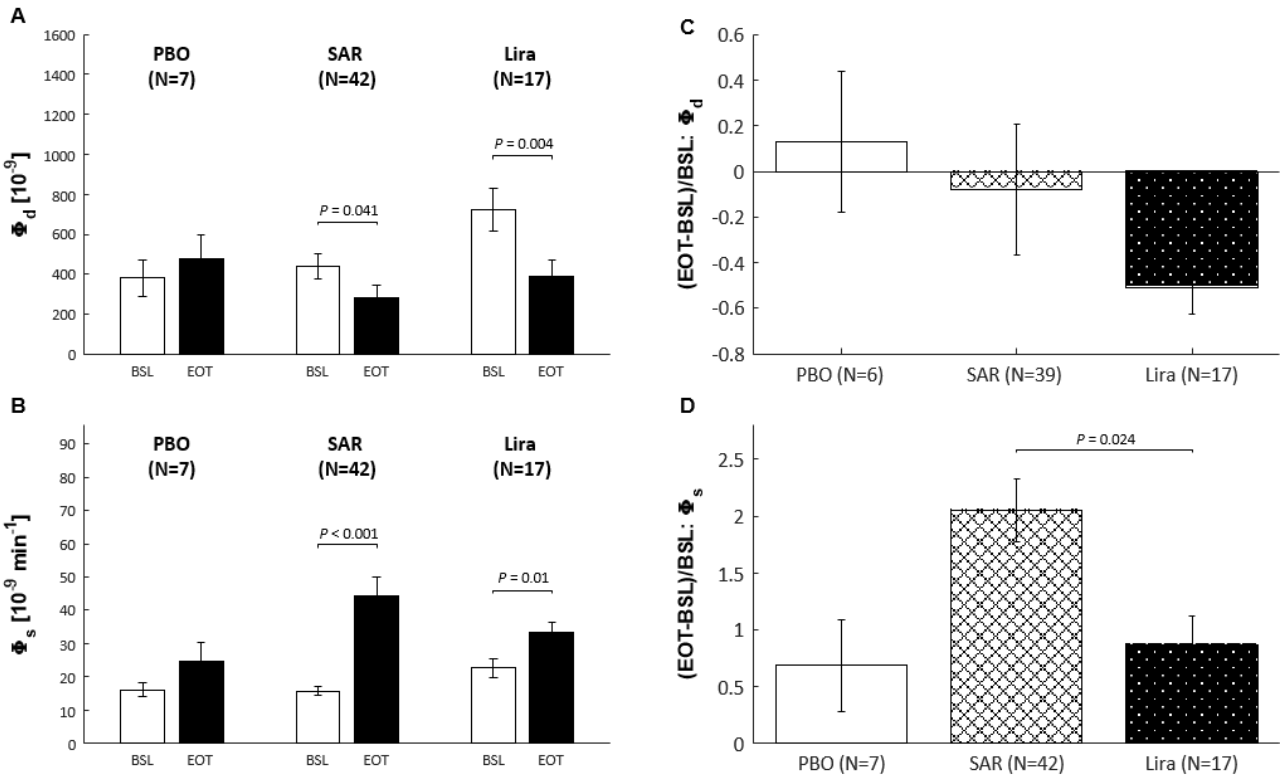
SUPPLEMENTARY TABLE I
SUBJECTS' DEMOGRAPHICS

VARIABLE	VISIT	COHORT				
		PBO (N=7)	***SAR 0.12 mg (N=21)***	***SAR 0.16 mg (N=15)***	***SAR 0.20 mg (N=10)***	***Lira 1.80 mg (N=17)***
BW [kg]	BSL	89.7 [83.2, 103.9]	91.5 [83.5, 108.1]	95.3 [84.4, 114.3]	92.9 [81.5, 112.1]	103.9 [83.1, 120.5]
	EOT	87.4 [81.6, 97.8]	89.9 [76.2, 103.4]	90.4 [81.3, 100.8]	88.9 [73.0, 102.0]	98.0 [81.0, 112.1]
	p-value	*0.031*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*
BMI [kg/m^2]	BSL	33.8 [29.0, 35.3]	32.1 [30.2, 36.4]	33.5 [32.1, 38.1]	32.2 [29.6, 35.1]	34.8 [28.5, 39.9]
	EOT	33.6 [28.4, 34.6]	31.2 [27.9, 34.8]	32.2 [30.2, 33.8]	30.0 [28.1, 34.9]	33.0 [28.9, 37.7]
	p-value	*NS*	*< 0.001*	*< 0.001*	*0.002*	*< 0.001*
HbA1c [%]	BSL	8.3 [7.6, 9.3]	8.0 [7.4, 8.4]	8.1 [7.7, 8.8]	8.2 [7.4, 10.0]	8.0 [7.7, 8.5]
	EOT	7.1 [6.9, 8.4]	6.2 [5.7, 6.6]	6.4 [6.0, 7.0]	6.0 [5.7, 7.1]	6.6 [6.0, 7.0]
	p-value	*0.021*	*< 0.001*	*< 0.001*	*< 0.001*	*< 0.001*

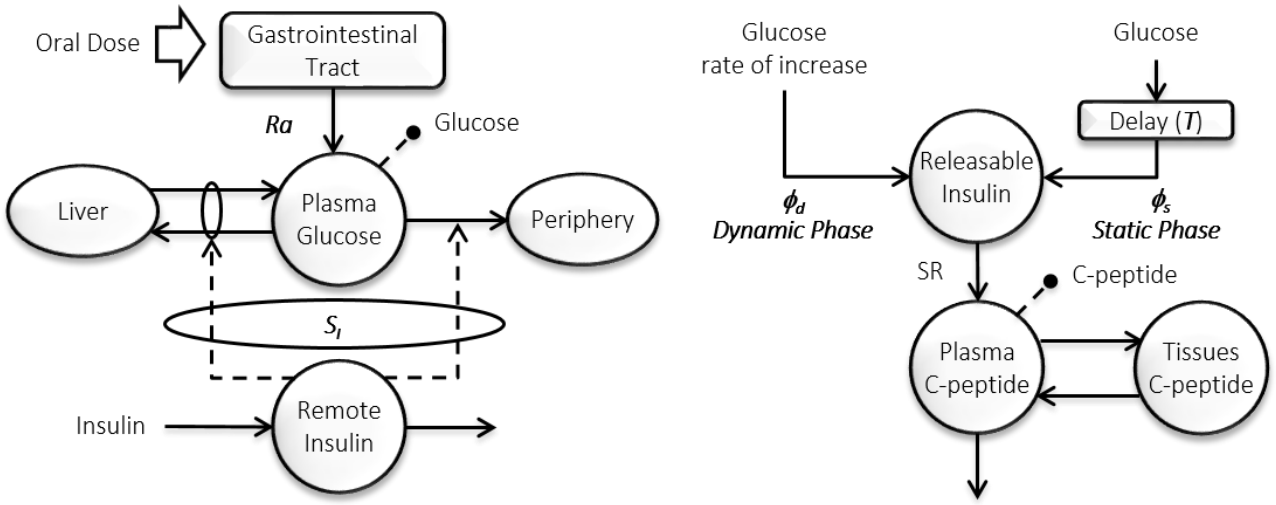
Supplementary Table I. Median [25th, 75th] percentile of body weight (BW), body mass index (BMI) and HbA1c. For each cohort and metrics, comparison was performed between Baseline (BSL) vs. End of Treatment (EOT) visits based on parameters' distribution: paired t-test for normally distributed values, Wilcoxon Signed-Rank test otherwise (p-value<0.05 was considered statistically significant).



Supplementary Figure 1. Mean ± standard error (SE) of dynamic and static β-cell responsiveness (Φ_d, and Φ_s, panels A and B respectively) and the respective percent deviation between BSL vs. EOT values, i.e. (EOT – BSL)/BSL, (panels C and D respectively). Comparison between BSL vs. EOT was performed using paired T-test, for normally distributed variables, and Wilcoxon Signed-Rank test otherwise (p-value<0.05 was considered statistically significant). Comparison between cohorts was performed by one-way analysis of variance (ANOVA) followed by post-hoc analysis using Tukey-Kramer correction for multiple comparisons, for normally distributed variables, and Kruskall-Wallis test followed by post-hoc analysis using Dunn-Sidak correction for multiple comparisons otherwise (p-value<0.05 was considered statistically significant).

The Oral Minimal Model Method

The oral minimal model (OMM) method (1)(2)(3), which combines the so-called oral glucose (2) and C-peptide minimal models **Error! Reference source not found.**, was used to assess insulin action, β-cell function and gastro-intestinal glucose absorption during the meal from postprandial glucose, insulin and C-peptide data.



Supplementary Fig. 2: The oral glucose (left) and C-peptide (right) minimal models (adapted from (1)).

The oral glucose minimal model (1) describes plasma glucose dynamics using plasma insulin concentration and carbohydrates content of the meal as known inputs and provides an estimate of insulin sensitivity (S_I), a parameter quantifying the ability of insulin to suppress endogenous glucose production and promote glucose disposal, as well as an estimate of the time profile of meal glucose rate of appearance (Ra) (2). In particular, such parameters are simultaneously estimated (S_I and time profile of Ra), thus allowing to intrinsically account for any changes in the time profile of Ra on SI estimation. In this model, Ra is described as a piecewise linear function (Eq. S.1) with known breakpoint t_i, and unknown amplitude α_i:

$$Ra(\alpha, t) = \begin{cases} \alpha_{i-1} + \dfrac{\alpha_i - \alpha_{i-1}}{t_i - t_{i-1}} \cdot (t_i - t_{i-1}) & for\ t_{i-1} \le t \le t_i \\ 0 & otherwise \end{cases} \quad \text{(S.1)}$$

As reported in the manuscript, here we assumed that the meal is completely absorbed within 360 min (t_{end} = *360 min*) as done in (4)(5). In addition, to better quantify the potential effect of the drug on meal glucose absorption, the AUC of model predicted Ra in the first 120 min after meal ingestion, normalized by the total orally absorbed glucose, was calculated (AUC($Ra_{0\text{-}120}$)).

The C-peptide minimal model (3) describes the plasma C-peptide concentration in relation to the observed changes in glucose concentration and provides an estimate of the overall beta-cell responsivity to glucose (Φ_{tot}). Specifically, such index is given by a combination of two components: the dynamic ($\Phi_{dynamic}$) and static (Φ_{static}) responsivity indices. In particular, $\Phi_{dynamic}$ quantifies the secretion of promptly releasable insulin and is assumed to be stimulated by the rate of increase in glucose concentration; while Φ_{static} quantifies the delayed, by a time constant T, provision of new releasable insulin above a certain threshold level (h). This is given by (Eq. S.2):

$$\phi_{tot} = \phi_s + \frac{\phi_d \cdot (G_{max} - G_b)}{\int_0^{\tau} (G(t) - h) dt} \quad \text{(S.2)}$$

where G_{max} (mg/dL) is the maximum glucose concentration value achieved during the experiment, h the threshold level is here fixed, as done in (8), to pre-meal (basal) glucose level (G_b) and τ (min) is the time at which the system is assumed to return to steady-state conditions after the perturbation (here assumed τ = 300 min). In addition, to complete the picture of β-cell responsivity, the index of basal beta-cell responsivity (Φ_b) was also calculated, from fasting plasma C-peptide and glucose data, as the ratio of basal secretion per unit basal glucose concentration **Error! Reference source not found.**.

Finally, the disposition index (DI), defined as $\Phi_{tot} \times S_I$, was calculated to evaluate β-cell function in light of the prevailing S_I (6)(7).

References

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