Summary of results

PROPRIETARY DRUG NAME® / GENERIC DRUG NAME: Insulin Glargine (Lantus®, Solostar®) and Insulin Aspart (Novorapid®, Flexpen®)

PROTOCOL TITLE:

English title: An open, single-centre, non-controlled feasibility study of the performance of a tablet based workflow and decision support system with incorporated software algorithm used for glycaemic management in non-critically ill patients with type 2 diabetes at the general ward

German title: Eine offene, monozentrische, nicht kontrollierte Machbarkeitsstudie mit einem Tablet-basierten Arbeitsprozess- und Entscheidungsunterstützungssystems mit integriertem Softwarealgorithmus für das Blutzuckermanagement bei nicht kritisch kranken Patienten mit Typ-2-Diabetes auf der Allgemeinstation

Research Article title:

A Mobile Computerized Decision Support System to Prevent Hypoglycemia in Hospitalized Patients With Type 2 Diabetes Mellitus: Lessons Learned From a Clinical Feasibility Study

Sponsor Details:

Organisation Details

Principal investigator and Sponsor: Univ. Prof. Dr. Thomas Pieber, Medical University of Graz, email: thomas.pieber@medunigraz.at

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Study Centers:

Medical University of Graz (Division of Endocrinology and Metabolism)

Study Initiation and Final Completion Dates:

FPFV	19-Nov-2012
LPLV	20-Mar-2013

Study Objectives:

The primary objective was to investigate the performance (safety) of the GlucoTab system for glycaemic management in non-critically ill patients with type 2 diabetes at the general ward for the length of hospital stay, with a maximum of 21 days.

The secondary study objectives included usability and efficacy parameters of the GlucoTab system for glycaemic management in non-critically ill patients with type 2 diabetes at the general ward for the length of hospital stay, with a maximum of 21 days.

METHODS:

Table – Baseline characteristics of study population

	Subject 001-015	**Subject 016-030**
n	15	15
Gender, f/m (n)	4/11	7/8
Age (years)	69 ± 10	73 ± 11
BMI (kg/m²)	29.1 ± 5.6	30.1 ± 6.8
Race: Caucasian	15	15
Serum creatinine (mg/dl)	1.3 ± 0.5	1.4 ± 0.6
HbA1c (%)	76 ± 30	62 ± 18
Diabetes duration (years)	14 ± 9	17 ± 16
Length of study	8.4 ± 3.9	8.3 ± 5.2
Diabetes therapy (n)		
No previous Insulin	9	7
Previous Insulin	6	8
Admission diagnosis (%)		
Hematological disease	0	7
Endocrine	47	20
Cardiovascular disease	40	27
Infectious disease	13	47

Number of Subjects: n=30

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

- Informed consent obtained after being advised of the nature of the study
- Male or female aged 18 - 90 years (both inclusive)
- Type 2 diabetes treated with diet, oral agents, non-insulin injected anti-diabetic medicine, insulin therapy or any combination of the four

Main Exclusion criteria

- Impaired renal function (serum creatinine ≥ 3.0mg/dL)
- Any disease or condition which the investigator or treating physician feels would interfere with the trial or the safety of the patient
- Pregnancy
- Any mental condition rendering the patient incapable of giving his consent

Safety assessments:

Risk Benefit Assessment: Subcutaneous insulin therapy is an established method in hospital practice and recommended to control glycaemia in the hospital setting. In previous investigations glycaemic control could be established safely following the advice of the REACTION algorithm and was superior as compared to routine care. A recent audit of local glycaemic management revealed levels above the recommended target range. Thus, the patients may directly benefit from the implementation of the GlucoTab system by means of improved blood glucose control.

The nursing staff could at any time decide to take an additional blood glucose measurement and/or neglect the decision as suggested by the GlucoTab system in case an advice generated is implausible and could possibly endanger the patient's health. For glucose measurement, routine standard devices was used (Accuchek Inform®). For subcutaneous insulin injection standard insulin (Insulin Lantus®, Insulin Novorapid®) as it is also used under routine conditions in the hospital was used during this study.

A risk analysis with needed actions was performed by a multidisciplinary team to identify and prevent possible risks for the patients. Beside this, all patients were treated according to the standard clinical practice of the hospital. After discharge the trial had no consequences for the patients. The patients, who were treated with insulin during the hospital stay, received after discharge their usual anti-diabetic medication unless a further insulin therapy is indicated by the treating physician.

Adverse Events (AEs) were defined as any undesirable experience occurring to a patient during the trial, whether or not considered related to the method under investigation. An ADE (Adverse device effect) was an AE that was (possibly or probably) related to the use of a medical device. All AEs / ADEs reported spontaneously by the patient or observed by the investigator or the nurses were recorded.

Statistical analysis:

All manually entered data and all calculated data (eg, suggested/ordered insulin doses) were stored automatically on the backend server. In addition, we used paper source forms to verify the correct documentation of data in the electronic system. The paper source forms were then transcribed into electronic case report forms (eCRF) for data analysis.

The glucose profiles were analyzed based on recommendations for standardizing analysis and presentation of glucose monitoring data (ambulatory glucose profile). Glucose variability was calculated as standard deviation (SD). The level of glycaemic control was calculated as patient-day-weighted mean, based on the daily premeal BG measurements. For the ambulatory glucose profile, “BG values in different ranges” was defined as “% of BG readings” within a well-defined range, such as 100-140 mg/dl.

All metric outcome variables were checked for normality by means of Shapiro-Wilk’s test. In case of significant deviations from normality, results are represented as median and range instead of mean and SD. Pearson’s $\chi 2$ test was used to analyze nominal data. The level of significance was set to 5% for all tests. Due to the descriptive character of this feasibility study no power calculation was performed. Statistical analysis was carried out using the statistical software R 3.0.1.

Results:

Primary Endpoint: 98.1% of documentation of the blood glucose measurement, 97.4% of basal insulin administrations, and 93.5% of bolus insulin administrations were successfully performed with the GlucoTab system. Non-performance of blood glucose measurements and insulin administrations with the GlucoTab system are related to technical bugs which have been fixed during the clinical trial, and user errors which have been considered in a more detailed training of end users.

Secondary Endpoints: Mean daily blood glucose was 163 mg/dl in part 1 and 148 mg/dl in part 2 of the study. Guidelines recommend a target range of 100-140 mg/dl. Regarding the times of the day the following mean blood glucose values were achieved:

Table - Mean blood glucose distribution over the day

	ClinDiab03 – part 1	**ClinDiab03 – part 2**
Morning	156 mg/dl	145 mg/dl
Noon	195 mg/dl	156 mg/dl
Evening	144 mg/dl	143 mg/dl

Night	153 mg/dl	146 mg/dl

Mean BG (patient-day weighted mean) values showed a peak at noon in ClinDiab03 – part 1 and a significant reduction of the peak after redistribution of bolus insulin in ClinDiab03 – part 2.

13 hypoglycaemic events (6 in the first part and 7 in the second part of the trial) were documented for six different patients (3 in the first and 3 in the second part of the trial) during the clinical trial. All of these hypoglycaemic events were mild according the definition of the study protocol (> 40 mg/dl). In summary, 1.9 % of all measurements were hypoglycaemic events and none of them were critical for patient safety with regards to medical symptoms. Redistribution of bolus insulin shifted hypoglycaemic events from night to noon.

98.7 % of the suggested new total insulin dose was accepted by the physicians. 95.7 % of the bolus insulin suggestions and 96.2 % of the basal insulin suggestions were accepted by the nurses.

Eight bugs were reported during the study. Six of these bugs were fixed in GlucoTab R1.4.1. The remaining two bugs were fixed in GlucoTab R2.0. None of these bugs led to a safety critical situation for a patient.

Serious adverse events/adverse events:

Table - Overview and Categorization of Adverse Events

<table>
<tr><th>Adverse Events</th><th>Not device related</th><th colspan="2">Device related</th><th></th></tr>
<tr><td rowspan="2">Non serious</td><td>AE
Adverse events not device related</td><td colspan="2">ADE
adverse device-related event</td><td>AE + ADE</td></tr>
<tr><td>20</td><td colspan="2">0</td><td>20</td></tr>
<tr><td rowspan="4">Serious</td><td>SAE
Serious adverse event</td><td colspan="2">SADE
Serious adverse device-related event</td><td>SAE + SADE</td></tr>
<tr><td rowspan="3">4</td><td colspan="2">0</td><td rowspan="3">4</td></tr>
<tr><td>ASADE
Anticipated serious adverse device related events</td><td>USADE
Unexpected serious adverse device related events</td></tr>
<tr><td>0</td><td>0</td></tr>
</table>

Conclusion:

Hypoglycaemic events: According to the U.K. Diabetes inpatient Audit 2011 (Rayman & National Health Service, 2012), 23.4% of inpatients with diabetes had at least one mild hypoglycaemic episode (BG measurement 54-72 mg/dl) and 10.6% had at least one severe hypoglycaemic episode (BG < 54 mg/dl). In this study, 16,7% of patients had at least one mild hypoglycaemic episode. One patient (3.3% of all patients) had a severe hypoglycaemic episode according to the above definition. There was no severe hypoglycaemic episode according to the definition used for this study (< 40 mg/dl). In the RCT "RABBIT-2 surgery" (Umpierrez et al., 2011), rates of patients with hypoglycaemia were 3.8% and 11.5% for BG <40 mg/dl and BG <60 mg/dl, respectively. These numbers did not show a significant difference in the frequency of hypoglycaemic events compared to sliding scale insulin therapy. In conclusion, the number of hypoglycaemic events in this study was lower than in clinical practice and in a comparable and well performed clinical trial.

Blood glucose control: In this study, a satisfactory blood glucose control could be achieved. Mean daily blood glucose was 163 mg/dl in part 1 and 148 mg/dl in part 2 of the study. Guidelines recommend a target range of 100-140 mg/dl. In this study, only 3 % (in part 1) and 2 % (in part 2) of all blood glucose measurements were 300 mg/dl or higher. In the ward where the study was performed (endocrinology), before introduction of any intervention, a retrospective assessment was performed, which revealed mean blood glucose level of 175 mg/dl for routine care (Neubauer et al., 2013). Therefore it can safely be stated that blood glucose control was improved and the rate of hyperglycaemic events was not increased compared to standard care.

Adherence to decision support: Successful application of the GlucoTab system was generally high. More than 98 % of blood glucose measurements and basal insulin administrations and 93 % of bolus insulin administrations were performed with the GlucoTab. In exceptional cases, processing steps could not be performed due to software bugs which were documented and partly already fixed in part 2 of the study and partly scheduled for correction in a later release after the end of the study.

Generally the adherence with the GlucoTab process was very satisfying. The GlucoTab was used throughout the glucose management process, and the adherence by the healthcare professionals with the suggested insulin doses was very high.

Overall conclusion:

- In this study, a satisfactory blood glucose control could be achieved.
- The number of hypoglycaemic events in this study was lower than in clinical practice and lower than in a comparable and well performed clinical trial (Umpierrez et al., 2011)
- A very high adherence to the suggestions of decision support system can be noted.

In summary, it can be stated that the study showed that the GlucoTab system was efficient, provided good usability, and was safe for patients.