Phase 1 clinical trial to evaluate TOTUM-63, a botanical complex for managing prediabetes

Sirvent P1, Bargetto M1, Chavanelle V1,2, Macian N3, Boulliau S1, Ducheix G3, Duale C1, Dubray C3, Pickering G3, Peltier SL1

Laboratoire AME2P, Université Clermont-Auvergne, France, 1VALBIOTIS, La Rochelle, France, 2Centre d’Investigation Clinique, Clermont-Ferrand, France

**ABSTRACT**

The IDF estimates that the number of individuals with diabetes will rise by 80% to 438 million people with TOTUM-63 (3). Different studies have shown that diet and lifestyle changes as effective, patients rarely adhered to them on the long term. The use of food supplements in prediabetes, has already been considered. We have developed TOTUM-63, a botanical complex (BC) that aims to reverse prediabetes and to prevent each dysfunction and/or its consequences independently. The ability of the BC to control fasting glycemia, HbA1c, insulin sensitivity, and hepatic triglycerides, and weight gain through a specific effect on fat mass has been demonstrated in different animal models (CD/di, C57BL/6 high-fat diet, C57BL/6N and Syrian hamster normal diet). In order to determine the safety and the efficacy of a first Phase I clinical trial on eight overweight male volunteers (NCT02790489). The design of the study included an initial period of supplementation with 2.5g/day of the BC for 4 weeks (V1; V2:V1+4weeks) followed by an intermediary analysis and a wash-out period of 2 weeks, then 4 weeks of supplement period 2 with 5g/day (V3; V2:V3+4weeks). Different safety parameters, in particular hepatic, urinary, renal and hemodynamic, were assessed at all visits. Glycemia and insulinemia were also monitored from catheter samples after taking a standardized breakfast (Breakfast Test Tolerance BT) at V3 and V4. Fourteen volunteers completed the trial, 1 volunteer left the study after V2 due to a persistent health problem identified on inclusion that was independent of the BC. The results do not show any clinically significant increase in the various safety parameters, objectively verifying the good tolerability of the BC for the two doses tested. In addition, BC did not induce an increase in insulin secretion during the BT. Conversely, we observed a decrease in the insulinemia AUC (V4:32886324 vs V3:54534014 U, p = 0.0384), and a downward trend for the glycerol AUC (V4:181328 vs V3:998236 mmol/L, p = 0.0286). The candidate BC is currently undergoing a Phase 2a trial on 60 prediabetic subjects with abdominal obesity (NCT02868177).

**METHODS**

**DESIGN OF THE STUDY**

The present study is a controlled, cross-over, sequential, monocenter, prospective, pilot tolerance study. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki, 1964, as amended in Edinburgh in October 2000 and Somersfield West, South Africa, 1996. This study was conducted in conformance with good clinical practice (GCP). Each participant personally and freely gave his/her informed consent before being enrolled in the study. The experimental design used intra-individual comparison in the same group of subjects. Each subject included participated to 2 periods of 4 weeks during which two different doses of the botanical complex were given daily (period 1 (V1 to V2): 2.5g per day and period 2 (V3 to V5): 5g per day). Between these two periods, there were a 2-week washout period (V2 to V3). Blood and urine samples were taken, an electrocardiogram was obtained, and the subject’s heart rate, blood pressure, body weight and waist size measured during visits 2, 3 and 4 (V0, V2, V3 and V4). Finally, two oral carbohydrate tolerance tests were carried out during visits 3 and 4 (V3 and V4).

**RESULTS**

**ADVERSE EVENTS**

None of the adverse event observed during the study in some patients (head ache, cold, low back pain, flatulence...), were classed as serious and related to the botanical complex TOTUM-63 could not be established.

**BIOLICAL PARAMETERS**

Some changes in biological measures were noticed and were considered by the investigators as being non clinically relevant (Table 1).

**CONCLUSION**

The primary evaluation criterion was the good tolerability of subjects to two doses of the botanical complex TOTUM-63. This good tolerance was characterized by stable biological, hemodynamic and anthropometric parameters following administration of TOTUM-63. No clinically relevant adverse event has been reported. Considering safety conclusions TOTUM-63 is a well-tolerated product. Moreover, the results observed at V4 (after the 4 weeks with 5g/day of TOTUM-63 supplementation) indicate that this dose of TOTUM-63 might improve insulin-sensitivity during oral carbohydrate tolerance test. Taken together, TOTUM-63 is a very promising candidate to pre-diabetes management. Well-conducted phase II clinical trial in targeted populations should be conducted to confirm the clear proof of concept brought by this first study in humans.

**REFERENCES**

1. Sirvent P1, Bargetto M1, Chavanelle V1,2, Macian N3, Boulliau S1, Ducheix G3, Duale C1, Dubray C3, Pickering G3, Peltier SL1
2. 2001 Lancet 357:31-45

**TABLES**

Table 1: biological parameters

**FIGURES**

Figure 1: Design of the study

Figure 2: Carbohydrate tolerance test. Before the tolerance test (t=0), the subjects were catheterized and a blood sample was collected to measure the main study endpoints. Five minutes later (t=5), the volunteers ingested 250 ml of water (V1) at the dose of TOTUM-63 (5g, with 200 mg of phytosterols/mL) after eating a standardized breakfast in twelve minutes (V0). Blood glucose and insulin levels were determined for 6 blood samples taken before and after eating breakfast at time -10 (pre challenge), -5' (pre challenge), +15', +30', +45', +60', +90' and +120'.

Figure 3: Glucose during oral carbohydrate tolerance test. AUC Area under the curve. Cmax Peak glucose concentration.

Figure 4: insulin sensitivity index (ISI) during carbohydrate tolerance test, ISI was calculated by the following formula: ISI=GLucose/Insulin/SquareRoot(ISI)