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Safety and efficacy of an oral insulin (Capsulin) in patients with early-stage type 2 diabetes: A dose-ranging phase 2b study

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Abstract

Aim: To compare the pharmacodynamic properties of different doses of regular human insulin administered in capsule form twice daily in a randomised twelve-week open-label study.

Methods: A total of 100 individuals (48 males, 52 females) with type 2 diabetes on metformin completed the study according to the protocol. The mean (SD) age was 48.5 (6.7) years, body mass index 25.7 (2.8) kg/m^2 and HbA1c 8.10% (0.65%). Subjects randomized upon admission were assigned to one of three groups receiving formulated regular insulin at dose levels of 75 iu BD, 150 iu insulin BD, or 300 iu BD, all in enteric-coated capsules. The primary and secondary endpoints were change from baseline in HbA1c and fasting plasma glucose (FPG), respectively.

Results: The study met its primary clinical endpoint of a decrease in HbA1c of 0.5% or higher (least square mean decrease 0.52%; $P = .004$, median decrease 0.6%) in the dose group receiving 150 iu BD. In a subset of this population, with starting HbA1c values of 9% to 9.5%, an average decrease of 1.575% was observed. In the total population, least square mean decreases in HbA1c for the 75 and 300 iu BD groups were −0.11% and −0.42%, respectively. Mean change in FPG in the 150 iu BD dose group was −18.8 mg/dl ($P = .017$) and −14.8 and −2.7 mg/dl for the 75 and 300 iu BD groups, respectively. A decrease of 20% for triglycerides (−40 mg/dl) was observed in the 150 iu BD dose group. No significant increases in body weight were observed, and significant decreases in systolic blood pressure were seen in all groups. No serious treatment-related adverse events were recorded, and no incidence of hypoglycaemia was reported throughout the entire 12-week study period.

Conclusions: Capsulin oral insulin administered twice per day at a dose of 150 iu per capsule is safe, with no confirmed treatment-linked hypoglycaemic events, and results in significant decreases from baseline in HbA1c, FPG and triglycerides.

KEYWORDS
clinical trial, drug development, glycaemic control, insulin therapy, phase 1-2 study, type 2, diabetes

1 | INTRODUCTION

While the general perception among patients is that oral insulin provides a method of administration that is more convenient and less painful, the additional major advantage of an oral formulation over injected insulin is the different pharmacokinetics that can be achieved, with direct delivery to the liver, thereby avoiding peripheral hyperinsulinaemia, and enabling the liver to play a major role in controlling blood glucose levels.

In previous studies it has been shown that plasma insulin levels do not exceed physiological concentration when administered orally,[1] because the insulin delivered is absorbed by the liver before it can reach the bloodstream.

Because of the potential for avoidance of hypoglycaemia, administration of insulin in oral form can be contemplated at a much earlier stage than in current practice in patients with type 2 diabetes, and can therefore be considered as a treatment alongside other oral antidiabetic medicines prescribed shortly after diagnosis of the disease. Indeed, several studies have clearly shown[2-6] that treatment of patients with insulin during the early stages of the disease is beneficial in terms of improving prognosis of the disease. This observation thus leads to the possibility that insulin may be considered as one of the first treatment options, rather than the last.

A number of approaches to non-invasive delivery of insulin have been pursued in the clinic,[7-12] but to date, no capsule form of oral insulin has received regulatory approval. The formulation employed here, Capsulin, is an enteric-coated size four capsule that passes readily through the stomach and opens up in the small intestine. The capsule contains insulin as a dry white powder in combination with excipients that are pharmacopoeial or generally recognised as safe (GRAS), the two principal components being a natural bile salt and an antioxidant. The excipients are able to protect the insulin from degradation by proteases in the gut, then enable it to penetrate the mucin layer, and finally aid its uptake by and across intestinal cells, after which it drains into the portal vein, and then travels directly to the liver. The insulin employed here is unmodified human recombinant insulin, which has no chemical interaction with the excipients, and is able to reach the liver in its native form. The mechanism of uptake is probably via natural pathways that are active in the intestine at all times for enabling transcellular transport of dietary components across enterocytes, but which are upregulated transiently by the formulation when the capsule releases its components. The formulation is simple to manufacture, with a stability of 18 months at +4°C and 6 months or longer at room temperature.

2 | METHODS

2.1 | Participants

This phase 2b open-label, randomized comparative study was conducted to evaluate the safety and efficacy of Capsulin, an oral insulin capsule formulation, in subjects with type 2 diabetes uncontrolled with metformin hydrochloride treatment. This study was conducted at 15 centres across different geographical locations in India from January 2019 to July 2020, and was monitored by JSS Clinical Research Pty. Two hundred and four subjects were screened and 153 were enrolled in the study. The inclusion criteria for the trial were:

1. Male or female aged 35-60 years (inclusive).
2. Type 2 diabetes diagnosed < 2 years prior to enrolment.
3. HbA1c ≥ 7% and ≤ 9.5%.
4. On stable oral monotherapy with metformin hydrochloride (1000 to 2500 mg/d) and regular diet and exercise regimen at least 12 weeks prior to enrolment.
5. Body mass index (BMI) = 18-30 kg/m^2.

Exclusion criteria included receipt of treatment with insulin, sulphonylureas or alpha-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists or sodium-glucose co-transporter-2 inhibitors or meglitinides or pramlintide or thiazolidinediones within 3 months prior to enrolment.

It was originally intended to treat 195 subjects, but because of the onset of the COVID-19 pandemic, which made visits to clinics difficult, the trial was terminated early, with a total of 137 subjects completing the full course. Of these, 37 subjects were removed, since they were unable to attend clinics at the end of the study, because of logistical challenges caused by lockdown restrictions. A CONSORT flow diagram of the study is provided in Appendix S1.

The study was conducted conforming to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E6 guidelines. It was registered with the Clinical Trials Registry—India (www.ctri.nic.in [CTRI/2018/08/015519]) and Human Subjects approval was received. Informed consent was obtained from each enrolled patient.

Drug accountability and compliance were assessed through the patient diary (each subject completed the diary after medication had been taken) and an accountability check was performed at the site on the basis of the number of capsules dispensed to the subjects (as per the dose) versus the number of capsules used and returned in the capsule strips. The average level of compliance was 97%.

2.2 | Study design

All subjects had metformin as pretrial antidiabetic therapy, and stayed on metformin for the duration of the trial. No other antidiabetic medications were employed. Subjects were randomized, using an interactive web response system, in a ratio of 1:1:1 to any one of the following three treatment groups:

- Group A: Capsulin 75 iu (2.5 mg), BD for 12 weeks.
- Group B: Capsulin 150 iu (5 mg), BD for 12 weeks.
- Group C: Capsulin 300 iu (10 mg), BD for 12 weeks.

The 300 iu dose was provided in the form of two 150iu capsules. Subjects allocated to the 150 and 300 iu BD dose groups underwent a run-in period of 1 week with each previous lower dose/s, prior to initiation of the assigned fixed dose of Capsulin. The overall duration of treatment with Capsulin for subjects in the 150 and 300 iu BD dose groups was thus 13 and 14 weeks, respectively. The solid-dose capsules were taken 1 hour before breakfast and dinner, orally with water. Once the subjects started receiving their full allocated dose, this dose was fixed throughout the study, and there was no titration in relation to blood glucose levels. Eight study visits were performed for all groups as follows: visit 1, screening; visit 2, randomization/enrolment and treatment start; visits 3-6, in-study monitoring; visit 7, end of treatment; and visit 8, post-treatment follow-up 1 month after the end of the study. The time between the first Hba1c measurement at screening and start of treatment was no longer than 21 (mean 11) days, making it improbable that significant changes in HbA1c either way could occur prior to commencement of the active phase of the study. A simplified Schedule of Assessments, outlining activities conducted during each visit, is included in Appendix S1.

A placebo group was not included in the study because of concerns that the health of patients with poorly controlled diabetes early after diagnosis could be jeopardized if issues arose during the 12-week period, bearing in mind the protocol stipulation that no changes in diabetes medication could be made throughout the course of the treatment. In such circumstances there could be extensive requirement for rescue medication, which would prejudice the analysis of the data, with loss of patients, reducing the statistical significance. This would have made the study larger, and recruitment times longer, thus further compounding the problems that emerged with the arrival of the COVID-19 pandemic.

As an additional safety measure, patients with 'uncontrolled hyperglycaemia', defined as having fasting plasma glucose (FPG) levels above 270 mg/dl on two successive occasions, were excluded. As the trial progressed, a small number of subjects, five in total, were identified as being above this limit on the basis of laboratory-measured glucose, and, with one exception, were removed from the study before completing treatment. Three of these subjects only received treatment for 2 weeks before their removal.

2.3 | Procedures

Prior to commencement, and at each visit, blood samples were taken, and FPG and 2-hour postprandial plasma glucose (PPG) concentrations were measured at a central laboratory. A standardized glucose/carbohydrate challenge was not employed across the multiple centres involved in testing, because accepted local practices were adopted at each centre instead. HbA1c levels were measured by High-Performance Liquid Chromatography (using a Tosoh G8 automated analyser) at the beginning and at the end of the study (see the Schedule of Assessments in Appendix S1). Standard biochemical variables were measured as part of the safety assessment, and anti-insulin antibody levels were determined using a commercial enzyme-linked immunosorbent assay (Orgentec; cut-off point, 10 U/ml) to investigate the possibility of a treatment-emergent antibody response.

In addition, subjects self-monitored their glucose levels on a regular basis by finger-prick test to safeguard against the incidence of hypoglycaemia.

2.4 | Outcomes

2.4.1 | Primary endpoint

The primary endpoint was the change in HbA1c level post 12-week twice-daily administration of selected fixed dose of Capsulin (75, 150 or 300 iu BD) from baseline.

2.4.2 | Secondary endpoints

The secondary endpoints consisted of

- Changes in FPG and 2-hour PPG levels in each treatment group post 12-week administration of Capsulin.
- Treatment-emergent adverse events that occurred during the study period, including the occurrence of hypoglycaemic episodes in each treatment group during the study period.
- Changes in laboratory investigations post 12-week administration of Capsulin.

2.5 | Statistical analysis

All data were tested for normality according to the method of Shapiro–Wilk, and continuous variables were compared within the same dose group using a paired *t*-test, while an independent sample *t*-test was used for comparison between the dose groups for continuous measurement. In cases where normality was not observed, the Wilcoxon signed rank test was used to compare within the dose groups. However, departure from normality was not seen in any groups for the primary endpoint, nor for the 150 iu BD dose group secondary endpoints.

2.5.1 | Datasets analysed

The randomized population consisted of all the subjects who were randomized in the study. The safety population consisted of all the subjects who were randomized and who received at least one dose of the investigational medicinal product.

The full analysis set (FAS) population consisted of all the subjects who were randomized into the study, received at least one dose of the investigational medicinal product from the assigned dose by randomization and had at least one postbaseline assessment.

The per protocol (PP) population comprised all the subjects in the FAS population who completed the study and did not have any major protocol deviation at visits 1 and 7. The results of primary and secondary endpoints reported here were derived from the PP population.

The majority of subjects in the safety population, but not the FAS, were excluded because of personal reasons, having withheld consent. Most of the remaining subjects excluded from the PP population had protocol violations relating to measurement of variables at sites other than the central laboratory, which were deemed to be unreliable for the purposes of this analysis. Most of these situations arose because patients were unable to visit the trial centre in person because of COVID-19 restrictions (see CONSORT Flow Diagram in Appendix).

3 | RESULTS

3.1 | Demographic data

Patients were recruited into one of a total of 15 different sites throughout India. Baseline characteristics are shown in Table 1. No significant unintentional bias was seen between the groups for any of the starting variables recorded. All data presented below are baseline versus 12 weeks.

3.2 | Changes in HbA1c

Although the population studied was homogeneous in terms of the basic physical variables at the start of the study, there was considerable spread in the range of HbA1c values at the start and in the response to treatment, as would be expected in patients whose diabetes was poorly controlled with metformin alone. Such variations notwithstanding, there was a statistically significant decrease in HbA1c for both the Capsulin 150 iu BD group from baseline (least square mean of decrease −0.52%; $P = .004$) and the Capsulin 300 iu BD group (least square mean decrease −0.42%, $P = .009$), shown in figure 1. The least square mean decrease for Capsulin 75 iu BD (−0.11%) was not statistically significant ($P = .522$). Analysis of covariance (ANCOVA) indicated no significant differences between any of the groups ($P = .09$ for comparison of the 75 iu BD with the 150 iu BD dose group). At the end of the study, the absolute value of mean HbA1c for each of the 150 and 300 iu BD dose groups was 7.6%, which is within the recommended HbA1c range for treatment by the American College of Physicians[13] (Table 2).

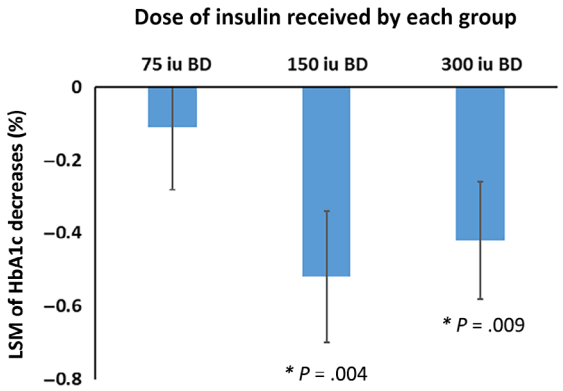

FIGURE 1 Least square mean (LSM) changes in HbA1c from baseline for individual participants over 12 weeks. Median values for HbA1c decreases were −0.6% and −0.55% for the 150 and 300 iu BD dose groups, respectively

TABLE 1 Baseline variables for subjects completing the study according to the protocol

Variables	75 iu BD	150 iu BD	300 iu BD
Number of subjects in study	33	29	38
Sex			
Male	13 (39%)	13 (45%)	22 (58%)
Female	20 (61%)	16 (55%)	16 (42%)
Age, y	48.8 (6.4)	46.6 (6.3)	49.7 (7.1)
Bodyweight, kg	63.9 (8.3)	66.1 (8.8)	66.9 (12.5)
BMI, kg/m^2	25.6 (3.0)	25.8 (2.7)	25.7 (2.9)
HbA1c, %	8.27 (0.66)	8.13 (0.65)	7.93 (0.61)
Fasting plasma glucose, mg/dl	148.8 (53.0)	148.2 (39.0)	136.7 (47.8)

Note: Data are *n* (%) or mean (SD). All subjects had metformin as pretrial antidiabetic therapy, and stayed on metformin for the duration of the trial. No other antidiabetic medications were employed.
Abbreviation: BMI, body mass index.

TABLE 2 Absolute decreases in HbA1c levels for each dose

Mean ± SD	75 iu BD	150 iu BD	300 iu BD
HbA1c at start	8.27 ± 0.66	8.13 ± 0.65	7.93 ± 0.61
HbA1c at conclusion	8.07 ± 1.03	7.60 ± 0.98	7.62 ± 0.95
Least squares mean decrease in HbA1c	−0.11 ± 0.97	−0.52 ± 0.97	−0.42 ± 0.99

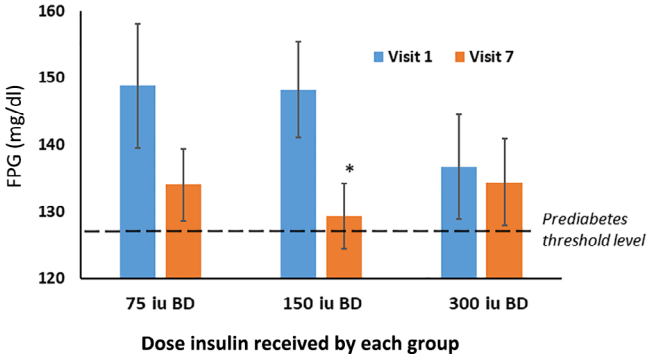

FIGURE 2 Mean fasting plasma glucose (FPG) values in each group at the start and finish of the trial. Error bars are standard errors of the mean. *Significant decrease ($P = .017$)

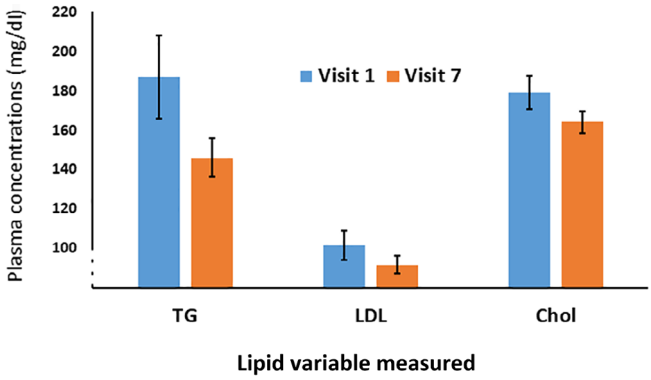

FIGURE 3 Decreases in lipid variables (triglycerides [TG], low-density lipoprotein [LDL] cholesterol and total cholesterol [Chol]) in the 150 iu BID dose group at the start and finish of the trial. Error bars are standard errors of the mean. The decrease in TG is statistically significant. In healthy individuals, the normal range for TG is less than 150 mg/dl, while below 200 and 100 mg/dl are normal for Chol and LDL cholesterol, respectively

3.3 | Changes in plasma glucose

A decrease was seen in FPG for all three groups (Figure 2), although statistical significance was only achieved for the 150 iu BD group. Interpretation is difficult, because the starting FPG values differed between the groups. Decreases in PPG after 12 weeks were seen in all groups, spanning a range of 17 to 31 mg/dl, although the differences were not significant. FPG and PPG levels measured for all visits are provided in Appendix S1.

3.4 | Lipid variables

Lipid variables were measured in a fasting state. Decreases in mean values of the order of 10% were seen in the 150 iu BD dose group for LDL cholesterol (−9.9 mg/dl) and total cholesterol (−15 mg/dl; $P = .12$), and 20% for triglycerides (TG) (−40 mg/dl). The level of HDL cholesterol in the 150 iu BD dose group remained essentially unaltered (44 to 43.2 mg/dl), and no significant increases in body weight were observed in any of the groups. In the case of both TG and LDL cholesterol, mean starting values were above the thresholds considered normal (149 mg/dl for TG and 100 mg/dl for LDL), but were reduced to below these thresholds at the end of the 3-month treatment period (Figure 3). Smaller decreases in these variables were observed in the other groups.

Least squares mean analysis of the decreases across all treatment groups for TG showed statistically significant decreases from baseline for both the 150 and 300 iu BD groups (Figure 4), but not for the 75 iu BD group.

Ten patients were receiving lipid-lowering medication prior to starting the trial, of which 6 were in the 150 iu BD dose group, but when the data from those patients were excluded, a mean decrease in TG of 20.9 mg/dl was still seen for the 150 iu BD dose group.

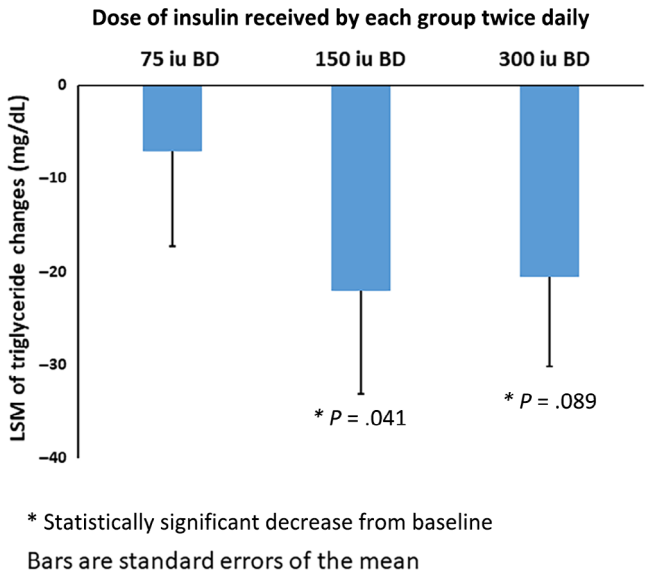

FIGURE 4 Decreases in triglycerides across all treatment groups between the start and finish of the trial. LSM, least square mean

3.5 | Safety

Throughout the entire study, with more than 25 000 dosing events, no adverse (including gastrointestinal) events occurred that could be attributed to the study medication, and no confirmed treatment-related hypoglycaemic events were recorded, even at the highest dose.

Only five subjects had anti-insulin antibody concentrations registered as above baseline levels at the end of the study, but the median level was little different from that recorded in patients prior to treatment (2.3 vs. 1.9 U/L).

4 | DISCUSSION

The current study was conducted in India from January 2019 to July 2020. There was originally an intention to treat 195 subjects, but because of the onset of the COVID-19 pandemic, which made recruitment difficult, the trial was terminated early, with a total of 132 subjects completing the full course. Of these, 32 subjects were removed, because they were unable to attend the central clinic at the end of the study, mainly because of challenges in logistics resulting from lockdown. However, even before the removal of dropouts, a significant decrease in HbA1c from baseline was observed ($P = .015$) when combining all three groups continuing treatment in the FAS (132 subjects in total, including final out-of-protocol measurements made in local clinics). Random variation led to a lower number of patients remaining in the target dose (150 iu BD). Nevertheless, the study met its endpoint, and was able to show a strongly statistically significant outcome with the target dose.

The absence of serious adverse events, and particularly of hypoglycaemic incidents, involving 25 000 dosing events, even in subjects receiving the highest dose, clearly shows the potential safety of this treatment in patients during the early phase of progression of the disease, and suggests that this medication may be used as an early, insulin-based intervention, as recommended by several authors, to improve the prognosis of the disease.[2-6]

The inclusion criteria specified that patients must have been diagnosed with diabetes no more than 2 years prior to the start of the study. Consequently, the patient population tested here had significantly lower body weight, BMI and baseline HbA1c range (7%-9.5%) than are commonly encountered in other studies. A population with these characteristics is exactly the population that one could be targeting if aiming to commence treatment in subjects with diabetes in the early phases of the disease, before HbA1c and FPG levels have risen too high and body weight is still close to normal levels. The results of the current study, and those of a previous phase 2 glucose clamp study[1] in patients with HbA1c and BMI at higher levels, also indicate a role for Capsulin in the treatment of patients at a later stage of the disease.

It has been reported that the starting conditions for subjects with diabetes strongly influence the magnitude of decrease in HbA1c that can be expected with a given insulin medication.[14] In patients with high HbA1c levels (> 8%), this value can be reduced significantly after insulin treatment, whereas in patients with an HbA1c of 8% or lower, reduction of HbA1c is proportionately more difficult. It is interesting to note that a similar trend is observed in our own data collected here: although the number of patients is small, the decreases in HbA1c are higher in that subset of the population with higher starting HbA1c values (Figure 5). In those starting at an HbA1c of 9% or higher, the decrease was 1.575%.

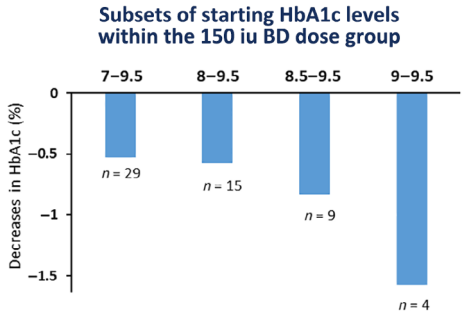

FIGURE 5 Mean decreases in HbA1c of patients in the 150 iu BD dose group according to starting HbA1c levels (overall target dose group decrease of 0.53%; $P = .004$, $n = 29$)

Although a limitation of this study is that it did not include a placebo, data in the literature[15,16] show that, in trials with patients on adjunct therapy with metformin (the condition pertaining in the current study), an HbA1c decrease in placebo of no more than 0.2% can be expected. It is evident, therefore, that decreases observed in HbA1c for each of the higher doses tested in the current study, particularly those in patients with higher starting HbA1c levels, cannot be attributed to a study effect.

As expected, the low dose of insulin performed less well than the two higher doses in the whole patient population, showing a least squares mean decrease in HbA1c of 0.11% compared with 0.52% and 0.42% for the 150 and 300 iu BD doses, respectively. This established an outer boundary of any possible placebo effect in the study. The result for the 150 iu BD group was a statistically significant difference from baseline, while the difference between the 75 and 150 iu BD groups in ANCOVA failed to achieve significance, perhaps in part because the study had to be curtailed early because of the impact of COVID-19, which meant that the number of patients recruited was lower than originally intended. It is interesting to note that HbA1c was reduced to the same level in both the 150 and 300iu BD dose groups. However, the fact that the 300 iu BD dose failed to outperform the 150 iu BD dose is not surprising, in light of observations made by our research group in a previous iso-glycaemic clamp study in patients with poorly controlled type 2 diabetes.[1] In that study it was seen that the plateaux of glucose-infusion rate attained were essentially identical for both of the doses administered orally. This can be attributed to the fact that the level of control by the liver on blood glucose is determined by the level of glucose in the blood itself, rather than by the amount of insulin delivered through portal circulation directly to the liver. The underlying basis for this, and the difference in behaviour from injected insulin, are explained below.

Unlike muscle or adipose tissue, liver cells have receptors that act as sensors for the level of glucose in the bloodstream, namely, GLUT-2[17] and glucokinase (GK),[18] and which, in concert, regulate the glucose-processing activity of the liver in accord with the concentration of glucose in the peripheral bloodstream. When insulin binds to its receptor on liver cells, signalling cascades lead to upregulation of GK, with large quantities being stored in the nucleus, complexed with its repressor molecule. Glucose in the cytoplasm stimulates indirect

release of GK in free form, which then regulates disposal of glucose taken up from the bloodstream.

Thus, while the binding of insulin to its receptor primes the liver to initiate measures for blood glucose control, it is the glucose-sensing mechanism that regulates the rate at which the liver executes this task. We hypothesize here that, because the shunting of GK from nucleus to cytoplasm is not under the control of insulin, but is triggered by cytoplasmic glucose levels, glucose disposal will proceed at a rate determined by blood glucose regardless of the insulin dose to which the liver has been exposed. Thus, in the study conducted here, where the blood glucose levels will be the same in patients receiving either 150 or 300 iu BD, the responses of the liver to control glucose levels will be identical. The only difference that the size of the insulin dose will make is in the size of the newly synthesized GK pool stored in the nucleus, but not upon its rate of deployment. The larger the pool of GK, the longer that dose of insulin will maintain the liver in a primed state. This fits with an observation made during a previous clamp study conducted by the authors (unpublished data), which showed that, in patients with similar blood glucose levels, the only difference between 150 and 300 iu BD doses was the duration of action, with the activity of one capsule containing 150 iu BD lasting 9-10 hours, and that of 300 iu BD 12-14 hours.

One implication of the above is that, in patients with higher blood glucose levels (and higher HbA1c), the glucose disposal activity of the liver will be higher than if the blood glucose levels are lower. This may explain, in part, why patients with a higher starting HbA1c recorded greater decreases after 12 weeks than those with a lower starting HbA1c. Finally, so long as patients have glucose levels above normal, one can expect that Capsulin will continue working as time progresses, to bring glucose levels back to normal, and HbA1c levels to below 7.6%. It is worth noting that, when using the liver-mediated approach, there is no limit to the decrease that can in principle be achieved (until a normal HbA1c level is reached), but that the rate of decrease may be slower than that achieved with other approaches. This argues against the need to increase the insulin dose, provided sufficient time is allowed for the treatment to exhibit its maximal effect.

The ability of the formulation employed in Capsulin to deliver peptides via the portal vein has been shown in preclinical studies using exendin as an archetypal peptide therapeutic.[19] When the peptide is insulin, receptors on hepatocyte membranes bind to the insulin, so that the peptide is sequestered in the liver, and only a small amount appears in the peripheral bloodstream. This is in contrast to other technologies used for administering insulin via the oral route,[20,21] where elevated levels of insulin are observed in the outer circulation, suggesting that insulin is entering the body via routes other than the portal vein. This is certainly the case with Oral-Lyn buccal spray, where the insulin crosses the mucosa in the oral cavity, and does not reach the intestine.

FPG and PPG levels measured for all visits are shown in Appendix S1. Although no statistically significant differences were seen between the different groups, the observation of decreases in these variables is consistent with a decrease in HbA1c. Although there is no direct correlation between glucose changes and HbA1c, the greatest decreases in HbA1c and FPG are both seen in the 150 iu BD dose group. Interestingly, changes in both FPG and PPG only appear during the late stages of treatment.

For any indication related to metabolic syndrome, control of blood cholesterol and TG is essential if the patient is going to benefit from the medication in the long term. It was encouraging, therefore, to see that in the group receiving the target dose of 150 iu BD, levels of TG in the bloodstream were reduced over the course of treatment, with the decrease in TG achieving statistical significance. It is worth noting that in the previous phase 2a study with the same formulation,[1] small but statistically significant decreases in TG ($P < .05$) were also seen over a 2-week period. In the current study, it was noted that the TG/HDL ratio (a potential indicator of insulin resistance[22,23]) was reduced from 3.9 to 3.45. Significant decreases in systolic blood pressure of 2%-3% were also seen in all groups.

In conclusion, the data collected here show that the oral insulin formulation tested is safe, and is able to induce significant decreases from baseline in HbA1c, FPG and TG. In just 12 weeks, FPG levels were reduced to levels close to the prediabetes threshold of 126 mg/dl. The absence of hypoglycaemic events is particularly important, because in this study patients had HbA1c levels that were comparatively low, and where it might be expected that such adverse effects may be more easily incurred by an efficacious oral diabetes product. All three important markers of efficacy—HbA1c, FPG and lipid variables—have shown changes together indicative of a reduction in the severity of the disease. In light of this, it is considered that Capsulin at a dose of 150 iu BD is appropriate for the treatment of patients with type 2 diabetes, even during the early stages of the disease.

AUTHOR CONTRIBUTION

Roger R. C. New is responsible for Design of Study, Technical Input, Conduct of Study, Data Analysis and Writing of Paper. R. Sukumar is responsible for Design of Study. Varsha Chaudhari is responsible for Technical Input. Michal Bogus is responsible for Technical Input. Glen N. Travers is responsible for Design of Study. Gajanan Namjoshi is responsible for Design of Study, Conduct of Study and Data Analysis.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data available on request from the authors, subject to third-party restrictions.

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REFERENCES

1. Luzio SD, Dunseath G, Lockett A, Broke-Smith TP, New RR, Owen DR. The glucose lowering effect of an oral insulin (capsulin) during an isoglycaemic clamp study in persons with type 2 diabetes. *Diabetes Obes Metab*. 2010;12:82-87.
2. Weng JP, Li YB, Xu W, et al. Effect of intensive insulin therapy on β-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet*. 2008;371:1753-1760.
3. Meneghini LF. Early insulin treatment in type 2 diabetes: What are the pros? *Diabetes Care*. 2009;32:S226-S269.
4. Owens DR. Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. *Diabetes Technol Ther*. 2013;15:776-785.
5. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2013;1:28-34.
6. Zhang W, Wang HD, Liu FC, et al. Effects of early intensive insulin therapy on endothelial progenitor cells in patients with newly diagnosed type 2 diabetes. *Diabetes Ther*. 2022;13:679-690.
7. Eldor R, Neutel J, Homer K, Kidron M. Efficacy and safety of 28-day treatment with oral insulin (ORMD-0801) in patients with type 2 diabetes mellitus - a randomised placebo-controlled trial. *Diabetes Obes Metab*. 2021;23:2529-2538.
8. Halberg IB, Lyby K, Wassermann K, Heise T, Zijlstra E, Plum-Mörschel L. Efficacy and safety of oral basal insulin versus subcutaneous insulin glargine in type 2 diabetes: a randomised, double-blind, phase 2 trial. *Lancet Diabetes Endocrinol*. 2019;7:179-188.
9. Malkov D, Angelo R, Wang HZ, Flanders E, Tang H, Gomez-Orellana I. Oral delivery of insulin with the *eligen*® technology: mechanistic studies. *Curr Drug Deliv*. 2005;2:191-197.
10. Khedkar A, Lebovitz H, Fleming A, et al. Pharmacokinetics and pharmacodynamics of insulin Tregopil in relation to premeal dosing time, between meal interval, and meal composition in patients with type 2 diabetes mellitus. *Clin Pharmacol Drug Dev*. 2020;9:74-86.
11. Guevara-Aguirre J, Guevara M, Saavedra J, Mihic M, Modi P. Oral spray insulin in treatment of type 2 diabetes: a comparison of efficacy of the oral spray insulin (Oralin) with subcutaneous (SC) insulin injection, a proof of concept study. *Diabetes Metab Res Rev*. 2004;20:472-478.
12. Hoogwerf BJ, Pantalone KM, Basina M, Jones MC, Grant M, Kendall DM. Results of a 24-week trial of Technosphere insulin versus insulin Aspart in type 2 diabetes. *Endocr Pract*. 2021;27:38-43.
13. Qaseem A, Wilt TJ, Kansagara D, Horwitch C, Barry MJ, Forciea MA. Hemoglobin A1c targets for glycemic control with pharmacologic therapy for nonpregnant adults with type 2 diabetes mellitus: a guidance statement update from the American College of Physicians. *Ann Intern Med*. 2018;168:569-576.
14. Davies MJ, Leiter LA, Guerci B, et al. Impact of baseline glycated haemoglobin, diabetes duration and body mass index on clinical outcomes in the Lixilan-O trial testing a titratable fixed-ratio combination of insulin glargine/lixisenatide (iGlarLixi) vs insulin glargine and lixisenatide monocomponents. *Diabetes Obes Metab*. 2017;19:1798-1804.
15. Khan A, Fahl Mar K, Schilling J, Brown WA. Magnitude and pattern of placebo response inclinical trials of oral antihyperglycaemic agents: data from the Food and Drug Administration 1999-2015. *Diabetes Care*. 2018;41:994-1000.
16. Levine M. Empagliflozin for type 2 diabetes mellitus: an overview of phase 3 clinical trials. *Curr Diabetes Rev*. 2017;12:405-423.
17. Thorens B. GLUT2, glucose sensing and glucose homeostasis. *Diabetologia*. 2015;58:221-232.
18. Massa ML, Gagliardino JJ, Francini F. Liver glucokinase: an overview on the regulatory mechanisms of its activity. *IUBMB Life*. 2011;63:1-6.
19. New RRC, Hahn U, Bogus M, Burnet M. Oral administration of Exendin, using Diabetology's Axcess formulation: a preclinical study. *ADA Symposium* 2021; 70: poster 89LB.
20. Cernea S, Kidron M, Wohlgelernter J, Modi P, Raz I. Dose-response relationship of oral insulin spray in healthy subjects. *Diabetes Care*. 2005;28:1353-1357.
21. Zhang YF, Zhou WW, Shen LY, et al. Safety, pharmacokinetics, and pharmacodynamics of oral insulin administration in healthy subjects: a randomized, double-blind, phase 1 trial. *Clin Pharmacol Drug Dev*. 2022;11:606-661.
22. Bertsch RA, Merchant MA. Study of the use of lipid panels as a marker of insulin resistance to determine cardiovascular risk. *Perm J*. 2015;19:4-10.
23. Pantoja-Torres B, Toro-Huamanchumo CJ, Urrunaga-Pastor D, et al. High triglycerides to HDL-cholesterol ratio is associated with insulin resistance in normal-weight healthy adults. *Diabetes Metab Syndr Clin Res Rev*. 2019;13:382-388.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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