil (IN-105). Insulin tregopil, administered orally, acts primarily on the liver. It is absorbed from the gastrointestinal tract (GIT) and has a first pass through portal circulation before reaching the systemic circulation. The primary portal insulin delivery is associated with several clinical advantages, such as (1) lower incidence of hypoglycemia (including nocturnal hypoglycemia), (2) lower peripheral hyperinsulinemia, (3) weight neutrality, and (4) improvement in patient-related outcomes like QoL (e.g., mobility, ease of self-care, less pain/discomfort), better compliance [7, 11], and better uptake of insulin initiation.

Elevated PPG is one of the earliest abnormalities of glucose homeostasis observed in T2DM. In patients with established DM, defective insulin secretion leads to post prandial hyperglycemia and the glucose levels do not return to normoglycemia over 1-2 hours post-meal [12]. Compared to the 2-h PPG levels, 1-h PPG levels more closely account for overall glycemic control as the rate of abnormal glucose values are high during the first hour after a meal, especially in patients with gestational DM [13–15]. When glycated hemoglobin A_{1c} (HbA_{1c}) levels approach 53 mmol/mol (7.0%) and fasting plasma glucose (FPG) levels are within the recommended range (4.4–7.2 mmol/L [80–130 mg/dL]), PPG has been found to majorly impact the residual hyperglycemia [16]. Post-prandial glucose is also an independent risk factor for the cardiovascular (CV) disease, with a demonstrated linear relationship between PPG and the risk of death due to CV [17]. Adding prandial insulins to basal insulins effectively control PPG levels and optimizes overall glycemic control [16].

Insulin tregopil has an ultra-fast onset (~ 10–20 min) and short duration of action (approximately 2- to 3 h post-meal). Clinical studies of insulin tregopil have shown an excellent control of 1-h PPG; its effect is more pronounced on 2-h PPG when FPG is under control. This action profile can help restore the first phase of insulin release deficiency in patients with T2DM who are on basal insulin, while the short duration of action reduces the risk of post-prandial hypoglycemia [18]. Pre-clinical and clinical studies have also demonstrated a good safety profile of insulin tregopil [18, 19]. In addition, the advanced phase clinical trial data suggest that insulin tregopil can potentially be used to manage PPG, further leading to improved HbA_{1c} levels, especially in the FPG-controlled patients with T2DM.

This article highlights the clinical development journey of an ultra-fast, short-acting insulin (insulin tregopil) to control PPG excursion in patients with DM.

2 Discovery Strategy and Historical Development of Oral Insulin Tregopil

The oral drug delivery technology involves chemically attaching amphiphilic oligomers to specific and pre-selected locations on peptides, proteins, and tiny organic molecules to modify them [20]. Nobex Corporation initiated the development of HIM products and designed oral HIM2 by facilitating conjugation with hydrophobic moieties. Clinical studies with HIM2 included Phase I/II trials in patients with T1DM and Phase II trials in patients with T2DM [9, 21–23]. These studies indicated that oral HIM2 was safe and effectively controlled post-prandial hyperglycemia when added to basal insulin. The clinical development of HIM2 was envisaged to position it as a treatment for T2DM and to supplement the reduced insulin secretion from pancreas observed in these patients [24]. In 2004, Biocon collaborated with Nobex Corporation and embarked on a development plan to generate a portfolio of orally delivered drugs to treat metabolic diseases [24, 25]. The clinical development of insulin tregopil by Biocon included global clinical trials to investigate the bioavailability, food effect, overall efficacy and safety, across different countries with a major focus on India (Fig. 1).

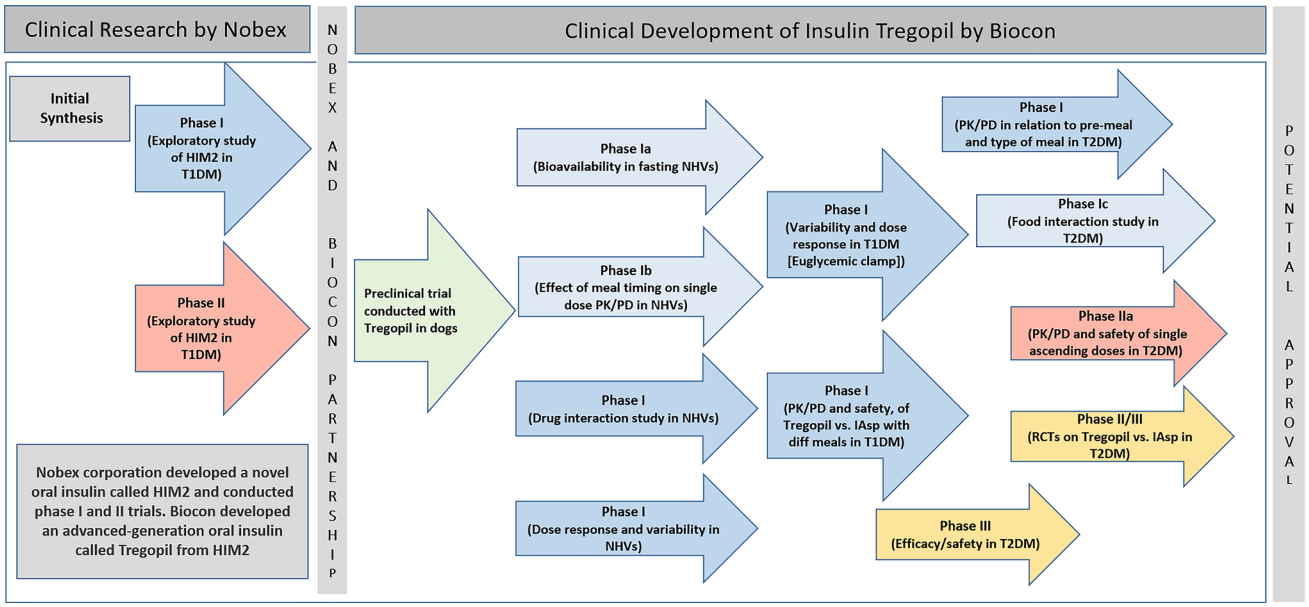

Fig. 1 Developmental milestones of insulin tregopil. *HIM2* hexyl-insulin monoconjugate 2, *IAsp* insulin aspart, *NHVs* normal healthy volunteers, *PD* pharmacodynamics, *PK* pharmacokinetics, *RCT* randomized controlled trial, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

3 Structure of Insulin Tregopil

Insulin tregopil ($C_{267}H_{401}N_{65}O_{82}S_6$) is a recombinant human insulin, with a single short-chain amphiphilic oligomer structurally akin to human insulin [26]. The activated methoxy tri-ethylene glycol reacts with any of the three free amino groups (N-terminal of the B chain [$PheB_1$], N-terminal of the A-chain [$GlyA_1$] and ε-amino group of amino acid [$Lys\beta_{29}$]) in insulin analog to produce the mixture of a conjugated product called methoxy-PEG3-propionyl-insulin at $Lys\beta_{29}$: IN-105 (Fig. 2) [27]. The conjugation process enhances oral hydrophobicity, protein stability, and resistance to enzymatic degradation [27, 28].

The purification of insulin tregopil is performed using reverse-phase high-performance liquid chromatography, and the elution pool is further polished using cation exchange chromatography. The cation exchange elution pool is crystallized and lyophilized to generate zinc insulin Tregopil crystals with 98.5% purity [29]. The molecular weight of insulin tregopil is 6026 g/mol [30], which is in the range of native insulin and other insulin analogs (insulin 5808; insulin glargine 6063; insulin aspart [IAsp] 5826; insulin detemir 5917; insulin degludec 6104; all in g/mol).

3.1 Insulin Tregopil with Permeation Enhancer

Insulin tregopil is a hydrophilic molecule that solubilizes very quickly in the presence of an aqueous medium and approximately 97–99% of the drug is dissolved within 5–10 min. The rapid and complete release of insulin tregopil from the drug product ensures quick availability of insulin tregopil in the GIT for absorption and demonstration of the pharmacological effect. Hydrophilic molecules, such as proteins and peptides, are generally not passively absorbed across the gut. Permeation enhancers such as sodium caprate (C10) unlock the tight junctions and promote the permeability of insulin and other proteins and peptides [7] through the gut, thereby increasing bioavailability [31].

4 Mechanism of Action of Insulin Tregopil

Endogenous insulin secreted from the pancreas enters the liver through the portal vein. It is believed to act by binding to the insulin receptors; in the liver, it inhibits glucose output and in the skeletal muscle and fat cells, it facilitates cellular uptake of glucose, and thus effects a lowering of blood glucose levels. Insulin exits the circulation at the microvasculature level, reaching the muscle and fat cells, and stimulating glucose transporter type-4 (GLUT4) translocation and glucose uptake [32, 33].

The liver is exposed to 2.5- to 3-fold higher insulin concentrations than the brain, fat, or other tissues. In contrast, when insulin is infused into a peripheral vein, hepatic insulin levels are ~20% lower than arterial levels. Insulin administered through the parenteral route causes peripheral hyperinsulinemia, thus leading to several unfavorable metabolic consequences, especially in the post-prandial setting. Insulin tregopil, through its hepato-preferential action, may reduce

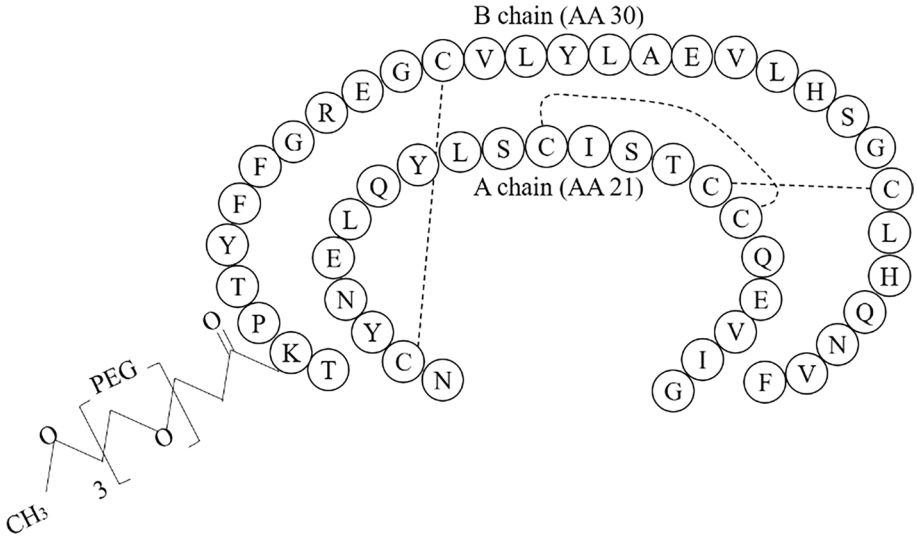

Fig. 2 Amino acid (AA) structure of insulin tregopil. *PEG* polyethylene glycol

the peripheral insulin levels by enhancing hepatic uptake of glucose and suppressing hepatic glucose production, consequently, reducing the risk of adverse effects [34].

Insulin tregopil, a recombinant human insulin analog, behaves similar to endogenous insulin, attaining higher hepatic exposure, than SC insulin administration. The intracellular insulin signaling mechanism in liver begins with the insulin receptor (INSR), a hetero-tetrameric protein consisting of two extracellular alfa units and two transmembrane beta units. Insulin binds to the alfa subunit of INSR in the liver, muscle, adipose tissue and consequently stimulates tyrosine kinase activity. Further, INSR auto-phosphorylates and activates the membrane-bound protein such as protein kinase (AKT), phosphatidylinositol-3 kinase, and insulin receptor substrate. Insulin predominantly acts via AKT signaling mechanism to activate glycogenesis, lipogenesis, and protein synthesis [35].

Endogenous insulin stimulates the growth hormone receptor to synthesize insulin-like growth factor-1 (IGF-1), which plays a central role in cell metabolism and growth regulation. Insulin upregulates IGF-1 bioactivity and downregulates hepatic production of insulin-like growth factor binding protein-1 (IGFBP-1) at the transcriptional level [36]. Data from study IN105-CT1-002-07 demonstrated the reduction of IGFBP-1 levels from baseline by insulin tregopil (15 mg and 20 mg doses) after 2 h, while the IGF-1 levels remained unchanged (data on file). Oral delivery of insulin leads to lower systemic concentration with a more favorable portal:peripheral concentration ratio, thus, resulting in reduced hypoglycemia potential in the later post-meal period, a lower incidence of obesity, and overall improvement in patients' QoL [11, 37] (Fig. 3).

5 Pre-clinical Development of Insulin Tregopil

Pre-clinical development of insulin tregopil was successfully conducted under various in vitro conditions. One of these studies showed a rapid dissolution (i.e., > 85% of insulin tregopil dissolution within 15 min). This rapid dissolution in gastric fluid ensured that the drug would be completely dissolved in the stomach before reaching the absorption site (also see Sect. 3.1). In vitro enzyme stability studies demonstrated that insulin tregopil had a two-fold greater resistance to chymotrypsin degradation than human insulin, which correlated to a higher concentration of insulin tregopil available for absorption in the GIT.

5.1 Toxicity Profile

The toxicity levels of insulin tregopil have been evaluated in three single-dose and eight repeat-dose animal studies over 14–180 days. These studies were conducted across three animal species, viz., Wistar rats/Sprague Dawley rats, New Zealand White rabbits, and Beagle dogs to assess their toxicity levels and pharmacokinetic (PK)/pharmacodynamic (PD) profiles (Online Resource—Table S1). The dose range and exposure in these studies were limited to observing the expected pharmacologic effect of hypoglycemia.

The single-dose studies showed no clinical signs of toxicity or lethality. There were no treatment-related changes in the body weight, food consumption, or gross pathology at all doses up to 400 mg/kg/day in rats, 150 mg/kg/day in rabbits, and 10 mg/kg/day in dogs. Similarly, repeat doses for up to 180 days showed no treatment-related changes in the body weight, food consumption, hematology, clinical chemistry, urinalysis, and macroscopic and microscopic evaluations. The expected pharmacological effect of blood

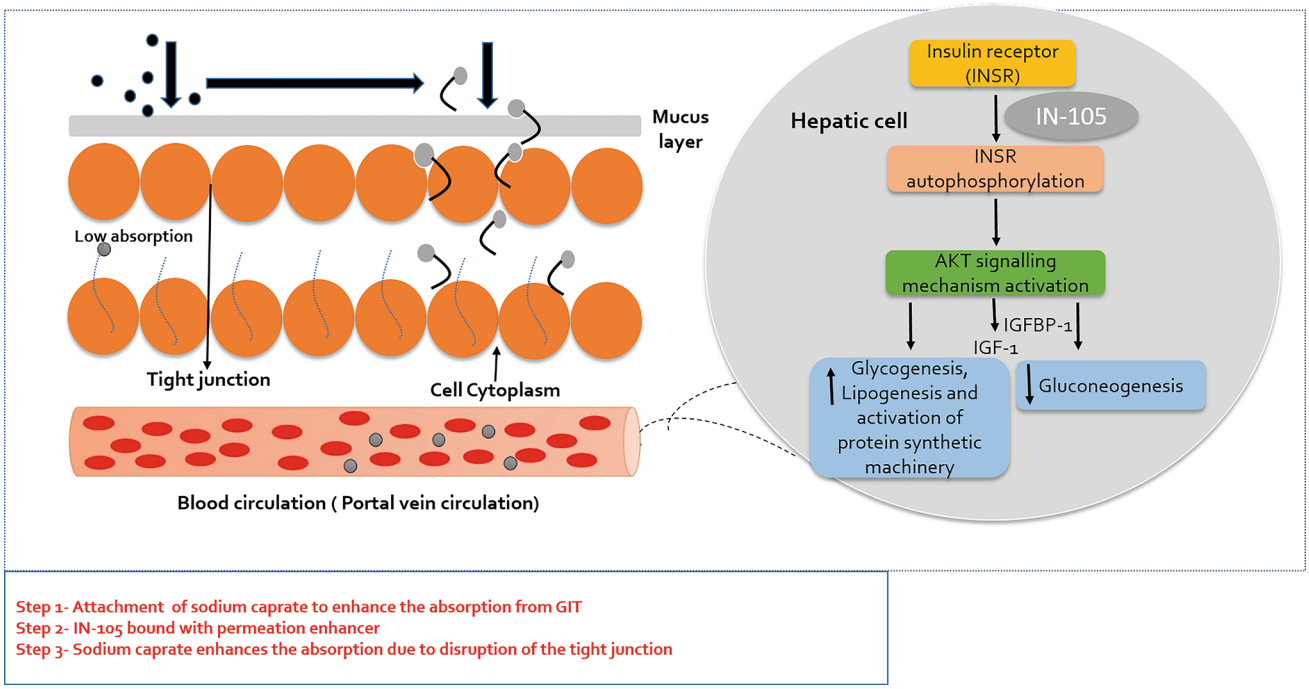

Fig. 3 Schematic representation of absorption of insulin tregopil from the GIT and metabolic effects in the liver. *AKT* protein kinase, *GIT* gastrointestinal tract, *IGFBP* insulin-like growth factor-binding proteins, *IGF* insulin-like growth factor, *INSR* insulin receptor, *IN-105* insulin tregopil

glucose-lowering was observed in all these studies. In the 180-day repeat-dose chronic toxicity study in rats and dogs, clinical signs of hypoglycemia were observed with increasing doses limiting the investigation of higher dose levels. No adverse changes were observed in the electrocardiogram and blood pressure measurements in dogs. A 90-day study in rats showed a positive response for anti-insulin tregopil antibodies, and in 90-day and 180-day studies in dogs, none of the tested saliva and serum samples were positive (i.e., presence of anti-insulin tregopil antibodies) for either IgG or IgA response. (Online Resource—Table S2).

Treatment with insulin tregopil did not affect any of the parameters, including body weight, food intake, maternal and litter effect, and fetal external, visceral, and skeletal parameters. The reproductive toxicity studies in Wistar rats showed no treatment-related changes in the fertility parameters, sperm motility, and cauda epididymal sperm counts.

In vitro and in vivo genotoxicity studies showed that insulin tregopil was not mutagenic (as demonstrated by bacterial reverse mutation test and micronucleus test in Swiss Albino mice). The teratology studies in rats and rabbits showed no clinical signs of teratogenicity or mortality in any of the study groups at any treatment level (Online Resource—Table S2). Based on the animal toxicology studies, the derived maximum human equivalent dose of insulin tregopil was calculated to be 387.6 mg for a 60-kg man (or 6.46 mg/kg/day) [38].

5.2 Pre-clinical Pharmacokinetics (PK) and Pharmacodynamics (PD)

Studies in conscious dogs demonstrated that insulin tregopil has a rapid onset (15 min) and short duration (2-h) of action towards reducing the PPG and C-peptide levels.

To quantify the PK/PD profiles of insulin tregopil, four approaches were used in this study:

1. The bio-effectiveness of insulin tregopil versus human insulin was compared when delivered at an equimolar infusion into the portal vein: Human insulin was infused intraportally in the comparator group at a dose of 3.6 pmol/kg/min for the first 120 min, followed by 12.0 pmol/kg/min for the next 120 min. In the intervention group, insulin tregopil was infused intraportally at the same doses (3.6 pmol/kg/min [600 µU/kg/min]/120 min) as human insulin (Online Resource—Table S3). The results showed that the intra-portal delivery of insulin tregopil and human insulin have similar PK profiles and equivalent PD profiles [19].
2. The dose response relationship for escalating doses of insulin tregopil was determined. It was observed that high-dose infusions of (0.25 mg/kg) of insulin tregopil showed a significant change in the PK/PD profiles compared to lower doses. Thus, a threshold amount of

0.25 mg/kg of insulin tregopil needed to be exceeded to achieve a significant PD effect [19].

3. The reproducibility of insulin tregopil's PD response was established. The higher dose (10 mg) of insulin tregopil was associated with an increased response compared to the low doses (3 mg and 6 mg), and there was a reasonable reproducibility of PK/PD profiles for consecutive doses of insulin tregopil [19].
4. The PK/PD profile of insulin tregopil was compared between inhaled human insulin and SC-injected human insulin in an exploratory analysis. Insulin tregopil and inhalational insulin showed rapid absorption (time of first occurrence of C_{max} [T_{max}] = 20 min) and SC administration insulin showed slower absorption rates (T_{max} = 88 min). The time needed to return to baseline plasma insulin levels was approximately 90, 210, and 360 min for insulin tregopil, inhaled, and SC insulin, respectively [19].

Pharmacokinetic studies in rats and rabbits showed that insulin tregopil was rapidly absorbed after the oral gavage, reaching peak plasma concentration between 10- and 30-min post-dose, depending upon the species and formulation. There was a dose-related increase in plasma insulin with a corresponding decrease in serum glucose in all the species tested. High variability in the absorption was a consistent finding. However, the corresponding reduction in glucose concentrations was more consistent. Therefore, the high PK variability of insulin tregopil may not be translating into PD variability, thus, resulting in a consistent plasma glucose reduction.

6 Clinical Development

The clinical development of insulin tregopil, thus far, includes 11 completed Phase I to Phase III clinical trials conducted across India, the USA, and Europe. All trials were of open-label design involving either normal healthy volunteers [NHV] (four trials), or patients with T1DM (two trials), and patients with T2DM (five trials). Trial details are presented in Table 1 (Phase II/III) and Online Resource—Table S4 (Phase I).

Single or multiple doses of insulin tregopil (5–60 mg three times per day [TID] prior to major meals) have been evaluated in various populations. A recent Phase I multiple ascending dose study in patients with T1DM evaluated the safety, PK, and PD of insulin tregopil following administration at pre-prandial doses of 30 mg, 45 mg, and up to 60 mg, TID.

6.1 Clinical Pharmacology

6.1.1 PK

The PK of insulin tregopil was evaluated in NHV and in patients with T1DM and T2DM under fasting and fed conditions across various Phase I/II trials (Online Resource—Table S4). Subjects were administered insulin tregopil in ascending doses (5–60 mg TID prior to major meals). The first-in-human dose of insulin tregopil (10–30 mg) was determined based on the no observed adverse effect level (NOAEL) derived from in vivo toxicology studies. The safety analysis from the dose range finding study revealed that all the treatments (placebo, 10 mg, 15 mg, 20 mg, and 30 mg) of insulin tregopil when administered as a single dose after an overnight fast of 10 h, 20 min before a standardized breakfast meal of 600 kcal, were well tolerated [39].

6.1.1.1 Bioavailability, $C_{max,}$ and $t_{1/2}$ In an open-label, five-treatment, five-period study, the effect of a single administration of insulin tregopil (5 mg and 10 mg) was evaluated in NHV. The subjects attained maximum plasma concentrations approximately 10–20 min post-dosing. Median time to reach maximum plasma concentration ranged between 20- and 30-min post-dose and the median half-life ($t_{1/2}$) of insulin tregopil (with doses up to 30 mg per meal) was observed to be 9 min and 16 min in studies conducted with NHV and T2DM patients, respectively. In a T1DM study, the plasma concentration of insulin tregopil was observed to increase rapidly (t_{max} = 0.4–0.5 h [24–30 min]) and the half-life ($t_{1/2}$) of insulin tregopil was 0.2–0.3 h (12–18 min).

Higher doses of oral insulin tregopil resulted in higher mean maximum plasma concentrations (C_{max}) whereas the same was lower with peripherally administered insulins (SC). The area under the serum concentration–time curve (AUC) from 0 to 180 min increased linearly in NHV and T2DM patients in doses up to 30 mg. In a Phase I, open-label, multiple ascending dose study, the increase in systemic availability of insulin tregopil in patients with T1DM was dose-dependent in the higher dose groups (45 mg and 60 mg) compared with the lower dose group (30 mg) (data on file). However, a distinct dose proportionality for bioavailability of insulin tregopil could not be established for the three dose groups studied.

Overall, the PK and PD parameters exhibited a dose-dependent increase with increasing doses of insulin tregopil only up to 30 mg beyond which, the increase was more than dose proportionate. The formal dose proportionality assessments indicated the PK response to be inconclusive for $AUC_{ins0–3h}$ and not proportional for C_{insmax}. The relative bioavailability of insulin tregopil in the peripheral circulation is ~2–3% and is approximately 8–11% in the portal circulation compared to IAsp. The portal peripheral

Table 1 Phase II and Phase III clinical trials of insulin tregopil conducted by Biocon

Study details	Intervention and comparator	Indication and dose	Eligibility criteria	Key outcomes
Study ID: IN-105-CT2-003-07 [41] **Study center:** India **Study design:** Five-period, open-label, placebo-controlled study **Study phase:** IIa	Insulin tregopil ($n=20$) and placebo ($n=20$)	**Indication:** T2DM **Doses:** 10 mg, 15 mg, 20 mg, and 30 mg	**Inclusion criteria:** (i) Subjects whose FBS was ≥ 130 mg/dL (ii) Subjects whose HbA_{1c} concentration was 7.5–9.5% (iii) Subjects who have been treated with metformin extended-release tablet with dose ranging between 500 and 1500 mg/day, including previous 12 weeks **Exclusion criteria:** (i) Subjects treated with insulin to control diabetes (ii) Subjects who had already participated in any other clinical study in the past 12 weeks of commencement of the study (iii) History of any other complications (iv) Subjects who had two or more serious hypoglycemic episodes within the 6 months prior to study	(i) PK and PD parameters for insulin and, C-peptide, and glucose for −2 to 180 min, −2 to 80 min, and −2 to 140 min after dosing (ii) AEs (iii) Abnormal laboratory findings
Study ID: IN-105-CT3-004-08 [42] **Study center:** India **Study design:** Multi-center, randomized, double-blind, placebo-controlled, parallel assignment, efficacy/safety study **Study phase:** III	Insulin Tregopil ($n=195$) and placebo ($n=66$)	**Indication:** T2DM **Doses:** 10 mg, 15 mg, 20 mg, and 30 mg	**Inclusion criteria:** (i) HbA_{1c} concentrations of > 7.5% and ≤ 10% (ii) On stable dose of metformin ER tablets at doses ranging between 1 and 2 g/day for at least 12 weeks prior to the screening visit (iii) Fasting plasma C-peptide > 0.6 ng/mL at screening **Exclusion criteria:** (i) History of hypersensitivity to study drugs and severe or multiple allergies (ii) T1DM (iii) History of other complications (iv) Patients currently on other oral hypoglycemic agents other than metformin	(i) Change in HbA_{1c} from randomization to Week 24 (ii) PPG—Standardized test meal and SMBG (iii) FPG (iv) AEs including clinically significant laboratory abnormalities (v) Hypoglycemia
Study ID: TREGO-DM2-03-I-01 and NCT03430856 [42] **Study center:** India **Study design:** Multicenter, randomized, parallel assignment, open-label study **Study phase:** II/III	Insulin Tregopil ($n=61$) and IAsp ($n=30$)	**Indicationn:** T2DM **Dose:** 30 mg and 45 mg	**Inclusion criteria:** (i) Patients with a T2DM for the duration of 6 months with the screening as per ADA 2017 guidelines (ii) Stable dose of metformin for the period of 3 months prior to screening (iii) HbA_{1c} of 7.5–10.0% **Exclusion criteria:** (i) Patients with T1DM (ii) Treatment with glucagon-like peptide 1 agonists within 12 weeks prior to screening (iii) History of severe hypoglycemia and other complications	(i) CFB in HbA_{1c} at 24 weeks (ii) Number of severe or clinically significant hypoglycemia events during 24 weeks of treatment period

ADA American Diabetic Association, *AE* adverse event, *CFB* change from baseline, *ER* extended release, *FBS* fasting blood sugar, *FPG* fasting plasma glucose, *HbA_{1c}* hemoglobin A1c, *PPG* post-prandial glucose, *PK* pharmacokinetics, *PD* pharmacodynamics, *SMBG* self-monitored blood glucose, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

insulin gradient indicates a significantly (2.5- to 3-fold) higher insulin concentration in the portal vein compared to the systemic circulation [32].

6.1.1.2 Effect of Meal Insulin tregopil absorption was significantly affected by meals. In a study evaluating pre-meal dosing time, between meal interval and type of meal in T2DM patients [18], insulin tregopil administered 10–20 min before a meal resulted in an optimal post-meal exposure (AUC) and demonstrated better PPG-lowering effect compared with the 30-min administration group. Insulin tregopil's exposure (plasma AUC) showed a progressive increase through 4-h, 5-h, and 6-h of between-meal interval. The 6-h between-meal interval resulted in better absorption of insulin tregopil compared with the 4-h and 5-h intervals. However, no significant differences were observed in PD parameters except for higher glucose $AUC_{0–180\ min}$ in the insulin tregopil 4-h group during the afternoon meal compared to the morning meal. A high-fiber meal had the least impact on absorption of insulin tregopil and resulted in the highest reduction in plasma glucose levels in the afternoon. Reduction in absorption of insulin tregopil occurred after a high-fat afternoon meal; however, PD response was not diminished significantly. In the same study, insulin tregopil showed a rapid onset of action of approximately 10 min. When administered 10–20 min before a meal, insulin tregopil demonstrated up to 13–18% reduction in blood glucose levels compared with baseline. A 5-h between-meal interval minimizes the impact of a meal on absorption of subsequent (afternoon) insulin tregopil dose, and the PD response of insulin tregopil is not altered by meal composition.

In T1DM patients, insulin tregopil administered 10 min before a meal led to a steep rise in the insulin concentrations, which reached a maximum in all dose groups (30 mg, 45 mg, 60 mg, and 60 mg + 30 mg post-prandial rescue) within 12–20 min, followed by a steep decline, with concentrations falling below the quantification limit within 1-h to 2-h of administration (data on file). Bioavailability of insulin tregopil was reduced after a meal. No rise in systemic insulin concentration was observed after administration of additional 30 mg post-prandial rescue dose in the insulin tregopil 60 mg cohort in the Phase I trial conducted in patients with T1DM.

6.1.1.3 Variability in PK One of the deficiencies of parenteral insulin analogs has been variability in PD effect, which in turn reflects variability in their absorption (20–55%) [40–42]. Oral peptide drugs typically have low bioavailability, which further amplifies the variability in their absorption, hence, the PK variability for oral insulin analogs can be expected to be higher than their parenteral counterparts. Inter-subject and intra-subject variability of insulin tregopil evaluated in patients with T1DM (cohort 2 [30 mg], G-16 euglycemic clamp study, [Online Resource—Table S4]) and T2DM (cohort 2 [30 mg], G-14 study, [Online Resource—Table S4]) showed high PK variability, which was more pronounced for intra- than for inter-subject variability. In the T1DM patients, the intra- and inter-subject coefficient of variation (CV%) was greater in the insulin tregopil group (80.3% and 38.1%) as compared with IAsp (18.3% and 30.5%), respectively, for the $AUC_{ins0–3\ h}$ parameter. Similarly, for the C_{insmax} parameter, the intra- and inter-subject CV% was higher in insulin tregopil (51.0% and 33.6%) than IAsp (33.2% and 25.8%). In T2DM patients, the inter- and intra-subject CV% for insulin tregopil was 124.7% and 64.7% for the C_{max} parameter; whereas the same for the $AUC_{0–last}$ parameter was 144.0% and 81.5%, respectively (Online Resource—Table S5). The higher variability in the PK of insulin tregopil is potentially due to high variation in the rates of absorption due to multiple factors such as high molecular weight, diffusion through mucin barrier, proteolytic cleavage, etc., along with the oral route of administration and extraction by the liver both significantly contributing to this variability. However, this variability may not be of a significant concern clinically as insulin tregopil is quickly extracted by the body cells during circulation.

Individual PPG levels in patients with T1DM from all cohorts (four-cohort Phase I, open-label, multiple ascending dose study) showed significant variation within and between patients and treatment days (data on file).

6.1.1.4 Interaction An open-label, randomized, placebo-controlled, single-dose study observed no apparent effect of insulin tregopil or placebo on metformin exposure (C_{max} and $AUC_{0–inf}$) under fed condition (Online Resource—Table S4).

6.1.2 PD

The PD of insulin tregopil was assessed in the NHV, T1DM, and T2DM populations. Insulin tregopil has an ultra-fast onset of action within ~ 10–20 min and median time to peak effect (i.e., minimum glucose level) is observed ~ 30–40 min post-dose (Online Resource—Table S4).

In an open-label, placebo-controlled Phase I study in NHV, a single dose of insulin tregopil administered at 5–15 mg under fasting conditions caused a 26–36% fall in plasma glucose levels compared with baseline (pre-dose) [41]. In another open-label, sequential ascending dose study in T2DM patients under fed condition, the average maximum percentage drop in glucose from baseline after administration of 10 mg, 15 mg, 20 mg, and 30 mg doses of IN-105 tablets was 18.1%, 26.1%, 29.0%, and 30.8%, respectively. The time to peak PD effect ranged between 35.5 and 42.3 min for insulin tregopil dosed between 10

and 30 mg [40]. A significant drop in plasma glucose levels was observed across all the investigated doses (single and multiple) of insulin tregopil. In the study mentioned above in T2DM, both the maximum drop in plasma glucose levels as well as the average change in glucose at 2-h (140 min) post-dose were dose dependent [40]. Similarly, the PD effect measured as glucose infusion rate was dose-dependent (10 mg, 20 mg, 30 mg, and 45 mg of insulin tregopil) in a study conducted in patients with T1DM. In another recently concluded study in T1DM patients, administration of insulin tregopil resulted in a brief decrease of PPG concentrations within 10–30 min after dosing, followed by a rapid increase to maximum limits within 150–180 min, which is in accordance with the fast- and short-acting PK profile of insulin tregopil (data on file). This resulted in requiring a rescue insulin dose in most T1DM patients. The additional rescue dosage of 30 mg insulin tregopil was not adequately effective in decreasing the PPG levels, necessitating the frequent administration of additional IAsp. Pharmacodynamic outcomes with the additional rescue dose were not consistently different from the PD outcomes observed in the 60 mg insulin tregopil T1DM patient cohort.

6.1.2.1 Effect of Meal Food affects the glucose-lowering effect of insulin tregopil. As with the PK, the gluco-dynamic effect of insulin tregopil was related to the effective time interval between the administration of insulin tregopil and meal. Longer intervals resulted in a greater fall in plasma glucose levels. Among the dosing time options tested in NHV and T2DM patient studies, insulin tregopil dosing 10 or 20 min before a meal resulted in a robust PD effect. Overall, there was no significant effect of the type of meal on PD parameters of insulin tregopil. In the multiple-dose, placebo-controlled study in T2DM patients, insulin tregopil at the 10-mg dose decreased the PD parameters across the day when it was administered in the following order—morning dose (before breakfast) > afternoon dose (before lunch) > evening dose (before dinner). Overall, insulin tregopil administration between 10- and 20-min before each meal with a 5-h interval showed rapid absorption, achieved adequate post-meal exposure, and effectively reduced PPG excursions in T2DM patients [18].

6.1.2.2 Variability in PD The variability in insulin tregopil exposure is not reflected to the same extent in the glucose reduction effect. When an insulin product is administered orally, at least 50% of the insulin is extracted in its first pass through the liver, resulting in 2.5- to 3-fold higher insulin concentrations in the liver than in the systemic circulation [32]. This is probably the reason for the presence of insulin tregopil in high concentrations in the portal circulation and more variability in the PK parameters in the peripheral evaluations. However, since the PD effect is a combination of action both at the liver and the peripheral tissues, the variability in PD effect is not as high as that observed with the PK parameters. In the single-ascending dose euglycemic glucose clamp study in T1DM patients, the inter-subject and intra-subject PK variability observed with insulin tregopil (doses up to 45 mg) was higher than that with IAsp. Compared with IAsp, insulin tregopil peaks more rapidly and decreases sooner, and this may contribute to the apparent higher variability in the peripheral effect (Online Resource—Table S5). Clear dose-dependent association between insulin tregopil doses and plasma glucose endpoints was not evident in this study. There was considerable inter- and intra-subject variability with respect to PPG among TIDM patients following insulin tregopil administration.

6.2 Clinical Efficacy

In T2DM patients, post-prandial hyperglycemia is one of the major abnormalities in glucose homeostasis and worsens the fasting hyperglycemia and disease progression [43]. As HbA_{1c} levels approach 53 mmol/mol (7.0%) and FPG levels are within target range (4.4–7.2 mmol/L [80–130 mg/dL]), PPG has been found to play a significant role in residual hyperglycemia [44]. Also, post-prandial hyperglycemia is independent of FPG and despite normal HbA_{1c}, is shown to double the risk of death from CV disease [45]. Post-prandial hyperglycemia is the rate-limiting factor for achieving optimal glycemic control in T2DM patients [17, 45].

After establishing the ultra-fast onset and short duration action profile of insulin tregopil in clinical pharmacology studies, its efficacy as a prandial/bolus insulin was demonstrated in three important studies. The proof-of-concept study established the glucose-lowering effect of insulin tregopil in the post-prandial setting (Phase II study), in T2DM patients, followed by two long-term studies conducted to investigate its efficacy, a placebo-controlled study (IN105-CT03-004-08) and an active-controlled study comparing subcutaneous IAsp (TREGO-DM2-03-I-01) in T2DM patients. Although the primary objective of these studies was to investigate the efficacy of insulin tregopil on HbA_{1c} reduction, the evidence/data that emerged from Phase I/II/III studies showed that insulin tregopil mainly acts through PPG control.

The Phase II study (IN-105-CT2-003-07) (refer Table 1 for study design details) examined the effect of single ascending doses (10 mg, 15 mg, 20 mg, and 30 mg) of insulin tregopil and placebo on the PK, PD, safety, and tolerability, under fed conditions in T2DM patients, who were previously on metformin therapy [39]. The multicenter, randomized, double-blind, multiple-dose placebo-controlled study (IN-105-CT3-004-08) evaluated the efficacy of insulin

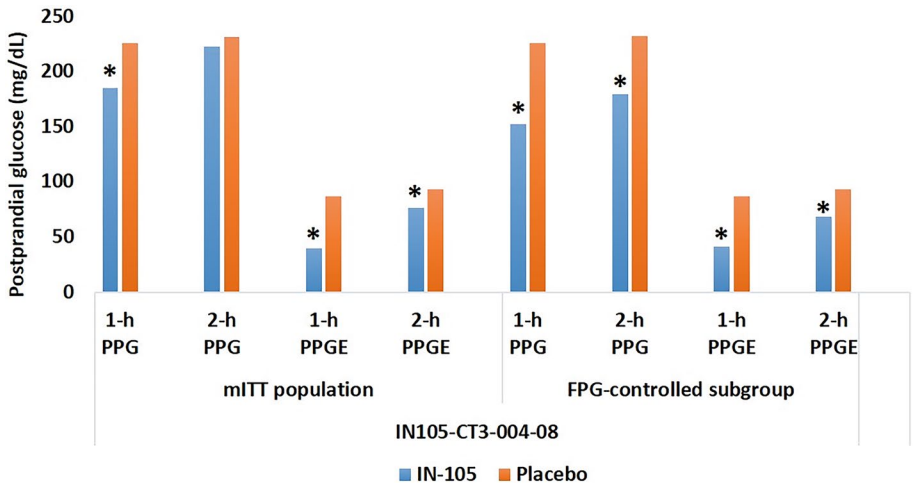

Fig. 4 Clinical efficacy of insulin tregopil compared with placebo: 1-h and 2-h post-prandial glucose (PPG) and PPG excursion (mg/dL) in IN105-CT03-004-08 trial. *$p < 0.05$ (IN-105 vs placebo). *dL* deciliter, *FPG* fasting plasma glucose, *IN-105* insulin tregopil, *mg* milligram, *mITT* modified intention-to-treat, *PPG* post-prandial glucose, *PPGE* post-prandial glucose excursion. mITT population—this population included all patients who met study inclusion criteria and did not meet any exclusion criteria, were randomized to the double-blind therapy, and had at least 1 HbA_{1c} value after at least 56 days of double-blind treatment. FPG-controlled subgroup—patients with standardized test meal (STM) FPG < 130 mg/dL

tregopil in terms of HbA_{1c} and PPG control. It determined the safety in a treatment period of up to 24 weeks. Patients who participated in the study received 10 mg, 15 mg, 20 mg, and 30 mg of insulin tregopil or placebo, TID pre-prandial (10 min before each major meal), as applicable. In this study, the primary analyses were performed in a modified intent-to-treat (mITT) population and post hoc analyses in the FPG-controlled subgroup (defined as patients in the insulin tregopil arm with standardized test meal [STM] FPG < 130 mg/dL at Week 24). The results for the combined dose group referred to as insulin tregopil arm are presented in Fig. 4. The study was followed by a 24-week Phase II/III active-controlled study (TREGO-DM2-03-I-01 and NCT03430856), which evaluated the efficacy and safety of two doses (30 mg and 45 mg) of insulin tregopil versus IAsp in T2DM patient, who were previously on a stable dose of metformin and insulin glargine (please refer Table 1 for design details). In this study, insulin tregopil was administered 10 ± 2 min before the three major meals, and IAsp was administered within 5 min prior to the meals [46]. The HbA_{1c} was analyzed in a subgroup of patients with well-controlled FPG (< 120 mg/dL by self-monitored blood glucose [SMBG]) and other parameters. The three efficacy studies showed that insulin tregopil was pharmacologically active while consistently establishing the achievement of PPG control (1- and 2 h PPG and PPG excursion) [39, 46]. Due to the prandial nature of insulin tregopil, its effect on PPG control is presented first followed by HbA_{1c}.

6.2.1 Post-prandial Glucose (PPG) Levels (1-h and 2-h) and PPG Excursion

In the single-dose placebo-controlled study in T2DM patients, the highest dose of insulin tregopil 30 mg showed a significant reduction in 1- and 2-h PPG and the corresponding excursion compared to placebo with mean 1- and 2-h PPG value of 146.56 mg/dL and 204.22 mg/dL, respectively. The 2-h PPG excursion showed a linear dose response relationship for insulin tregopil doses up to 30 mg used in this study.

Both multiple-dose Phase III studies in T2DM patients evaluated PPG under standardized conditions following an STM as this is imperative for analyzing the efficacy of prandial insulins like insulin tregopil. Overall, insulin tregopil demonstrated significant improvement in early post-prandial hyperglycemia compared to placebo and active comparator IAsp. In doses of 30 mg and 45 mg, it was more effective than IAsp in 1-h PPG control and as effective as IAsp in the 2-h PPG control and the mean 1-h PPG level was well below 180 mg/dL.

In the placebo-controlled study, at Week 24, a significant reduction in 1-h PPG was observed in patients in the insulin tregopil arm (1-h PPG: 184.95 mg/dL, mean change from baseline − 42.51 mg/dL and mean difference (standard deviation [SD]) from placebo, − 39.92 (9.28) mg/dL, $p < 0.0001$). The 1-h PPG control was improved further in the FPG-controlled subgroup with levels below 155 mg/dL (152.40 mg/dL, mean change from baseline, − 64.38 (65.16) mg/dL, difference from placebo, − 58.27 (− 80.02, − 36.51) mg/dL, $p = 0.000$) (Fig. 4). The 1-h PPG levels of

< 155 mg/dL is predicted to be a critical cut-off value linked to cardiovascular and microvascular complications/outcome [47, 48]. Similarly, a numerical reduction in the 2-h PPG levels in the insulin tregopil arm (2-h PPG: 222.54 mg/dL) and a significant reduction in the FPG-controlled subgroup was also observed (2-h PPG: 179.33 mg/dL, mean change from baseline, − 51.86 (66.67) mg/dL and mean difference (95% CI) from placebo, − 37.72 (− 60.05, − 15.39) mg/dL, $p = 0.001$, respectively) (Fig. 4). There was a significant reduction in the 1-h excursion in the insulin tregopil arm (change from baseline [SD], − 47.87 mg/dL (57.84), difference from placebo, − 48.18 mg/dL (− 65.37, − 30.99) and its FPG-controlled subgroup compared with placebo (change from baseline, − 46.33 (55.49) mg/dL, and difference from placebo, − 46.27 (− 62.53, − 30.01) mg/dL), $p = 0.000$) (Fig. 4). There was also a significant reduction in 2-h PPG excursion in the insulin tregopil arm (change from baseline, − 32.45 (57.50) mg/dL, difference from placebo, − 22.59 (− 40.40, − 4.78) mg/dL, $p = 0.013$) as well as in the FPG-controlled subgroup compared with placebo (change from baseline [SD], − 33.81 (56.75) mg/dL, difference from the placebo, − 24.67 (− 41.43, − 7.91) mg/dL, $p = 0.004$) (Fig. 4). The results indicated that insulin tregopil has significantly better PPG control compared with placebo. Overall, the effect on PPG control was accentuated with significant improvement in both 1-h and 2-h PPG control in a subgroup of patients treated with insulin tregopil with good FPG control, compared to placebo.

It was observed that the HbA_{1c} levels improved to the normal range in the FPG-controlled subgroup of the insulin tregopil arm (7.34%), and patients in this subgroup had a better PPG control. Though limited by a small sample size, in the insulin tregopil arm, the 1-h PPG target (< 155 mg/dL) was achieved by 25% patients, while it was achieved by 43% in the FPG-controlled subgroup. The 2-h PPG target (< 180 mg/dL) was achieved by 26% and 54% patients in the two subgroups, respectively.

In the active-controlled study, insulin tregopil was found to reduce PPG levels within 20 min of administration. Insulin tregopil at a 45 mg daily dose resulted in an average 1-h PPG level of 157.9 mg/dL (Fig. 5). Insulin tregopil was more effective than IAsp (as assessed by SMBG) in reducing 1-h PPG excursion at breakfast and lunch and 2-h PPG levels at breakfast. The 1-h excursion following the STM was significantly lesser in the insulin tregopil group compared with IAsp (change from baseline, estimated treatment difference, 95% CI − 45.33 mg/dL [− 71.91, − 18.75], $p = 0.001$) [49]. PPG control by insulin tregopil at 2-h and later was less compared with IAsp. Results of post hoc analyses suggest that insulin tregopil's action is faster than IAsp and has an onset of action within 15 min, which supports its ultra-fast-acting profile [49].

The integrated analyses indicated that the reduction in 1-h PPG and 1-h PPG excursion was better than that observed with other prandial insulins such as IAsp and faster-acting IAsp (FIAsp) in the ONSET-2 trial [50]. In the same study, the 2-h PPG and PPG excursion values were comparable to those observed with insulin tregopil; however the change from baseline values were lower with insulin tregopil; a higher dose of insulin tregopil could improve the 2-h PPG control comparable to that of IAsp and FIAsp [50].

6.2.2 Glycated Hemoglobin

Glycated hemoglobin A_{1c} was the primary endpoint assessed from baseline to Week 24 in the multiple-dose placebo-controlled and active-controlled clinical studies in T2DM patients. Insulin tregopil demonstrated more effective reduction of HbA_{1c} in patients with sustained well-controlled FPG, reflecting an effective PPG control. In the placebo-controlled study (IN105-CT3-004-08), there was no significant improvement in HbA_{1c} at Week 24 compared with placebo (adjusted mean change from baseline) standard error (SE) was − 0.42% (0.07), 95% CI (− 0.56, − 0.29) vs − 0.46% (0.12) (− 0.69, − 0.23), mean difference (SE), 0.04% (0.14) (− 0.23, 0.30), $p = 0.7962$. However, based on the post hoc analyses, the mean change from baseline in HbA_{1c} in the FPG-controlled subgroup of the insulin tregopil arm (− 0.89%) was better than that with placebo (− 0.46%). This is similar to the observed HbA_{1c} reduction (0.7–1%) with other prandial anti-diabetic drugs like acarbose and nateglinide [51, 52]. Dipeptidyl peptidase-4 inhibitors, with a major effect on PPG control, have also produced HbA_{1c} reduction in the range of 0.7–1% in different studies [53, 54]. The difference in the mean change from baseline in HbA_{1c} in the FPG-controlled subgroup of insulin tregopil compared with placebo (full analysis set) (− 0.43%, $p = 0.004$) was statistically significant as per guidelines and was also clinically relevant. However, this was not observed when compared with the FPG-controlled placebo subgroup, possibly due to the lower number of patients in this placebo subgroup ($n = 20$).

In the active-controlled study (TREGO-DM2-03-I-01), the observed HbA_{1c} did not improve over the treatment period. The mean change from baseline in observed HbA_{1c} at Week 24 was 0.15%, 0.22%, and − 0.77% in the insulin tregopil 30 mg, 45 mg and IAsp groups, respectively. However, in the post hoc analysis, a clinically relevant HbA_{1c} reduction of 0.3% from baseline was observed in 40% of patients in the 30 mg insulin tregopil group, 45.1% of patients in the 45 mg insulin tregopil group, and 66.6% of patients in the IAsp group. Approximately 50% and 45.61% of patients in the insulin tregopil 30 mg and 45 mg groups, respectively, achieved any reduction in HbA_{1c} at Week 24

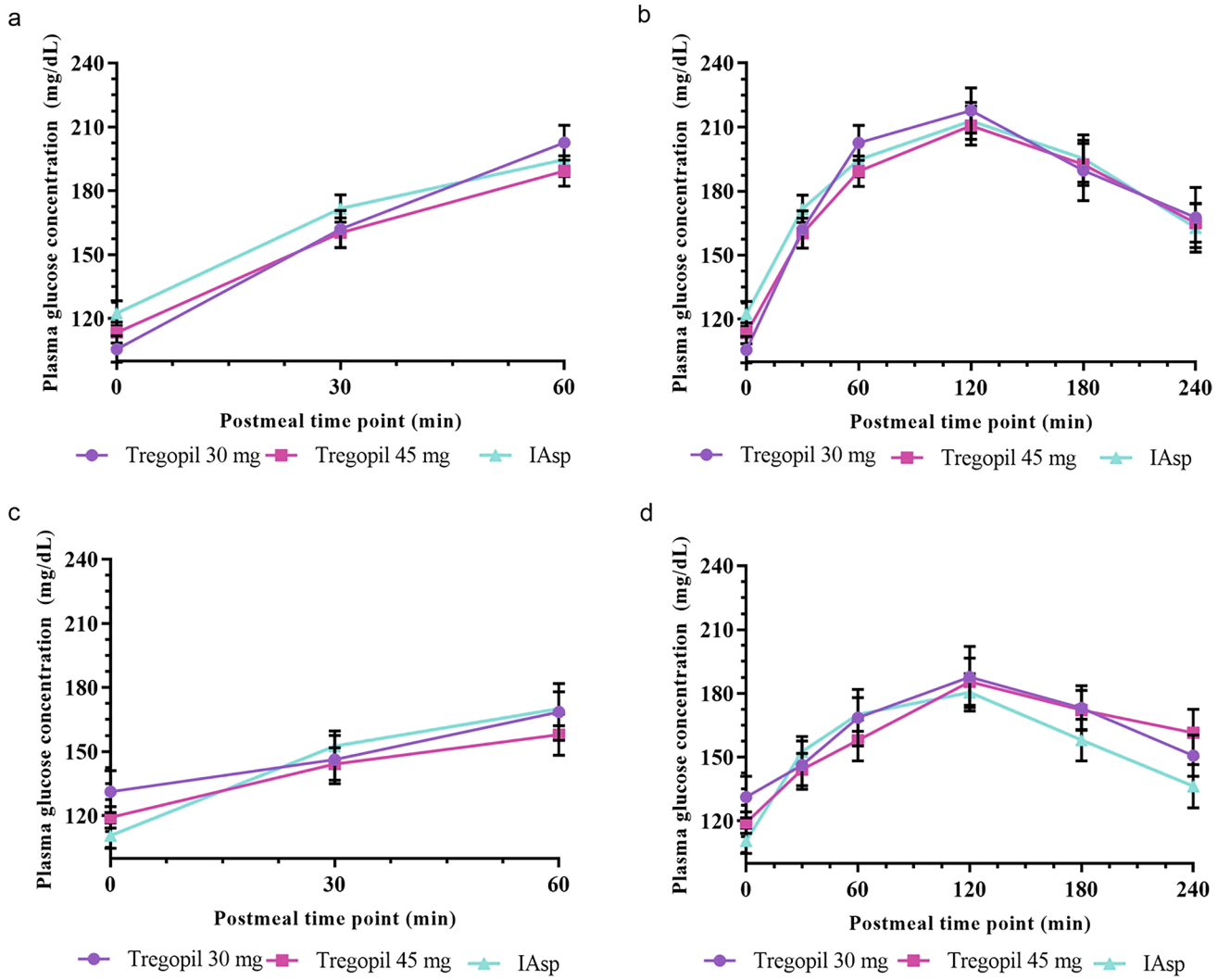

Fig. 5 Clinical efficacy of insulin tregopil compared with insulin aspart evaluated as mean PPG versus time during STM in TREGO-DM2-03-I-01 trial **a** at pre-treatment up to 1-h (60 min); **b** at pre-treatment up to 4-h (240 min); **c** at week-24 up to 1-h (60 min); **d** at Week-24 up to 4-h (240 min). Mean with SEM is presented in the above plots. Post-meal-time point—0 min indicates, 10 min after the dose, i.e., meal start time. *dL* deciliter, *IAsp* insulin aspart, *mg* milligram, *min* minutes, *PPG* post-prandial glucose, *STM* standardized test meal

compared with baseline and were considered as HbA_{1c} responders (Fig. 6). About 85.7% (12/14) and 100% (8/8) of the patients in the FPG-controlled subgroup (age > 40 years, duration of diabetes 2–10 years, on oral antidiabetic agents [OADs] in addition to metformin and glargine and FPG < 120 mg/dL [SMBG]) at 24 weeks responded to treatment with insulin tregopil and IAsp, respectively. A reduction in HbA_{1c} of 0.55% (30 mg: 0.29% and 45 mg: 0.81%) and 0.91% from baseline was observed at Week 24 in the same insulin tregopil and IAsp subgroups.

Based on the learnings from the previous studies, the randomization criteria for the active-controlled study were set as follows: (1) patients with poor glucose control (HbA_{1c} range in 9–10% or greater); (2) patients with improved control of the FPG (HbA_{1c} in the range of 8–9%), with a set target pattern of pre-lunch, pre-supper, and bedtime glucose levels; and (3) patients with target patterns of PPG elevation with unachieved optimal HbA_{1c} levels (~7–8% or even less) [55]. Insulin tregopil improves PPG control in all T2DM patients, and its contribution to HbA_{1c} reduction is best reflected in patients who continue to maintain the FPG control.

HbA_{1c} has a major discordance with the PPG control in the following criteria: (1) calculated and measured HbA_{1c} levels show variation with glucose control, and (2) PPG contributes majorly to HbA_{1c} at levels < 7.3% and contribution of FPG is significant at levels above 9.3% [56]. In the active-controlled study (TREGO-DM2-03-I-01), measured HbA_{1c}

levels were observed to vary with the calculated HbA_{1c} levels. The findings from this study indicated that HbA_{1c} may not be the most appropriate measure of glycemic control and other plasma glucose parameters like PPG and PPGE estimated by STM and SMBG may be more appropriate in truly reflecting the actions of insulin tregopil. The potential reason behind this discordance is due to the unique features of insulin tregopil action beyond its effect on plasma glucose that could affect HbA_{1c}. It is possible that insulin tregopil may have a direct or indirect effect on the glycation pathway or that it may influence the metabolism/survival of red blood cells and thereby increase HbA_{1c} levels, which needs further investigation.

7 Safety

Data gathered so far from the clinical studies across various population groups, i.e., NHV [57, 58], T1DM (IN-105-DM-01-G-16, TREGO-DM1-01-G-02 [NCT04141423]; data on file) and T2DM [18, 39, 49] (Online Resource—Table S4) suggest that insulin tregopil at the doses tested is safe and well tolerated. Tregopil does not cause any gastrointestinal (GI) side effects owing to its oral administration and hence, any upper GI pathology is not expected to impact its absorption. In the active-controlled study, a lower incidence of clinically significant hypoglycemia was reported in the insulin tregopil group (30 mg: 53.3%, 38 events; 45 mg: 41.9%, 27 events) compared with the IAsp group (56.7%, 47 events). The risk ratio for hypoglycemia showed lower potential for causing hypoglycemia compared with other prandial fast-acting insulins such as FIAsp, which shows higher incidence of hypoglycemia when co-administered with basal insulin and metformin. In the active-controlled study, the risk ratio of insulin tregopil groups (30 mg + 45 mg) versus IAsp group for all hypoglycemia events was 0.64 and for clinically significant hypoglycemia events, the ratio was 0.69. The incidence of clinically significant hypoglycemia (ADA classification) in terms of event rate per 100-year exposure was lower in the insulin tregopil groups (282.9 and 193.3/per 100-year exposure [PYE] with insulin tregopil 30 mg and 45 mg, respectively) compared with IAsp (346.3 PYE). There were much higher rates observed in other studies with rapid-acting insulins (event rate for IAsp was 1790 events PYE) [50]. Insulin tregopil was also safe and well-tolerated at all doses as established from the evaluation of non-glycemic adverse events from a Phase I study in T1DM patients (Online Resource—Table S4). Administration of different doses of insulin tregopil (30 mg, 45 mg, 60 mg, and 60 mg + 30 mg post-prandial rescue) TID before meals in patients on basal insulin glargine showed no safety concerns except hypoglycemia, which is an expected pharmacological adverse action of insulin treatment. However, none of the reported hypoglycemic events were severe and all the patients recovered completely. Hypoglycemic episodes, which occurred early after pre-prandial administration due to the rapid action of insulin tregopil, did not elevate with the increase in insulin tregopil dosage and could be managed with administration of rescue insulin dose and absorbable carbohydrates, based on the requirement. Early treatment with insulin tregopil can provide a good glycemic control with potential benefits of weight neutrality and beta-cell sparing effect, while mitigating disease progression. The overall results from the

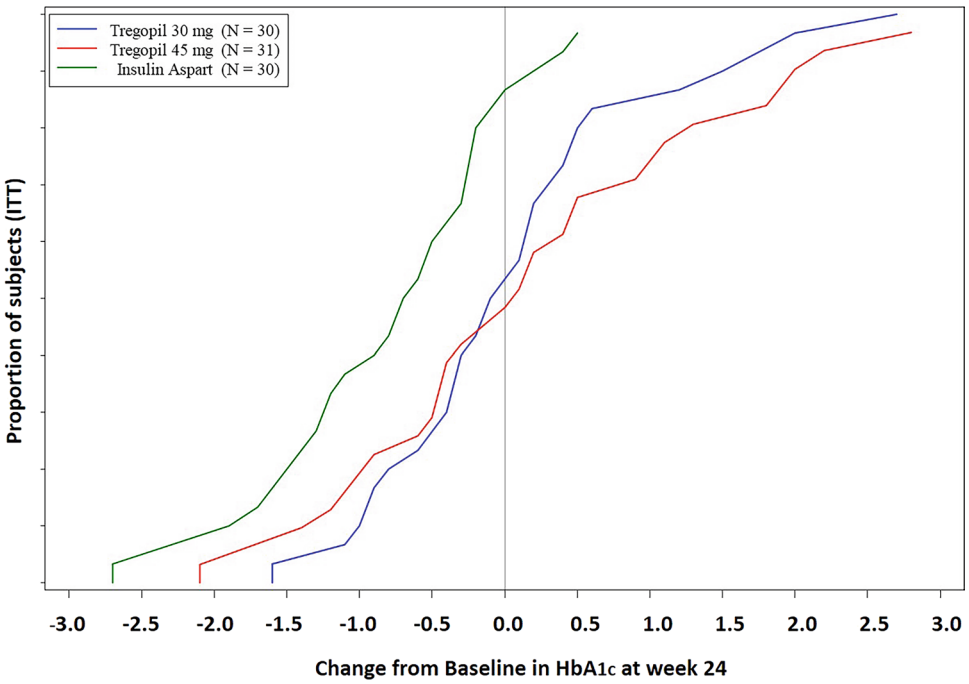

Fig. 6 Change from baseline in HbA_{1c} (%) at week 24—cumulative distribution function: ITT analysis set. *HbA_{1c}* glycated hemoglobin A_{1c}, *ITT* intention-to-treat, *mg* milligram, *N* sample population

clinical development of insulin tregopil indicate that it has considerable benefits in managing DM and has the potential to improve patients' QoL.

8 Prescribing Information

Insulin tregopil is available as a 15-mg intact tablet to be swallowed with water. Treatment regimen with insulin tregopil is initiated with a 30-mg daily dosage and then increased based on 1-h and 2-h PPG levels for each major meal during the day. It may be combined with permitted oral anti-diabetic agents, long-acting insulins, or both, to optimize the glycemic control.

8.1 Proposed Indications T2DM

8.1.1 Contraindications

Insulin tregopil is contraindicated in patients with hypersensitivity to insulin tregopil and its excipients (sodium caprate, mannitol, crospovidone, colloidal silicon dioxide, magnesium stearate). In addition, it is also contraindicated during episodes of hypoglycemia.

8.1.2 Special Precautions and Warnings

In general, patients must be instructed in diabetes self-management skills and addressing special scenarios such as an inadequate or skipped insulin dose, inadvertent insulin overdose when taking insulin tregopil in combination with other anti-diabetic medications. Caution should be exercised when prescribing insulin tregopil in patients with signs and symptoms of congestive heart failure, weight gain, and edema. Hypoglycemia can occur when patients take doses of insulin tregopil that are higher than advised, or when the food is not consumed within a specified time frame (10 min) following administration of insulin tregopil. Insulin tregopil usage should be discontinued in the case of elevated hepatic enzymes (alanine transaminase, aspartate transaminase, and alkaline phosphatase).

9 Oral Insulin Development by Competitors

Recently, several attempts have been made to develop oral insulins by leading pharmaceutical organizations worldwide because of their potential benefits of an oral formulation. Various approaches such as conjugation with hydrophobic oligomers and micro- or nano-encapsulations have been employed in developing oral insulins [59], and these approaches must pass through several phases of clinical development and overcome potential challenges before the drug is available to the patients. Despite these difficulties, there are several products under different stages of development to make oral insulins successful. Some of the products include Capsulin OAD by Diabetology Ltd. [60, 61]; oral hepatocyte-directed vesicle technology (HDV) insulin by Diasome Pharmaceuticals [62, 63]; NN1952, OI338GT (NN1953), and OI362GT (NN1954) by Novo Nordisk [64–69]; and Oshadi Icp by Oshadi Drug Administrations [70–72], which are in the Phase I or Phase II clinical trial stages (Online Resource—Table S6).

Apart from insulin tregopil, ORMD-0801 developed by Oramed Pharmaceuticals was another oral insulin formulation whose clinical development has been discontinued following results from a Phase III study recently. Although the product showed promising results in Phase I and Phase II clinical trials, similar challenges as with insulin tregopil have also been encountered during the development of ORMD-0801 [6, 73–75], such as dose limitation beyond which there is improvement in efficacy, challenges in estimating PK at the primary site of action, i.e., portal circulation and challenges in reporting correlation between peripheral drug concentration and PD effects. The fact that to date, no other oral insulins have reached the level of obtaining global approval status points to the difficulties at the research and development of oral insulins in general. Despite the recognized challenges, Biocon has made significant progress in the global development of insulin tregopil by overcoming the key challenges in drug development. Phase I to Phase III trials with insulin tregopil have already been completed, where the effect of this oral insulin on PPG control, particularly in the crucial early post-meal period, has been well demonstrated. Insulin tregopil differs from Oramed's, ORMD-0801 in the following aspects:

1. Insulin tregopil has an ultra-fast onset and short-acting profile, making it ideal for prandial glucose control in T2DM.
2. Peripheral concentrations of insulin tregopil can be quantified by a unique method developed to measure its PK. This method compares the PK properties of insulin tregopil against active control (IAsp) thereby providing a near-exact estimate of the parameters.
3. A dose-dependent response in glucose reduction (although may not be dose proportionate) has been observed for the doses of insulin tregopil studied thus far.
4. Development of insulin tregopil is based on a strong foundation of clinical studies using HIM2 products, and is more advanced in clinical development, thereby facilitating the assimilation of more information in the field of oral insulins.

One of the key limitations of insulin tregopil is that the HbA_{1c} control with this oral insulin does not translate into the same effectiveness as the control over PPG. This aspect is currently under study. In this regard, sustained FPG control seems to be currently the most appropriate method of predicting responders who may benefit from treatment with insulin tregopil. Insulin tregopil is expected to be beneficial in a subset of patients with established needle phobia and those unable to comply with regular use of injectable insulins affecting patients' QoL. During periods of travel or other situations, when using injectable insulins could be challenging, oral insulins can be especially useful. Since it is ultra-fast and short acting, patients can time the administration of oral tregopil only when they are able to consume the meal, which is useful in those patients with unpredictable meal timings.

10 Conclusion

Insulin tregopil, is generally found to be safe in patients with T1DM on a stable basal-bolus regimen. However, at the doses tested, the prandial glucose is reduced for a shorter period of time with inadequate meal coverage. Insulin tregopil shows a potential for reducing the dose and number of prandial insulin injections; however, higher doses in combination with the basal insulin pose the risk of hypoglycemia. In T2DM, insulin tregopil has demonstrated efficacy in PPG control, especially during the early post-meal period. In a sub-set of patients, the early PPG control was observed to be better than IAsp. Adding insulin tregopil to a regimen of basal insulin and OADs with continued FPG optimization can be useful in patients with good FPG control.

Insulin tregopil can potentially benefit in special settings such as when patients on prandial insulins are traveling or other short-term social situations where injectable administration is inconvenient. Insulin tregopil, being hepato-preferential, can be explored in other indications such as non-alcoholic steatohepatitis, which shares common risk factors with T2DM. Insulin tregopil, similar to other oral peptide formulations, faces challenges regarding high variability in its bioavailability. The current formulation, although promising, can be further improved to overcome the above challenge with further advancements in the oral peptide drug delivery.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-023-01925-1.

Acknowledgements The authors acknowledge Ashwini Vishweswaramurthy for her contributions towards the development of this monograph, Shivani Mittra and Geetanjali Tonpe for writing support and Jayanti Panda for operational support. Authors also acknowledge Molecular Connections Analytics Pvt. Ltd., Bengaluru, for providing editorial support towards its development.

Declarations

Disclosures Shashank Joshi has received Speaker/Advisory/Research Grants from Abbott, Alkem, Astra Zeneca, Bayer, Biocon, Boehringer Ingelheim, Eli Lilly, Franco Indian, Glenmark, Lupin, Marico, MSD, Novartis, Novo Nordisk, Roche, Sanofi, Serdia, Torrent Pharma, Twin Health and Zydus. Sandeep N. Athalye, Subramanian Loganathan, and Vathsala Jayanth are currently employed with Biocon Biologics Ltd and Vasan K. Sambandamurthy is previous employee of Biocon Limited.

Funding Biocon Limited.

Conflict of Interest S.N.A, S.L, V.J, and V.K.S. hold stocks in Biocon. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest or financial conflict with the subject matter or materials discussed in the review apart from those disclosed. For S.J., please refer to 'Disclosures'.

Data Availability The data supporting the study findings are available from the corresponding author, Subramanian Loganathan, upon reasonable request.

Ethics Approval The ethical standards of independent ethics committees or institutional review board were followed during the conduct of the clinical trials included in this review.

Consent to Participate All the subjects involved in the clinical trials mentioned in this review received informed consent prior to the study-related procedures, which was duly signed by the subjects and the investigators.

Consent for Publication Not applicable.

Code Availability Not applicable.

Author Contributions S.J., V.J., S.L., V.K.S., and S.N.A. designed and conceptualized the review article. All the authors were involved in writing, reviewing and approving the manuscript. As the guarantor of this work, S.L., takes full responsibility for the work, including the decision to submit and publish the manuscript.

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