

SUPPLEMENTARY DATA

Supplementary Table 1. Baseline Demographics and Disease Characteristics^{*}

| Characteristic | GLIM (n = 482) | CANA 100 mg (n = 483) | CANA 300 mg (n = 485) | Total (N = 1,450) |
|------------------------------------|-----------------------------|----------------------------------|----------------------------------|------------------------------|
| Age, years | 56.3 ± 9.0 | 56.4 ± 9.5 | 55.8 ± 9.2 | 56.2 ± 9.2 |
| Sex, n (%) | | | | |
| Male | 263 (54.6) | 252 (52.2) | 241 (49.7) | 756 (52.1) |
| Female | 219 (45.4) | 231 (47.8) | 244 (50.3) | 694 (47.9) |
| Race, n (%) [†] | | | | |
| White | 322 (66.8) | 323 (66.9) | 333 (68.7) | 978 (67.4) |
| Black or African American | 22 (4.6) | 20 (4.1) | 18 (3.7) | 60 (4.1) |
| Asian | 93 (19.3) | 99 (20.5) | 93 (19.2) | 285 (19.7) |
| Other [‡] | 45 (9.3) | 41 (8.5) | 41 (8.5) | 127 (8.8) |
| Ethnicity, n (%) | | | | |
| Hispanic or Latino | 76 (15.8) | 86 (17.8) | 80 (16.5) | 242 (16.7) |
| Not Hispanic or Latino | 403 (83.6) | 395 (81.8) | 404 (83.3) | 1,202 (82.9) |
| Other [§] | 3 (0.6) | 2 (0.4) | 1 (0.2) | 6 (0.4) |
| A1C, % (mmol/mol) | 7.8 ± 0.8 (62 ± 8.7) | 7.8 ± 0.8 (62 ± 8.7) | 7.8 ± 0.8 (62 ± 8.7) | 7.8 ± 0.8 (62 ± 8.7) |
| FPG, mmol/L (mg/dL) | 9.2 ± 2.1 (165.8 ± 37.8) | 9.2 ± 2.1 (165.8 ± 37.8) | 9.1 ± 2.0 (164.0 ± 36.0) | 9.2 ± 2.1 (165.8 ± 37.8) |
| Body weight, kg | 86.5 ± 19.8 | 86.9 ± 20.1 | 86.6 ± 19.5 | 86.6 ± 19.8 |
| BMI, kg/m ² | 30.9 ± 5.5 | 31.0 ± 5.3 | 31.2 ± 5.4 | 31.0 ± 5.4 |
| eGFR, mL/min/1.73 m ² | 89.5 ± 17.5 | 89.7 ± 19.3 | 91.4 ± 19.4 | 90.2 ± 18.7 |
| Duration of type 2 diabetes, years | 6.6 ± 5.0 | 6.5 ± 5.5 | 6.7 ± 5.5 | 6.6 ± 5.3 |

GLIM, glimepiride; CANA, canagliflozin; FPG, fasting plasma glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation.

^{*}Data are mean ± SD unless otherwise indicated.

[†]Percentages may not total 100.0% due to rounding.

[‡]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, and other.

[§]Includes not reported and unknown.

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Supplementary Table 2. Summary of Changes From Baseline in Blood Pressure and Fasting Plasma Lipids at Week 104 (LOCF)

| Parameter | GLIM | CANA 100 mg | CANA 300 mg |
|-------------------------------------|---------------------------|---------------------------|---------------------------|
| Systolic BP, n | 480 | 480 | 480 |
| Mean ± SD baseline, mmHg | 129.5 ± 13.5 | 130.0 ± 12.4 | 130.0 ± 13.8 |
| LS mean ± SE change | 1.7 ± 0.6 | -2.0 ± 0.6 | -3.1 ± 0.6 |
| Difference vs GLIM (95% CI) | | -3.7 (-5.2, -2.3) | -4.8 (-6.2, -3.4) |
| Diastolic BP, n | 480 | 480 | 480 |
| Mean ± SD baseline, mmHg | 79.0 ± 8.4 | 78.7 ± 8.0 | 79.2 ± 8.4 |
| LS mean ± SE change | -0.02 ± 0.38 | -1.3 ± 0.4 | -2.2 ± 0.4 |
| Difference vs GLIM (95% CI) | | -1.3 (-2.2, -0.3) | -2.2 (-3.1, -1.3) |
| Triglycerides, n | 467 | 465 | 462 |
| Mean ± SD baseline, mmol/L (mg/dL) | 1.9 ± 1.2 (170.0 ± 110.2) | 2.1 ± 1.5 (186.0 ± 128.5) | 2.2 ± 2.1 (190.7 ± 183.4) |
| LS mean ± SE change, mmol/L (mg/dL) | 0.06 ± 0.06 (5.8 ± 5.0) | -0.05 ± 0.06 (-4.2 ± 5.0) | 0.01 ± 0.06 (0.7 ± 5.0) |
| Median (IQR) percent change | 7.0 (-19.2, 37.7) | -4.3 (-25.8, 22.4) | -2.4 (-24.0, 23.5) |
| LS mean ± SE percent change | 13.9 ± 2.6 | 4.5 ± 2.7 | 8.0 ± 2.6 |
| Difference vs GLIM (95% CI) | | -9.4 (-15.9, -2.8) | -5.9 (-12.5, 0.6) |
| LDL-C, n | 461 | 463 | 456 |
| Mean ± SD baseline, mmol/L (mg/dL) | 2.7 ± 0.9 (102.8 ± 34.0) | 2.6 ± 0.9 (99.7 ± 35.4) | 2.8 ± 0.9 (106.7 ± 36.2) |
| LS mean ± SE change, mmol/L (mg/dL) | 0.06 ± 0.04 (2.3 ± 1.4) | 0.14 ± 0.04 (5.6 ± 1.4) | 0.24 ± 0.04 (9.4 ± 1.4) |
| Median (IQR) percent change | -1.0 (-13.1, 18.5) | 4.5 (-10.2, 22.1) | 6.0 (-7.7, 25.1) |
| LS mean ± SE percent change | 6.3 ± 2.1 | 11.2 ± 2.1 | 14.3 ± 2.1 |
| Difference vs GLIM (95% CI) | | 4.9 (-0.4, 10.1) | 8.0 (2.7, 13.3) |
| HDL-C, n | 466 | 465 | 461 |
| Mean ± SD baseline, mmol/L (mg/dL) | 1.2 ± 0.3 (46.6 ± 11.3) | 1.2 ± 0.3 (46.9 ± 12.5) | 1.2 ± 0.3 (47.0 ± 12.0) |
| LS mean ± SE change, mmol/L (mg/dL) | 0.00 ± 0.01 (-0.2 ± 0.4) | 0.10 ± 0.01 (3.8 ± 0.4) | 0.11 ± 0.01 (4.2 ± 0.4) |
| Median (IQR) percent change | 0.0 (-11.4, 9.6) | 6.6 (-2.7, 17.7) | 7.5 (-2.4, 18.2) |
| LS mean ± SE percent change | 0.7 ± 0.9 | 9.4 ± 0.9 | 10.0 ± 0.9 |
| Difference vs GLIM (95% CI) | | 8.7 (6.5, 10.8) | 9.3 (7.1, 11.4) |
| LDL-C/HDL-C, n | 461 | 463 | 456 |
| Mean ± SD baseline, mol/mol | 2.3 ± 0.9 | 2.3 ± 0.9 | 2.4 ± 0.9 |
| LS mean ± SE change | 0.04 ± 0.03 | -0.07 ± 0.03 | -0.01 ± 0.03 |
| Median (IQR) percent change | 0.4 (-14.8, 23.6) | -0.9 (-16.7, 15.6) | -0.3 (-16.4, 17.5) |
| LS mean ± SE percent change | 7.7 ± 2.3 | 4.3 ± 2.3 | 5.3 ± 2.3 |

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| Difference vs GLIM (95% CI) | | -3.4 (-9.1, 2.3) | -2.4 (-8.1, 3.4) |
|---|----------------------------------|----------------------------------|----------------------------------|
| Non-HDL-C, n | 466 | 465 | 461 |
| Mean \pm SD baseline, mmol/L (mg/dL) | 3.5 \pm 1.0 (136.3 \pm 39.7) | 3.5 \pm 1.0 (135.8 \pm 40.3) | 3.7 \pm 1.1 (142.6 \pm 42.3) |
| LS mean \pm SE change, mmol/L (mg/dL) | 0.10 \pm 0.04 (3.9 \pm 1.6) | 0.14 \pm 0.04 (5.3 \pm 1.6) | 0.26 \pm 0.04 (10.0 \pm 1.6) |
| Median (IQR) percent change | 1.4 (-9.6, 15.0) | 2.5 (-9.8, 17.3) | 4.4 (-7.5, 18.2) |
| LS mean \pm SE percent change | 6.1 \pm 1.3 | 6.4 \pm 1.3 | 10.3 \pm 1.3 |
| Difference vs GLIM (95% CI) | | 0.3 (-3.0, 3.6) | 4.3 (1.0, 7.6) |

LOCF, last observation carried forward; GLIM, glimepiride; CANA, canagliflozin; BP, blood pressure; SD, standard deviation; LS, least squares; SE, standard error; CI, confidence interval; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

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Supplementary Table 3. Summary of Overall Safety and Selected Adverse Events (Weeks 52-104; Extension Period)*

| Patients, n (%) | GLIM (n = 381) | CANA 100 mg (n = 393) | CANA 300 mg (n = 377) |
|--------------------------------|---------------------------|----------------------------------|----------------------------------|
| Any AE | 243 (63.8) | 218 (55.5) | 224 (59.4) |
| AEs leading to discontinuation | 8 (2.1) | 5 (1.3) | 14 (3.7) |
| AEs related to study drug† | 51 (13.4) | 35 (8.9) | 42 (11.1) |
| Serious AEs | 31 (8.1) | 24 (6.1) | 22 (5.8) |
| Deaths | 0 | 3 (0.8)‡ | 1 (0.3)§ |
| Selected AEs | | | |
| UTI | 20 (5.2) | 28 (7.1) | 17 (4.5) |
| Genital mycotic infection | | | |
| Male ¶ | 3 (1.4) | 7 (3.3) | 5 (2.7) |
| Female#,** | 1 (0.6) | 9 (5.0) | 8 (4.2) |
| Osmotic diuresis-related AEs†† | 2 (0.5) | 1 (0.3) | 3 (0.8) |
| Volume depletion AEs‡‡ | 4 (1.0) | 0 | 3 (0.8) |

GLIM, glimepiride; CANA, canagliflozin; AE, adverse event; UTI, urinary tract infection.

* All AEs are reported for regardless of rescue medication.

† Possibly, probably, or very likely related to study drug, as assessed by investigators.

‡ One patient died due to acute chemical poisoning; 1 patient due to hemorrhage intracranial; and 1 patient due to pulmonary embolism and acute renal failure.

§ One patient died due to a road traffic accident.

|| GLIM, n = 218; CANA 100 mg, n = 214; CANA 300 mg, n = 187.

¶ Including balanitis, balanoposthitis, genital candidiasis, genital infection fungal, and posthitis.

GLIM, n = 163; CANA 100 mg, n = 179; CANA 300 mg, n = 190.

** Including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.

†† Including dry mouth, pollakiuria, and polyuria.

‡‡ Including dehydration, dizziness postural, hypotension, orthostatic hypotension, and syncope.

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Supplementary Table 4. Summary of Laboratory Parameters at Baseline and Week 104

| Parameter | GLIM | CANA 100 mg | CANA 300 mg |
|------------------------------------|-------------|-------------|-------------|
| ALT, n | 310 | 338 | 316 |
| Mean baseline, U/L | 29.1 | 28.8 | 28.6 |
| Mean (SD) percent change | 9.4 (47.2) | 0.9 (60.7) | -9.2 (40.0) |
| AST, n | 310 | 335 | 314 |
| Mean baseline, U/L | 23.7 | 23.7 | 23.3 |
| Mean (SD) percent change | 10.7 (39.8) | 1.7 (31.7) | -1.0 (35.6) |
| Bilirubin, n | 311 | 339 | 316 |
| Mean baseline, µmol/L | 8.9 | 9.0 | 8.6 |
| Mean (SD) percent change | 1.5 (34.4) | 6.4 (35.7) | 13.1 (40.8) |
| BUN, n | 312 | 339 | 319 |
| Mean baseline, mmol/L | 5.3 | 5.3 | 4.9 |
| Mean (SD) percent change | 6.1 (25.1) | 17.0 (32.1) | 20.2 (32.6) |
| Creatinine, n | 312 | 339 | 319 |
| Mean baseline, µmol/L [*] | 73.1 | 71.9 | 69.0 |
| Mean (SD) percent change | 6.7 (13.4) | 2.2 (13.8) | 4.4 (14.5) |
| Magnesium | 312 | 339 | 319 |
| Mean baseline, mmol/L | 0.8 | 0.8 | 0.8 |
| Mean (SD) percent change | 0.4 (10.3) | 5.9 (11.0) | 7.7 (9.9) |
| Urate, n | 312 | 339 | 319 |
| Mean baseline, µmol/L | 323.0 | 328.1 | 309.8 |
| Mean (SD) percent change | 8.3 (21.0) | -8.9 (18.8) | -9.6 (17.1) |
| Hemoglobin, n | 297 | 326 | 306 |
| Mean baseline, g/L [†] | 140.7 | 140.2 | 139.8 |
| Mean (SD) percent change | -1.8 (7.5) | 3.0 (7.4) | 3.5 (8.2) |

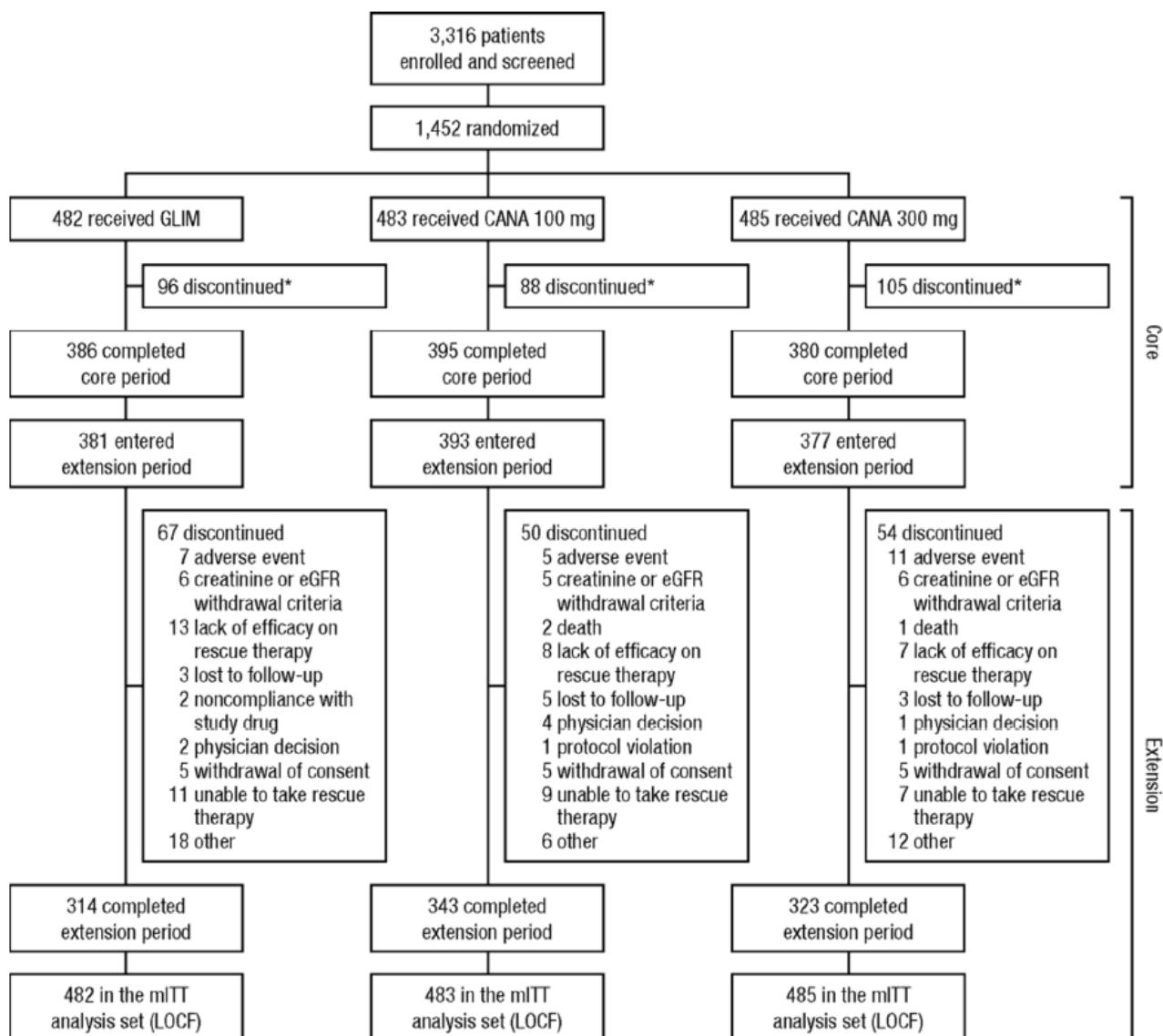
GLIM, glimepiride; CANA, canagliflozin; ALT, alanine aminotransferase; SD, standard deviation; AST, aspartate aminotransferase; BUN, blood urea nitrogen.

*Conversion factor for mg/dL of 0.0113.

†Conversion factor for g/dL of 0.10.

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Supplementary Figure 1. Study flow diagram.



GLIM, glimepiride; CANA, canagliflozin; eGFR, estimated glomerular filtration rate.

*Reasons for discontinuation in core period have been previously reported (12).