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TOTUM-63 lowers fasting glycemia in subjects with prediabetes: a phase II clinical trial

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Disclosure

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

Context & objectives

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.

Method

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 hours OGTT glycemia, insulin sensitivity, anthropometric parameters, hemodynamic parameters, lipid profile, safety

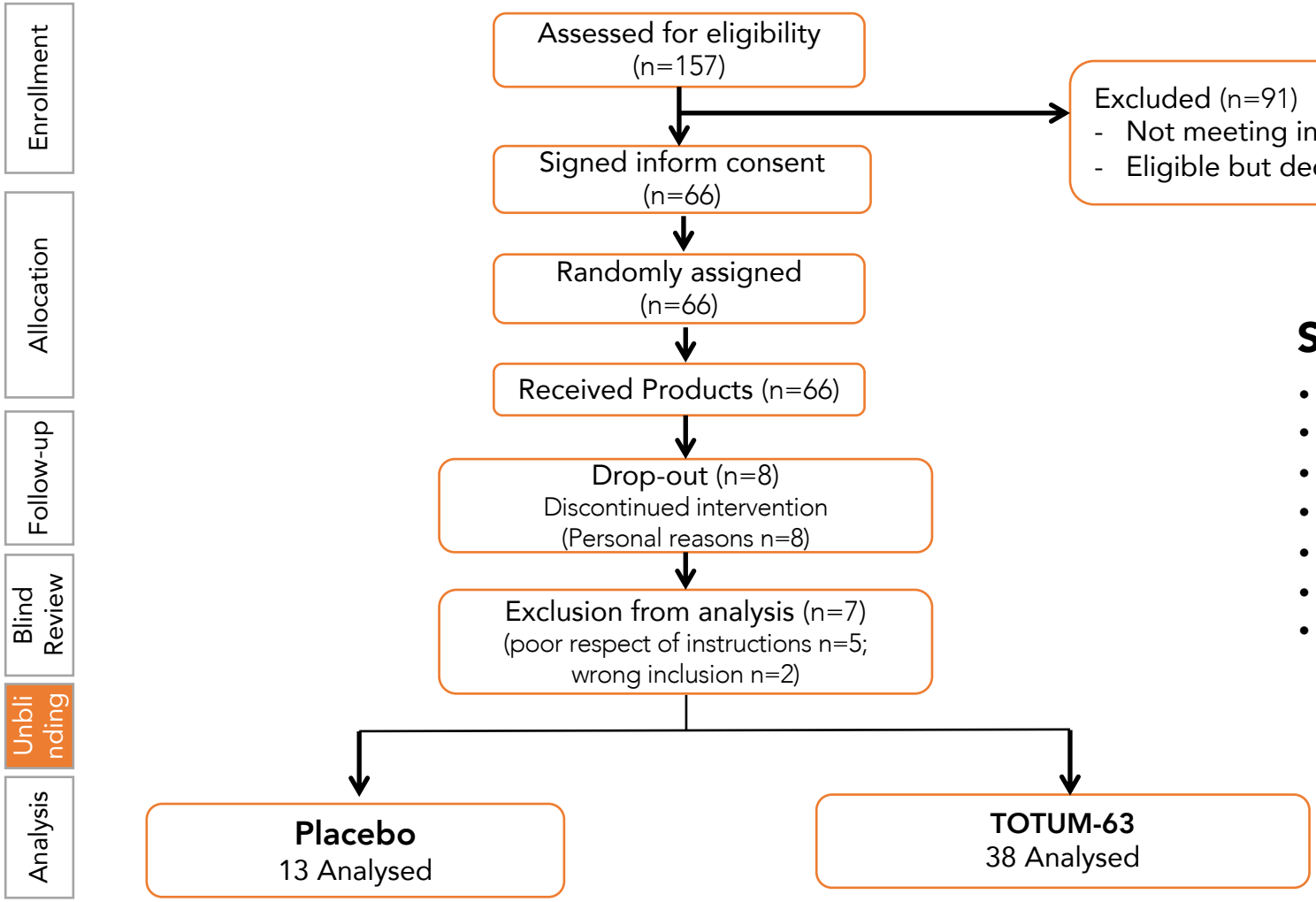
Statistics

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.

Main inclusion criteria

- Age between 35 and 75 years (limits included).
- Fasting glycemia > 6.1 mmol/L. (1.1g/L).
- 2 hours glycemia (OGTT) > 7.8 mmol/L (1.4g/L).
- HbA1c < 7%
- Waist circumference > 94 cm for men or > 80 cm for women.
- Triglyceridemia > 1.5 g/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).

Flow chart

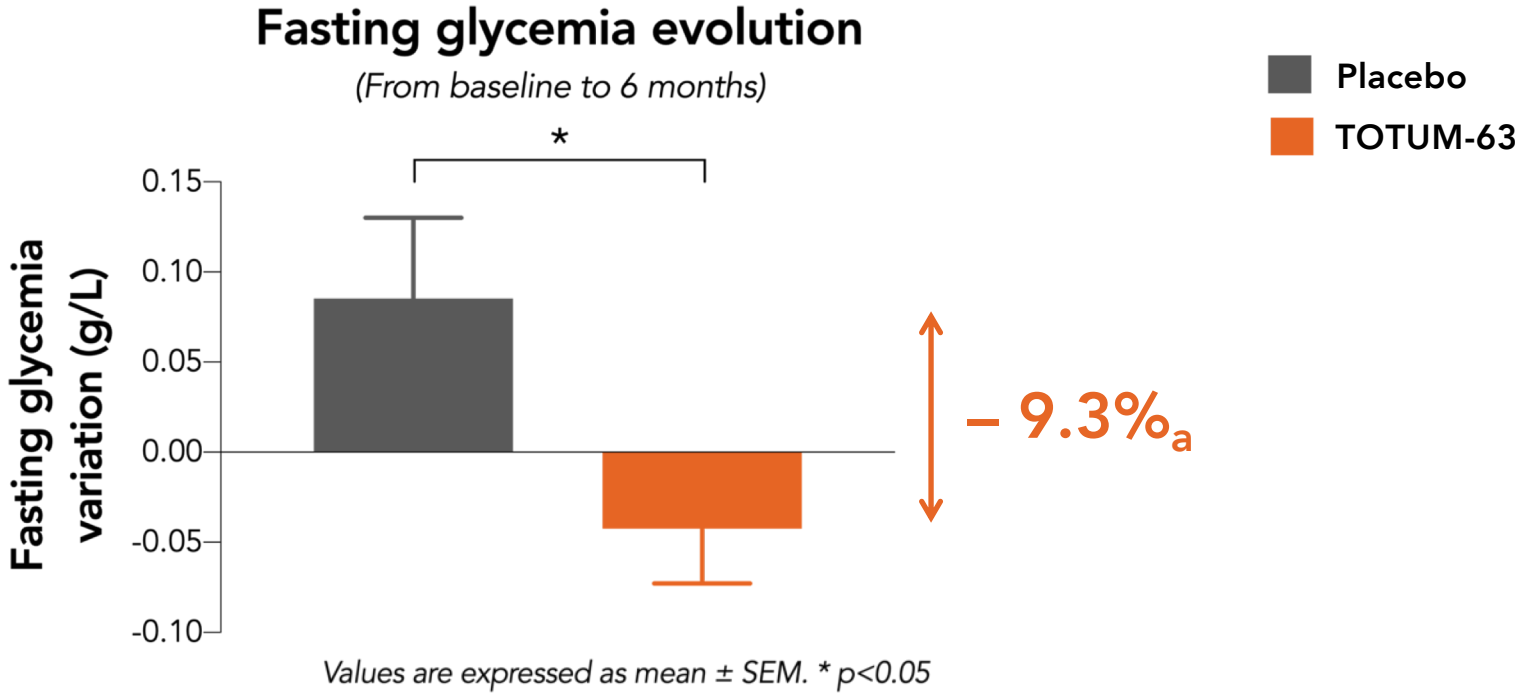


Study population at baseline

- **Age*:** 57.1 years (± 1.4)
- **Gender:** 35 female, 16 male
- **BMI*:** 31.3 kg/m^2 (± 0.8)
- **Fasting glycemia*:** 1.26 g/L (± 0.02)
- **2 hours OGTT glycemia*:** 1.85 g/L (± 0.08)
- **HbA1c*:** 6.0 % (± 0.6)
- **Fasting triglycerides*:** 1.78 g/L (± 0.10)

** Mean values ± SEM*

Primary endpoint reached: reduction in fasting glycemia *vs.* placebo



	Fasting glycaemia (g/L)				
	Baseline	3 months	6 months	Variation V3-V1	Statistics
Placebo (n=13)	1.26 (± 0.07)	1.22 (± 0.16)	1.35 (± 0.08)	+ 0.09 (± 0.04)	p < 0.05
TOTUM-63 (n=38)	1.24 (± 0.03)	1.24 (± 0.27)	1.20 (± 0.02)	- 0.04 (± 0.02)	

a Difference of means of individual variations

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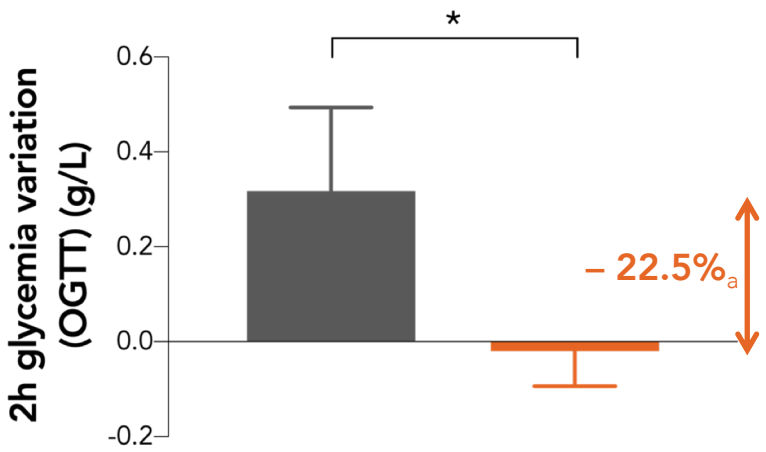
Main secondary endpoints: reduction in 2h OGTT glycemia, body weight and waist circumference *vs.* placebo

2h glycemia evolution (OGTT)

(From baseline to 6 months)

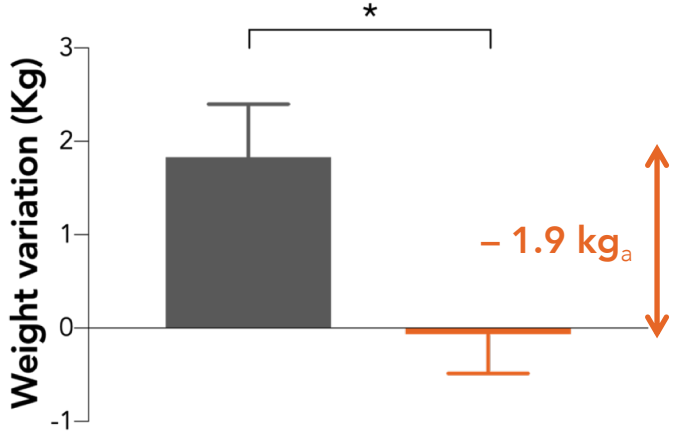


*Values are expressed as mean ± SEM. * p<0.05*

	2 hours OGTT glycemia (g/L)			
	Baseline	6 months	Variation V3-V1	Statistics
Placebo (n=13)	1.94 (± 0.12)	2.26 (± 0.17)	+ 0.32 (± 0.17)	p < 0.05
TOTUM-63 (n=38)	1.82 (± 0.09)	1.80 (± 0.09)	- 0.02 (± 0.07)	

Weight evolution

(From baseline to 6 months)

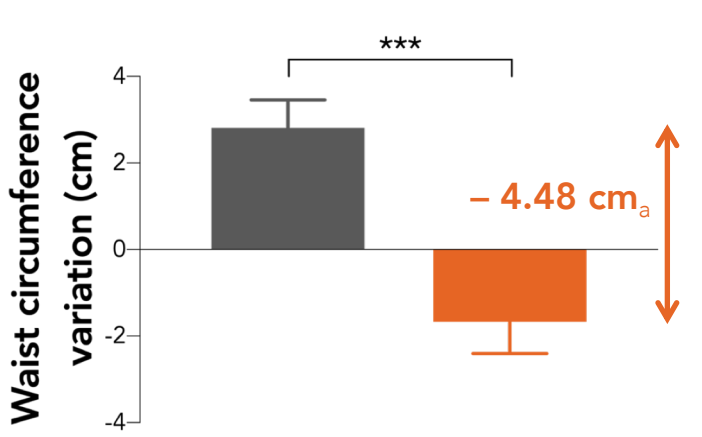


*Values are expressed as mean ± SEM. * p<0.05*

	Body weight (Kg)			
	Baseline	6 months	Variation 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)	

Waist circumference evolution

(From baseline to 6 months)



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

	Waist circumference (cm)			
	Baseline	6 months	Variation 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)	

Placebo TOTUM-63

a Difference of means of individual variations

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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	1.26	*0.07*	1.35	*0.08*	0.09	*0.04*	1.24	*0.03*	1.20	*0.02*	-0.04	*0.02*	*< 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	6.23	*0.13*	6.40	*0.19*	0.17	*0.10*	5.92	*0.08*	5.93	*0.09*	0.01	*0.05*	*NS*
2-hour OGTT glycemia	1.94	*0.12*	2.26	*0.17*	0.32	*0.17*	1.82	*0.09*	1.80	*0.09*	-0.02	*0.07*	*< 0.05*
Glucose iAUC	97.90	*9.50*	105.30	*8.67*	7.35	*9.33*	88.50	*5.32*	87.20	*4.85*	-0.16	*3.90*	*NS*
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	1.47	*0.18*	1.62	*0.17*	0.16	*0.15*	1.87	*0.13*	1.55	*0.14*	-0.31	*0.10*	*< 0.01*
Total Cholesterol	2.02	*0.11*	2.15	*0.13*	0.13	*0.10*	2.16	*0.06*	2.05	*0.05*	-0.10	*0.05*	*< 0.05*
LDL Cholesterol	1.25	*0.10*	1.33	*0.10*	0.08	*0.07*	1.34	*0.05*	1.27	*0.04*	-0.07	*0.04*	*< 0.05*
HDL cholesterol	0.48	*0.03*	0.50	*0.03*	0.02	*0.02*	0.44	*0.02*	0.47	*0.02*	0.02	*0.01*	*NS*
Free Fatty Acids	0.49	*0.05*	0.47	*0.05*	-0.02	*0.05*	0.56	*0.03*	0.46	*0.03*	-0.10	*0.04*	*NS*
SBP	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	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 n (%)	Events n	Subjects n (%)	Events 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

- Serious AE recorded for TOTUM-63 subject was not tied to the product according to the investigator (tachychardia with chest pain).
- 10 AEs whose relationship with study's product were not excluded, were Gastrointestinal disorders (abdominal pain, diarrhea or nausea).

No statistically significant difference between groups on the proportion of subjects with:

- Serious AE (p=1.00)
- Severe AEs (p=0.22)
- Moderate or severe AEs (p=0.63)
- AEs in relationship with research (p=1.00)
- AEs in relationship with the study's product (p=0.67)

Conclusion

- TOTUM-63 **was very well tolerated** and no change was observed in safety parameters (blood cell count, renal function, hepatic function, hemodynamics).
- 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: -1.9Kg; $p<0.05$) **and waist circumference** (-4.5cm; $p<0.001$).
- 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 FBG 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.

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