

SUPPLEMENTARY APPENDIX 1

Collaborators

PRIME-V study group

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WHO Trial Registration Data Set

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	UMIN000015170
Date of registration in primary registry	21 September, 2014
Secondary identifying numbers	Institutional Review Board of Chiba University approved number: G26009
Source(s) of monetary or material support	Chiba University
Primary sponsor	Chiba University 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan +81-43-222-7171
Secondary sponsor(s)	Astellas Pharma Inc. 2-5-1, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan +81-3-3244-3000
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Public title	Prospective and randomized controlled study on the efficacy and safety of ipragliflozin and metformin for visceral fat reduction in patients being treated with dipeptidyl peptidase-4 (DPP-4) inhibitors for poor glycemic controlled type-2 diabetes (PRIME-V)
Scientific title	Prospective and randomized controlled study on the efficacy and safety of ipragliflozin and metformin for visceral fat reduction in patients being treated with DPP-4 inhibitors for poor glycemic controlled type-2 diabetes (PRIME-V)
Countries of recruitment	Japan
Health condition(s) or problem(s) studied	Type 2 diabetes mellitus
Intervention(s)	Treatment group: DPP-4 inhibitor sitagliptin 50 mg, ipragliflozin 50 mg Control group: DPP-4 inhibitor sitagliptin 50 mg, metformin 1000 mg (can be increased up to 1500 mg after 12 weeks from the initial 500 mg)
Key inclusion and exclusion criteria	Inclusion criteria Eligible patients are those who meet the following inclusion criteria: (a) diagnosis of type 2 diabetes, confirmed in accordance with Japanese guidelines[16]; (b) age between 20 and 75 years; (c) inadequate control of plasma glucose levels despite treatment with 50 mg of the DPP-4 inhibitor sitagliptin for >12 weeks; (d) glycosylated hemoglobin (HbA1c, which provides an indication of the average blood glucose concentration of a patient over the previous 3 months) level >7.0% or <10.0% (according to the National Glycohemoglobin Standardization Program [NGSP]); (e) body mass index (BMI) >22 kg/m ² ; (f) estimated glomerular filtration rate >50 mL/min/1.73 m ² ; and (g) an adequate understanding of the contents of the trial and provision of written

DATA CATEGORY	INFORMATION
	<p>informed consent.</p> <p>Exclusion criteria</p> <p>Patients meeting any of the following criteria will be excluded from the trial: (a) diagnosis of type 1 diabetes; (b) history of metabolic acidosis, diabetic coma, and/or pre-coma up to 6 months prior to providing consent; (c) history of serious infections requiring insulin treatment, prior/upcoming surgeries, and/or severe injuries; (d) considerable loss of kidney function (blood creatinine level >1.3 mg/dL in men or >1.2 mg/dL in women) and/or need for dialysis (including peritoneal dialysis); (e) serious liver damage; (f) history of stroke, myocardial infarction, heart failure, or other severe cardiovascular complications requiring hospitalization; (g) use of oral hypoglycemic agents other than DPP-4 inhibitors at the start of the trial; (h) pregnancy, nursing, or plans to become pregnant; (i) history of chemical sensitivity to DPP-4 inhibitors, Sodium-dependent glucose transporter-2 inhibitors, and/or metformin; (j) current diagnosis of, or at risk for, urinary tract infection and/or dehydration; (k) positive for ketone bodies; (l) history of lactic acidosis; (m) excessive alcohol consumption; (n) history of bone fracture caused by osteoporosis; (o) need for computed tomography (CT) scan within 3 months prior to providing written consent; and/or (p) determination of ineligibility by the attending physician for any other reason.</p>
Study type	<p>Interventional</p> <p>Allocation: randomized</p> <p>Intervention model: parallel assignment by computer program</p> <p>Masking: blind (outcomes assessor)</p> <p>Primary purpose: reductions in visceral fat</p> <p>Phase IV</p>
Date of first enrolment	January 2015
Target sample size	106
Recruitment status	No longer recruiting
Primary outcome(s)	The rate of change in the total area of visceral fat in each group, as measured via CT following the 24-week treatment period

DATA CATEGORY	INFORMATION
Key secondary outcomes	(a) HbA1c (NGSP); (b) body weight and BMI; (c) waist circumference; (d) bone markers (alkaline phosphatase, bone alkaline phosphatase, and tartrate-resistant acid phosphatase-5b; (e) muscle strength; (f) fasting plasma glucose level, homeostatic model assessment (HOMA)-b, and HOMA-R; (g) cholesterol level (total cholesterol, low-density lipoprotein cholesterol as calculated using the Friedewald Equation, fasting triglycerides, and high-density lipoprotein cholesterol); (h) blood pressure; (i) adipocytokine (adiponectin) and inflammatory markers; (j) subcutaneous fat area and total fat area; (k) respiratory quotient, basal metabolism, whole body dual-energy x-ray absorption, eating behavior questionnaire, and calorie and glucose intake; (l) area of abdominal muscle as measured via CT; and (m) bone density in the fourth lumbar vertebra as measured via CT.

Protocol Version and Amendment Tracking

Version Number/Amendment	Date
1.0	27/May/2014
1.1 Revision	30/June/2014
1.2 Revision	8/September/2014
1.3 Revision	1/December/2014
1.4 Revision	6/February/2015
1.5 Revision	25/March/2015
1.6 Revision	19/May/2015
1.7 Revision	7/September/2015
1.8 Revision	24/November/2015
1.9 Revision	1/March/2016
2.0 Revision	21/September/2016

Research Organization

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5) Study Coordinating Management Office

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6) Auditors

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7) Patient Registration Center / Allocation / Data Management

Chiba University Clinical Trial Data Center

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The clinical data entry (double data entry), coding, data management, the allocation sequence generation, and reporting will be performed using the data management system ACRess (Fujitsu, Tokyo, Japan).

8) Statistical Analysis

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10) Project Support Organizations

Central Laboratory: LSI Medience Corporation (Tokyo, Japan)

Image processing Contact Research Organization (CRO): Micron Inc. (Tokyo, Japan)

11) Monitoring

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12) Other

To conduct this study, an agreement was signed between Chiba University and Astellas Pharma Inc. (Tokyo, Japan). Astellas Pharma Inc. funds this study.