

STATISTISKA KONSULTGRUPPEN		Statistical Analysis Plan	
Protocol: A randomized trial of the effect of continuous glucose monitoring (CGM) in individuals with type 1 diabetes treated with multiple daily insulin injections (MDI)		Protocol No: CGMMDI - GOLD	
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Statistical Analysis Plan

FINAL

DexComG4 (DexCom Corporation) CGMMDI GOLD-Study

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

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Approvals

Name/Title: Nils-Gunnar Pehrsson / Statistiska Konsultgruppen, Study Statistician	
Signature:	Date:
Name/Title: Marcus Lind / NU-Hospital Organization, Uddevalla, Principal Investigator	
Signature:	Date:

Revisions

Version	Description of Changes	Date

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LIST OF ABBREVIATIONS

Abbreviation	Definition
A/C	Albumin/Creatinine
AE	Adverse Events
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CRF	Case Report Form
CRP	C-reactive Protein
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DTSQc	Diabetes Treatment Satisfaction Questionnaire – Change
DTSQs	Diabetes Treatment Satisfaction Questionnaire – Status
FAS	Full Analysis Set
HCQ	Hypoglycaemic Confidence Questionnaire
HDL	High-Density Lipoprotein
IPAQ	International Physical Activity Questionnaire
LDL	Low-Density Lipoprotein
LOCF	Last Observation Carried Forward
LSM	Least Square Means
MAGE	Mean Amplitude of Glycaemic Excursions
MDI	Multiple Daily Insulin injections
MedDRA	Medical Dictionary for Regulatory Activities
PCI	Percutaneous Coronary Intervention
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SMBG	Self-Monitoring of Blood Glucose
SOC	System Organ Class
SWE-HFS	Swedish Hypoglycaemia Fear Scale
SWE-PAID-20	Swedish version of the Problem Areas in Diabetes
WHO-5	World Health Organization-Five Well-Being Index

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1 STUDY DETAILS

This Statistical Analysis Plan (SAP) has been developed by an independent party, by Statistiska konsultgruppen. The SAP has been finalised before the database lock and before the Case Report Form (CRF) data has been available for the programmers.

1.1 Study Objectives

The primary objective of this study is to determine whether Continuous Glucose Monitoring (CGM) therapy reduces HbA1c in type 1 diabetic patients treated with Multiple Daily Insulin (MDI) injections compared to conventional therapy using Self-Monitoring of Blood Glucose (SMBG).

The secondary objectives of this study are comparisons of the following variables during CGM use versus non-use of CGM:

- Mean blood glucose level as measured by CGM
- Mean Amplitude of Glycaemic Excursions (MAGE) as measured by CGM
- Standard deviation of blood glucose level as measured by CGM
- Treatment satisfaction, measured using the Diabetes Treatment Satisfaction Questionnaire – Status (DTSQs) and DTSQ – Change (DTSQc)
- Quality of life, according to the Swedish version of the Problem Areas in Diabetes (SWE-PAID-20) and World Health Organization-Five Well-Being Index (WHO-5)
- Fear of hypoglycaemia, estimated by the Swedish Hypoglycaemia Fear Scale (SWE-HFS)
- Time of low glucose levels as measured by CGM (below 3.0 mmol/l and below 3.9 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%) or more
- Reduction of HbA1c by 10 mmol/mol (1%) or more
- Number of severe hypoglycaemic events defined as unconsciousness due to hypoglycaemia or need of assistance from another person to resolve the hypoglycaemia
- Mean number of capillary glucose measurements per day

1.2 Study Design

This is a multi-center, randomized, non-blinded, cross-over clinical trial. After a maximum run-in period of six weeks patients were randomized to either CGM or continued conventional therapy. During the run-in period blinded CGM was performed during two weeks. After the blinded CGM period patients who did not believe they would 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), were not randomized. Consenting patients were randomized to CGM or conventional therapy for 26 weeks and then the opposite treatment for 26 weeks, with an intermittent wash-out period for 17 weeks. Patients were initially randomized 1:1, stratified by site, to CGM or conventional therapy.

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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.

	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, HCQ	DTSQc	Insulin dose	Concomitant medications	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 SMBG measuring 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.

1.3 Treatment Periods

The treatment periods in this study are:

- CGM (DexCom G4)
- Conventional therapy

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1.4 Sample Size

The study was powered to detect a difference of 0.3% (3 mmol/mol) in HbA1c between CGM and conventional therapy, at 90% power, assuming a standard deviation of 1.1%, which requires 144 participants. Assuming a drop-out rate of 10% 160 individuals were required to be enrolled.

2 STUDY POPULATIONS

2.1 Definition of Study Populations

2.1.1 Full Analysis Set

The Full Analysis Set (FAS) population consists of all randomized patients who have at least one follow-up measurement of any efficacy variables in each study period.

2.1.2 Safety Population

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

3 STUDY VARIABLES

3.1 Baseline Variables

3.1.1 Demographics and Baseline Characteristics

The following demographics and baseline characteristics will be described:

- Age
- Sex
- Race
- Ethnicity
- Years from diabetes onset
- Smoking (current, previous, never)

3.1.2 Medical and Surgical History

The following medical and surgical history will be described:

- Previous laser photocoagulation of the retina
- Previous myocardial infarction
- Previous bypass-graft
- Previous Percutaneous Coronary Intervention (PCI)
- Previous stroke
- Previous amputation
- Previous diabetic foot (or leg) ulcer
- Current diabetic foot (or leg) ulcer
- Average number of experienced hypoglycaemia per week during the last two months (not based on blood glucose values, but subjective estimation)
- Number of severe hypoglycaemias past year

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- Number of severe hypoglycaemias past 5 years

3.1.3 Prior and Concomitant Medication

The prior and concomitant medication is continuously collected during the study and will be coded by using Anatomical Therapeutic Chemical (ATC) Classification System and summarized according to higher-level class and generic term.

3.1.4 Physical Examination

The physical examination is collected at Visit 2, Week 26, Week 43 and Week 69 and will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized per study treatment phase according to System Organ Class (SOC) and Preferred Term (PT) as clinically significant and clinically not significant events.

3.2 Efficacy Variables

3.2.1 Primary Efficacy Variable

The primary efficacy variable is difference in HbA1c between the last visit in each treatment phase, weeks 26 and 69.

3.2.2 Secondary Efficacy Variables

The secondary efficacy variables are as following:

- The difference in mean glucose level (measured by CGM during 2 weeks) between weeks 23-26 and 66-69. The corresponding time period of the CGM phase will be selected as the one available for the blinded CGM data during the conventional therapy phase, i.e. the same number of days/hours from the last blinded CGM data available. This rule is valid for all CGM endpoints stated below.
- The difference in MAGE (measured by CGM during 2 weeks) between weeks 23-26 and 66-69. The MAGE is a parameter assessing glycaemic variability and is calculated based on the arithmetic mean of differences between consecutive peaks and nadirs of differences >1 Standard Deviation (SD) of mean glucose values.
- The difference in SD of glucose levels measured by CGM during 2 weeks between weeks 23-26 and weeks 66-69, measured by CGM.
- The difference in DTSQs scores between weeks 26 and 69. Each item 1-8 will be summarized separately. The total score computed by using items 1, 4, 5, 6, 7 and 8 and items 2 and 3 will be analyzed. See Appendix 1 for further details.
- DTSQc score at week 69. Each item 1-8 will be summarized separately. The total score computed by using items 1, 4, 5, 6, 7 and 8 and items 2 and 3 will be analyzed. See Appendix 1 for further details.
- The difference in WHO-5 scores between weeks 26 and 69. Each item 1-5 will be summarized separately. The total score will be analyzed. See Appendix 2 for further details. If there is an item with missing data at a certain visit then the total score will be set to missing at that visit.
- The difference in SWE-HFS scores between weeks 26 and 69. Each item 1-23 will be summarized separately. Two subscales will be calculated, Behaviour/Avoidance (mean of first 10 items), Worry (mean of last 13 items) and analyzed. If >2 items have missing data at a certain visit for a subscale then that subscale will be set to missing at that visit. If <=2 items are missing

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for a subscale then the subscale will be calculated as the mean of the remaining (completed) items.

- The difference in SWE-PAID-20 scores between weeks 26 and 69. Each item 1-20 will be summarized separately. The total score will be computed as the sum of the items multiplied by 1.25. If >3 items have missing data at a certain visit then the total score will be set to missing at that visit. If ≤3 items are missing then total score will be calculated as the mean score of the remaining (completed) items.
- The difference in the proportion of time with low glucose levels measured by CGM during 2 weeks between week 23-26 and week 66-69 measured by CGM (below 54 mg/dl [3.0 mmol/l] and below 72 mg/dl [3.9 mmol/l] respectively)
- The difference in the proportion of time with high glucose levels measured by CGM during 2 weeks between week 23-26 and week 66-69 measured by CGM (above 180 mg/dl [10.0 mmol/l] and above 250 mg/dl [13.9 mmol/l] respectively)
- The difference in the proportion of time with euglycemic levels measured by CGM during 2 weeks between weeks 23-26 and weeks 66-69 (99-180 mg/dl [5.5-10.0 mmol/l] and 70-180 mg/dl [3.9 -10.0 mmol/l] respectively)
- The difference in the proportion of patients reducing their HbA1c by 0.5% (5 mmol/mol) or more
- The difference in the proportion of patients lowering their HbA1c 1% (10 mmol/mol) or more
- The difference in the occurrence (Yes/No) of severe hypoglycaemic events between the CGM and the conventional therapy handled as two independent samples defined as unconsciousness due to hypoglycaemia or need of assistance from another person to resolve the hypoglycaemia
- The difference in the mean number of severe hypoglycaemic events between the CGM and the conventional therapy handled as two independent samples defined as unconsciousness due to hypoglycaemia or need of assistance from another person to resolve the hypoglycaemia
- The event rate (number of events per patient years) of severe hypoglycaemic events between the CGM and the conventional therapy
- The difference in mean number of capillary glucose measurements per day between weeks 4-26 (data from weeks 1-4 should be used in case there is no data available between weeks 4-26) and weeks 47-69 (data from weeks 43-47 should be used in case there is no data available between weeks 47-69), from time periods when values are available in glucometers reported in the CRF.

3.2.3 Exploratory Efficacy Variables

Following exploratory variables will be analysed:

- The difference in IPAQ scores between weeks 26 and 69. Each item 1-4 will be summarized separately and the total categorical score and continuous score will be analysed. The IPAQ sitting question is not included as part of the summary scores and will be reported separately as median values and interquartile range. For more details see Appendix 3.
- The difference in HCQ scores between weeks 26 and 69. Each item 1-9 will be summarized separately. The total score will be calculated as mean value of all items and analyzed. If an individual misses more than 1 item at a certain visit, the total score will be set to missing at that visit. If there is a single missing item, then the score for the missing item will be imputed by the mean score of the remaining (completed) items.

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- The difference in Coefficient of Variation (CV), defined as SD/mean, of glucose levels measured by CGM during 2 weeks between weeks 23-26 and weeks 66-69, measured by CGM.
- The prediction questionnaire will be used in the analyses of possible predictors to the efficacy variables
- The proportion of time of nocturnal hypoglycaemia will also be investigated for CGM and conventional therapy
- The insulin dose will be investigated for CGM and conventional therapy
- Evaluations will also be performed whether the frequency of patient looking at the CGM system has an effect on the various effect variables

Following exploratory laboratory variables will be analyzed:

- The difference in Creatinine ($\mu\text{mol/L}$) between week 26 and week 69
- The difference in sensitive C-reactive Protein (CRP) (mg/L) between week 26 and week 69
- The difference in total cholesterol (mmol/L) between week 26 and week 69, as long as lipid lowering medications are stable
- The difference in Low-Density Lipoprotein (LDL) cholesterol (mmol/L) between week 26 and week 69, as long as lipid lowering medications are stable
- The difference in High-Density Lipoprotein (HDL) cholesterol (mmol/L) between week 26 and week 69, as long as lipid lowering medications are stable
- The difference in triglycerides (mmol/L) between week 26 and week 69, as long as lipid lowering medications are stable
- The difference in Apolipoprotein A1 (g/L) between week 26 and week 69, as long as lipid lowering medications are stable
- The difference in Apolipoprotein B (g/L) between week 26 and week 69, as long as lipid lowering medications are stable
- The difference in Albumin/Creatinine (A/C) ratio between week 26 and week 69

Following exploratory body measurements and vital signs variables will be analyzed:

- The difference in Body Mass Index (BMI) (kg/m^2) between week 26 and week 69
- The difference in waist circumference (cm) between week 26 and week 69
- The difference in waist/hip ratio between week 26 and week 69
- The difference in Systolic Blood Pressure (SBP) (mmHg) between week 26 and week 69, as long as antihypertensive medications are stable
- The difference in Diastolic Blood Pressure (DBP) (mmHg) between week 26 and week 69, as long as antihypertensive medications are stable

In the subgroup analyses of the primary and the selected secondary variables following parameters, but not limited to those, will be investigated:

- Age
- Sex
- Baseline HbA1c
- Exposure time

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3.3 Safety Variables

3.3.1 Exposure of Study Treatment

Exposure to CGM sensor and the conventional therapy will be described as number of days the patient has been in each treatment phase in total, as well as the number of patients completing each study visit. The compliance to CGM sensor usage will be expressed in percent of total time as well as the number and percent of patients having a compliance of at least 80%, both between the study visits and in total. The total time in-between the visits will be set to maximum of 30 days.

3.3.2 Adverse Events

Adverse Events (AE) have been continuously reported during the study. Information about start, stop, severity, actions taken, relationship to CGM/conventional therapy, outcome and seriousness for each AE has also been recorded.

Only treatment-emergent AEs will be included in the summaries for safety population. The treatment-emergent AE for each study period is defined as the AE that has started on or after that particular study period or an AE that has started before but has increased in severity, relationship to the study treatment or seriousness. All AEs will be coded MedDRA and summarized per study treatment phase according to System Organ Class (SOC) and Preferred Term (PT).

4 STATISTICAL METHODOLOGY

4.1 General Methodology

All continuous variables will be summarized with number, mean, SD, median and range for the CGM period, conventional therapy period and for the difference between the CGM and the conventional therapy period. All ordered categorical variables and all dichotomous variables will be summarized with number and percentages for the CGM period, conventional therapy period and with number and percentages of decreases, increases and unchanged for CGM period compared to conventional therapy period. The 95% Confidence Intervals (CI) for event rates for severe hypoglycaemia will be computed by using exact Poisson confidence limits.

Due to the crossover study design, all statistical analyses regarding the main comparison of CGM with conventional therapy will be adjusted for both period effect and patient effect in the following way:

- For the primary efficacy analysis, HbA1c will be analysed using SAS procedure PROC GLM with sequence, patient(sequence), period and treatment as class variables.
- For secondary efficacy analyses of normally distributed variables the same analysis will be applied as for the primary efficacy analysis, i.e. by using SAS procedure, PROC GLM with sequence, patient(sequence), period and treatment as class variables.
- For the secondary efficacy analyses of obviously non-normal continuous variables (assessed by review of data histograms) except for the mean number of severe hypoglycaemic events, for each patient the differences between period A and period B will be calculated (for DTSQc the variable is already given as change from period A to period B) and compared between the group randomized to CGM in the first period and the group randomized to conventional therapy in the first period by using Fisher's non-parametric two

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sample permutation test. For the secondary variable mean number of severe hypoglycaemic events the difference between CGM and conventional therapy will be handled as two independent samples and will be tested by using Fisher's non-parametric two sample permutation test.

- For the secondary efficacy analyses of dichotomous and ordered categorical variables except for the severe hypoglycaemic events Yes/No the difference between period A and period B will be calculated as worse (-1), equal (0) or better (+1), and then compare these differences (-1, 0,+1) between the group randomized to CGM in the first period and the group randomized to conventional therapy in the first period with Fisher's non-parametric two sample permutation test.
- For the secondary efficacy analysis of occurrence of severe hypoglycaemic events the difference between CGM and conventional therapy will be handled as two independent samples and will be tested by using Fisher's Exact test.
- For the secondary efficacy analysis of the event rate of severe hypoglycaemic events the difference between the CGM and the conventional therapy will be handled as two independent samples and will be tested by using a test based on the Poisson distribution.

From the GLM analyses the Least Square Means (LSM) with 95% CI will be presented for the difference between the treatments.

If efficacy measurements, concerning both primary and secondary efficacy variables, from 26 and 69 weeks follow-up, respectively, are missing, the Last Observation Carried Forward (LOCF) principle will be applied. LOCF will not be applied to the measurements at the first visit in each treatment period (randomization and week 43).

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

The theory of sequential multiple test procedures will be applied for the primary analysis and for secondary analyses. If a test gives a significant result at the 5% significance level, the total test mass will be transferred to the following number in the test sequence until a non-significant result is achieved. All these significant tests will be considered confirmative.

All tests will be two-tailed and conducted at 0.05 significance level. All analyses will be performed by using SAS® v9.4 (Cary, NC).

4.2 Patient Disposition and Data Sets Analyzed

The number of patients included in each of the FAS and safety populations will be summarized for each treatment period and overall. The number and percentage of patients randomized and treated will be presented. Patients who completed the study and patients who withdrew from study prematurely will also be presented with a breakdown of the reasons for withdrawal by treatment period for the FAS and safety populations.

4.3 Protocol Violations/Deviations

The number of patients with protocol deviations will be listed per treatment period for FAS population.

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4.4 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the FAS population.

4.5 Medical and Surgical History

Medical and surgical history will be summarized as number and percent of all patients included in the FAS population.

4.6 Prior and Concomitant Medication

The prior medication and concomitantly used medication for different treatment periods will be summarized for FAS population.

4.7 Physical Examinations

The physical examination will be summarized for different treatment periods, subdivided into clinically significant and clinically not significant, for FAS population.

4.8 Efficacy Analyses

4.8.1 Primary Efficacy Analysis

The primary efficacy analysis of the difference in HbA1c at weeks 26 and 69 between CGM and conventional therapy will be analyzed for the FAS population by using a general linear model adjusted for both period's effect and patient effect. This implies that treatment effect will be analyzed within patients and period's effect will be handled correctly.

For graphical purpose the HbA1c data will be described in boxplots over time.

4.8.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be performed as described in General Methodology above.

The continuous variables will be described graphically as boxplots and categorical variables as bar charts.

4.8.3 Exploratory Efficacy Analyses

The exploratory efficacy variables will be analyzed and presented graphically in similar way as the secondary efficacy variables.

The subgroup analyses might be investigated by introducing the interaction term between the variable and the treatment in the model or by looking at different subgroups of patients separately.

Exploratory analyses of the primary endpoint and selected secondary endpoints during the first treatment phase (weeks 1-26) will also be performed. The list of

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selected secondary variables will be chosen later as these are the exploratory analyses.

4.9 Safety Analyses

4.9.1 Exposure of Study Treatment

Duration of therapy will be summarized for each treatment in total as well as the number and percent of patients completed each visit. Compliance will be summarized for CGM use at Randomization (end of run-in period) or Week 43 (end of wash-out period), Week 2 or 45, Week 4 or 47, Week 13 or 56 and Week 26 or 69, depending on what period the patient was randomized to CGM as well as for the total CGM period. The compliance will also presented for the blinded CGM use during the conventional therapy at Randomization (end of run-in period) or Week 43 (end of wash-out period) depending on what period the patient was randomized to conventional therapy alone.

The summaries will be provided for safety population.

4.9.2 Adverse Events

A summary of patients reporting at least one of the following AEs will be presented in an overview table by treatment:

- Any AE
- Any Serious Adverse Event (SAE)
- Any treatment-related AE
- Any treatment-related SAE
- Any AE leading to discontinuation
- Any severe hypoglycaemia
- Any serious severe hypoglycaemia
- Any treatment related severe hypoglycaemia
- Any severe hypoglycaemia leading to discontinuation
- Death

All cases of hypoglycaemia collected in this study are severe hypoglycaemia.

Summaries per SOC and PT presenting n (%) of AEs and n (%) of patients with at least one AE by treatment will be provided for:

- All AEs (includes all serious and non-serious AEs)
- All AEs by maximum reported intensity
- All AEs by causality
- All SAEs
- All AEs leading to discontinuation

5 CHANGES OF ANALYSIS FROM PROTOCOL

The changes to the protocol are as per following:

1. The PP population will not be defined and analyzed.
2. The variable Time of low glucose levels as measured by CGM (below 3.0 mmol/l and below 4.0 mmol/l) has been updated to Time of low glucose levels as measured by CGM (below 3.0 mmol/l and below 3.9 mmol/l)

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6 LISTING OF TABLES AND FIGURES

6.1 Listing of Tables

Table Number	Table Title
1.1	Patient Disposition and Data Sets Analyzed (FAS Population)
1.2	Listing of Protocol Deviations (FAS Population)
1.3	Demographics and Baseline Characteristics (FAS Population)
1.4	Medical and Surgical History (Population)
1.5	Physical Examinations by Clinical Significance (FAS Population)
1.6.1	Prior Medications (FAS population)
1.6.2	Concomitant Medications (FAS population)
2.1	Primary Efficacy Analysis (FAS Population)
2.2.1	Secondary Efficacy Analysis (FAS Population)
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	<i>Etc for other secondary efficacy variables as boxplots or bar-charts...</i>

Protocol:

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

Protocol No:

CGMMDI - GOLD

Version:

1.0

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7 APPENDIX

7.1 Appendix 1: DTSQs and DTSQc

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[..\scoring_short_ipaq_april04.pdf](#)