SUPPLEMENTARY APPENDIX 1

Collaborators

PRIME-V study group

Asahi General Hospital: Hidetaka Yoko, Shunichiro Onishi and Kazuki Kobayashi
Chiba Aoba Municipal Hospital: Takashi Terano, Tomohiko Yoshida, Kyohei Yamamoto, Hanna Deguchi and Tomohiro Ohno
Chiba Chuo Geka Naika: Akina Kobayashi and Kou Ishikawa
Chiba Kaihin Municipal Hospital: Takahiro Ishikawa and Kaneyuki Watanabe
Chiba Rosai Hospital: Masahiro Mimura, Kouichiro Nemoto, Emi Tsuchiya and Yukari Maeda
Chiba University: Kou Ishikawa, Masaya Koshizaka, Kenichi Sakamoto, Masaya Yamaga, Mayumi Shoji, Akiko Hattori, Shintaro Ide, Kana Ide, Akina Kobayashi, Hidetaka Yoko, Takahiro Ishikawa, Yoshiro Maezawa, Minoru Takemoto, Koutaro Yokote, Sho Takahashi, Kengo Nagashima, Yasunori Sato and Takuro Horikoshi
Funabashi Central Hospital: Hidetaka Yoko and Masaya Koshizaka
Funabashi Municipal Medical Center: Hideaki Iwaoka, Tatsushi Shimoyama and SyunSyuke Nakamura
Hotaruno Central Naika: Daigaku Uchida and Susumu Nakamura
Inage Hospital: Minoru Takemoto, Harukiyo Kawamura and Kenichi Sakamoto
Izumi Chuo Hospital: Minoru Takemoto
Kimitsu Chuo Hospital: Ryouichi Ishibashi, Tomoko Takiguchi and Kenji Takeda
National Hospital Organization Chiba Medical Center: Norio Shimada, Hirotake Tokuyama, Tetsuya Okazaki, Kenchi Yui and Emi Ohara
Kujyukuri Home Hospital: Kou Ishikawa
Kouyukai Memorial Hospital: Akiko Hattori and Masaya Yamaga
Sannou Hospital: Ryouta Shimousa
Seirei Sakura Citizen Hospital: Kana Ide, Mayumi Shoji and Ryouti Ishibashi
Sousa Citizen Hospital: Yusuke Baba, Masaya Yamaga and Ryoichi Ishibashi

Tamura Memorial Hospital: Kenichi Sakamoto and Shintaro Ide

Toho University Sakura Medical Center: Ichiro Tatsuno, Atsuto Saiki and Yasuhiro Watanabe

Tokuyama Clinic: Takahiko Tokuyama

Tokyo Women’s Medical University Yachiyo Medical Center: Jun Ogino, Naotake Hashimoto, Chihiro Yoneda and Kana Tajima
## WHO Trial Registration Data Set

<table>
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<th>DATA CATEGORY</th>
<th>INFORMATION</th>
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<td>Primary registry and trial identifying number</td>
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<td>Date of registration in primary registry</td>
<td>21 September, 2014</td>
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<td>Secondary identifying numbers</td>
<td>Institutional Review Board of Chiba University approved number: G26009</td>
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<tr>
<td>Source(s) of monetary or material support</td>
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<td>Primary sponsor</td>
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<tr>
<td></td>
<td>1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan</td>
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<tr>
<td></td>
<td>+81-43-222-7171</td>
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<tr>
<td>Secondary sponsor(s)</td>
<td>Astellas Pharma Inc.</td>
</tr>
<tr>
<td></td>
<td>2-5-1, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan</td>
</tr>
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<td>+81-3-3244-3000</td>
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<tr>
<td>Contact for public queries</td>
<td>Masaya Koshizaka, MD, PhD [+81-43-222-7171] [<a href="mailto:overslope@chiba-u.jp">overslope@chiba-u.jp</a>]</td>
</tr>
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<td></td>
<td>Ko Ishikawa, MD, PhD [+81-43-222-7171] [<a href="mailto:ishikawako@chiba-u.jp">ishikawako@chiba-u.jp</a>]</td>
</tr>
<tr>
<td></td>
<td>Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Japan, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan</td>
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<td>DATA CATEGORY</td>
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</table>
| Contact for scientific queries      | Koutaro Yokote, MD, PhD  
[+81-43-226-2092][kyokote@faculty.chiba-u.jp]  
Professor, Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine, Japan, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan |
| 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/m²; (f) estimated glomerular filtration rate >50 mL/min/1.73 m²; and (g) an adequate understanding of the contents of the trial and provision of written consent. |
**DATA CATEGORY** | **INFORMATION**
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informed consent.  

Exclusion criteria  
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.

| Study type | Interventional  
Allocation: randomized  
Intervention model: parallel assignment by computer program  
Masking: blind (outcomes assessor)  
Primary purpose: reductions in visceral fat  
Phase IV |
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<td>Date of first enrolment</td>
<td>January 2015</td>
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<tr>
<td>Target sample size</td>
<td>106</td>
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<td>Recruitment status</td>
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<td>Primary outcome(s)</td>
<td>The rate of change in the total area of visceral fat in each group, as measured via CT following the 24-week treatment period</td>
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<td>Key secondary outcomes</td>
<td>(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.</td>
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<td>Version Number/Amendment</td>
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<td>30/June/2014</td>
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Masaya Koshizaka, MD, PhD
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4) Study Coordinating Management Committee
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Professor, Department of Medicine, Division of Diabetes, Metabolism and Endocrinology, Chiba University Hospital
Hideki Hanaoka
Clinical Research Center, Chiba University Hospital
Ko Ishikawa, MD, PhD
Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine
Takatoshi Sato
Clinical Research Center, Chiba University Hospital

5) Study Coordinating Management Office
Clinical Research Center, Chiba University Hospital

6) Auditors
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7) Patient Registration Center / Allocation / Data Management
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Mayumi Negishi, Mayumi Matsui and Mayumi Ogawa
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
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8) Statistical Analysis
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Kengo Nagashima and Yasunori Sato
Department of Global Clinical Research / Biostatistics, Chiba University, Graduate School of
Medicine

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Kaori Tachibana, MD, PhD
Department of Diabetes/Metabolic Endocrinology, Japanese Red Cross Narita Hospital
Tsuyoshi Matsumoto, MD, PhD
Department of Diabetes/Metabolism, Funabashi Central Hospital

10) Project Support Organizations
Central Laboratory: LSI Medience Corporation (Tokyo, Japan)
Image processing Contact Research Organization (CRO): Micron Inc. (Tokyo, Japan)

11) Monitoring
Increase Co., Ltd. (Tokyo, Japan)

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.