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# Efficacy and safety of Glycebal (PDM011011) capsules as adjuvant therapy in subjects with type 2 diabetes mellitus: an open label, randomized, active controlled, phase II trial

## ABSTRACT

**Background.** *Momordica charantia* is a medicinal plant used traditionally for treatment of various diseases including diabetes.

**Objective.** To evaluate the efficacy and safety of PDM011011 capsules (1.2 g/day) as an adjuvant therapy in subjects with type 2 diabetes mellitus (T2DM).

**Methods.** Each PDM011011 capsule contained 400 mg dry fruit juice powder of *Momordica charantia*. Ninety three T2DM patients receiving at least one oral hypoglycemic treatment were screened. The eligible 85 subjects were randomized into 3:1 ratio in drug treatment (PDM011011 capsules) and placebo arm. Sixty-four patients received three 400 mg PDM011011 capsules (1.2 g/day) while 21 patients received three placebo capsules per day for 90 days respectively. The primary efficacy endpoints were mean change in FPG, PPG level and HbA<sub>1c</sub>% from baseline to day 30, 60 and 90 after interventions.

**Results.** PDM011011-capsule (1.2 g/day) showed significant reduction in FPG level by 14.59% after 90 days treatment, while patients receiving placebo capsules exhibited a marginal increase of 2.12%. The reduction in FPG level was statistically significant ( $p = 0.013$ ) as compared with the placebo group. It also reduced PPG level by 22.21% as compared to the 3.71% reduction ( $p = 0.002$ ) in placebo group. The encouraging reduction in HbA<sub>1c</sub>% in the drug group was 0.78 as compared to the placebo group with only 0.20 ( $p = 0.066$ ). PDM011011 capsule showed no adverse events, serious adverse events and death in the study population. **Conclusion.** PDM011011-capsule (1.2 g/day) showed good efficacy and safety; and it can be prescribed as an adjuvant therapy in subjects with T2DM. (Clin Diabet 2016; 5, 3: 88–94)

**Key words:** type 2 diabetes mellitus, *Momordica charantia*, Glycebal, PDM011011 capsule, hypoglycemic, antidiabetic

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## Introduction

Diabetes mellitus (DM) is a progressive metabolic disorder characterized by increased blood glucose level for a long duration, insulin deficiency and insulin resistance with disturbances of carbohydrate, fat and protein metabolism [1]. The long term hyperglycemia is associated

with macro and microvascular complications (dysfunction or failure of vital organs including eyes, heart, kidney, nerves and blood vessels) [2]. As per annual report of the international diabetes federation, 387 million people have DM and it will reach to 592 million by 2035 [3]. DM is predicted to affect 79.4 million people in India by 2030 and the prevalence is increasing in rural population [4].

Type 2 DM (T2DM) predominantly occurs between age 45–64 and its development is based on various factors, including genetics, physical inactivity, sedentary lifestyle, obesity, smoking and substantial consumption of alcohol [5]. Pathophysiological conditions in T2DM are due to impaired insulin secretion by pancreatic  $\beta$  cells and insulin resistance or both. The reduction in insulin secretion is established gradually and comprises glucose and lipid toxicity [6].

In available treatment options, oral hypoglycemic agents and insulin supplement is backbone for management of DM. However, these are associated with side effects and fail to alter the progress of complications [7]. The most common side effects observed are hypoglycemia, increased body weight (Sulfonylureas, Meglitinides), peripheral edema, impaired liver function (Thiazolidinediones) [8] and gastrointestinal disorders (Dipeptidyl Peptidase-4 Inhibitors) [9]. Thiazolidinedione class is also allied with adverse effects mainly high risk of heart attack and bladder cancer [10, 11].

Herbal medicines are now in great demand for the treatment of DM as they are efficacious, produce relatively less or no side effects and are of relatively low cost compared with insulin and other oral hypoglycemic drugs [12, 13].

*Momordica charantia* (family Cucurbitaceae), bitter melon or bitter gourd is a medicinal plant used traditionally for treatment of various diseases and known for various pharmacological activities [14]. Studies conducted in streptozotocin induced diabetic rats and mice with Bitter melon have shown significant reduction of blood glucose levels [15]. Khanna et al. isolated polypeptide-p, from *M. charantia* which has shown effective hypoglycemic activity [16]. In many clinical studies *M. charantia* has shown beneficial effects in diabetic subjects [17, 18]. *M. charantia* is identified to contain several compounds such as mormordin, carotenoids, flavonoids, vitamin C, and polyphenols. The important compounds that have isolated from *M. charantia* and known as hypoglycemic agents include charantin (a steroid glycoside), and polypeptide-p or plant insulin [19].

Existing marketed formulations containing bitter melon juice powder prepared by traditional methods may have risk of degradation of biomolecules before use. We developed a patented, novel method for the preparation of *M. charantia* juice powder which assures

the stability of heat sensitive biomolecules. The present study was performed to evaluate the efficacy and safety of PDM011011 capsule as an adjuvant therapy in subjects with T2DM.

## Materials and methods

### Patients

Male or female patients of age > 30 and < 70 years with a clinical diagnosis of T2DM, stable for 6 months on any other anti-diabetic agents, prior to screening were recruited from 5 centers in India. Patients having fasting plasma glucose of  $\geq 110$  mg/dl and  $\leq 250$  mg/dl; HbA<sub>1c</sub> > 7%, but < 10% at the time of randomization were included. Pregnant and lactating women, women of childbearing potential and men not agreeing to use adequate contraception methods during study, were excluded. Other exclusion criteria were subjects with type 1 DM, secondary DM, and clinically significant cardiac disease, endocrine abnormalities other than stable thyroid disease or patients requiring insulin therapy and serum creatinine level more than 1.5 mg/dl.

The study was approved by an Institutional Review Boards and conducted in accordance with the ethical principles described in the Declaration of Helsinki. Written informed consent was taken from all subjects prior to start of the study.

### Plant material and drug preparation

Unripe green fruits of *M. charantia*, collected from the fields of Maharashtra, India were authenticated in Piramal Life Sciences Limited (PLSL), Mumbai India. The extraction process focuses on the juice expression of whole fruits with seeds, which is then processed and converted into a free-flowing natural green colored powder with a characteristic odor and taste. The processing of juice is a patented step, developed for the stabilization of heat sensitive bioactives. Each PDM011011-capsule contained 400 mg of dry standardized fruit juice powder with not less than 0.4 mg of Uridine as a chemical marker.

### Study design

The present study was an open-label, randomized, active-controlled, phase II trial to evaluate efficacy and safety of PDM011011 capsules as an adjuvant therapy in subjects with T2DM. The study design consisted of total 5 visits; a screening visit, baseline visit, followed by three visits on day 30, 60 and 90, at which safety and efficacy assessments were performed. A total of 93 patients were screened and 85 patients were enrolled at 5 sites in India. The eligible 85 subjects were randomized into 3:1 ratio in drug treatment (PDM011011-capsule) and placebo arm. Sixty-four patients received

**Table 1. Patient disposition in the study**

Disposition	Number (%) of patients		Total N = 85
	Study drug (PDM 011011) N = 64	Placebo N = 21	
Enrolled subjects	64 (75.29%)	21 (24.70%)	85 (100%)
Subjects dosed	64 (75.29%)	21 (24.70%)	85 (100%)
Completed	62 (78.48%)	17 (21.51%)	79 (92.94%)
Prematurely withdrawn from study	02 (3.12%)	04 (9.52%)	06 (4.70%)
Consent withdrawn	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigator decision	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ineligibility/Not meeting incl. criteria	0 (0.00%)	0 (0.00%)	0 (0.00%)
AE	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lost to follow-up	2 (3.12%)	4 (9.52%)	6 (19.04%)
SAE/Death	0 (0.00%)	0 (0.00%)	0 (0.00%)
Other	0 (0.00%)	0 (0.00%)	0 (0.00%)

N — number of patients; AE — adverse events; SAE — serious adverse events

PDM011011 capsules (1.2 g/day) while 21 patients received placebo capsules for 90 days. Drug treatment arm received one PDM011011-capsule (400 mg) in the morning and two capsules in evening daily half-an-hour before breakfast and dinner respectively. Similarly placebo capsules were received in the placebo arm.

### Efficacy and safety assessment

The primary efficacy endpoints were mean change in fasting plasma glucose (FPG), postprandial blood sugar level (PPG) level and glycosylated hemoglobin (HbA<sub>1c</sub>) % from baseline to day 30, 60 and 90 after interventions. HbA<sub>1c</sub> % should be  $\geq 7$ . The secondary efficacy endpoints were lipid profile and the general well-being of subjects during the treatment. Safety was monitored by assessing patient's reported adverse events, physical examinations, vital signs, clinical laboratory parameters as well as complete blood count.

### Sample size and randomization

Determination of sample size was based on the outcome of oral treatment of the same drug and study's assumption was done as follows: efficacy of the test drug (70%, 42 out of 60) and placebo (40%, 8 out of 20) will have about 90% power to detect differences at  $\alpha = 0.05$ . The randomization of all enrolled subjects was carried out by block randomization in 3:1 ratio (drug:placebo).

### Statistical analysis

Statistical analysis was performed by using SPSS V 10.0 package (Statistical Package for the Social Sciences, Version 10.0). Data was given as Mean  $\pm$  SD or Frequency (Percentage) as per the type of data. Stu-

dent's paired 't' tests were applied to compare means of related (before–after) data. Student's unpaired 't' tests were applied to compare means of unrelated data. Level of significance was taken as  $p = 0.05$ .

## Results

### Demographic and baseline characteristics

Out of 85 enrolled subjects, 79 completed the study, including 62 patients from PDM011011 group and 17 from the placebo group (Table 1). Six patients were lost to follow up; 2 from treatment group and 4 from the placebo group and hence could not complete the study (Figure 1). The trial was performed in a real-world clinical setting involving 5 Indian sites, started in June 26, 2012 and completed in October 17, 2012.

The demographic data evaluation was performed. The protocol population and the baseline characteristics were found comparable between the two groups (Table 2). The range of age in the study drug was 31–60 years and in the placebo group it was 31–55, thus similar age-wise distribution in both the groups was observed.

The baseline disease characteristics (Table 2) in terms of FPG, PPG level and HbA<sub>1c</sub> % were evaluated. The mean baseline FPG level in PDM 011011-group was  $150.02 \pm 35.2$  mg/dl while in the placebo group it was  $148.76 \pm 34.8$  mg/dl. The mean baseline PPG level was  $202.40 \pm 56.7$  mg/dl in the treatment group and  $190.24 \pm 54.3$  mg/dl in the placebo group. The mean baseline HbA<sub>1c</sub> % level in the treatment group was  $7.87 \pm 1.0$  and in the placebo group  $7.83 \pm 1.1$  respectively.

### Efficacy analysis

Primary efficacy endpoint assessments consisted of three parameters — FPG level, PPG level and HbA<sub>1c</sub> %

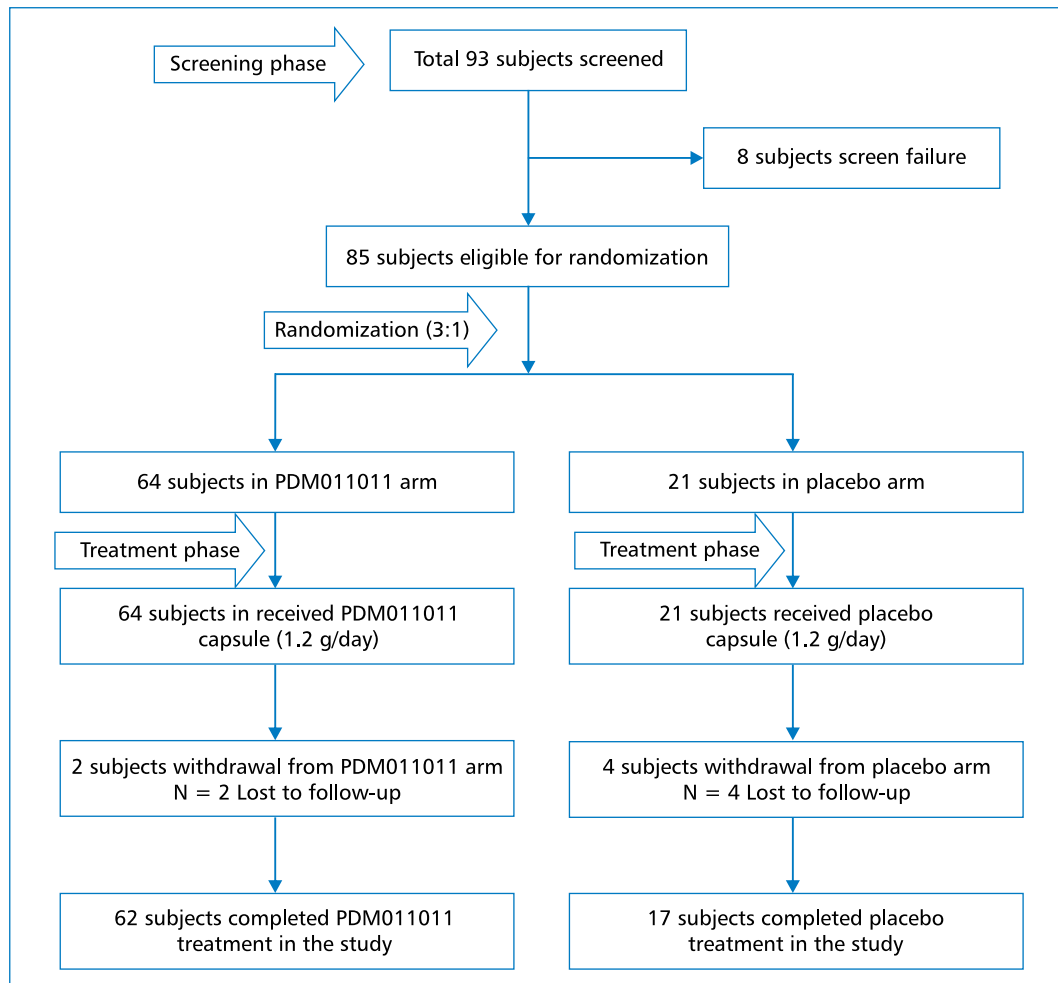


Figure 1. CONSORT Flow Diagram (Patient disposition)

Table 2. Patient demographics and baseline characteristics

Parameter	PDM 011011 treatment group N = 62	Placebo group N = 17
Gender, n (%)		
Male	39 (62.90%)	10 (58.82%)
Female	23 (37.09%)	07 (41.50%)
Age		
Mean age $\pm$ SD	41.33 $\pm$ 7.59	41.31 $\pm$ 6.88
Age range	31–60	31–55
Mean baseline FPG level $\pm$ SD [mg/dl]	150.02 $\pm$ 35.2	148.76 $\pm$ 34.8
Mean baseline PPG level $\pm$ SD [mg/dl]	202.40 $\pm$ 56.7	190.24 $\pm$ 54.3
Mean baseline HbA <sub>1c</sub> level $\pm$ SD	7.87 $\pm$ 1.0	7.83 $\pm$ 1.1
Past/Receiving medications		
Glibenclamide	14	03
Gliclazide	02	01
Metformin	19	07
Gliclazide with metformin	16	05
Glimpride	05	00
Herbal	02	01
Unknown	05	02

FPG — fasting plasma glucose level; PPG — postprandial blood sugar level; HbA<sub>1c</sub> — glycosylated hemoglobin

**Table 3. Summary statistics of fasting, postprandial blood sugar level and HbA<sub>1c</sub> %**

Variable	Group	Baseline	Day 30	Day 60	Day 90
FPG [mg/dl]	Drug	150.02 ± 35.2	142.5 ± 21.2	135.43 ± 24.8	128.12 ± 16.8
	Placebo	148.76 ± 34.8	145.35 ± 21.0	146.35 ± 21.3	150.88 ± 22.8
PPG [mg/dl]	Drug	202.4 ± 56.7	179.16 ± 22.6	170.01 ± 26.4	157.45 ± 17.9
	Placebo	190.23 ± 54.2	182.23 ± 28.3	182.76 ± 32.1	183.17 ± 30.5
HbA <sub>1c</sub> %	Drug	7.87 ± 1.0	–	–	7.08 ± 0.9
	Placebo	7.83 ± 1.1	–	–	7.62 ± 0.9

Values expressed as mean ± SD; Drug — PDM011011 capsule; FPG — fasting plasma glucose level; PPG — postprandial blood sugar level; HbA<sub>1c</sub> — glycosylated hemoglobin

**Table 4. Percent change in primary efficacy parameters after treatment**

Parameters	FPG [mg/dl]		PPG [mg/dl]		HbA <sub>1c</sub> (%)	
	Drug	Placebo	Drug	Placebo	Drug	Placebo
Baseline	150.02	148.76	202.40	190.24	7.87	7.83
Post treatment (90 days)	128.13	150.88	157.45	183.18	7.08	7.62
Plasma glucose decrease during treatment period	21.89	-2.12	44.95	7.06	–	–
Plasma glucose decrease (%)	14.59	-1.42	22.21	3.71	0.78	0.20
p value	*p = 0.013		**p = 0.002		p = 0.066	

Data was evaluated using Student's unpaired t test; \*Significant values at p < 0.05 compared to the placebo; \*\*Significant values at p < 0.01 compared to the placebo; Drug — PDM011011 capsule; FPG — fasting plasma glucose level; PPG — postprandial blood sugar level; HbA<sub>1c</sub> — glycosylated hemoglobin

**Table 5. Lipid profiling of subjects after treatment**

Variable	Treatment	Baseline	Day 90
Serum cholesterol [mg/dl]	PDM011011 Drug	152.69 ± 27.27	146.48 ± 28.74
	Placebo	154.23 ± 30.11	152.35 ± 29.11
HDL cholesterol [mg/dl]	PDM011011 Drug	48.56 ± 5.93	47.52 ± 9.28
	Placebo	48.52 ± 5.83	48.06 ± 7.71
LDL cholesterol [mg/dl]	PDM011011 Drug	81.82 ± 24.15	77.45 ± 26.10
	Placebo	84.16 ± 25.22	81.99 ± 23.38
VLDL cholesterol [mg/dl]	PDM011011 Drug	22.31 ± 4.20	21.51 ± 3.95
	Placebo	21.54 ± 4.68	22.31 ± 4.64
Triglycerides [mg/dl]	PDM011011 Drug	111.55 ± 20.98	107.56 ± 19.75
	Placebo	107.71 ± 23.40	111.53 ± 23.18

Values expressed as mean ± SD; HDL — high density lipoprotein; LDL — low density lipoprotein; VLDL — very low density lipoprotein

as depicted in Table 3. The study drug showed significant reduction of FPG level by 14.59% after 90 days treatment, while placebo group exhibited a marginal increase of 2.12% (Table 4). This reduction was statistically significant (p = 0.013) when compared with the placebo group. The study drug also reduced PPG level by 22.21% as compared to the 3.71% reduction (p = 0.002) in the placebo group. However, there was no significant reduction observed in HbA<sub>1c</sub> % in both drug and placebo treated groups. The reduction in

HbA<sub>1c</sub> % in the drug group which was 0.78 as compared to the placebo group with only 0.20 (p = 0.066) was encouraging.

Secondary efficacy endpoint assessments contain the lipid profiling of serum cholesterol, HDL (high density lipoprotein), LDL (low density lipoprotein), VLDL (very low density lipoprotein) and triglycerides. There was a reduction in the mean change from baseline to day-90 observed in both treatment and placebo group (Table 5).

## Safety analysis

Safety analysis was carried out in terms of incidence of adverse events, hematological parameters, vital signs and physical examination. Treatment of PDM011011-capsule was well tolerated throughout the study. During 90 days treatment with PDM011011-capsule no adverse events or serious adverse events as well as no death was recorded. There was no significant change in the hematological parameters, blood chemistry and vital signs seen.

## Discussion

The treatment with PDM011011-capsule significantly reduced FPG level and PPG level, which confirms good hypoglycemic activity of the treatment drug. Treatment with PDM011011 capsules (1.2 g/day) for 3 months reduced the FPG level by 14.59%, while slight increase of 2.12% was observed in patients receiving placebo capsules. The reduction in FPG level was statistically significant ( $p = 0.013$ ) as compared with the placebo group. Rahman et al. mentioned significant reduction of the FPG level after treatment of 2 g/day and 4 g/day bitter melon powder for 10 weeks in T2DM patients [20]. In another study, it was observed that a 2 g/day dose of bitter melon for 4-weeks in T2DM patients significantly reduced blood glucose level by  $26.7 \pm 40.8$  mg/dl however the effect was less as compared to 1 g/day dose of metformin [21]. In our study, results reported with lower dose (1.2 g/day) are found similar to the results reported with higher doses (2 g/day and 4 g/day) in other studies [20, 21].

In this study, the PPG level was also reduced by 22.21% as compared to the 3.71% reduction ( $p = 0.002$ ) in placebo after 90 days treatment. John et al. reported non-significant reduction ( $p > 0.05$ ) in PPG level after treatment with bitter melon tablets (total 6 g/day) for 4 weeks in T2DM patients. The change in PPG was 30 mg/dl observed from baseline to endpoint [22]. In our study the most significant change in PPG was 44.95 mg/dl seen from baseline to day-90.

The measurement of HbA<sub>1c</sub>% is the hallmark for overall control of diabetes and preventing associated complications [23]. A decline of 1% HbA<sub>1c</sub> might avert about 30–35% microvascular and 14–16% macrovascular complications [24]. Our study-results denote that, a reduction in HbA<sub>1c</sub>% from baseline to end point in patients receiving PDM011011 capsules is higher than the placebo treated group. At day-90 the difference between mean reductions in HbA<sub>1c</sub>% was not statistically significant. These results were found similar to the study reported by Dans et al. in which non-significant decline in HbA<sub>1c</sub>% levels was seen in T2DM patients treated with bitter melon extract [25]. Rahman et al. also reported

non-significant reduction in HbA<sub>1c</sub>% in T2DM patients receiving bitter melon powder for 10 weeks [20].

In our previous study, we assessed the effect of PDM011011-capsule (400 mg) bid in T2DM patients ( $n = 20$ ) for 90 days. The reduction of FPG and PPG levels were 18.65% and 22.03% respectively, and 1.1% reduction in the level of HbA<sub>1c</sub>% were observed. The outcomes of this pilot-study were comparable with present study. In addition, approximately 5% reduction in the body weight was observed in obese diabetes patients ( $n = 6$ ) with weight (80 Kg) receiving PDM011011 capsules. Overall, 2.2% weight reduction was observed in diabetes patients and 0.6% weight gain was seen in patients receiving metformin tablets. The weight reduction is also an added improvement of PDM011011 capsule.

In the present study, the treatment of PDM011011-capsule in T2DM patients showed a mean reduction in levels of serum cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides from baseline to the endpoint. These findings are similar to the study outcomes reported by Rahman et al. where the groups treated with bitter melon powder exhibited favorable changes in the blood lipid levels but not reached statistical significance excluding the 4 g/day group [20].

PDM011011 capsule (1.2 g/day) was well tolerated and found to be safe during this study. Hematological parameters and vital signs were reported normal in both treatment and placebo group. In the overall response assessed at the end of the study, all subjects showed excellent response to PDM011011-treatment, 80% (49 out of 62). The remarkable reduction in the fasting glucose level, postprandial blood glucose level and HbA<sub>1c</sub>% confirms the anti-diabetic potential of PDM011011-capsule. It can be prescribed with other anti-diabetic drugs as adjuvant therapy in T2DM patients. Although PDM011011-capsule showed good efficacy, longer duration of clinical study is necessary to confirm the long term safety of the drug.

## Conclusion

Glycebal-PDM011011 capsule showed good efficacy and safety; and it can be prescribed as an adjuvant therapy in subjects with type 2 diabetes mellitus.

## Conflict of interest statement

The authors declare no conflict of interests.

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