TOTUM-63 LOWERS FASTING GLYCEMIA IN SUBJECTS WITH PREDIABETES: A PHASE II CLINICAL TRIAL

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BACKGROUND AND AIMS

Over 1 billion people worldwide live with prediabetes, which is defined by increased fasting blood glucose (FBG), glucose intolerance and/or higher A1c hemoglobin. Prediabetes is considered a risk factor for Type 2 Diabetes (T2D).

TOTUM-63 is a plant-based product designed to reduce T2D risk factors. TOTUM-63 has been demonstrated to significantly improve body weight and glucose homeostasis in animal models of obesity and type 2 diabetes (db/db and C57BL/6 fed a high-fat diet). In a Phase I/II clinical trial, TOTUM-63 had shown its safety, good tolerance and beneficial effects on post-prandial glucose control in individuals living with overweight.

The aim of this multicenter, randomized and double-blind placebo-controlled Phase II trial was to assess the effects of TOTUM-63 on glucose homeostasis in individuals with impaired fasting glycemia and glucose intolerance.

MATERIALS AND METHODS

Study design

- Multicenter, randomized, unbalanced (3 : 1, TOTUM-63 : Placebo) and double-blind placebo controlled study, 2 parallel-groups.
- Supplementation period: 6 months, 5 g/day (3 intakes).
- **Primary endpoint:** change in fasting glycemia between baseline and 6 months.
- **Main secondary endpoints**: 2-hour OGTT glycemia, insulin sensitivity, anthropometric parameters, hemodynamic parameters, lipid profile, safety.

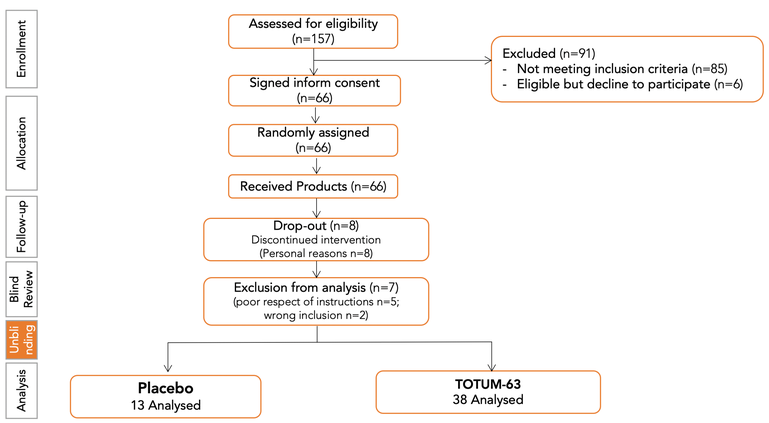
Main inclusion criteria

- Age between 35 and 75 years (limits included).
- Fasting glycemia > 6.1 mmol/L (1.1 g/L).
- 2-hour glycemia (OGTT) > 7.8 mmol/L (1.4 g/L).
- HbA1c < 8.6 mmol/L.
- Waist circumference > 94 cm for men or > 80 cm for women.
- Triglyceridemia > 1.7 mmol/L.
- With reported body weight variation < 5% in the 3 months prior the randomization.
- Without significant change in food habits or in physical activity in the 3 months before randomization and agreeing to keep them unchanged throughout the study (no hyper-hypocaloric diet nor start-stop of sport activity planned in the next 7 months).

Statistics

- Statistical analyses (Stata software, Texas, USA) were conducted with linear mixed models to take into account the between and within participant variability (subject as random-effect) and to measure the following fixed effects: group (placebo *vs.* TOTUM-63), time (V1 and V3) and their interaction. Baseline value of the dependent variable was considered as an adjustment covariate.

FLOW CHART



RESULTS

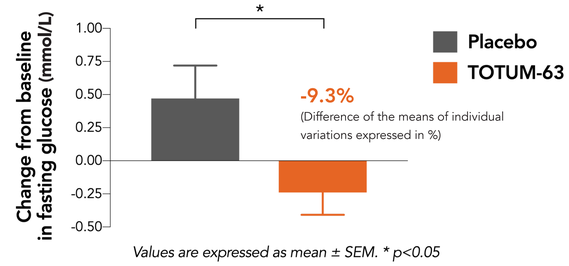
Study population at baseline

- **Age***: 57.1 years (± 1.4)
- **Gender**: 35 female, 16 male
- **BMI***: 31.3 kg/m² (± 0.8)
- **Fasting glycemia***: 6.93 mmol/L (± 0.17)
- **2-hour OGTT glycemia***: 10.25 mmol/L (± 0.42)
- **HbA1c***: 6.98 mmol/L (± 0.11)
- **Fasting triglycerides***: 1.99 mmol/L (± 0.13)

Here are the characteristics of the study population at baseline. No statistical difference was evidenced between groups at baseline.

* Mean values ± SEM

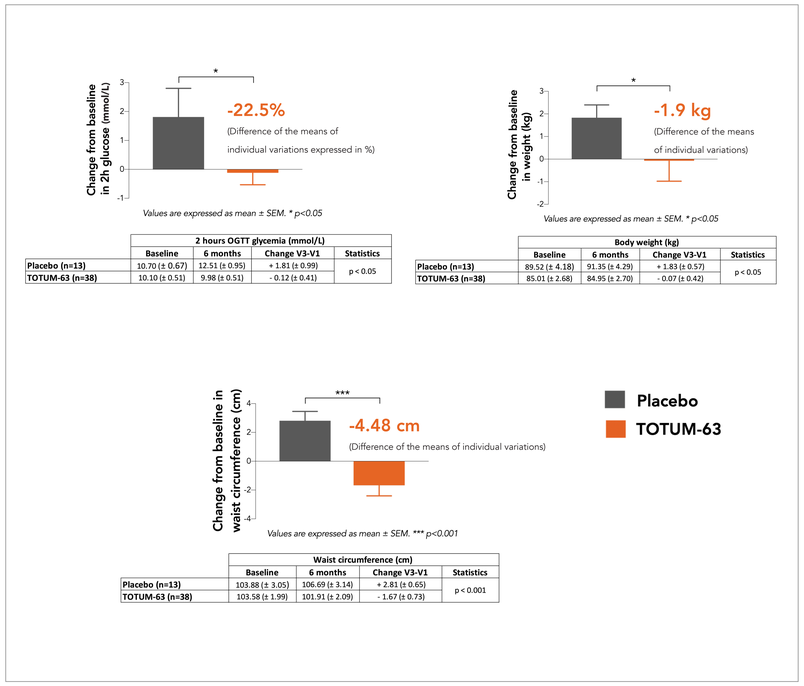
Primary endpoint reached: reduction in fasting glycemia *vs.* placebo, from baseline to 6 months.



*Values are expressed as mean ± SEM. * p<0.05*

	Fasting Glycemia (mmol/L)			
	Baseline	6 months	Change V3-V1	Statistics
Placebo (n=13)	7.00 (± 0.41)	7.47 (± 0.45)	+ 0.47 (± 0.25)	p < 0.05
TOTUM-63 (n=38)	6.90 (± 0.18)	6.66 (± 0.13)	- 0.24 (± 0.17)	

Main secondary endpoints: reduction in 2-hour OGTT glycemia, body weight and waist circumference *vs.* placebo, from baseline to 6 months.



*Values are expressed as mean ± SEM. * p<0.05*

	2 hours OGTT glycemia (mmol/L)			
	Baseline	6 months	Change V3-V1	Statistics
Placebo (n=13)	10.70 (± 0.67)	12.51 (± 0.95)	+ 1.81 (± 0.99)	p < 0.05
TOTUM-63 (n=38)	10.10 (± 0.51)	9.98 (± 0.51)	- 0.12 (± 0.41)	

*Values are expressed as mean ± SEM. * p<0.05*

	Body weight (kg)			
	Baseline	6 months	Change V3-V1	Statistics
Placebo (n=13)	89.52 (± 4.18)	91.35 (± 4.29)	+ 1.83 (± 0.57)	p < 0.05
TOTUM-63 (n=38)	85.01 (± 2.68)	84.95 (± 2.70)	- 0.07 (± 0.42)	

*Values are expressed as mean ± SEM. *** p<0.001*

	Waist circumference (cm)			
	Baseline	6 months	Change V3-V1	Statistics
Placebo (n=13)	103.88 (± 3.05)	106.69 (± 3.14)	+ 2.81 (± 0.65)	p < 0.001
TOTUM-63 (n=38)	103.58 (± 1.99)	101.91 (± 2.09)	- 1.67 (± 0.73)	

Results overview

	Placebo (n=13)						TOTUM-63 (n=38)						
	Baseline (V1)		6 months (V3)		V3-V1 Δ		Baseline (V1)		6 months (V3)		V3-V1 Δ		
Parameters	Mean	*SEM*	Mean	*SEM*	Mean Δ	*SEM*	Mean	*SEM*	Mean	*SEM*	Mean Δ	*SEM*	*p*
Fasting Glycemia	7.00	*0.41*	7.47	*0.45*	0.47	*0.25*	6.90	*0.18*	6.66	*0.13*	-0.24	*0.17*	*< 0.05*
Fasting Insulinemia	21.24	*5.41*	18.56	*3.75*	-2.68	*2.21*	20.96	*2.21*	18.83	*1.75*	-2.14	*2.27*	*NS*
HOMA-IR	7.40	*2.56*	6.45	*1.61*	-0.96	*1.07*	6.50	*0.76*	5.54	*0.52*	-0.97	*0.83*	*NS*
HbA1c	7.3	*0.2*	7.6	*0.3*	0.3	*0.1*	6.8	*0.1*	6.9	*0.1*	0.1	*0.1*	*NS*
2-hour OGTT glycemia	10.70	*0.67*	12.51	*0.95*	1.81	*0.99*	10.10	*0.51*	9.98	*0.51*	-0.12	*0.41*	*< 0.05*
Body weight	89.52	*4.18*	91.35	*4.29*	1.83	*0.57*	85.01	*2.68*	84.95	*2.70*	-0.07	*0.42*	*< 0.05*
BMI	33.25	*1.69*	33.93	*1.73*	0.68	*0.20*	30.60	*0.81*	30.59	*0.84*	-0.01	*0.15*	*< 0.05*
Waist Circumference	103.88	*3.05*	106.69	*3.14*	2.81	*0.65*	103.58	*1.99*	101.91	*2.09*	-1.67	*0.73*	*< 0.001*
Hip Circumference	113.00	*3.66*	113.77	*3.87*	0.77	*0.84*	107.01	*1.56*	107.08	*1.55*	0.07	*0.67*	*NS*
Fasting triglycerides	1.66	*0.20*	1.83	*0.19*	0.18	*0.17*	2.11	*0.15*	1.75	*0.16*	-0.36	*0.11*	*< 0.01*
Total Cholesterol	5.23	*0.30*	5.57	*0.33*	0.33	*0.26*	5.58	*0.15*	5.31	*0.14*	-0.27	*0.13*	*< 0.05*
LDL Cholesterol	3.22	*0.26*	3.43	*0.26*	0.21	*0.18*	3.46	*0.13*	3.28	*0.12*	-0.17	*0.10*	*< 0.05*
HDL cholesterol	1.24	*0.07*	1.29	*0.08*	0.05	*0.05*	1.14	*0.06*	1.22	*0.05*	0.05	*0.03*	*NS*
Free Fatty Acids	0.49	0.05	0.47	0.05	-0.02	0.05	0.56	0.03	0.46	0.03	-0.1	0.04	*NS*
SBP (mmHg)	131.92	*3.38*	139.46	*5.67*	7.54	*3.30*	130.76	*2.29*	127.74	*2.01*	-3.03	*1.66*	*< 0.01*
DBP (mmHg)	82.31	*4.20*	84.15	*3.22*	1.85	*1.96*	82.26	*1.52*	80.55	*1.20*	-1.71	*1.46*	*NS*

Safety outcomes

Adverse events		PLACEBO (n=15)		TOTUM-63 (n=51)	
		Subjects	Events	Subjects	Events
		n (%)	n	n (%)	n
All the adverse events		11 (73.3%)	19	31 (60.8%)	65
All serious adverse events		0 (0.0%)	0	1 (2.0%)	1
Intensity of the event	Mild	7 (46.7%)	7	15 (29.4%)	16
	Moderate	8 (53.3%)	8	27 (52.9%)	47
	Severe	2 (13.3%)	4	2 (3.9%)	2
Relationship with the research	Excluded	10 (66.7%)	17	27 (52.9%)	59
	Not excluded	2 (13.3%)	2	6 (11.8%)	6
Relationship with the study's product	Excluded	10 (66.7%)	18	27 (52.9%)	56
	Not excluded	1 (6.7%)	1	7 (13.7%)	9
Action taken on the study product	Not applicable	1 (6.7%)	1	10 (19.6%)	12
	No action	9 (60.0%)	16	27 (52.9%)	43
	Product definitively stopped	2 (13.3%)	2	4 (7.8%)	4
	Product interrupted	0 (0.0%)	0	3 (5.9%)	6
Evolution of adverse event	End of AE	11 (73.3%)	16	26 (51.0%)	54
	Evolution of the AE inducing a new AE	0 (0.0%)	0	2 (3.9%)	2
	Still in progress at the end of the study	2 (13.3%)	3	8 (15.7%)	9
Adverse events by body system	Cardiovascular	0 (0.0%)	0	3 (5.9%)	4
	Respiratory	2 (13.3%)	2	2 (3.9%)	2
	Gastrointestinal	2 (13.3%)	2	12 (23.5%)	14
	Neurologic / Psychiatric	2 (13.3%)	2	10 (19.6%)	15
	ENT	5 (33.3%)	5	11 (21.6%)	12
	Mucocutaneous	1 (6.7%)	1	1 (2.0%)	1
	Musculoskeletal	3 (20.0%)	5	8 (15.7%)	10
	Other	2 (13.3%)	2	6 (11.8%)	7

Serious adverse event recorded for TOTUM-63 subject was not tied to the product according to the investigator (tachychardia with chest pain).

10 adverse events whose relationship with study's product were not excluded, were gastro-intestinal disorders (abdominal pain, diarrhea or nausea).

No statistically significant difference between groups on the proportion of subjects with:
- Serious AE.
- Severe AEs.
- Moderate or severe AEs.
- AEs in relationship with research.
- AEs in relationship with the study's product.

CONCLUSION

- TOTUM-63 was very well tolerated and no change was observed in safety parameters (blood cell count, renal function, hepatic function).
- At the end of the supplementation period, FBG (primary endpoint) was reduced in TOTUM-63 group compared to placebo group (placebo-corrected difference from baseline: -9.3%, p<0.05).
- Similarly, 2-hour OGTT glycemia was improved in TOTUM-63 group, *vs.* placebo (placebo-corrected difference from pre-protocol value: -22.5%, p<0.05).
- Moreover, TOTUM-63 had a significant lowering effect on body weight (placebo-corrected difference from baseline: -1.9 Kg, p<0.05) and waist circumference (-4.5 cm, p<0.001).
- Furthermore, TOTUM-63 also improved lipid profile and reduced systolic blood pressure.

This randomized and double-blind placebo-controlled Phase II trial showed that TOTUM-63 contributed to lower fasting blood glucose in individuals with impaired fasting glycemia and glucose intolerance. Moreover, TOTUM-63 also improved many metabolic and anthropometric parameters often impaired in individuals living with prediabetes and T2D. This study opens the door to larger trials and makes TOTUM-63 a promising candidate for T2D risk prevention.

Disclosure: Sébastien PELTIER is CEO of VALBIOTIS. Vivien CHAVANELLE, Yolanda OTERO, Maxime BARGETTO, Murielle CAZAUBIEL and Pascal SIRVENT are employed by VALBIOTIS