

## 1 Title Page

Protocol Number:	CGMMDI
Protocol Title:	A randomized trial of the effect of continuous glucose monitoring (CGM) in individuals with type 1 diabetes treated with multiple daily insulin injections (MDI)
Sponsor:	Investigator-initiated trial. The study sponsor is Marcus Lind. MD, PhD, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and Department of Medicine, NU-Hospital Organization, Uddevalla, Sweden
CGM System:	DexComG4 (DexCom Corporation)
Protocol Release date:	13 January 2014
GCP Statement:	This study will be performed in full compliance with ICH and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by competent authorities.

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## Synopsis

A keystone in preventing diabetic complications in patients with type 1 diabetes is good glycaemic control. Frequent self-measurements of blood glucose (SMBG) levels has been an essential part of insulin dosing before meals. However, in recent years continuous glucose monitoring (CGM) has become a treatment option for notifying the patient on trends in glucose levels and warning when these are estimated to be too high and too low.

In some countries today, Sweden among others, CGM is reimbursed in combination with continuous subcutaneous insulin infusions (CSII) in patients with very poor glycaemic control or a history of repeated severe hypoglycaemia in adult type 1 diabetic patients. This is based on existing clinical trials showing a beneficial effect on HbA1c by combining CGM with CSII. However, the majority of adult type 1 diabetic patients are treated with multiple daily insulin injections (MDI). Clinical trial data are sparse on the effect of CGM in adult type 1 diabetic patients treated with MDI, and there are no clinical trial data including only patients on MDI.

The aim of the current study is to evaluate effectiveness, safety and treatment satisfaction among adult type 1 diabetic patients on CGM treated with MDI. The design is a 69-week, cross-over clinical trial, including 26 weeks treatment with CGM, 26 weeks treatment with conventional SMBG and a wash-out period of 17 weeks. In total 120 patients will be included at 5 sites in Sweden. The study will have 80% power to detect a 3 mmol/mol (0.3 percentage unit) change in HbA1c resulting from CGM.

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## **2 List of Abbreviations and Definitions of Terms**

ADA=American Diabetes Association

AE = Adverse Event

BMI = Body Mass Index

CGM = Continuous Glucose Monitoring

CSII = Continuous Subcutaneous Insulin Infusion

FPG = Fasting Plasma Glucose

HbA1c = Glycated Haemoglobin

MAGE = Mean Amplitude of Glycemic Excursions

MDI = Multiple Daily Insulin Injections = Basal insulin + meal time insulin to at least all major meals

PG = Plasma Glucose

PT=Preferred Term

SAE=Serious Adverse Event

SD=Standard Deviation

SMBG=Self-Measurement of Blood Glucose

SOC=System Organ Class

STAR-3=Sensor Augmented Pump Therapy for A1C Reduction

### **3 Study conduct & Oversight**

#### **3.1 Sponsor and Principal Investigator (PI)**

This is an investigator-initiated trial. The Principal Investigator (PI) and sponsor is Marcus Lind, MD, PhD, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and NU-Hospital Organization, Uddevalla, Sweden.

#### **3.2 CGM-system**

DexCom Corporation will provide CGM systems (DexCom G4) and sensors during the trial.

#### **3.3 Executive committee**

Marcus Lind, MD, PhD

Department of Molecular and Clinical Medicine, Sahlgrenska Academy University of Gothenburg, Gothenburg, Sweden and NU-Hospital Organization, Uddevalla, Sweden

William H. Polonsky, PhD, CDE

Chief Executive Officer, Behavioral Diabetes Institute, Associate Clinical Professor, University of California, San Diego, San Diego, California, United States

Irl B. Hirsch, MD, Professor of Medicine, University of Washington School of Medicine, Seattle, Washington, United States

Jan Bolinder, Professor in Diabetology, Karolinska University Hospital, Stockholm, Sweden

Tim Heise, MD, Profil, Neuss, Germany

David Owens, Institute of Molecular and Experimental Medicine, Cardiff University, University Hospital of Wales, Cardiff, UK

#### **3.4 Site Monitoring**

Gothia Forum, Gothenburg, Sweden will be responsible for study monitoring performed according to rules of the Swedish Drug Administration (LVFS 2003:11) regarding standards for monitoring of medical devices (SS\_EN ISO 14155:2011).

#### **3.5 Lab**

The central laboratory at the Karolinska University Hospital will be responsible for all analyses during the trial except urine albumin creatinine ratio, which will be analysed at local laboratories.

#### **3.6 Investigators and sites**

Marcus Lind, MD, PhD, NU-hospital Organization, Uddevalla, Sweden

Magnus Ekelund, MD, PhD, Department of Medicine, Helsingborg Hospital, Helsingborg, Sweden

Peter Moström, MD, Department of Medicine, Allingsås Hospital, Sweden

Marie Sjönander MD, Angered's Närsjukhus, Gothenburg, Sweden

### **3.7 Data Management & Statistics**

Gothia Forum will provide the eCRF system to be used in the study.

Data Management (including the randomization system) and statistical analysis will be performed by Statistiska Konsultgruppen, Gothenburg, Sweden.

## **4 Introduction & Background Information**

### **4.1 Background**

A keystone in preventing diabetic complications in patients with type 1 diabetes is good glycaemic control (1). Today, intensive glycaemic treatment is generally achieved through multiple daily insulin injections (MDI) or an insulin pump, also termed continuous subcutaneous insulin infusion (CSII, [2]). Regular capillary self-measured blood glucose values have been most crucial in obtaining good glycaemic control and guiding the patient on insulin doses (3, 4, 5).

During recent years continuous glucose monitoring (CGM) has become a treatment option for guiding the patient on insulin dosage and other activities (6). CGM has the advantage of informing the patient on estimated glucose values continuously, not the least important of which is to illustrate trends on increases or decreases in glucose levels.

Data from several clinical trials on CGM has shown divergent results on its glycaemic control effects (7). In some clinical trials, only patients on CSII have been included or have initiated CGM and CSII simultaneously as an intervention. In other trials both patients with MDI and CSII have been included, and post hoc analyses have also resulted in divergent findings whether the effect on glycaemic control potentially differs when combining CGM with MDI or CSII (8, 9, 10). Although the absolute majority of adult type 1 diabetic patients are treated with MDI, clinical trials initiating CGM in a pure MDI-treated group are absent.

The current trial is a cross-over design and 69 weeks in duration, where patients will be randomized patients to CGM-treatment for 26 weeks, conventional therapy for 26 weeks and a wash-out period for 17 weeks. The primary endpoint is the effect on HbA1c.

### **4.2 Study Population**

Adult patients in Sweden with type 1 diabetes treated with MDI and with inadequate glycaemic control. A random sample of type 1 patients from each site will be questioned regarding participation in the trial.

### **4.3 Purpose/aim of the study**

The aim of this study is to analyse the effect of CGM on glycaemic control measured by A1C, high and low glucose levels measured by CGM, and quality of life in patients with type 1 diabetes treated with MDI.

### **4.4 Primary Objective**

The primary objective is to determine whether CGM-therapy reduces HbA1c in type 1 diabetic patients treated with MDI compared to conventional therapy using SMBG.

### **4.5 Secondary Objectives**

Secondary objectives are comparisons of the following variables during CGM use versus non-use of CGM:

- Mean blood glucose level as measured by CGM
- Standard deviation of blood glucose level as measured by CGM
- MAGE as measured by CGM
- Treatment satisfaction, measured using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)
- Quality of life, according to the Diabetes Distress Scale and WHO 5
- Fear of hypoglycaemia, estimated by the Swedish Hypoglycaemia Fear Scale
- Time of low glucose levels as measured by CGM (below 3.0 mmol/l and below 4.0 mmol/l)
- Time of high glucose levels as measured by CGM (above 10.0 mmol/l and above 13.9 mmol/l)
- Time of euglycaemia as measured by CGM (5.5-10.0 mmol/l and 3.9-10.0 mmol/l)
- Reduction of HbA1c by 5 mmol/mol (0.5% in DCCT) or more
- Reduction of HbA1c by 10 mmol/mol (1% in DCCT) or more
- Number of severe hypoglycaemic events defined as unconsciousness due to hypoglycaemia or need of assistance from another person to resolve the hypoglycaemia
- Total insulin dose

## **5 Trial Design**

### **5.1 Design**

Multi-center, non-blinded, cross-over clinical trial.

### **5.2 Treatments**

The studied intervention will be CGM (DexCom G4, Dexcom Corporation) which will be compared to conventional therapy using only self-measurements of blood glucose levels (SMBG) for guiding the dosage of insulin.

Dexcom Corporation will provide the DexCom G4 systems and sensors.

### **5.3 Randomization**

After a maximum run-in period of four weeks patients will be randomized to either CGM or continued conventional therapy. During the run-in period blinded CGM will be performed during one week. After the blinded CGM period patients that do not believe they will wear a CGM sensor more than 80% of the study time during the period of randomization to CGM, or patients who did not perform adequate calibrations during the run-in period (on average at least 12 of 14 during a 7-day period), will not be randomized. The patient will be shown an example picture of glucose curves (not their own curves) with trend arrows, explained by the physician/diabetic educator to give the patient a better chance to judge how often they will use the sensor. Consenting patients will be randomized to CGM or conventional therapy for 26 weeks and conventional therapy for 26 weeks, with an intermittent wash-out period for 17 weeks.

Patients will be initially randomized 1:1, stratified by site, to CGM or conventional therapy. A centralised web system (handled by Statistiska Konsultgruppen) will be used for randomisation. Each patient will be assigned a unique and anonymous Subject ID at randomisation.

### **5.4 Duration**

The expected study duration for each participant is 72 weeks, including an assumed mean run-in period of 3 weeks. The total study period is expected to be 84 weeks, including a recruitment period of 12 weeks.

### **5.5 Endpoints**

#### *5.5.1 Primary endpoint*

The primary endpoint is the difference in HbA1c between week 26 and week 69.

### 5.5.2 Secondary endpoints

Secondary endpoints are the following:

The difference in mean glucose level (measured by CGM during two weeks) between week 23-26 and 66-69.

The difference in MAGE (measured by CGM during two weeks) between week 23-26 and 66-69.

The difference in standard deviation of glucose levels measured by CGM during two weeks between weeks 23-26 and weeks 66-69, measured by CGM

The difference in DTSQ scores between weeks 26 and 69

DTSQc score at week 69

The difference in WHO 5 scores between weeks 26 and 69

The difference in SWE-HFS scores between weeks 26 and 69

The difference in SWE-PAID-20 scores between weeks 26 and 69

The difference in the proportion of time with low glucose levels measured by CGM during two weeks between week 23-26 and week 66-69 measured by CGM (below 3.0 mmol/l and below 4.0 mmol/l respectively)

The difference in the proportion of time with high glucose levels measured by CGM during two weeks between week 23-26 and week 66-69 measured by CGM ((above 10.0 mmol/l and above 13.9 mmol/l respectively)

The difference in the proportion of time with euglycaemic levels measured by CGM during two weeks between weeks 23-26 and weeks 66-69 (5.5-10.0 mmol/l and 3.9-10.0 mmol/l respectively)

The difference in the proportion of patients reducing their HbA1c by 5 mmol/mol (0.5% in DCCT) or more

The difference in the proportion of patients lowering their HbA1c 10 mmol/mol (1% in DCCT) or more

The difference in the mean number of severe hypoglycaemic events between weeks 1-26 and weeks 44-69 defined as unconsciousness due to hypoglycaemia or need of assistance from another person to resolve the hypoglycaemia

The difference in total insulin dose between weeks 26 and 69

Primary and secondary endpoints will be intention to treat as well as per protocol in individuals that use sensors > 80% of the time

Compare outcomes with frequency of receiver interactions

## 6 Selection and withdrawal of subjects

Patients fulfilling all inclusion and no exclusion criteria will have their HbA1c levels analysed by the central laboratory.

The study is planned to include 120 patients randomized 1:1, stratified by site, to CGM or conventional therapy. Treatment will be for 26 weeks for each group, with a wash-out period of 17 weeks between treatment. An expected drop-out rate is assumed to be 5%-10% without replacement.

### 6.1 Inclusion and exclusion criteria

#### 6.1.1 Inclusion criteria

1. Type 1 diabetes
2. Adults 18 years or older
3. Written Informed Consent
4. HbA1c greater than or equal to 58 mmol/mol (7.5% DCCT standard)

#### 6.1.2 Exclusion criteria

1. Pregnancy, planned pregnancy for the study duration or pregnancy during the last six months
2. Severe cognitive dysfunction or other disease, which is judged by the physician to be not suitable for inclusion.
3. Required continuous use of paracetamol. Paracetamol must not have been used the week before the study and shall not be used during CGM-use because it disturbs the interpretation of blood glucose levels estimated by the DexComG4. However, other pain killers can be used throughout the study duration.
4. Current CGM use. (within the past 4 months)
5. History of allergic reaction to any of the CGMS materials or adhesives in contact with the skin.
6. History of allergic reaction to chlorhexidine or alcoholanti-septic solution.
7. Abnormal skin at the anticipated glucose sensor attachment sites (excessive hair, burn, inflammation, infection, rash, and/or tattoo).
8. Patient is uncomfortable by using the sensor during the blinded run-in period and believes it is unlikely that he/she will use the sensor more than 80% of the time during the trial.
9. The patient has on average performed 12 or less calibrations per week during the run-in period.

10. Insulin pump therapy=Continuous subcutaneous insulin infusion (CSII)
11. Diabetes duration < 1 year
12. Participation in another study.
13. Own insulin production (If this is not clear, C-peptide should be checked by a local blood sample)
14. Other investigator-determined criteria making patients unsuitable for participation.

### *6.1.3 Rescreening*

Rescreening of patients is possible in the study, but maximally at two times. There is no time limit for rescreening. It can be performed at any interval from previous screening. Rescreening can be performed for any inclusion/exclusion criterion that did not fit the inclusion criteria or fulfilled any exclusion criteria at the previous screening. However, there should be a possibility that this criterion can fit this inclusion criterion or not fit the exclusion criterion at the rescreening visit; e.g. that the glycaemic control has worsened since last screening and HbA1c did not fit inclusion criteria at the previous screening visit.

## **7 Investigational Product & Treatment of Subjects**

The trial product will be dispensed to each subject as required according to treatment group. The centralized web randomization system will allocate CGM use or non-use to the participant.

### **7.1 Treatment procedures**

All participants will receive the glucometer Bayer Contour XT for self measurements of blood glucose during the study. The meter's accuracy will be checked with a control solution before blinded CGM at run-in and week 40-43 and at visit week 13 and 56. During the run-in period all patients will have blinded CGM during two weeks. If the patient believes after performing blinded CGM that he/she will not be able to wear the sensor and use the CGM-system during the majority of the study period (more than 80% of the time) when randomized to CGM, he/she will be excluded from randomization. In addition, subjects not adherent with calibration procedures (require on average > 12 out of 14 calibrations over a 7 days period). There should be at least 10 days with valid blinded CGM data before randomization.

All patients in the trial will be instructed regarding basic information on insulin dosing, such as bolus correction, types of food elevating glucose levels and the effect of physical activity on glucose control. This information will be provided at the same level as in clinical practice for patients with type 1 diabetes, i.e. to guarantee that all patients have basic skills for dosing insulin. All patients will also be educated on the proportion of rapid acting insulin analogues remaining at various timepoints after injection (figure 3 in ref 11). Patients will be educated how to use the Bayer Contour XT meter and the DexCom 4G system. Care-givers will download data from the Bayer Contour XT meter both when randomized to SMBG and CGM, and additionally from the DexCom 4G system at all clinical visits. The main reason why SMBG data will also be downloaded at randomization to CGM is to have the possibility to retrospectively evaluate how the SMBG frequency changes when using CGM. At

clinical visits the care-giver will discuss glucose levels measured by SMBG and CGM data with the patient for possible improvements in the diabetes care. This will be performed in correspondence with intensive therapy used in clinical practice. All patients will have the possibility to contact the responsible staff for the trial at each site for additional support between the visits if needed, e.g. technical problems with SMBG meters or the DexCom 4G system, but extra visits will not be planned with the aim of improving the glycaemic control.

During at least the first week of randomization to CGM there will be no alarm levels set on the CGM, other than a constantly active acute alarm to low glucose levels. The reason is that the patient shall be taught to be active in judging trends of CGM and not only reacting at certain levels for alarms.

Alarm settings will be introduced 2 weeks after randomization, at the latest. At each visit the patient will be motivated to be active using the information from the CGM at least every 1-2 hours during daytime. In correspondence, patients will be motivated in measuring blood glucose levels when randomized to conventional therapy in accordance with guidelines, i.e. at least 4 times a day. At the 2 initial visits of each treatment period patients will be checked for general skills adopted on dosing insulin, types of foods that elevate glucose levels and the influence of physical activity on glucose levels. BG-values will be evaluated at the visits for patients receiving conventional therapy for possible improvements in dosing insulin, food intake and physical activity. In correspondence, CGM-curves will be analysed as well as algorithms for dosage of insulin from CGM-data and physical activity and influence of eating habits on glucose levels. When randomized to CGM patients will be instructed at the start point of the treatment phase and the two consecutive visits on a predefined algorithm for adjusting insulin according to the algorithm below:

### **Ten Guidelines to Improve Glucose Control Using CGM**

Guideline #1: Wear the CGM as much as possible. It will not help you if it is sitting in a drawer!

Guideline #2: Look at you receiver frequently. Knowing where you glucose was and where it is going will help you make better diabetes management decisions.

Guideline #3: Maintain reasonable expectations for your CGM. It is an awesome device, but it is not perfect (nor are your blood glucose measurements). The twice daily calibrations are important and will minimize false readings and alarms that may occasionally occur.

Guideline #4: Alerts and alarms should be helpful, especially if you respond to them. When you get a high or low glucose alert, you should think about both the actions you took that led to the high or low and the actions you should take *now*. If you are getting too many alerts, don't give up on your CGM. Instead, discuss changes in your diabetes management and/or your alert settings with your diabetes team.

Guideline #5: Know your personal glucose targets and take actions to reach them.

My pre-meal target is \_\_\_\_ - \_\_\_\_ mg/dl.

My post-meal target is < \_\_\_\_ mg/dl at 2 hours after the start of a meal.

Guideline #6: Have a plan for how to prevent or to respond to hypoglycemia. If you are low, try to not panic and over-react. Eat some carbs and repeat a fingerstick blood glucose measurement 15 minutes later if your glucose isn't back up or rising.

If your glucose is in your target range but is falling rapidly:

- Once again, avoid over-reacting but do not wait for the low glucose alert. Eat some carbohydrates. Remember, it may take 15 minutes or more for the carbohydrates to reverse the falling glucose.
- Keep a close watch on your glucose for the next 30-60 minutes.
- Be careful with your activity as exercise may further lower your glucose. Thinking back, if exercise contributed to the low, consider if a snack or insulin reduction would have helped.

Guideline #7: Don't keep your CGM results too private. You should have at least one person in your life you can share it with—both your successes and your frustrations.

Guideline #8: Generally speaking, try to take your mealtime insulin about 15 minutes before eating and remember that a blood glucose measurement should be used to determine your mealtime insulin dose. However, you should use your CGM trends to adjust your mealtime insulin as needed. Consider these 3 possible scenarios that could occur when you are determining your mealtime insulin dose.

Scenario 1- It's right before a meal and the trend arrow is horizontal: Do what you would normally do.

Scenario 2- The trend arrow or trend graph indicates your glucose is rising: Increase your mealtime insulin dose by:

\_\_\_\_ units for a slow increase (slanted arrow).

\_\_\_\_ units for a rapid increase (1 or 2 arrows straight up).

- Consider allowing more time between your insulin dose and your meal and/ or starting your meal with proteins and fats, not carbohydrates
- Thinking back, consider that if you had a snack earlier, perhaps you should have taken an extra insulin injection. Or if your glucose was low earlier, perhaps you over-treated it.

Scenario 3- The trend arrow or trend graph indicates your glucose is falling: Decrease your meal insulin dose by:

\_\_\_\_ units for a slow decrease (slanted arrow).

\_\_\_\_ units for a rapid decrease (1 or 2 arrows straight down).

- Consider allowing less time between your insulin dose and your meal or taking your meal insulin after you eat and/or starting your meal with carbohydrates, not fats and proteins.

Guideline #9: Respond to high glucose but be careful about "stacking" insulin and don't over-react. Remember, the rapid- acting insulin you take at meals may still be working 4 hours after your injection. Specifically, if it's 2 hours or more since the start of your last meal insulin dose and THE ARROW OR TREND GRAPH IS INDICATING THAT YOUR GLUCOSE IS STILL RISING:

- Take an extra dose of rapid acting insulin:
  - \_\_\_\_ units for a slow increase (slanted arrow).
  - \_\_\_\_ units for a rapid increase (1 or 2 arrows straight up).
- Keep a careful watch on your glucose over the next hour or two.
- Consider what you would do differently the next time with your meal and/ or your mealtime insulin dose to avoid the high and rising glucose. Thinking back, perhaps at your last meal you accidentally skipped your insulin or took less insulin than you should have.

Guideline #10: Take time for reflection. You can learn a lot from your CGM. Many CGM users develop a habit of looking back at their 24 hour trend graph view every morning or night. If you do this, think about what decisions you made that worked well (when your glucose was where you wanted it) and what changes you could make to prevent high or low glucose or rapidly changing glucose.

Your CGM tracings, downloaded from your CGM receiver, also help your health care team detect patterns of high, low and normal glucose that occur over time. This will help them determine if you need to make adjustments to your long-acting insulin dose or how you determine your meal insulin doses. Consider the following examples:

- During the past week, you have woken up in your target range most mornings. This suggests that your long-acting insulin dose is probably what it needs to be. If you stayed high throughout most nights or have woken up high most mornings, your long-acting insulin dose may need to be increased.
- During the past week, you recognize you are having frequent low glucose before lunch. This suggests you may need less insulin before breakfast or eat a mid-morning snack. If you observe your glucose is high most nights at bedtime, you may need more meal insulin at dinner.

You may also be able to install the software on your home computer and download your CGM receiver to help you identify your own patterns. Your health care team will help you make appropriate adjustments to your diabetes management.

In addition, these suggestions will be reviewed with each patient at their followup visits.

Blinded CGM will be performed for all participants during two weeks before baseline and two weeks before the starting point of the second treatment phase. Participants randomized to conventional therapy will also have CGM during 2 of the 4 last weeks of each treatment period (performed 23-26 and 66-69 respectively).

HbA1c will be recorded at the starting point of each treatment period and all subsequent study visits except week 2 and week 45.

At all visits SMBG and CGM data will be downloaded for randomized patients, and a diabetes educator or physician will discuss potential improvements for optimising glycaemic control with the patient. SMBG-data will be downloaded also for patients with CGM-treatment.

## **7.2 Rescue Criteria**

If the clinician or diabetic educator determines that CGM use is associated with severe risks, e.g., severe hypoglycaemia, CGM treatment shall be stopped and the patient will receive conventional treatment.

## **7.3 Procedures for monitoring subject compliance.**

Protocol compliance and adherence will be checked at each patient contact. The percentage of sensor time used will be evaluated and recorded at each visit.

## **7.4 Treatment Satisfaction and quality of life**

The DTSQ has been used in many diabetes therapy clinical trials and is a validated questionnaire consisting of 8 questions. Two versions are used, the DTSQs and DTSQc, where the DTSQs is used for recording the current treatment satisfaction and the DTSQc for patients to retrospectively compare various treatments.

SWE-HFS consists of 23 questions concerning actions to prevent hypoglycemia and fears about hypoglycaemia. The Swedish translation has been well validated (12).

SWE-PAID-20 consists of 20 questions regarding situations about diabetes that may be a problem to the individual.

WHO-5 consists of 5 questions assessing patient well-being.

IPAQ consists of 4 questions of various levels of physical activity during the last 7 days. (13)

The questionnaires will be completed at the study site. The patients will be allowed to individually complete the questionnaires in a reasonably quiet environment. It will be emphasized that patients complete the questionnaires prior to clinical measurements and before meeting a doctor. Questionnaires should be answered by the patient alone; however, the nurse/assistant will be informed to help patients complete the questionnaires, if necessary, but without influencing patients' responses. Only the anonymous Subject ID will be used to identify questionnaires to ensure patient confidentiality. Study nurses/assistants should check questionnaires for completeness. The PI shall ensure that appropriate study training is provided.

## **7.5 Biobank**

Blood samples for biobank will be stored at the Karolinska University Hospital for potential use in diabetes-related research. One serum, one plasma and one sample of whole blood will be stored for biobank samples. The samples will be stored for a maximum time period of 15 years. Samples are coded and code keys will be kept by the care provider. The origin can be traced to the human from whom it was taken.

If a subject withdraws consent to the use of their biological samples, donated samples will be disposed/destroyed, if not already analyzed and documented and the subject is withdrawn from further study participation.

The principle investigator ensures the central laboratory holding the samples is informed about the withdrawal and that the samples are disposed/destroyed and the action is documented and returned to the study site.

## **7.6 Risks associated with DexCom G4**

### *7.6.1 Paracetamol*

Use of paracetamol is not allowed during the study, since it will disturb glucose levels measured by the DexCom-system, resulting in the system showing higher than actual blood glucose values. The

false high glucose is related to the level of paracetamol in the body. Calibrating the CGM while paracetamol is in the body will lead to inaccurate CGM readings

## 8 Trial Procedures

Trial procedure during the run-in phase and trial is schematically shown below:

	Information	Informed Consent	Check criteria	Blinded CGM	Demographics, medical history	HbA1c	Creatinine, sensitive CRP, blood lipids, apolipoproteins, biobank samples	BMI, waist circumf. waist-hip ratio	Blood pressure	A/C ratio	DTSQs, WHO 5, SWE-HFS, SWE-PAID-20, IPAQ	DTSQC	Insulin dose	Concomitant medication	Optimization by CGM / SMBG only	AE, SAE	Download SMBG	Download CGM, evaluate use	Wash-out period	Meter or CGM receiver Download and Review
Visit 1	x																			
Visit 2		x	x																	
Run-in				x							x					x	x			x
Randomization					x	x	x	x	x	x			x	x	x	x	x	x		x
Week 2															x	x	x	x		x
Week 4						x									x	x	x	x		x
Week 13						x									x	x	x	x		x
Week 23-26				x																
Week 26						x	x	x	x	x	x		x	x		x	x	x		x
Week 27-43																			x	
Week 40-43				x							x					x	x			x
Week 44						x	x	x	x	x			x	x	x	x	x	x		x
Week 45															x	x	x	x		x
Week 47						x									x	x	x	x		x
Week 56						x									x	x	x	x		x
Week 66-69				x																x
Week 69						x	x	x	x	x	x	x	x	x		x	x	x		x

Physical examination is to be performed at visit 2-inclusion, visit 9-week 26, visit 11-week 44, and visit 16-week 69

Education on Bayer Contour XT and DexCom 4G system will be performed at baseline, week 2 and week 4 in each period.

At randomization and week 44, basic knowledge of insulin dosing will be checked and, if necessary, patients will be educated about basic insulin dosing.

At visit week 13 and week 26 (and corresponding week 56 and week 69) participants using CGM shall be asked how frequently they look at the receiver screen.

## **8.1 Visit 1 - Information**

*Recruitment visit/Telephone contact* : Patients will be given a brief overview of the study either at a clinical visit or via telephone and written information approved by ethical committee sent/given to the patient.

## **8.2 Visit 2 - Inclusion**

Patients will be permitted to ask questions about the study after reading the written information and receive further explanation . If the patient gives written and verbal informed consent to participate, inclusion/exclusion criteria will be assessed and a physical examination will be performed.

## **8.3 Visit 3 - Run-in period**

The frequency of SMBG performed during the last month will be recorded. This will if the patients own meter is available be checked by downloading data or checking in the meter, else the average number of SMBG/day will be estimated by the patient him-/herself.

DTSQs, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires will be filled in. This will be performed before blinded CGM is performed to minimize the influence from trial-related activities. All participants will receive the Bayer Contour XT glucometer for SMBG during the study. During run-in blinded CGM will be performed during 2 weeks. CGM values during at least 10 days shall be recorded, otherwise a novel sensor shall be set to obtain this time period.

## **8.4 Visit 4 - Randomization**

Patients meeting all inclusion and no exclusion criteria will be randomized if believing that he/she will use the sensor the majority of the time during the trial (more than 80% of the time) and performed adequate calibrations during the run-in period (on average at least 12 of 14 during a 7-day period). The patient will be shown an example picture of glucose curves (not their own curves) with trend arrows, explained by the physician/diabetic educator to give the patient a better chance to judge how often they will use the sensor. Randomization will take place 6 weeks after visit 2 at the latest.

Patients will be randomized to receive CGM (Dexcom G4) or SMBG with Bayer Contour XT. Education of how to use the Bayer Contour XT and DexCom 4G system will be performed. The following variables will be recorded:

- Age, sex
- HbA1c, creatinine, sensitive CRP, samples for biobank
- Weight, waist-circumference, waist-hip ratio, height
- Blood lipids and apolipoproteins
- Systolic and diastolic blood pressure
- Urine albumin creatinine ratio
- Insulin dose

- Diabetes onset
- Smoking (current, previous, never)
- Concomittant medications
- Previous laser photocoagulation of the retina
- Previous myocardial infarction
- Previous bypass-graft
- Previous PCI
- Amputation
- Previous diabetic foot ulcer
- Current diabetic foot ulcer
- Basic knowledge of insulin dosing will be checked and, if necessary, patients will be educated about basic insulin dosing.
- Number of severe hypoglycaemias last year
- Number of severe hypoglycaemias last 5 years
- AE, SAE

### **8.5 Visit 5 - Week 2**

A check will be performed that the patient has understood how the Bayer Contour XT meter works and how the DexCom 4G system works. SMBG data and CGM-data will be downloaded. For both randomized groups interpreting and discussing possible improvements in optimising glycaemic control will be performed. Glucose levels will be evaluated by SMBG or CGM data.

For patients using SMBG intensive therapy in accordance with clinical practice optimization will be performed including recommendations of optimal insulin dosage and extension of SMBG measurements if judged clinically indicated. For patients randomized to CGM, in addition the predefined treatment algorithm will be discussed with the patient. The patient will also be motivated in wearing the sensor, calibrating the CGM-system in accordance with recommendations and checking information of the CGM-system at least 1-2 times per hour daytime.

Alarms for high and low glucose levels shall be set at the latest at this visit. Generally, the upper alarm is initially set relatively high at around 14-15 mmol/l, and then with time lowered to around 10-11 mmol/l. However, this must be judged individually, patients with very poor glycaemic control may need an even higher initial alarm level and those with better glycaemic control may need a lower initial level. It shall also be considered if the patient benefits from the snooze function in the beginning, i.e. only reminded of the alarm for high levels every third hour. This enables the patient to get used to alarms before activating it properly, thus avoiding stress and irritation.

Check for AE, SAE.

### **8.6 Visit 6 - Week 4**

HbA1c will be measured. The same procedure for SMBG and CGM will be performed as at visit 5. Check for AE, SAE.

### **8.7 Visit 7 - Week 13**

HbA1c will be measured. The same procedure for SMBG and CGM will be performed as at visit 5. Check for AE, SAE.

### **8.8 Visit 8 – Week 23-26**

Blinded CGM will be performed during 2 of the 4 last weeks of the treatment period (week 23-26) for patients randomized to SMBG. This visit is solely due to perform the blinded CGM-period, no treatment procedures such as discussing insulin doses or glucose levels shall be performed. Patients randomized to CGM will not come to a corresponding visit.

Check for AE, SAE.

### **8.9 Visit 9 - Week 26**

SMBG and CGM-data will be downloaded.

The following variables will be measured:

- HbA1c, creatinine, sensitive CRP, samples for biobank
- Weight, waist-circumference, waist-hip ratio
- Blood lipids and apolipoproteins
- Systolic and diastolic blood pressure
- DTSQs, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires
- Urine albumin creatinine ratio
- Insulin dose
- AE, SAE

### **8.10 Visit 10, week 40-43**

DTSQs, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires will be filled in. This will be performed before blinded CGM is performed to minimize the influence from trial-related activities. Blinded CGM will be set for all participants to be performed during 2 weeks, of week 40-43. CGM should be completed over at least 10 days before treatment according to the second treatment phase is initiated.

### **8.11 Visit 11, Week 44**

Education of how to use the Bayer Contour XT and DexCom 4G system will be performed. The following variables will be recorded:

- HbA1c, creatinine, sensitive CRP, samples for biobank
- Weight, waist-circumference, waist-hip ratio
- Blood lipids and apolipoproteins
- Systolic and diastolic blood pressure
- DTSQs, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires
- Urine albumin creatinine ratio
- Insulin dose
- Concomittant medications
- Basic knowledge of insulin dosing will be checked and, if necessary, patients will be educated about basic insulin dosing.
- AE, SAE.

### **8.12 Visit 12 - Week 45**

A check will be performed that the patient has understood how the Bayer Contour XT meter works and how the DexCom 4G system works. SMBG data and CGM-data will be downloaded. For both

randomized groups interpreting and discussing possible improvements in optimising glycaemic control will be performed. Glucose levels will be evaluated by SMBG or CGM data.

For patients using SMBG intensive therapy in accordance with clinical practice optimization will be performed including recommendations of optimal insulin dosage and extension of SMBG measurements if judged clinically indicated. For patients randomized to CGM, in addition the predefined treatment algorithm will be discussed with the patient. The patient will also be motivated in wearing the sensor, calibrating the CGM-system in accordance with recommendations and checking information of the CGM-system at least 1-2 times per hour daytime.

Alarms for high and low glucose levels shall be set at the latest at this visit. Generally, the upper alarm is initially set relatively high at around 14-15 mmol/l, and then with time lowered to around 10-11 mmol/l. However, this must be judged individually, patients with very poor glycaemic control may need an even higher initial alarm level and those with better glycaemic control may need a lower initial level. It shall also be considered if the patient benefits from the snooze function in the beginning, i.e. only reminded of the alarm for high levels every third hour. This enables the patient to get used to alarms before activating it properly, thus avoiding stress and irritation.

Check for AE, SAE.

### **8.13 Visit 13, Week 47**

HbA1c will be measured. The same procedure for SMBG and CGM will be performed as at visit 12. Check for AE, SAE.

### **8.14 Visit 14 - Week 56**

HbA1c will be measured. The same procedure for SMBG and CGM will be performed as at visit 12. Check for AE, SAE.

### **8.15 Visit 15 –Week 66-69**

Blinded CGM will be performed during 2 of the 4 last weeks of the treatment period (week 66-69) for patients randomized to SMBG. This visit is solely due to perform the blinded CGM-period, no treatment procedures such as discussing insulin doses or glucose levels shall be performed. Patients randomized to CGM will not come to a corresponding visit.

Check for AE, SAE.

### **8.16 Visit 16 - Week 69**

SMBG and CGM-data will be downloaded.

The following variables will be measured:

- HbA1c, creatinine, sensitive CRP, samples for biobank
- Weight, waist-circumference, waist-hip ratio
- Blood lipids and apolipoproteins
- Systolic and diastolic blood pressure
- DTSQs, DTSQc, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires
- Urine albumin creatinine ratio
- Insulin dose

- Concomittant medication
- AE, SAE.

## **9 Assessment of Efficacy (Both intention to treat and per-protocol)**

### **9.1 Primary efficacy variable**

The primary efficacy variable is the difference in HbA1c between week 26 and week 69

### **9.2 Secondary efficacy variable**

Secondary efficacy variables are:

The difference in mean glucose level between week 23-26 and 66-69, measured by CGM

The difference in standard deviation of glucose levels between week 23-26 and week 66-69, measured by CGM

The difference in MAGE of glucose levels between week 23-26 and week 66-69, measured by CGM

The difference in DTSQs scores between week 26 and 69

The difference in the proportion of time where low glucose levels were measured by CGM between week 23-26 and week 66-69 (below 3.0 mmol/l and 4.0 mmol/l respectively)

The difference in the proportion of time where high glucose levels were measured by CGM between week 23-26 and week 66-69 (above 10.0 mmol/l and 13.9 mmol/l respectively)

The difference in the proportion of time with euglycaemia were measured by CGM between week 23-26 and week 66-69 (3.9-10.0 and 5.5-10.0 respectively)

The difference in the proportion of patients lowering HbA1c by 5 mmol/mol (0.5% DCCT standard) between weeks 26 and 69

The difference in the proportion of patients lowering HbA1c by 10 mmol/mol (1.0% DCCT standard) between weeks 26 and 69

The difference in mean number of severe hypoglycaemic events between weeks 1-26 and weeks 39-69

Difference in total insulin dose between weeks 26 and 69

## **10 Assessment of Safety**

### **10.1 Hypoglycaemia**

Periods of hypoglycaemia will be compared using blinded CGM versus randomization to open CGM during the corresponding time period. The regular definitions of hypoglycaemia using SMBG will be difficult to compare since patients using CGM will detect asymptomatic hypoglycaemia due to CGM

and be more alert to symptoms of hypoglycaemia. The number of severe hypoglycaemic events, defined as unconsciousness due to hypoglycaemia or need of assistance from another person to resolve hypoglycemia, will be recorded. The time with low glucose values will be analysed by comparing active treatment with CGM with blinded CGM for the corresponding time period.

## 10.2 Adverse Events (AE)

### 10.2.1 Definition of AE

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered or intended for administration of a pharmaceutical product, including placebo. An AE does not necessarily have a causal relationship with treatment. An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. This may include changes in laboratory values, diagnostic test results or physical examination findings
- Any new disease or exacerbation of an existing disease. Medical conditions/diseases present prior to starting the study are considered AEs if they worsen during the study
- Any deterioration in measurements of laboratory values or other clinical tests (e.g., ECG or x-ray) that results in symptoms, a change in treatment or discontinuation from study drug
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline

### 10.2.2 Hypoglycaemias

Hypoglycaemia is an AE by definition, but non-severe hypoglycaemias will not be considered an AE in this study since non-severe hypoglycaemias are common among type 1 diabetic patients in clinical practice. Non-severe hypoglycaemias will not be recorded on the AE pages of the CRF.

### 10.2.3 Reporting of Adverse Events (AE)

Recording and follow up of AEs will be made from the time of the first study related activity until the completion of the final study visit (SAEs will be followed up until resolved or the event or sequelae stabilizes, see 10.3).

AEs will be recorded on the AE pages of the CRF. For each AE, the following information will be recorded:

- AE (e.g. headache)
- Start/stop date
- Severity
- Action taken
- Relationship to CGM/self-measurement of blood glucose
- Outcome
- Seriousness

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g., fever, elevated WBCs, cough, abnormal chest x-ray, etc. should all be reported as “pneumonia”).

## **10.3 Serious Adverse Events (SAE)**

### *10.3.1 Definition of SAE*

An SAE is any medical occurrence at any dose that:

- Results in death
- Is life-threatening (i.e. the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study medication)
- Is a medically important event or reaction (see below)

Other important medical events that may not be immediately life-threatening or result in death or hospitalisation but may, based on appropriate medical judgment, jeopardise the subject or require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Examples of such events are intensive treatments in an emergency room or at home for allergic bronchospasm, blood dyscrasias or seizures that do not result in hospitalisation, or development of drug dependency or drug abuse. These events may be considered to need rapid reporting by the Sponsor to competent authorities.

### *10.3.2 Reporting of SAE*

All SAEs will be reported to the Sponsor within 24 hours on an SAE report form.

All SAEs will be recorded on the AE pages of the CRF. Subjects with SAEs must be followed until the event resolves, or the event or sequelae stabilise.

## **11 Statistics**

### **11.1 Populations**

#### *11.1.1 Full analysis set (ITT-population)*

The full analysis set (ITT-population) consists of all randomised patients who received at least one follow-up of HbA1c at week 13 or 26 after the starting point of each study period.

#### *11.1.2 Per-Protocol population*

The Per-Protocol population (PP-population) consists of all patients in the ITT-population who used sensors more than 80% of the time during the trial. The PP-population is defined at the clean-file meeting before the database is locked.

#### *11.1.3 Safety Population*

The safety population consists of all randomized patients who received CGM during any time period. In the safety analysis a patient will belong to the treatment given not to the randomised treatment.

### **11.2 General Statistical Methodology**

The study design is a randomized two period open cross-over study with 17 weeks wash-out period.

All statistical analyses regarding the main comparison of CGM with SMBG will be adjusted for both period effect and subject effect in the following ways:

For the primary efficacy analysis, HbA1c will be analysed using SAS procedure PROC GLM with sequence, subject(sequence), period and treatment as class variables.

For secondary efficacy analyses of normal distributed variables apply the same analysis as primary efficacy analysis SAS procedure, PROC GLM with sequence, subject(sequence), period and treatment as class variables.

For the secondary efficacy analyses of non-normal continuous variables, for each subject we calculate the differences between period A and period B. We compare these differences between the group that was randomised to CGM in the first period with the group that was randomised to SMBG in the first period with Fisher's non-parametric two sample permutation test.

Secondary efficacy analyses of dichotomous or ordered categorical variables will be analyzed in the following way: For each subject we calculate the differences between period A and period B, as worse, equal or better. We compare these differences (-1, 0,+1) between the group that was randomised to CGM in the first period with the group that was randomised to SMBG in the first period with Fisher's non-parametric two sample permutation test.

All significance tests will be two-sided and conducted at the 5% significance level.

The main primary and secondary analyses will be done on the ITT and PP population.

All continuous variables will be summarized with number, mean, SD, median and range for the CGM period, SMBG period and for the difference between the CGM and the SMBG period. All ordered categorical variables and all dichotomous variables will be summarized with number and percentages for the CGM period, SMBG period and with number and percentages of decreases, increases and unchanged when CGM period compared to SMBG period

### **11.3 Efficacy analyses**

#### *11.3.1 Primary efficacy analysis CGM compared to SMBG*

The primary efficacy analysis is the analysis of HbA1c at weeks 26 and 69 between CGM and SMBG for ITT population. The comparison of HbA1c after 26 weeks in CGM with SMBG will be adjusted for both period effect and subject effect using PROC GLM in SAS. Two-sided test with significance level 0.05.

If HbA1c from 26 and 69 weeks follow-up, respectively, is missing the last observation carried forward (LOCF) principle from 2, 4, and 13 weeks in each study period will be applied. All measurements obtained after rescue therapy should be excluded in all efficacy analyses.

#### *11.3.2 Secondary efficacy analyses*

All the secondary efficacy analyses will be performed on all secondary efficacy variable according to the principles given in section 12.2, General Statistical Methodology above.

All secondary efficacy analyses will be two-sided, conducted at the 5% significance level on the ITT-population.

The theory of sequentially multiple test procedures (1) will be applied for the primary analysis and for the 4 first secondary analyses. If a test gives a significant result on 5% significant level, the test total test mass will be transferred to the following number in the test sequence until a non-significant result is achieved.

The above efficacy analyses will also be performed on the PP-population.

#### **11.4 Statistical Analysis Plan**

A Statistical Analysis Plan that contains a detailed description of all planned analysis will be written and signed before the database is locked.

#### **11.5 Sample Size Calculation**

The study is designed to detect a difference in HbA1c of 3 mmol/mol (0.3%) between week 26 and week 69, at 80% power, assuming a SD of 1.1% which requires 108 participants. Assuming a drop-out rate of 10% the study will include 120 individuals.

#### **11.6 Safety analyses**

All safety analyses will be performed on the safety population.

All AE and SAE will be coded using the MedDRA dictionary and tabulated by treatment group.

Number of events, number of patients with events and percentage of patients with events will be given for:

- All events
- All SOC-classes
- All PT-codes within each SOC –code.

### **12 Premature termination of the trial**

The Sponsor or the Investigator may decide to stop the trial or part of the trial at any time.

If a trial is prematurely terminated or suspended, the Investigator should promptly inform the patients and ensure appropriate therapy and follow-up. Furthermore, the Investigator should promptly inform the IEC (Independent Ethics Committee) and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

If changes to the principal features of the confirmatory statistical analyses described in the protocol are required, a protocol amendment must be prepared. Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

### **13 Data Handling and Record Keeping**

#### **13.1 Data Collection**

Study data will be collected using electronic Case Record Forms (eCRF). No personal identifiers will be recorded in the eCRF but only the anonymous Subject ID number assigned to each subject in the study will be used.

Central laboratory data will be acquired as electronic data files. No personal identifiers other than the anonymous Subject ID will be included in the data files.

CGM data will be downloaded by the investigator sites using software supplied with the CGM device. No personal identifiers other than the anonymous Subject ID will be recorded in the CGM system.

The downloaded data files will be used for study analysis. CGM mean and standard deviation values will also be recorded on the CRF, but the values recorded on the CRF will only be used in the event any electronic files cannot be obtained due to technical issues during the download process.

## **13.2 Data Management**

A Data Management Plan (DMP) will be written to detail data management activities during the trial.

### *13.2.1 Study Database & Data Entry*

An eCRF will be set up for data entry by Investigator site personnel.

### *13.2.2 Data Validation & Data Clarifications*

Data management will periodically run data validation procedures on the data entered into the database. The data validation procedures will be specified in a Data Validation Plan (DVP). Where applicable, a Data Clarification Form (DCF) will be sent to the investigator site to clarify any data inconsistencies or suspected errors. Changes to the values reported on the original CRF will not be made to the study database until a completed and signed DCF has been returned by the Investigator.

### *13.2.3 Clean File & Database Lock*

Once all study data has been collected and entered, and prior to breaking the randomization codes, the database will be reviewed for completeness, accuracy and consistency. At a formal Clean File meeting the database will be declared locked, after which point the database will be write protected and the randomisation codes may be broken and analysis start.

## **13.3 Data Retention & Archiving**

Study sites should keep study documents and records, including printout copies of the eCRF and CGM records, for 10 years after the study ends.

After the study has been closed, printout copies of the eCRF and raw datasets (eCRF, central lab, and CGM data) will be transferred to the Sponsor for archiving in accordance with data archiving requirements.

## **14 Access to Source Data/Documents**

The investigator will permit trial-related monitoring, audits, IRB/EC review, and regulatory inspection(s), providing direct access to source data/documents.

## **15 Quality Control and Quality Assurance**

Site monitoring will be performed by Gothia Forum.

## **16 Ethics**

The trial will be conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. The protocol is subject to review and approval by relevant ethics committee.

### **16.1 Declaration of Ethical Conduct**

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and the applicable

regulatory requirements. It will be conducted in accordance with Good Clinical Practice (GCP) guidelines as required by the following:

1. Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Patients”), and all its accepted amendments to date concerning medical research in humans.
2. ICH Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use. (Note for Guidance on Good Clinical Practice, 2002).
3. European Union (EU) Clinical Trials Directive 2001/20/EC on the regulation of clinical trials in the EU and the implementation of GCP.
4. GCP Directive 2005/28/EC

This study will be conducted in accordance with national and local laws (e.g. drug and narcotics laws of the countries where study sites are located).

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in the protocol and to adhere to the principles of ICH Good Clinical Practice to which the protocol conforms as well as all governing local regulations and principles for medical research.

## **16.2 Ethical Review**

Prior to commencement of the trial, the protocol, any amendments, patient information/Informed Consent Form, any other written information to be provided to the patient, SPC, information about payments and compensation available to patient if not mentioned in the subject information, the physician’s current CV and/or other documentation evidencing qualifications, and other documents as required by the local Independent Ethics Committee (IEC) should be submitted. The submission letter should clearly identify (by including version number and/or date of the document) which documents have been submitted to the IEC. Written approval/favourable opinion must be obtained from IEC prior to commencement of the trial.

During the trial, the Investigator must promptly report the following to the IEC unexpected SAEs where a causal relationship cannot be ruled out, amendments to the protocol, notes of administrative changes, deviations to the protocol implemented to eliminate immediate hazards to the trial patients, new information that may affect adversely the safety of the patients or the conduct of the trial and other documents as required by the local IRB/IEC.

Amendments must not be implemented before approval/favourable opinion, unless necessary to eliminate hazards to patients.

The Investigator must maintain an accurate and complete record of all submissions made to the IEC. The records should be filed in the physician’s Trial File.

In case of early termination of the study, the Investigator should promptly inform the IEC and provide a detailed written explanation. The pertinent regulatory authorities should be informed according to national regulations.

## **16.3 Subject Information & Consent**

Informed consent should be obtained by means of a patient information sheet (PIS) and informed consent form (ICF), prepared in accordance with ICH E6 section 4.8.10 and applicable local regulations, written in non-technical language. The ICF should list all risks associated with treatment with DexCom 4G that are listed in the Swedish SmPC. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol. As part of administering the ICF, the Investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study

is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the PIS and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. The original signed ICF for each subject will be verified by the Sponsor monitor and kept in the study site investigational site files. Each subject will be given a copy of the signed ICF and written information.

## **17 Protocol Adherence & Amendments**

### **17.1 Adherence to Protocol**

The Investigator will conduct the study in strict accordance with the protocol, which has been written to enable the Investigator's compliance with ICH E6, Section 4, "Investigator Guideline for Good Clinical Practices."

There are to be no waivers to inclusion/exclusion criteria and no Investigator-led deviations from the schedules and procedures set out within this protocol. Any subject whose treatment deviates from the protocol or who is not qualified for study participation may be ineligible for analysis and may compromise the study.

Subjects who have not signed an EC approved ICF cannot participate in any trial activities.

The Investigator and research team must comply with ICH E6 principles and all applicable local regulatory laws and regulations.

### **17.2 Protocol Amendments**

Any changes to the protocol will be made by formal amendment. For changes potentially increasing risks to study participants, approval of a protocol amendment must be obtained from the IRB/EC prior to implementation of the change. Changes required to ensure the immediate safety of study participants may be made prior to IRB/EC approval or notification of the Sponsor, but will require prompt, full IRB/IEC notification and acknowledgement after the fact. Administrative changes not influencing subject treatment must be reported to the IRB/EC in accordance with its procedures and must at least be acknowledged in writing by the chairperson of the IRB/EC ("expedited approval"). The IRB/EC letter approving each protocol modification and identifying both the amendment or administrative change and the date of the meeting at which it was approved must be retained by the Investigator and a copy must be provided to the sponsor. The ICF must be revised to reflect protocol modifications affecting participants' treatment or risks, to provide new information potentially influencing participants' willingness to initiate or continue study participation, or to advise of important administrative changes (e.g., change of addresses, phone numbers, IRB/EC or subject ombudsman contact). Following IRB/EC approval, the revised ICF must be signed in a timely fashion by all current study participants. The earlier versions of IRB/EC-approved ICFs must be archived with study records.

## **18 Financing and Insurance**

A separate financial protocol will be set up. Subjects are insured according to the Swedish patient insurance scheme.

## **19 Publication Policy**

The trial will be posted on <http://clinicaltrials.ifpma.org/> before trial start.

The results of the trial will be published by the Investigators in an international scientific journal.

## **20 Supplements/Appendices**

### **20.1 Amendments**

Before the Investigator commences the trial, the following documents must be available:

- Regulatory approval and/or notification as required (independent ethics committee and the Medical Products Agency - Sweden)
- Signed and dated agreement on the final protocol
- Curricula vitae of the Investigator and Sub-Investigator(s) (current, dated and signed and/or supported by an official regulatory document)

### **20.2 Personnel Information**

The Investigator is responsible for the conduct of the trial. If any tasks are delegated, the Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant trial-related duties

## 21 References

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**Protocol Amendment**

Number: 1  
Study Code: CGM-MDI  
Date: 2013-12-30

## **A randomized trial of the effect of continuous glucose monitoring (CGM) in individuals with type 1 diabetes treated with multiple daily insulin injections (MDI)**

### **Sponsor:**

Marcus Lind, MD, PhD, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and NU-Hospital Organization, Uddevalla, Sweden

### **Section(s) of protocol to be amended:**

<b>Previous text</b>	<b>Revised text</b>
1. 4.2 A random sample of type 1 patients from each site will be questioned regarding participation in the trial.	4.2 Type 1 patients at each site will be questioned regarding participation in the trial.
2. 5.3 After a maximum run-in period of four weeks...	5.3 After a maximum run-in period of six weeks...
3. 5.3 During the run-in period blinded CGM will be performed during one week.	5.3 During the run-in period blinded CGM will be performed during two weeks.
4. 6 Patients fulfilling all inclusion and no exclusion criteria will have their HbA1c levels analysed by the central laboratory.	6 Removed
5. 6.1.2 Own insulin production (If this is not clear, C-peptide should be checked by a local blood sample)	6.1.2 Fasting C-peptide level of 0.3 nmol/l or higher
6. 6.1.2 No previous text	6.1.2 eGFR < 30 ml/min (estimated from creatinine, age and sex at the inclusion visit by the MDRD-formula)
7. 6.1.2 No previous text	6.1.2 Planned house move during the next 1.5 years, making it difficult to come to study visits

<b>Previous text</b>	<b>Revised text</b>
8. 6.1.3 Rescreening of patients is possible in the study, but maximally at two times.	6.1.3 Rescreening of patients is possible in the study, but maximally at one time.
9. 7.1 All participants will receive the glucometer Bayer Contour XT for self measurements of blood glucose during the study. The meter's accuracy will be checked with a control solution before blinded CGM at run-in and week 40-43 and at visit week 13 and 56.	7.1 Removed.
10. 7.1 Patients will be educated how to use the Bayer Contour XT meter and the DexCom 4G system. Care-givers will download data from the Bayer Contour XT meter both when randomized to SMBG and CGM...	7.1 Patients will be educated how to use the DexCom G4 system. All patients' knowledge regarding use of glucometer will be checked, and if judged clinically indicated education will be performed. Care-givers will download data from the patient's glucometer both when randomized to SMBG and CGM...
11. 7.1 Guideline #8: Generally speaking, try to take your mealtime insulin about 15 minutes before eating and remember that a blood glucose measurement should be used to determine your mealtime insulin dose.	7.1 Guideline #8: Consider taking your mealtime insulin 15 minutes before the meal if you note from the CGM curve that the insulin effect does not match the glucose rise from the meal.
12. 7.1 No previous text	7.1 The patients will be offered to install the SMBG-software on their home computer and download SMBG data to identify glucose patterns. The health care team will help the patients make appropriate adjustments to their diabetes management.
13. 7.4 No previous text	7.4 Hypoglycaemia confidence questionnaire consists of 9 questions regarding how confident the patients are regarding handling of hypoglycaemia Predictor variables questionnaire consists of 19 questions regarding possible predictors of CGM-effect.

Previous text	Revised text
14. 7.7 No previous text	<p>7.7 Downloading of SMBG and CGM data</p> <p>7.7.1 SMBG</p> <p>At all visits, SMBG data will be downloaded and the number of blood glucose values will be recorded. The serial number of the glucometer shall be recorded. If the patient has more than one meter all shall be downloaded and serial numbers recorded. If downloading of SMBG data is not possible, the glucometer shall be checked manually regarding the number of blood glucose values. If the memory of the glucometer does not cover the whole period, the time point for the first measurement in the meter will be considered the start point.</p> <p>At the start point of blinded CGM during the run-in period and the wash-out period, the number of measurements during the past 60 days will be recorded.</p> <p>At randomization visit, week 2, week 4, week 44, week 45 and week 47, the number of measurements since previous visit will be recorded.</p> <p>At week 13, week 26, week 56 and week 69, the number of measurements during the past 60 days will be recorded.</p> <p>7.7.2 CGM</p> <p>Blinded CGM will be performed at three time points, each 14 days long. When downloading blinded CGM-data, valid information shall exist during at least 10 whole days, else a novel sensor shall be set to obtain this time period.</p> <p>At all visits when downloading CGM data the number of days with sensor use will be recorded together with the mean value and SD. In analyses the mean value and the SD will only be used if raw data do not exist due to technical problems.</p> <p>At week 2, week 4, week 45 and week 47, the number of days with sensor use, since the previous visit will be recorded.</p> <p>At week 13, week 26, week 56 and week 59, the number of days with sensor use during the past 30 days will be recorded.</p>
15. 8 Education on Bayer Contour XT and DexCom 4G system will be performed at baseline, week 2 and week 4 in each period.	8 Education on DexCom G4 system will be performed at baseline, week 2 and week 4 in each period. Knowledge on how to perform SMBG will be checked and education will be performed if judged clinically indicated.
16. 8.2 No previous text	8.2 HbA1c, creatinine and fasting C-peptide will be analysed by the central laboratory.

<b>Previous text</b>	<b>Revised text</b>
17. 8.2 No previous text	8.2 The following variables will be recorded: <ul style="list-style-type: none"> <li>-Age, sex</li> <li>-Race, ethnicity</li> <li>-Diabetes onset</li> <li>-Smoking (current, previous, never)</li> <li>-Previous laser photocoagulation of the retina</li> <li>-Previous myocardial infarction</li> <li>-Previous bypass-graft</li> <li>-Previous PCI</li> <li>-Stroke</li> <li>-Amputation</li> <li>-Previous diabetic foot ulcer</li> <li>-Current diabetic foot ulcer</li> <li>-Average number of experienced hypoglycaemia per week during the last two months (not based on blood glucose values, but subjective estimation)</li> <li>-Number of severe hypoglycaemias past year</li> <li>-Number of severe hypoglycaemias past 5 years</li> </ul>
18. 8.3 No previous text	8.3 The patient should be randomized at the latest six weeks after the inclusion visit.
19. 8.3 All participants will receive the Bayer Contour XT glucometer for SMBG during the study.	8.3 Removed.
20. 8.3 DTSQs, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires will be filled in.	8.3 DTSQs, WHO-5, SWE-HFS, SWE-PAID-20, IPAQ, Hypoglycaemia confidence and Predictor variables questionnaires will be filled in.
21. 8.4 Patients meeting all inclusion and no exclusion criteria will be randomized...	8.4 Patients meeting all inclusion and no exclusion criteria at inclusion visit (visit 2) will be randomized...
22. 8.4 Patients will be randomized to receive CGM (Dexcom G4) or SMBG with Bayer Contour XT. Education of how to use the Bayer Contour XT and DexCom 4G system will be performed.	8.4 Patients will be randomized to receive CGM (DexCom G4) as a complement to glucose monitoring with SMBG or only to glucose monitoring with SMBG. Education of how to use the DexCom G4 system will be performed. All patients' knowledge regarding use of glucometer will be checked, and if judged clinically indicated education will be performed.

<b>Previous text</b>	<b>Revised text</b>
23. 8.4 -Age, sex -Diabetes onset -Smoking (current, previous, never) -Previous laser photocoagulation of the retina -Previous myocardial infarction -Previous bypass-graft -Previous PCI -Amputation -Previous diabetic foot ulcer -Current diabetic foot ulcer -Number of severe hypoglycaemias last year -Number of severe hypoglycaemias last 5 years	8.4 Removed
24. 8.4, 8.6, 8.7, 8.9, 8.11, 8.13, 8.14, 8.16 No previous text	8.4, 8.6, 8.7, 8.9, 8.11, 8.13, 8.14, 8.16 Blood samples will be analysed by the central laboratory.
25. 8.4, 8.9, 8.11, 8.16 -Urine albumin creatinine ratio	8.4, 8.9, 8.11, 8.16 -Urine albumin creatinine ratio (measured as morning sample, if the patient has no morning sample, a sample will be taken at the clinic)
26. 8.5 A check will be performed that the patient has understood how the Bayer Contour XT meter works and how the DexCom 4G system works.	8.5 A check will be performed that the patient has understood how the DexCom G4 system works, and how to perform SMBG.
27. 8.5, 8.6, 8.7 8.12, 8.13, 8.14 No previous text	Concomittant medications shall be recorded
28. 8.5, 8.6, 8.12, 8.13 No previous text	8.5, 8.6, 8.12, 8.13 This visit will take place within $\pm$ 5 days from the exact date.
29. 8.6, 8.7, 8.13, 8.14 No previous text	8.6, 8.7, 8.13, 8.14 It shall be considered whether the alarm levels of CGM shall be adjusted.
30. 8.7, 8.9, 8.14, 8.16 No previous text	8.7, 8.9, 8.14, 8.16 This visit will take place within $\pm$ 10 days from the exact date.
31. 8.7, 8.9, 8.14, 8.16 No previous text	8.7, 8.9, 8.14, 8.16 It shall be recorded how many times participants using CGM judges that he/she looks at the receiver screen on average per day.
32. 8.9 No previous text	-Concomittant medications

<b>Previous text</b>	<b>Revised text</b>
33. 8.9, 8.10, - DTSQs, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires	8.9, 8.10 - DTSQs, WHO-5, SWE-HFS, SWE-PAID-20, IPAQ and Hypoglycaemia confidence questionnaires
34. 8.11 Education of how to use the Bayer Contour XT and DexCom 4G system will be performed.	8.11 Education of how to use the DexCom G4 system will be performed. All patients' knowledge regarding use of glucometer will be checked, and if judged clinically indicated education will be performed.
35. 8.11 - DTSQs, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires	8.11 Removed
36. 8.12 A check will be performed that the patient has understood how the Bayer Contour XT meter works and how the DexCom 4G system works.	8.12 A check will be performed that the patient has understood how the DexCom G4 system works, and how to perform SMBG.
37. 8.16 - DTSQs, DTSQc, WHO-5, SWE-HFS, SWE-PAID-20 and IPAQ questionnaires	8.16 - DTSQs, DTSQc, WHO-5, SWE-HFS, SWE-PAID-20, IPAQ and Hypoglycaemia confidence questionnaires

**Reason for Amendment:**

1. Necessary adjustments have been made to clarify the study procedure and to make the protocol more coherent.
2. eGFR < 30 ml/min has been added as exclusion criterion since the DexCom G4 is less well studied in this population.
3. The patients' own glucometers will be used in the study since they are used to handling it and glucometers used in Sweden are checked regarding their accuracy.
4. Two questionnaires have been added to evaluate confidence of hypoglycaemia and possible predictors for the effect of CGM.

**Actions to be taken:**

Amendment till CSP. Amendmentet bifogas CSP på samtliga studiecenter

**Signed agreement to the Amendment:**

I agree to the terms of this Protocol Amendment.  
Study Code: CGM-MDI

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Date  
(day month year)

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Principal investigator  
Marcus Lind

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**Protocol Amendment**

Number: 2  
Study Code: CGM-MDI  
Date: 2014-01-30

**A randomized trial of the effect of continuous glucose monitoring (CGM) in individuals with type 1 diabetes treated with multiple daily insulin injections (MDI)****Sponsor:**

Marcus Lind, MD, PhD, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and NU-Hospital Organization, Uddevalla, Sweden

**Section(s) of protocol to be amended:**

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<b>Previous text</b>	<b>Revised text</b>
1. 8.5 Visit 5 – Week 2, 8.12 Visit 12 – Week 45 It shall also be considered if the patient benefits from the snooze function in the beginning, i.e. only reminded of the alarm for high levels every third hour. This enables the patient to get used to alarms before activating it properly, thus avoiding stress and irritation.	It shall also be considered if the patient benefits from the snooze function, i.e. being reminded of the alarm for high or low levels after a certain amount of time if the blood glucose is still above/below their alarm level.

**Reason for Amendment:**

1. Change of incorrect description of the snooze function.

**Actions to be taken:**

Amendment till CSP. Amendmentet bifogas CSP på samtliga studiecenter

**Signed agreement to the Amendment:**

I agree to the terms of this Protocol Amendment.  
Study Code: CGM-MDI

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Date  
(day month year)

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Principal investigator  
Marcus Lind

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**Protocol Amendment**

Number: 3  
Study Code: CGM-MDI  
Date: 2014-06-05

## **A randomized trial of the effect of continuous glucose monitoring (CGM) in individuals with type 1 diabetes treated with multiple daily insulin injections (MDI)**

### **Sponsor:**

Marcus Lind, MD, PhD, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and NU-Hospital Organization, Uddevalla, Sweden

### **Section(s) of protocol to be amended:**

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<b>Previous text</b>	<b>Revised text</b>
1. Synopsis In total 120 patients will be included at 5 sites in Sweden. The study will have 80% power to detect a 3 mmol/mol (0.3 percentage unit) change in HbA1c resulting from CGM.	In total 160 patients will be included at 14 sites in Sweden. The study will have 90% power to detect a 3 mmol/mol (0.3 percentage unit) change in HbA1c resulting from CGM.
2. 3.6 No previous text	Görel Sundbeck, Hallands Sjukhus Kungälv, Kungälv, Sweden Helene Holmer, Centralsjukhuset Kristianstad, Kristianstad, Sweden Erik Schwarcz, Universitetssjukhuset Örebro, Örebro, Sweden Jarl Hellman, Akademiska Sjukhuset, Uppsala, Sweden Ulf Rosenqvist, Motala Lasarett, Motala, Sweden Anders Kempe, Öbackakliniken, Härnösand, Sweden Anders Nilsson, Ängelholms Sjukhus, Ängelholm, Sweden Zeineb Al-Tahir, Trelleborgs Lasarett, Trelleborg, Sweden Anders Frid, Malmö Universitetssjukhus, Malmö, Sweden Thomas Nyström, Södersjukhuset, Stockholm, Sweden Removed
3. 5.5.2 The difference in total insulin dose between weeks 26 and 69	
4. 5.5.2 No previous text (same position in list as above endpoint had)	Difference in mean number of capillary glucose measurements per day between weeks 1-26 and weeks 43-69, from time periods when values are available in glucometers
5. 5.5.2 ... weeks 44-69...	... weeks 43-69...
6. 6 ... 120 patients...	... 160 patients...
7.7.1 (Amendment no 1) ... week 44...	... week 43...

<b>Previous text</b>	<b>Revised text</b>
8. 8, 8.11 Week 44	Week 43
9. 8.4 No previous text	All patients will also be educated on the proportion of rapid acting insulin analogues remaining at various timepoints after injection (figure 3 in ref 11)
10. 8.11 No previous text	This visit will take place within $\pm$ 10 days from the exact date
11. 9.2 Difference in total insulin dose between weeks 26 and 69	Removed
12. 9.2 No previous text (same position as above variable had)	Difference in mean number of capillary glucose measurements per day between weeks 1-26 and weeks 43-69, from time periods when values are available in glucometers
13. 11.5. The study is designed to detect a difference in HbA1c of 3 mmol/mol (0.3%) between week 26 and week 69, at 80% power, assuming a SD of 1.1% which requires 108 participants. Assuming a drop-out rate of 10% the study will include 120 individuals.	The study is designed to detect a difference in HbA1c of 3 mmol/mol (0.3%) between week 26 and week 69, at 90% power, assuming a SD of 1.1% which requires 144 participants. Assuming a drop-out rate of 10% the study will include 160 individuals.

#### **Reason for Amendment:**

1. 160 patients instead of 120 to increase the power to 90%
2. To include more patients
3. CGM does not likely affect insulin resistance
4. Patients may measure fewer blood glucose values when having CGM
5. Previous miswriting
6. 160 patients instead of 120 to increase the power to 90%
7. Previous miswriting
8. Previous miswriting
9. It was not mentioned in the visit description
10. Interval was previously missing in the protocol
11. CGM does not likely affect insulin resistance
12. Patients may measure fewer blood glucose values when having CGM
13. 160 patients instead of 120 to increase the power to 90%

**Actions to be taken:**

Amendment till CSP. Amendmentet bifogas CSP på samtliga studiecenter

**Signed agreement to the Amendment:**

I agree to the terms of this Protocol Amendment.

Study Code: CGM-MDI

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Date  
(day month year)

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Principal investigator  
Marcus Lind

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**Protocol Amendment**

Number: 4  
Study Code: CGM-MDI  
Date: 2015-05-24

## **A randomized trial of the effect of continuous glucose monitoring (CGM) in individuals with type 1 diabetes treated with multiple daily insulin injections (MDI)**

### **Sponsor:**

Marcus Lind, MD, PhD, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden and NU-Hospital Organization, Uddevalla, Sweden

### **Section(s) of protocol to be amended:**

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<b>Previous text</b>	<b>Revised text</b>
1. 3.3 Executive committee David Owens, Institute of Molecular and Experimental Medicine, Cardiff University, University Hospital of Wales, Cardiff, UK	3.3 Executive committee (removed)
2. 3.3 Executive committee (no previous text)	3.3 Executive committee Sofia Dahlqvist, Department of Medicine, NU Hospital Group, Uddevalla, Sweden
3. 11.1.1 Full analysis set (ITT-population) The full analysis set (ITT- population) consists of all randomised patients who received at least one follow-up of HbA1c at week 13 or 26 after the starting point of each study period.	11.1.1 Full analysis set (ITT-population) The full analysis set (ITT-population) consists of all randomised patients who received at least one follow-up measurement of any efficacy measurements in each study period.
4. 11.3.1 Primary efficacy analysis CGM compared to SMBG If HbA1c from 26 and 69 weeks follow-up, respectively, is missing the last observation carried forward (LOCF) principle from 2, 4, and 13 weeks in each study period will be applied.	11.3.1 Primary efficacy analysis CGM compared to SMBG If efficacy measurements from 26 and 69 weeks follow-up, respectively, is missing the last observation carried forward (LOCF) principle will be applied. Last observation carried forward (LOCF) principle will NOT be applied from measurements at the first visit in each study period.

**Reason for Amendment:**

1. David Owens is removed from the executive committee because he was not able to participate in developing the protocol.
2. Sofia Dahlqvist is added to the executive committee because she has been involved in design and other essential processes of the study.
3. In the ITT-population generally all patients with any follow-up measurement are included to evaluate as many individuals as possible regarding the effect of the intervention.
4. The ITT-analysis should not be restricted to only HbA1c. All patients should have any follow-up measurement after starting treatment in each study period to have the possibility of evaluating treatment effect.

**Actions to be taken:**

Amendment till CSP. Amendmentet bifogas CSP på samtliga studiecenter

**Signed agreement to the Amendment:**

I agree to the terms of this Protocol Amendment.  
Study Code: CGM-MDI

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Date  
(day month year)

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Principal investigator  
Marcus Lind