

Table S1: Summary of demographics by treatment sequence

Parameters	Statistics	Cohort 1						Cohort 2		
		DABC	DACB	DBAC	DBCA	DCAB	Total	EF	FE	Total
N		4	4	4	4	4	24	12	12	24
Gender	Female n (%)	3(75.00)	3(75.00)	2(50.00)	2(50.00)	2(50.00)	12(50.00)	6(50.00)	6(50.00)	12(50.00)
	Male n (%)	1(25.00)	1(25.00)	2(50.00)	2(50.00)	2(50.00)	12(50.00)	6(50.00)	6(50.00)	12(50.00)
Age (Years)	Mean(±SD)	42.50(± 9.04)	48.50(± 4.43)	44.00(± 5.35)	33.25(± 10.31)	43.25(± 13.60)	41.25(± 10.02)	37.33(± 9.21)	36.58(± 11.69)	36.96(± 10.30)
	Median	43.00	49.00	43.50	30.50	49.00	43.50	37.50	35.50	37.50
	Min, Max	31.00, 53.00	43.00, 53.00	39.00, 50.00	24.00, 48.00	23.00, 52.00	23.00, 53.00	25.00, 53.00	24.00, 51.00	24.00, 53.00
BMI (Kg/M²)	Mean(±SD)	28.40(± 2.62)	29.53(± 1.79)	27.83(± 3.88)	28.43(± 3.08)	27.83(± 1.34)	28.93(± 2.77)	27.81(± 4.23)	26.73(± 3.54)	27.27(± 3.85)
	Median	29.30	29.30	26.80	28.95	27.55	28.50	27.80	26.55	27.05
	Min, Max	24.70, 30.30	27.70, 31.80	24.40, 33.30	24.50, 31.30	26.60, 29.60	24.40, 34.90	21.50, 34.00	20.60, 31.90	20.60, 34.00
Height (Cm)	Mean(±SD)	160.78(± 4.90)	162.88(± 12.40)	166.40(± 9.61)	169.75(± 5.32)	159.00(± 10.10)	164.06(± 9.04)	165.97(± 8.64)	164.56(± 10.19)	165.26(± 9.27)
	Median	160.00	163.75	168.25	170.00	158.50	164.25	163.50	165.00	163.50
	Min, Max	156.00, 167.10	149.00, 175.00	154.10, 175.00	163.00, 176.00	149.00, 170.00	149.00, 181.20	152.40, 183.00	149.00, 178.00	149.00, 183.00
Weight (Kg)	Mean(±SD)	73.50(± 8.55)	79.13(± 16.56)	77.10(± 12.20)	81.85(± 9.66)	70.32(± 5.92)	78.05(± 10.97)	77.09(± 16.04)	72.11(± 9.42)	74.60(± 13.11)
	Median	72.35	78.85	78.80	81.25	69.70	77.35	76.75	75.40	76.05
	Min, Max	64.80, 84.50	61.40, 97.40	61.80, 89.00	70.80, 94.10	64.90, 77.00	61.40, 97.40	52.40, 113.00	57.80, 83.60	52.40, 113.00

Treatment A – metformin (2 g) was administered with breakfast 20 min after one insulin tregopil (10 mg) tablet Treatment B – metformin (2 g) was administered with breakfast 20 min after 1 placebo tablet

Treatment C – metformin (2 g) was administered with breakfast 20 min after 3 placebo tablets

Treatment D – metformin (2 g) was administered with breakfast

Treatment E – metformin (2 g) was administered in fasting condition 20 min before breakfast

Treatment F – 3 placebo tablets and metformin (2 g) were administered in fasting condition 20 min before breakfast.