EFFECTS OF EARLY USE OF DUAL THERAPY OF DAPAGLIFLOZIN WITH METFORMIN ON GLYCEMIC VARIABILITY IN MEXICAN PATIENTS WITH TYPE 2 DIABETES MELLITUS. AN OPEN-LABEL RANDOMIZED CLINICAL TRIAL.

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Statistical Analysis Plan

The sample size was determined using the mean difference formula: n = (Zα / 2 + Zß) 2 * 2 * σ2 / d2 a reduction in GV was estimated from 4.85 to 2.2 with an expected standard deviation of 2.8 in the MAGE index according to RR. Henry et al. [19]with an alpha value of 0.05 and a power of 0.80, resulting in a sample size of 88 subjects, with 44 subjects in each treatment group.

Patient recruitment began in October 2019 and was interrupted due to the SARS-COV-2 pandemic in March 2020. Nevertheless, patients who were already enrolled were followed up. Recruitment was normally restarted in March 2021; one of the inclusion criteria was adjusted, allowing HbA1c <13.0%, prior limit <12.0%. The last patient was recruited on December 6th, 2021.The complete study was concluded in March 2021.

A total of 88 patients met the selection criteria, signed the informed consent, and were randomized 1:1 on www.randomization.com (complete list of it is showed as supplementary material) to receive daily either DAPA 10 mg + MET 2000mg or MET 2000mg for 12 weeks. Both groups were monitored for GV using a CGM system for 7 days at baseline (W0) and on week 12 (W12).

Pre-randomization: patients were given 2000mg of MET daily for two weeks, only patients who tolerated this dose were included in the study and a treatment was randomly assigned.

Treatment: subjects who met the pre-randomization period and tolerated treatment were randomized 1:1 to receive either DAPA 10 mg/day + MET 2000 mg/day or MET 2000 mg/day for 12 weeks.

Of the total of 264 patients surveyed, a sample of 88 met the inclusion criteria and none of the exclusion criteria randomization DAPA+MET n=42 and MET n= 46. During the study, 7 patients discontinued (DAPA+MET n=1 and MET n=6). 80 patients concluded the study for 12 weeks (DAPA+MET n=41 and MET n=39). One patient was removed from the study (MET n=1) because he did not comply his medication intake nor the instructions during CGM. Study flowchart is displayed in Figure 1.

The baseline characteristics were, the age [53.7 ±8.6 years DAPA+MET versus 50.9± 11.8 years MET; p=0.2], TIR% Target: 70-180 mg/dL [55.5% (12.6-80.6) DAPA+MET versus 82.7%(26.1-95.1) MET; p=0.02], BMI [30.9±6.9 kg/m2 DAPA+MET versus 30.1± 3.2 MET; p=0.24], glucose [202.4 ±70.5 mg/dL DAPA+MET) versus 179.0± 62.9 mg/dL MET; p=0.11], insulin [12.2 ± 13.3 µU/mL DAPA+MET versus 10.9 ± 6.6 µU/mL MET; p=0.57]. Complete baseline characteristics of the subjects included are summarized in Table 1.

All the measurements were carried out fasting. Student's T test was performed for normal variables to obtain significance. Skewed distribution variables are expressed with median and interquartile values of 25% and 75%, significance for these variables was obtained with the Mann Whitney U test.