Supplemental Online Content

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eTable 1. Summary List of Pivotal Clinical Trials by Treatment Indication and Generic Name

eTable 2. Detailed Age Distribution by Treatment Indication

This supplemental material has been provided by the authors to give readers additional information about their work.
|   | Treatment Indication | Generic Name   | Clinical Trial Number | Enrolled Participants, n<sup>a</sup> |
|---|----------------------|----------------|------------------------|--------------------------------------|
| 1 | Depression           | Vilazodone     | NCT00285376            | 397                                  |
| 2 | Depression           | Vilazodone     | NCT00683592            | 466                                  |
| 3 | Depression           | Vilazodone     | NCT01473394            | 505                                  |
| 4 | Depression           | Vilazodone     | NCT01473381            | 853                                  |
| 5 | Depression           | Vortioxetine   | NCT00839423            | 313                                  |
| 6 | Depression           | Vortioxetine   | NCT00735709            | 417                                  |
| 7 | Depression           | Vortioxetine   | NCT01140906            | 458                                  |
| 8 | Depression           | Vortioxetine   | NCT01153009            | 445                                  |
| 9 | Depression           | Vortioxetine   | NCT01163266            | 457                                  |
|10 | Depression           | Vortioxetine   | NCT00811252            | 300                                  |
|11 | Depression           | Vortioxetine   | NCT00596817            | 396                                  |
|12 |                  | Levomilnacipran<sup>f</sup> | NCT00969709 | 704 |
|13 |                  | Levomilnacipran<sup>f</sup> | NCT01377194 | 557 |
|14 |                  | Levomilnacipran<sup>f</sup> | NCT01034462 | 429 |
|15 |                  | Levomilnacipran<sup>f</sup> | NCT02288325 | 324 |
|16 |                  | Esketamine<sup>f</sup> | NCT02418585 | 236 |
|17 |                  | Esketamine<sup>f</sup> | NCT02493868 | 720 |
|18 | Heart Failure       | Ivabradine     | NCT02441218            | 6559                                 |
|19 | Heart Failure       | Ivabradine     | NCT00143507            | 10917                                |
|20 | Heart Failure       | Sacubitril; Valsartan | NCT01035255 | 8442 |
|21 | Insomnia            | Lemborexant    | NCT02952820            | 949                                  |
|22 | Insomnia            | Lemborexant    | NCT02783729            | 743                                  |
|23 | Insomnia            | Suvorexant     | NCT01097616            | 1023                                 |

<sup>a</sup> n = number of participants enrolled in the clinical trial.
|   | Non-small Cell Lung Cancer (NSCLC) |   |   |
|---|-----------------------------------|---|---|
| 24 | NCT01097629                        | 1021 |   |
| 25 | NCT00792298                        | 253  |   |
| 26 | Erlotinibf                         | NCT00556712 | 889 |
| 27 | Crizotinib                         | NCT00446225 | 173 |
| 28 | Afatinib                           | NCT01328951 | 643 |
| 29 | NCT01154140                        | 343  |   |
| 30 | NCT00932893                        | 347  |   |
| 31 | NCT00949650                        | 345  |   |
| 32 | NCT01121393                        | 364  |   |
| 33 | Ramucirumab                        | NCT01168973 | 1253 |
| 34 | Ceritinib                          | NCT01828099 | 376 |
| 35 | NCT02039674                        | 123  |   |
| 36 | NCT02578680                        | 646  |   |
| 37 | Pembrolizumab                      | NCT02142738 | 305 |
| 38 | NCT02220894                        | 1274 |   |
| 39 | NCT01905657                        | 1033 |   |
| 40 | NCT02775435                        | 559  |   |
| 41 | Nivolumab                          | NCT01673867 | 582 |
| 42 | NCT01642004                        | 272  |   |
| 43 | Gefitinib\(^f\)                    | NCT00322452 | 1217 |
| 44 | Osimertinib                        | NCT02296125 | 556 |
| 45 | NCT02151981                        | 419  |   |
| 46 | Necitumumab                        | NCT00981058 | 1094 |
| 47 | Alectinib                          | NCT02075840 | 303 |

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|   |   |   |
|---|---|---|
|49 | Atezolizumab | NCT02367781 | 723 |
|50 | Atezolizumab | NCT02366143 | 1202 |
|51 | Atezolizumab | NCT02008227 | 1225 |
|52 | Brigatinib | NCT02094573 | 222 |
|53 | Durvalumab | NCT02125461 | 713 |
|54 | Dacomitinib | NCT01774721 | 452 |
|55 | Albumin-bound paclitaxel | NCT00540514 | 1052 |
|56 | Pemetrexed | NCT00087711 | 1725 |
|57 | Pemetrexed | NCT00102804 | 663 |
|58 | Pemetrexed | NCT00789373 | 539 |
|59 | Non-valvular Atrial Fibrillation (NVAF) Stroke Prevention | Dabigatran | NCT00262600 | 18113 |
|60 | Non-valvular Atrial Fibrillation (NVAF) Stroke Prevention | Rivaroxaban | NCT00403767 | 14264 |
|61 | Non-valvular Atrial Fibrillation (NVAF) Stroke Prevention | Apixaban | NCT00412984 | 18201 |
|62 | Non-valvular Atrial Fibrillation (NVAF) Stroke Prevention | Apixaban | NCT00496769 | 5598 |
|63 | Non-valvular Atrial Fibrillation (NVAF) Stroke Prevention | Edoxaban | NCT00781391 | 21105 |
|64 | Osteoporosis | Denosumab | NCT00089791 | 7808 |
|65 | Osteoporosis | Denosumab | NCT00980174 | 242 |
|66 | Osteoporosis | Denosumab | NCT01575873 | 795 |
|67 | Bazedoxifene acetate + conjugated estrogen | NCT00675688 | 3101 |
|68 | Bazedoxifene acetate + conjugated estrogen | NCT00808132 | 590 |
|69 | Abaloparatide | NCT01343004 | 1645 |
|70 | Romosozumab-aqqg | NCT01575834 | 7180 |
|71 | Romosozumab-aqqg | NCT01631214 | 4093 |
|72 |   | NCT01081834 | 584 |
|73 |   | NCT01106677 | 1284 |
|   | Type 2 Diabetes (T2D) | Canagliflozin | NCT01809327 | 1186 |
|---|----------------------|---------------|-------------|------|
| 75 |                      |               | NCT00968812 | 1450 |
| 76 |                      |               | NCT01032629 | $127^b+1718^c$ |
| 77 |                      |               | NCT01106625 | 469  |
| 78 |                      |               | NCT02025907 | 218  |
| 79 |                      |               | NCT01137812 | 755  |
| 80 |                      |               | NCT01106690 | 342  |
| 81 |                      |               | NCT01106651 | 714  |
| 82 |                      |               | NCT01064414 | 269  |
| 83 |                      | Canagliflozin | NCT00528372 | 485  |
| 84 |                      |               | NCT00736879 | 282  |
| 85 |                      |               | NCT00859898 | 638  |
| 86 |                      | Dapagliflozin | NCT00643851 | 598  |
| 87 |                      |               | NCT00528879 | 546  |
| 88 |                      |               | NCT00660907 | 814  |
| 89 |                      |               | NCT00680745 | 596  |
| 90 |                      |               | NCT01392677 | 218  |
| 91 |                      |               | NCT00683878 | 420  |
| 92 |                      |               | NCT00984867 | 451  |
| 93 |                      |               | NCT00673231 | 807  |
| 94 |                      |               | NCT02229396 | 694  |
| 95 |                      |               | NCT02413398 | 321  |
| 96 |                      |               | NCT01177813 | 986  |
| 97 |                      |               | NCT01159600 | $637^d+666^e$ |
| 98 |                      |               | NCT01719003 | 1364 |

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|   | Empagliflozin |   | Ertugliflozin |   | Linagliptin |   |
|---|--------------|---|--------------|---|------------|---|
| 99 | NCT01422876  | 686 | NCT01958671  | 461 | NCT00740051 | 227 |
| 100| NCT01167881  | 1545| NCT02033889  | 621 | NCT00621140 | 503 |
| 101| NCT01210001  | 498 | NCT01999218  | 1326| NCT00601250 | 701 |
| 102| NCT01011868  | 494 | NCT02036515  | 463 | NCT00798161 | 791 |
| 103| NCT01306214  | 563 | NCT02099110  | 1233| NCT00622284 | 1560|
| 104| NCT01164501  | 738 | NCT02226003  | 291 | NCT00641043 | 389 |
| 105|              |    |              |    | NCT00819091 | 245 |
| 106|              |    |              |    | NCT00602472 | 1058|
| 107|              |    |              |    | NCT00954447 | 1261|
| 108|              |    |              |    | NCT00800683 | 133 |
| 109|              |    |              |    | NCT00286455 | 329 |
| 110|              |    |              |    | NCT00395512 | 655 |

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|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
| 124 |   | Alogliptin | NCT01023581 | 784 |
| 125 |   |   | NCT00286442 | 527 |
| 126 |   |   | NCT00328627 | 1554 |
| 127 |   |   | NCT00286494 | 493 |
| 128 |   |   | NCT00432276 | 803 |
| 129 |   |   | NCT00286468 | 500 |
| 130 |   |   | NCT00286429 | 390 |
| 131 |   | Liraglutide | NCT00294723 | 746 |
| 132 |   |   | NCT00318461 | 1091 |
| 133 |   |   | NCT00700817 | 665 |
| 134 |   |   | NCT00856986 | 988 |
| 135 |   |   | NCT00318422 | 1041 |
| 136 |   |   | NCT00331851 | 581 |
| 137 |   |   | NCT00518882 | 464 |
| 138 |   |   | NCT00333151 | 530 |
| 139 |   |   | NCT01620489 | 277 |
| 140 |   | Lixisenatide | NCT00688701 | 241 |
| 141 |   |   | NCT00763451 | 323 |
| 142 |   |   | NCT01169779 | 391 |
| 143 |   |   | NCT00707031 | 634 |
| 144 |   |   | NCT00713830 | 859 |
| 145 |   |   | NCT00763815 | 484 |
| 146 |   |   | NCT00715624 | 496 |
| 147 |   |   | NCT00866658 | 311 |
| 148 |   |   | NCT00975286 | 446 |
|   |   |   | Semaglutide sc |   |   |
|---|---|---|---------------|---|---|
|149|   |   | NCT01768559   | 894|   |
|150|   |   | NCT02054897   | 388|   |
|151|   |   | NCT01930188   | 1231|   |
|152|   |   | NCT01885208   | 813|   |
|153|   |   | NCT02128932   | 1089|   |
|154|   |   | NCT02305381   | 397|   |
|155|   |   | NCT02906930   | 703|   |
|156|   |   | NCT02863328   | 822|   |
|157|   |   | NCT02607865   | 1864|   |
|158|   | Semaglutide oral⁵ | NCT02863419   | 711|   |
|159|   |   | NCT02827708   | 324|   |
|160|   |   | NCT03021187   | 731|   |
|161|   | Insulin degludec | NCT00982644   | 1030|   |
|162|   |   | NCT01068665   | 457|   |
|163|   |   | NCT01059799   | 435|   |
|164|   |   | NCT01006291   | 687|   |
|165|   |   | NCT00972283   | 992|   |
|166|   |   | NCT01046110   | 447|   |

a: Clinical trial population is collected from FDA’s internal database.
b: Refers to study 1 (Add-on Combination Therapy With Sulfonylurea)
c: Refers to study 2 (Add-On Combination Therapy With Insulin (With or Without Other Antihyperglycemic Agents))
d: Refers to study 1 (Empagliflozin vs. Placebo as add-on to Metformin)
e: Refers to study 2 (Empagliflozin vs. Placebo as add-on to Metformin Plus Sulfonylurea)
f: Drugs not included as part of the FDA, CDER’s annual approved new molecular entities list from 2010-2019 but approved for treatment indications during this time period.
| Age Range (yrs) | Depression (n=7977) | Heart Failure (n=25918) | Insomnia (n=3989) | Non-small Cell Lung Cancer (n=22427) | Non-valvular Atrial Fibrillation Stroke Prevention (n=77281) | Osteoporosis (n=25454) | Type 2 Diabetes (n=66512) |
|-----------------|---------------------|-------------------------|-------------------|-------------------------------------|---------------------------------------------------------------|------------------------|--------------------------|
| 15-19           | 106 (1)             | 6 (0)                   | 9 (0)             | 7 (0)                               | 1 (0)                                                         | 0 (0)                  | 13 (0)                   |
| 20-24           | 546 (7)             | 26 (0)                  | 66(2)             | 22 (0)                              | 4 (0)                                                         | 1 (0)                  | 106 (0)                  |
| 25-29           | 735 (9)             | 59 (1)                  | 131(3)            | 90 (0)                              | 21 (0)                                                        | 3 (0)                  | 312 (0)                  |
| 30-34           | 749 (9)             | 134 (1)                 | 176 (4)           | 197 (1)                             | 51 (0)                                                        | 12 (0)                 | 915 (1)                  |
| 35-39           | 803 (10)            | 295 (1)                 | 211(5)            | 407 (2)                             | 150 (0)                                                       | 13 (0)                 | 2203 (3)                 |
| 40-44           | 984 (12)            | 600 (2)                 | 277 (7)           | 808 (4)                             | 393 (1)                                                       | 66 (0)                 | 4309 (6)                 |
| 45-49           | 1065 (13)           | 1193 (5)                | 316 (8)           | 1518 (7)                            | 978 (1)                                                       | 395 (2)                | 7394 (11)                |
| 50-54           | 1029 (13)           | 2180 (8)                | 329 (8)           | 2574 (11)                           | 2922 (4)                                                      | 1406 (6)               | 10455 (16)               |
| 55-59           | 854 (11)            | 4771 (18)               | 586 (15)          | 3750 (17)                           | 5561 (7)                                                      | 1552 (6)               | 12672 (19)               |
| 60-64           | 546 (7)             | 4454 (17)               | 451 (11)          | 4346 (19)                           | 8882 (11)                                                     | 3257 (13)              | 12397 (19)               |
| 65-69           | 342 (4)             | 4617 (18)               | 708 (18)          | 4130 (18)                           | 13268 (17)                                                    | 5054 (20)              | 8621 (13)                |
| 70-74           | 162 (2)             | 3828 (15)               | 476 (12)          | 2916 (13)                           | 15540 (20)                                                    | 6371 (25)              | 4813 (7)                 |
| 75-79           | 43 (1)              | 2573 (10)               | 177 (4)           | 1261 (6)                            | 16886 (22)                                                    | 4465 (18)              | 1900 (3)                 |
| 80-84           | 10 (0)              | 959 (4)                 | 63 (2)            | 305 (1)                             | 9309 (12)                                                     | 2188 (9)               | 328 (0)                  |
| ≥85             | 3 (0)               | 223 (1)                 | 13 (0)            | 64 (0)                              | 3315 (4)                                                      | 671 (3)                | 55 (0)                   |
| NAa             | -                   | -                       | -                 | 32(0)                               | -                                                             | -                      | 19(0)                    |

The number zero “0” in parenthesis represents a rounded off number less than 0.5% of the actual value.

a: missing age