

Supplementary Table S1. Additional metabolic characteristics of the study subjects before starting Lumacaftor/Ivacaftor and after 12-18 months of treatment. Data are expressed as mean (standard deviation) or median (IQR), unless otherwise specified. Abbreviations: *HbA1c* glycated haemoglobin; *PG* plasma glucose; *min* minutes; *PI* plasma insulin; *CP* C-peptide; *IGI* Insulinogenic Index; *DI* Disposition Index; *HOMA-IR* Homeostasis model assessment insulin resistance.

| Variables | Baseline | After 12-18 months of Lumacaftor/Ivacaftor | <i>p</i> |
|----------------------------|--|--|--------------|
| HbA1c (% , mmol/mol) | 5.8 (5.3 – 6.1), 39.5 (37.2 – 42.5) | 5.6 (5.4 – 5.9), 38.0 (36.2 – 40.5) | 0.59 |
| Fasting PG (mg/dL, mmol/L) | 81.5 [77.5 – 87.8], 4.52 [4.29 – 4.86] | 89.0 [82.5 – 94.8], 4.94 [4.57 – 5.25] | 0.032 |
| 30 min PG (mg/dL, mmol/L) | 132.0 [123.0 – 157.8], 7.32 [6.82 – 8.75] | 146.0 [132.6 – 154.0], 8.10 [7.37 – 8.55] | 0.71 |
| 60 min PG (mg/dL, mmol/L) | 159.0 [133.3–187.8], 8.82 [7.39 – 10.42] | 183.0 [156.8 – 207.8], 10.15 [8.70 – 11.53] | 0.45 |
| 90 min PG (mg/dL, mmol/L) | 138.0 [119.0 –196.0], 7.66 [6.60 – 10.88] | 149.0 [131.8 – 165.5], 8.27 [7.31 – 9.18] | 0.87 |
| 120 min PG (mg/dL, mmol/L) | 121.0 [105.0 – 157.5], 6.71 [5.83 – 8.74] | 125.0 [108.3 – 143.3], 6.94 [6.05 – 7.95] | 0.69 |
| Fasting PI (pmol/L) | 37.2 [24.3 – 75.2] | 49.0 [29.0 – 58.0] | 0.87 |
| 30 min PI(pmol/L) | 132.3 [97.7 – 249.8] | 169.5 [140.8 – 266.9] | 0.68 |
| 60 min PI (pmol/L) | 258.0 [193.8 – 393.4] | 315.0 [210.8 – 513.4] | 0.57 |
| 90 min PI (pmol/L) | 379.2 [189.0 – 472.4] | 391.7 [273.1 – 500.6] | 0.50 |
| 120 min PI(pmol/L) | 263.9 [126.4 – 533.0] | 274.3 [224.7 – 412.9] | 0.75 |
| Fasting CP (nmol/L) | 0.37 [0.21 – 0.59] | 0.37 [0.31 – 0.50] | 0.97 |
| 30 min CP (nmol/L) | 1.11 [0.54 – 2.08] | 1.08 [0.83 – 1.30] | 0.82 |
| 60 min CP (nmol/L) | 1.78[1.12 – 3.01] | 2.05 [1.39 – 2.47] | 0.97 |
| 90 min CP (nmol/L) | 2.25 [1.70 – 2.99] | 2.29 [1.97 – 2.87] | 0.24 |
| 120 min CP (nmol/L) | 2.18 [1.30 – 3.64] | 2.38 [1.80 – 3.02] | 0.68 |
| IGI | 0.29 [0.21 – 0.42] | 0.31 [0.24 – 0.56] | 0.75 |
| DI | 2.40 [1.78 – 3.16] | 1.88 [1.41 – 3.17] | 0.60 |
| HOMA-IR | 1.07 [0.68 – 2.00] | 1.43 [0.98 – 1.99] | 0.60 |
| Matsuda Index | 7.88 [4.20 – 11.02] | 5.46 [3.98 – 6.98] | 0.25 |

Supplementary Table S2. Additional metabolic characteristics of the study subjects before starting Exacaftor/Ivacaftor/Tezacaftor therapy and after 12-18 months of treatment. Data are expressed as mean (standard deviation) or median [IQR], unless otherwise specified. Abbreviations: *HbA1c* glycated haemoglobin; *PG* plasma glucose; *min* minutes; *PI* plasma insulin; *CP* C-peptide; *IGI* Insulinogenic Index; *DI* Disposition Index; *HOMA-IR* Homeostasis model assessment insulin resistance.

| Variables | Baseline | After 12-18 months of Exacaftor/Ivacaftor/Tezacaftor | P |
|----------------------------|--|---|-------------|
| HbA1c (% , mmol/mol) | 5.8 [5.2-6.6], 40.0 [33.0-48.5] | 5.4 [4.8 – 5.8], 36.0 [29.5-40.0] | 0.04 |
| Fasting PG (mg/dL, mmol/L) | 84.0 [71.50 – 104.0], 4.66 [3.97-5.77] | 90.0 [86.5-103], 4.99 [4.80-5.72] | 0.50 |
| 30 min PG (mg/dL, mmol/L) | 161.0 [130.0-217.5], 8.94 [7.22-12.07] | 180.00 [146.0-209.0], 9.99 [8.10-11.60] | 0.59 |
| 60 min PG (mg/dL, mmol/L) | 221.0 [129.0-261.5], 12.27 [7.16-14.52] | 183.0 [149.5-246.0], 10.16 [8.30-13.66] | 0.69 |
| 90 min PG (mg/dL, mmol/L) | 181.0 [104.0-238.5], 10.05 [5.77-13.24] | 189.0 [130.0-227.5], 10.49 [7.22-16.62] | 0.69 |
| 120 min PG (mg/dL, mmol/L) | 133.00 [103.0-202.0], 7.38 [5.72-11.21] | 142.00 [111.0-182.5], 7.88 [6.16-10.13] | 0.89 |
| Fasting PI (pmol/L) | 34.73 [16.67-75.35] | 46.53 [24.31-75.35] | 0.69 |
| 30 min PI (pmol/L) | 214.6 [111.5-339.6] | 275.0 [174.3-284.4] | 0.69 |
| 60 min PI (pmol/L) | 323.6 [171.5-704.6] | 323.6 [214.6-677.1] | 1.00 |
| 90 min PI (pmol/L) | 316.7 [181.3-509.8] | 397.3 [284.8-771.2] | 0.23 |
| 120 min PI (pmol/L) | 310.4 [236.1-443.1] | 425.7 [238.2-594.8] | 0.14 |
| Fasting CP (nmol/L) | 0.34 [0.30-0.54] | 0.49 [0.42-0.55] | 0.35 |
| 30 min CP (nmol/L) | 1.12 [0.65-1.50] | 1.26 [0.86-1.81] | 0.08 |
| 60 min CP (nmol/L) | 2.00 [1.07-3.26] | 2.30 [1.46-2.89] | 0.69 |
| 90 min CP (nmol/L) | 1.67 [1.56-3.19] | 2.42 [1.76-3.85] | 0.23 |
| 120 min CP (nmol/L) | 1.92 [1.67-3.13] | 2.85 [2.06-3.12] | 0.5 |
| IGI | 0.25 [0.13-0.62] | 0.33 [0.31-0.34] | 0.15 |
| DI | 1.22 [0.36-4.48] | 2.64 [1.05-4.49] | 0.72 |
| HOMA-IR | 2.10 [0.45-5.40] | 1.40 [0.75-2.70] | 0.50 |
| Matsuda Index | 4.88 [3.54-7.95] | 8.14 [3.15-14.51] | 0.47 |