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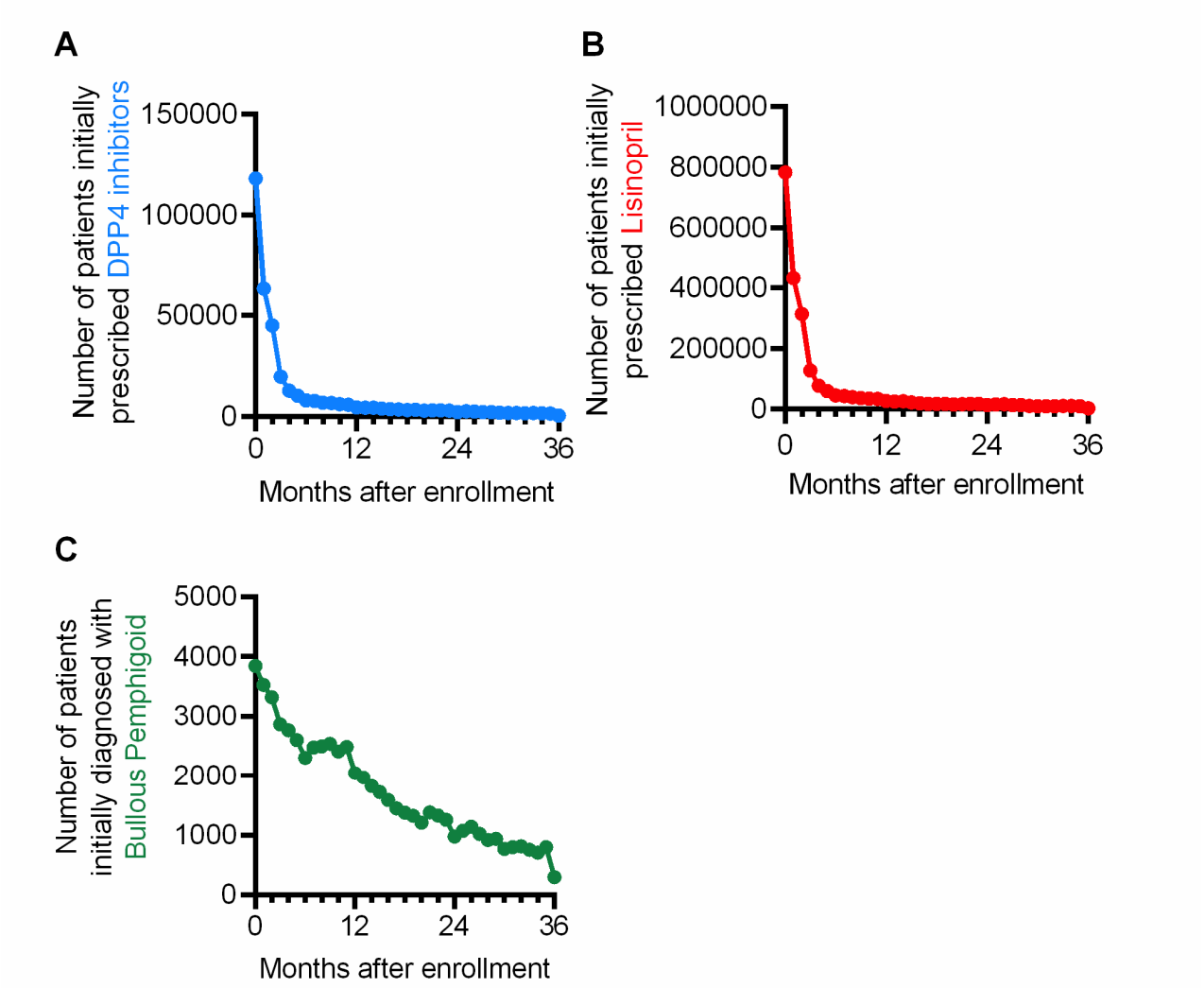
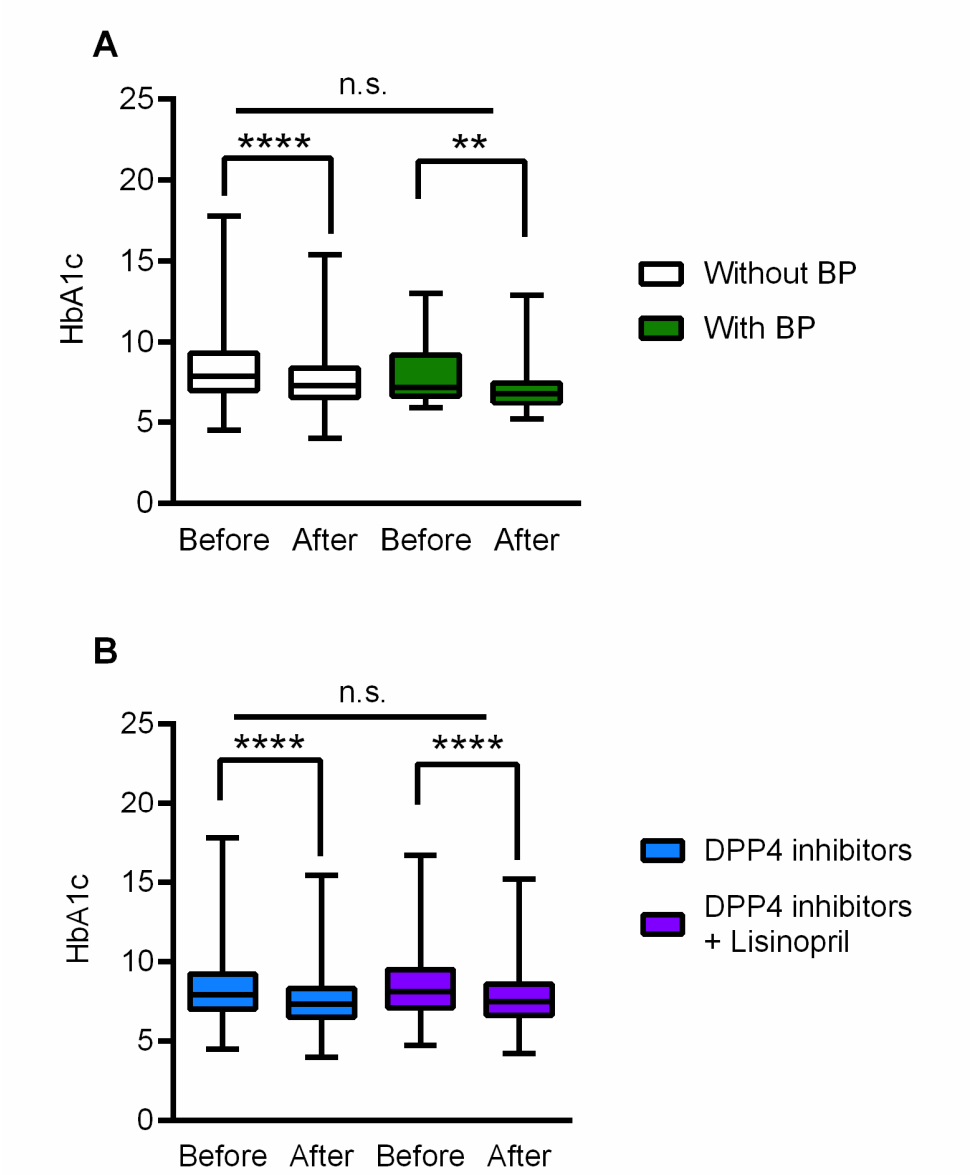
Supplementary Material



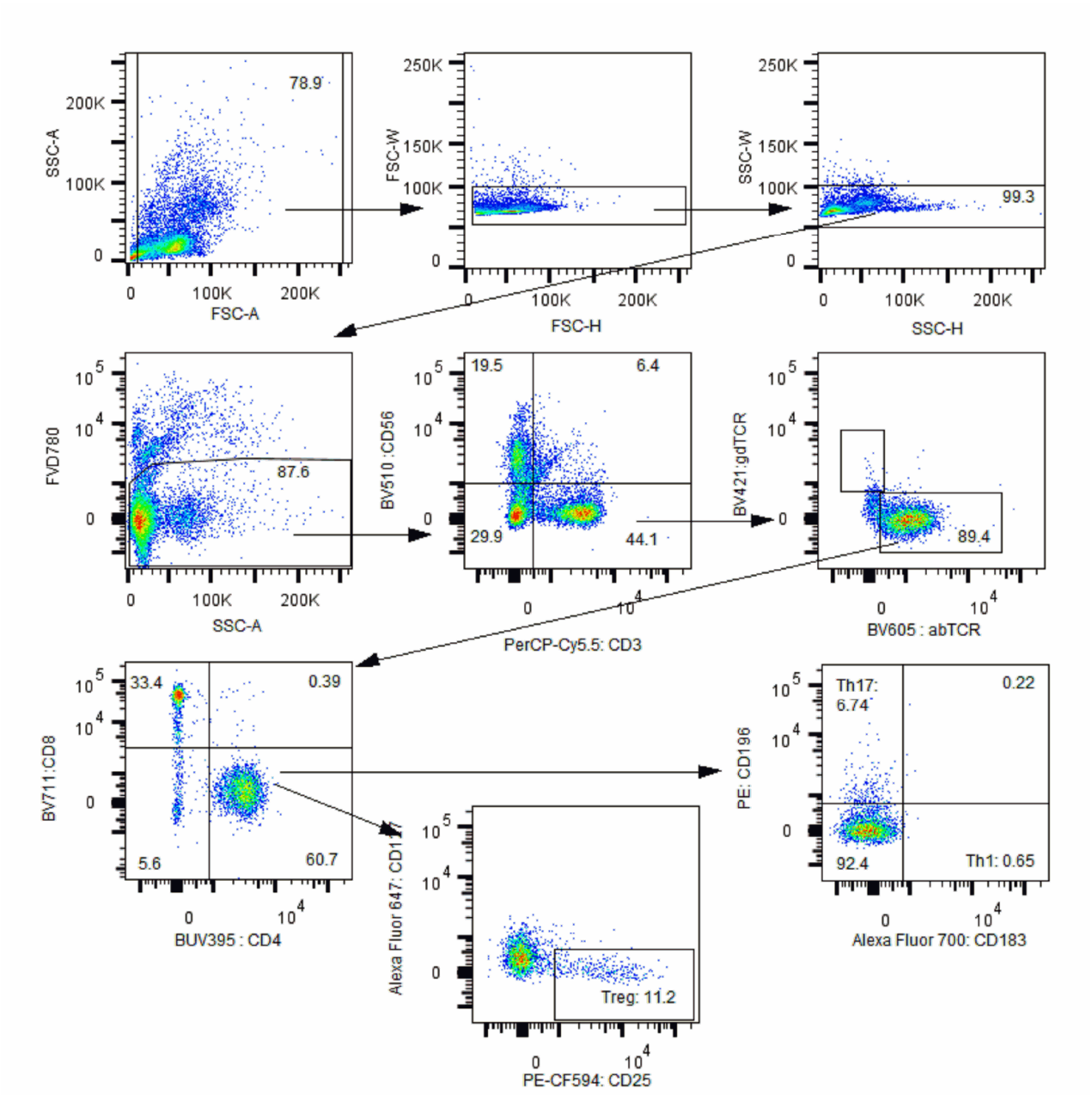
Supplemental Figure 1.

Time distribution of the first event after enrolment in the MarketScan database. (**A**) Time interval from patient enrollment to the first prescription of DPP4 inhibitors. (**B**) Time interval from patient enrollment to the first prescription of lisinopril. (**C**) Time interval from patient enrollment to initial BP diagnosis. The number of patients is presented on a monthly basis.



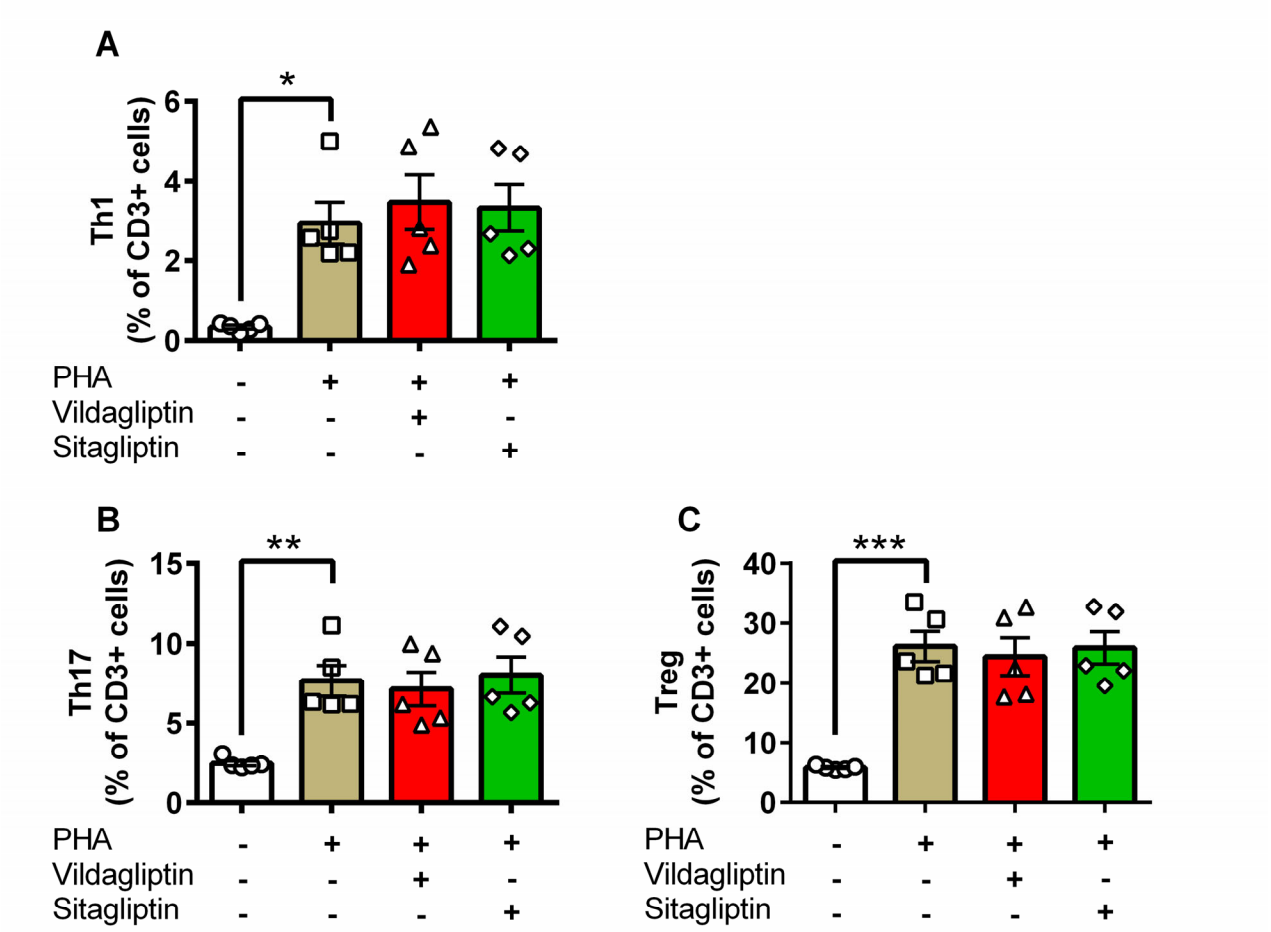
Supplemental Figure 2.

Chronological changes in the HbA1c levels of patients receiving DPP4 inhibitors. HbA1c levels before and after DPP4 inhibitor prescription. (**A**) Patients prescribed any DPP4 inhibitor were divided into two groups, i.e., those who did and those who did not experience BP onset within the observation period. HbA1c values at the first and last measurements were compared before and after treatment, respectively. (**B**) Patients prescribed any DPP4 inhibitor were divided into two groups, i.e., those who received and those who did not receive lisinopril simultaneously. HbA1c values at the first and last measurements were compared before and after treatment, respectively. Statistical significance was determined using a two-tailed Wilcoxon matched-pair signed-rank test, ** $p < 0.01$; **** $p < 0.0001$. Statistical analysis for comparing HbA1c changes between groups was performed using the unpaired *t*-test with Welch's correction. n.s., not significant.



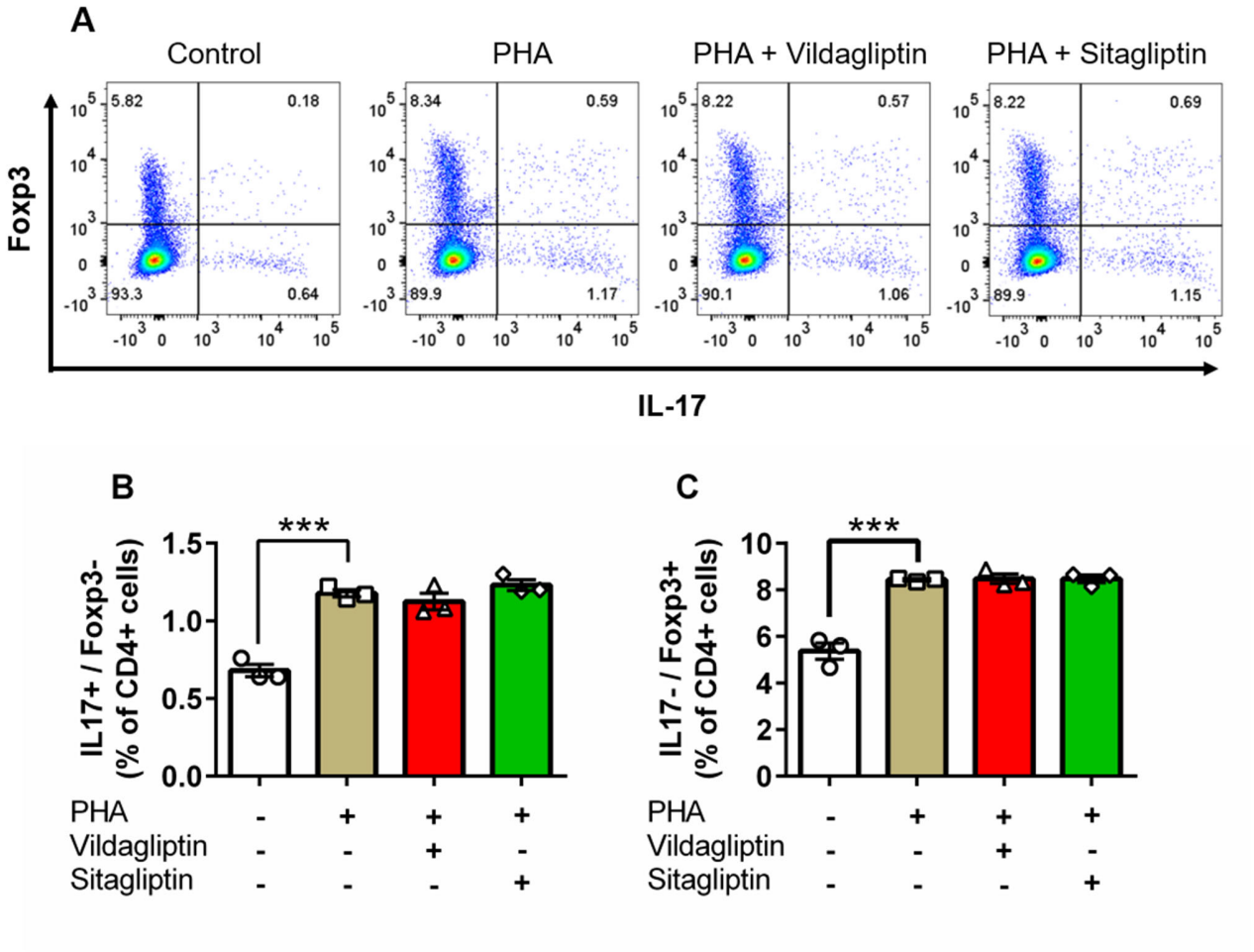
Supplemental Figure 3.

Gating strategy for T cell subsets using cell surface marker. Flow cytometry data corresponding to hPBMCs from healthy volunteers are shown as an example to demonstrate the gating strategy used to identify Th1, Th17, and Treg cells. Each cell type, including $CD4^+$ T cells ($CD3^+$ $CD56^-$ $\alpha\beta TCR^+$ $\gamma\delta TCR^-$ $CD8^-$ $CD4^+$), Th1 cells ($CD4^+$ T cells $CD196^-$ $CD183^+$), Th17 cells ($CD4^+$ T cells $CD196^+$ $CD183^-$), and Tregs ($CD4^+$ T cells $CD25^+$ $CD127^-$), was identified.



Supplemental Figure 4.

DPP4 inhibitors showing no effect on T cell phenotype. hPBMCs were stimulated with PHA with or without DPP4 inhibitors for 48 h. T cell subsets were characterized using cell surface markers (Supplemental Figure 3). (**A**) Percentage of Th1 cells among living $CD3^+$ cells. (**B**) Percentage of Th17 cells among living $CD3^+$ cells. (**C**) Percentage of Treg cells among living $CD3^+$ cells. Individual data are shown as the mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.005$



Supplemental Figure 5

T cell subsets characterized based on IL-17 and Foxp3 expression. (**A**) Dot plots representing each condition. (**B**) Percentage of IL-17^{+}/Foxp3^{-} cells among living CD4^{+} cells. (**C**) Percentage of Foxp3^{+}/IL-17^{-} cells among living CD4^{+} cells. Individual data are shown as the mean ± SEM. ***$p <$ 0.005.

Supplemental Table 1. Overall results of disproportionality analysis for BP in the FDA Adverse Event Reporting System (FAERS) database.

Filename: Supplemental Table 1.xlsx (contains 2 tables)

Sheet: BP_DrugA

Individuals in the FAERS database were divided into the following four groups: (*a*) individuals who received the drug of interest (drug A) and exhibited BP; (*b*) individuals who received drug A, but did not exhibit BP; (*c*) individuals who did not receive drug A and exhibited BP; and (*d*) individuals who did not receive drug A and did not exhibit BP. The reporting odds ratio (ROR) and 95% confidence interval (CI) as well as the *Z* score for DPP4 inhibitor-associated BP were calculated using the following respective equations:

$$\mathrm{ROR} = \frac{a/b}{c/d}$$

$$95\%\ \mathrm{CI} = exp\left\{\log(\mathrm{ROR}) \pm 1.96\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}\right\}$$

$$Z\ \mathrm{score} = \frac{\log(\mathrm{ROR})}{\sqrt{\left(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}\right)}}$$

where *a*, *b*, *c*, and *d* represent the number of individuals in each group, respectively.

Sheet: DPP4iBP_DrugB

Individuals who received any DPP4 inhibitor were divided into the following four groups: (*a1*) individuals who received a concomitant drug of interest (drug B) and exhibited BP; (*b1*) individuals who received drug B, but did not exhibit BP; (*c1*) individuals who did not receive drug B and exhibited BP; and (*d1*) individuals who did not receive drug B and did not exhibit BP. The ROR and 95% CI as well as the *Z* score for DPP4 inhibitor-associated BP were calculated using the following respective equations:

$$\mathrm{ROR} = \frac{a1/b1}{c1/d1}$$

$$95\%\ \mathrm{CI} = exp\left\{\log(\mathrm{ROR}) \pm 1.96\sqrt{\left(\frac{1}{a1}+\frac{1}{b1}+\frac{1}{c1}+\frac{1}{d1}\right)}\right\}$$

$$Z\ \mathrm{score} = \frac{\log(\mathrm{ROR})}{\sqrt{\left(\frac{1}{a1}+\frac{1}{b1}+\frac{1}{c1}+\frac{1}{d1}\right)}}$$

where *a1*, *b1*, *c1*, and *d1* refer to the number of individuals in each group, respectively.

Supplemental Table 2. Formulations of DPP4 inhibitors and lisinopril in the analysis of MarketScan data. The ingredients of formulations and the number of patients are shown.

Drug class	Formulations	Route	No. of patients
DPP4 inhibitor	Sitagliptin Phosphate	Oral	213,357
	Metformin Hydrochloride/Sitagliptin Phosphate	Oral	113,958
	Linagliptin	Oral	42,792
	Empagliflozin/Linagliptin	Oral	12,340
	Saxagliptin Hydrochloride	Oral	11,472
	Linagliptin/Metformin Hydrochloride	Oral	8,762
	Metformin Hydrochloride/Saxagliptin Hydrochloride	Oral	7,092
	Alogliptin Benzoate	Oral	3,468
	Alogliptin Benzoate/Pioglitazone Hydrochloride	Oral	1,503
	Alogliptin Benzoate/Metformin Hydrochloride	Oral	1,240
	Dapagliflozin/Saxagliptin	Oral	542
	Ertugliflozin/Sitagliptin	Oral	290
Lisinopril	Lisinopril	Oral	1,965,744
	Hydrochlorothiazide/Lisinopril	Oral	586,790

Supplemental Table 3. Definition of bullous pemphigoid in the analysis of MarketScan data. The number of patients for each ICD10 code is shown.

ICD10	Detail	No. of patients
L10	(Non-Billable Dx) Pemphigus	32
L100	Pemphigus vulgaris	1,693
L101	Pemphigus vegetans	101
L102	Pemphigus foliaceous	338
L103	Brazilian pemphigus [fogo selvagem]	18
L104	Pemphigus erythematosus	103
L105	Drug-induced pemphigus	21
L1081	Paraneoplastic pemphigus	25
L1089	Other pemphigus	323
L109	Pemphigus, unspecified	1,258
L12	(Non-Billable Dx) Pemphigoid	6
L120	Bullous pemphigoid	3,326
L121	Cicatricial pemphigoid	1,022
L122	Chronic bullous disease of childhood	36
L1230	Acquired epidermolysis bullosa, unspecified	184
L1231	Epidermolysis bullosa due to drug	22
L1235	Other acquired epidermolysis bullosa	57
L128	Other pemphigoid	319
L129	Pemphigoid, unspecified	729
L270	Generalized skin eruption due to drugs and medicaments taken internally	55,717

Supplemental Table 4. Cell surface marker antibodies used during flow cytometry.

Antibody	Dilution	Fluorophore	Clone	Company	Catalog Number
CCR6(CD196)	1:50	PE	11A9	BD Biosciences	559562
CD127	1:20	Alexa Fluor® 647	HIL-7R-M21	BD Biosciences	558598
CD25	1:50	PE-CF594	M-A251	BD Biosciences	562403
CD3	1:5	PerCP-Cy5.5	SK7	BD Biosciences	340949
CD4	1:100	BUV395	RPA-T4	BD Biosciences	564724
CD56	1:100	BV510	NCAM16.2	BD Biosciences	563041
CD8	1:200	BV711	RPA-T8	BD Biosciences	563677
CXCR3(CD183)	1:50	Alexa Fluor® 700	1C6/CXCR3	BD Biosciences	561320
TCRαβ	1:100	BV605	IP26	Biolegend	306732
TCRγδ	1:50	BV421	B1	BD Biosciences	562560