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

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## ABSTRACT

The IDF estimates that the number of individuals with diabetes will rise by almost 55% to 640 million by 2040. According to the ADA, 86 million Americans aged 20 years and over are prediabetic. We have developed an innovative 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, serum and hepatic triglycerides, and weight gain through a specific effect on fat mass has been demonstrated in different animal models (db/db, C57BL/6 high fat diet, C57BL/6NR and Syrian hamster normal diet). Following these results, a first Phase I open trial was initiated on slightly overweight male volunteers (NCT02790489). 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 supplementation with 5.0g/day (V3, V2+2weeks; V4: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 Tolerance Test: BTT) 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, objectifying the very good tolerance of the BC for the two doses tested. In addition, BC did not induce an increase in insulin secretion during the BTT. Conversely, we observed a decrease in the insulinemia AUC (V4:32863624 versus V3:544531240mUI.min/L, -40%, p=0.02), and a downward trend for the glycemia AUC (V4:118328 versus V3:168328mmol.min/L, -30%, p=0.08). The candidate BC is currently undergoing a Phase 2a trial on 80 prediabetic subjects with abdominal obesity (NCT02868177).

## BACKGROUND

Worldwide, the number of people with type 2 diabetes is estimated at nearly 592 million[(1)]. The estimated total cost of healthcare in the United States and in Europe as a result of type 2 diabetes was 456 billion in 2014.

According to the World Health Organization, **prediabetes** is defined by a fasting glycemia between 6.1 and 7.0 mmol/L and/or glycemia between 7.8 and 11.1 mmol/L two hours after taking oral glucose (IGT)[(2)]. According to experts from the American Diabetes Association, **potentially 70% of prediabetics will develop diabetes**[(3)]. Different studies have shown that implementing diet and lifestyle changes, and even a therapeutic treatment, can decrease the risk of prediabetics developing diabetes[(4,5)]. **It is thus possible to regress from prediabetes back to normoglycemia**[(3)]. However, even if diet and lifestyle changes are effective, patients rarely adhere to them on the long term. The use of food supplements in addition to lifestyle changes to prevent type 2 diabetes, in particular for prediabetics, has already been considered. Nevertheless, no food supplement has yet demonstrated satisfactory tolerance and efficacy.

We have developed TOTUM-63, a botanical complex (BC) that aims to reverse prediabetes and to prevent each dysfunction and/or its consequences independently. Preclinical studies conducted with TOTUM-63 in healthy mice and hamsters, high-fat fed obese mice and diabetic db/db mice showed a particularly significant effect of TOTUM-63 on fasting glycaemia and insulin sensitivity. In addition, TOTUM-63 has shown very good tolerance.

**The objective of the present study is to objectify the good tolerance of the botanical complex TOTUM-63 on different blood, urine and hemodynamic biological parameters, and during an oral carbohydrate tolerance test in overweight subjects.**

## METHODS

### DESIGN OF THE STUDY

The present study is a controlled, cross-over/sequential, interventional, 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 Somerset 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 Totum-63 were taken daily (period 1 (V1 to V2): 2.5g per day and period 2 (V3 to V4): 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 recorded, and the subject's heart rate, blood pressure, body weight and waist size measured during visits 0, 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).

The primary evaluation criterion was the good tolerability of subjects to two doses of the botanical complex Totum-63. Secondary evaluation criteria was blood glucose and insulin kinetics during an oral carbohydrate tolerance test.

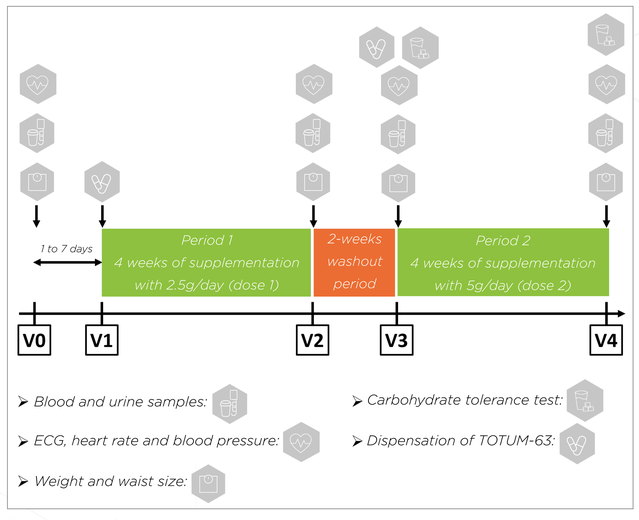


*Figure 1: Design of the study*

### SUBJECTS

The study took place in the Clinical Pharmacology Centre, CHU Clermont-Ferrand. Principal criteria for inclusion were: male subjects between 45 and 65 years, with BMI between 25 and 30 kg/m$^2$, stable weight, physical activity level and eating habits for three months before the start of the study. Principal criteria for non-inclusion were: anti-diabetic treatment, lipid-regulating or anti-dyslipidemia drugs, subjects taking treatment that could interfere with the evaluation of the study endpoints, subjects consuming dietary supplements or food products supplemented with phytosterols, beta-glucans, konjac and/or cinnamon, subject with extreme eating habits, subject with unstable blood pressure equal to or over 160/95.

17 subjects were screened and 15 included in the study. 1 subject was withdrawn from the study due to Wolff-Parkinson-White (WPW) syndrome occurring only intermittently. Thus only 14 subjects completed the study. The baseline characteristics of the subjects were (mean ± SD) age: 51.5 ± 6.2 years; height: 172 ± 3.8 cm; weight: 82 ± 6.6 Kg; BMI: 27.7 ± 1.9 Kg/cm$^2$.

### STATISTICS

Following analysis of normality and homoscedasticity of the variables, the results for the two doses used in the study were compared using a Student's t-test for paired groups.

## RESULTS

### ADVERSE EVENTS

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

### BIOLOGICAL PARAMETERS

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

| | V0 | | V2 | | V3 | | V4 | |
|---|---|---|---|---|---|---|---|---|
| | Mean | *SD* | Mean | *SD* | Mean | *SD* | Mean | *SD* |
| ASAT (UI/L) | 23.8 | *5.5* | 23.2 | *2.9* | 24.0 | *5.4* | 24.9 | *3.5* |
| ALAT (UI/L) | 40.9 | *13.4* | 38.2 | *13.2* | 36.6 | *14.5* | 39.0 | *10.8* |
| γGT (UI/L) | 47.3 | *31.9* | 45.8 | *34.1* | 44.1 | *34.1* | 51.6 | *35.2* |
| ALKALINE PHOSPHATASE (UI/L) | 61.0 | *20.0* | 60.8 | *19.1* | 60.7 | *19.0* | 59.5 | *18.1* |
| UREA (mmol/L) | 5.7 | *1.4* | 6.0 | *1.4* | 6.3 | *1.7* | 6.2 | *1.4* |
| BILIRUBIN (µmol/L) | 9.2 | *2.7* | 9.8 | *2.8* | 8.7 | *2.8* | 10.3 | *2.4* |
| BLOOD CREATINE (µmol/L) | 75.9 | *7.9* | 79.4 | *8.3* | 81.3 | *10.0* | 76.7 | *9.0* |
| URINARY CREATINE (mmol/L) | 17.6 | *6.6* | 16.5 | *6.7* | 17.6 | *6.4* | 17.5 | *4.9* |
| TOTAL CHOLESTEROL (mmol/L) | 4.8 | *0.9* | 4.6 | *0.9* | 4.7 | *0.8* | 4.4 | *0.8* |
| TRIGLYCERIDE (mmol/L) | 1.3 | *0.6* | 1.1 | *0.6* | 1.4 | *0.5* | 1.2 | *0.6* |
| HDL-CHOLESTEROL (mmol/L) | 1.4 | *0.4* | 1.5 | *0.5* | 1.4 | *0.4* | 1.4 | *0.4* |
| LDL-CHOLESTEROL (mmol/L) | 2.8 | *0.9* | 2.5 | *0.8* | 2.6 | *0.9* | 2.5 | *0.7* |
| LDL-CHOLESTEROL OXIDIZED (mmol/L) | 39.6 | *12.5* | 37.4 | *14.9* | 35.4 | *11.2* | 33.8 | *11.4* |
| BLOOD GLUCOSE (mmol/L) | 4.7 | *0.4* | 4.8 | *0.5* | 4.6 | *0.4* | 4.8 | *0.6* |
| INSULIN (mUI/L) | 7.7 | *6.5* | 8.1 | *8.6* | 8.8 | *9.8* | 8.4 | *8.1* |
| FRUCTOSAMINE (µmol/L) | 215.6 | *13.9* | 219.8 | *11.1* | 213.4 | *16.2* | 205.4 | *15.5* |

*Table 1: biological parameters*

### VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Any changes of the vital signs (PAS, PAD, FC, body temperature, respiratory rate, QTc interval and O2 saturation), were considered by the investigators as being non clinically relevant (Table 2).

| | V0 | | V2 | | V3 | | V4 | |
|---|---|---|---|---|---|---|---|---|
| | MEAN | *SD* | MEAN | *SD* | MEAN | *SD* | MEAN | *SD* |
| Weight (kg) | 81.5 | *6.5* | 81.3 | *6.9* | 81.6 | *6.8* | 81.6 | *6.7* |
| BMI (kg/m²) | 27.6 | *1.8* | 27.5 | *2.0* | 27.5 | *2.1* | 27.6 | *2.0* |
| Waist size (cm) | 97.9 | *6.1* | 97.9 | *7.3* | 97.1 | *6.9* | 97.4 | *7.3* |
| BP systolic (mmHg) | 135.6 | *16.3* | 132.9 | *11.6* | 134.5 | *15.3* | 133.8 | *15.2* |
| BP diastolic (mmHg) | 85.9 | *10.1* | 84.6 | *11.6* | 83.3 | *7.6* | 83.9 | *9.8* |
| $O_2$ saturation (%) | 97.3 | *1.7* | 98.6 | *1.6* | 98.0 | *1.5* | 98.1 | *1.4* |
| HF (bpm) | 57.4 | *11.5* | 57.5 | *10.7* | 59.3 | *9.7* | 57.9 | *13.0* |
| PR (ms) | 167.8 | *19.3* | 168.3 | *24.1* | 169.3 | *20.9* | 170.9 | *21.4* |
| QRS (ms) | 88.1 | *5.4* | 89.4 | *6.0* | 90.6 | *6.5* | 88.5 | *5.6* |
| QT (ms) | 398.6 | *39.1* | 399.9 | *28.9* | 404.6 | *34.5* | 395.2 | *26.6* |
| QTc (ms) | 385.4 | *29.6* | 387.7 | *24.6* | 398.3 | *19.2* | 383.1 | *26.9* |
| Axe QRS (ms) | 26.1 | *29.6* | 24.1 | *27.4* | 26.9 | *29.5* | 24.2 | *29.3* |

*Table 2: Other data related to safety*

### CARBOHYDRATE TOLERANCE TEST

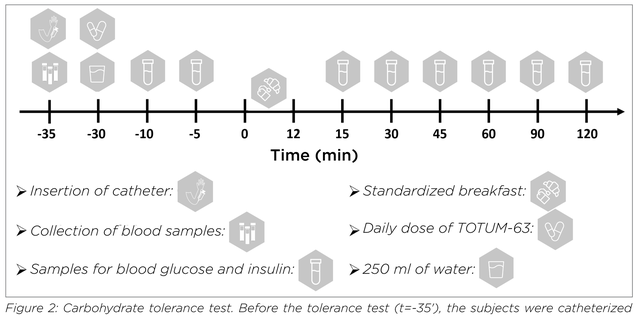


*Figure 2: Carbohydrate tolerance test. Before the tolerance test (t=-35'), the subjects were catheterized and a blood sample was collected to measure the main study endpoints. Five minutes latter (t=-30'), the subjects drank 250 mL of water (V3) or the daily dose of TOTUM-63 (5g) with 250 mL of water (V4), before eating a standardized breakfast in twelve minutes (t=0'). Blood glucose and insulin kinetics were determined from the 8 blood samples taken before and after eating breakfast at time -10' (pre challenge), -5' (pre challenge), +15', +30', +45', +60', +90' and +120'.*

### GLUCOSE DURING ORAL CARBOHYDRATE TOLERANCE TEST

After 4 weeks of supplementation with TOTUM-63 (5g/day), glucose tolerance during oral carbohydrate tolerance test was improved, as shown by the reduced maximal glycaemia (Cmax, Fig. 3).

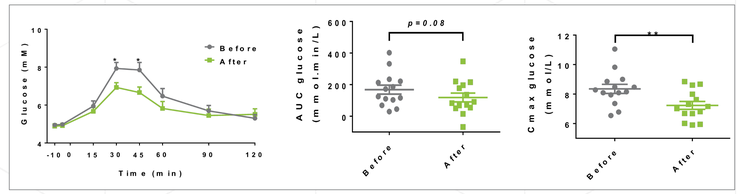


*Figure 3: Glucose during carbohydrate tolerance test. AUC: Area under the curve. Cmax: Peak glucose concentration. *p<0.05 **p<0.01*

### INSULIN DURING ORAL CARBOHYDRATE TOLERANCE TEST

After 4 weeks of supplementation with Totum-63 (5g/day), insulin response during oral carbohydrate tolerance test was lowered, as shown by the reduced area under the curve and maximal concentration for insulin (AUC and Cmax respectively, Fig. 4).

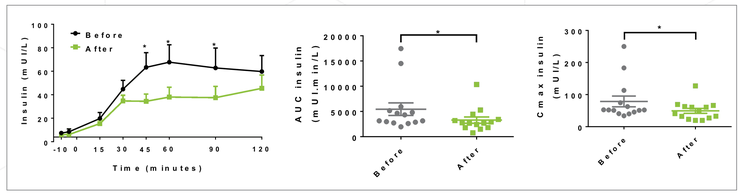


*Figure 4: Insulin during carbohydrate tolerance test. AUC: Area under the curve. Cmax: Peak insulin concentration. *p<0.05*

### INSULIN SENSITIVITY

After 4 weeks of supplementation with TOTUM-63 (5g/day), the insulin sensitivity index (ISI) calculated during the oral carbohydrate tolerance test based on glucose and insulin responses, was improved (Fig. 5).

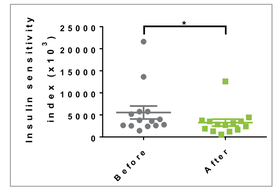


*Figure 5: Insulin sensitivity index (ISI) during carbohydrate tolerance test. ISI was calculated by the following formula: ISI=AUCglucose x AUCinsulin. *p<0.05*

## 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

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