A Phase 2b Study of Oral Insulin (Capsulin™) Administered to Patients with Type 2 Diabetes

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Presenter Disclosure

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This study was supported by Diabetology Ltd. Manufacture of the API was performed by USV Private Ltd, and clinical studies and preparation of the report were conducted by JSS Ltd, New Delhi, India

Study Protocol

The study was performed at 15 sites in India in patients within two years of having been diagnosed with Type 2 diabetes.

The patients, assessed as out of control, were receiving treatment with metformin prior to the trial, and continued this treatment unchanged throughout the study.

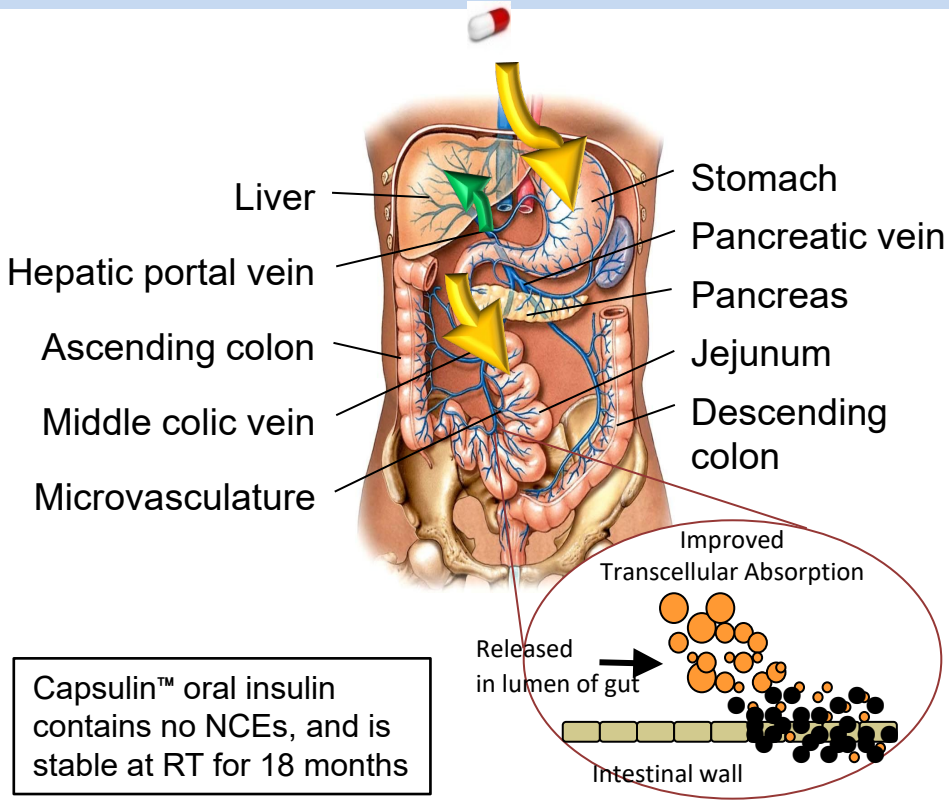
Starting HbA1c for the whole population was 8.1% (inclusion criteria 7 – 9.5%) and mean BMI was 25.7kg/m^2 .

137 patients in the full analysis set (100 in total completing the study per protocol) were divided into three groups, receiving the Capsulin™ formulation twice daily, and an insulin dose of 75iu, 150iu, or 300iu per capsule.

The study period was of 12 weeks duration, after a run-in period for each of the higher doses of one week on the lower insulin doses. A placebo group was not included on ethical grounds, but the lowest dose provides an indication of the uppermost boundary for placebo response.

Patient were monitored at regular intervals, and the primary endpoint, HbA1c fall at 12 weeks greater than 0.5% below baseline was met. Significant falls in FPG and triglycerides were also observed, and no safety issues noted.

Axcess™ Delivery Technology



Capsulin™ oral insulin contains no NCEs, and is stable at RT for 18 months

1) Enteric-coated capsule protects insulin in its passage past the stomach
2) Coating dissolves on rise in pH and releases formulation in small intestine
3) Excipients in the formulation ***inhibit protease activity transiently***
4) Formulation has ***mucolytic activity***
5) Excipients ***stimulate uptake*** into and across intestinal cells

Insulin enters the intestinal micro-vasculature and passes into the portal vein.

Demographics

Baseline parameters for subjects completing the study within protocol

	Group A (75 iu BD)	Group B (150 iu BD)	Group C (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, years	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, %	8.3 (0.7)	8.1 (0.7)	7.9 (0.6)
Fasting plasma glucose, mg/dL	148.8 (53.0)	148.2 (39.0)	136.7 (47.8)

Data are n (%) or mean (SD). All subjects had metformin as pre-trial antidiabetic therapy, and stayed on metformin for the duration of the trial. No other antidiabetic medications were employed.

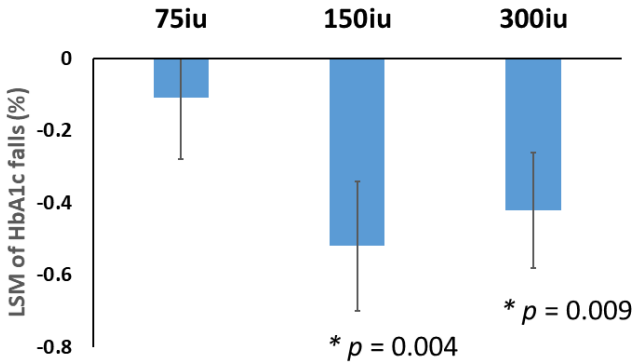
The study was curtailed earlier than planned, because of logistical challenges arising from the onset of the Covid-19 pandemic. Although this meant that fewer patients than anticipated completed the study according to protocol, statistically significant differences were nevertheless still achieved for both the primary and secondary endpoints.

It is worthy of note that the population entering the study had low BMIs and mean HbA1c levels relative to the type 2 diabetes population as a whole, as a result of being diagnosed with diabetes no longer than two years before start of the study.

The observation of statistically significant changes in the 150iu target dose group, coupled with the absence of hypoglycaemia or other adverse effects, suggests that this formulation is a candidate not only for replacement of injected insulin, but also as a treatment to be taken as an oral antidiabetic agent early after the initial diagnosis of the disease.

Falls in HbA1c

Dose of Insulin Received by Each Group Twice Daily

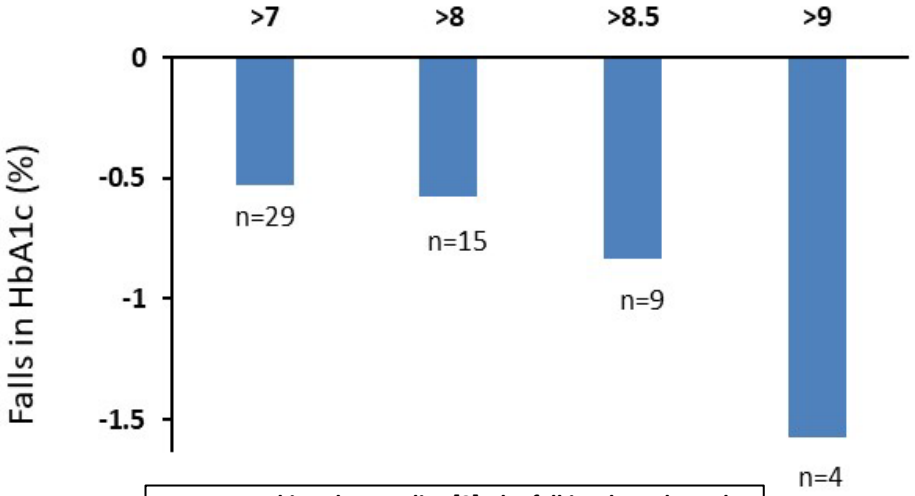


* Falls from baseline statistically significant
Bars are standard errors of the mean

The study met it primary endpoint of fall in HbA1c > 0.5% below baseline. A clear difference between 75iu and 150iu dose groups was seen, while the effect reached a plateau at higher doses, as was noted in a previous phase 2a glucose clamp study [1]. This is attributed to the fact that the liver responds according to the magnitude of the blood glucose level, regardless of the insulin dose it receives, once saturation of the receptors is reached.

In the 150iu group, HbA1c is brought down to 7.5%, withing the 7-8% range recommended by the American College of Physicians.

Relationship between Starting HbA1c and Fall after Treatment



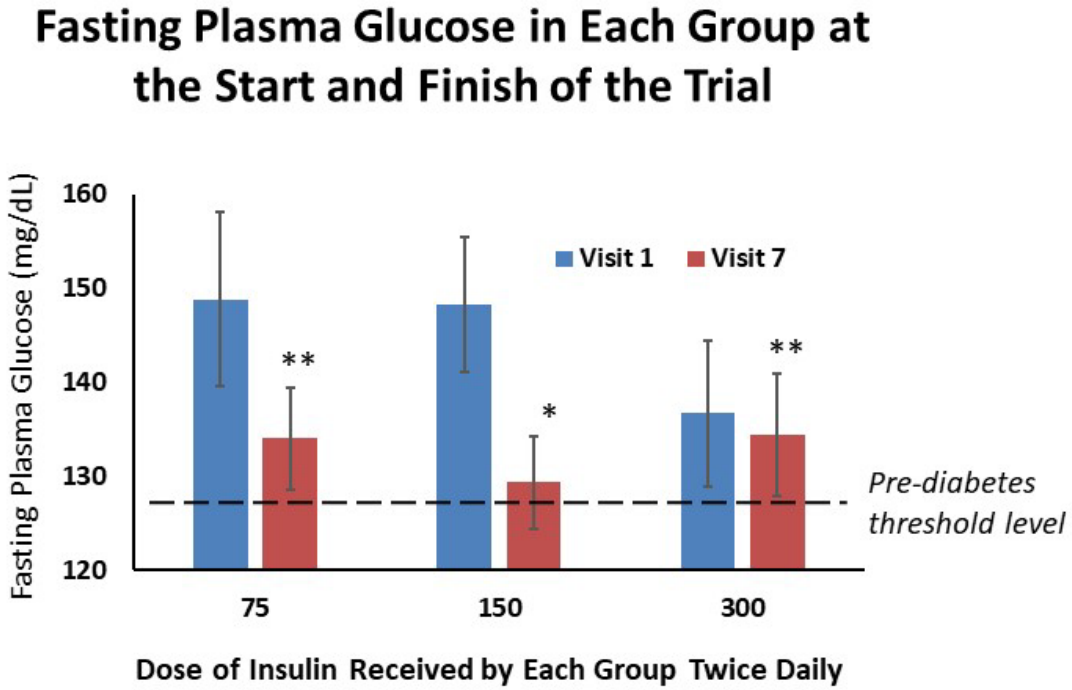
As reported in other studies [2], the fall in HbA1c brought about a given dose of insulin is highly dependent on the starting level of HbA1c in the patient population.

A sub-group analysis in the 150iu dose group demonstrated that, in those patient taking part in the study with starting HbA1c levels higher than 9%, a fall of greater than 1.5% below baseline was observed.

[1]Luzio et al. The glucose lowering effect of an oral insulin (Capsulin) during an isoglycaemic clamp study in persons with type 2 diabetes. *Diabetes, Obesity and Metabolism*, 2009 doi: 10.1111/j.1463-1326.2009.01146.x

[2]Davies MJ 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.

Fasting Blood Glucose



A fall was seen in fasting plasma glucose (FPG) for all three groups studied, and statistical significance was achieved for the 150iu BD group (p = 0.017).

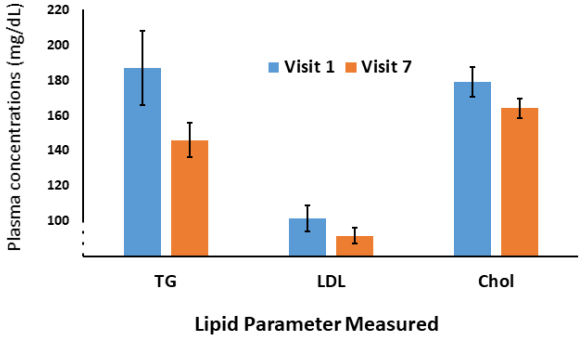
Interpretation is difficult, since the starting FPG values differed between groups. It is noteworthy, however, that in group B, the FPG values went down close to the pre-diabetes threshold level of 126 mg/dL.

Falls in post-prandial glucose were seen in all groups spanning a range of 17 to 31 mg/dL, although the differences were not significant.

Error bars are standard errors of the mean
*Significant fall (p = 0.017) ** Falls not significant

Lipid Parameters

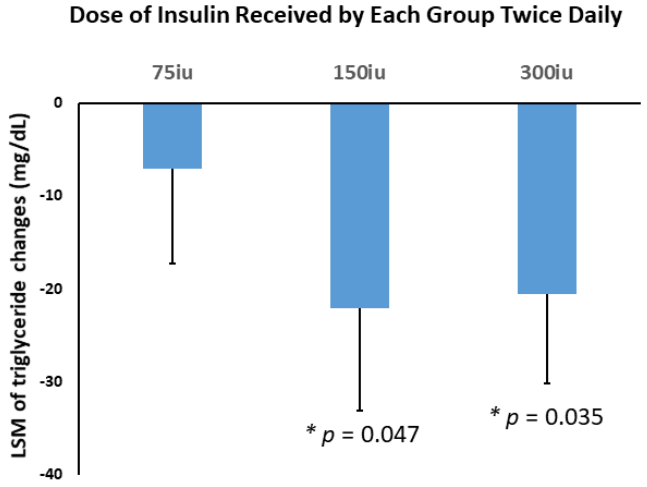
Falls in Lipid Biomarkers in Group B at the Start and Finish of the Trial



Error bars are standard errors of the mean

Falls in mean values of the order of 10% were seen for group B for LDL cholesterol and total cholesterol, and 20% for triglycerides. The level of HDL cholesterol in group B remained unaltered, and no significant increases in body weight were observed in any of the groups. In the case of both triglycerides and LDL cholesterol, mean starting values were above the thresholds considered normal (149mg/dL for triglyceride and 100mg/dL for LDL), but were brought down to below these thresholds at the end of the study. Smaller falls in these parameters were seen in the other groups

Significant Falls in Triglycerides for Groups B and C between the Start and Finish of the Trial



* Falls from baseline statistically significant

Bars are standard errors of the mean

Safety

No recorded instances of hypoglycaemia were seen throughout the whole twelve-week study period (comprising over 25,000 dosing events).

No treatment-linked incidence of gastro-intestinal adverse effects were documented in any of the groups.

No change in levels of anti-insulin antibodies was seen, with means at baseline levels both before and after the end of the study.

The formulation contains no new chemical entities, and all excipients have a long history of safe use in man via the oral route at doses high than used here.

Conclusions

1. A trial in patients with early-stage type 2 diabetes was conducted using Diabetology's Capsulin™ oral insulin formulation in 100 patients receiving 75, 150 or 150iu insulin BD for 12 weeks, (over 25,000 dosing events).

2. The study met its primary endpoint of >0.5% fall in HbA1c below baseline (p = 0.004) for the target dose group of 150iu BID (5 mg recombinant human insulin per capsule).

3. Significant falls in FPG (p = 0.017) and triglycerides (p = 0.047) were also observed, and no rises in HDL or BMI were seen.

4. No hypoglycaemic events were observed throughout the 12 weeks of the study; no treatment-related adverse events were recorded (including gastro-intestinal); mean anti-insulin antibodies remained at baseline levels.

5. The data obtained show the ability of the formulation to bring HbA1c, FPG and lipid levels down to safe levels in a patient population early in the progression of the disease.

6. A sub-group analysis suggested the potential of the 150iu dose group to bring HbA1c levels down by as much as 1.5% in patients with a starting HbA1c level above 9%.

7. The data collected give confidence that future studies in a population with a wider range of HbA1c will yield statistically significant and clinical meaningful results.