Study No. V4 By-Ins

Prediction of the efficacy of Exenatide treatment in suboptimally controlled type 2 diabetic patients by “Metabolic Fingerprint” and evidence-based KADIS® decision support: a clinical observation

Observational, multi-center study in type 2 diabetic subjects

Final Report

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Content

List of abbreviations

BG	blood glucose
BMI	body mass index
BP	blood pressure
BU	bread units
CGM	continuous glucose monitoring
CHO	carbohydrates
DD	duration of diabetes
IDK	Institute of Diabetes “Gerhardt Katsch” Karlsburg
IU	insulin units
KADIS®	Karlsburg Diabetes Management System
MBG	mean blood glucose
MODD	mean of daily differences
pp	post prandial
p	level of statistical significance
Range	difference between maximum and minimum in daily glucose profiles
RR_{systol}	systolic blood pressure
$RR_{diastol}$	diastolic blood pressure
SD	standard deviation
$t_{BG>8.9mmol/l}$	duration of hyperglycemic episodes

Background

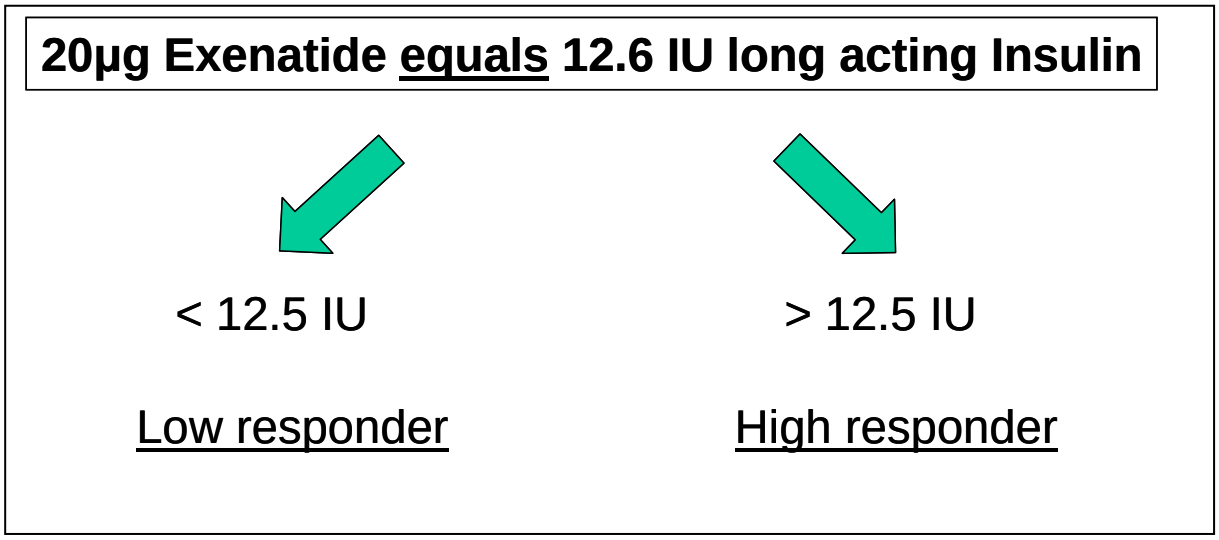
Incretin analogues such as Exenatide are a new class of anti-hyperglycemic agents that have the ability to improve glycemic control similar to natural incretin hormones. Initial application of incretin analogues have demonstrated that some patients meet the expected effects on glycemic control while others fail. However, at present, no practicable, pre-clinical method is available to predict LOW or HIGH Exenatide responder prior therapeutic application.

Recently it could convincingly be demonstrated how accurately the effectiveness of therapeutic adjustments can be assessed by estimating the "Metabolic Fingerprint" using the KADIS®-based decision support system. KADIS® is a computer-based interactive management system that enables individualized prediction of glucose profiles in response to different metabolic intervention. Assessment of patients´ metabolic control requires an input of baseline characteristics such as age, gender, type of diabetes, BMI, and of self-control data, such as conventional or continuous glucose monitoring data, insulin dosage, meal intake, and physical activity. KADIS® is based on a mathematical model that originally described glucose-insulin metabolism in type 1 diabetes. Most recently, KADIS® has been extended for application in type 2 and in pre-diabetes by including a static and dynamic control model of insulin release describing basal and glucose-stimulated insulin secretion and the therapy with oral anti-diabetics. As a therapy simulator, KADIS® calculates patient-specific parameters to assist physicians in choosing individual diabetes management regimes most appropriate for achieving glycemic targets. Following input of the data, the program is able to generate a visual copy of glucose control ("Metabolic Fingerprint") and allows interactive simulations of a patient's daily therapeutic regimen to optimize glycemic profiles. Furthermore, KADIS® can visualize 24-hour absorption patterns of carbohydrate intake, insulin equivalents of exercise action profiles of exogenous insulin and, in the case of type 2 diabetes, also of endogenous insulin, and of oral hypoglycemics in relation to diurnal changes in insulin sensitivity (Appendix: KADIS® supported diabetes management).

In combination with CGM, KADIS® enables individualized evaluation of glucose profiles in relation to metabolic intervention. By estimating the "Metabolic Fingerprint", patients in whom suboptimal glycemic control is

mainly due to either large glucose fluctuations or, specifically, to exaggerated postprandial glucose excursions, can accurately be identified and assigned to the appropriate therapy regimen by evaluating *in silico* the glycemic effects of a given anti-diabetic drug.

In *in silico* studies previously performed by the IDK with stored data of 58 non-insulin treated type 2 diabetic patients, KADIS® was evaluated for its ability of predicting the therapeutic effects of Exenatide on daily glucose profiles, and consequently, to assign patients to LOW or HIGH responder groups to Exenatide prior to the therapeutic intervention. It was estimated that the overall glycemic lowering effect of 20 µg Exenatide is about 0.8 mmol/l [~14 mg/dl] and equals the therapeutic application of about 12.6 IU of long acting insulin.

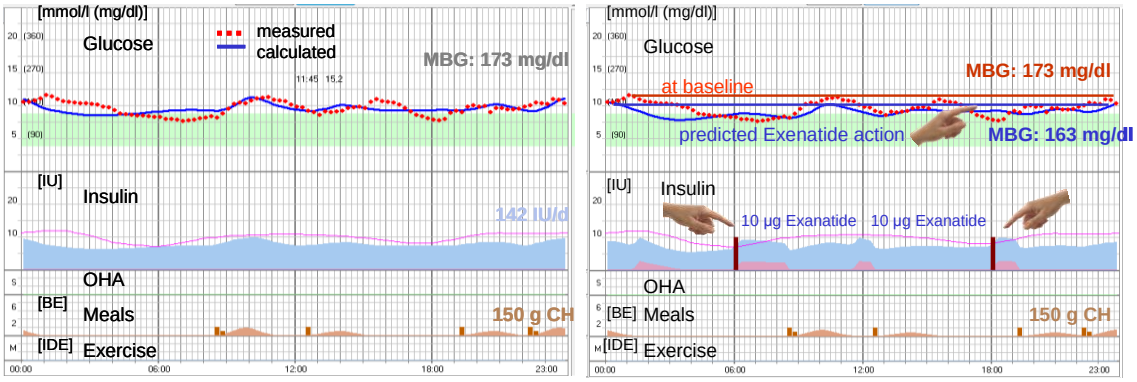


This result provides the possibility to assign patients with an Exenatide equivalence factor of insulin action <12.6 IU to LOW responders and patients with an Exenatide equivalence factor >12.6 IU to HIGH responders. Two typical examples which demonstrate the estimation procedure for a LOW responder and for a HIGH responder to an Exenatide therapy are given in the following figures.

Low Exenatide Responder

Patient P2: female; age: 59y; duration of disease: 8y; BMI: 43.3 kg/m²

KADIS®-based estimation of the personalized "Metabolic Fingerprint" | ***In silico* simulation of the incretin effect**



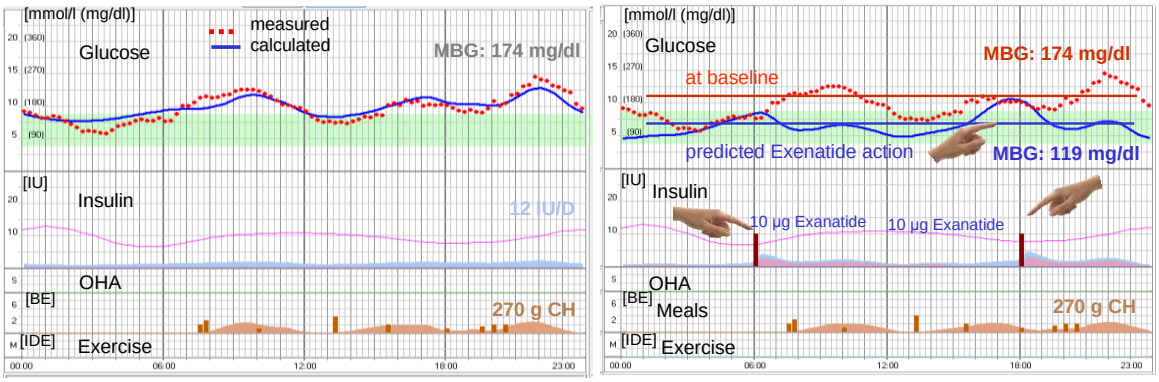
Exenatide Equivalence Factor of Insulin Action: 8.1 IU

ΔMBG: 10 mg/dl

High Incretin Responder

Patient P1: male; age: 67y; duration of disease: 7y; BMI: 28.7 kg/m²

KADIS®-based estimation of the personalized "Metabolic Fingerprint" | ***In silico* simulation of the incretin effect**



Incretin Equivalence Factor of Insulin Action: 15.5 IU

ΔMBG: 55 mg/dl

It was concluded that estimation of the personalized "Metabolic Fingerprint" and KADIS®-based decision support may be appropriate tools for identifying patients in advance who would chiefly benefit from Exenatide treatment.

Objectives

The basic objectives of this observational study were to evaluate the efficacy of the personalized decision support program KADIS® for

- its ability to identify patients as LOW or HIGH responders to an Exenatide therapy prior to therapy **correctly** by *in silico* simulation procedure and
- its ability to **accurately** predict the therapeutic outcome of Exenatide or Lantus application by comparing predicted and observed HbA1c, MBG, and glucose profiles, baseline vs. endpoint of the observational period.

Secondary aims were to evaluate the metabolic effects of Exenatide and of Lantus on metabolic control by comparison of

- body weight/BMI,
- plasma insulin/C-peptide levels,
- triglycerides/cholesterol,
- blood pressure,
- CHO intake,
- KADIS®-based calculated endogenous insulin secretion,
- KADIS®-based estimate of pp incretin effects
- hypoglycemic episodes

at baseline vs. endpoint of the 6-months observational period.

Study procedure

The study was performed as an open-label, multi-center, two-arm, clinical observational study using CGM and personalized "Metabolic Fingerprint" to evaluate **correctness** of KADIS®-based assignment to LOW or HIGH responder to Exenatide therapy prior to therapy and to evaluate **accuracy** of KADIS®-based prediction by comparing the outcomes (baseline vs. endpoint) of 6 months of Exenatide or Lantus treatment, respectively. There was no randomization because the patients were assigned to both study arms according to the KADIS®-based analyses of their personalized "Metabolic Fingerprint".

The entire test procedure was performed as follows:

Procedure A	Multiple continuous glucose monitoring with the CGM™ (Medtronic Inc.) over 72 h periods at the beginning and at week 24 of the study
Procedure B	Exenatide injection at an escalating dose of 5 to 10 µg twice daily **(Exenatide group).**
Procedure C	Lantus injection according to an individual dose titration algorithm as provided by KADIS®-based recommendations once daily **(Lantus group).**

After giving written informed consent, study participants were subjected to a routine examination by their responsible physicians. This examination was considered as "baseline observation" in terms of the observational study. If the patient met the inclusion criteria, then the patient was included into the study and subjected to the 1st CGM.

To be enrolled, a study patient had to meet with al of the following inclusion criteria:

- type of diabetes: type 2
- age >30 years
- age at onset: > 30 years
- diabetes duration: ≥ 1 years
- glycemic control: HbA1c ≥ 7.0 %
- on sulfonylurea/biguanide therapy
- sex: male and female
- ethnic origin: Caucasian
- written informed consent

The observational study was conducted in four major steps including all study patients enrolled:

- Baseline examination (**study week 1**)
- 1st insertion of the glucose sensor and 1st 72-h CGM (**study week 1**)
- Initiation of Exenatide or Lantus treatment according to the KADIS®-based assignment, respectively (**study week 3**)
- Exenatide dose escalation and Lantus dosing control, respectively (**study week 7**)
- 2nd insertion of the glucose sensor and 2nd 72-h CGM (**study week 24**)
- Post Study Examination (**study week 25**)

The patients included in the observational study were under direct routine control of their physicians during the study. All study subjects followed strictly the advice of their physicians and the procedures of the study protocol.

The study participants were asked to report any adverse events spontaneously. The subjects were made aware of the symptoms of potential side-effects, such as hypo/hyperglycemia or gastrointestinal problems. If any such signs or symptoms appeared, subjects had to report to the Investigator(s) immediately. None of the study patients reported any adverse events during the entire observational period of the study.

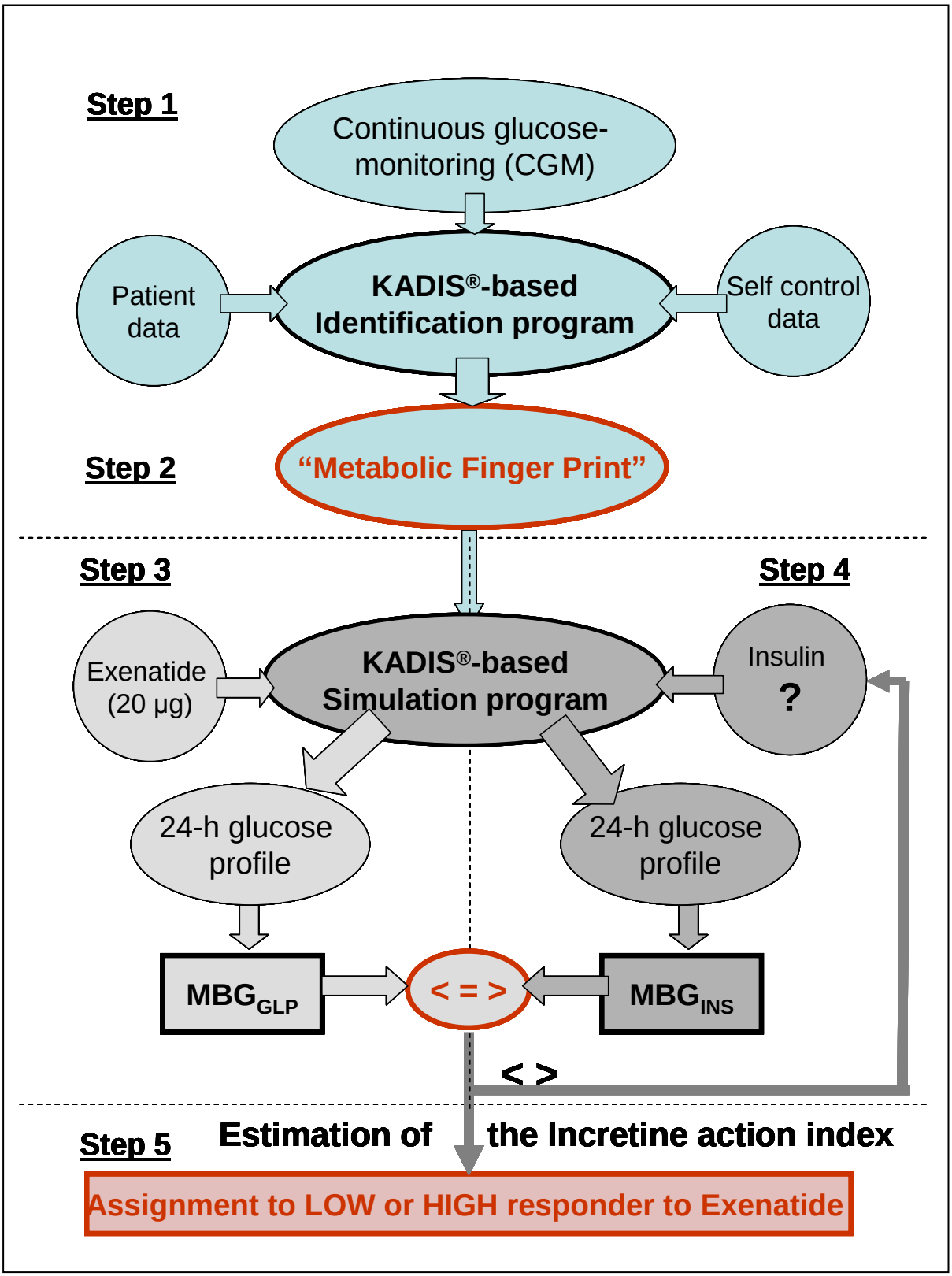
Standard methods for clinical laboratory parameters were used. Documentation of the methods and normal values were part of the clinical file. Routine clinical-chemical parameters were determined by certified clinical laboratories either affiliated with the general practitioners or diabetologists according to the rules of laboratory diagnostics or by certified central laboratories.

Self-monitoring was performed by the study patients for assessment of blood glucose control. Over the trial period, glucose strips were provided. During the 1st and 2nd CGM period, each study patient was obliged to make daily entries into a self-test record diary of blood glucose levels, type and dosage of Exenatide and Lantus, respectively, or other medication, food intake, physical exercise and events, such as illness and new situations.

The clinical study was performed according to the regulations for observational studies and conducted in agreement with the guidelines for routine diabetes care.

Data handling and statistics

The procedure of KADIS®-based assignment to LOW (Lantus group) or HIGH (Exenatide goup) responders to Exenatide therapy is schematically presented in the following figure:



Flow chart of KADIS®-based *in silico* simulation procedure to identify and to assign LOW or HIGH responder to Exenatide therapy

The entire KADIS®–based assignment procedure comprised 5 steps:

1st step: CGM for 3 to 5 days,

2nd step: KADIS®-based estimation of the personalized "Metabolic Fingerprint",

3rd step: KADIS®-based calculation of the outcome of application of 20 µg Exenatide on the expected mean glucose value (MBG_{GLP}) of the simulated daily glucose profile,

4th step: Estimation of the dose of Lantus that provides a comparable glucose lowering effect as 20 µg Exenatide by KADIS®-based titration of the outcome of Lantus application on the mean glucose value (MBG_{INS}) of the simulated daily glucose profile,

5th step: Assignment of the study patient to LOW responders (Lantus group) if the KADIS®-based estimated equivalent dose of Lantus was <12.6 IU or to HIGH responders (Exenatide group) if the KADIS®-based estimated dose of Lantus was >12.6 IU.

Evaluation of correctness of KADIS®-based assignment

The evaluation of the correctness, i.e. the predictive power of KADIS®-based assignment to LOW or HIGH responder to Exenatide therapy was performed by comparing the KADIS®-based predicted HbA1c and MBG values at T=0 with the monitored HbA1c and MBG values after 6 months (T=6 months) of application of Exenatide or Lantus therapy. For the predicted values of HbA1c and MBG a model-related uncertainty factor of ±15% was added to the predicted mean values, which is related to the EU recommendations for the accuracy of glucose measuring devices. This procedure resulted in the predictive range of mean ±15% for the KADIS®-based predicted HbA1c and MBG values.

To calculate the predictive range for the HbA1c levels, at first the HbA1c values had to be estimated. This was done by using the equation of Nathan et al. (MBG=1.75HbA1c–3.81; Diabetologia 50, 2239-2244, 2007)

$$\mathbf{HbA1c = 0.335\ MBG + 4.818}$$

whereas the equation and its parameters were adapted by regression analysis to the paired data of HbA1c and about 2,500 CGM patient records (which is equivalent to about 2,160,000 single glucose measurements) of the Karlsburg diabetes patient register.

The KADIS®-based assignment was regarded as **correct**, if the measured HbA1c and/or MBG values after 6 months were reduced as to be expected from the KADIS®-based prediction and, in contrast, as **failed**, if the measured HbA1c and/or MBG values increased.

Evaluation of the accuracy of KADIS®-based prediction

To evaluate the accuracy of KADIS®-based prediction of the outcome of Exenatide or Lantus therapy on HbA1c and MBG prior to therapeutic application, the measured CGM profiles at T=0 (baseline) and at T=6 months were compared with the KADIS®-based predicted outcome CGM profiles. If the measured HbA1c and the MBG of the 2nd CGM met the KADIS®-based predicted ranges for HbA1c and MBG, then the prediction was regarded as accurate. Two examples of the evaluation procedure are provided in the following figures on the next pages.

Evaluation of the secondary outcome parameters

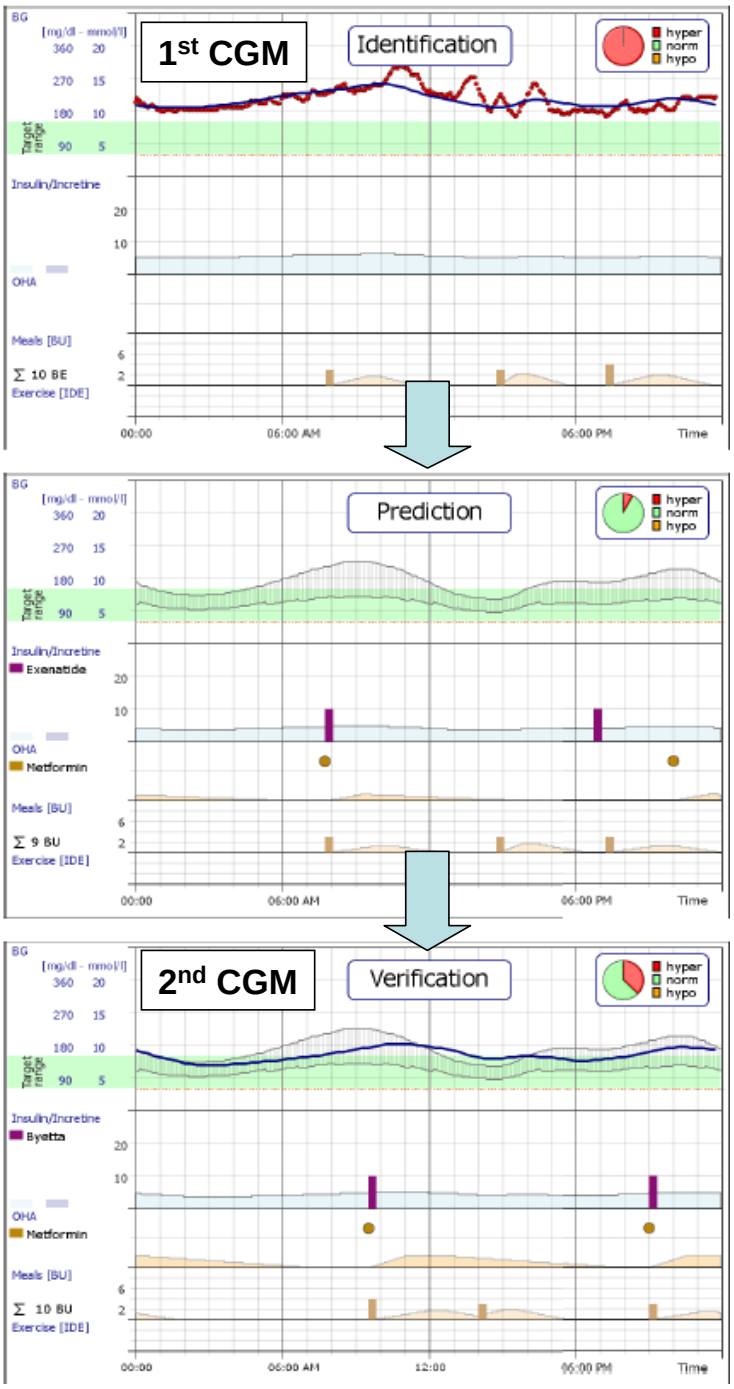
Changes in the secondary outcome parameters such as weight, BMI, CHO intake, calculated endogenous insulin secretion $IU_{endo+exo}$, the percentage of incretin action on pp insulin secretion, fasting BG, fasting insulin, fasting C-peptide, blood pressure parameters, triglyceride, and cholesterol were evaluated in the two study arms of the observational study by comparing the measured and calculated values at baseline vs. endpoint of the 6-months observational period. Significant differences were analyzed by using the t-test.

The glucose variability parameters were analyzed by applying a new evaluation score (Q-score), which summarize the parameters MBG, Range, duration of hyper-/hypoglycemic episodes, and MODD to only one evaluation parameter (Appendix: Q-Score).

The Statistical Package for the Social Sciences (version 12.0; SPSS, Chicago, Ill.) was used for all statistical analyses.

P-800017

KADIS®: "Study Lilly-Inkretine" [P-00800017]



T = 0
Age: 52 years
DD: 2 years
BMI: 38.0 kg/m²
HbA1c: 10.3 %
MBG: 11.9 mmol/l [214 mg/dl]
Weight: 123 kg

KADIS®-based analysis and assignment:

High Responder!

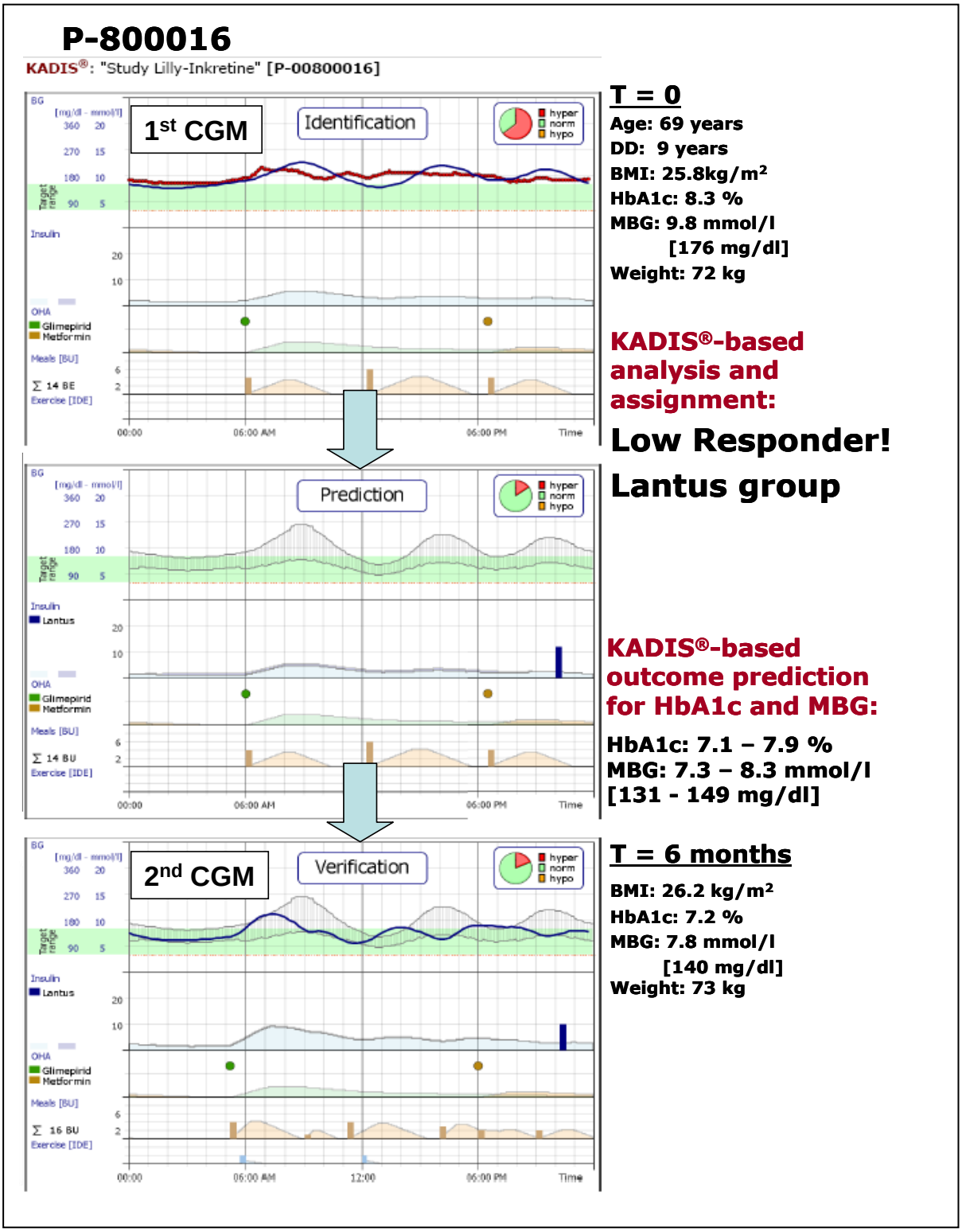
Exenatide group

KADIS®-based outcome prediction for HbA1c and MBG:

HbA1c: 6.8 – 7.6 %
MBG: 6.3 – 6.9 mmol/l [113 - 124 mg/dl]

T = 6 months
BMI: 34.9 kg/m²
HbA1c: 7.1 %
MBG: 8.7 mmol/l [157 mg/dl]
Weight: 113 kg

Schematic presentation of the procedure to evaluate the accuracy of KADIS®-based outcome prediction (Exenatide group)



Schematic presentation of the procedure to evaluate the accuracy of KADIS®-based outcome prediction (Lantus group)

Results

Recruitment of study patients and KADIS®-based assignment to LOW or HIGH responders to Exenatide therapy

66 study patients were recruited from the clientele of patients of **12** general practitioners/diabetologists in Saxonia (Appendix: List of participating practitioner settings) cooperating with the study center in Karlsburg. According to the KADIS®-based simulation procedure to detect LOW or HIGH responder for Exenatide therapy, they were assigned to the two study arms: **Exenatide group** or **Lantus group**, as far as they met the inclusion criteria (Fig. 1)

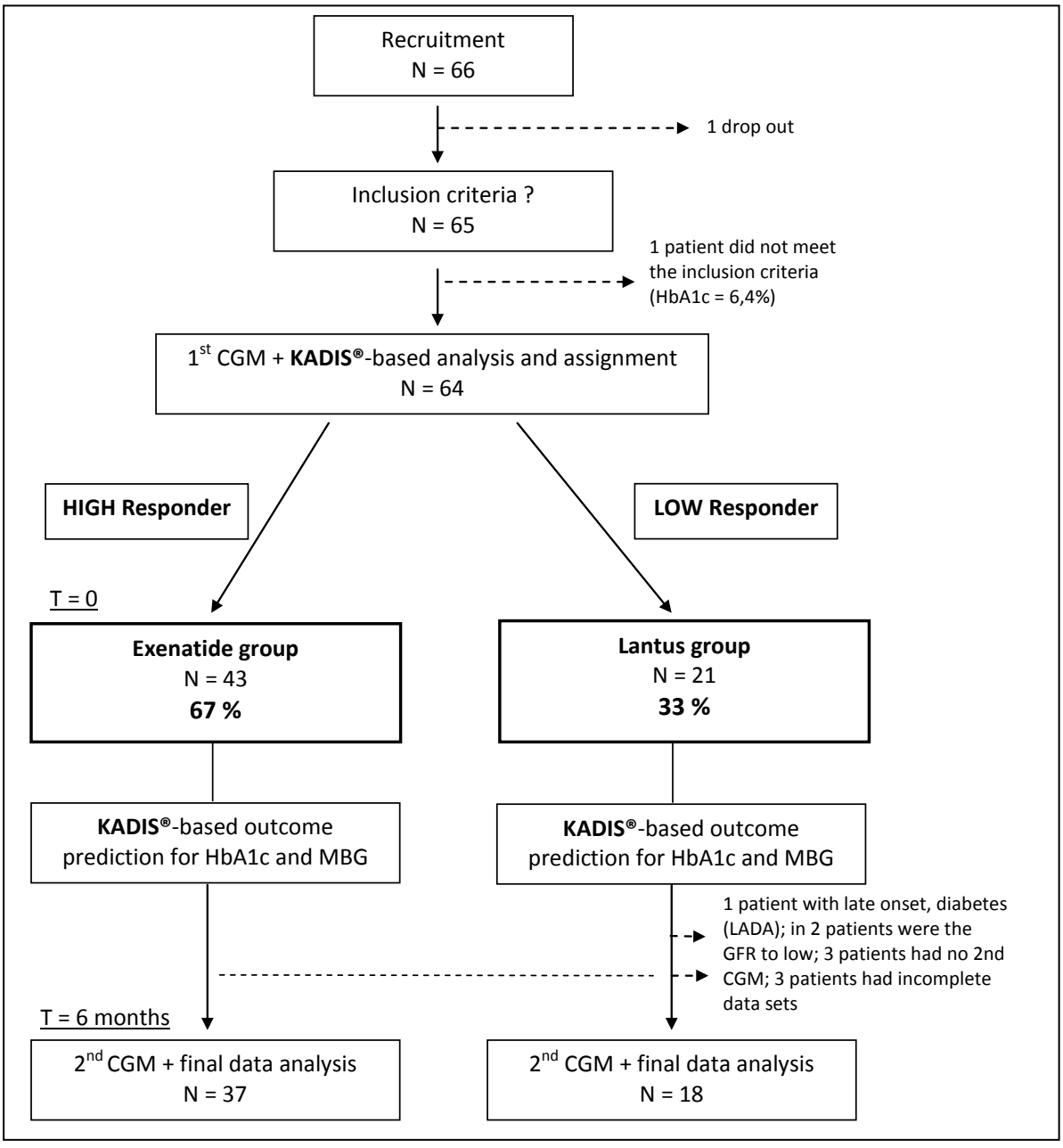


Figure 1: Recruitment and KADIS®-based analysis and assignment of the study patients to the two study arms: Exenatide group and Lantus group

From the 66 recruited study patients one patient dropped out and one patient did not meet the inclusion criteria (HbA1c = 6.4%). The remaining 64 patients performed the 1st CGM and were assigned to the two study arms according to the results of the KADIS®-based *in silico* simulation procedure. **43 study patients (67%)** were identified as HIGH responders and assigned to the study arm Exenatide group and **21 study patients (33%)** were identified as LOW responders to an Exenatide therapy and assigned therefore to the study arm Lantus group.

After KADIS®-based prediction of the outcomes to be expected for the HbA1c and MBG levels after 6 months of observation, in the Exenatide group the incretin therapy and in the Lantus group the insulin therapy were initiated (**T = 0**) and performed during the following 6 months of the observational period.

At the end of the observational period the study patient performed the 2nd CGM in both study arms.

For 37 study patients of the Exenatide group and for 18 study patients of the Lantus group complete data sets could be generated. These study patients were subjected to the final data analysis. The characteristics of these study patients at baseline (T=0) are summarized in Tab. 1.

At baseline the patients of the Exenatide group had a significantly higher body weight (99 vs. 93 kg, $p<0.001$), BMI (34.3 vs. 28.9 kg/m^2, $p<0.001$) and KADIS®-based calculated endogenous insulin secretion (104.3 vs. 70.3 IU, $p<0.009$) in comparison to the Lantus group. On the other hand, a significantly higher percentage of study patients of the Lantus group were on blood pressure therapy at baseline (83 vs. 54%, $p<0.034$). Also the duration of hyperglycemic episodes at baseline washigher in the Lantus group (13.0 vs. 8.8 h, $p<0.039$).

Tab. 1: Characteristics of study patients included into the final data analysis (T = 0)

Parameter	total	Exenatide group	Lantus group	p
N	55	37	18	
Age (years)	61.2 ± 8.3	60.9 ± 8.2	63.9 ± 8.8	
Gender (f/m)	29/26	19/18	10/8	
DD (years)	8.2 ± 6.2	8.4 ± 6.6	7.7 ± 5.4	
Weight (kg)	93.3 ± 17.6	98.7 ± 17.5	93.0 ± 16.3	0.001
BMI (kg/m^2)	32.6 ± 5.6	34.3 ± 5.5	28.9 ± 4.2	0.001
CHO intake (BU/d)	13.0 ± 2.0	13.0 ± 2.1	13.3 ± 2.3	
HbA1c (%)	8.0 ± 1.0	8.0 ± 1.1	8.0 ± 1.0	
MBG (mmol/l)	8.9 ± 2.3	8.7 ± 2.5	9.3 ± 1.8	
[mg/dl]	[160 ± 41]	[157 ± 45]	[167 ± 32]	
SD (mmol/l)	1.8 ± 0.6	1.8 ± 0.6	1.8 ± 0.4	
[mg/dl]	[32 ± 11]	[32 ± 11]	[32 ± 7]	
Range (mmol/l)	7.8 ± 2.1	7.7 ± 2.3	8.2 ± 1.8	
[mg/dl]	[140 ± 38]	[139 ± 41]	[148 ± 32]	
$t_{MBG>8.9\ mmol/l}$ (h)	10.3 ± 7.1	8.8 ± 6.7	13.0 ± 7.2	0.039
Q-Score	9.0 ± 3.3	8.5 ± 3.5	10.0 ± 2.7	
calculated $IU_{endo+exo}$ (IU)	93.2 ± 46.5	104.3 ± 50.4	70.3 ± 25.4	0.009
incretin effect on $IU_{endo,pp}$ (%)	5.1 ± 9.9	4.4 ± 8.9	6.4 ± 12.0	
fasting BG (mmol/l)	9.0 ± 2.4	9.2 ± 2.5	8.5 ± 2.2	
[mg/dl]	[162 ± 43]	[166 ± 45]	[153 ± 40]	
fasting insulin (pmol/l)	109.1 ± 74.8	108.0 ± 70.5	111.8 ± 87.0	
fasting C-peptide (nmol/l)	1.31 ± 0.62	1.32 ± 0.66	1.28 ± 0.54	
$RR_{diastol}$ (mmHg)	81.2 ± 5.9	80.6 ± 5.2	82.3 ± 7.1	
RR_{systol} (mmHg)	136.6 ± 12.6	134.9 ± 10.6	139.9 ± 15.6	
BP therapy (%)	63.6	54.1	83.3	0.034
Triglceride (mmol/l)	2.52 ± 1.82	2.60 ± 2.04	2.30 ± 1.04	
Choloster (mmol/l)	5.27 ± 1.21	5.11 ± 1.35	5.73 ± 0.50	

Data: mean ± SD; DD: diabetes duration; BMI: body mass index; CHO: carbohydrates; BU (1 BU equals 10 g CHO): bread units; MBG: mean blood glucose; $t_{MBG>8.9\ mmol/l}$: time above target glucose range; Q-Score: complex evaluation score for glucose profiles (Appendix: Q-Score); $IU_{endo+exo}$: KADIS®-based calculated endogenous insulin secretion rate; $IU_{end,pp}$: percentage of incretin action on post prandial insulin secretion; BG: blood glucose; BP: blood pressure

Correctness of KADIS®-based assignment

37 out of the 43 study patients of the Exenatide group performed successfully the 2nd CGM and could therefore included into the final data analysis to evaluate the correctness of the KADIS®-based assignment to the Exenatide group.

In **89%** of the study patients (N=33) the KADIS®-based assignment was classified as correct (Fig. 2) according to the defined evaluation criteria for correctness. In only 11% (N=4) of the Exenatide group the KADIS®-based assignment failed.

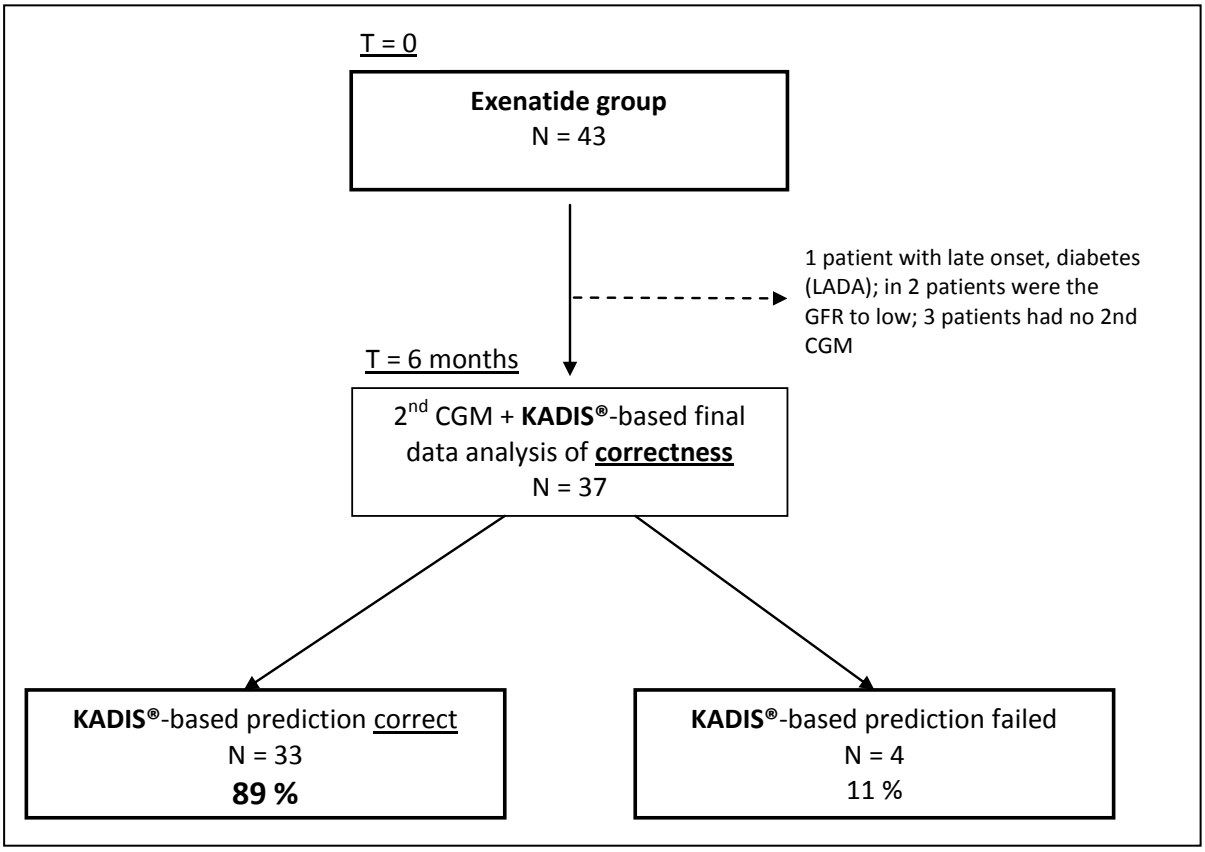


Figure 2: Evaluation of the correctness of KADIS®-based assignment in the Exenatide group
(Attention: the LADA patient and the low GFR were identified by the post study examination!)

With the exception of HbA1c (8.1 vs. 7.6%, p<0.001), there were no differences in the evaluation parameters at baseline (T=0) between the correctly assigned study patients and the study patients in whom the KADIS®-based assignment failed (Tab. 2).

Tab. 2: Characteristics of study patients, who were assigned to the Exenatide group by KADIS®-based simulation procedure (T = 0)

Parameter	Exenatide group	KADIS®-based assignment	
N	37	correct (N=33)	failed (N=4)
Age (years)	60.9 ± 8.2	61.1 ± 8.1	59.0 ± 9.4
Gender (f/m)	19/18	16/17	3/1
DD (years)	8.4 ± 6.6	7.9 ± 5.9	12.0 ± 11.7
Weight (kg)	98.7 ± 17.5	96.9 ± 16.8	113.5 ± 18.5
BMI (kg/m^2)	34.3 ± 5.5	33.8 ± 5.3	38.5 ± 5.6
CHO intake (BU/d)	13.0 ± 2.1	13.0 ± 2.2	13.5 ± 1.7
HbA1c (%)	8.0 ± 1.1	8.1 ± 1.1	7.6 ± 0.5[1)]
MBG (mmol/l)	8.7 ± 2.5	8.8 ± 2.6	7.9 ± 0.7
[mg/dl]	[157 ± 45]	[158 ± 47]	[142 ± 13]
SD (mmol/l)	1.7 ± 0.6	1.8 ± 0.7	1.6 ± 0.3
[mg/dl]	[31 ± 11]	[32 ± 13]	[29 ± 5]
Range (mmol/l)	7.7 ± 2.3	7.8 ± 2.4	7.0 ± 1.0
[mg/dl]	[139 ± 41]	[140 ± 43]	[126 ± 18]
$t_{MBG>8.9\ mmol/l}$ (h)	8.8 ± 6.7	9.0 ± 7.0	7.5 ± 0.9
Q-Score	8.5 ± 3.5	8.6 ± 3.6	7.1 ± 0.5
calculated $IU_{endo+exo}$ (IU)	104.3 ± 50.4	99.9 ± 49.4	140.8 ± 49.6
incretin effect on $IU_{endo,pp}$ (%)	4.4 ± 8.9	4.9 ± 9.3	0.7 ± 0.5
fasting BG (mmol/l)	9.2 ± 2.5	9.2 ± 2.6	8.9 ± 1.5
[mg/dl]	[166 ± 45]	[166 ± 47]	[160 ± 27]
fasting insulin (pmol/l)	108.0 ± 70.5	106.9 ± 68.2	117.1 ± 98.5
fasting C-peptide (nmol/l)	1.32 ± 0.66	1.29 ± 0.68	1.53 ± 0.45
$RR_{diastol}$ (mmHg)	80.6 ± 5.2	80.9 ± 5.4	78.5 ± 2.4
RR_{systol} (mmHg)	134.9 ± 10.6	135.1 ± 9.8	133.8 ± 18.0
BP therapy (%)	54.1	51.5	75.0
Triglycerides (mmol/l)	2.60 ± 2.04	2.65 ± 2.14	2.22 ± 0.92
Cholosterol (mmol/l)	5.11 ± 1.35	5.08 ± 1.43	5.33 ± 0.74

Data: mean ± SD; DD: diabetes duration; BMI: body mass index; CHO: carbohydrates; BU (1 BU equals 10 g CHO): bread units; MBG: mean blood glucose; $t_{MBG>8.9\ mmol/l}$: time above target glucose range; Q-Score: complex evaluation score for glucose profiles (Appendix: Q-Score); $IU_{endo+exo}$: KADIS®-based calculated endogenous insulin secretion rate; $IU_{end,pp}$: percentage of incretin action on post prandial insulin secretion; BG: blood glucose; BP: blood pressure

[1)] $p < 0.001$

In the Lantus group 18 out of the 21 study patients performed successfully the 2nd CGM and were therefore included into the final data analysis to evaluate the correctness of the KADIS®-based assignment to the Lantus group.

In **78%** of the study patients (N=14) the KADIS®-based assignment was classified as correct (Fig. 3) according to the defined evaluation criteria for correctness. In 22% (N=4) of the Lantus group the KADIS®-based assignment failed.

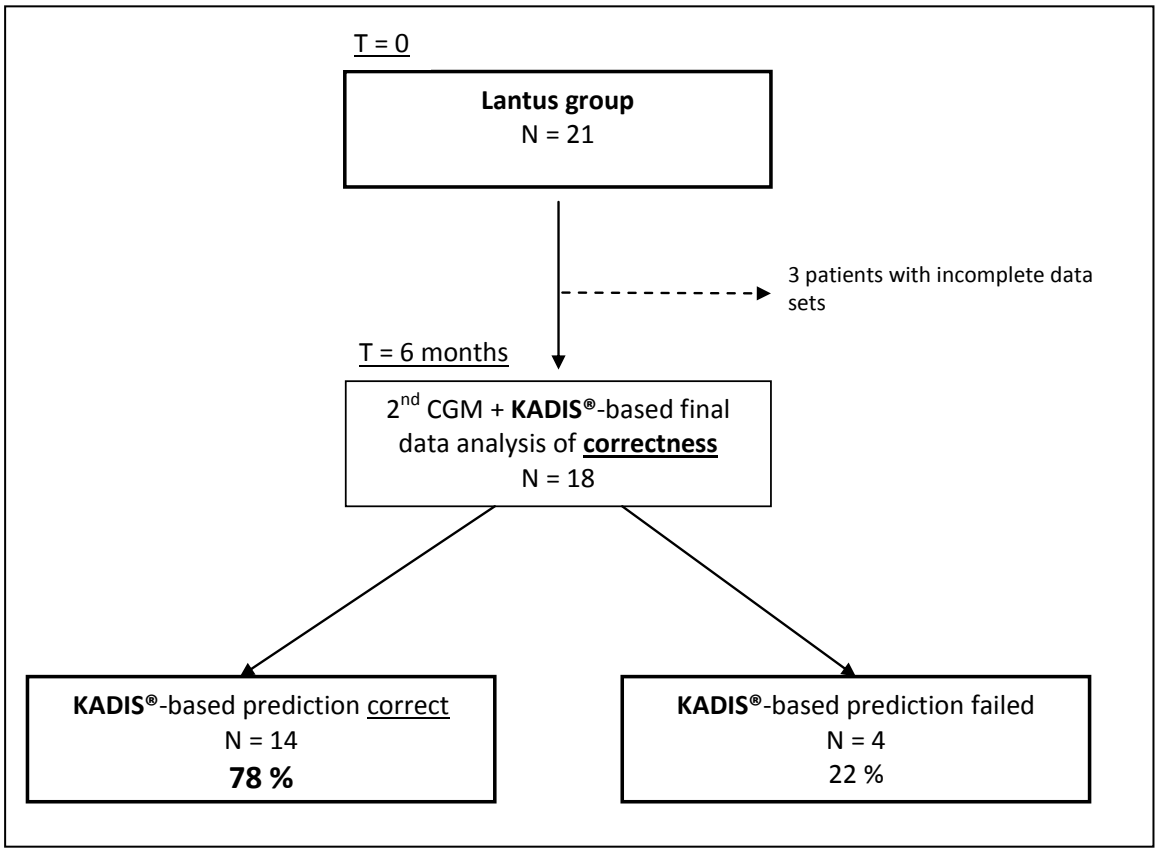


Figure 3: Evaluation of the correctness of KADIS®-based assignment in the Lantus group

With exception of HbA1c (8.0 vs. 8.7%, p<0.001) and the percentage of patients on blood pressure therapy (92.9 vs. 50.0%, p<0.05), there were no differences in the evaluation parameters at baseline (T=0) between the correctly assigned study patients to the Lantus group and the study patients in whom the KADIS®-based assignment failed (Tab. 3).

Tab. 3: Characteristics of study patients, who were assigned to the Lantus group by KADIS®-based simulation procedure (T = 0)

Parameter	Lantus group	KADIS®-based prediction	
N	18	correct (N=14)	failed (N=4)
Age (years)	63.9 ± 8.8	64.2 ± 7.8	63.0 ± 13.1
Gender (f/m)	10/8	8/6	2/2
DD (years)	7.7 ± 5.4	8.3 ± 5.1	5.8 ± 6.8
Weight (kg)	93.0 ± 16.3	80.4 ± 11.8	88.5 ± 11.1
BMI (kg/m^2)	28.9 ± 4.2	28.4 ± 4.0	30.9 ± 4.8
CHO intake (BU/d)	13.3 ± 2.3	13.1 ± 2.1	12.5 ± 1.7
HbA1c (%)	8.0 ± 1.0	7.8 ± 1.0	8.7 ± 1.1[1)]
MBG (mmol/l)	9.3 ± 1.8	9.4 ± 1.9	9.1 ± 1.8
[mg/dl]	[167 ± 32]	[169 ± 34]	[164 ± 32]
SD (mmol/l)	1.8 ± 0.4	1.9 ± 0.4	1.7 ± 0.1
[mg/dl]	[32 ± 7]	[34 ± 7]	[31 ± 2]
Range (mmol/l)	8.2 ± 1.8	8.3 ± 2.0	7.8 ± 0.4
[mg/dl]	[148 ± 32]	[149 ± 36]	[140 ± 7]
$t_{MBG>8.9\ mmol/l}$ (h)	13.0 ± 7.2	13.1 ± 7.2	12.9 ± 8.1
Q-Score	10.0 ± 2.7	10.2 ± 2.8	9.4 ±2.5
calculated $IU_{endo+exo}$ (IU)	70.3 ± 25.4	67.1 ± 19.6	81.3 ± 42.4
incretin effect on $IU_{endo,pp}$ (%)	6.4 ± 12.0	5.8 ± 11.2	8.6 ± 16.2
fasting BG (mmol/l)	8.5 ± 2.2	8.7 ± 2.3	7.7 ± 0.9
[mg/dl]	[153 ± 40]	[157 ± 41]	[139 ± 16]
fasting insulin (pmol/l)	111.8 ± 87.0	125.7 ± 90.9	56.4 ± 42.5
fasting C-peptide (nmol/l)	1.28 ± 0.54	1.30 ± 0.62	1.21 ± 0.21
$RR_{diastol}$ (mmHg)	82.3 ± 7.1	82.9 ± 7.3	80.0 ± 7.1
RR_{systol} (mmHg)	139.9 ± 15.6	140.6 ± 15.7	137.5 ± 17.1
BP therapy (%)	83.3	92.9	50.0[2)]
Triglycerides (mmol/l)	2.30 ± 1.04	2.40 ± 1.09	1.95 ± 0.94
Cholosterol (mmol/l)	5.73 ± 0.50	5.61 ± 0.57	5.98 ± 0.31

Data: mean ± SD; DD: diabetes duration; BMI: body mass index; CHO: carbohydrates; BU (1 BU equals 10 g CHO): bread units; MBG: mean blood glucose; $t_{MBG>8.9\ mmol/l}$: time above target glucose range; Q-Score: complex evaluation score for glucose profiles (Appendix: Q-Score); $IU_{endo+exo}$: KADIS®-based calculated endogenous insulin secretion rate; $IU_{end,pp}$: percentage of incretin action on post prandial insulin secretion; BG: blood glucose; BP: blood pressure

[1)] $p < 0.001$; [2)] $p < 0.05$

Accuracy of KADIS®-based outcome prediction of HbA1c and MBG

In the correctly assigned Exenatide subgroup (N=33) the KADIS®-based outcome prediction met accurately the individually predicted ranges for **HbA1c in 91%** and for **MBG in 70%** (Fig. 4).

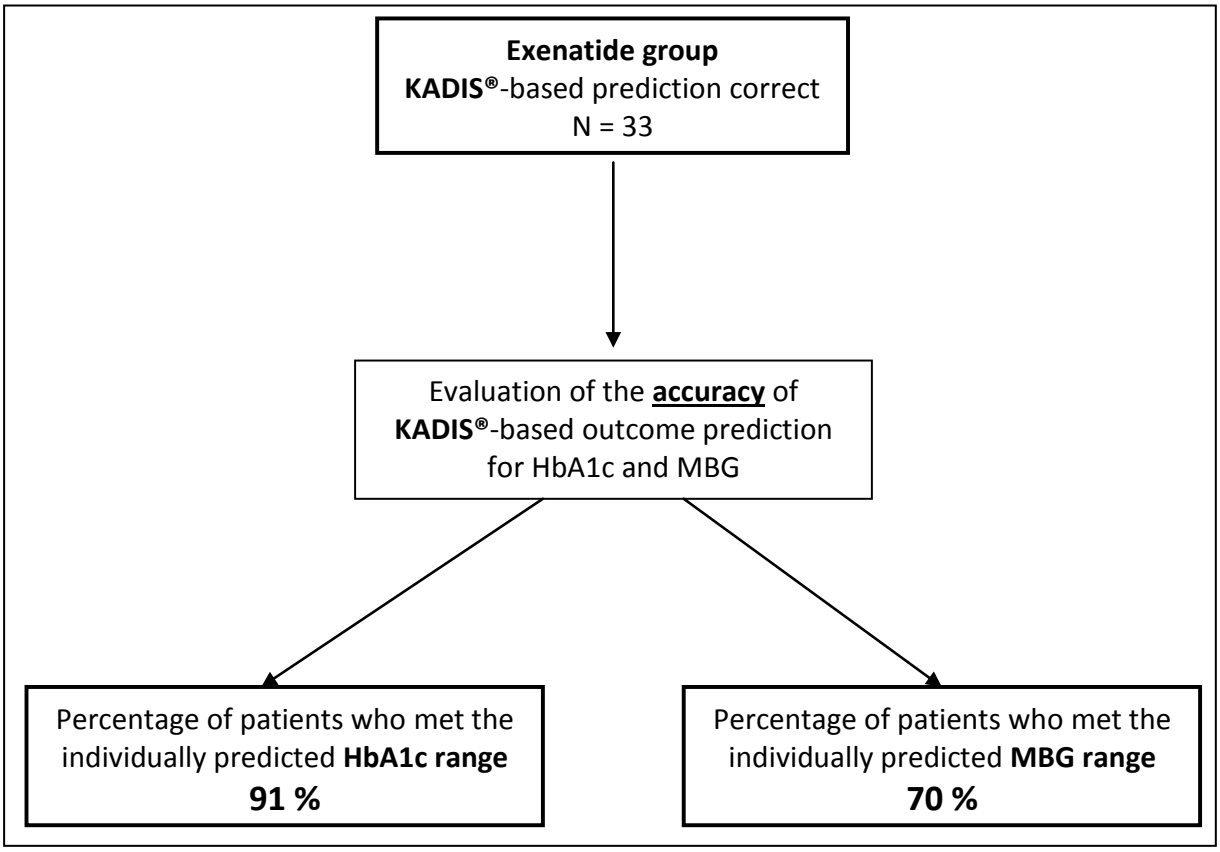


Figure 4: Evaluation of the accuracy of KADIS®-based outcome prediction for HbA1c and MBG

The mean HbA1c in the Exantide subgroup with correct KADIS®-based assignment was 8.1% and the MBG was 8.7 mmol/l [157 mg/dl] at baseline.

For HbA1c, KADIS®-based analysis predicted an outcome of HbA1c between 6.3 to 8.3%. The measured mean HbA1c after 6 months was 7.1%.

For MBG, KADIS®-based analysis predicted an outcome between 6.4 to 8.4 mmol/l [115 to 157 mg/dl]. The measured MBG after 6 months of observation was 7.8 mmol/l [140 mg/dl].

The individual data for baseline HbA1c and MBG (T=0), predicted ranges and measured outcomes (T=6 mo.) are summarized in Tab. 4 and Appendix: Case records.

Tab. 4: Evaluation of the ACCURACY of KADIS®-based prediction of patient focused HbA1c and MBG
Exenatide group (basic assignment correct, N = 33)

	HbA1c (%)			MBG (mmol/l) [mg/dl]		
Pat.-ID	**T = 0**	**Prediction**	**T = 6 mo.**	**T = 0**	**Prediction**	**T = 6 mo.**
P-800001	6.9	6.1 – 8.1	6.2	8.2 [148]	5.9 – 7.9 [106-142]	7.1 [128]
P-800004	8.8	6.6 – 9.0	8.4	16.8 [302]	7.4 –10.2 [133-184]	12.0 [216]
P-800005	8.8	6.6 – 9.0	7.9	10.3 [185]	7.4 –10.2 [133-184]	10.3 [185]
P-800006	7.0	6.1 – 8.1	7.6	7.4 [133]	5.8 – 7.8 [104-140]	7.7 [139]
P-800010	9.4	6.2 – 8.2	9.1	8.5 [153]	6.0 – 8.0 [108-144]	7.7 [139]
P-000017	10.3	6.0 – 8.0	7.1	11.9 [214]	5.4 – 7.4 [97-133]	8.7 [157]
P-800019	7.1	6.0 – 8.0	6.9	6.5 [117]	5.6 – 7.6 [101-137]	7.2 [130]
P-800020	8.7	6.2 – 8.3	7.5	8.9 [160]	6.1 – 8.1 [110-146]	9.1 [164]
P-800021	7.1	6.5 – 8.5	7.1	7.6 [137]	6.7 – 9.1 [121-164]	8.1 [146]
P-800022	7.1	6.1 – 8.1	6.1	7.6 [137]	6.0 – 8.0 [108-144]	6.3 [113]
P-800024	7.8	6.0 – 8.0	6.2	6.9 [124]	5.6 – 7.6 [101-137]	6.3 [113]
P-800025	7.7	6.1 – 8.1	6.3	7.8 [140]	5.9 – 7.9 [106-142]	6.2 [112]
P-800027	7.7	6.2 – 8.2	7.3	7.2 [130[	6.1 – 8.1 [110-146]	8.0 [144]
P-800030	7.1	6.3 – 8.7	7.4	8.5 [153]	6.9 – 9.3 [124-167]	7.1 [128]
P-800031	8.9	6.8 – 9.2	7.0	12.2 [220]	8.0 –10.8 [144-194]	9.5 [171]
P-800034	8.3	6.0 – 8.0	7.6	7.4 [133]	5.5 – 7.3 [99-131]	8.3 [149]
P-800035	7.5	6.7 – 9.1	6.3	9.3 [167]	6.1 – 8.1 [110-146]	7.3 [131]
P-800036	7.2	6.2 – 8.2	6.9	8.4 [151]	6.1 – 8.1 [110-146]	7.7 [139]
P-800037	7.7	6.2 – 8.2	7.4	7.9 [142]	6.0 – 8.0 [108-144]	7.9 [142]
P-800038	10.8	7.2 – 9.6	7.3	11.2 [202]	9.0–12.2 [162-220]	7.4 [133]
P-800039	7.2	6.1 – 8.1	7.2	7.1 [128]	5.8 – 7.8 [104-140]	6.8 [122]
P-800040	9.3	6.5 – 8.9	7.3	8.9 [160]	7.3 –10.1 [131-182]	8.8 [158]
P-800041	7.1	6.4 – 8.4	6.5	8.6 [155]	6.5 – 8.9 [117-160]	6.8 [122]
P-800043	10.4	7.1 – 8.9	8.9	18.0 [324]	6.9 – 9.3 [124-167]	10.2 [184]
P-800044	8.5	6.3 – 8.7	5.6	7.0 [126]	6.7 – 9.1 [121-164]	4.9 [88]
P-800047	7.1	6.1 – 8.1	6.7	7.8 [140]	5.9 – 7.9 [106-142]	7.0 [126]
P-800054	6.5	6.0 – 8.0	6.2	8.5 [153]	6.4 – 8.8 [125-158]	7.9 [142]
P-800056	7.4	6.4 – 8.4	7.5	6.2 [112]	6.3 – 8.7 [113-157]	8.1 [146]
P-800057	6.8	6.1 – 8.1	6.4	7.0 [126]	5.7 – 7.7 [103-139]	6.9 [124]
P-800058	9.2	6.3 – 8.7	8.0	6.2 [112]	6.8 – 9.2 [122-166]	9.8 [176]
P-800059	8.3	6.1 – 8.1	6.1	7.6 [137]	5.8 – 7.8 [104-140]	5.7 [103]
P-800060	7.4	6.4 – 7.8	6.5	8.8 [158]	5.9 – 7.9 [106-142]	6.7 [121]
P-800064	8.1	6.2 – 7.6	7.5	7.6 [137]	5.3 – 7.1 [95-128]	5.6 [101]
N = 33 ±SD	**8.1 ±1.1**	**6.3 – 8.3**	**7.1 ±0.8**	**8.8 [158] ±2.5 [45]**	**6.4 – 8.4 [115-157]**	**7.8 [140] ±1.5 [27]**

In the not correctly assigned Exenatide subgroup (N=4), the KADIS®-based outcome prediction did not meet the individually predicted ranges for HbA1c and for MBG (Tab. 5, Appendix: Case records).

Tab. 5: Evaluation of the ACCURACY of KADIS®-based prediction of patient focused HbA1c and MBG
Exenatide group (basic assignment failed, N = 4)

	HbA1c (%)			MBG (mmol/l) [mg/dl]		
Pat.-ID	T = 0	Prediction	T = 6 mo.	T = 0	Prediction	T = 6 mo.
P-800013	7.2	6.0 – 8.0	7.8	7.0 [126]	5.4 – 7.4 [97-133]	7.9 [142]
P-800033	8.2	6.2 – 8.2	9.3	8.4 [151]	6.1 – 8.1 [110-146]	10.4 [187]
P-800045	7.2	6.2 – 8.2	8.7	8.4 [151]	6.1 – 8.1 [110-146]	8.9 [160]
P-800062	7.8	6.1 – 8.1	8.5	7.7 [139]	5.7 – 7.7 [103-139]	7.9 [142]
N = 4 ±SD	**7.6 ±0.5**	**6.1 – 8.1**	**8.6 ±0.6**	**7.9 [142] ±0.7 [13]**	**5.8 – 7.8 [104-140]**	**8.8 [158] ±1.2 [22]**

The mean HbA1c in the Exantide subgroup with incorrect KADIS®-based assignment was 7.6% and the MBG was 7.9 mmol/l [142 mg/dl] at baseline.

For HbA1c KADIS®-based analysis predicted an outcome of HbA1c between 6.1 to 8.1%. The measured HbA1c after 6 months was 8.6%.

For MBG, KADIS®-based analysis predicted an outcome between 5.8 to 7.8 mmol/l [104 to 140 mg/dl]. The measured MBG after 6 months of observation was 8.8 mmol/l [158 mg/dl].

In the correctly assigned Lantus group (N=14) the KADIS®-based outcome prediction met accurately the individually predicted ranges for **HbA1c in 100%,** and for **MBG in 78%** (Fig. 5).

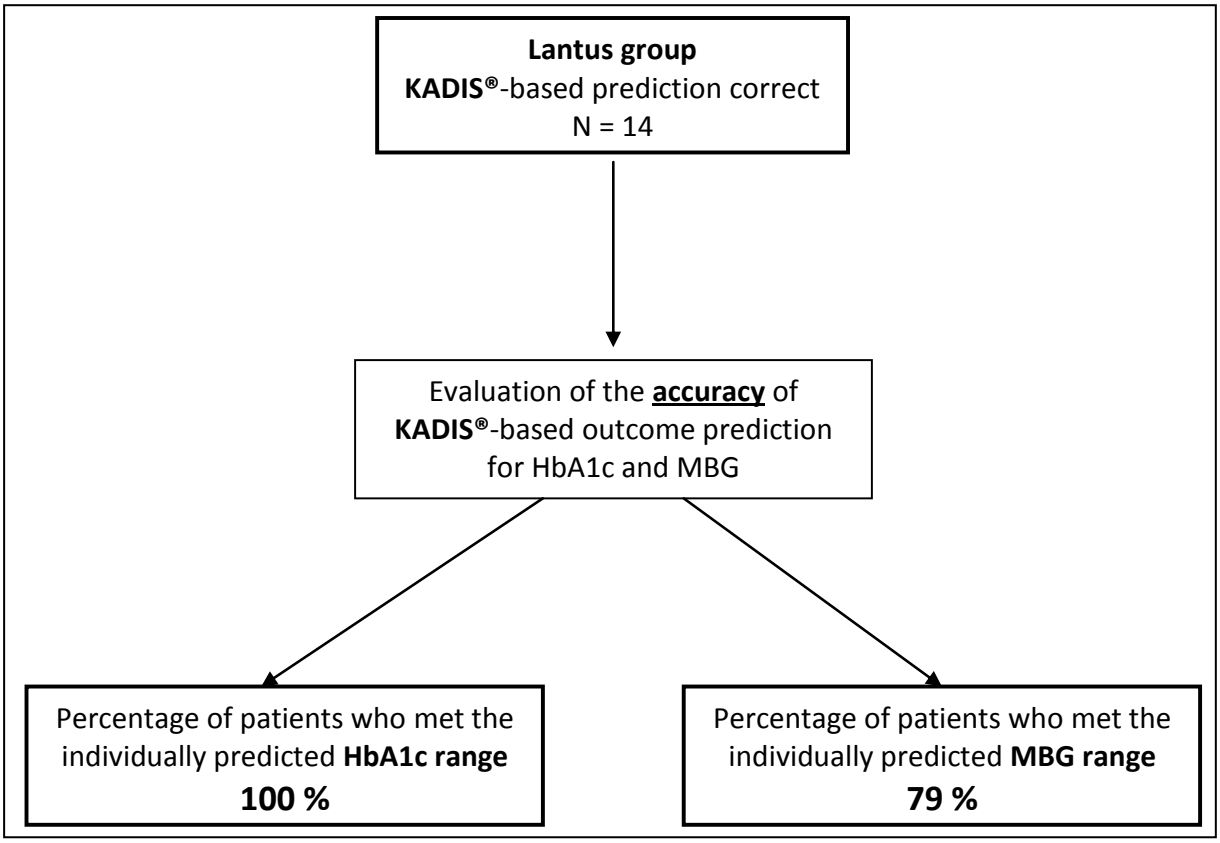


Figure 5: Evaluation of the accuracy of KADIS®-based outcome prediction for HbA1c and MBG

The mean HbA1c in the Lantus subgroup with correct KADIS®-based assignment was 7.8% and the MBG was 8.8 mmol/l [158 mg/dl] at baseline.

For HbA1c, KADIS®-based analysis predicted an outcome between 6.2 to 8.2%. The measured HbA1c after 6 months was 7.1%.

For MBG, KADIS®-based analysis predicted an outcome between 6.2 to 8.2 mmol/l [112 to 148 mg/dl]. The measured MBG after 6 months of observation was 8.1 mmol/l [146 mg/dl].

The individual data for baseline HbA1c and MBG (T=0), predicted ranges and measured outcomes (T=6 mo.) are summarized in Tab. 6 and Appendix: Case records.

Tab. 6: Evaluation of the ACCURACY of KADIS®-based prediction of patient focused HbA1c and MBG
Lantus group (basic assignment correct, N = 14)

Pat.-ID	HbA1c (%)			MBG (mmol/l) [mg/dl]		
	T = 0	Prediction	T = 6 mo.	T = 0	Prediction	T = 6 mo.
P-800002	7.2	6.2 – 8.2	6.8	6.5 [117]	6.2 – 8.2 [112-148]	6.2 [112]
P-800003	7.4	6.4 – 8.4	6.7	8.0 [144]	5.6 – 7.6 [101-137]	7.9 [142]
P-800007	6.7	6.4 – 8.4	7.6	8.9 [160]	6.5 – 8.9 [117-160]	8.2 [148]
P-800012	9.0	6.4 – 8.4	6.5	9.5 [171]	6.4 – 8.8 [125-158]	8.3 [149]
P-800016	8.3	6.3 – 8.3	7.2	9.8 [176]	6.3 – 8.7 [113-157]	7.8 [140]
P-000018	8.4	6.2 – 8.2	6.2	12.3 [221]	6.0 – 8.0 [108-144]	6.7 [121]
P-800023	6.9	6.4 – 8.4	7.3	9.4 [169]	6.5 – 8.9 [117-160]	8.9 [160]
P-800028	7.9	6.2 – 8.2	7.7	8.0 [144]	6.0 – 8.0 [108-144]	7.6 [137]
P-800029	7.7	6.2 – 8.2	7.0	11.0 [198]	6.0 – 8.0 [108-144]	7.8 [140]
P-800046	6.9	6.4 – 8.4	6.9	8.0 [144]	6.6 – 9.0 [119-162]	7.0 [126]
P-800048	8.0	6.1 – 8.1	6.8	8.6 [155]	5.7 – 7.7 [103-139]	8.1 [146]
P-800050	9.7	6.1 – 8.1	7.9	12.0 [216]	5.8 – 7.8 [104-140]	13.9 [250]
P-800055	9.0	6.2 – 8.2	7.4	12.2 [220]	6.1 – 8.1 [110-146]	7.2 [130]
P-800063	7.0	6.4 – 8.4	7.0	7.4 [133]	6.5 – 8.9 [117-160]	7.7 [139]
N = 14 ±SD	**7.8 ±1.0**	**6.2 – 8.2**	**7.1 ±0.5**	**8.8 [158] ±2.7 [49]**	**6.2 – 8.2 [112-148]**	**8.0 [144] ±0.6 [11]**

In the not correctly assigned Lantus subgroup (N=4), the KADIS®-based outcome prediction did not meet the individually predicted ranges for HbA1c and for MBG (Tab. 7, Appendix: Case records).

Tab. 7: Evaluation of the ACCURACY of KADIS®-based prediction of patient focused HbA1c and MBG
Lantus group (basic assignment failed, N = 4)

Pat.-ID	HbA1c (%)			MBG (mmol/l) [mg/dl]		
	T = 0	Prediction	T = 6 mo.	T = 0	Prediction	T = 6 mo.
P-800014	9.0	6.2 – 8.2	10.0	7.1 [128]	6.0 – 8.0 [108-144]	10.5 [189]
P-800049	7.3	6.2 – 8.2	7.9	8.2 [148]	6.0 – 8.0 [108-144]	8.6 [155]
P-800051	9.9	6.4 – 8.4	10.1	10.5 [189]	6.4 – 8.8 [125-158]	13.8 [248]
P-800052	8.6	6.2 – 8.2	9.5	10.8 [194]	6.2 – 8.2 [112-148]	12.3 [221]
N = 4 ±SD	**8.7 ±1.1**	**6.2 – 8.2**	**9.4 ±1.0**	**9.2 [166] ±1.8 [32]**	**6.2 – 8.2 [112-148]**	**11.3 [203] ±2.2 [40]**

Comparison of different metabolic and non-metabolic parameters T = 0 vs. T = 6 months in both study arms

In both study arms significant improvements in metabolic control were achieved if the KADIS®-based assignment to the study groups was correct (Tab. 8 and Tab. 9).

In the Exenatide group significant improvements of the following parameters were observed:
- body weight (96.9 to 91.4 kg, p<0.000),
- BMI (33.8 to 31.9 kg/m^2, p<0.000),
- HbA1c (8.1 to 7.1 %, p<0.000),
- MBG (8.8 to 7.7 mmol/l, p<0.006),
- Q-Score (8.6 to 6.8, p<9.005),
- incretin effect on $IU_{endo,pp}$ (4.9 to 38.7%, p<0.000),
- fasting BG (9.2 to 7.7 mmol/l, p<0.002),
- BP therapy (54.1 to 81.8 %, p<0.009).

No changes were found for the following parameters:
CHO intake, calculated $IU_{endo+exo,}$ fasting insulin, fasting C-peptide, $RR_{diastol}$, RR_{systol}, triglycerides, cholesterol.

In the Lantus group significant improvements of the following parameters were seen:
- HbA1c (7.8 to 7.1%, p<0.016),
- MBG (9.4 to 8.1 mmol/l, p<0.032),
- Q-Score (10.2 to 7.9, p<9.001),
- incretin effect on $IU_{endo,pp}$ (5.8 to 14.2 %, p<0.021),
- fasting C-peptide (1.30 to 0.96 nmol/l, p<0.007),

No changes could be evaluated for the following parameters:
body weight, BMI, CHO intake, calculated $IU_{endo+exo,}$ fasting BG, fasting insulin, $RR_{diastol}$, RR_{systol}, triglycerides, cholesterol.

Tab. 8: Efficacy of KADIS®-based outcome prediction (Exenatide group)

Parameter	Exenatide group		
N = 33	**T = 0**	**T = 6 months**	**p**
Age (years) Gender (f/m) DD (years)	61.1 ± 8.1 16/17 7.9 ± 5.9		
Weight (kg) BMI (kg/m^2) CHO intake (BU/d)	96.9 ± 16.8 33.8 ± 5.3 13.0 ± 2.2	91.4 ± 15.8 31.9 ± 4.9 13.4 ± 2.3	0.000 0.000
HbA1c (%)	8.1 ± 1.1	7.1 ± 0.8	0.000
MBG (mmol/l) [mg/dl] SD (mmol/l) [mg/dl] Range (mmol/l) [mg/dl] $t_{MBG>8.9\ mmol/l}$ (h) Q-Score	8.8 ± 2.6 [158 ± 47] 1.8 ± 0.7 [32 ± 13] 7.8 ± 2.4 [140 ± 43] 9.0 ± 7.0 8.6 ± 3.6	7.7 ± 1.5 [139 ± 27] 1.4 ± 0.5 [25 ± 9] 6.1 ± 2.3 [110 ± 41] 6.0 ± 6.3 6.8 ± 2.8	0.006 0.001 0.002 0.021 0.005
calculated $IU_{endo+exo}$ (IU) incretin effect on $IU_{endo,pp}$ (%)	99.9 ± 49.4 4.9 ± 9.3	86.5 ± 33.7 38.7 ± 14.7	 0.000
fasting BG (mmol/l) [mg/dl] fasting insulin (pmol/l) fasting C-peptide (nmol/l)	9.2 ± 2.6 [166 ± 47] 106.9 ± 68.2 1.29 ± 0.68	7.7 ± 1.7 [139 ± 31] 140.0 ± 113.0 1.25 ± 0.59	0.002
$RR_{diastol}$ (mmHg) RR_{systol} (mmHg) BP therapy (%)	80.9 ± 5.4 135.1 ± 9.8 54.1	81.6 ± 7.1 134.7 ± 11.7 81.8	 0.009
Triglycerides (mmol/l) Cholosterol (mmol/l)	2.65 ± 2.14 5.08 ± 1.43	2.41 ± 1.39 5.21 ± 1.37	

Data: mean ± SD; DD: diabetes duration; BMI: body mass index; CHO: carbohydrates; BU (1 BU equals 10 g CHO): bread units; MBG: mean blood glucose; $t_{MBG>8.9\ mmol/l}$: time above target glucose range; Q-Score: complex evaluation score for glucose profiles (Appendix: Q-Score); $IU_{endo+exo}$: KADIS®-based calculated endogenous insulin secretion rate; $IU_{end,pp}$: percentage of incretin action on post prandial insulin secretion; BG: blood glucose; BP: blood pressure

Tab. 9: Efficacy of KADIS®-based outcome prediction (Lantus group)

Parameter	Lantus group		
N = 14	**T = 0**	**T = 6 months**	**p**
Age (years) Gender (f/m) DD (years)	64.2 ± 7.8 8/6 8.3 ± 5.1		
Weight (kg) BMI (kg/m^2) CHO intake (BU/d)	80.4 ± 11.8 28.4 ± 4.0 13.1 ± 2.1	78.9 ± 10.9 27.9 ± 3.9 14.0 ± 2.6	
HbA1c (%)	7.8 ± 1.0	7.1 ± 0.5	0.016
MBG (mmol/l) [mg/dl] SD (mmol/l) [mg/dl] Range (mmol/l) [mg/dl] $t_{MBG>8.9\ mmol/l}$ (h) Q-Score	9.4 ± 1.9 [169 ± 34] 1.9 ± 0.4 [34 ± 7] 8.3 ± 2.0 [149 ± 36] 13.1 ± 7.2 10.2 ± 2.8	8.1 ± 1.8 [146 ± 32] 2.3 ± 1.6 [41 ± 29] 7.4 ± 1.7 [133 ± 31] 7.1 ± 5.3 7.9 ± 2.8	0.032 0.011 0.001
calculated $IU_{endo+exo}$ (IU) incretin effect on $IU_{endo,pp}$ (%)	67.1 ± 19.6 5.8 ± 11.2	80.9 ± 33.9 14.2 ± 11.8	 0.021
fasting BG (mmol/l) [mg/dl] fasting insulin (pmol/l) fasting C-peptide (nmol/l)	8.7 ± 2.3 [157 ± 41] 125.7 ± 90.9 1.30 ± 0.62	7.5 ± 2.3 [135 ± 41] 87.6 ± 86.3 0.96 ± 0.50	 0.007
$RR_{diastol}$ (mmHg) RR_{systol} (mmHg) BP therapy (%)	82.9 ± 7.3 140.6 ± 15.7 92.9	83.3 ± 7.6 136.7 ± 10.8 100.0	
Triglycerides (mmol/l) Cholosterol (mmol/l)	2.40 ± 1.09 5.61 ± 0.57	1.80 ± 0.94 5.26 ± 1.51	

Data: mean ± SD; DD: diabetes duration; BMI: body mass index; CHO: carbohydrates; BU (1 BU equals 10 g CHO): bread units; MBG: mean blood glucose; $t_{MBG>8.9\ mmol/l}$: time above target glucose range; Q-Score: complex evaluation score for glucose profiles (Appendix: Q-Score); $IU_{endo+exo}$: KADIS®-based calculated endogenous insulin secretion rate; $IU_{end,pp}$: percentage of incretin action on post prandial insulin secretion; BG: blood glucose; BP: blood pressure

Conclusions

The results obtained from this observational, two-arm, multi-center study in suboptimally controlled type 2 diabetic patients indicate convincingly the ability, the efficacy and the correctness of KADIS®-based assignment to LOW or HIGH responder groups to an Exenatide therapy prior to the therapeutic intervention.

In correctly assigned patients, the expected outcome of an incretin or insulin therapy in terms of HbA1c and MBG levels can be accurately predicted with high precision by applying KADIS®-based decision support and, moreover, the metabolic control is significantly improved.

In contrast, in incorrectly assigned patients the metabolic outcome failed to meet the KADIS®-based predictions and the metabolic control deteriorate.

The metabolic background for LOW or HIGH responder to an Exenatide therapy could not be defined exactly within the frame of this observational study. But there are some indications that differences in body weight, endogenous insulin secretion, and insulin resistance might be of importance. Further RCT studies are necessary to find correct answers.

In summary it can be concluded that the KADIS®-based *in silico* simulation strategy is an appropriate tool to identify LOW or HIGH responders to an Exenatide therapy prior to therapy applicationand may have therefore great potential to become an efficient part in routine diabetes care and management.