**SUPPLEMENTARY APPENDIX**

**TABLE S1** Prespecified and post hoc analyses

| Age groups | Prespecified | Defined post hoc |
|------------|--------------|------------------|
| Primary and key secondary endpoints (3-point MACE, 4-point MACE, treatment sustainability) |               |                  |
| <70, ≥70 years | ✓ |                  |
| <65, ≥65 years | ✓ |                  |
| <65, 65 to <75, ≥75 years | | ✓ |
| <65, 65 to <75, 75 to <80, ≥80 years | | ✓ |
| Other secondary and tertiary endpoints (including CV endpoints other than 3-point MACE/4-point MACE, body weight and HbA1c) | |                  |
| <65, 65 to <75, ≥75 years | | ✓ |
| <65, 65 to <75, 75 to <80, ≥80 years | | ✓ |
| Adverse events | |                  |
| <65, 65 to <75, ≥75 years | | ✓ |
| <70, 70 to <80, ≥80 years | | ✓ |
| <65, 65 to <75, 75 to <80, ≥80 years | | ✓ |

Abbreviations: CV, cardiovascular; HbA1c, glycated haemoglobin; MACE, major adverse CV events.
TABLE S2 Baseline characteristics of participants

|                        | Age <65 years | Age 65 to <75 years | Age ≥75 years |
|------------------------|---------------|---------------------|---------------|
|                        | Linagliptin   | Glimepiride        | Linagliptin   | Glimepiride | Linagliptin | Glimepiride |
|                        | (n = 1556)    | (n = 1502)         | (n = 1057)    | (n = 1072)  | (n = 410)   | (n = 436)   |
| Age, years             | 56.3 (6.0)    | 56.3 (6.0)         | 69.7 (2.9)    | 69.6 (2.8)  | 77.8 (2.6)  | 77.8 (2.6)  |
| Sex, n (%)             |               |                     |               |             |             |             |
| Male                   | 968 (62.2)    | 906 (60.3)         | 641 (60.6)    | 622 (58.0)  | 229 (55.9)  | 253 (58.0)  |
| Female                 | 588 (37.8)    | 596 (39.7)         | 416 (39.4)    | 450 (42.0)  | 181 (44.1)  | 183 (42.0)  |
| Race, n (%)*           |               |                     |               |             |             |             |
| White                  | 1075 (69.1)   | 1001 (66.6)        | 805 (76.2)    | 825 (77.0)  | 337 (82.2)  | 364 (83.5)  |
| Asian                  | 334 (21.5)    | 333 (22.2)         | 154 (14.6)    | 158 (14.7)  | 43 (10.5)   | 39 (8.9)    |
| Black/African-American | 97 (6.2)      | 116 (7.7)          | 46 (4.4)      | 41 (3.8)    | 12 (2.9)    | 12 (2.8)    |
| American Indian/Alaska Native | 38 (2.4) | 42 (2.8)          | 50 (4.7)      | 45 (4.2)    | 18 (4.4)    | 21 (4.8)    |
| Hawaiian/Pacific Islander | 4 (0.3) | 2 (0.1)          | 1 (0.1)       | 1 (0.1)     | 0           | 0           |
| Ethnicity, n (%)*      |               |                     |               |             |             |             |
| Not Hispanic/Latino    | 1313 (84.4)   | 1258 (83.8)        | 865 (81.8)    | 882 (82.3)  | 317 (77.3)  | 347 (79.6)  |
| Hispanic/Latino        | 235 (15.1)    | 236 (15.7)         | 191 (18.1)    | 188 (17.5)  | 93 (22.7)   | 89 (20.4)   |
| Smoking status, n (%)* |               |                     |               |             |             |             |
| Never smoker           | 622 (40.0)    | 680 (45.3)         | 518 (49.0)    | 516 (48.1)  | 216 (52.7)  | 246 (56.4)  |
| Ex-smoker              | 455 (29.2)    | 389 (25.9)         | 424 (40.1)    | 423 (39.5)  | 172 (42.0)  | 165 (37.8)  |
| Current smoker         | 471 (30.3)    | 425 (28.3)         | 114 (10.8)    | 131 (12.2)  | 22 (5.4)    | 25 (5.7)    |
| CV risk entry criteria |               |                     |               |             |             |             |
|                                | Age <65 years | Age 65 to <75 years | Age ≥75 years |
|--------------------------------|--------------|---------------------|--------------|
|                                | Linagliptin  | Glimepiride        | Linagliptin  | Glimepiride        | Linagliptin  | Glimepiride        |
|                                | (n = 1556)   | (n = 1502)          | (n = 1057)   | (n = 1072)          | (n = 410)   | (n = 436)          |
| Previous vascular disease      | 533 (34.3)   | 495 (33.0)          | 380 (36.0)   | 384 (35.8)          | 138 (33.7)  | 159 (36.5)          |
| Microvascular complications†   | 157 (10.1)   | 160 (10.7)          | 157 (14.9)   | 169 (15.8)          | 86 (21.0)   | 89 (20.4)           |
| Age ≥70 years                  | 0 (0.0)      | 0 (0.0)             | 595 (56.3)   | 589 (54.9)          | 410 (100.0) | 436 (100.0)         |
| ≥2 CV risk factors             | 1352 (86.9)  | 1305 (86.9)         | 800 (75.7)   | 810 (75.6)          | 264 (64.4)  | 279 (64.0)          |
| None of above or missing data  | 15 (1.0)     | 12 (0.8)            | 1 (0.1)      | 3 (0.3)             | 0           | 0                   |
| Heart failure (narrow SMQ ‘cardiac failure’), n (%) | 48 (3.1) | 62 (4.1) | 52 (4.9) | 52 (4.9) | 22 (5.4) | 35 (8.0) |
| Atherosclerotic CV disease, n (%)* | 623 (40.0) | 584 (38.9) | 465 (44.0) | 475 (44.3) | 184 (44.9) | 191 (43.8) |
| Coronary artery disease        | 458 (29.4)   | 432 (28.8)          | 367 (34.7)   | 362 (33.8)          | 143 (34.9)  | 143 (32.8)          |
| Cerebrovascular disease        | 172 (11.1)   | 160 (10.7)          | 140 (13.2)   | 135 (12.6)          | 59 (14.4)   | 61 (14.0)           |
| Peripheral artery occlusive disease | 105 (6.7) | 90 (6.0) | 72 (6.8) | 71 (6.6) | 30 (7.3) | 39 (8.9) |
| Hypertension, n (%)*           | 1396 (89.7)  | 1369 (91.1)         | 963 (91.1)   | 944 (88.1)          | 361 (88.0)  | 385 (88.3)          |
| Microvascular disease, n (%)*  | 420 (27.0)   | 393 (26.2)          | 293 (27.7)   | 352 (32.8)          | 134 (32.7)  | 136 (31.2)          |
| Diabetic neuropathy            | 265 (17.0)   | 223 (14.8)          | 170 (16.1)   | 192 (17.9)          | 80 (19.5)   | 80 (18.3)           |
| Diabetic nephropathy           | 159 (10.2)   | 163 (10.9)          | 130 (12.3)   | 146 (13.6)          | 63 (15.4)   | 63 (14.4)           |
| Diabetic retinopathy           | 110 (7.1)    | 113 (7.5)           | 74 (7.0)     | 91 (8.5)            | 28 (6.8)    | 32 (7.3)            |
| eGFR (MDRD), mL/min/1.73 m²‡    | 82.5 (19.6)  | 83.2 (19.2)         | 72.3 (17.4)  | 73.3 (18.4)         | 64.9 (17.3) | 64.9 (17.0)         |
| eGFR (MDRD), n (%)‡            |              |                     |              |                     |              |                     |
| ≥90 mL/min/1.73 m²             | 495 (31.8)   | 502 (33.4)          | 165 (15.6)   | 187 (17.4)          | 33 (8.0)    | 33 (7.6)            |
| ≥60–<90 mL/min/1.73 m²         | 879 (56.5)   | 855 (56.9)          | 636 (60.2)   | 650 (60.6)          | 211 (51.5)  | 235 (53.9)          |
| Age <65 years | Age 65 to <75 years | Age ≥75 years |
|---------------|---------------------|--------------|
|               | Linagliptin (n = 1556) | Glimepiride (n = 1502) | Linagliptin (n = 1057) | Glimepiride (n = 1072) | Linagliptin (n = 410) | Glimepiride (n = 436) |
| ≥30−<60 mL/min/1.73 m² | 165 (10.6) | 134 (8.9) | 250 (23.7) | 231 (21.5) | 161 (39.3) | 160 (36.7) |
| ≥15−<30 mL/min/1.73 m² | 4 (0.3) | 3 (0.2) | 4 (0.4) | 2 (0.2) | 5 (1.2) | 8 (1.8) |
| <15 mL/min/1.73 m² | 2 (0.1) | 0 (0.0) | 1 (0.1) | 0 | 0 | 0 |
| UACR, mg/g, median (25th−75th percentile)§ | 8.8 (5.3–24.8) | 8.8 (4.4–23.9) | 9.7 (5.3–33.6) | 9.7 (5.3–33.6) | 15.9 (7.1–50.4) | 13.3 (6.2–45.1) |
| UACR, n (%)§ | 1199 (77.1) | 1155 (76.9) | 769 (72.8) | 783 (73.0) | 260 (63.4) | 296 (67.9) |
| BMI, kg/m²‖ | 30.90 (5.45) | 30.88 (5.20) | 29.59 (4.79) | 29.37 (4.96) | 28.94 (4.51) | 28.46 (4.28) |
| HbA1c, %¶ | 7.18 (0.58) | 7.21 (0.61) | 7.12 (0.55) | 7.10 (0.55) | 7.10 (0.51) | 7.13 (0.56) |
| HbA1c, mmol/mol¶ | 54.95 (6.36) | 55.28 (6.67) | 54.33 (5.98) | 54.03 (5.98) | 54.07 (5.58) | 54.45 (6.15) |
| Fasting plasma glucose, mg/dL# | 141.0 (32.3) | 140.7 (31.8) | 139.1 (27.9) | 139.3 (28.8) | 139.4 (31.5) | 138.1 (29.1) |
| Diabetes duration, years, median (25th−75th percentile)** | 5.2 (2.4–10.0) | 5.0 (2.3–9.9) | 7.2 (3.9–11.8) | 7.4 (4.0–11.8) | 8.0 (3.9–12.4) | 7.7 (4.0–11.8) |
| Diabetes duration ≤5 years, n (%)* | 743 (47.8) | 739 (49.2) | 353 (33.4) | 337 (31.4) | 128 (31.2) | 136 (31.2) |
| Systolic blood pressure, mmHg†† | 133.93 (15.14) | 133.61 (15.50) | 137.31 (16.61) | 137.46 (16.40) | 141.13 (17.05) | 139.90 (17.04) |
| Diastolic blood pressure, mmHg†† | 80.65 (9.04) | 81.03 (8.96) | 78.04 (9.62) | 77.25 (9.65) | 76.84 (10.05) | 76.54 (9.44) |
| Glucose-lowering therapy, n (%)* | 1345 (86.4) | 1303 (86.8) | 860 (81.4) | 871 (81.3) | 305 (74.4) | 336 (77.1) |
| Metformin | 1345 (86.4) | 1303 (86.8) | 860 (81.4) | 871 (81.3) | 305 (74.4) | 336 (77.1) |
|                      | Age <65 years | Age 65 to <75 years | Age ≥75 years |
|----------------------|---------------|---------------------|---------------|
|                      | Linagliptin   | Glimepiride        | Linagliptin   | Glimepiride | Linagliptin | Glimepiride |
|                      | (n = 1556)    | (n = 1502)         | (n = 1057)    | (n = 1072) | (n = 410)   | (n = 436)   |
| SU                   | 432 (27.8)    | 398 (26.5)         | 299 (28.3)    | 327 (30.5) | 138 (33.7)  | 121 (27.8)  |
| Alpha-glucosidase inhibitor | 54 (3.5)    | 38 (2.5)           | 30 (2.8)      | 40 (3.7)   | 13 (3.2)    | 14 (3.2)    |
| Glinide (meglitinide) | 11 (0.7)      | 12 (0.8)           | 8 (0.8)       | 20 (1.9)   | 9 (2.2)     | 6 (1.4)     |
| Number of background glucose-lowering therapies, n (%)* |                |                     |               |            |             |             |
| 0                    | 120 (7.7)     | 118 (7.9)          | 106 (10.0)    | 106 (9.9)  | 48 (11.7)   | 48 (11.0)   |
| 1                    | 1023 (65.7)   | 1006 (67.0)        | 704 (66.6)    | 675 (63.0) | 257 (62.7)  | 301 (69.0)  |
| 2                    | 394 (25.3)    | 361 (24.0)         | 241 (22.8)    | 280 (26.1) | 101 (24.6)  | 84 (19.3)   |
| 3                    | 11 (0.7)      | 9 (0.6)            | 5 (0.5)       | 9 (0.8)    | 4 (1.0)     | 3 (0.7)     |
| Antihypertensives, n (%)* | 1353 (87.4) | 1346 (90.1)        | 945 (89.5)    | 951 (88.9) | 364 (88.8)  | 385 (88.3)  |
| ACE inhibitors       | 711 (45.9)    | 701 (46.9)         | 459 (43.5)    | 464 (43.4) | 160 (39.0)  | 177 (40.6)  |
| β-Blockers           | 572 (37.0)    | 549 (36.7)         | 453 (42.9)    | 445 (41.6) | 168 (41.0)  | 165 (37.8)  |
| Diuretics            | 501 (32.4)    | 528 (35.3)         | 414 (39.2)    | 417 (39.0) | 184 (44.9)  | 192 (44.0)  |
| Angiotensin receptor blockers | 462 (29.8) | 445 (29.8)         | 368 (34.8)    | 339 (31.7) | 126 (30.7)  | 144 (33.0)  |
| Calcium antagonists  | 394 (25.5)    | 380 (25.4)         | 352 (33.3)    | 355 (33.2) | 145 (35.4)  | 150 (34.4)  |
| Acetylsalicylic acid (aspirin), n (%)* | 672 (43.4)    | 652 (43.6)         | 540 (51.1)    | 547 (51.1) | 198 (48.3)  | 214 (49.1)  |
| Statins, n (%)*      | 1001 (64.7)   | 987 (66.1)         | 675 (63.9)    | 715 (66.8) | 237 (57.8)  | 285 (65.4)  |

Abbreviations: BMI, body-mass index; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; MDRD, Modification of Diet in Renal Disease study equation; SMQ, Standardized MedDRA Query from the Medical Dictionary for Regulatory Activities version 21.0; SU, sulphonylurea; UACR, urinary albumin-to-creatinine ratio.
|                  | Age <65 years | Age 65 to <75 years | Age ≥75 years |
|------------------|---------------|---------------------|--------------|
| Linagliptin (n = 1556) | Glimepiride (n = 1502) | Linagliptin (n = 1057) | Glimepiride (n = 1072) | Linagliptin (n = 410) | Glimepiride (n = 436) |

Data are mean (SD) unless otherwise stated.

*Data missing for 8 linagliptin participants/8 glimepiride participants aged <65 years, and 1 linagliptin participant/2 glimepiride participants aged 65 to <75 years.

†Microvascular complications: eGFR 30–59 mL/min/1.73 m², UACR ≥30 µg/mg, or proliferative retinopathy.

‡Data missing for 11 linagliptin participants/8 glimepiride participants aged <65 years, and 1 linagliptin participant/2 glimepiride participants aged 65 to <75 years.

§Data missing for 13 linagliptin participants/15 glimepiride participants aged <65 years, 2 linagliptin participants/5 glimepiride participants aged 65 to <75 years, and 1 linagliptin participant/2 glimepiride participants aged ≥75 years.

‖Data missing for 10 linagliptin participants/10 glimepiride participants aged <65 years, and 1 linagliptin participant/3 glimepiride participants aged 65 to <75 years.

¶Data missing for 9 linagliptin participants/8 glimepiride participants aged <65 years, and 1 linagliptin participant/2 glimepiride participants aged 65 to <75 years.

#Data missing for 11 linagliptin participants/11 glimepiride participants aged <65 years, 4 linagliptin participants/3 glimepiride participants aged 65 to <75 years, and 3 glimepiride participants aged ≥75 years.

**Data missing for 13 linagliptin participants/19 glimepiride participants aged <65 years, 7 linagliptin participants/8 glimepiride participants aged 65 to <75 years, and 2 linagliptin participants/1 glimepiride participant aged ≥75 years.

††Data missing for 8 linagliptin participants/9 glimepiride participants aged <65 years, and 1 linagliptin participant/3 glimepiride participants aged 65 to <75 years.
**TABLE S3** Duration of treatment and observation

| Age          | Linagliptin (n = 1556) | Glimepiride (n = 1502) | Linagliptin (n = 1057) | Glimepiride (n = 1072) | Linagliptin (n = 410) | Glimepiride (n = 436) |
|--------------|------------------------|------------------------|------------------------|------------------------|-----------------------|------------------------|
| Age <65 years| 6.1                    | 6.1                    | 5.8                    | 5.8                    | 5.5                   | 5.4                    |
| Age 65 to <75 years | 5.8                    | 5.8                    |                        |                        |                       |                        |
| Age ≥75 years |                        |                        | 6.2                    | 6.3                    | 6.1                   | 6.1                    |
| Age Category | Linagliptin (n = 1548) | Glimepiride (n = 1494) | Linagliptin (n = 1056) | Glimepiride (n = 1070) | Linagliptin (n = 410) | Glimepiride (n = 436) |
|--------------|------------------------|------------------------|------------------------|------------------------|-----------------------|------------------------|
| Any glucose-lowering therapy | 677 (43.7) | 653 (43.7) | 405 (38.4) | 388 (36.3) | 155 (37.8) | 151 (34.6) |
| Insulin | 291 (18.8) | 302 (20.2) | 196 (18.6) | 204 (19.1) | 74 (18.0) | 71 (16.3) |
| GLP-1 receptor agonist | 26 (1.7) | 25 (1.7) | 4 (0.4) | 8 (0.7) | 2 (0.5) | 2 (0.5) |
| Oral glucose-lowering therapy | 524 (33.9) | 492 (32.9) | 287 (27.2) | 268 (25.0) | 111 (27.1) | 109 (25.0) |
| Glitazone (thiazolidinedione) | 250 (16.1) | 219 (14.7) | 109 (10.3) | 91 (8.5) | 30 (7.3) | 31 (7.1) |
| Alpha-glucosidase inhibitor | 110 (7.1) | 118 (7.9) | 36 (3.4) | 31 (2.9) | 13 (3.2) | 12 (2.8) |
| SU | 107 (6.9) | 89 (6.0) | 73 (6.9) | 72 (6.7) | 33 (8.0) | 31 (7.1) |
| Metformin | 89 (5.7) | 96 (6.4) | 71 (6.7) | 62 (5.8) | 23 (5.6) | 32 (7.3) |
| DPP-4 inhibitor | 50 (3.2) | 61 (4.1) | 49 (4.6) | 60 (5.6) | 28 (6.8) | 28 (6.4) |
| Other | 47 (3.0) | 61 (4.1) | 23 (2.2) | 19 (1.8) | 3 (0.7) | 9 (2.1) |
| Glinide (meglitinide) | 11 (0.7) | 7 (0.5) | 16 (1.5) | 8 (0.7) | 8 (2.0) | 3 (0.7) |

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SU, sulphonylurea.
Data are n (%) of participants.
### TABLE S5 Incidence rate of adverse events in age groups <65, 65 to <75, and ≥75 years

| Age Group | Any AE* | Any hospitalization | Hypersensitivity reactions*† | Pemphigoid*‡ | Skin lesions*§ | Cancer‖ | Colorectal cancer§ | Gastric cancer# | Thyroid cancer** | Fall*‡ | Bone fractures*†† | Hypoglycaemia* |
|-----------|---------|---------------------|----------------------------|--------------|--------------|---------|-------------------|--------------|--------------|--------|-----------------|---------------|
| Age <65 years | Linagliptin (n = 1556) | 112.29 | 7.39 | 2.91 | 0.01 | 0.04 | 0.85 | 0.07 | 0.03 | 0 | 0.94 | 1.52 |
| | Glimepiride (n = 1502) | 131.34 | 7.28 | 2.49 | 0 | 0.04 | 1.03 | 0.08 | 0.02 | 0.75 | 1.29 | 8.23 |
| Age 65 to <75 years | Linagliptin (n = 1057) | 127.26 | 10.39 | 3.14 | 0.06 | 0.08 | 2.24 | 0.25 | 0.09 | 1.56 | 1.29 | 1.21 |
| | Glimepiride (n = 1072) | 153.22 | 11.70 | 2.40 | 0 | 0.02 | 2.42 | 0.23 | 0.03 | 1.56 | 1.52 | 9.00 |
| Age ≥75 years | Linagliptin (n = 410) | 152.34 | 13.85 | 2.99 | 0.06 | 0.11 | 3.06 | 0.39 | 0 | 2.30 | 2.18 | 1.24 |
| | Glimepiride (n = 436) | 180.53 | 15.08 | 3.16 | 0 | 0 | 2.71 | 0.33 | 0.04 | 4.12 | 2.97 | 7.56 |

**Abbreviations:** AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Query.

Data are n patients per 100 years.

*Data for 1548 linagliptin and 1494 glimepiride participants aged <65 years, 1056 linagliptin and 1070 glimepiride participants aged 65 to <75 years.

†MedDRA narrow SMQ “hypersensitivity”.

‡MedDRA narrow SMQ “hypersensitivity”.

§MedDRA narrow SMQ “hypersensitivity”.

‖MedDRA narrow SMQ “hypersensitivity”.

§§Moderate or severe hypoglycaemia.
‡MedDRA preferred term.
§MedDRA narrow SMQ “Severe cutaneous adverse reactions”.
‖MedDRA narrow SMQs “Malignant Tumors” and “Tumors of unspecified malignancy”.
¶MedDRA high level term “Colorectal neoplasms malignant”.
†MedDRA high level term “Gastric neoplasms malignant”.
‖†MedDRA high level term “Thyroid neoplasms malignant”.
‡Based on 84 MedDRA preferred terms for bone fractures.
‡‡Investigator-reported episode of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL.
§§Requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
|                         | Any AE     | Bone fractures* | Hyperglycaemia | Nasopharyngitis | Hypertension | Back pain | Diarrhoea | Bronchitis | Upper respiratory tract infection | Arthralgia | Headache | Dizziness | Cough | Urinary tract infection | Osteoarthritis | Anaemia | Cataract |
|-------------------------|------------|-----------------|----------------|-----------------|--------------|-----------|-----------|-----------|---------------------------------|------------|----------|-----------|-------|------------------------|---------------|---------|----------|
| **Age <65 years**       |            |                 |                |                 |              |           |           |           |                                 |            |          |           |       |                        |                |         |          |
| Linagliptin (n = 1548)  | 1432 (92.5)|                | 283 (18.3)     | 252 (16.3)      | 222 (14.3)   | 217 (14.0)| 177 (11.4)| 169 (10.9) | 164 (10.6)                             | 159 (10.3) | 157 (10.1)| 140 (9.0) | 133 (8.6)| 125 (8.1)              | 117 (7.6)     | 87 (5.6)| 84 (5.4)  |
| Glimepiride (n = 1494) | 1416 (94.8)|                | 302 (20.2)     | 259 (17.3)      | 224 (15.0)   | 182 (12.2)| 146 (9.8) | 159 (10.6) | 167 (11.2)                             | 159 (10.6) | 169 (11.3)| 162 (10.8)| 131 (8.8) | 134 (9.0)              | 132 (8.8)     | 70 (4.7)| 70 (4.7)  |
| **Age 65 to <75 years** |            |                 | 993 (94.0)     | 207 (19.6)      | 148 (14.0)   | 132 (12.5)| 133 (12.6)| 113 (10.7) | 115 (10.9)                             | 125 (11.8) | 87 (8.2) | 105 (9.9) | 109 (10.3)| 144 (13.6)              | 101 (9.6)     | 70 (4.7)| 70 (4.7)  |
| Linagliptin (n = 1056)  | 1017 (95.0)|                | 144 (13.5)     | 191 (17.9)      | 164 (15.3)   | 127 (11.9)| 124 (11.6)| 122 (11.4) | 123 (11.5)                             | 106 (9.9)  | 98 (9.2) | 130 (12.1)| 103 (9.6) | 142 (13.3)              | 123 (11.5)     | 70 (4.7)| 70 (4.7)  |
| Glimepiride (n = 1070) | 31 (9.8)   |                | 32 (10.1)      | 58 (18.4)       | 59 (18.7)    | 28 (8.9) | 45 (14.2) | 30 (9.5)   | 33 (10.4)                             | 25 (7.9)   | 20 (6.3) | 38 (12.0) | 34 (10.8) | 50 (15.8)              | 36 (11.4)     | 35 (11.1)| 35 (11.1) |
| **Age 75 to <80 years** |            |                 | 305 (96.5)     | 320 (96.1)      | 32 (9.6)     | 54 (16.2) | 37 (11.1) | 46 (13.8) | 24 (7.2)                              | 38 (11.4)  | 24 (7.2) | 52 (15.6) | 42 (12.6) | 43 (12.9)              | 40 (12.0)     | 35 (10.5)| 34 (10.5) |
| Linagliptin (n = 316)   | 91 (96.8)  |                 | 32 (10.1)      | 54 (16.2)       | 10 (10.6)    | 16 (17.0) | 12 (1.5)  | 16 (17.0) | 5 (5.3)                              | 7 (7.4)    | 5 (5.3)  | 9 (9.6)   | 10 (10.6)| 17 (18.1)              | 10 (10.6)     | 9 (9.6) | 10 (6.0)  |
| Glimepiride (n = 333)   | 102 (99.0) |                 | 32 (9.6)       | 13 (13.8)       | 10 (10.6)    | 19 (18.4) | 12 (2.7)  | 16 (15.5) | 8 (7.8)                              | 13 (12.6)  | 6 (5.8)  | 9 (9.6)   | 16 (15.5)| 16 (15.5)              | 11 (10.7)     | 9 (8.7) | 8 (7.8)   |
| **Age ≥80 years**       |            |                 | 91 (96.8)      | 102 (99.0)      | 32 (9.6)     | 13 (13.8) | 9 (9.6)   | 10 (10.6) | 8 (7.8)                              | 13 (12.6)  | 6 (5.8)  | 9 (9.6)   | 16 (15.5)| 16 (15.5)              | 11 (10.7)     | 9 (8.7) | 8 (7.8)   |
| Linagliptin (n = 94)    | 91 (96.8)  |                 | 32 (9.6)       | 13 (13.8)       | 10 (10.6)    | 19 (18.4) | 12 (2.7)  | 16 (15.5) | 8 (7.8)                              | 13 (12.6)  | 6 (5.8)  | 9 (9.6)   | 16 (15.5)| 16 (15.5)              | 11 (10.7)     | 9 (8.7) | 8 (7.8)   |
| Glimepiride (n = 103)   | 102 (99.0) |                 | 32 (9.6)       | 13 (13.8)       | 10 (10.6)    | 19 (18.4) | 12 (2.7)  | 16 (15.5) | 8 (7.8)                              | 13 (12.6)  | 6 (5.8)  | 9 (9.6)   | 16 (15.5)| 16 (15.5)              | 11 (10.7)     | 9 (8.7) | 8 (7.8)   |
| Condition          | Age <65 years | Age 65 to <75 years | Age 75 to <80 years | Age ≥80 years |
|--------------------|---------------|---------------------|---------------------|--------------|
|                    | Linagliptin   | Glimepiride         | Linagliptin         | Glimepiride  |
| Constipation       | 83 (5.4)      | 54 (3.6)            | 86 (8.1)            | 81 (7.6)     |
|                    | 20 (6.3)      | 29 (8.7)            | 10 (10.6)           | 11 (10.7)    |
| Pneumonia          | 65 (4.2)      | 59 (3.9)            | 63 (6.0)            | 75 (7.0)     |
|                    | 28 (8.9)      | 29 (8.7)            | 4 (4.3)             | 14 (13.6)    |
| Fall               | 57 (3.7)      | 56 (3.7)            | 78 (7.4)            | 77 (7.2)     |
|                    | 26 (8.2)      | 44 (13.2)           | 13 (13.8)           | 28 (27.2)    |
| Contusion          | 53 (3.4)      | 50 (3.3)            | 50 (4.7)            | 55 (5.1)     |
|                    | 22 (7.0)      | 22 (6.6)            | 6 (6.4)             | 12 (11.7)    |
| Atrial fibrillation| 46 (3.0)      | 48 (3.2)            | 70 (6.6)            | 70 (6.5)     |
|                    | 22 (7.0)      | 33 (9.9)            | 5 (5.3)             | 12 (11.7)    |
| Dyspnoea           | 46 (3.0)      | 48 (3.2)            | 38 (3.6)            | 48 (4.5)     |
|                    | 13 (4.1)      | 14 (4.2)            | 4 (4.3)             | 14 (13.6)    |

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Data are n (%) of participants.
*Based on 84 MedDRA preferred terms for bone fracture.
†MedDRA preferred terms.
‡Hypoglycaemia and cardiac failure are not shown, as they were analyzed separately.
TABLE S7 Incidence rate of adverse events in age groups <65, 65 to <75, 75 to <80, and ≥80 years

| Age Group          | Linagliptin (n = 1548) | Glimepiride (n = 1494) | Linagliptin (n = 1056) | Glimepiride (n = 1070) | Linagliptin (n = 316) | Glimepiride (n = 333) | Linagliptin (n = 94) | Glimepiride (n = 103) |
|--------------------|------------------------|------------------------|------------------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|
| Any AE             | 112.29                 | 131.34                 | 127.35                 | 153.25                 | 147.69                | 167.71                 | 170.33                | 237.49                 |
| Bone fractures*    | 0.94                   | 1.29                   | 1.29                   | 1.52                   | 2.34                  | 2.51                   | 1.62                  | 4.60                   |
| Individual AEs† in ≥10% of any group‡ |                       |                        |                        |                        |                       |                        |                       |                        |
| Hyperglycaemia     | 4.17                   | 4.56                   | 2.13                   | 3.07                   | 2.43                  | 2.27                   | 2.46                  | 2.85                   |
| Nasopharyngitis    | 3.69                   | 3.91                   | 4.68                   | 4.35                   | 4.83                  | 4.02                   | 3.82                  | 3.64                   |
| Hypertension       | 3.17                   | 3.29                   | 3.14                   | 3.62                   | 4.88                  | 4.20                   | 2.77                  | 4.09                   |
| Back pain          | 3.08                   | 2.60                   | 2.75                   | 2.69                   | 2.14                  | 4.07                   | 4.19                  | 2.82                   |
| Diarrhoea          | 2.46                   | 2.05                   | 2.78                   | 2.63                   | 3.57                  | 2.69                   | 3.87                  | 6.17                   |
| Bronchitis         | 2.33                   | 2.24                   | 2.33                   | 2.58                   | 2.32                  | 3.39                   | 5.09                  | 5.18                   |
| Upper respiratory tract infection | 2.29                 | 2.40                   | 2.40                   | 2.63                   | 2.59                  | 1.68                   | 1.38                  | 2.02                   |
| Arthralgia         | 2.18                   | 2.24                   | 2.59                   | 2.22                   | 1.91                  | 2.78                   | 1.92                  | 3.42                   |
| Headache           | 2.17                   | 2.41                   | 1.78                   | 2.06                   | 1.52                  | 1.68                   | 1.35                  | 1.50                   |
| Dizziness          | 1.91                   | 2.32                   | 2.17                   | 2.79                   | 3.01                  | 3.96                   | 2.58                  | 4.46                   |
| Cough              | 1.80                   | 1.83                   | 2.26                   | 2.15                   | 2.65                  | 3.05                   | 2.77                  | 4.40                   |
| Urinary tract infection | 1.69                 | 1.86                   | 3.04                   | 2.99                   | 3.92                  | 3.12                   | 5.04                  | 4.16                   |
| Osteoarthritis     | 1.57                   | 1.83                   | 2.08                   | 2.60                   | 2.81                  | 2.89                   | 2.78                  | 2.83                   |
| Anaemia            | 1.15                   | 0.95                   | 1.75                   | 1.53                   | 2.70                  | 2.44                   | 2.49                  | 2.23                   |
| Cataract           | 1.11                   | 0.94                   | 2.17                   | 2.26                   | 2.63                  | 2.45                   | 2.89                  | 2.01                   |
| Condition        | Age <65 years |          | Age 65 to <75 years |          | Age 75 to <80 years |          | Age ≥80 years |          |
|------------------|---------------|----------|---------------------|----------|---------------------|----------|---------------|----------|
|                  | Linagliptin   | Glimepiride | Linagliptin   | Glimepiride | Linagliptin   | Glimepiride | Linagliptin   | Glimepiride |
| Constipation     | 1.10          | 0.73     | 1.74               | 1.65     | 1.49               | 2.02     | 2.83          | 2.71     |
| Pneumonia        | 0.85          | 0.79     | 1.24               | 1.52     | 2.09               | 2.00     | 1.08          | 3.52     |
| Fall             | 0.74          | 0.75     | 1.56               | 1.56     | 1.94               | 3.18     | 3.61          | 7.66     |
| Contusion        | 0.69          | 0.67     | 0.98               | 1.11     | 1.65               | 1.53     | 1.65          | 3.10     |
| Atrial fibrillation | 0.60         | 0.64     | 1.39               | 1.41     | 1.64               | 2.34     | 1.36          | 3.05     |
| Dyspnoea         | 0.60          | 0.64     | 0.74               | 0.96     | 0.96               | 0.95     | 1.08          | 3.58     |

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.
Data are n patients per 100 years.
*Based on 84 MedDRA preferred terms for bone fracture.
†MedDRA preferred terms.
‡Hypoglycaemia and cardiac failure are not shown, as they were analyzed separately.
FIGURE S1 Time to all-cause mortality. CI, confidence interval; HR, hazard ratio.
FIGURE S2 Time to CV death. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
C ≥75 years

HR 0.89
(95% CI 0.60, 1.30)

| Year | Linagliptin (n) | Glimepiride (n) |
|------|----------------|-----------------|
| 0.0  | 410            | 436             |
| 0.5  | 404            | 432             |
| 1.0  | 399            | 427             |
| 1.5  | 398            | 421             |
| 2.0  | 392            | 415             |
| 2.5  | 387            | 410             |
| 3.0  | 380            | 399             |
| 3.5  | 370            | 389             |
| 4.0  | 355            | 381             |
| 4.5  | 345            | 370             |
| 5.0  | 338            | 357             |
| 5.5  | 320            | 327             |
| 6.0  | 214            | 226             |
| 6.5  | 129            | 138             |
FIGURE S3  Time to non-CV death. CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
C ≥75 years

No. of participants

| Linagliptin (n) | Glimepiride (n) |
|----------------|-----------------|
| 410            | 436             |
| 404            | 432             |
| 399            | 427             |
| 398            | 421             |
| 392            | 415             |
| 387            | 410             |
| 380            | 399             |
| 370            | 389             |
| 370            | 381             |
| 355            | 370             |
| 345            | 357             |
| 338            | 327             |
| 320            | 226             |
| 214            | 138             |

HR 0.81
(95% CI 0.56, 1.17)
FIGURE S4 Clinical outcomes. 3-point MACE, 3-point major adverse CV events (CV death, non-fatal myocardial infarction, or non-fatal stroke); CI, confidence interval; CV, cardiovascular. *95.47% CI.

| Clinical outcomes | Linagliptin | Glimepiride | Hazard ratio (95% CI) | Hazard ratio (95% CI) | P-value for treatment-by-age-group interaction |
|-------------------|------------|------------|----------------------|----------------------|---------------------------------------------|
|                   | n with event / N analyzed (%) | Rate per 100 patient-years | n with event / N analyzed (%) | Rate per 100 patient-years |                                          |
| 3-point MACE      |            |            |                      |                      |                                            |
| <65 years         | 356/3023 (11.8) | 2.07 | 362/3010 (12.0) | 2.12 | 0.98 (0.84, 1.14) | 0.5925 |
| 65 to <75 years   | 144/1558 (9.3) | 1.60 | 126/1502 (8.4) | 1.44 | 1.11 (1.08, 1.14) |                                            |
| 75 to <80 years   | 121/1067 (11.4) | 2.01 | 130/1072 (12.6) | 2.28 | 0.88 (0.89, 1.12) |                                            |
| 75+ years         | 68/318 (20.9) | 3.87 | 67/333 (20.1) | 3.70 | 1.05 (0.94, 1.17) |                                            |
| 250 years         | 5/25 (20.0) | 5.45 | 3/24 (12.5) | 0.31 | 0.99 (0.71, 1.36) |                                            |
| All-cause mortality | 308/3023 (10.2) | 1.68 | 336/3016 (11.2) | 1.84 | 0.51 (0.78, 1.06) | 0.001 |
| <65 years         | 89/1556 (5.9) | 0.96 | 80/1502 (5.3) | 0.99 | 1.00 (0.79, 1.21) |                                            |
| 65 to <75 years   | 116/1067 (11.2) | 1.65 | 130/1072 (12.1) | 2.01 | 0.92 (0.71, 1.18) |                                            |
| 75 to <80 years   | 63/318 (20.1) | 3.79 | 61/333 (24.3) | 4.22 | 0.90 (0.65, 1.24) |                                            |
| 75+ years         | 29/25 (30.0) | 5.02 | 41/243 (16.9) | 7.40 | 0.74 (0.49, 1.19) |                                            |
| CV death          | 169/3023 (5.6) | 0.92 | 168/3010 (5.6) | 0.92 | 1.00 (0.81, 1.24) | 0.7134 |
| <65 years         | 57/1556 (3.7) | 0.50 | 50/1502 (3.3) | 0.54 | 1.10 (0.75, 1.61) |                                            |
| 65 to <75 years   | 64/1067 (6.0) | 1.00 | 61/1072 (5.7) | 0.95 | 1.00 (0.75, 1.30) |                                            |
| 75 to <80 years   | 34/318 (10.8) | 1.87 | 36/333 (10.8) | 1.88 | 1.00 (0.62, 1.59) |                                            |
| 75+ years         | 14/94 (14.9) | 2.71 | 21/153 (13.7) | 3.81 | 0.70 (0.33, 1.52) |                                            |
| Non-CV death      | 130/3023 (4.3) | 0.76 | 139/3016 (5.0) | 0.92 | 0.82 (0.66, 1.03) | 0.0839 |
| <65 years         | 35/1556 (2.2) | 0.36 | 33/1502 (2.2) | 0.37 | 0.59 (0.46, 0.77) |                                            |
| 65 to <75 years   | 54/1067 (5.1) | 0.85 | 60/1072 (5.7) | 0.94 | 0.79 (0.55, 1.13) |                                            |
| 75 to <80 years   | 35/318 (11.1) | 1.92 | 45/333 (13.5) | 2.24 | 0.82 (0.53, 1.27) |                                            |
| 75+ years         | 35/94 (10.0) | 2.91 | 20/153 (19.4) | 3.65 | 0.78 (0.40, 1.52) |                                            |
| Fatal or non-fatal myocardial infarction | 153/3023 (5.1) | 0.88 | 148/3010 (4.9) | 0.88 | 1.03 (0.82, 1.29) | 0.5767 |
| <65 years         | 65/1556 (4.2) | 0.75 | 63/1502 (4.2) | 0.71 | 1.05 (0.74, 1.48) |                                            |
| 65 to <75 years   | 51/1067 (4.8) | 0.84 | 56/1072 (5.4) | 0.95 | 0.88 (0.69, 1.11) |                                            |
| 75 to <80 years   | 28/318 (8.8) | 1.50 | 19/333 (5.7) | 1.03 | 1.45 (0.83, 2.53) |                                            |
| 75+ years         | 9/94 (9.5) | 1.66 | 8/153 (5.2) | 1.57 | 1.07 (0.40, 2.84) |                                            |
| Fatal or non-fatal stroke | 104/3023 (3.4) | 0.59 | 120/3010 (4.0) | 0.69 | 0.86 (0.66, 1.12) | 0.3659 |
| <65 years         | 43/1556 (2.8) | 0.47 | 37/1502 (2.5) | 0.42 | 1.13 (0.73, 1.75) |                                            |
| 65 to <75 years   | 31/1067 (2.9) | 0.51 | 48/1072 (4.5) | 0.78 | 0.65 (0.41, 1.02) |                                            |
| 75 to <80 years   | 21/318 (6.6) | 1.29 | 23/333 (6.9) | 1.24 | 0.97 (0.54, 1.75) |                                            |
| 75+ years         | 15/94 (15.8) | 2.40 | 12/153 (7.8) | 2.43 | 0.79 (0.33, 1.85) |                                            |
| Hospitalization for heart failure or CV death | 236/3023 (7.8) | 1.34 | 234/3010 (7.8) | 1.34 | 1.00 (0.84, 1.21) | 0.1774 |
| <65 years         | 77/1556 (4.9) | 0.84 | 60/1502 (4.0) | 0.67 | 1.25 (0.89, 1.75) |                                            |
| 65 to <75 years   | 82/1067 (7.8) | 1.33 | 98/1072 (9.1) | 1.59 | 0.84 (0.62, 1.21) |                                            |
| 75 to <80 years   | 59/318 (18.7) | 3.42 | 50/333 (15.0) | 2.68 | 1.28 (0.88, 1.86) |                                            |
| 75+ years         | 18/94 (19.1) | 3.75 | 26/153 (16.9) | 5.11 | 0.73 (0.40, 1.33) |                                            |

Favours Linagliptin Favours Glimepiride
FIGURE S5 Change in HbA1c. Baseline values are descriptive; post-baseline values are from a mixed model for repeated measures. BL, baseline; CI, confidence interval; HbA1c, glycated haemoglobin; SE, standard error. Part A reprinted with permission from Rosenstock et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322;1158-1166.
C 65 to <75 years

Weighted average mean difference up to week 256:
0.01% (95% CI: −0.06, 0.08)
0.07 mmol/mol (95% CI: −0.71, 0.85)

D ≥75 years

Weighted average mean difference up to week 256:
0.04% (95% CI: −0.08, 0.15)
0.42 mmol/mol (95% CI: −0.84, 1.69)
FIGURE S6 Change in body weight. Baseline values are descriptive; post-baseline values are from a mixed model for repeated measures. BL, baseline; CI, confidence interval; SE, standard error. Part A reprinted with permission from Rosenstock et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322;1158-1166.
FIGURE S7 “Treatment sustainability” key secondary endpoints. CI, confidence interval; HbA1c, glycated haemoglobin. *Receiving treatment and maintaining HbA1c ≤7.0% at final visit (onwards from titration) without the need for rescue medication, without any moderate/severe hypoglycaemic episodes, and without >2% weight gain; moderate hypoglycaemia defined as investigator-reported episode of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL, severe hypoglycaemia defined as event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. †Receiving treatment and maintaining HbA1c ≤7.0% at final visit (onwards from titration) without the need for rescue medication and without >2% weight gain.
**FIGURE S8** Association between moderate or severe hypoglycaemia and subsequent falls or bone fractures. Preceding hypoglycaemia was determined at the time of fall or bone fracture event/censoring only for n/N (%), while hazard ratios (95% CIs) and P-values result from Cox regression with time-varying covariate for hypoglycaemia. CI, confidence interval. *Investigator-reported episode of symptomatic hypoglycaemia with plasma glucose ≤70 mg/dL or episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. †Based on 84 preferred terms for bone fractures from the Medical Dictionary for Regulatory Activities version 21.0.

| Outcome          | Preceding hypoglycaemia | No preceding hypoglycaemia | Hazard ratio (95% CI) | P-value | P-value for treatment-by-time-dependent hypoglycaemia-event interaction |
|------------------|-------------------------|----------------------------|-----------------------|---------|-----------------------------------------------------------------------|
| Falls or bone fractures† | 120/1085 (11.1)          | 528/4926 (10.7)            | 1.32 (1.07, 1.63)     | 0.0093  |                                                                       |
| Linagliptin      | 13/196 (7.0)             | 279/2825 (9.9)             | 0.96 (0.55, 1.68)     | 0.8916  | 0.2159                                                               |
| Glimepiride      | 107/899 (11.9)           | 249/2101 (11.9)            | 1.41 (1.12, 1.77)     | 0.0036  |                                                                       |
| Falls            | 67/1098 (6.1)            | 312/4913 (6.4)             | 1.27 (0.96, 1.68)     | 0.0949  |                                                                       |
| Linagliptin      | 6/186 (3.2)              | 166/2823 (6.0)             | 0.73 (0.32, 1.68)     | 0.4540  | 0.1430                                                               |
| Glimepiride      | 61/910 (6.7)             | 144/2090 (6.9)             | 1.40 (1.03, 1.90)     | 0.0094  |                                                                       |
| Fractures†       | 77/1103 (7.0)            | 320/4908 (6.5)             | 1.30 (1.00, 1.69)     | 0.0533  |                                                                       |
| Linagliptin      | 9/192 (4.7)              | 165/2819 (5.9)             | 1.09 (0.56, 2.13)     | 0.8032  | 0.5740                                                               |
| Glimepiride      | 68/911 (7.5)             | 155/2089 (7.4)             | 1.34 (1.01, 1.79)     | 0.0451  |                                                                       |

No preceding hypoglycaemia  Preceding hypoglycaemia