

SUPPLEMENT 1:

Stereoselective bioanalysis of carvedilol and its metabolites

Plasma samples were analysed for carvedilol enantiomers and their metabolites using a previously validated high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS) method ([Nardotto et al., 2016](#)). The metabolites 5OHC and 4OHC were analysed together as (R)-(+)-OHC and (S)-(-)-OHC because the method was not able to separate the two moieties. The lower limits of quantification for carvedilol, OHC and DMC were 0.05, 0.05 and 0.02 ng/mL, respectively. The coefficients of variation obtained in the study of inter- and intra-assay precision and accuracy were less than 15%. Quality control samples (low, medium and high analyte concentrations) were analysed with each batch of samples and calibration standards.

Reference:

Nardotto, G.H.B., Coelho, E.B., Marques, M.P., Lanchote, V.L., 2016. Chiral analysis of carvedilol and its metabolites hydroxyphenyl carvedilol and O-desmethyl carvedilol in human plasma by liquid chromatography-tandem mass spectrometry: Application to a clinical pharmacokinetic study. *J. Chromatogr. B* 1015–1016, 173–180.

Table S1: Summary of the baseline clinical biochemistry and demographic characteristics of the subjects enrolled into the clinical study.

| | Healthy subjects (n=13) | | | T2DM patients (n=14) | | |
|--------------------------------------|-------------------------|--------|------------------|----------------------|--------|------------------|
| | 25 th | median | 75 th | 25 th | median | 75 th |
| Creatinine clearance (μmol/L) | 97.9 | 102.2 | 104.0 | 86.4 | 90.6 | 100.6 |
| Microalbuminuria per litter (mg/L) | 4.5 | 10.6 | 15.6 | 10.1 | 12.8 | 15.5 |
| Microalbuminuria per minute (μg/min) | 5.6 | 6.8 | 8.1 | 1.7 | 6.3 | 9.5 |
| Total Bilirubin (mg/dL) | 0.4 | 0.5 | 0.6 | 0.40 | 0.5 | 0.7 |
| Direct bilirubin (mg/dL) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.2 |
| Indirect bilirubin (mg/dL) | 0.3 | 0.4 | 0.5 | 0.3 | 0.3 | 0.5 |
| HbA1c (%) | 5.3 | 5.4 | 6.2 | 6.4 | 6.7 | 6.8 |
| Na (mmol/L) | 139.0 | 139.9 | 140.5 | 136.2 | 136.8 | 139.0 |
| K (mmol/L) | 4.1 | 4.4 | 4.5 | 3.9 | 4.5 | 4.8 |
| Gama GT (U/L) | 23.0 | 24.0 | 41.0 | 22.0 | 25.0 | 42.0 |
| Fasten glucose (mg/dL) | 89.0 | 90.0 | 94.0 | 118.0 | 119.5 | 122.8 |
| TGP (U/L) | 22.1 | 30.2 | 33.0 | 19.0 | 26.0 | 28.9 |
| TGO (U/L) | 19.0 | 23.0 | 30.0 | 16.0 | 18.0 | 24.0 |
| Urea (mg/dL) | 28.0 | 31.0 | 35.0 | 22.0 | 24.0 | 32.7 |

| | | | | | | |
|-----------------------------|-------|-------|-------|-------|-------|-------|
| Cholesterol (mg/dL) | 170.0 | 183.0 | 211.0 | 130.0 | 177.0 | 183.0 |
| Triglycerides (mg/dL) | 100.0 | 130.0 | 140.0 | 132.0 | 142.0 | 149.0 |
| HDL (mg/dL) | 39.0 | 46.0 | 47.0 | 28.0 | 35.0 | 42.0 |
| LDL (mg/dL) | 97.0 | 110.0 | 136.0 | 69.7 | 98.5 | 111.5 |
| Weight (kg) | 66.6 | 69.2 | 72.5 | 64.9 | 71.1 | 75.3 |
| BMI (kg/m ²) | 24.8 | 25.4 | 26.1 | 25.3 | 26.4 | 27.3 |