

## SUPPLEMENTARY DATA

### Supplementary Table 1. Exclusion criteria

- 1) type 1 diabetes, (or secondary forms of diabetes - gestational diabetes, transplant-associated, glucocorticoid-associated, latent-onset diabetes of the adult, or known monogenic forms of diabetes);
- 2) congestive heart failure, cardiomyopathy, clinically significant valvular heart disease (moderate or severe), or pulmonary hypertension;
- 3) estimated GFR <50 mL/min/1.73m<sup>2</sup>;
- 4) known secondary cause of hypertension;
- 5) current pregnancy, or recent pregnancy within the last 3 months, or current breast-feeding. Female patients of child bearing potential (premenopausal, or not surgically sterile) who are unwillingly to have a baseline serum pregnancy test, and/or who are unwillingly to use active contraception throughout the duration of the study;
- 6) use within the last 4 weeks of any DPP-4 inhibitor, GLP-1 receptor agonist (GLP-1RA), SGLT-2 inhibitor;
- 7) prior hypersensitivity reaction to any DPP-4 inhibitor;
- 8) liver disease either indicated by a known history of severe liver disease or by elevated liver enzymes and/or liver function tests more than 3X the upper limit of normal on two readings;
- 9) alcohol or substance abuse problem that would interfere with the study as defined by the investigator;
- 10) prior history of pancreatitis (acute or chronic), or a history of medullary thyroid cancer, c-cell hyperplasia or history of multiple endocrine neoplasia syndromes;
- 11) systolic blood pressure >160 mmHg or diastolic blood pressure ≥100 mmHg, as measured by an automated oscillometric blood pressure device during screening;
- 12) individuals who are unwilling to reduce their dose of sulphonylurea by 50% at visit 1 and for the duration of the study;
- 13) current involvement, or any recent involvement (within 3 months) in any other clinical trial involving an investigational product;
- 14) unwillingness to take study drug;
- 15) individuals with a medical condition of a serious nature such as an active malignancy (excluding dermal basal cell or dermal squamous cell carcinomas) or any of the medical conditions listed above including hepatic dysfunction, eGFR <50 ml/min/1.73m<sup>2</sup>, significant cardiac or respiratory conditions, or other medical conditions according to the investigator's opinion.

## SUPPLEMENTARY DATA

**Supplementary Table 2. Acute and chronic renal hemodynamic outcome measures in response to sitagliptin compared to placebo**

Variables	Baseline	placebo (n=16)			Baseline	sitagliptin (n=16)			p-value
		1Hr	2Hr	3Hr		1Hr	2Hr	3Hr	
<b>Acute (single dose)</b>									
GFR(mL/min/1.73m <sup>2</sup> )	118.3±27.1	121.8±24.7	119.5±30.6	122.4±34.9	108.2±20.3	108.7±22.5	113.5±25.6	118.1±30.6	0.33
ERPF(mL/min/1.73m <sup>2</sup> )	537.4±133.2	553.3±128.5	578.3±135.0	591.7±138.1	541.1±109.6	549.2±132.0	604.1±228.1	563.3±134.2	0.28
RBF(mL/min/1.73m <sup>2</sup> )	876.4±217.0	894.2±207.8	933.3±221.6	951.9±223.3	887.0±188.8	903.2±226.6	989.8±385.7	917.4±220.8	0.11
RVR(mmHg/L/min)	0.11±0.03	0.11±0.03	0.10±0.03	0.11±0.03	0.11±0.03	0.11±0.02	0.11±0.03	0.11±0.02	0.88
FF	0.22±0.03	0.22±0.03	0.21±0.04	0.21±0.04	0.20±0.03	0.20±0.04	0.20±0.05	0.21±0.04	0.08
P <sub>GLO</sub> (mmHg)	57.8±5.8	58.4±4.9	57.7±6.4	58.1±7.0	55.7±4.8	55.8±5.4	56.5±5.1	57.5±6.2	0.21
R <sub>A</sub> (dyne•s•cm <sup>-5</sup> )	2956.8±1756.9	3140.4±1381.2	3296.3±1556.9	3334.7±1809.4	3137.8±1067.0	3265.4±895.9	3409.9±1488.2	3208.1±1175.0	0.28
R <sub>E</sub> (dyne•s•cm <sup>-5</sup> )	2093.2±323.3	2108.2±283.4	1963.8±355.1	1955.7±391.6	1861.7±327.2	1857.7±424.0	1841.0±553.7	1977.8±436.4	0.11
<b>Chronic (1 month)</b>									
GFR(mL/min/1.73m <sup>2</sup> )	118.7±23.0	117.1±24.7	116.6±25.8	120.6±29.3	114.8±16.6	115.6±17.0	118.6±18.8	122.1±2	0.40
ERPF(mL/min/1.73m <sup>2</sup> )	542.4±109.0	537.2±100.0	556.2±107.9	567.0±152.2	580.6±114.1	565.5±123.1	592.9±120.6	594.4±147.0	0.29
RBF(mL/min/1.73m <sup>2</sup> )	860.7±181.0	847.2±159.8	878.9±185.5	890.5±250.9	935.2±195.8	907.9±202.5	946.1±200.0	950.9±237.3	0.36
RVR(mmHg/L/min)	0.11±0.03	0.10±0.02	0.11±0.03	0.11±0.04	0.10±0.02	0.10±0.02	0.10±0.02	0.11±0.03	0.40
FF	0.22±0.04	0.22±0.05	0.21±0.04	0.22±0.04	0.20±0.03	0.21±0.04	0.21±0.04	0.21±0.03	0.43
P <sub>GLO</sub> (mmHg)	56.7±5.0	56.4±5.4	56.1±5.3	56.9±6.0	55.4±3.6	55.7±3.4	56.1±4.1	56.8±4.1	0.80
R <sub>A</sub> (dyne•s•cm <sup>-5</sup> )	3104.6±1463.3	2556.8±868.8	3308.1±1494.9	3619.1±1913.2	2869.3±887.8	2803.7±636.8	2968.9±726.4	3423.1±1282.5	0.87
R <sub>E</sub> (dyne•s•cm <sup>-5</sup> )	2155.6±466.5	2163.6±508.1	2050.8±406.0	2111.4±418.9	1892.8±355.5	1986.3±402.1	1952.4±422.0	1971.0±293.6	0.36

Data are mean ± SD. ERPF (effective renal plasma flow), FF (filtration fraction), GFR (glomerular filtration rate), P<sub>GLO</sub> (glomerular hydrostatic pressure), R<sub>A</sub> (renal afferent resistance), R<sub>E</sub> (renal efferent resistance), RVR (renal vascular resistance). p-values presented are for comparisons of sitagliptin vs. placebo (baseline-subtracted) at 3Hr for variable indicated, comparisons at other time points are not presented were not statistically significant.

## SUPPLEMENTARY DATA

**Supplementary Table 3. Acute and chronic systemic hemodynamic outcome measures by NICOM in response to sitagliptin compared to placebo**

Variables	Baseline	placebo (n=16)			Baseline	sitagliptin (n=16)			p-value
		1Hr	2Hr	3Hr		1Hr	2Hr	3Hr	
<b>Acute (single dose)</b>									
CO (L/min)	6.5±1.5	7.1±2.1	6.9±1.8	7.1±2.1	7.3±1.1	8.5±1.6	8.1±1.5	7.7±1.5	0.70
SV (mL/beat)	92.8±28.7	94.0±28.6	91.3±30.0	93.3±30.5	107.3±22.40	115.5±30.5	107.2±30.9	108.1±28.6	0.93
TPR(dynes•sec/cm <sup>2</sup> /m <sup>2</sup> )	1195.4±348.2	1116.9±343.4	1134.7±330.93	1168.3±377.5	1072.9±209.8	938.3±197.9	924.5± 180.2	1016.2±230.2	0.66
TFC kohm(-1)	38.5±7.6	40.1±7.8	40.5±7.8	41.0±8.1	36.9±5.4	37.9±5.9	38.8±6.2	39.0± 6.3	0.69
SBP(mmHg)	125.9±13.1	128.1±16.0	127.3±14.2	131.5±13.1	131.6±15.3	131.0±19.9	128.6±15.6	130.1±18.5	0.07
DBP(mmHg)	73.6±9.4	71.2±10.4	72.3±10.2	75.9±9.1	76.0±8.0	75.1±7.1	74.7±9.8	76.7±10.5	0.35
MAP(mmHg)	91.0±8.8	90.2±10.3	90.6±9.2	94.4±8.7	94.4±9.2	93.7±10.3	92.7±10.8	94.5±12.0	0.12
HR (bpm)	71.8±12.0	77.2±13.4	78.1±11.9	77.2±11.6	69.2±11.2	75.2±10.0	74.5±9.9	72.8±9.3	0.34
<b>Chronic (1 month)</b>									
CO (L/min)	6.4±1.5	7.1±2.1	6.6±1.8	6.2±1.7	7.3±1.6	8.7±1.7	8.3±1.8	7.9±1.5	0.17
SV (mL/beat)	89.5±27.3	93.7±29.3	86.1±27.6	84.4±28.0	109.9±25.0	110.9±28.2	115.8±27.0	107.9±28.5	0.70
TPR(dynes•sec/cm <sup>2</sup> /m <sup>2</sup> )	1160.9±287.3	1136.5±315.7	1216.3±383.4	1370.2±586.6	1083.5±269.8	1029.8±287.3	964.1±208.0	1058.4±253.6	0.16
TFC kohm(-1)	38.4±6.1	43.1±20.2	39.1±6.9	39.5±7.3	37.1±6.2	37.9±6.6	38.9±6.7	39.1± 6.8	0.40
SBP(mmHg)	124.5±14.7	129.0±14.8	123.0±18.3	131.6±17.1	126.1±12.9	129.5±13.5	132.2±15.8	135.8±13.3	0.42
DBP(mmHg)	72.4±9.1	74.5±9.7	75.5±11.0	76.6±10.0	75.4±7.5	75.6±6.3	77.2±10.2	80.8±6.3	0.53
MAP(mmHg)	89.7±9.4	91.4±9.5	93.6±11.6	94.9±10.1	92.2±7.9	93.6±7.5	95.5±11.2	99.1±7.9	0.38
HR (bpm)	72.8±10.8	76.9±11.9	78.4±11.5	75.0±11.4	67.5±10.6	71.1±9.2	72.8±10.3	73.2±11.4	0.02*

Data are mean ± SD. CO (cardiac output), SV (stroke volume), NICOM (non-invasive cardiac output monitoring), TFC (thoracic fluid content), TPR (total peripheral resistance). p-values presented are for comparisons of sitagliptin vs. placebo (baseline-subtracted) at 3Hr for variable indicated (comparisons at other time points are not presented however were not statistically significant).

## SUPPLEMENTARY DATA

**Supplementary Table 4. Neurohormones, markers of oxidative stress and 24 hour urine parameters**

	placebo (n=16)				sitagliptin (n=16)			
	Day 1 Baseline/3Hr		1 Month Baseline/3Hr		Day 1 Baseline/3Hr		1 Month Baseline/3Hr	
24-Hr sodium/Cr	22.03[14.6,37.26]		16.5[13.5,25.6]		15.8[12.9,19.8]		16.6[11.3,19.6]	
24-Hr ACR (mg/mmol)	1.75[0.87,5.50]		2.25[1.30,5.21]		1.67[0.83,3.21]		2.13[0.87,7.54]	
Timed 3-Hr Urine Volume (mL)	229.18 ± 112.96		193.33 ± 92.75		169.11 ± 75.59		201.21 ± 94.06	
PRC (ng/L)	10[7,17]	6[4,14]	12[5,44]	5[3,9]	16[6,46]	7[3,28]	20[11,58]	9[6,16]
Aldosterone (pmol/L)	127.59±36.5	120.6±36.2	155.7±86.6	130.2±50.1	137.6±55.4	115.5±34.4	141.1±42.7	111.2±29.6
ANP (pg/mL)	3358±522	3440±742	3527±559	3479±605	3238±886	3257±630	3152±618	3246±517
Nitric oxide (μmol/L)	30.0±27.9	19.6±13.04	27.4±17.5	21.2±10.8	22.7±10.6	16.4±7.7	21.0±7.6	20.4±10.0
Nitric oxide:UCr	0.09±0.07	0.09±0.06	0.09±0.06	0.09±0.09	0.07±0.04	0.06±0.03	0.08±0.06	0.09±0.06
cGMP (plasma) (pmol/L)	1.8±0.5	1.5±0.6	1.5±0.4	1.4±0.5	1.8±0.6	1.6±0.6	1.9±0.7	1.5±0.4
cGMP:Cr (pmol/mmol)	302±290	308±245	256±164	317±228	203±114	263±190	238±150	264±118
Uric acid (μmmol/L)	329.6±77.4		342.4±79.6		348.3±86.4		351.3±76.2	
8-isoprostanate/Cr (pg/μmol)	233±118	239±150	246±120	210±110	192±79	203±57	212±108	174±92
8-deoxy-2-guanosine/Cr (ng/μmol)	29.9±14.9	29.3±13.2	31.2±11.7	27.1±8.0	22.6±6.0	20.1±8.7	22.9±11.2	<b>26.5±10.4<sup>*δ</sup></b>

Data are expressed mean±SD or median [interquartile range]. ACR, albumin:creatinine ratio; ANP, atrial natriuretic peptide; cGMP, cyclic guanosine monophosphate; PRC, plasma renin concentration, UCr, urinary creatinine; Cr, creatinine

\*indicates significance, p-value=0.030 for comparison of acute 3 Hr change at 1 month, indicates significance, p-value=0.030 for comparison of 3Hr change (single dose compared to 1 month).

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**Supplementary Table 5. Urinary cytokines, chemokines, growth factors, and receptors**

	placebo (n=16)		sitagliptin (n=16)		p-value
	Baseline	1 Month (3Hr)	Baseline	1 Month (3Hr)	
<b>Interferon-<math>\alpha</math>2 (IFN<math>\alpha</math>2)</b>	2.16 ± 2.18	1.78 ± 3.35	1.98 ± 5.17	0.84 ± 0.62	0.057
<b>Interferon-<math>\gamma</math> (IFN<math>\gamma</math>)</b>	<b>0.68 ± 0.53</b>	<b>0.55 ± 0.29</b>	<b>0.27 ± 0.27</b>	<b>0.51 ± 0.27</b>	<b>0.030</b>
<b>Interleukin-1<math>\alpha</math> (IL-1<math>\alpha</math>)</b>	0.35 ± 0.58	0.38 ± 0.67	0.48 ± 1.38	0.24 ± 0.37	0.51
<b>Interleukin-1<math>\beta</math> (IL-1<math>\beta</math>)</b>	0.08 ± 0.10	0.18 ± 0.16	0.10 ± 0.14	0.25 ± 0.46	0.63
<b>Interleukin-1Ra (IL-Ra)</b>	36.91±55.44	60.25 ±78.68	27.66±34.62	39.02 ±48.67	0.47
<b>Interleukin-2 (IL-2)</b>	0.06 ± 0.11	0.06 ± 0.08	0.05 ± 0.08	0.04 ± 0.04	0.79
<b>Interleukin-3 (IL-3)</b>	0.07 ± 0.05	0.07 ± 0.03	0.04 ± 0.04	0.18 ± 0.49	0.24
<b>Interleukin-4 (IL-4)</b>	0.78 ± 0.74	0.50 ± 0.48	0.32 ± 0.54	0.27 ± 0.18	0.23
<b>Interleukin-5 (IL-5)</b>	0.04[0.02,0.07]	0.05[0.04,0.10]	0.02[0.01,0.04]	0.04[0.03,0.05]	0.93
<b>Interleukin-6 (IL-6)</b>	0.23 ± 0.21	0.26 ± 0.28	0.23 ± 0.24	0.17 ± 0.20	0.39
<b>Interleukin-7 (IL-7)</b>	0.14[0.04,0.33]	0.04[0.02,0.28]	0.06[0.02,0.12]	0.05[0.02,0.17]	0.96
<b>Interleukin-8 (IL-8)</b>	0.35[0.08,0.98]	0.45[0.14,1.06]	0.28[0.10,1.26]	0.24[0.04,3.76]	0.30
<b>Interleukin-9 (IL-9)</b>	0.05[0.04,0.10]	0.06[0.04,0.11]	0.03[0.02,0.07]	0.06[0.04,0.08]	0.85
<b>Interleukin-10 (IL-10)</b>	0.13 ± 0.13	0.14 ± 0.10	0.05 ± 0.06	0.09 ± 0.06	0.50
<b>Interleukin-12 (IL-12P40)</b>	0.76 ± 0.90	0.87 ± 0.73	0.37 ± 0.74	0.62 ± 0.71	0.73
<b>Interleukin-12 (IL-12P70)</b>	0.05 ± 0.05	0.06 ± 0.09	0.04 ± 0.09	0.04 ± 0.04	0.59
<b>Interleukin-13 (IL-13)</b>	0.24 ± 0.29	0.32 ± 0.21	0.13 ± 0.09	0.28 ± 0.19	0.54
<b>Interleukin-15 (IL-15)</b>	0.10 ± 0.13	0.12 ± 0.24	0.08 ± 0.09	0.03 ± 0.03	0.36
<b>Interleukin-17A (IL-17A)</b>	0.02 ± 0.03	0.01 ± 0.02	0.07 ± 0.18	0.05 ± 0.11	0.58
<b>Interleukin-18 (IL-18)</b>	2.52 ± 1.88	2.71 ± 1.71	1.40 ± 0.99	4.16 ± 9.91	0.30
<b>Interferon-inducible protein-10 (IP-10)</b>	1.96[0.46,8.97]	4.77[1.62,8.17]	4.21[1.74,5.82]	2.80[1.10,8.17]	0.58
<b>Monocyte chemoattractant protein-1 (MCP-1)</b>	57.94[29.56,97.10]	63.42[42.71,126.19]	46.82[37.77,68.16]	54.00[33.24,61.59]	0.76
<b>Monocyte chemoattractant protein-3 (MCP-3)</b>	0.54[0.23,1.25]	0.74[0.57,1.55]	0.25[0.09,1.20]	0.64[0.26,1.77]	0.44
<b>Macrophage-derived chemokine (MDC)</b>	7.52[4.11,14.86]	9.41[5.58,12.79]	3.05[2.07,6.08]	6.65[2.93,11.90]	0.24
<b>Macrophage inflammatory proteins-1a (MIP-1a)</b>	0.63[0.34,1.03]	0.76[0.45,1.26]	0.34[0.14,1.00]	0.72[0.38,0.87]	0.82
<b>Macrophage inflammatory proteins-1b (MIP-1b)</b>	0.49[0.24,1.05]	0.58[0.25,1.51]	0.35[0.27,0.64]	0.37[0.13,0.81]	0.42
<b>Platelet derived growth factor-AA (PDGF-AA)</b>	2.51 [1.47,5.20]	2.36[2.03,4.82]	2.20[1.13,2.88]	2.29[1.65,2.96]	0.36
<b>Platelet derived growth factor-AB/BB (PDGF-AB/BB)</b>	0.32 ± 0.36	0.55 ± 0.76	0.34 ± 0.41	0.30 ± 0.28	0.21
<b>Regulated on Activation Normal T-Cell Expressed and Secreted (RANTES)</b>	1.15 ± 0.97	1.66 ± 3.43	1.08 ± 0.66	0.95 ± 1.09	0.46
<b>sCD40Ligand (sCD40K)</b>	0.11 ± 0.10	0.09 ± 0.06	0.05 ± 0.05	0.07 ± 0.04	0.20
<b>Transforming growth factor-a (TGFa)</b>	0.33 ± 0.16	0.49 ± 0.22	0.40 ± 0.31	0.43 ± 0.17	0.22
<b>Tumour necrosis factor-a (TNFa)</b>	0.04 ± 0.03	0.04 ± 0.07	0.04 ± 0.06	0.04 ± 0.05	0.99
<b>Tumour necrosis factor-b (TNFb)</b>	0.18 ± 0.27	0.09 ± 0.10	0.08 ± 0.22	0.05 ± 0.09	0.57
<b>Vascular endothelial growth factor (VEGF)</b>	5.75 ± 2.94	5.35 ± 6.09	4.82 ± 3.66	4.66 ± 3.45	0.89

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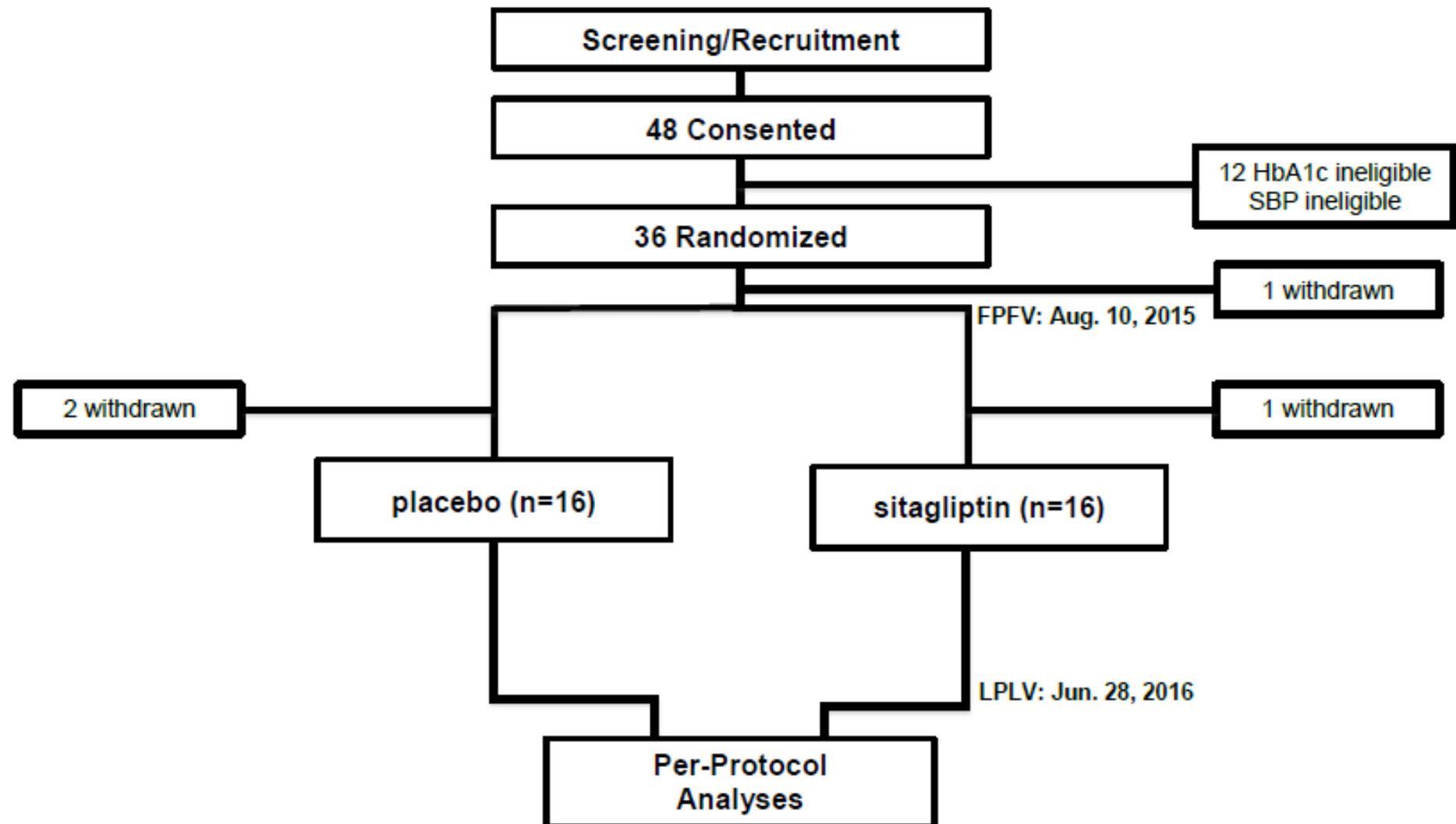
	placebo (n=16)		sitagliptin (n=16)		p-value
	Baseline	1 Month (3Hr)	Baseline	1 Month (3Hr)	
<b>Epidermal growth factor (EGF)</b>	1180.15±550.50	1189.35±407.91	1256.63±1376.00	1295.19±1169.71	0.95
<b>Fibroblast growth factor-2 (FGF-2)</b>	10.94 ± 9.17	10.65 ± 7.28	6.91 ± 5.04	11.17 ± 6.51	0.096
<b>Eotaxin</b>	0.31±0.51	0.61±1.02	0.43±0.67	0.76±1.07	0.23
<b>Flt-3 ligand (Fit-3L)</b>	1.50[0.74,1.65]	1.27[0.95,1.87]	0.96[0.76,1.37]	1.00[0.67,1.33]	0.6376
<b>Fractalkine</b>	11.85±9.42	9.80±9.91	8.74±8.35	7.47±5.01	0.94
<b>Granolucyte-colony stimulating factor (G-CSF)</b>	1.40 ± 1.26	1.32 ± 0.95	1.41 ± 2.12	1.36 ± 0.95	0.82
<b>Granolucyte-monocyte colony- stimulating factor (GM-CSF)</b>	2.57±2.08	2.46±1.38	2.18±2.63	2.38±1.25	0.073
<b>GRO pan (CXCL1/2/3) (GRO)</b>	4.66[2.33,7.04]	4.91[2.82,9.39]	3.02[1.94,7.44]	4.28[2.83,6.36]	0.75

Data are expressed mean±SD, or median [interquartile range].

Units for urinary analytes are expressed as pg per mmol urinary creatinine.

## SUPPLEMENTARY DATA

**Supplementary Figure 1. Patient flow diagram** Overview of patient recruitment, treatment allocation, and withdrawals throughout the study.

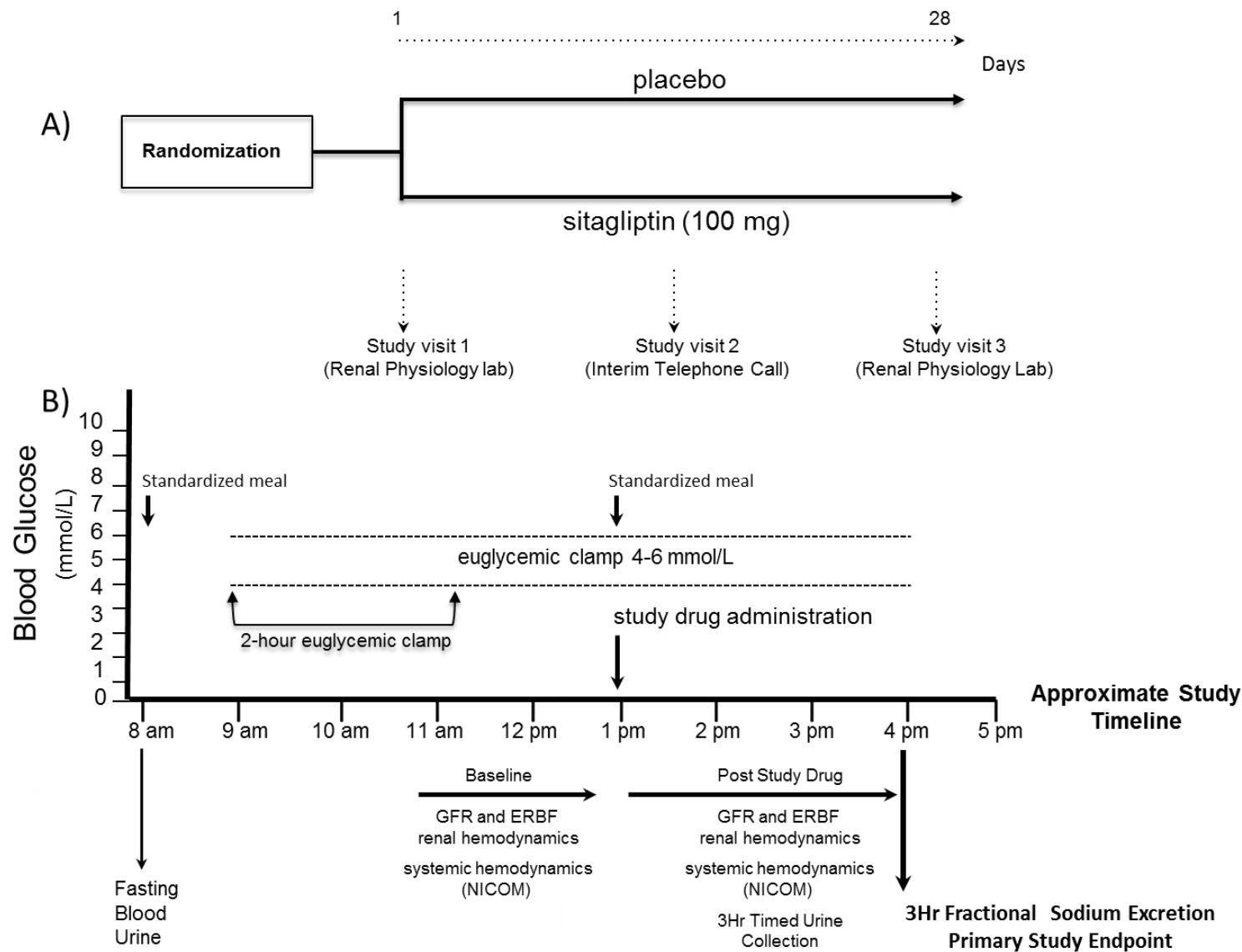


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**Supplementary Figure 2. Study design and experimental protocol** (A) Indicates the overall study design and timing of Study visits. (B) Specifies the timeline of the experimental procedures performed on Study visits at the renal physiology lab, Study visit 1 and Study visit 3 were identical.

ERPF, effective renal plasma flow; GFR, glomerular filtration rate; NICOM, non-invasive cardiac output monitoring.

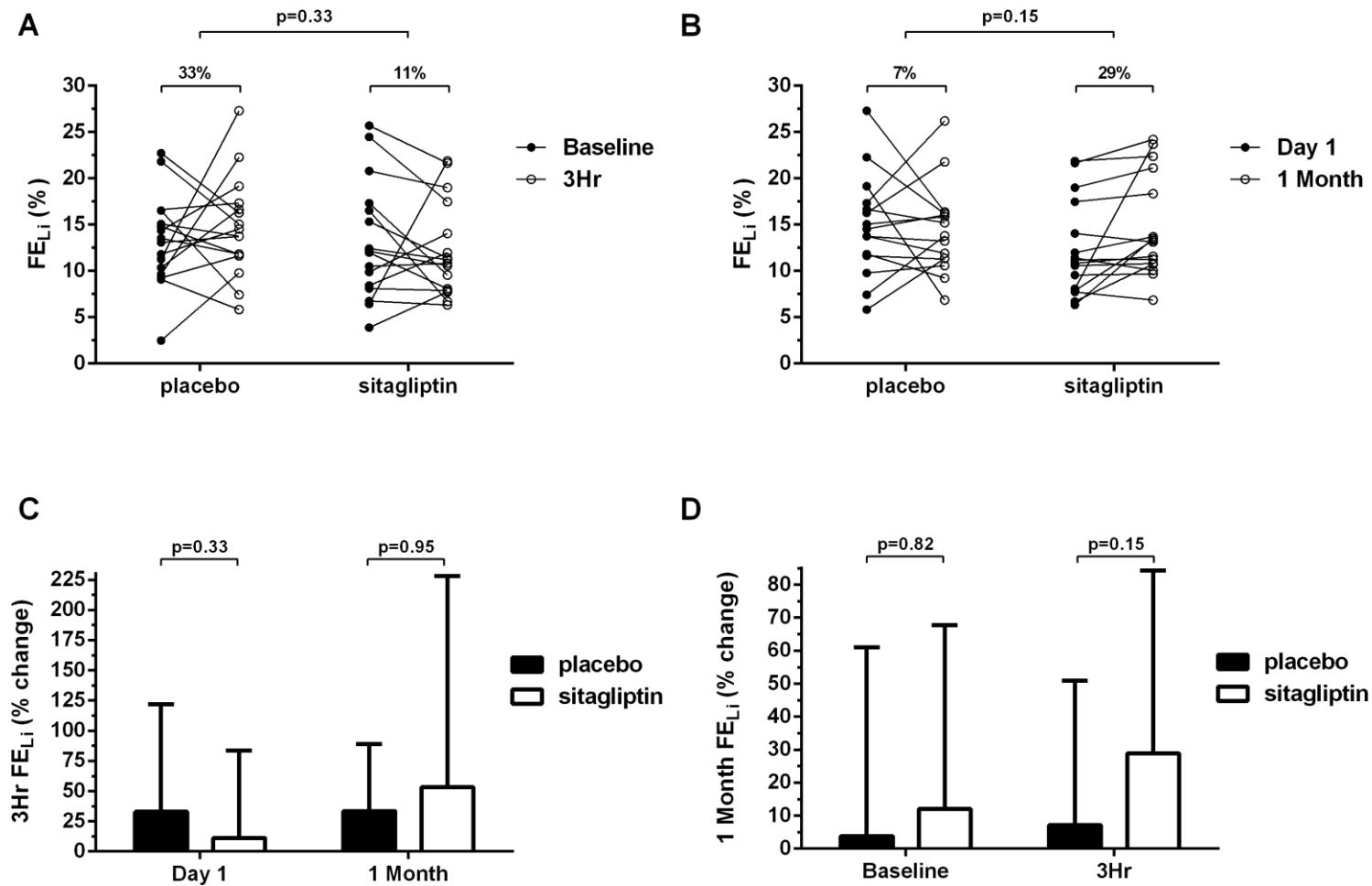
## SUPPLEMENTARY DATA



## SUPPLEMENTARY DATA

**Supplementary Figure 3. Acute and chronic fractional excretion of lithium ( $FE_{Li}$ ) in response to sitagliptin compared to placebo**

(A)  $FE_{Li}$  on Day 1 at 3Hr (compared to baseline) after a first dose of sitagliptin or placebo. (B)  $FE_{Li}$  at 1 month 3Hr after sitagliptin or placebo (compared to Day 1). (C) Percent change in  $FE_{Li}$  at 3Hr (compared to baseline) on Day 1 and after 1 month of sitagliptin or placebo. (D) Percent change in  $FE_{Li}$  at 1 Month (compared to Day 1) at baseline and at 3Hr after sitagliptin or placebo. In (A) and (B) horizontal bars indicate percent changes in group means.



SUPPLEMENTARY DATA

**Supplementary Figure 4. Correlation of plasma sitagliptin concentrations with (A) FE<sub>Na</sub>, and (B) plasma SDF-1 $\alpha^{1-67}$ .**

(A) Correlation of individual plasma sitagliptin concentrations on Day 1 (3Hr after first sitagliptin or placebo administration) with 1 Month change in fractional sodium excretion (FE<sub>Na</sub>) at 3Hr. (B) Correlation of individual plasma sitagliptin concentration on Day 1 (3Hr after first sitagliptin or placebo administration) with plasma SDF-1 $\alpha^{1-67}$  concentrations on Day 1. FE<sub>Na</sub>, fractional excretion of sodium.

