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# Evaluation of Efficacy and Safety of Polyherbal Capsule in Subjects with Type-II Diabetes Mellitus

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**ABSTRACT**

The prevalence of diabetes mellitus (DM) has steadily increased throughout the years worldwide; diabetes mellitus has become a major concern for both developing countries and developed countries. Approximately 6-7% of the world's population is affected by this disease. In this current study, forty subjects aged between 35-65 yrs diagnosed with T2DM was recruited, randomly allocated to either OCDM15 or placebo arm and supplemented with two capsules twice daily for 90 days. During the study period, baseline and other follow up assessments were collected. Comparing the change from baseline and treatment versus placebo groups was performed using appropriate statistical methods. As a result of this study, the OCDM15 groups showed a reduction of 18.56% in HbA1C, while in the placebo group, the HbA1C level was reduced by 7.60%. The valuable insights were provided regarding the potential efficacy and safety profile of OCDM15 capsules in the management of type 2 diabetes. With the potential to improve glycemic control as well as overall management of T2DM, OCDM15 capsules may prove to be a promising adjunctive therapy for individuals with T2DM.

## INTRODUCTION

The prevalence of diabetes mellitus is a major health problem affecting a large number of people worldwide. Statistical data indicate a continuous rise in diabetes incidence worldwide across nearly all demographics. There is a substantial challenge to healthcare systems around the world, which they may not be able to handle on an effective basis due to this increasing trend. [1, 2]. Diabetes mellitus is characterized by high blood sugar levels (hyperglycemia) caused by abnormal blood sugar metabolism. It can be caused either by a lack of insulin production or by resistance to insulin produced by the body. Pancreatic beta cells secrete insulin, which regulates glucose uptake into cells through the secretion of insulin from the Islets of Langerhans. When glucose is produced, it is used as a primary energy source by muscle and adipose tissues as well as stored in the liver. It is possible to have high blood glucose levels, poor protein synthesis, and acidosis when insulin is deficient, defective, or insensitive. [3, 4].

The prevalence of diabetes mellitus (DM) continues to rise throughout the world; it has become a major concern for both developed and developing countries. It affects over 67% of the world's population.

Over 95% of all noncommunicable diseases are caused by type-2 diabetes. Nearly 7% of the world's population suffers from diabetes. Diabetes patients with DNP have a significant risk of developing ESRD, one of the most serious chronic health conditions. Diabetes-related neuropathy occurs in approximately one third of patients with the disease. As part of follow-up and control of the disease, specific markers should be detected early, lifestyle factors adjusted, and treatments administered [5, 6].

## METHODOLOGY

### Study design

In this study, OCDM15 capsule was randomized, double blinded, placebo controlled, and assessed for safety and efficacy in subjects with Type 2 Diabetes. There are five visits consisting of screening/randomization, days 15, 30, 60, and 90 in the study. Informed consent was obtained from subjects prior to screening for inclusion and exclusion criteria.

The following activities were performed during screening visit:

History of medical problems (including drug allergies, and conditions for which medications were taken). Height, weight, BMI, physical examinations, and demographic information were collected on each subject. The vital signs (blood pressure, respiratory rate, pulse rate, and temperature) were evaluated after 5 minutes of rest. It was recorded whether there were any concurrent illnesses or concomitant medications.

**Methods**

**Subject Recruitment and Screening**

One center with adequate facilities for evaluating subject with diabetes and compliance with ICH – GCP were selected.

**Assigning Study Groups**

According to the sponsor's code, eligible subjects were assigned to either study arm in a 1:1 ratio. One or more of the following regimens are contained in the investigational product.

- OCDM15- Two capsules twice daily
- Placebo- Two capsules twice daily

**Data Collection and Follow-up for Discontinued Subjects**

Despite the premature withdrawal of subjects from the study, it was imperative that safety data be collected as long as possible on such subjects. Early withdrawal could be related to the safety profile of the study medication, so such data was critical to the integrity of the final study analysis. Attempts were made to obtain safety data after withdrawal of consent if a subject had withdrawn their consent. The safety follow up was conducted regularly with those subjects who dropped out of the study due to intolerability issues. After three documented attempts (phone calls) to contact a subject, it was considered lost to follow up.

**Inclusion criteria**

The following inclusion criteria were used for screening and enrolment of the subjects in the trial:

To qualify for enrollment in the study:

1. Male or female subjects in the age group of 35-65 years

2. Subjects newly diagnosed with mild to moderate Type 2 diabetes

3. Subjects having fasting plasma glucose level ≥ 126 mg/dl

4. Subjects having HbA1c level range ≥ 6.5%

5. Subjects with a body mass index (BMI) ≥ 25 kg/$m^2$ and ≤ 40 kg/$m^2$

6. A negative pregnancy test must be taken at the Screening Visit by women of childbearing potential who have been using a medically acceptable birth control method for at least one month prior to screening (3 months on oral contraceptives). In order to be considered for this trial, non-childbearing women must have been amenorrheic for at least a year or have had a hysterectomy or bilateral oophorectomy.

**Exclusion criteria**

1. Subjects with any acute or chronic diabetes- associated complications and type 1 diabetes

2. Subjects with severe cardiac disease including congestive cardiac failure, unstable angina and myocardial infarction.

3. Subjects with chronic or acute pancreatic disease, hypertension (systolic pressure≥180mmHg and/ or diastolic pressure≥110mmHg)

4. Women who were lactating, pregnant or planning to become pregnant during the study.

5. Subject who used any herbal drugs and dietary supplements for Type 2 diabetes.

6. History of drugs or alcohol abuse

7. History of surgical procedures undergone in past six months

8. Participation in a study of another investigational drug within 1 month prior to study start.

**Study procedures and schedule**

During each study visit, the following procedures were conducted on each subject.

**Table 1: Schedule of events**

| Procedures | Screening Visit/Randomization visit (Day -7 to Day 0) Visit 1 | Treatment Period | | | |
|---|---|---|---|---|---|
| | | Day 15 (Visit 2) | Day 30 (Visit 3) | Day 60 (Visit 4) | Day 90 (Visit 5) |
| Signed Informed Consent | × | | | | |
| Inclusion/Exclusion Reviewed | × | × | × | × | × |
| Medical/Surgical/Medication History | × | | | | |
| Physical Examination | × | × | × | × | × |
| Vital Signs | × | × | × | × | × |
| Height*, Weight, BMI* | × | × | × | × | × |
| Clinical Laboratory Tests (hematology, Biochemistry, urinalysis) | × | | | | × |
| Fasting plasma glucose level | × | × | × | × | × |
| HbA1c | × | | | | × |
| Insulin level in blood | × | | | | × |
| Lipid Profile | × | | | × | × |
| Urine Pregnancy Test (if applicable) | × | × | × | × | × |
| Trial medication allocation | × | | | | |
| Dispense Subject Diary | × | × | × | × | |
| Collect/Review Subject Diary | | × | × | × | × |
| Provide Directions for Concomitant Medication Use if any | × | | | | |
| Review Product Accountability | | × | × | × | × |
| Dispense New Investigational Product | × | × | × | × | |
| Assess use of Concomitant Medications | | × | × | × | × |
| Adverse Events Assessed | | × | × | × | × |

*- Height and BMI was assessed only in screening visit.

**Methods of data collection**

**Primary Efficacy Parameter**

- The mean change of HbA1c from baseline to end of the study.

**Secondary Efficacy Parameter**

- Change in fasting plasma glucose from baseline to Day 15, Day 30, Day 60 and Day 90. Change in insulin level from baseline to Day 90. Change in lipid profile from baseline to day 60 and day 90. Adverse event profile, frequency and severity.

**Statistical Procedures**

Descriptive statistics were also provided by treatment group for FPG, Insulin level in blood and Lipid profile. These were generated during study as absolute values and also change from baseline. In addition, individual results were reviewed for any treatment emergent changes of possible clinical significance. Statistical testing was planned to be two-sided and performed using in-house software. The analyses were performed based on the data from the intent-to-treat (ITT) population, defined as all subjects who received at least one study medication dose, and on the data from the PP population; all subjects completed the study without any major protocol violations. In order to assess the efficacy of the study medication within and between groups, a student t-test was used [7 - 10].

**RESULTS**

**Subject disposition**

A total of forty participants with type 2 diabetes mellitus were randomized between the OCDM15 group and the placebo group after meeting the inclusion and exclusion criteria.

**Table 2: Subject Disposition**

| | **OCDM15 (N=20)** | **Placebo (N=20)** |
|---|---|---|
| **Number of Subjects completed the study** | 17 (85.0) | 19 (95.0) |
| **No. of subject dropped out** | 03 (15.0) | 01 (05.0) |

**Baseline and demographic characteristic**

Baseline and demographic parameters were evaluated for the study group and are given in table no.3.

**Table 3: Baseline and demographic characteristics**

| | ***OCDM15*** **(N=20)** | **Placebo (N=20)** |
|---|---|---|
| Age | 44.7±09.1 | 45.1±07.2 |
| Sex | | |
| Male, N (%) | 08 (40) | 05 (25) |
| Female, N (%) | 12 (60) | 15 (75) |
| Weight (Kg) | 69.6±08.8 | 70.1±08.7 |
| Height (cm) | 160.6±09.4 | 156.7±07.2 |
| BMI ($kg/m^2$) | 26.83±01.8 | 28.6±04.2 |
| Blood pressure (mm/Hg) | | |
| Systolic Blood pressure | 120.9±08.0 | 131.2±10.2 |
| Diastolic Blood pressure | 73.6±07.4 | 77.4±09.3 |
| Pulse Rate | 91.0±08.8 | 95.9±10.0 |

Forty seven subjects were screened in the study, in that 40 were randomized into two groups in 1:1 ratio. A total of 13 males and 27 females participated in the study. The average age of subjects in OCDM15 group was 44.7±09.1 and in placebo group was 45.1±07.2. The male to female ratio was 8:12 and 05: 15 in OCDM15 and placebo group respectively and the ratio between the groups was not statistically significant (p=0.5000).

**Table 4: Assessment of Primary efficacy- HbA1c level**

| | OCDM15 | | | Placebo | | | p value |
|---|---|---|---|---|---|---|---|
| | N | Mean | P value | N | Mean | P value | |
| Visit 1 | 17 | 7.89±0.55 | | 19 | 7.75±0.39 | | |
| Visit 5 | 17 | 6.42±1.00 | 0.0001* | 19 | 7.16±0.45 | <0.0001* | 0.0051^ |
| Change from baseline | | | | | | | |
| Visit 5 | 17 | 1.46±1.40 | 0.0001* | 19 | 0.59±0.40 | <0.0001* | 0.0051^ |

**- p-value statistically significant from baseline*

*^-p value between the groups*

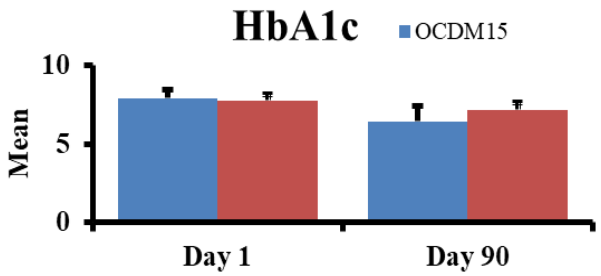


**Figure 1: Assessment of primary efficacy- HbA1c (Mean)**

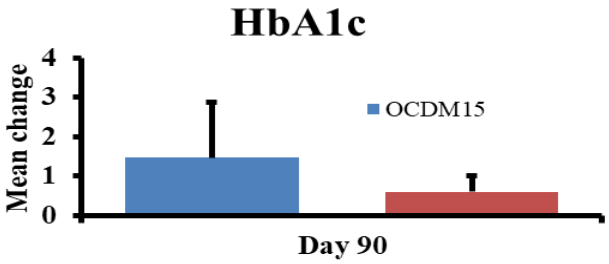


**Figure 2: Assessment of primary efficacy- HbA1c (Mean Change)**

The result showed a statistical significant difference in HbA1c level in both the groups as compared to baseline. The mean change from baseline was found to be 1.46±1.40 in OCDM15 group and in placebo it was 0.59±0.40. The difference between the groups was found to be statistically significant.

**Assessment of secondary efficacy variables**

**Change in fasting plasma glucose level**

The plasma glucose level is the method for diagnosing diabetes mellitus. It was measured in fasting state for the subjects in all the visits. The change from baseline was analyzed using t test within group and between the groups.

**Table 5: Assessment of secondary efficacy- FPG level**

| | OCDM15 | | | Placebo | | | P value |
|---|---|---|---|---|---|---|---|
| | N | Mean | P value | N | Mean | P value | |
| Visit 1 | 17 | 159.71±27.07 | | 19 | 145.68±21.21 | | |
| Visit 2 | 17 | 143.94±27.33 | 0.0002* | 19 | 141.21±22.56 | 0.0132* | 0.0034^ |
| Visit 3 | 17 | 142.18±34.06 | 0.0001* | 19 | 137.63±22.06 | 0.0001* | 0.0107^ |
| Visit 4 | 17 | 138.53±31.56 | 0.0001* | 19 | 133.05±24.66 | 0.0001* | 0.0156^ |
| Visit 5 | 17 | 129.35±33.01 | 0.0001* | 19 | 126.79±20.68 | 0.0001* | 0.0053^ |
| Change from baseline | | | | | | | |
| Visit 5 | 17 | 30.35±19.39 | 0.0001* | 19 | 15.74±8.69 | 0.0001* | 0.0053^ |

**- p-value statistically significant from baseline*

*^-p value between the groups*

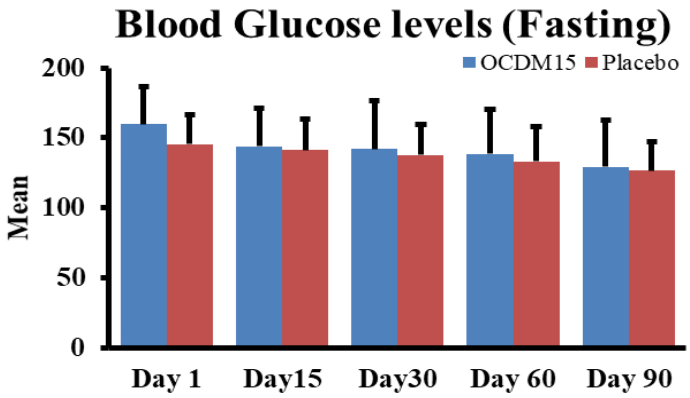


**Figure 3: Assessment of secondary efficacy- FPG (Mean)**

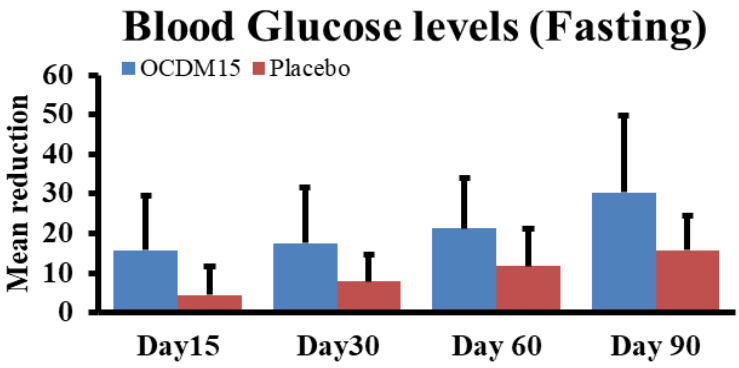


**Figure 4: Assessment of secondary efficacy- FPG (Mean reduction)**

**Change in insulin level**

Insulin level was measured at visit 1 and visit 5 and the change from baseline was analyzed using t test between the groups and within the group.

**Table 6: Assessment of secondary efficacy- Insulin level**

| | OCDM15 | | | Placebo | | | P value |
|---|---|---|---|---|---|---|---|
| | N | Mean | P value | N | Mean | P value | |
| Visit 1 | 17 | 9.06±7.52 | | 19 | 8.96±6.94 | | |
| Visit 5 | 17 | 10.34±7.61 | 0.0419 | 19 | 8.28±5.81 | 0.3899 | 0.0051^ |
| Change from baseline | | | | | | | |
| Visit 5 | 17 | 1.28±1.74 | 0.0419 | 19 | 0.68±3.36 | 0.3899 | 0.0051^ |

**- p-value statistically significant from baseline*

*^-p value between the groups*

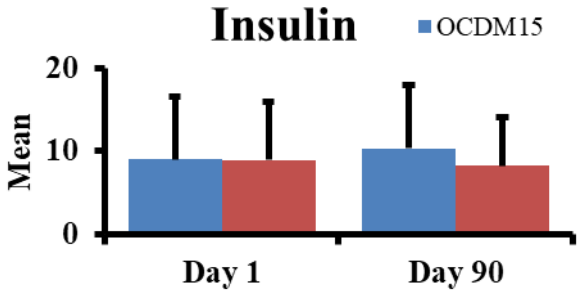


**Figure 5: Assessment of secondary efficacy- Insulin level (Mean)**

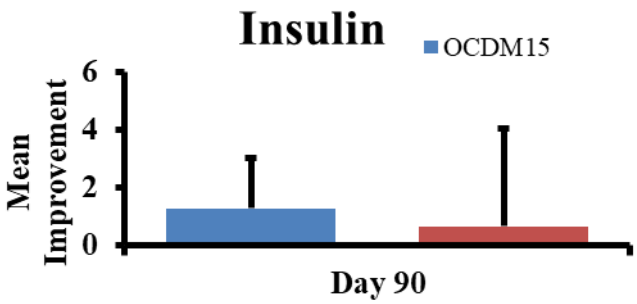


**Figure 6: Assessment of secondary efficacy- Insulin level (Mean Improvement)**

**Change in triglycerides level**

Almost all fat in food and in the body exists as triglycerides. Blood plasma is also a source of lipids, which together with cholesterol form plasma lipids. There has been a stronger correlation between triglyceride levels and waist circumference (abdominal obesity) than between triglyceride levels and body mass index. A key feature of the metabolic syndrome is atherogenic dyslipidemia. This is marked by hypertriglyceridemia and low levels of high-density lipoprotein cholesterol [HDL].

**Table 7: Assessment of secondary efficacy- Triglycerides**

| | OCDM15 | | | Placebo | | | P value |
|---|---|---|---|---|---|---|---|
| | N | Mean | P value | N | Mean | P value | |
| Visit 1 | 17 | 163.00±53.60 | | 19 | 161.58±50.97 | | |
| Visit 4 | 17 | 122.47±30.43 | 0.0042* | 19 | 151.11±49.47 | 0.0000* | 0.0145^ |
| Visit 5 | 17 | 113.82±19.81 | 0.0010* | 19 | 142.00±48.00 | 0.0056* | 0.0339^ |
| Change from baseline | | | | | | | |
| Visit 5 | 17 | 49.18±50.92 | 0.0010* | 19 | 19.58±27.15 | 0.0056 | 0.0339^ |

**- p-value statistically significant from baseline*

*^-p value between the groups*

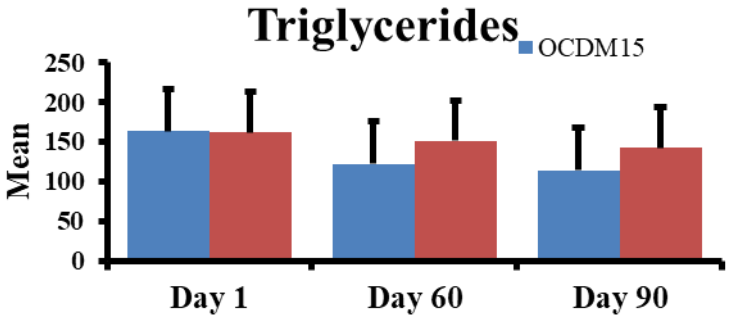


**Figure 7: Assessment of secondary efficacy- Triglycerides (Mean)**

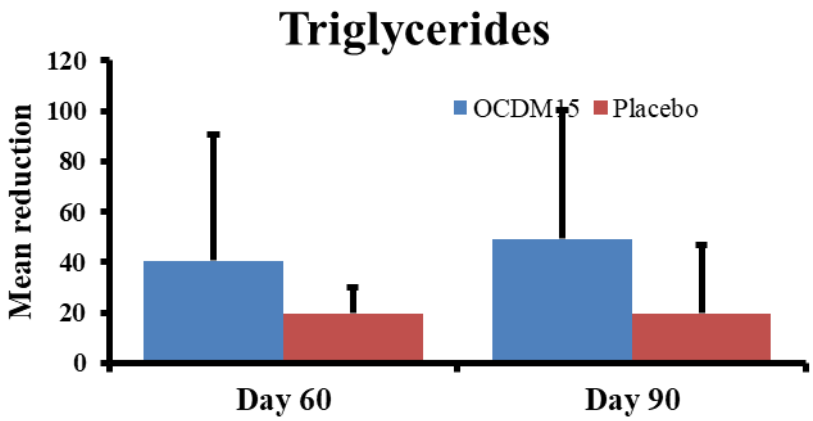


**Figure 8: Assessment of secondary efficacy- Triglycerides (Mean reduction)**

The mean change in triglycerides was found to be 49.18±50.92 in OCDM15 group and in placebo group it was reduced only by 19.58±27.15. Subjects in OCDM15 group showed more response in reduction of triglycerides level compared to placebo. OCDM15 was statistically significant compared to placebo. OCDM15 helps in reducing the triglycerides level which is the main cause for developing cardio vascular disease in type 2 diabetes subjects.

**SAFETY**

**Extent of exposure**

The safety evaluation was done on all 40 subjects who received at least one dose of *OCDM15* or placebo.

**Adverse events**

Out of 40 subjects 9 subjects reported adverse events. The incidence of AE in each group was 15% in OCDM15 group whereas in placebo group it was 30%. The incidence of AE was compared between the groups and it was not statistically significant. The event which was reported by subjects were listed in table 8,

**Table 8: Assessment of adverse events**

| **Adverse event** | **System organ class** | **OCDM15 N=20** | **Placebo N=20** | **Total N=40** |
|---|---|---|---|---|
| Urinary infection | Infection and infestation | 1 (5) | 2 (10) | 3 (7.5) |
| Body pain | Musculoskeletal and connective tissue disorder | 2 (10) | 4 (20) | 6 (15) |

The most commonly reported Adverse Events were in the SOC "musculoskeletal and connective tissue disorder" with a total number of 6 Adverse Events, out of which 02 Adverse Events were from OCDM15 and 4 from Placebo. In this category body pain was noticed. The next most common conditions fell into the "Infection and infestations" category with 3 AE. Out of all the Adverse Events, 3 events (Urinary infection) were reported as might be related to the study drug and the rest were not related to the study drug. All the AEs are of mild intensity and were completely recovered.

**DISCUSSION**

OCDM15 was tested for its safety and efficacy in treating type 2 diabetes mellitus subjects in a randomized, placebo-controlled double blind study. Following informed consent, 47 subjects were screened and divided into two groups in a 1:1 ratio. Fourty subjects were recruited, 36 of whom completed the study and three of whom dropped out of OCDM15 and one of whom dropped out of placebo. A total of five visits are required for the study: Visit 1 (screening visit), Visit 2, Visit 3, Visit 4, and Visit 5. Changes in HbA1C level were considered primary endpoints, while changes in insulin level, lipid profile, and fasting plasma glucose level were deemed secondary endpoints. A measurement of HbA1C and insulin

efficacy was taken at Visit 1 and Visit 5, a lipid profile was taken at Visits 1, 4 and 5, and a measurement of fasting plasma glucose was taken at each visit. A statistically significant difference was found between OCDM15 and Placebo under study conditions, as well as a significant difference within group. Both groups showed statistically significant changes in HbA1C levels at the end of the study. In the OCDM15 group, the HbA1C level was reduced by 18.56%, while in the placebo group, the HbA1C level was reduced by 7.60%. According to the results, OCDM15 was effective at controlling glucose levels during the study period. OCDM15 and placebo groups experienced significant changes in fasting blood glucose levels from baseline. There was a 19 % reduction in FPG level in the OCDM15 group and a 10.80 % reduction in the placebo group. Insulin level was significantly different between and within OCDM15 group and not between placebo group. The OCDM15 group increased 14.12 %, while the placebo group increased 7.57 %. Cardiovascular disease and coronary heart disease are caused by moderately elevated triglycerides in diabetic dyslipidemia. Supplementing with OCDM15 resulted in a reduction in triglyceride levels of 30.16% and 12.11 % in the placebo group. Accordingly, OCDM15 is effective in reducing triglycerides levels and most subjects' triglycerides levels fell within the normal range after taking the medicine. The supplementation of OCDM15 resulted in a reduction of glucose levels as well as a reduction in lipid levels, which is a major cause of heart disease. It was reported that adverse events occurred in both groups. There were 15% and 30% of AE incidents in OCDM15 and placebo, respectively. The study medication was not related to two of the adverse events associated with OCDM15 and four of the adverse events associated with placebo. It is important to note that all the events have been fully recovered [11, 12]. During the study, vital signs, weight, and clinical laboratory parameters were measured, and no significant changes were found in either group. According to the results, neither OCDM15 nor placebo affected vital parameters.

## CONCLUSION

OCDM15 capsule was found to be safe and effective in subjects with Type 2 Diabetes Mellitus (T2DM) in a randomized, double-blinded, placebo-controlled proof-of-concept study according to the guidelines outlined in the ICH Good Clinical Practices (ICH GCP) guidelines. These findings indicate that OCDM15 capsule may be a treatment option for Type 2 Diabetes Mellitus based on the results of this study. In order to shed light on the mechanism of action of OCDM15 capsule in the treatment of Type 2 diabetes, more research is needed, including larger-scale studies and long-term follow-up studies.

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