SUPPLEMENTARY DATA

Participating Investigators:

Executive Committee: Jeffrey L. Probstfield, University of Washington Division of Cardiology; Irl B. Hirsch, University of Washington Diabetes Care Center; Barry R. Davis, University of Texas Health Science Center at Houston, School of Public Health; Kevin O'Brien, University of Washington Division of Cardiology; Hertzel C. Gerstein, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada; Matthew C. Riddle, Oregon Health & Science University, Section of Diabetes, Portland, OR; Richard Bergenstal, International Diabetes Center at Park Nicollet, St. Louis Park, MN; Ian de Boer, University of Washington Division of Nephrology and Kidney Research Institute; Jeanne Poole, University of Washington Division of Cardiology; Sara Pressel, University of Texas Health Science Center at Houston, School of Public Health; Dorrine Khakpour, University of Washington Diabetes Care Center; Connie Kingry, University of Washington Division of Cardiology.
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Holter/ ECG Reading Center (University of Washington): Jeanne Poole, Susan
Data Center: University of Texas Health Science Center at Houston, School of Public Health: Barry R. Davis*, Sara Pressel*, Dejian Lai*, Cecilia Lara*.
*Denotes Membership Operations Committee
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Central Chemistry Laboratory: Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA: Santica Marcovina, Jessica Harting.
Medicomp, Inc: Dan Balda, Mauri Wilson.
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*Left study

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Supplementary Table 1. Criteria for Eligibility

A. Inclusion criteria

1. Type 2 diabetes for >12 months, defined according to current ADA criteria.
2. C-peptide >0.17 nmol/L – after informed consent has been signed, samples will be drawn fasting and sent to a central lab.
3. All participants must be on insulin therapy. Diabetes, blood pressure, and lipid therapy must be stable (in both dose and agent) for ≥3 months (dose of any 1 drug has not changed by more than 2-fold, and new agents not been added within the previous 3 months).
4. HbA1c 58-69 mmol/mol (7.5-8.5%) for enrollment.
5. Age at enrollment (screening): 40-75 years (inclusive) when there is a history of cardiovascular disease (defined below in 'a'), or 55 to 75 years (inclusive) when there is not a history of cardiovascular disease but two or more risk factors (with or without treatment) are present (defined below in 'b'). *
    a. Established cardiovascular disease defined as presence of ***one*** of the following:
        i. Previous myocardial infarction (MI). (most recent must be > 3 months prior enrollment)
        ii. Previous stroke. (most recent must be > 3 months prior enrollment).
        iii. History of coronary revascularization (e.g., coronary artery bypass graft surgery, stent placement, percutaneous transluminal coronary angioplasty, or laser atherectomy). (most recent must be > 3 months prior enrollment).
        iv. History of carotid or peripheral revascularization (e.g., carotid endarterectomy, lower extremity atherosclerotic disease atherectomy, repair of abdominal aortic aneurysm, femoral or popliteal bypass). (most recent must be > 3 months prior enrollment).
        v. Angina with either ischemic changes on a resting ECG, or ECG changes on a graded exercise test, or positive cardiac imaging study.
        vi. Ankle/brachial index <0.9.
        vii. Left Ventricular Hypertrophy with strain by ECG or ECHOcardiogram.
        viii. >50% stenosis of a coronary, carotid, renal, or lower extremity artery.
        ix. Urine albumin to urine creatinine ratio of >30 mg albumin/g creatinine in 2 samples, separated by at least 7 days, within past 12 months) [Target of 50% of study population].
    b. Increased CVD risk defined as presence *of two* or more of the following:
        i. Untreated LDL-C >3.4 mmol/L or on lipid treatment.
        ii. Low HDL-C (<1.0 mmol/L for men and <1.3 mmol/L for women).
        iii. Untreated systolic BP >140 mmHg, or on antihypertensive treatment.
        iv. Current cigarette smoking.
        v. Body mass index 25-40 (Asian populations 23-40) kg/m^2.
6. No expectation that participant will be moving out of the area of the clinical center during the next 8 months, unless the move will be to an area served by another trial center.
7. Ability to speak and read English.

B. **Exclusion criteria:**

Participants who meet any of the following criteria are not eligible for the trial:

1. The presence of a physical disability, significant medical or psychiatric disorder; substance abuse; or use of a medication that in the judgment of the investigator will affect the use of CGM,

wearing of the sensors, Holter or Telemetry monitor, complex medication regimen, or the completion of any aspect of the protocol.

2. Cannot have had any cardiovascular event or interventional procedure, (MI, stroke, or revascularization) or been hospitalized for unstable angina within the last 3 months.
3. Inability or unwillingness to discontinue use of acetaminophen products during CGM use.
4. Inability or unwillingness to discontinue use of all other diabetes agents other than insulin and metformin during trial (including insulin pump participants who will need to convert to BBI).
5. Intolerance of metformin dose <500 mg/day.
6. Inability or unwillingness to perform blood glucose testing a minimum of 3 times per day.
7. Creatinine level ≥132.6 µmol/L for males, or ≥123.8 µmol/L for females.
8. ALT level ≥ 3 times upper limit of normal.
9. Current symptomatic heart failure, history of NYHA Class III or IV congestive heart failure at any time, or ejection fraction (by any method) < 25% .
10. Inpatient psychiatric treatment in the past 6 months.
11. Currently participating in an intervention trial.
12. Chronic inflammatory diseases, such as collagen vascular diseases or inflammatory bowel disease.
13. History of pancreatitis.
14. BMI >40 kg/m^2 **
15. For females, pregnant or intending to become pregnant during the next 7 months *(Pregnancy is an exclusion because exenatide is a category C drug).*

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* Changed to following with Amendment 1 (12-3-2012): Age at enrollment (screening): 40-75 years (inclusive) when there is either a history of cardiovascular disease (defined below in 'a'), or when there is not a history of cardiovascular disease but two or more risk factors (with or without treatment) are present (defined below in 'b')

******** *Changed to following with Amendment 2 (12-3-2012): BMI >45kg/m^2*

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Supplementary Table 2. Schedule of visits, examinations and procedures

	-8 to-10w	-6 to -8 w	-2 to -3w	0	10d ±3d	4w ±1w	11-12 w[3]	13w ±1w	19w ±1w	24-25 w[3]	26w±1w
	Screen Visit	Screen Visit #1b[2]	CGM/ Holter Visit	BSL Visit			CGM/Holter Visit			CGM/Holter Visit	Final Visit
Visit #	1	1b -If indicated	2	3	4	5	6	7	8	9	10
Contact (phone or email)*											
Consent	X										
General Physical Exam	X										
Special skin evaluations	X		X	X	X	X	X	X	X	X	X
History, BP, HR, and weight	X			X	X	X		X	X		X
Waist-Hip Ratio				X							X
Review DM Management	X		X	X	X	X	X	X	X	X	X
HbA1c (POC)	X		X	X	X	X	X	X	X	X	X
HbA1c (central lab)	X		X					X			X
C-Peptide[1^]	X										
Albumin creatinine ratio (ACR) [1]	X			X				X		X	X
Creatinine[1]	X		X					X			X
ALT[1]	X										X
Inflammatory markers^											
Serum SAA, CRP & IL-6 and urine 8-iso-prostaglandin F2-alpha				X				X			X
Adiponectin[4^]				X				X			X
1,5 AG[4]				X				X			X
HDL proteomics[4^]				X							X
Metabolomics[4^]				X							X

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HGM Download (SMBG)			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
HGM Upload (SMBG)				**X**				**X**			**X**
Masked CGM Placement[3]			**X**				**X**			**X**	
Data Download (CGM)[5]				**X**				**X**			**X**
Holter monitor Placement			**X**				**X**			**X**	
Holter & Telemetry monitor download				**X**				**X**			**X**

[1]Samples used for eligibility screening

[2]A second screening visit may be necessary to verify lab tests or after washout of pre-trial medications at screening visit #1

[3]Masked CGM used by all participants at Screening, 11-13 weeks, and 24-26 week (for 7 days)

[4]Adiponectin, 1,5 AG, HDL proteomics and metabolomics will be performed on a 60 participant subset (30/group) of the whole cohort.

[5]Participants will return to the clinic for downloading the masked CGM data.

**One protocol-specified phone call will occur between <u>each visit</u> – self-management/education will be completed at the time of calls.*

^Fasting samples

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Supplementary Table 3. Summary of FLAT-SUGAR Screening and Reasons for Ineligibility

	Prescreen		Visit 1		Visit 2		
	Eligible or Ineligible Subjects	**Dropout**	**Eligible or Ineligible Subjects**	**Dropout**	**Eligible or Ineligible Subjects**	**Dropout**	**BBI/GLIP Randomized Participants**
Total	**255**		**200**		**123**		
Eligible/ineligible	204 / 51	4	131 / 69	7	104 / 19	1	102
Reasons for ineligibility (not mutually exclusive):							
HbA1c out of range	37		47		17		
C-peptide level ≥ 0.5 ng/mL	1		16				
Creatinine level ≥132.6μmol/L for males, or ≥123.8μmol/L for females	3		1		1		
Stable diabetes, BP and lipid therapy	4						
History of pancreatitis	2						
BMI >40 kg/m^2	2						
Intolerance of metformin dose <500 mg/day					2		
Participant has an insulin pump	2						
ALT level ≥ 3 times upper limit of normal			1				
No CVD events specified	1						
Other	5		5		4		

ALT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; CVD = cardiovascular disease.

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Supplementary Table 4. CONSORT Checklist

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	8-12
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	12-13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	14
	13b	For each group, losses and exclusions after randomisation, together with reasons	NA

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Recruitment	14a	Dates defining the periods of recruitment and follow-up	13
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	27-28
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	NA
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	NA
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	NA
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	NA
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	NA
Other information			
Registration	23	Registration number and name of trial registry	7
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19

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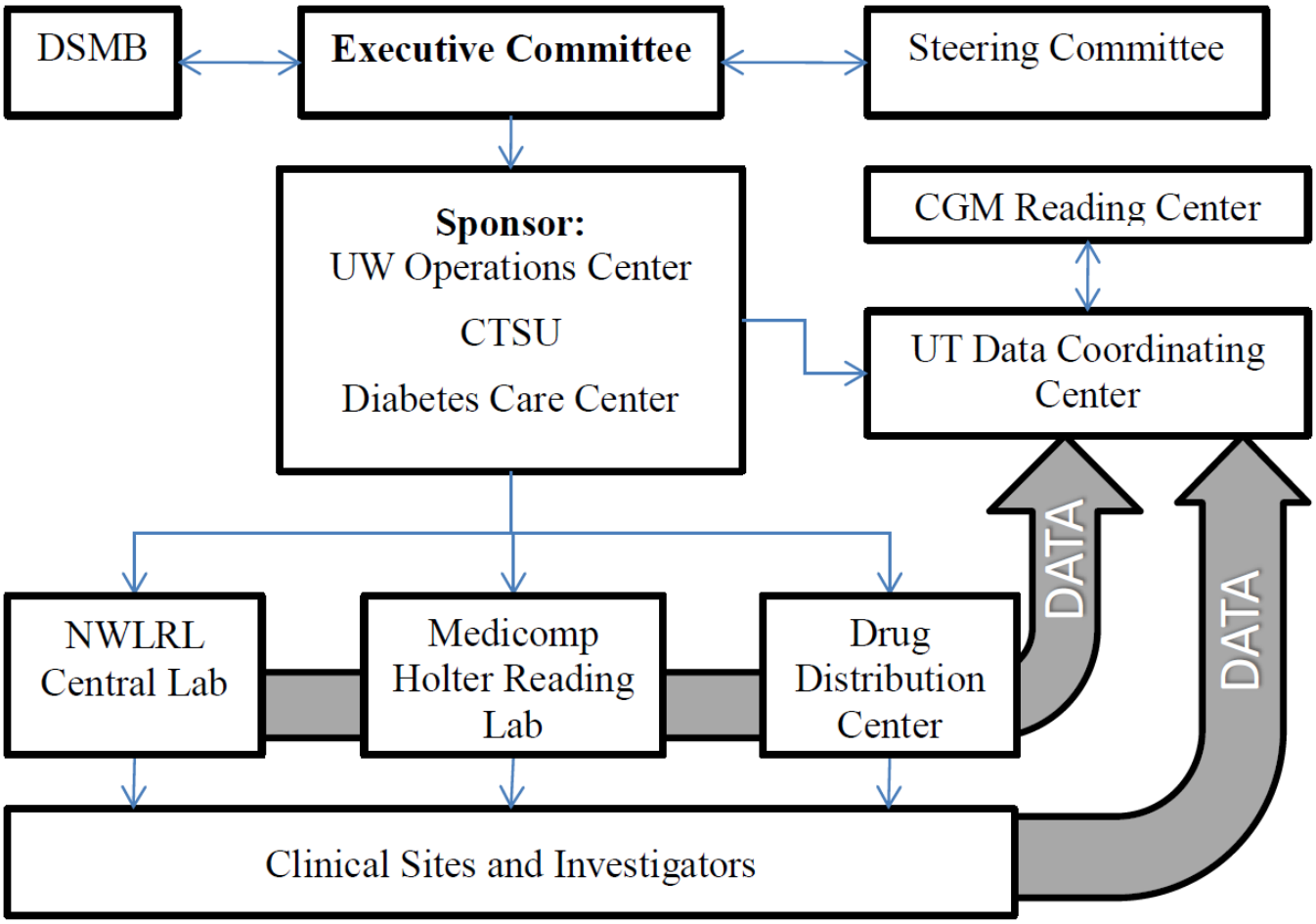
Supplementary Figure 1. Study organization. *DSMB* – Data Safety Monitoring Board which reports to the Executive Committee. *Executive Committee* – Consisting of diabetologists and clinical trialists who provided guidance and counsel to the Steering Committee and the UW Operations Centers. *Steering Committee* – An expanded group of investigators including the Executive Committee and leading personnel at clinical sites and other units. *Sponsor* – The University of Washington, including the Clinical Trials Service Unit (CTSU) and the Diabetes Care Center. *UT Data Coordinating Center* – Located at the University of Texas School of Public Health in Houston. *NWRL Central Laboratory* – Northwest Lipid Metabolism and Diabetes Research Laboratories located at the University of Washington. *Medicomp* - Medicomp Corporation provides ambulatory cardiac monitoring for patients/participants globally 24 hours a day in multiple state-of-the art facilities, staffed by certified clinicians. Core Holter reading and analysis done at the University of Washington. *Drug Distribution Center* – Located at the VA Cooperative Research Center in Albuquerque, NM. *Clinical Sites* – 12 clinical centers served as participant clinical centers for the study.



SUPPLEMENTARY DATA

Supplementary Figure 2. Study design. BBI - basal bolus insulin; CGM - continuous glucose monitoring; HGM - (SMBG) - self monitoring of blood glucose; ICF - Informed Consent Form; RAA - Rapid acting analogue; VB - variability biomarker.