**Appendix**

**Search Strategy**

**Pubmed**

("exenatide"[Supplementary Concept] OR "byetta"[tiab] OR "bydureon"[tiab] OR "exendin 4"[tiab] OR "exenatide"[tiab] OR “liraglutide”[Supplementary Concept] OR "liraglutide"[tiab] OR "victoza"[tiab] OR "Glucagon-Like Peptide 1"[Mesh] OR "Glucagon-Like Peptide 1"[tiab] OR “NN 2211”[tiab] OR "lixisenatide"[tiab] OR "ZP10A peptide"[Supplementary Concept] OR “AVE 0010”[tiab] OR "ZP10A peptide"[tiab] OR "lyxumia"[tiab] OR "taspoglutide"[Supplementary Concept] OR "taspoglutide"[tiab] OR "teduglutide"[Supplementary Concept] OR "teduglutide"[tiab] OR "albiglutide"[Supplementary Concept] OR "albiglutide"[tiab] OR "semaglutide"[tiab] OR "LC15-0444"[Supplementary Concept] OR "LC15-0444"[tiab] OR "dipeptidyl-peptidase IV inhibitors"[Supplementary Concept] OR "dipeptidyl-peptidase IV inhibitors"[Mesh] OR "dipeptidyl-peptidase IV inhibitors"[tiab] OR "dipeptidyl-peptidase IV inhibitor"[Supplementary Concept] OR "dipeptidyl-peptidase IV inhibitor"[Mesh] OR "dipeptidyl-peptidase IV inhibitor"[tiab] OR "vildagliptin"[Supplementary Concept] OR "vildagliptin"[tiab] OR "galvus"[tiab] OR “eucreas”[tiab] OR “icandra”[tiab] OR “jalra”[tiab] OR “xiliarx”[tiab] OR “zomarist”[tiab] OR "sitagliptin"[Supplementary Concept] OR "sitagliptin"[tiab] OR "MK 0431"[tiab] OR "januvia"[tiab] OR “efficib”[tiab] OR “janumet”[tiab] OR “ristaben”[tiab] OR “ristfor”[tiab] OR “tesavel”[tiab] OR “velmetia”[tiab] OR “xelevia”[tiab] OR "janumet" [Supplementary Concept] OR "saxagliptin"[Supplementary Concept] OR "saxagliptin"[tiab] OR "BMS 477118"[tiab] OR "5-hydroxysaxagliptin"[Supplementary Concept] OR "5-hydroxysaxagliptin"[tiab] OR "komboglyze"[tiab] OR "onglyza"[tiab] OR "linagliptin"[Supplementary Concept] OR "linagliptin"[tiab] OR “jentadueto”[tiab] OR "tradjenta"[tiab] OR "BI 1356"[tiab] OR "alogliptin"[Supplementary Concept] OR "alogliptin"[tiab] OR "SYR 322"[tiab]) OR "septagliptin"[tiab] OR "anagliptin"[tiab] OR "bisegliptin"[tiab] OR "carmegliptin"[Supplementary Concept] OR "carmegliptin"[tiab] OR "denagliptin"[Supplementary Concept] OR "denagliptin"[tiab] OR "dutogliptin"[Supplementary Concept] OR "dutogliptin"[tiab] OR "gosogliptin"[Supplementary Concept] OR "gosogliptin"[tiab] OR "isoleucine thiazolidide"[Supplementary Concept] OR "isoleucine thiazolidide"[tiab] OR "valine pyrrolidide"[Supplementary Concept] OR "valine pyrrolidide"[tiab] OR "evogliptin"[tiab] OR "gemigliptin"[tiab] OR "melogliptin"[tiab] OR "omarigliptin"[tiab] OR "psn 9301"[tiab] OR "teneligliptin"[tiab] OR "trelagliptin"[tiab]) AND ("Pancreatic Neoplasms"[Mesh] OR "Pancreatitis"[Mesh] OR "pancreas"[tiab] OR "pancreatitis"[tiab] OR "pancreatic"[tiab] OR "pancreatic cancer"[tiab] OR "serum amylase"[tiab] OR "serum lipase"[tiab] OR "Islet Cell Adenoma"[tiab] OR "Insulinoma"[tiab] OR "Islet Cell Carcinoma"[tiab] OR "Gastrinoma"[tiab] OR "Glucagonoma"[tiab] OR "Somatostatinoma"[tiab] OR "Vipoma"[tiab] OR "[Pancreatic Ductal](http://www.ncbi.nlm.nih.gov/mesh/68021441) Carcinoma"[tiab] OR "Islet Cell Adenomas"[tiab] OR "Insulinomas"[tiab] OR "Islet Cell Carcinomas"[tiab] OR "Gastrinomas"[tiab] OR "Glucagonomas"[tiab] OR "Somatostatinomas"[tiab] OR "Vipomas"[tiab] OR "[Pancreatic Ductal](http://www.ncbi.nlm.nih.gov/mesh/68021441) Carcinomas"[tiab]) AND English[lang] NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))

**Appendix Table 1**. Characteristics of GLP-1 based agents in randomized controlled trials included in analysis of pancreatic events

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study Source (author, year) | Location (number of centers) | Year of Study Completion | Total Duration (weeks) | Duration of GLP-1 exposure (weeks) | Participant Disease | Arms | Number of participants | Mean age, years (SD) | Female, N (%) |
| Ross et al, 2012[21] (NCT01012037) | Multi-national (84 centers in 9 countries) | 2010 | 43 | 12 | Type 2 Diabetes | Linagliptin 2.5mg bid | 223 | 58.7  (9.9) | 85  (38.1) |
| Linagliptin 5mg qd | 224 | 58.4 (10.6) | 103 (46.0) |
| Placebo | 44 | 59.9 (10.7) | 23  (52.3) |
| Haak et al, 2012[22]  (NCT00798161) | Multi-national (133 clinics in 14 countries) | 2010 | 73 | 24 | Type 2 Diabetes | Linagliptin 5mg qd | 142 | 56.2 (10.8) | 62 (43.7) |
| Metformin 500mg bid | 144 | 52.9 (10.4) | 62 (43.1) |
| Metformin 1000mg bid | 147 | 55.2 (10.6) | 69 (46.9) |
| Linagliptin 2.5mg qd + Metformin 500mg bid | 143 | 55.6 (11.2) | 73 (49.0) |
| Linagliptin 2.5mg qd + Metformin 1000mg bid | 143 | 56.4 (10.7) | 66 (46.2) |
| Placebo | 72 | 55.7 (11.0) | 36 (50) |
| NCT00328172[23] | Multi-national (71 sites in 6 countries) | 2007 | 65 | 12 | Type 2 Diabetes | Linagliptin 0.5mg | 58 | 58.0 (9.4) | 13 (22.4) |
| Linagliptin 2.5mg | 57 | 59.8 (10.3) | 30 (52.6) |
| Linagliptin 5.0mg | 55 | 56.6 (9.6) | 24 (43.6) |
| Metformin | 65 | 53.7 (10.7) | 26 (40.0) |
| Placebo | 67 | 58.6 (8.9) | 34 (50.7) |
| Yki-Jarvinen et al, 2013[24, 25]  (NCT00954447) | Multi-national (169 sites in 19 countries) | 2011 | 108 | 52 | Type 2 Diabetes | Linagliptin 5.0mg | 631 | 59.7 (9.9) | 302 (47.9) |
| Placebo | 630 | 60.4 (10.0) | 301 (47.8) |
| NCT00654381[26] | Japan | 2010 | 91 | 12 | Type 2 Diabetes | Linagliptin 5.0mg | 159 | 60.3  (9.4) | 48 (30.2) |
| Linagliptin 10.0mg | 160 | 61.3 (10.0) | 48 (30.0) |
| Voglibose | 162 | 58.5  (9.9) | 47 (29.0) |
| Placebo | 80 | 59.7  (8.9) | 23 (28.7) |
| NCT00622284[27] | Multi-national (221 sites in 16 countries) | 2010 | 146 | 104 | Type 2 Diabetes | Linagliptin | 776 | 59.8  (9.4) | 314  (40.5) |
| Glimepiride | 775 | 59.8  (9.4) | 304  (39.2) |
| BI Trial No: 1218.15/ U09-2519-01[28] | Multi-national (43 sites in 7 countries) | 2009 | 61 | 24 | Type 2 Diabetes | Linagliptin 5mg + Pioglitazone 30mg | 259 | NR | NR |
| Pioglitazone 30mg + Placebo | 130 | NR | NR |
| BI Trial No: 1218.52/U11-1782-01[29] | Multi-national (101 sites in 14 countries) | 2011 | 102 | 54 | Type 2 Diabetes | Linagliptin 2.5mg + Metformin (500mg and 1000mg bid) | 396 | NR | NR |
| Metformin 1000mg bid | 170 | NR | NR |
| BI Trial No: 1218.63/U11-1781-02[30] | Multi-national (33 sites in 5 countries) | 2011 | 67 | 24 | Type 2 Diabetes | Linagliptin 5mg | 162 | NR | 46 (28.4) |
| Placebo | 79 | NR | 30 (38.0) |
| BI Trial No: 1218.75/U12-3204-01[31] | Multi-center study (Black/African American patients only) | 2011 | 55 | 24 | Type 2 Diabetes | Linagliptin 5mg | 106 | NR | NR |
| Placebo | 120 | NR | NR |
| BI Trial No: 1218.61/U13-3124-01[32] | Multi-national study (4 countries) | 2012 | 123 | 24 | Type 2 Diabetes | Linagliptin 5mg | 183 | NR | NR |
| Placebo | 89 | NR | NR |
| BI Trial No: 1218.65/U12-2143-01[33] | Multi-national study (19 sites in 3 countries) | 2012 | 74 | 24 | Type 2 Diabetes | Linagliptin 5mg | 205 | 82%(<65  years) | NR |
| Placebo | 100 | 83% (<65 years) | NR |
| BI Trial No: 1218.64/U13-1283-01[34] | Multi-national study (52 sites in 9 countries) | 2012 | 117 | 52 | Type 2 Diabetes | Linagliptin 5mg | 113 | NR | 43 (38.1) |
| Placebo (first 12 weeks)/ Glimepiride (next 40 weeks) | 122 | NR | 43 (35.2) |
| BI Trial No: 1218.66/U12-2076-01[35] | Multi-national study (19 sites in 3 countries | 2012 | 80 | 24 | Type 2 Diabetes | Linagliptin 5mg | 200 | 84.0% (<65 years) | NR |
| Placebo | 99 | 89.9% (<65 years) | NR |
| Rosenstock et al, 2009[36] (NCT00286429) | Multi-national study (110 sites in 13 countries) | 2007 | 65 | 26 | Type 2 Diabetes | Alogliptin 12.5 mg | 131 | 55.4 (9.8) | 76 (58) |
| Alogliptin 25 mg | 129 | 55.9 (10.2) | 85 (66) |
| Placebo | 130 | 55.0 (10.6) | 68 (52) |
| White et al, 2013[37] (NCT00968708) | Multi-national study (898 centers in 49 countries) | 2013 | 193 | 76 (median) | Type 2 Diabetes | Alogliptin | 2701 | 36.0% (≥65 years) | 873 (32.3) |
| Placebo | 2679 | 34.9% (≥65 years) | 856 (32.0) |
| NCT01318135[38] | Japan (58 sites) | 2010 | 52 | 52 | Type 2 Diabetes | Alogliptin 12.5mg qd + Glimepiride 1-6mg qd or bid | 150 | 38.0% (≥65 years) | 53 (35.3) |
| Alogliptin 25mg qd + Glimepiride 1-6mg qd or bid | 152 | 30.9% (≥65 years) | 52 (34.2) |
| NCT01289119[39] | Multi-national study (21 sites in 3 countries) | 2011 | 52 | 16 | Type 2 Diabetes | Alogliptin monotherapy | 92 | 51.6 (10.41) | 37 (40.2) |
| Metformin | 98 | 53.2 (9.46) | 50 (51.0) |
| Metformin + Alogliptin Add-on Therapy | 99 | 53.0 (9.88) | 48 (48.5) |
| Pioglitazone | 63 | 51.8 (10.37) | 24 (38.1) |
|  |  |  |  |  |  | Pioglitazone + Alogliptin Add-on Therapy | 61 | 52.6 (9.44) | 33 (54.1) |
| Placebo | 93 | 53.1 (8.88) | 39 (41.9) |
| NCT01263496[40] | Japan (58 sites) | 2008 | 72 | 52 | Type 2 Diabetes | Alogliptin 6.25mg qd | 96 | 28.1 (≥65 years) | 26 (27.1) |
| Alogliptin 12.5 mg qd | 101 | 33.7 (≥65 years) | 29 (28.7) |
| Alogliptin 25mg qd | 97 | 34.0 (≥65 years) | 22 (22.7) |
| Alogliptin 50mg qd | 97 | 32.9 (≥65 years) | 29 (29.9) |
| Voglibose 0.2mg tid | 83 | 38.6 (≥65 years) | 27 (32.5) |
| NCT00328627[41] | Multi-national study (90 sites in 19 countries) | 2008 | 93 | 26 | Type 2 Diabetes | Alogliptin 12.5mg + Placebo | 128 | 53.1  (9.59) | 61 (47.6) |
| Alogliptin 25mg + Placebo | 129 | 53.7  (9.31) | 79 (61.2) |
| Placebo | 129 | 55.2  (9.89) | 68 (52.7) |
| NCT00395512[42] | Multi-national study (268 sites in 23 countries) | 2008 | 67 | 26 | Type 2 Diabetes | Alogliptin 25 mg + Pioglitazone 30 mg | 164 | 52.8   (11.01) | 91 (55.5) |
| Alogliptin 12.5 mg + Pioglitazone 30 mg | 164 | 53.5   (11.37) | 83 (50.6) |
| Pioglitazone 30 mg | 163 | 51.5   (10.72) | 73 (44.8) |
| Kikuchi et al, 2010[43] (NCT00325117) | Japan (26 sites) | 2007 | 52 | 12 | Type 2 Diabetes | Vildagliptin 50mg bid + glimepiride | 102 | 59.2  (9.8) | 27 (26.5) |
| Placebo + glimepiride | 100 | 60.3 (10.1) | 31 (31.0) |
| Lukashevich et al, 2011[44]  (NCT00646542) | Multi-national study (12 countries) | 2010 | 291 | 24 | Type 2 Diabetes | Vildagliptin 50mg qd (moderate RI) | 165 | 67.7  (8.8) | 69 (41.8) |
| Placebo (moderate RI) | 129 | 69.7  (7.3) | 49 (38.0) |
| Vildagliptin 50mg qd (severe RI) | 124 | 64.1  (9.2) | 59 (47.6) |
| Placebo (severe RI) | 97 | 64.5 (10.8) | 44 (45.4) |
| Strain et al, 2013[45]  (NCT01257451) | Multi-national study (45 centers in 7 countries) | 2012 | 64 | 24 | Type 2 Diabetes | Vildagliptin | 139 | 75.1  (4.3) | 66 (47.5) |
| Placebo | 139 | 74.4  (4.0) | 86 (61.9) |
| NCT00106340[46] (CLAF237A2308) | Multi-national study (402 centers in 25 countries) | 2008 | 166 | 104 | Type 2 Diabetes | Vildagliptin 50mg bid + Metformin | 1562 | 57.5 (9.07) | 733  (46.9) |
| Glimepiride up to 6mg qd + Metformin | 1556 | 57.5 (9.19) | 718 (46.1) |
| NCT00300287[47] (CLAF237A2307) | Multi-national study (69 centers in 6 countries) | 2006 | 85 | 52 | Type 2 Diabetes | Vildagliptin 50mg qd | 156 | 63.27 (10.18) | 63 (40.4) |
| Placebo | 150 | 62.84 (11.03) | 61 (40.7) |
| CLAF237A1301[48] | Japan (51 centers) | 2007 | 44 | 12 | Type 2 Diabetes | Vildagliptin 50mg bid | 188 | 60.3 (10.48) | 67 (35.6) |
| Voglibose 0.2mg tid | 192 | 58.0 (9.32) | 62 (32.3) |
| CLAF237A23119[49] | United States (796 centers) | 2007 | 53 | 12 | Type 2 Diabetes | Vildagliptin 100mg + Metformin | 1776 | 55.3 | 864 (48.6) |
| Thiazolinedione + Metformin | 888 | 56.2 | 467 (52.6) |
| NCT00110240[50] (CLAF237A2323) | Multi-national study (31 centers in 3 countries) | 2006 | 87 | 24 | Type 2 Diabetes | Vildagliptin 50mg bid | 441 | 51.79 (10.13) | 176 (40.0) |
| Acarbose up to 100mg tid | 220 | 51.93 (10.34) | 81 (37.0) |
| NCT00327015[51] | Multi-national study (211 sites in 13 countries) | 2007 | 78 | 24 | Type 2 Diabetes | Saxagliptin 5mg + Metformin 500mg | 320 | 51.95 (10.43) | 155 (48.4) |
|  |  |  |  |  |  | Saxagliptin 10mg + Metformin 500mg | 323 | 52.08 (11.59) | 177 (54.8) |
|  |  |  |  |  |  | Metformin 500mg + Placebo | 328 | 51.83 (10.74) | 165 (50.3) |
| Hollander et al, 2011[52]  (NCT00295633) | Multi-national study (133 sites in 7 countries) | 2007 | 82 | 24 | Type 2 Diabetes | Saxagliptin 2.5mg + TZD | 195 | 54.9 (9.7) | 89 (45.6) |
| Saxagliptin 5mg + TZD | 186 | 53.2 (10.6) | 97 (52.2) |
| Placebo + TZD | 184 | 54.0 (10.1) | 99 (53.8) |
| NCT00757588[53] | Multi-national study (80 sites in 10 countries) | 2010 | 73 | 24 | Type 2 Diabetes | Saxagliptin 5mg + Insulin | 304 | 57.2  (9.4) | 184 (60.5) |
| Placebo + Insulin | 151 | 57.3  (9.3) | 83 (54.9) |
| Scirica et al, 2013[54]  (NCT01107886) | Multi-national study (788 sites in 26 countries) | 2013 | 156 | 109 | Type 2 Diabetes | Saxagliptin | 8280 | 65.1  (8.5) | 2768 (33.4) |
| Placebo | 8212 | 65.0  (8.6) | 2687 (32.7) |
| Goke et al, 2013[55]  (NCT00575588) | Multi-national study (130 sites in 11 countries) | 2010 | 139 | 104 | Type 2 Diabetes | Saxagliptin + Metformin | 428 | 57.5 (10.26) | 216 (50.5) |
| Glipizide + Metformin | 430 | 57.59 (10.37) | 198  (46.1) |
| NCT003160825[6] | Multi-national study (74 sites in 4 countries) | 2007 | 74 | 24 | Type 2 Diabetes | Saxagliptin 2.5/5 mg QAM | 71 | 54.28 (10.93) | 34 (47.9) |
| Saxagliptin 2.5 mg QAM | 74 | 55.24 (10.44) | 49 (66.2) |
| Saxagliptin 5 mg QAM | 74 | 54.66 (9.71) | 36 (48.6) |
| Saxagliptin 5 mg QPM | 72 | 55.11 (10.35) | 39 (54.2) |
| Placebo | 74 | 55.57 (10.32) | 39 (52.7) |
| NCT00614939[57] | Multi-national study (74 sites in 14 countries) | 2009 | 74 | 12 | Type 2 Diabetes | Saxagliptin | 85 | 66.8  (8.3) | 53 (62.4) |
| Placebo | 85 | 66.2  (9.1) | 44 (51.8) |
| Chan et al, 2008[58, 59]  (NCT00095056) | Multi-national study (30 sites in 13 countries) | 2006 | NR | 54 | Type 2 Diabetes | Sitagliptin 50mg or 25mg once daily | 65 | 68.9  (9.8) | 34  (52.3) |
| Glipizide | 26 | 65.3  (9.7) | 10  (38.5) |
| Kojima et al, 2013[60]  (UMIN000006278) | Japan (Japanese Red Cross Medical Center) | 2011 | 65 | 12 | Type 2 Diabetes | Sitagliptin | 20 | 63.85 (12.92) | 5  (0.25) |
| Nateglinide | 16 | 66.44 (9.02) | 4  (0.25) |
| NCT00509262  (Arjona Ferreira JC et al, 2013[61, 62]) | Multi-national study | 2011 | 178 | 54 | Type 2 Diabetes | Sitagliptin | 211 | 64.2 (10.7) | 80 (37.9) |
| Glipizide | 212 | 64.2  (9.4) | 90 (42.5) |
| NCT00722371[63, 64] (Henry RR et al, 2014) | Multi-national study | 2010 | 108 | 54 | Type 2 Diabetes | Sitagliptin 100mg/Pioglitazone 15mg | 230 | NR | 112 (48.7) |
| Sitagliptin 100mg/Pioglitazone 30 mg | 231 | NR | 96 (41.6) |
| Sitagliptin 100mg/Pioglitazone 45mg | 230 | NR | 95 (41.3) |
| Pioglitazone 15mg | 230 | NR | 82 (35.7) |
| Pioglitazone 30mg | 233 | NR | 106 (45.5) |
| Pioglitazone 45 mg | 230 | NR | 117 (50.9) |
| NCT00337610[65, 66]  (Raz I et al, 2008) | Multi-national study (30 sites in 13 countries) | 2007 | 47 | 30 | Type 2 Diabetes | Sitagliptin 100mg | 96 | 53.6  (9.5) | 47 (48.9) |
| Placebo | 94 | 56.1  (9.5) | 55 (58.5) |
| NCT01131182[67] | NR | 2010 | 22 | 4 | Type 2 Diabetes | Sitagliptin | 507 | 55.0 (11.0) | 238 (46.9) |
| Sulfonylurea | 514 | 55.0 (11.0) | 259 (50.4) |
| NCT00103857 (Goldstein BJ et al, 2007) [68, 69] | Multi-national study | 2006 | 69 | 54 | Type 2 Diabetes | Sitagliptin 50mg bid + Metformin 500mg bid | 190 | 54.1 (10.0) | 85 (44.7) |
| Sitagliptin 50mg bid + Metformin 1000mg bid | 182 | 53.3 (9.6) | 105 (57.7) |
| Sitagliptin 50mg bid + Metformin 1000mg bid (Open Label Cohort) | 117 | 52.6 (10.0) | 50 (42.7) |
| Metformin 500mg bid | 182 | 53.4 (10.2) | 93 (51.1) |
| Metformin 1000mg bid | 182 | 53.2  (9.6) | 100 (54.9) |
| Placebo/Metformin 1000mg bid | 176 | 53.6 (10.0) | 83 (47.2) |
| NCT00701090[70, 71] (Arechavaleta et al, 2011) | Multi-national study | 2009 | 74 | 30 | Type 2 Diabetes | Sitagliptin | 516 | 56.3  (9.7) | 232 (44.9) |
| Glimepiride | 519 | 56.2 (10.1) | 240 (46.2) |
| NCT00086515[72, 73]  (Charbonnel et al, 2006) | Multi-national study | 2007 | 135 | 24 | Type 2 Diabetes | Sitagliptin 100mg | 464 | 54.4 (10.4) | 205 (44.2) |
| Placebo/Glipizide 5mg | 237 | 54.7  (9.7) | 96 (40.5) |
| NCT00637273[74, 75]  (Bergenstal et al, 2010) | Multi-national study (62 sites in 3 countries) | 2009 | 56 | 26 | Type 2 Diabetes | Exenatide once weekly | 160 | 52.4 (10.41) | 71 (44.4) |
| Sitagliptin | 166 | 52.2 (10.54) | 80 (48.2) |
| Pioglitazone | 165 | 53.0 (9.92) | 86 (52.1) |
| NCT00094757[76] | Multi-national study | 2006 | 78 | 54 | Type 2 Diabetes | Sitagliptin 100mg | 205 | 54.5 (10.0) | 95 (46.3) |
| Sitagliptin 200mg | 206 | 55.4  (9.2) | 102 (49.5) |
| Placebo/Pioglitazone | 110 | 55.5 (10.1) | 41 (37.3) |
| NCT00094770[77] | Multi-national study (173 sites in 27 countries) | 2006 | 139 | 104 | Type 2 Diabetes | Sitagliptin 100mg | 588 | 56.8  (9.3) | 252 (42.8) |
| Glipizide | 584 | 56.6  (9.8) | 226 (38.7) |
| NCT01137812[78, 79] (Schernthaner et al, 2013) | Multi-national study (182 sites in 17 countries) | 2012 | 87 | 52 | Type 2 Diabetes | Sitagliptin 100mg | 378 | 56.6 (9.33) | 163 (43.1) |
| Canagliflozin 300mg | 377 | 56.5 (9.62) | 170 (45.1) |
| NCT00482729[80] | Multi-national study (209 sites in United States) | 2008 | 74 | 44 | Type 2 Diabetes | Sitagliptin/Meformin-Fixed Dose Combination | 625 | 49.5 (10.5) | 272 (43.5) |
| Metformin | 621 | 50.0 (10.5) | 266 (42.8) |
| Bunck et al, 2009  (NCT00097500) [81] | Multi-national study (3 sites in 3 countries) | 2007 | 154 | 52 | Type 2 Diabetes | Exenatide | 36 | 58.4  (1.4) | 13  (36.1) |
| Insulin glargine | 33 | 58.3  (1.3) | 11  (33.3) |
| Diamant et al, 2010[82]  (NCT00641056) | Multi-national study (72 sites in 7 countries) | 2009 | 53 | 26 | Type 2 Diabetes | Exenatide | 233 | 58.0 (10.0) | 113 (48.0) |
| Insulin glargine | 223 | 58.0  (9.0) | 100 (45.0) |
| Inagaki et al, 2012[83]  (NCT0093553) | Japan (22 sites) | 2010 | 61 | 26 | Type 2 Diabetes | Exenatide once weekly | 215 | 57.07 (10.44) | 73 (34.0) |
| Insulin glargine once daily | 212 | 56.44 (11.16) | 64 (30.2) |
| Russell-Jones et al, 2012[84]  (NCT00676338) | Multi-national study (106 sites in 22 countries) | 2010 | 82 | 26 | Type 2 Diabetes | Exenatide 2mg once weekly + Oral placebo | 248 | 53.7 (10.91) | 109 (43.9) |
| Sitagliptin 100mg/day + SC placebo | 163 | 52.3 (11.05) | 69 (42.3) |
| Metformin starting at 1000mg/day + SC placebo | 246 | 53.7 (11.08) | 92 (37.4) |
| Pioglitazone starting at 30mg/day+ SC placebo | 163 | 55.3 (10.96) | 66 (40.5) |
| NCT01003184[85] | 34 sites in Ireland and United Kingdom | 2011 | 91 | 26 | Type 2 Diabetes | Exenatide once weekly | 111 | 59.2 (9.86) | 40 (36.04) |
| Insulin Detemir twice daily | 105 | 57.8 (9.48) | 33 (31.4) |
| Astrup et al, 2012[86]  (NCT00480909) | Multi-national study (19 sites in 8 European countries) | 2009 | 117 | 104 | Type 2 Diabetes | Liraglutide 1.2mg | 95 | 47.18 (9.72) | 73 (76.8) |
| Liraglutide 1.8mg | 90 | 45.53 (10.9) | 68 (75.6) |
| Liraglutide 2.4 mg | 93 | 45.01 (11.09) | 71 (76.3) |
| Liraglutide 3.0 mg | 93 | 45.91 (10.71) | 70 (75.3) |
| Placebo | 98 | 45.86 (10.28) | 74 (75.5) |
| Garber et al, 2009[87]  (NTC00294723) | 126 sites in United States and 12 sites in Mexico | 2007 | 91 | 52 | Type 2 Diabetes | Liraglutide 1.2 mg | 251 | 53.7 (11.0) | 134 (53.4) |
| Liraglutide 1.8 mg | 247 | 52.0 (10.8) | 126 (51.0) |
| Glimepiride 8 mg | 248 | 53.4 (10.9) | 115 (46.4) |
| Nauck et al, 2009[88]  (NCT00318461) | Multi-national study (170 sites in 21 countries) | 2007 | 52 | 26 | Type 2 Diabetes | Once daily Liraglutide (0.6mg) | 242 | 56.0 (11.0) | 91 (37.6) |
| Once daily Liraglutide (1.2mg) | 241 | 57.0  (9.0) | 111 (46.1) |
| Once daily Liraglutide (1.8mg) | 242 | 57.0  (9.0) | 100 (41.3) |
| Once daily Glimepiride (4mg) | 244 | 57.0  (9.0) | 103 (42.2) |
| Placebo | 122 | 56.0  (9.0) | 49 (40.2) |
| Marre et al, 2009[89] | Multi-national study (116 sites in 21 countries) | NR | NR | 26 | Type 2 Diabetes | Liraglutide 0.6mg | 233 | 55.7  (9.9) | 107 (46.0) |
| Liraglutide 1.2mg | 228 | 57.7  (9.0) | 125 (55.0) |
| Liraglutide 1.8mg | 234 | 55.6 (10.0) | 110 (47.0) |
| Placebo | 114 | 54.7 (10.0) | 60 (53.0) |
| Zinman et al, 2009[90]  (NCT00333151) | 90 sites in United States and Canada | 2007 | 65 | 26 | Type 2 Diabetes | Liraglutide 1.2mg | 178 | 55.0 (10.0) | 77 (43.0) |
| Liraglutide 1.8 mg | 178 | 55.0 (11.0) | 87 (49.0) |
| Placebo | 177 | 55.0 (10.0) | 67 (38.0) |
| Raz et al, 2012[91]  (NCT00744926) | Multi-national study (53 centers in 11 countries) | 2011 | 134 | 24 | Type 2 Diabetes | Taspoglutide 10mg | 116 | NR | NR |
| Taspoglutide 20mg | 129 | NR | NR |
| Placebo | 123 | NR | NR |
| Rosenstock et al, 2009[92]  (NCT00518115) | Multi-national study (118 sites in 4 countries) | 2008 | 56 | 16 | Type 2 Diabetes | Albiglutide 4 mg weekly | 35 | 50.4 (10.3) | 20  (57.1) |
| Albiglutide 15 mg weekly | 35 | 55.5 (10.5) | 17  (48.6) |
| Albiglutide 30 mg weekly | 31 | 54.2  (9.7) | 23  (74.2) |
| Albiglutide 15 mg biweekly | 33 | 52.5  (9.6) | 19  (57.6) |
| Albiglutide 30 mg biweekly | 32 | 55.5  (9.9) | 16  (50.0) |
| Albiglutide 50 mg biweekly | 35 | 51.1 (10.3) | 16  (45.7) |
| Albiglutide 50 mg monthly | 35 | 54.1 (11.3) | 18  (51.4) |
| Albiglutide 100 mg monthly | 34 | 54.4  (9.9) | 15  (44.1) |
| Placebo | 51 | 54.0 (10.6) | 23  (45.1) |
| Seino et al, 2012[93] | Multi-national study (57 centers in 4 Asian countries) | NR | NR | 24 | Type 2 Diabetes | Lixisenatide (10ug for 1 week, 15 ug for 1 week, then 20ug-maintenance dose) | 154 | 58.7 (10.2) | 85 (55.2) |
| Placebo | 157 | 58.0 (10.1) | 77 (49.0) |
| Umpierrez et al, 2011[94]  (NCT00630825) | 36 sites in United States and 3 in Puerto Rico | 2008 | 39 | 16 | Type 2 Diabetes | LY2189265 (LY 0.5/1.0) | 66 | 59.0 (12.0) | 31  (47.0) |
| LY2189265 (LY 1.0/1.0) | 65 | 57.0 (12.0) | 30  (46.0) |
| LY2189265 (LY 1.0/2.0) | 65 | 54.0 (11.0) | 31  (48.0) |
| Placebo | 66 | 56.0 (12.0) | 37  (56.0) |

**Appendix Table 2**. Quality assessment of GLP-1 based agents in randomized controlled trials included in analysis of pancreatic events

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study Source | Sequence generation | Blinding | Allocation concealment | Was Pancreatitis an AE or SAE? | Adverse event (AE) monitoring | Arms | Withdrawal rate (%) | Loss to follow- up (%) |
| Ross et al, 2012[21] (NCT01012037) | Central computer based; randomization: block in a 5:5:1 ratio | Double blind | Adequate | AE | Safety and tolerability end-points were the incidence of adverse events (including adverse changes observed during physical examinations or ECGs), protocol-specified significant AEs, hypoglycemia and changes from baseline in vital signs, clinical laboratory parameters and body weight. | Linagliptin 2.5mg bid | 7.2 | 0 |
| Linagliptin 5mg qd | 4.5 | 0 |
| Placebo | 2.3 | 0 |
| Haak et al, 2012[22]  (NCT00798161) | NR | Double blind | Adequate | AE | Incidence of AEs, serious AEs, discontinuation due to AEs,12-lead ECGs, vital signs and clinical laboratory parameters. The causal relationships between study medications and AEs were evaluated by the investigators at the site. | Linagliptin 5mg qd | 14.8 | 2.1 |
| Metformin 500mg bid | 11.8 | 2.1 |
| Metformin 1000mg bid | 14.3 | 2.7 |
| Linagliptin 2.5mg qd + Metformin 500mg bid | 11.2 | 2.8 |
| Linagliptin 2.5mg qd + Metformin 1000mg bid | 7.7 | 0 |
| Placebo | 25.0 | 1.4 |
| NCT00328172[23] | NR | Double blind | NR | SAE | NR | Linagliptin 0.5mg | 24.1 | 1.7 |
| Linagliptin 2.5mg | 17.5 | 3.5 |
| Linagliptin 5.0mg | 23.6 | 1.8 |
| Metformin | 7.7 | 1.5 |
| Placebo | 32.8 | 1.5 |
| Yki-Jarvinen et al, 2013[24, 25]  (NCT00954447) | NR | Double blind | NR | SAE | NR | Linagliptin 5.0mg | 13.9 | 2.2 |
| Placebo | 17.5 | 1.3 |
| NCT00654381[26] | NR | Double blind | NR | SAE | NR | Linagliptin 5.0mg | 1.89 | 0 |
| Linagliptin 10.0mg | 3.13 | 0 |
| Voglibose | 2.5 | 0 |
| Placebo | 7.5 | 0 |
| NCT00622284[27] | NR | Double blind | NR | SAE | NR | Linagliptin | 24.4 | 1.4 |
| Glimepiride | 22.1 | 1.7 |
| BI Trial No: 1218.15/ U09-2519-0128 | Randomized into 1;2 ratio to receive either placebo or linagliptin | Double blind | Adequate | SAE | Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory parameters. | Linagliptin 5mg + Pioglitazone 30mg | 5.8 | NR |
| Pioglitazone 30mg + Placebo | 14.6 | NR |
| BI Trial No: 1218.15/ U09-2519-01[28] | NR | Double blind | NR | SAE | Safety endpoints were the incidence and intensity of adverse events (AEs), withdrawals due to AEs, clinically relevant new or worsening findings in physical examination, 12-lead ECG, vital signs and clinical laboratory parameters. | Linagliptin 2.5mg + Metformin (500mg and 1000mg bid) | 0 | NR |
| Metformin 1000mg bid | 0.6 | NR |
| BI Trial No: 1218.52/U11-1782-01[29] | NR | Double blind | NR | SAE | Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, 12-lead electrocardiogram (ECG), vital signs, clinical laboratory parameters. | Linagliptin 5mg | 1.23 | NR |
| Placebo | 1.26 | NR |
| BI Trial No: 1218.63/U11-1781-02[30] | NR | Double blind | NR | AE | Incidence and intensity of AEs, withdrawals due to AEs, clinically relevant changes from baseline in vital signs (blood pressure and pulse rate), clinically relevant new or worsening findings in 12-lead ECG as reported as AEs, clinically relevant changes from baseline in clinical laboratory assessments, cardiac and cerebrovascular events adjudicated Clinical Events Committee (CEC) | Linagliptin 5mg | 12.3 | NR |
| Placebo | 12.5 | NR |
| BI Trial No: 1218.75/U12-3204-01[31] | NR | Double blind | NR | AE | Incidence and intensity of AEs, primarily based on spontaneous AEs; withdrawal due to AEs; clinically relevant new or worsening findings in physical examination reported as AEs; changes from baseline in vital signs (BP and pulse); clinically relevant new or worsening findings in 12 lead ECG reported as AEs; changes from baseline in clinical lab assessments; and hypoglycemic events. | Linagliptin 5mg | 2.2 | NR |
| Placebo | 0 | NR |
| BI Trial No: 1218.61/U13-3124-01[32] | NR | Double blind | NR | SAE | Incidence and intensity of adverse events, withdrawals due to AEs, physical examination, ECGs, change from baseline in clinical lab parameters and cardiovascular events (Clinical Event Committee adjudication results) | Linagliptin 5mg | 0.98 | NR |
| Placebo | 3.0 | NR |
| BI Trial No: 1218.64/U13-1283-01[34] | NR | Double blind | NR | AE | Incidence and intensity of adverse events (AEs), withdrawals due to AEs, physical examination, vital signs, 12 lead ECG, change from baseline in clinical lab parameters | Linagliptin 5mg | 0 | NR |
| Placebo (first 12 weeks)/ Glimepiride (next 40 weeks) | 1.64 | NR |
| BI Trial No: 1218.66/U12-2076-01[35] | NR | Double blind | NR | SAE | Incidence and intensity of adverse events, withdrawals due to AEs, physical examination and vital signs, 12-lead ECG, clinical laboratory assessments | Linagliptin 5mg | 5.1 | NR |
| Placebo | 2.0 | NR |
| Rosenstock et al, 2009[36] (NCT00286429) | Automated interactive voice response system using a randomization schedule | Double blind | NR | SAE | During the treatment period, patients were reviewed for adverse event evaluations. Further safety assessments included clinical examination of skin and digits. Hematology, serum chemistry, vital signs, physical exam and ECG parameters were done. | Alogliptin 12.5 mg | 36.6 | 3.05 |
| Alogliptin 25 mg | 40.3 | 2.33 |
| Placebo | 57.7 | 1.54 |
| White et al, 2013[37] (NCT00968708) | NR | Double blind | NR | SAE | The principal secondary safety end point was the primary composite end point with the addition of urgent revascularization due to unstable angina within 24 hours after hospital admission. Additional safety end points included angioedema, hypoglycemia, pancreatitis, cancer, and the results of laboratory testing. | Alogliptin | NR | NR |
| Placebo | NR | NR |
| NCT01318135[38] | NR | Open Label | Inadequate | SAE (Pancreatic cancer only) |  | Alogliptin 12.5mg qd + Glimepiride 1-6mg qd or bid | NR | NR |
| Alogliptin 25mg qd + Glimepiride 1-6mg qd or bid | NR | NR |
| NCT01289119[39] | NR | Double blind | NR | SAE | Treatment-emergent adverse events (TEAE) were defined as any adverse events that started on or after the date of the first dose of double-blind study drug and within 14 days after the date of the last dose of double-blind study drug. | Alogliptin monotherapy | 9.78 | 3.26 |
| Metformin | 9.18 | 0 |
| Metformin + Alogliptin Add-on Therapy | 6.06 | 0 |
| Pioglitazone | 7.94 | 0 |
| Pioglitazone + Alogliptin Add-on Therapy | 6.56 | 1.64 |
| Placebo | 9.78 | 0 |
| NCT01263496[40] | NR | Open Label | Inadequate | SAE | A treatment-emergent adverse event (TEAE) is defined as an adverse event with an onset that occurs after receiving study drug and within 30 days after receiving the last dose of study drug | Alogliptin 6.25mg qd | NR | NR |
| Alogliptin 12.5 mg qd | NR | NR |
| Alogliptin 25mg qd | NR | NR |
| Alogliptin 50mg qd | NR | NR |
| Voglibose 0.2mg tid | NR | NR |
| NCT00328627[41] | NR | Double blind | NR | SAE | NR | Alogliptin 12.5mg + Placebo | 24.2 | 1.56 |
| Alogliptin 25mg + Placebo | 21.7 | 1.55 |
| Placebo | 45.7 | 3.1 |
| NCT00395512[42] | NR | Double blind | Adequate | SAE | NR | Alogliptin 25 mg + Pioglitazone 30 mg | 17.1 | 3.05 |
| Alogliptin 12.5 mg + Pioglitazone 30 mg | 23.2 | 3.05 |
| Pioglitazone 30 mg | 22.7 | 3.68 |
| Kikuchi et al, 2010[43] (NCT00325117) | Dynamic randomization | Double blind | NR | SAE | Adverse events were recorded at each visit, and these AEs were assessed for severity and suspected relationship to the study drug. Hematology, biochemistry and urinalysis were performed at each scheduled visit. All laboratory assessments were processed at a central testing to ensure consistency | Vildagliptin 50mg bid + glimepiride | 2.9 | NR |
| Placebo + glimepiride | 4.0 | NR |
| Lukashevich et al, 2011[44]  (NCT00646542) | NR | Double blind | NR | SAE | All treatment emergent AEs were recorded and assessed by the investigator as to severity and potential relationship to study drug. Particular attention was paid to hepatic, infections, skin, pancreatitis as well as edema and cardiovascular safety. | Vildagliptin 50mg qd (moderate RI) | 10.3 | 2.4 |
| Placebo (moderate RI) | 10.9 | 1.6 |
| Vildagliptin 50mg qd (severe RI) | 13.7 | 1.6 |
| Placebo (severe RI) | 13.4 | 2.1 |
| Strain et al, 2013[45]  (NCT01257451) | Validated automated system | Double blind | Adequate | AE | All AEs and their severity, serious AEs, and their presumed relation with the study drug were monitored and recorded at each study visit. | Vildagliptin | 5.8 | 0.72 |
| Placebo | 5.8 | 0 |
| NCT00106340[46] (CLAF237A2308) | NR | Double blind | NR | SAE | Safety assessments included monitoring and recording all AEs, SAEs and pregnancies; regular monitoring of hematology, blood chemistry, and urine (performed at a central lab); and regular assessments of vital signs, ECG, physical condition and body weight. Severity and relationship to study drug were recorded for all AEs and SAEs | Vildagliptin 50mg bid + Metformin | 36.4 | 0 |
| Glimepiride up to 6mg qd + Metformin | 38.8 | 0 |
| NCT00300287[47] (CLAF237A2307) | NR | Double blind | NR | SAE | Safety assessments included monitoring and recording all AEs, SAEs with their severity and presumed relationship to study drug and pregnancies, recording of hypoglycemic events, the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, body weight, and ECGs | Vildagliptin 50mg qd | 14.7 | 0.6 |
| Placebo | 12.7 | 0.7 |
| CLAF237A1301[48] | NR | Double blind | NR | AE (elevated pancreatic enzymes) | Safety assessments included monitoring and recording all AEs, SAEs with their severity and presumed relationship to study drug and pregnancies, recording of hypoglycemic events, the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, body weight, and ECGs | Vildagliptin 50mg bid | 4.8 | NR |
| Voglibose 0.2mg tid | 5.2 | NR |
| CLAF237A23119[49] | NR | Open Label | NA | SAE | Safety assessments included monitoring and recording all AEs, SAEs with their severity and presumed relationship to study drug and pregnancies, recording of hypoglycemic events, the regular monitoring of hematology, blood chemistry and urine, and regular assessments of vital signs, physical condition, body weight, and ECGs | Vildagliptin 100mg + Metformin | 10.4 | 2.5 |
| Thiazolinedione + Metformin | 11.8 | 2.1 |
| NCT00110240[50] (CLAF237A2323) | NR | Double Blind | NR | SAE | Safety assessments included adverse events, hypoglycemic events and serious adverse events, physical examination, vital signs , laboratory evaluations, and ECGs | Vildagliptin 50mg bid | 9.5 | 1.6 |
| Acarbose up to 100mg tid | 12.7 | 1.4 |
| NCT00327015[51] | NR | Double Blind | NR | SAE | Safety and tolerability end-points included incidence of AEs, SAEs, discontinuation due to AEs, physical and ECG examinations, vital signs and results of clinical laboratory tests | Saxagliptin 5mg + Metformin 500mg | 28.4 | 6.9 |
| Saxagliptin 10mg + Metformin 500mg | 28.5 | 7.1 |
| Metformin 500mg + Placebo | 33.2 | 6.7 |
| Hollander et al, 2011[52]  (NCT00295633) | NR | Double Blind | NR | SAE | Safety assessments included incidence of AEs, SAEs and discontinuation due to AEs, changes from baseline lab parameters; changes from baseline vital signs; and incidence of marked clinical laboratory abnormalities. | Saxagliptin 2.5mg + TZD | 31.8 | NR |
| Saxagliptin 5mg + TZD | 36.0 | NR |
| Placebo + TZD | 41.3 | NR |
| NCT00757588[53] | Interactive voice response system | Double Blind | NR | SAE | Safety end points included AEs, hypoglycemia and weight gain | Saxagliptin 5mg + Insulin | 11.8 | 0.98 |
| Placebo + Insulin | 11.3 | 3.31 |
| Scirica et al, 2013[54]  (NCT01107886) | Central computerized telephone or web based system | Double Blind | NR | NR (Safety End Point) | A clinical events committee comprising specialists in cardiovascular and pancreatic medicine, all of whom were unaware of the study group assignments, adjudicated | Saxagliptin | NR | NR |
| Placebo | NR | NR |
| Goke et al, 2013[55]  (NCT00575588) | NR | Double Blind | NR | SAE | Safety and tolerability assessments included AEs and SAEs, lab measurements, vital signs, physical examination and ECG testing | Saxagliptin + Metformin | 61.4 | 0.23 |
| Glipizide + Metformin | 65.8 | 0.69 |
| NCT003160825[6] | NR | Double Blind | NR | SAE | NR | Saxagliptin 2.5/5 mg QAM | 38.0 | 9.9 |
| Saxagliptin 2.5 mg QAM | 44.6 | 9.5 |
| Saxagliptin 5 mg QAM | 29.7 | 8.1 |
| Saxagliptin 5 mg QPM | 36.1 | 11.1 |
| Placebo | 35.1 | 8.1 |
| NCT00614939[57] | Interactive voice response system | Double Blind | NR | SAE | Safety and tolerability assessments included AEs, SAEs, treatment-related AEs, discontinuations of randomized study medication because of AEs, deaths, AEs of special interest and hypoglycemic events | Saxagliptin | 71.8 | NR |
| Placebo | 80.0 | NR |
| Chan et al, 2008[58, 59]  (NCT00095056) | Computer generated randomization schedule | Double Blind | Adequate | SAE | Assessment of safety and tolerability included evaluation of the data from physical examinations, vital signs and ECGs collected at specified study visits. All adverse experiences were rated by the investigators for intensity and relationship to study drug. | Sitagliptin 50mg or 25mg once daily | 29.2 | NR |
| Placebo/Glipizide | 23.1 | NR |
| Kojima et al, 2013[60]  (UMIN000006278) | Random allocation sequence performed centrally | Open label | NA | AE | NR | Sitagliptin | NR | NR |
| Nateglinide | NR | NR |
| NCT00509262  (Arjona Ferreira JC et al, 2013[61, 62]) | Computer generated randomization schedule | Double Blind | NR | SAE | Safety measurements included evaluation of AEs, physical exam and vital signs, and ECG. Lab safety studies included serum chemistry, hematology and urinalysis. All AEs were rated by the investigator for intensity and relationship to study drug | Sitagliptin | 210 |  |
| Glipizide | 212 |  |
| NCT00722371[63, 64] (Henry RR et al, 2014) | NR | Double blind | NR | SAE | Safety and tolerability were evaluated throughout the study by physical examination, monitoring of vital signs and safety lab measurements that included serum chemistry, hematology and urinalysis. AEs were monitored and evaluated by the investigators for intensity (severity), duration, outcome and relationship to study drug | Sitagliptin 100mg/Pioglitazone 15mg | 20.9 | 3.5 |
| Sitagliptin 100mg/Pioglitazone 30 mg | 22.9 | 6.9 |
| Sitagliptin 100mg/Pioglitazone 45mg | 22.2 | 5.7 |
| Pioglitazone 15mg | 31.3 | 6.1 |
| Pioglitazone 30mg | 27.9 | 9.0 |
| Pioglitazone 45 mg | 27.4 | 5.7 |
| NCT00337610[65, 66]  (Raz I et al, 2008) | Computer generated schedule | Double blind | NR | SAE | Safety and tolerability were evaluated by physical examination, vital signs and lab measurements that included routine serum chemistry, hematology, urinalysis and pregnancy testing. AEs were monitored through the study for intensity, duration, outcome, relationship to study drug and level of severity | Sitagliptin 100mg | 17.7 | 3.13 |
| Placebo | 14.9 | 3.19 |
| NCT01131182[67] | NR | Open label | NA | SAE | NR | Sitagliptin | NR | NR |
| Sulfonylurea | NR | NR |
| NCT00103857 (Goldstein BJ et al, 2007) [68, 69] | NR | Double blind | NR | SAE | Data were collected regarding AEs, physical exam, vital signs, ECGs and body weight throughout the study. All AEs were rated by investigators for intensity and relationship to study drug. | Sitagliptin 50mg bid + Metformin 500mg bid | 22.1 | 2.6 |
| Sitagliptin 50mg bid + Metformin 1000mg bid | 22.5 | 5.5 |
| Sitagliptin 50mg bid + Metformin 1000mg bid (OLC) | 32.5 | 2.6 |
| Metformin 500mg bid | 30.8 | 2.2 |
| Metformin 1000mg bid | 25.8 | 3.8 |
| Placebo/Metformin 1000mg bid | 34.7 | 5.1 |
| NCT00701090[70, 71] (Arechavaleta et al, 2011) | Concealed computer-generated allocation schedule | Double blind | Adequate | SAE | Safety and tolerability were assessed by a review of all safety parameters including adverse experiences, laboratory safety parameters, body weight and vital signs. | Sitagliptin | 9.3 | 1.7 |
| Glimepiride | 9.8 | 1.7 |
| NCT00086515[72, 73]  (Charbonnel et al, 2006) | NR | Double blind | NR | SAE | Safety and tolerability were assessed throughout the study. Monitoring for adverse experiences, physical examinations, vital signs, body weight, 12-lead electrocardiograms (ECGs) (read at a central reading laboratory), and safety laboratory measurements comprising routine hematology, serum chemistry, and urinalysis were performed. | Sitagliptin 100mg | 10.6 | 0.86 |
| Placebo/Glipizide 5mg | 18.9 | 2.11 |
| NCT00637273[74, 75]  (Bergenstal et al, 2010) | Interactive voice response system | Double blind | Adequate | SAE | NR | Exenatide once weekly | 26.9 | 5.0 |
| Sitagliptin | 16.9 | 5.4 |
| Pioglitazone | 24.8 | 7.8 |
| NCT00094757[76] | NR | Double blind | NR | SAE | Data for adverse experiences, physical examinations, vital signs, ECGs, and body weight were collected throughout the study. | Sitagliptin 100mg | 25.8 | 1.5 |
| Sitagliptin 200mg | 30.1 | 2.4 |
| Placebo/Pioglitazone | 27.3 | 5.4 |
| NCT00094770[77] | NR | Double blind | NR | SAE | Data on adverse experiences, physical examinations, vital signs, ECGs and body weight were collected throughout the study. All adverse experiences were rated by the study site investigators for intensity and relationship to study drug. Laboratory safety evaluations included blood chemistry, haematology and urinalysis. | Sitagliptin 100mg | 34.4 | 3.2 |
| Glipizide | 29.5 | 1.7 |
| NCT01137812[78, 79] (Schernthaner et al, 2013) | Interactive Voice Response System/Interactive Web Response System | Double blind | Adequate | SAE | Safety evaluations included adverse events (AEs), clinical laboratory tests, vital sign measurements, physical examinations, self-monitored blood glucose, 12-lead electrocardiograms, and documentation of hypoglycemic episodes. | Sitagliptin 100mg | 44.4 | 2.1 |
| Canagliflozin 300mg | 32.6 | 1.6 |
| NCT00482729[80] | NR | Double blind | NR | SAE | NR | Sitagliptin/Meformin-Fixed Dose Combination | 34.7 (217/626) | 13.7 (86/626) |
| Metformin | 34.9  (218/624) | 10.6  (66/624) |
| Bunck et al, 2009  (NCT00097500) [81] | NR | Open Label | NA | SAE | NR | Exenatide | 16.7 | 0 |
| Insulin glargine | 9.1 | 3.03 |
| Diamant et al, 2010[82]  (NCT00641056) | Computer generated randomization sequence | Open Label | NA | SAE | Safety endpoints were adverse events, clinical lab assessments, vital signs, and hypoglycemia. We defined adverse events as those occurring at or after randomization or worsening during the study | Exenatide | 10.3 | 0.86 |
| Insulin glargine | 6.3 | 0.45 |
| Inagaki et al, 2012[83]  (NCT0093553) | Computer generated randomization sequence | Open Label | NA | AE | Safety profile end points included adverse events (AEs) and hypoglycemia. | Exenatide once weekly | 10.2 | 0.47 |
| Insulin glargine once daily | 5.2 | 0 |
| Russell-Jones et al, 2012[84]  (NCT00676338) | Computer generated randomization sequence | Double blind | Adequate | SAE | Safety end points were adverse events, clinical lab assessments, vital signs, hypoglycemia and antibodies to exenatide. Treatment emergent adverse events were defined as those occurring or worsening after the first dose of study drug | Exenatide 2mg once weekly + Oral placebo | 15.3 | 1.6 |
| Sitagliptin 100mg/day + SC placebo | 14.1 | 2.4 |
| Metformin starting at 1000mg/day + SC placebo | 13.4 | 0.4 |
| Pioglitazone starting at 30mg/day+ SC placebo | 1.8 | 1.8 |
| NCT01003184[85] | NR | Open label | NR | SAE | NR | Exenatide once weekly | 17.1 | 0.9 |
| Insulin Detemir twice daily | 11.4 | 0 |
| Astrup et al, 2012[86]  (NCT00480909) | NR | Double blind (first 20 weeks) Weeks 20-104: Open label | NR | SAE | Safety assessments included adverse events, recorded at every visit, standard lab tests and serum liraglutide antibodies. A safety committee for data surveillance was established | Liraglutide 1.2mg | 10.5 | 0 |
| Liraglutide 1.8mg | 17.8 | 0 |
| Liraglutide 2.4 mg | 21.5 | 0 |
| Liraglutide 3.0 mg | 11.8 | 0 |
| Placebo | 19.4 | 0 |
| Garber et al, 2009[87]  (NTC00294723) | Telephone based or web-based systems | Double blind | Adequate | SAE | Key safety assessments were tolerability (including nausea and other gastrointestinal adverse events), serum calcitonin and hypoglycemic episodes | Liraglutide 1.2 mg | 35.5 | NR |
| Liraglutide 1.8 mg | 29.7 | NR |
| Glimepiride 8 mg | 38.7 | NR |
| Nauck et al, 2009[88]  (NCT00318461) | Telephone based or web-based randomization systems | Double blind | Adequate | SAE | Safety variables included adverse events, vital signs, ECG, biochemical and hematology measures and subject reported hypoglycemic episodes | Once daily Liraglutide (0.6mg) | 14.0 | 0 |
| Once daily Liraglutide (1.2mg) | 18.0 | 0.4 |
| Once daily Liraglutide (1.8mg) | 21.0 | 0 |
| Once daily Glimepiride (4mg) | 14.0 | 0 |
| Placebo | 39.0 | 0 |
| Marre et al, 2009[89] | NR | Double blind | NR | SAE | Safety variables included hypoglycemic episodes, liraglutide antibodies, tolerability (gastrointestinal complaints) and pulse. AEs, vital signs, ECG, biochemical and hematology measures including calcitonin were also monitored | Liraglutide 0.6mg | 10.7 | NR |
| Liraglutide 1.2mg | 14.0 | NR |
| Liraglutide 1.8mg | 8.9 | NR |
| Placebo | 27.2 | NR |
| Zinman et al, 2009[90]  (NCT00333151) | Telephone based or web-based randomization systems | Double blind | Adequate | SAE | Safety variables included AEs, vital signs, ECG, biochemical and hematology measures and subject reported hypoglycemic episodes | Liraglutide 1.2mg | 14.0 | NR |
| Liraglutide 1.8 mg | 25.0 | NR |
| Placebo | 32.0 | NR |
| Raz et al, 2012[91]  (NCT00744926) | NR | Double blind | NR | SAE | Safety assessments included AEs, vital signs, physical examinations, clinical lab tests, ECG and hypoglycemia | Taspoglutide 10mg | 11.2 | NR |
| Taspoglutide 20mg | 13.2 | NR |
| Placebo | 3.3 | NR |
| Rosenstock et al, 2009[92]  (NCT00518115) | NR | Double blind | NR | SAE | Adverse event assessments and safety analyses were conducted throughout the study | Albiglutide 4 mg weekly | 48.6 | 5.7 |
| Albiglutide 15 mg weekly | 31.4 | 8.6 |
| Albiglutide 30 mg weekly | 32.3 | 3.2 |
| Albiglutide 15 mg biweekly | 45.5 | 9.1 |
| Albiglutide 30 mg biweekly | 24.2 | 0 |
| Albiglutide 50 mg biweekly | 42.9 | 2.9 |
| Albiglutide 50 mg monthly | 14.3 | 2.9 |
| Albiglutide 100 mg monthly | 44.1 | 2.9 |
| Placebo | 23.5 | 0 |
| Seino et al, 2012[93] | Interactive voice response system | Double blind | Adequate | SAE | Safety and tolerability included reported AEs and other safety information such as symptomatic hypoglycemia | Lixisenatide (10ug for 1 week, 15 ug for 1 week, then 20ug-maintenance dose) | NR | NR |
| Placebo | NR | NR |
| Umpierrez et al, 2011[94]  (NCT00630825) | Computer generated random sequence | Double blind | Adequate | SAE | Safety measures included AEs, vital signs, hypoglycemia events and lab tests. | LY2189265 (LY 0.5/1.0) | 12.1 | 1.5 |
| LY2189265 (LY 1.0/1.0) | 10.8 | 1.5 |
| LY2189265 (LY 1.0/2.0) | 13.8 | 1.5 |
| Placebo | 9.1 | 1.5 |

**Appendix Table 3.** Pancreatic cancer events in randomized controlled trials of GLP-1 agents

| Study Source (author, year) | Duration of GLP-1 exposure (weeks) | Arms | Number of participants | Number of cases |
| --- | --- | --- | --- | --- |
| NCT0065438126 | 52 | Linagliptin 5mg | 159 | 0 |
| Linagliptin 10mg | 160 | 1 |
| Voglibose | 162 | 0 |
| Placebo | 80 | 0 |
| NCT0062228427 | 104 | Linagliptin | 776 | 1 |
| Glimepiride | 775 | 2 |
| BI Trial No: 1218.15/ U09-2519-0128 | 24 | Linagliptin 5mg + Pioglitazone 30mg | 130 | 0 |
| Pioglitazone 30mg + Placebo | 259 | 1 |
| White et al, 2013[37]  (NCT00968708) | 76 | Alogliptin | 2701 | 0 |
| Placebo | 2679 | 0 |
| NCT01318135[38] | 52 | Alogliptin 12.5mg qd + Metformin 500mg bid or 750 mg tid | 142 | 1 |
| Metformin 500mg bid or 750 mg tid | 145 | 0 |
| NCT01263496[40] | 52 | Alogliptin 6.25mg qd | 96 | 0 |
| Alogliptin 12.5 mg qd | 101 | 0 |
| Alogliptin 25mg qd | 97 | 1 |
| Alogliptin 50mg qd | 97 | 0 |
| Voglibose 0.2mg tid | 83 | 0 |
| CLAF237A23119[49] | 12 | Vildagliptin 100mg + Metformin | 1756 | 1 |
| Thiazolinedione + Metformin | 871 | NR |
| NCT00757588[53] | 52 | Saxagliptin 5mg + Insulin | 304 | 1 |
| Placebo + Insulin | 151 | 0 |
| Scirica et al, 2013[54]  (NCT01107886) | 109 | Saxagliptin | 8280 | 5 |
| Placebo | 8212 | 12 |
| NCT00316082[56] | 24 | Saxagliptin 2.5/5 mg QAM | 71 | 1 |
| Saxagliptin 2.5 mg QAM | 74 | 0 |
| Saxagliptin 5 mg QAM | 74 | 0 |
| Saxagliptin 5 mg QPM | 72 | 0 |
| Placebo | 74 | 0 |
| Chan et al, 2008[58, 59]  (NCT00095056) | 54 | Sitagliptin 50mg or 25mg once daily | 65 | 1 |
| Placebo/Glipizide | 26 | 0 |
| NCT00509262 Arjona (Ferreira JC et al, 2013[61, 62]) | 54 | Sitagliptin | 210 | 1 |
| Glipizide | 212 | 0 |
| NCT00722371[63, 64] (Henry RR et al, 2014) | 54 | Pioglitazone 15mg | 230 | 0 |
| Pioglitazone 30mg | 233 | 0 |
| Pioglitazone 45 mg | 230 | 0 |
| Sitagliptin 100mg/Pioglitazone 15mg | 230 | 0 |
| Sitagliptin 100mg/Pioglitazone 30 mg | 231 | 1 |
| Sitagliptin 100mg/Pioglitazone 45mg | 230 | 0 |
| NCT00337610[65, 66]  (Raz I et al, 2008) | 30 | Sitagliptin 100mg | 96 | 0 |
| Placebo | 94 | 1 |
| NCT00103857  (Goldstein BJ et al, 2007) [68, 69] | 104 | Metformin 500mg bid | 182 | 0 |
| Metformin 1000mg bid | 182 | 0 |
| Sitagliptin 50mg bid + Metformin 500mg bid | 190 | 0 |
| Sitagliptin 50mg bid + Metformin 1000mg bid | 182 | 0 |
| Sitagliptin 50mg bid + Metformin 1000mg bid | 117 | 0 |
| Placebo/Metformin 1000mg bid | 176 | 1 |
| NCT00701090[70, 71] (Arechavaleta et al, 2011) | 30 | Sitagliptin | 516 | 1 |
| Glimepiride | 518 | 0 |
| NCT00086515[72, 73] (Charbonnel et al, 2006) | 104 | Sitagliptin 100mg | 464 | 1 |
| Placebo/Glipizide 5mg | 237 | 0 |
| NCT00094757[76] | 54 | Sitagliptin 100mg | 205 | 0 |
| Sitagliptin 200mg | 206 | 0 |
| Placebo/Pioglitazone | 110 | 1 |

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