

SUPPLEMENTARY DATA

**Supplementary Table S1.** Summary of data from 23 exclusively placebo-controlled clinical trials (47 treatment arms) conducted for efficacy approval by the US FDA for 15 oral hypoglycemic medications between 1999 and 2014. Protocol Number, Trial Duration, Primary Efficacy Blood Pressure Measure, Mean Baseline and Change Scores on Primary Efficacy Measure, Number of Patients Per Treatment Cell, P-Values, and Effect Sizes \* **bold treatment arms indicate success (p< 0.05)**

**Table 1. Exclusively Placebo-Controlled Trials**

Protocol Number Duration (weeks)	Primary Efficacy Variable	Placebo Baseline HbA <sub>1c</sub> / Decrease in HbA <sub>1c</sub> [N Patients]	Investigational Antihyperglycemic Baseline HbA <sub>1c</sub> / Decrease in HbA <sub>1c</sub> [N Patients]	P-Value <sup>a</sup> for Efficacy Calculation and Effect Size (Hedges' G)
Pioglitazone (1999)				
PNFP001 <sup>26 weeks</sup>	HbA <sub>1c</sub>	10.4/-0.74 [79]	<b>10.2/0.27 [79]</b> <b>10.2/0.27 [85]</b> <b>10.3/0.86 [76]</b>	P < 0.01 (0.67) P < 0.01 (0.66) P < 0.01 (1.05)
PNFP012 <sup>24 weeks</sup>	HbA <sub>1c</sub>	10.8/-0.93 [84]	<b>10.4/0.55 [87]</b> <b>10.6/0.60 [89]</b>	P < 0.01 (1.04) P < 0.01 (1.07)
PNFP 026 <sup>16 weeks</sup>	HbA <sub>1c</sub>	10.4/-0.76 [96]	<b>10.7/0.60 [101]</b>	P < 0.01 (0.84)
Rosiglitazone (1999)				
011 <sup>26 weeks</sup>	HbA <sub>1c</sub>	9.0/-0.92 [158]	<b>9.0/0.28 [166]</b> <b>8.8/0.56 [169]</b>	P < 0.0001 (0.96) P < 0.0001 (1.13)
024 <sup>26 weeks</sup>	HbA <sub>1c</sub>	8.9/-0.79 [173]	<b>8.9/0.02 [180]</b> <b>8.9/0.13 [158]</b> <b>8.9/0.31 [181]</b> <b>9.0/0.67 [187]</b>	P < 0.0001 (0.64) P < 0.0001 (0.73) P < 0.0001 (0.94) P < 0.0001 (1.17)
Glyburide and Metformin (2000)				
019 <sup>20 weeks</sup>	HbA <sub>1c</sub>	8.14/0.21 [147]	<b>8.2/1.48 [149]</b> <b>8.1/1.53 [152]</b>	P < 0.01 (1.49) P < 0.01 (1.54)
Metformin MR (2000)				
CV138-010 <sup>24 weeks</sup>	HbA <sub>1c</sub>	7.9/-0.19 [79]	<b>8.0/0.60 [156]</b>	P < 0.001 (1.07)
CV138-036 <sup>16 weeks</sup>	HbA <sub>1c</sub>	8.4/-0.11 [111]	<b>8.2/0.44 [115]</b> <b>8.4/0.60 [115]</b> <b>8.3/0.87 [111]</b> <b>8.4/0.83 [125]</b> <b>8.4/1.06 [112]</b>	P < 0.001 (0.64) P < 0.001 (0.83) P < 0.001 (1.16) P < 0.001 (1.08) P < 0.001 (1.38)
Metformin XT (2004)				
303 <sup>16 weeks</sup>	HbA <sub>1c</sub>	8.7/0.43 [33]	<b>8.5/1.26 [19]</b>	P= 0.028 (0.91)
Sitagliptin (2006)				
P021 <sup>24 weeks</sup>	HbA <sub>1c</sub>	8.0/-0.18 [253]	<b>8.0/0.61 [236]</b>	P < 0.001 (0.85)
P023 <sup>18 weeks</sup>	HbA <sub>1c</sub>	8.1/-0.12 [103]	<b>18.0/0.48 [193]</b>	P < 0.001 (0.63)
Sitagliptin and Metformin (2007)				
P036 <sup>24 weeks</sup>	HbA <sub>1c</sub>	8.7/-0.20 [165]	<b>8.8/1.4 [183]</b>	P < 0.001 (1.21)

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			<b>8.8/1.9 [178]</b>	P < 0.001 (1.60)
Saxagliptin (2009)				
CV181011 <sup>24 weeks</sup>	HbA <sub>1c</sub>	7.9/-0.19 [92]	<b>7.9/0.43 [100]</b> <b>8.0/0.47 [103]</b>	P < 0.05 (0.68) P < 0.05 (0.72)
CV181038 <sup>24 weeks</sup>	HbA <sub>1c</sub>	7.8/0.3 [68]	<b>8.0/0.7 [67]</b> <b>8.0/0.6 [69]</b> <b>7.9/0.7 [69]</b> <b>7.9/0.6 [70]</b>	P < 0.02 (0.48) P < 0.02 (0.36) P < 0.02 (0.48) P < 0.02 (0.36)
Linagliptin (2011)				
1218.16 <sup>24 weeks</sup>	HbA <sub>1c</sub>	8.00/-0.25 [163]	<b>8.00/0.44 [333]</b>	P < 0.0001 (0.76)
Linagliptin and Metformin (2012)				
1218.46 <sup>24 weeks</sup>	HbA <sub>1c</sub>	8.7/-0.13 [65]	<b>8.7/1.22 [137]</b> <b>8.7/1.59 [140]</b>	P < 0.0001 (1.46) P < 0.0001 (1.85)
Alogliptin (2013)				
MET-302 <sup>26 weeks</sup>	HbA <sub>1c</sub>	8.5/-0.2 [109]	<b>8.3/0.5 [112]</b> <b>8.4/0.6 [113]</b>	P < 0.001 (0.66) P < 0.001 (0.76)
PLC-010 <sup>26 weeks</sup>	HbA <sub>1c</sub>	8.0/0.0 [63]	<b>7.9/0.6 [131]</b> <b>7.9/0.6 [128]</b>	P < 0.001 (0.57) P < 0.001 (0.58)
Alogliptin and Metformin (2013)				
MET-302 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Same as above	<b>8.5/1.2 [111]</b> <b>8.4/1.6 [114]</b>	P < 0.001 (1.33) P < 0.001 (1.70)
Canagliflozin (2013)				
DIA 3005 <sup>26 weeks</sup>	HbA <sub>1c</sub>	8.0/-0.14 [189]	<b>8.1/0.77 [191]</b> <b>8.0/1.03 [193]</b>	P < 0.0001 (1.10) P < 0.0001 (1.41)
Dapagliflozin (2014)				
MB102013 <sup>24 weeks</sup>	HbA <sub>1c</sub>	7.8/0.23 [72]	<b>7.8/0.77 [61]</b> <b>8.0/0.89 [65]</b>	P = 0.0005 (0.60) P < 0.001 (0.73)
MB102032 <sup>24 weeks</sup>	HbA <sub>1c</sub>	7.8/-0.02 [68]	<b>7.9/0.82 [68]</b>	P < 0.0001 (0.84)
Empagliflozin (2014)				
1245.20 <sup>24 weeks</sup>	HbA <sub>1c</sub>	7.9/-0.08 [228]	<b>7.9/0.66 [224]</b> <b>7.9/0.78 [224]</b>	P < 0.0001 (0.98) P < 0.0001 (1.14)

<sup>a</sup> P-values: as reported from statistical analyses in the reviews.

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**Supplementary Table S2.** Summary of data from 27 augmented placebo-controlled clinical trials (49 treatment arms) conducted for efficacy approval by the US FDA for 13 oral hypoglycemic medications between 1999 and 2015. Protocol Number, Trial Duration, Primary Efficacy Blood Pressure Measure, Mean Baseline and Change Scores on Primary Efficacy Measure, Number of Patients Per Treatment Cell, P-Values, and Effect Sizes \* **bold treatment arms indicate success (p< 0.05)**

**Table 2. Augmented Placebo-Controlled Trials**

Protocol Number Duration (weeks)	Primary Efficacy Variable	Background Medication	Placebo Baseline HbA1c/Decrease in HbA1c [N Patients]	Investigational Antihyperglycemic BaselineHbA1c/ Decrease in HbA1c [N Patients]	P-Value <sup>a</sup> for Efficacy Calculation and Effect Size (Hedges' G)
Pioglitazone (1999)					
PNFP027 <sup>16 weeks</sup>	HbA <sub>1c</sub>	Metformin	9.7/-0.32 [153]	<b>9.9/0.67 [161]</b>	P < 0.05 (0.55)
Rosiglitazone (1999)					
094 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Metformin	8.6/-0.45 [113]	<b>8.9/0.56 [116]</b> <b>8.9/0.78 [110]</b>	P < 0.0001 (0.82) P < 0.0001 (1.03)
Metformin XR (2005)					
014 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Sulfonylureas	8.1/-0.07 [141]	<b>7.9/0.72 [144]</b> <b>7.8/0.82 [141]</b> <b>7.7/0.71 [146]</b>	P < 0.001 (0.77) P < 0.001 (0.87) P < 0.001 (0.81)
Sitagliptin (2006)					
P019 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Pioglitazone	8.0/0.15 [178]	<b>8.1/0.85 [175]</b>	P < 0.001 (0.83)
P020 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Metformin	8.0/0.02 [224]	<b>8.0/0.67 [453]</b>	P < 0.001 (0.64)
Bromocriptine (2009)					
K <sup>24 weeks</sup>	HbA <sub>1c</sub>	Sulfonylureas	9.4/-0.48 [123]	<b>9.3/0.01 [122]</b>	P = 0.001 (0.40)
L <sup>24 weeks</sup>	HbA <sub>1c</sub>	Sulfonylureas	9.5/-0.23 [127]	<b>9.3/0.37 [122]</b>	P < 0.001 (0.51)
Saxagliptin (2009)					
CV181013 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Glitazones	8.2/0.3 [180]	<b>8.3/0.66 [192]</b> <b>8.4/0.94 [183]</b>	P < 0.05 (0.35) P < 0.05 (0.63)
CV181040 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Glyburide	8.4/-0.08 [264]	<b>8.4/0.54 [246]</b> <b>8.5/0.64 [250]</b>	P < 0.05 (0.61) P < 0.05 (0.71)
CV181014 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Metformin	8.1/-0.13 [175]	<b>8.1/0.59 [186]</b> <b>8.1/0.69 [186]</b> <b>8.0/0.58 [180]</b>	P < 0.05 (0.76) P < 0.05 (0.87) P < 0.05 (0.76)
Linagliptin (2011)					
1218.17 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Metformin	8.00/-0.15 [175]	<b>8.1/0.49 [513]</b>	P < 0.0001 (0.73)
1218.18 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Metformin/ Sulfonylurea	8.1/0.10 [262]	<b>8.2/0.72 [778]</b>	P < 0.0001 (0.75)
Sitagliptin and Metformin XR (2012)					
P053 <sup>30 weeks</sup>	HbA <sub>1c</sub>	Metformin	9.1/0.0 [92]	<b>9.3/1.0 [95]</b>	P < 0.001 (1.03)

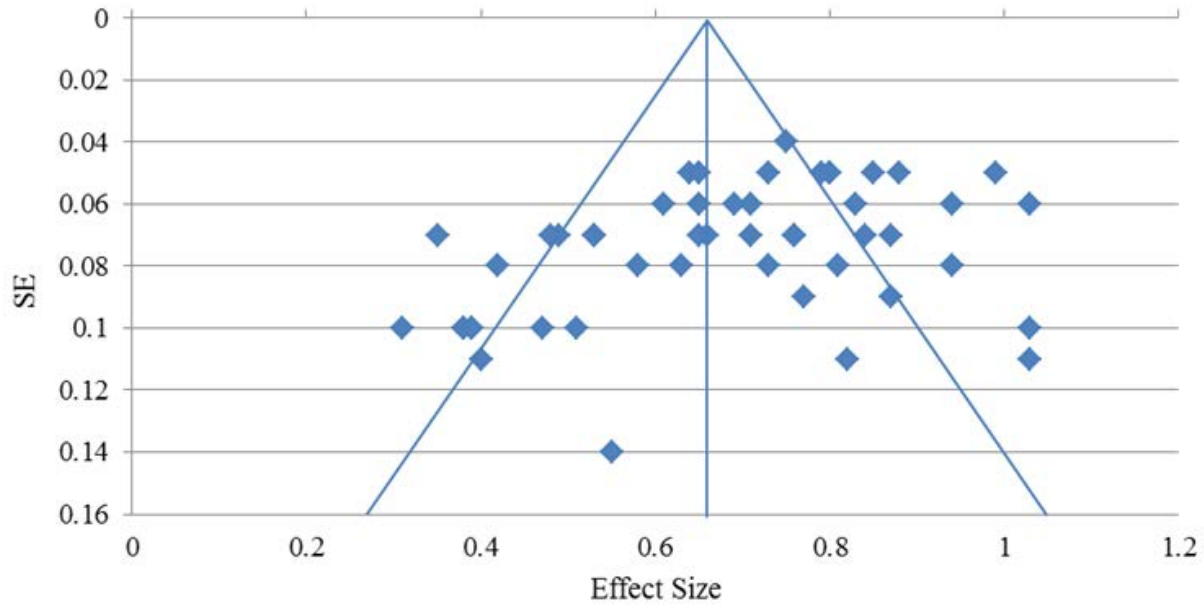
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Alogliptin (2013)					
MET-008 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Metformin	8.0/0.1 [103]	<b>7.9/0.6 [210]</b> <b>7.9/0.6 [203]</b>	P < 0.001 (0.38) P < 0.001 (0.38)
TZD-009 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Pioglitazone	8.1/0.2 [95]	<b>8.1/0.7 [195]</b> <b>8.0/0.8 [195]</b>	P < 0.001 (0.39) P < 0.001 (0.47)
SULF-007 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Sulfonylureas	8.2/0.0 [97]	<b>8.1/0.4 [201]</b> <b>8.1/0.5 [197]</b>	P < 0.001 (0.31) P < 0.001 (0.39)
Canagliflozin (2013)					
DIA 3006 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Metformin	8.0/0.17 [181]	<b>7.9/0.79 [365]</b> <b>8.0/0.94 [360]</b>	P < 0.0001 (0.80) P < 0.0001 (0.99)
DIA 3002 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Metformin/ Sulfonylureas	8.1/0.13 [150]	<b>8.1/0.85 [155]</b> <b>8.1/1.06 [152]</b>	P < 0.0001 (0.73) P < 0.0001 (0.94)
DIA 3012 <sup>26 weeks</sup>	HbA <sub>1c</sub>	Metformin/ Pioglitazone	8.0/0.26 [114]	<b>8.0/0.89 [113]</b> <b>7.8/1.03 [155]</b>	P < 0.0001 (0.84) P < 0.0001 (1.03)
Dapagliflozin (2014)					
MB102014 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Metformin	8.1/0.30 [137]	<b>8.2/0.70 [137]</b> <b>7.9/0.84 [135]</b>	P < 0.001 (0.49) P < 0.001 (0.66)
MB102028 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Glimepiride	8.3/0.13 [145]	<b>--/0.63 [142]</b> <b>--/0.82 [151]</b>	P < 0.001 (0.69) P < 0.001 (0.94)
MB102030 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Pioglitazone	8.3/0.42 [139]	<b>8.4/0.82 [141]</b> <b>8.4/0.97 [140]</b>	P < 0.001 (0.42) P < 0.001 (0.58)
MB102061 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Sitagliptin/ Metformin	8.3/-0.04 [224]	<b>--/0.45 [223]</b>	P < 0.001 (0.65)
Empagliflozin (2014)					
1245.19 <sup>24 weeks</sup>	HbA <sub>1c</sub>	Pioglitazone	8.2/0.11 [165]	<b>8.1/0.59 [165]</b> <b>8.1/0.70 [168]</b>	P < 0.0001 (0.53) P < 0.0001 (0.65)
1245.23a <sup>24 weeks</sup>	HbA <sub>1c</sub>	Metformin	7.9/0.13 [207]	<b>7.9/0.71 [217]</b> <b>7.9/0.77 [213]</b>	P < 0.0001 (0.80) P < 0.0001 (0.88)
1245.23b <sup>24 weeks</sup>	HbA <sub>1c</sub>	Metformin/ Sulfonylurea	8.2/0.18 [225]	<b>8.1/0.82 [225]</b> <b>8.1/0.77 [216]</b>	P < 0.0001 (0.85) P < 0.0001 (0.79)
Empagliflozin and Metformin (2015)					
1276.10 <sup>16 weeks</sup>	HbA <sub>1c</sub>	Metformin	7.7/0.28 [107]	<b>7.8/0.74 [219]</b> <b>7.8/0.7 [220]</b> <b>7.8/0.9 [219]</b> <b>7.7/0.78 [218]</b>	P < 0.05 (0.53) P < 0.05 (0.48) P < 0.05 (0.71) P < 0.05 (0.65)

<sup>a</sup> P-values: as reported in statistical analyses in the reviews.

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**Supplementary Figure S1.** Funnel plot assessing asymmetry based on selection bias for treatment arms from augmented placebo-controlled studies.



**Supplementary Figure S2.** Funnel plot assessing asymmetry based on selection bias for treatment arms from exclusively placebo-controlled studies.

