Diploma Thesis

Glycemic control with GlucoTab using insulin degludec in non-critically ill patients with type 2 diabetes at the general ward

submitted by

Lirie Bytyqi

to obtain the academic degree of

Doctor of Medicine (Dr^{in}. med. univ.)

at the

Medical University of Graz

conducted at the

Department of Internal Medicine -
Division of Endocrinology and Diabetology

under guidance of

Assoc. Prof.in Priv.-Doz.in Dr.in med. univ. Julia Mader
Priv.-Doz. Dr. med. univ. Dr. scient. med. Felix Aberer

Graz, 14th of July 2021

Statutory Declaration

I hereby declare that I have authored this diploma thesis fully on my own, that I have not used any other than the declared sources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Graz, 14th of July 2021 *Lirie Bytyqi eh*

Acknowledgements

During the writing process of this thesis, I have received much help and support from many sides, for which I am incredibly thankful.

Firstly, I would like to thank my supervisors Assoc. Prof.in Priv.-Doz.in Dr.in med. univ. Julia Mader, who always responds in record time and was incredibly helpful in creating this thesis, and Priv.-Doz. Dr. med. univ. Dr. scient. med. Felix Aberer for his guidance and help. Thank you both for your hard work.
Thank you to the team of the Division of Endocrinology and Diabetology for their outstanding work, too.

Huge thanks go out to my loved ones, the handful of special people in my life that make it worth living:

I don’t know where I would be today without my best friend Rike, who always seems to have the right words in every situation and never fails to make me laugh. You are golden. Thank you for everything you have done for me.

My friends Michelle and Melisa deserve a big thank you for always being there if I need someone to talk to. I can’t imagine what I would do without you.

Special thanks go out to my brother Kujtim, who in his infinite wisdom somehow always knows the answer to my questions. I’m so glad to have you as my little brother, no matter how annoying you sometimes are, but that is your job after all.

And last, but definitely not least, I would like to thank my parents for always supporting me in every way that they could, so I was able to focus on achieving my dreams, no matter how big.

You all make me a better, happier person and I love you.

Table of Content

Glossary and Abbreviations

%	Percent
©	Copyright
®	Registered trademark
°C	Degrees Celsius
ACE	Angiotensin Converting Enzyme
ADA	American Diabetes Association
ADE	Adverse Device Effect
AE	Adverse Event
BG	Blood Glucose
BMI	Body Mass Index
CE	Conformité Européenne (Certification that a product meets all legal requirements to be sold in the European Economic Area)
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
CT	Computed Tomography (scan)
DMP	Data Management Plan

dl	deciliter
DPP-4-inhibitor	Dipeptidyl-Peptidase-4- inhibitor
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
FPFV	First Patient First Visit
GCP	Good Clinical Practice
GLP-1	Glucagon-like Peptide 1
h	hours
HDL(-cholesterol)	High Density Lipoprotein
ICH-GCP	International Conference on Harmonization- Good Clinical Practice
ICU	Intensive Care Unit
i.v.	intravenous
kg	kilograms
LPLV	Last Patient Last Visit
mg	milligrams

mmHg	millimeter of mercury
mmol	millimole
MRI	Magnetic Resonance Imaging
NCT number	National Clinical Trial number
NPH- Insulin	Neutral Protamine Hagedorn- Insulin
OHA	Oral Antihyperglycemic Agents
oGTT	oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
PPAR-Ɣ	Peroxisome Proliferator-activated Receptor Gamma
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGLT-2	Sodium Dependent Glucose Transporter 2
U	Units
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

Table of Figures

List of Tables

Zusammenfassung

Einleitung: Eine gute Blutzuckereinstellung ist eng mit klinischen Outcomes bei Patienten mit Diabetes verknüpft. Mithilfe eines Systems zur Entscheidungsunterstützung (GlucoTab®) wurde in früheren Studien die Blutzuckereinstellung erleichtert. In dieser Studie wurde die Diabeteseinstellung unter Nutzung des GlucoTab®- Systems mit einem neuen Basalinsulinanalogon untersucht. (1–3)

Zielsetzung: Das Ziel dieser klinischen Studie war die Wirksamkeit, Sicherheit und Benutzerfreundlichkeit des GlucoTab®- Systems in Kombination mit dem ultra-langwirksamen Basalinsulin degludec und dem kurzwirksamen Insulin aspart bei stationären Patient*innen mit Diabetes mellitus Typ 2 zu untersuchen.

Methoden: GlucoTab® wurde für die Behandlung von 30 stationären nicht-intensivpflichtigen Patient*innen mit bekanntem Diabetes mellitus Typ 2 oder neu aufgetretener Hyperglykämie auf der Bettenstation der klinischen Abteilung für Endokrinologie und Diabetologie der Medizinischen Universität Graz eingesetzt. Das GlucoTab®- System wurde mit Insulin degludec (Tresiba®, ein ultra-langwirksames Basalinsulin) und Insulin aspart (NovoRapid®, ein kurzwirksames Bolusinsulin) betrieben. Blutzuckermessungen wurden mittels „Point of Care Testing“ vor Mahlzeiten und zur Schlafenszeit durchgeführt. Zudem wurde verblindetes kontinuierliches subkutanes Glukose-Monitoring (CGM) mithilfe des Abbott FreeStyle Libre Pro Flash Glucose Monitoring System angewandt.

Ergebnisse: 52,2 ± 10,2% (n=377) aller gemessenen Blutzuckerwerte (insgesamt 722) lagen im Zielbereich von 70 – 140 mg/dl. Die Rate an Hypoglykämien war gering, mit 1,25% der Messungen <70 mg/dl und 0,28% <54 mg/dl. Es kam zu keiner schweren Hypoglykämie. Die durch den Algorithmus vorgeschlagenen Insulindosen wurden in 93,6% der Fälle ab dem ersten Studientag eingehalten. Die Rate an Korrekturen durch die Benutzer*innen war ebenfalls gering, mit einer durchschnittlichen Korrektur von -0,8 ±1,7 Einheiten für Bolusinsulin und 0,0 ± 0,2 Einheiten für Basalinsulin.

Schlussfolgerung: Die Therapieunterstützung mithilfe des GlucoTab®- Systems mit Insulin degludec im Krankenhaus konnte sicher und effektiv erreicht werden.

Abstract

Introduction: Glycemic control is tightly linked to clinical outcomes in patients with diabetes. Using a clinical decision support system (GlucoTab®) improved glycemic control in previous studies, therefore we studied the effects of using GlucoTab® with a novel basal insulin analogue. (1–3)

Objective: The aim of this clinical trial was to investigate and analyze the clinical efficacy, safety, and usability of GlucoTab® for glycemic control, specifically in combination with the ultralong-acting basal insulin degludec and the rapid-acting insulin aspart in hospitalized patients with diabetes mellitus type 2.

Methods: GlucoTab® was used for diabetes management on 30 non-critically ill hospitalized patients at the Division of Endocrinology and Diabetology at the Department of Internal Medicine in Graz to investigate the efficacy of the system when used with insulin degludec. GlucoTab® uses an algorithm to support the management of patients with diabetes using insulin degludec (Tresiba®, an ultralong-acting basal insulin analogue) and insulin aspart (NovoRapid®, a rapid-acting insulin analogue). Blood glucose checks were performed pre-meal and at bedtime, as well as blinded continuous subcutaneous glucose monitoring (using the Abbott FreeStyle Libre Pro Flash Glucose Monitoring System) to better understand glycemic excursions over time.

Results: The blood glucose target range of 70 – 140 mg/dl was achieved with 52.2 ± 10.2% (n=377) of blood glucose measurements falling into that range from a total of 722 measurements. The rate of hypoglycemia was low, with only 1.25% of blood glucose measurements at <70 mg/dl, 0.28% <54 mg/dl and no severe hypoglycemic event. The adherence to the GlucoTab® suggestions was high (93.6% adherence since study start) and the number of dose corrections was low, with -0.8 ±1.7 U for bolus insulin and 0.0 ± 0.2 U for basal insulin.

Conclusion: Treatment support using the GlucoTab® system with Insulin Degludec in a hospital setting is safe and effective.

1 Introduction

Diabetes mellitus, or commonly known as *diabetes*, is a group of metabolic diseases that plays an increasingly important role in our current society. Most people have either heard of diabetes, know someone who suffers from it, or are even affected by the disease or its complications themselves. In Europe alone, there are around 60 million people affected by it, a number that makes up around 7% of the overall European population. (4)

As with a lot of other diseases, diabetes, even more so type 2 diabetes specifically, is highly linked to lifestyle factors and genetics. For patients with diabetes, the goal is to keep the blood glucose levels under control, as high blood glucose leads to an array of potential problems, specifically damaging the large and small blood vessels and nerves. This can lead to diabetic retinopathy, nephropathy, neuropathy, and many other complications further down the line. (5)

Careful management of patients with diabetes or hyperglycemia in the hospital is essential, seeing as these are risk factors for both mortality and adverse events during their hospital stay. Blood glucose management is not an easy task for the medical staff. Decision support systems that work via specific algorithms that provide suggestions for insulin dosing have started to gain traction, potentially aiding in overcoming insufficient in-hospital diabetes management. (6,7)

The goal of this study is to evaluate the efficacy of an already existing decision support system (GlucoTab®) with a new type of ultra-long-acting insulin (insulin degludec, Tresiba®). For this, a collective of 30 patients, both male and female, with type 2 diabetes or new-onset hyperglycemia that requires subcutaneous insulin therapy, regardless of the diagnosis that led to their hospital admission, have been included in this study.

But what exactly is diabetes and what factors contribute to this disease?

2 Diabetes mellitus type 2

As opposed to the lack of endogenous insulin secretion in diabetes mellitus type 1, type 2 diabetes is marked by a relative absence of the blood glucose-lowering hormone insulin, which usually happens as a combination of insulin resistance in the receptors in the body and an impaired secretion of insulin in the β-cells of the pancreas.

While the beta cells of the pancreas still produce insulin, the body is unable to respond adequately to it. Over time, the high demand for insulin can result in failure of secretion in the pancreas. Diabetes mellitus type 2 was more commonly found in older adults, giving it the name “adult-onset diabetes”. Nowadays, there is a rising number of affected children and younger adults, since the disease is linked with genetical factors, obesity, as well as an unbalanced diet and lack of movement. (5,8,9)

2.1 Epidemiology

As of 2019, the global number of people afflicted with both type 1 and type 2 diabetes was estimated to be around 463 million in people aged 20-79 years. This equals about 9.3% of all adults worldwide, most of which live in low- to middle-income countries. It is estimated that this number will further continue to rise over the years. (9)

Table 1: Global estimates and projections for diabetes (9)

At a glance	*2019*	*2030*	*2045*
Total world population	7.7 billion	8.6 billion	9.5 billion
Adult population (20-79 years)	5.0 billion	5.7 billion	6.4 billion
Diabetes (20-79 years)			
Global Prevalence	9.3%	10.2 %	10.9%
Number of people with diabetes	436 million	578.4 million	700.2 million
Number of deaths due to diabetes	4.2 million	-	-
Total health expenditures for diabetes	USD 760.3 billion	USD 824.7 billion	USD 845.0 billion

Hyperglycemia in pregnancy (20-49 years)			
Proportion of live births affected	15.8%	14.0%	13.3%
Number of live births affected	20.4 million	18.3 million	18.0 million
Impaired glucose tolerance (20-79 years)			
Global Prevalence	7.5%	8.0%	8.6%
Number of people with impaired glucose tolerance	373.9 million	453.8 million	548.4 million

Naturally, the numbers are higher in countries where people do not have easy access to healthcare or are unable to maintain to a healthy diet.
The latest numbers show that there are around 24 million adults with undiagnosed diabetes in Europe, worldwide this number reaches up to almost 232 million. (9) Europe has the second lowest prevalence compared to other International Diabetes Federation Regions, but there are still around 59.3 million people affected, which make up about 8.9% of the population. As for mortality, around 8.5% of all-cause mortality is attributed towards diabetes and its complications in people aged 20-79 years. (9)

2.2 Etiology and Pathophysiology

Type 2 diabetes is highly linked to obesity and genetic factors, making this a disease that is spreading rampantly, especially in industrialized countries. Overeating, lack of exercise, as well as the psychosocial environment all contribute to the development of type 2 diabetes. The increased amount of food intake results in an increased secretion of insulin, which in turn can cause insulin resistance in the peripheral cells. This means that the body needs to produce even more insulin for the cells to be able to absorb glucose, which can cause the pancreas to fail to respond to the demand of required insulin over time.
In a lot of patients, the insulin resistance starts years before the disease starts manifesting itself because it is masked by elevated insulin secretion. (4,8)
In the majority of cases patients develop type 2 diabetes on the basis of a metabolic syndrome, which is a combination of abdominal obesity and at least two of these following factors: high serum triglycerides, low serum HDL-cholesterol,

high blood pressure, and elevated blood glucose. This syndrome is arguably the biggest risk factor for diabetes, especially because it occurs at an increasingly younger age. (4,10)

A few pathophysiological processes happen in the body that make up type 2 diabetes, some of which are reversible especially in the early stages of the disease. With type 2 diabetes, the prandial secretion of insulin is dysfunctional, which results in hyperglycemia. As a contributing factor to this, the secretion of the blood glucose-raising hormone glucagon, which is produced in the α-cells of the pancreatic islets, is insufficiently suppressed despite high glucose levels. (10)
Periodically high levels of insulin cause the insulin receptors to lose sensitivity to it, which causes the body to produce even more insulin to compensate, creating a vicious circle. (8,10)
Another problem arises when the insulin-producing β-cells of the pancreas go into apoptosis, which again results in hyperglycemia. Coupled with insulin resistance and a reduced secretion and efficacy of incretins, which are hormones that regulate the postprandial release of insulin, the body fails to keep the blood glucose levels at a normal level. (10)

2.3 Clinical Manifestation

Type 2 diabetes starts off as a silent disease with symptoms that are not very obvious or impressive. While type 1 diabetes usually presents in younger people (usually between the ages of 15 to 25) with more fulminant symptoms, the progression of type 2 diabetes usually is quite slow and unremarkable.
Most patients are over the age of 40 years old and obese, a lot of the time the diagnosis is established at screenings performed during routine medical checkups. Often, symptoms are unspecific, ranging from fatigue and a decline in performance to the more classic polyuria, polydipsia, and weight loss. Some patients also suffer from pruritus, bacterial infections of the skin, paresthesia and pain in the legs, or loss of libido.

If the disease has been present for a longer period of time before the diagnosis is made, several secondary problems can present in the patient, the most common being polyneuropathy, peripheral arterial disease, or retinopathy. (8,10)

2.4 Complications

The reason why it is so important to keep blood glucose levels under control is that many complications can arise from diabetes. Some of them present acutely, while many happen slowly over time, but they all play a big role in disease management.

2.4.1 Acute complications

One of the most serious acute complications in patients is diabetic coma, a metabolic derailment that is considered a medical emergency.
The reason why this happens is usually infection and/or inadequate insulin therapy. There are two sub-forms of diabetes-associated coma: Ketoacidotic coma, commonly associated with type 1 diabetes, and hyperosmolar coma, which occurs in patients with type 2 diabetes. (8)
Ketoacidotic coma develops over a shorter period, usually over 24 hours. Symptoms like vomiting or nausea often occur, as well as exsiccosis and tachycardia. The complete lack of insulin as well as the secretion of counterregulatory hormones leads to gluconeogenesis, glycogenolysis, and an increased production of ketone bodies through lipolysis in the liver. In severe cases, patients can develop Kussmaul respiration (deep, rapid, labored breathing) and the typical fruity fetor on their breath. (8,11)
In case of ketoacidotic coma, the removal of ketone bodies and the substitution of insulin, fluids and electrolytes are to be initiated immediately. (8)
Contrary to ketoacidotic coma, hyperosmolar coma develops more slowly, over the course of several days or even weeks, and dehydration is mainly at the forefront. Blood glucose levels of 1000 mg/dl or higher are common, as most of the time, this is a result of inadequate treatment or undiagnosed type 2 diabetes. (12)

Due to the continued production of insulin, excessive lipolysis and the production of ketone bodies is thwarted. Patients often present with extreme exsiccosis and typical symptoms of diabetes like polyuria and polydipsia. This happens because of hyperosmolarity that is caused by elevated blood glucose. In turn, the kidneys' transport limits for glucose are exceeded, meaning that the excess glucose has to be eliminated via the urine. This results in osmotic diuresis with loss of water and electrolytes. (13)

Some patients with severe hyperglycemia suffer from neurological effects and even seizures, the final stage being the name-giving comatose stadium. Mortality for diabetic coma lies between 5-15%, although only around 1% of patients with type 2 diabetes experience hyperosmolar coma. (8,12,13)

Treatment for this complication consists mostly of administration of fluids, balancing out electrolytes and gradual blood glucose lowering via insulin, as well as patient monitoring. It is important to note that the replenishment of fluids should be done gradually, as to prevent a quick change in osmolarity. This could potentially lead to an osmotic gradient between extracellular and subarachnoid space, resulting in brain edema. Therefore, as a rule for diabetic coma, blood glucose should not be lowered by more than 50% in 4-8 hours. (8,12)

2.4.2 Chronic complications

Vascular complications make up the biggest part of diabetes mortality, with around 70-80% of patients with diabetes succumbing to problems with the large and small blood vessels, which affect a multitude of organs.

Both macro- and microangiopathy can become a big problem if a patient is not well controlled in their blood glucose levels, with microangiopathy being specifically associated with diabetes. The risks for stroke, myocardial infarction, and peripheral arterial disease are increased in patients with diabetes mellitus, even more so if the patients also suffer from further comorbidities like metabolic syndrome contributing to detrimental outcomes. (8,10)

2.4.2.1 Macroangiopathy

With the larger blood vessels also being affected, coronary heart disease, ischemic stroke, and peripheral arterial disease are common in patients with diabetes. “Silent” myocardial infarctions occur more often in these patients, which is why it is important to do regular electrocardiograms (ECGs) and checkups. Around 75% of patients with diabetes die from cardiovascular complications, although it is to be noted that diabetes and cardiovascular disease go hand in hand. (8,10)

2.4.2.2 Microangiopathy

This process of non-enzymatic glycosylation of proteins (hemoglobin, serum proteins, basal membranes) occurs because of chronic hyperglycemia, which changes the capillary basal membranes of the vessels. This results in dysfunctional oxygen transportation and a change in blood flow.
Hypertension and smoking further negatively influence this process. (8,13)

2.4.2.2.1 Diabetic retinopathy

Diabetic retinopathy describes changes in the retina of the eye caused by angiogenic growth factors. Risk factors include chronic hyperglycemia, as well as hormonal changes (in puberty or pregnancy), hypertension, and hyperlipidemia. Rapid lowering of the HbA_{1c} levels (start of intensive insulin therapy or a switch from oral to insulin therapy) is another risk factor of early worsening of diabetic retinopathy. (4,10)
This is most likely due to high doses of insulin acting synergistically with vascular endothelial growth factor (VEGF), a protein expressed by ischemic retina that spurs on blood vessel growth. Therefore, vascular proliferation is triggered, which worsens diabetic retinopathy in patients with pre-existing retinal abnormality. (14)
This form of microvascular long-term complication correlates with the duration of diabetes and metabolic control. Because of the long latency period where type 2 diabetes remains undiagnosed, complications like diabetic retinopathy have

already started when the disease starts manifesting itself. Diabetic retinopathy, other than glaucoma, is the most common reason for non-traumatic blindness in adults in industrialized countries. It is also the earliest symptom of microangiopathy. (8,10,13,15)
Every % of HbA_{1c} that is lowered in a patient results in 30-40% lower risk of developing retinopathy. (16)
Around one third of all type 2 patients show signs of retinopathy at the time of the diabetes diagnosis, and for many, it can develop over the course of the disease, which is why regular ophthalmological checkups are recommended. (4,10)

2.4.2.2.2 Diabetic neuropathy

The impairment of nerve tissue is dependent on disease duration, patient age, nicotine abuse, as well as metabolic adjustment, and several other risk factors. It is still unclear as to what exactly happens, but diabetic neuropathy primarily affects peripheral sensibility, the vegetative system, as well as reflexes. (10,13,17)
Around 50% of patients with diabetes show typical signs of polyneuropathy, most of which include somatosensory disorder, numbness, reduced perception of vibration, neuropathic pain, and changes in the skin (like discoloration, dryness, loss of hair, and sweat secretion). (4,17)
Around 80% of cases are classified as peripheral sensorimotor polyneuropathy, while autonomic neuropathy, which affects the vegetative nervous system, makes up the second-largest group of neuropathic disorders. The latter can cause arrhythmia and ventricular fibrillation, which can lead to sudden cardiac death. (10)
Furthermore, diabetic neuropathy often leads to diabetic foot syndrome, in which local traumata to the feet (ill-fitting shoes, wrong/ lack of podiatric care, lack of hygiene) can become infected and ulcerate. This is worsened by the fact that wound healing is impaired in patients with diabetes, so the ulcers heal slower. In the worst-case scenario, amputation can become necessary. Diabetic foot syndrome is the most common chronic complication of diabetes in patients. (8,10,17)

2.4.2.2.3 Diabetic nephropathy

Another potential complication in patients with insufficiently controlled diabetes is diabetic nephropathy, which has become the most common reason for hemodialysis and the leading cause of chronic kidney disease. About one fourth of all dialysis patients suffer from diabetic nephropathy, which comes with a high mortality rate of 23% survival over a span of 5 years. (8,10)
Around 10% of patients with type 2 diabetes develop this complication, which can manifest itself as proteinuria (specifically microalbuminuria in the early stages), hypertension, and a decreased estimated glomerular filtration rate (eGFR). (8,10)
The reason for this kidney disease is the development of glomerular lesions, which includes diffuse and nodular mesangial expansion, as well as the thickening of the glomerular basal membrane. In later stages, diffuse nodular glomerulosclerosis can occur, which are known as Kimmelstiel-Wilson nodules. In many cases, this is combined with arteriosclerotic changes to the blood vessels, which add to the nephropathy. (8,18)
As with most of the other potential complications of diabetes, this, too, can be controlled with lifestyle interventions, keeping the blood glucose levels under control, as well as optimization of blood pressure. (19)
The sooner therapy with angiotensin-converting-enzyme (ACE) -inhibitors in (borderline) hypertonic patients begins, the more progression of diabetic nephropathy towards terminal kidney failure and dialysis will be prevented. It also lowers cardiovascular complications and mortality in total. (10,19)

2.5 Diagnostic work ups

Taking a patient's history is essential to get closer to a working hypothesis and a potential diagnosis of any disease, especially one that is so heavily dependent on lifestyle factors and genetics. In patients who are likely to develop or suffer from type 2 diabetes, it is important to ask about the most common symptoms like polyuria, polydipsia, and weight loss. Family history, previous pregnancies and complications of those as well as potential symptoms of complications of diabetes

can also lead one towards a diagnosis. To solidify this, there are several tests that can rule out or establish the diagnosis of diabetes mellitus. (8)

2.5.1 Blood glucose management

The World Health Organization (WHO) and the American Diabetes Association (ADA) define diabetes as chronic hyperglycemia, which is marked by a fasting blood glucose level of 126 mg/dl or higher. This is measured after the patient has been fasting for at least 8 hours. (10,20)
If the blood glucose level exceeds 200 mg/dl at a random, non-fasting measurement in patient with symptoms of diabetes, the diagnosis can be established. It is important to repeat these tests to rule out laboratory mistakes. (Table 2) (8,10)

Table 2: Criteria for the diagnosis of diabetes (20)

Fasting blood glucose ≥126 mg/dl
OR
2-h-blood glucose ≥200 mg/dl during oGTT
OR
HbA_{1c} ≥6.5% (48 mmol/mol)
OR
In a patient with classic symptoms of hyperglycemia or a hyperglycemic crisis: a random blood glucose ≥200 mg/dl

2.5.2 HbA_{1c}

Another valuable method in diagnosing diabetes in a patient is the HbA_{1c} level in the blood. HbA_{1c} is a form of glycated hemoglobin that forms in the presence of glucose. Naturally, the more glucose is present, the more hemoglobin is glycated, which means higher levels of HbA_{1c}. It generally gives information about the average blood glucose levels in the last 8-12 weeks. In patients without diabetes,

the normal levels of HbA_{1c} are 5.7% (38.8 mmol/mol) or lower. Diabetes is diagnosed from a level of 6.5% (47.5 mmol/mol) or higher. (4,8,10)
Levels ranging from 5.7% to 6.5% are categorized as a higher risk for diabetes, which is why additional testing for fasting blood glucose and an oral glucose tolerance test (oGTT) are recommended. (21)
HbA_{1c} levels can be falsely elevated in patients suffering from advanced kidney disease, chronic alcohol abuse, hyperlipoproteinemia, or in the latter stages of pregnancy. They can also be falsely lower than they really are after blood transfusions or in patients with shortened erythrocyte life span because of hemolysis or hemoglobinopathy. In the first half of pregnancy, the levels can also be lower than expected. (10,20)
It is a more convenient form of diagnostics because it is less dependent on the patient and fasting, while also being less sensitive to potential value-changing factors like stress, illness, or diet changes. On the other hand, there are many other factors mentioned above that can falsely alter the levels of HbA_{1c} in the blood. (20,21)

2.5.3 Oral Glucose Tolerance Test

An oral glucose tolerance test (oGTT) can be scheduled if the fasting glucose levels are abnormal, when certain risk factors are present, including obesity or polycystic ovary syndrome (PCOS), or in patients with suspected gestational diabetes. For the test, the fasting patient must ingest a load of 75g of glucose orally at once. The blood glucose is measured at the beginning of the test, as well as 2h later. Blood glucose levels of 200mg/dl or higher after 2 hours would be classified as pathologic. (8,10)

2.5.4 Other Tests

There are other clinical tests that can rule out diabetes or help to distinguish between type 1 and type 2, although generally they are not as important or as significant as the aforementioned ones.
Glucose levels can be measured in the urine via test strips, although this has lost importance since blood glucose measurements have become very simple, fast, and accessible.
Under normal circumstances, there should be little to no glucose in the urine, because it gets reabsorbed by the kidneys. When blood glucose levels surpass the renal threshold of 180 mg/dl, glucose is expelled through the urine. This highly depends on whether the kidneys are affected by the disease or are dysfunctional for other reasons. Therefore, the lack of glucose in the urine cannot rule out diabetes mellitus. (8,10)
The level of C-peptide, which is a marker for active insulin secretion, can also be measured in the blood. In patients with manifest type 1 diabetes, C-peptide is nearly untraceable, because the pancreas does not produce insulin.
Contrary to that, in type 2 diabetes C-peptide levels are usually above the normal range. With longer disease duration and declining beta-cell function they can be normal or even below the normal range. (8,22)

2.6 Treatment

One relevant goal in the treatment of patients with type 2 diabetes is to establish good glycemic control (HbA_{1c} <53-58 mmol/mol) and prevent potential future complications of the disease, as well as dealing with manifest complications. One of the main issues and risk factors is obesity, which means that measures to keep that under control are one of the corner stones of diabetes treatment. (23,24)
Treatment goals however are largely dependent on patient age and comorbidities. The older a patient is and the more and severe comorbidities they have, the less stringent glycemic control is required.

2.6.1 Lifestyle Adjustment and patient education

As type 2 diabetes is a chronic disease and a result of western lifestyle, diabetes education and measures to adjust lifestyle are essential.
On top of a regulated diet, physical activity is a big part of diabetes treatment. A medium to high intensity workout of 150 minutes per week with additional muscle strengthening would be ideal to influence a patient's health positively, although for most of them, that is quite hard to achieve. Along with improving insulin resistance and secretion, it lowers cardiovascular risk. (25)
A key factor in compliance is patient education, which includes providing information about the condition in words that laypeople can understand, as well as giving reasons for why the lifestyle changes are necessary and must be kept up long-term. (8)

2.6.2 Pharmacological Treatment

As with any other disease, it is crucial to customize the therapy to each patient, depending on individual needs and preexisting conditions.
The main goals for pharmacological treatment are to prevent complications of hyperglycemia, to reduce or eliminate symptoms as well as to preserve the quality of life. The goal is to keep the HbA_{1c}-levels below 53-58 mmol/mol (7.0-7.5%) to prevent macro- and microvascular complications. In older, multimorbid patients, a HbA_{1c} of 64 mmol/mol, (8%) or higher might be acceptable, depending on comorbidities, life expectancy and risk of hypoglycemia. (26,27)

2.6.2.1 Oral antihyperglycemic agents

The first line oral antihyperglycemic agent (OHA) for the treatment of type 2 diabetes is metformin because it is highly efficient in decreasing HbA_{1c}, affordable, safe, and has shown a preferable outcome in cardiovascular events. Metformin prevents gluconeogenesis, thus improving peripheral insulin sensitivity. (26,27)

In many patients, metformin monotherapy, along with the previously mentioned lifestyle changes, enables sufficient glycemic control. (26)
Combination therapy usually becomes necessary after a few years because diabetes is a progressive disease. It is advised to add other agents to metformin step-by-step as needed, until sufficient glycemic control is achieved. (10,27,28)
Depending on the comorbidities of patients, there are a number of different OHAs that can be used:
The sodium glucose linked transporter (SGLT2) in the kidneys is responsible for the majority of the renal glucose reabsorption. These transporters are blocked by SGLT2- inhibitors, a commonly used OHA, which cause controlled glucosuria and thus lower blood glucose. Furthermore, they cause a decrease in HbA_{1c} and blood pressure, and they lower the risk of cardiovascular events. They are associated with weight loss (-2-3kg). On the other hand, SGLT-2 inhibitors can be the reason for frequent urogenital infections. (26)
Glucagon-like Peptide-1 (GLP-1) agonists mimic the effects of the natural protein in the body, which causes the glucose-dependent pancreatic insulin production to increase. They also delay gastric emptying, inhibit the release of glucagon, and cause a feeling of satiation. They differ from OHA because they are injected subcutaneously, similar to insulin. Depending on the substance, administration is required from daily to once a week. They, too, can cause weight loss and a reduction of cardiovascular risk, although gastrointestinal side effects like nausea and vomiting can occur. (26)
Dipeptidyl-Peptidase-IV (DPP-4) inhibitors prevent natural GLP-1 from breaking down and thus have similar effects as GLP-1 agonists. None of the previously mentioned agents cause hypoglycemia. DPP-4-inhibitors do not have a positive effect on body weight. They often are used in combination with metformin or other OHAs because of their low effect as monotherapy. (26)
Sulfonylurea reduces HbA1c by up to 1.5% through stimulation of pancreatic insulin secretion. However, they are putting patients at an increased risk of hypoglycemia as they increase insulin secretion from the islet cells irrespective of the patient’s current blood glucose. Patients are also at risk of gaining weight when therapy with sulfonylurea is initiated due to the increased endogenous insulin levels and potentially snacking against impending hypoglycemia. (26,29)
Thiazolidinediones are agonists of peroxisome proliferator-activated

receptor gamma (PPAR-Y), which they bind to in order to improve insulin sensitivity. Unwanted side effects of this drug include weight gain and a higher risk of edema because of fluid retention. Therefore, heart failure is a big contraindication for the use of thiazolidinedione, as well as liver dysfunction. Bone fractures can occur more frequently in menopausal women. (26,29,30)
It should be noted that thiazolidinedione and sulfonylurea are not state of the art OHA therapy anymore.
No matter the choice of OHA, it is very important to take each patient and their needs into consideration when prescribing drugs.
Every non-insulin agent that is added to metformin lowers the HbA_{1c} by approximately 0.7-1%. Every 3-6 months, glycemic control measured by HbA1c shall be reevaluated and if the HbA_{1c}- target has not been achieved, antihyperglycemic therapy needs to be adjusted. (27)
In patients with blood glucose levels higher than 300 mg/dl or with a HbA_{1c} of over 10% (86 mmol/mol), or if the patient shows symptoms of hyperglycemia, it is advisable to initiate insulin therapy. (27)

2.6.2.2 Insulin

Insulin is the only hormone in the body that can lower blood glucose. It is crucial in the therapy of diabetes or hyperglycemia, especially since as the disease progresses, many patients have to add insulin therapy to their existing therapy regimen. Usually, the indication for this is inadequate glycemic control with OHAs and lifestyle modifications. Another factor would be intolerance or contraindications for OHAs. Insulin therapy might also be initiated intermittently around surgeries or during acute medical conditions. (28)
It is important to train and educate patients when it comes to insulin treatment. Self-monitoring of blood glucose, diet, hypoglycemia, and the correct administration are essential aspects that the patient should be taught about. (27)
Insulin is administered subcutaneously, preferably into the abdominal area, the thigh, or the upper arm. To reduce the risk of lipodystrophy, injection sites should be switched regularly (see 2.6.3). (31)

There are three main types of insulin that are available for the treatment of diabetes mellitus: rapid-acting insulin, basal insulin, and premixed insulin. Insulin can be injected via insulin pens (most common form), insulin syringes or insulin pumps (rapid-acting insulin only). (10,28)
The insulins used in this study will be discussed in more detail in *chapter 3.1.2* and *3.1.3*.

2.6.2.2.1 Rapid-acting insulins

Rapid-acting insulins are administered at mealtimes to cover the blood glucose peaks that follow.
These agents take effect around 5-15 minutes after application, peak in about 30-90 minutes post-injection, and last for around 3-5 hours, depending on what specific compound is used. They are well suited to be used for lowering (post-) prandial blood glucose spikes due to their quick onset and short duration. (32,33)
One of two categories for these types of agents is regular insulin, which is becoming more and more obsolete with the availability of modern rapid acting insulin analogues as they are relatively slow in the on- and offset of insulin action. That is why rapid-acting insulin analogues are more commonly used nowadays. They include insulin aspart (NovoRapid®, Novo Nordisk, Denmark), insulin glulisine (Apidra®, Sanofi-Aventis, France), and insulin lispro (Humalog®, Eli-Lilly, USA). (10)
A subgroup includes ultra-rapid-acting insulins, which as the name suggests, have a shorter onset of action than rapid-acting insulins.
They are meant to mimic the fast onset of action of physiological insulin secretion with this faster onset time, thus reducing postprandial glucose excursions. They are absorbed quicker subcutaneously to achieve better control of postprandial plasma glucose levels.
This is most valuable to patients with reoccurring postprandial hyperglycemic episodes. Insulin lispro (Lyumjev®, Eli-Lilly, USA) and insulin aspart (Fiasp®, Novo Nordisk, Denmark) are part of this group. (34,35)

2.6.2.2.2 Basal insulins

2.6.2.2.2.1 Intermediate-acting basal insulins

By combining Insulin with protamine or zinc, or by changing the structure or concentration of the hormone, the duration of its effect can be prolonged. They can be administered into the subcutaneous adipose tissue of the abdomen or thigh. The goal for these was to flatten the response curve, as well as to increase the time of effectiveness, which reduces the number of injections and broadens the time frame in which they should be administered. (10,28)
NPH-insulin (Neutral Protamine Hagedorn insulin) is one of these agents. It has to be brought into suspension before application, which is why it can cause more hyper- and hypoglycemia than other drugs. The effect starts at around 60 minutes after administration, lasting from 9 – 18 hours. Usually, two injections per day are required to cover a 24-hour period. (10)

2.6.2.2.2.2 Long-acting basal insulin analogues

Long- and ultra-long-acting basal insulins are another form of insulin analogues that stem from changes in structure, amino-acid sequence, or concentration, which makes them last around 20 – 28 hours. They are meant to recreate the constant levels of insulin in between meals and at nighttime, while the long acting time lowers the number of injections needed for the patient. Insulin glargine (Lantus®, Sanofi, France) and insulin detemir (Levemir®, Novo Nordisk, Denmark) are both long-acting insulin analogues. While they are quite different on a molecular level, they share a lot of improved pharmacodynamic characteristics. They both have a reduced variability compared to NPH insulin and a reduced risk of nocturnal hypoglycemia. (10,33,36)

2.6.2.2.2.3 Ultra-long-acting basal insulin analogues

These insulin analogues have an even longer duration of insulin action than all the other previously mentioned ones. Insulin degludec (Tresiba®, Novo Nordisk, Denmark) and a higher concentrated insulin glargine (Toujeo®, Sanofi, France)

have been developed to last longer and to further simplify diabetes therapy by requiring fewer injections. Insulin degludec has a half-life of >25 hours, which is around twice the time of the long-acting insulin glargine that comes up to around 12 hours half-life. The reduced risk of nocturnal hypoglycemia, the longer duration of insulin action that is similar to physiological basal insulin, as well as the flexibility of injection times are all factors that contribute to these analogues being favored. (33,37)

2.6.2.2.3 Premixed insulins

This form of insulin covers both basal and prandial insulin demand and is usually administered 2-3 times a day.
Premixed insulins are best suited for elderly patients or patients for whom a simple regimen with a reduced number of injections per day is recommended, as well as patients with a set schedule who consume meals regularly. The effect of premixed analogues is closer to the physiological response, which is why it can be administered directly before or after a meal, whereas premixed human insulin has to be administered 30 minutes in advance. (10,28,33)
NovoMix® and IDegAsp (Ryzodeg®, Novo Nordisk, Denmark) are examples of premixed insulins. NovoMix contains insulin aspart and insulin aspart protamine, which is longer acting. It is available as NovoMix 30 (30% insulin aspart, 70% insulin aspart protamine), NovoMix 50 (50%/50% mix of both agents) and NovoMix 70 (70% insulin aspart and 30% insulin aspart protamine). NovoMix 30 may be used in children over the age of 10, while the other two may only be used in adults. IDegAsp is a newer agent, a combination of the ultra-long-acting insulin degludec and the rapid-acting insulin aspart. It is suitable for patients over the age of 2 years. (38,39)

Table 3: Properties of Insulin Preparations from (11)

Preparation	Time of Action		
	Onset, h	**Peak, h**	**Effective duration, h**
Rapid-acting			
Aspart	<0.25	0.5-1.5	2-4
Glulisine	<0.25	0.5-1.5	2-4
Lispro	<0.25	0.5-1.5	2-4
Regular	0.5-1.0	2-3	3-6
Long-acting			
Degludec	1-9	-	42
Detemir	1-4	-	12-24
Glargine	2-4	-	20-24
NPH	2-4	4-10	10-16
Examples of insulin combinations			
70/30-70% protamine aspart, 30% aspart	<0.25	Dual	15-18
50/50-50% protamine lispro, 50% lispro	<0.25	Dual	10-16
70/30-70% NPH, 30% regular insulin	0.5-1	Dual	10-16

2.6.3 Complications of insulin treatment

2.6.3.1 Hypoglycemia

One of the most common side effects of insulin therapy is hypoglycemia, which is graded into three levels according to the ADA. Level 1 of hypoglycemia is defined by a blood glucose level of <70 mg/dl but ≥54 mg/dl. The threshold for neuroendocrine responses in people without diabetes is set at <70 mg/dl, although many people with diabetes are unaware of symptoms of hypoglycemia or do not have any at all. Level 2 of hypoglycemia is defined as a blood glucose measurement of <54 mg/dl, which is when neuroglycopenic symptoms manifest in most patients. Immediate action is required to counteract the hypoglycemia and the patient's antihyperglycemic therapy should be investigated to avoid such

events in the future. In some cases, patients fail to recognize symptoms of hypoglycemia, which most likely is caused by hypoglycemia unawareness, leading them to experience hypoglycemic events more frequently.
Level 3 of hypoglycemia is considered a severe event with altered mental and/or physical functions. At this stage, a patient requires help from a third person to deal with the symptoms and treatment. (24)
Hypoglycemia can occur for a myriad of reasons, whether it be a change in diet or missed meals, excessive physical activity, stress, and acute illness. An administration of excess insulin or newly started blood glucose-lowering medication can also play a role, though they occur less frequently. (40–42)
Some risk factors for it that are often prevalent in hospitalized patients include older age, kidney failure, previous insulin therapy, change in nutritional intake like fasting periods before surgery, interruption of glucose monitoring, and the failure to adjust therapy. (43)
Typical symptoms include palpitations, sweating, tremor, and hunger. Often, patients have difficulty thinking or experience confusion during hypoglycemic events, in more severe cases it can even lead to seizures, coma, or death. Poor glycemic control can lead to postoperative infections and even kidney injury, with hypoglycemia being associated with increased morbidity and mortality in hospitalized patients. (40–44)
Preventing hypoglycemic events is a priority in diabetes therapy, which is why it is important to take risk factors into account. Clinical decision support tools can further facilitate glycemic control while raising the target levels of blood glucose for patients at risk for hypoglycemia can also help in prevention. Furthermore, less intense treatment with glucose-lowering therapy also reduces hypoglycemic events. (40,41)

2.6.3.2 Lipodystrophy

Another potential risk of insulin therapy is lipodystrophy at the injection sites, which is the most common cutaneous complication of insulin injection. This can result from inappropriate needle length for the subcutaneous tissue depth, a lack of rotation of injection sites, or from not changing needles between injections. Often,

patients are not educated well enough on proper injection techniques, which is why this is such a common complication. Lipodystrophy occurs in around 50% of patients and can manifest itself as lipohypertrophy or as lipoatrophy. The former presents itself as a thickened, “rubbery” lesion in the subcutaneous tissue, while the latter is a scarring lesion as the result of fatty tissue atrophy. The exact etiology is still unclear. The problem with lipodystrophy is that it impairs the absorption of insulin by up to 25%, which can result in poor glycemic control. Patients tend to favor areas with lipodystrophy, mostly because injections into those areas are less painful or because of habit, which is why patient education is important. Properly rotating injection sites, using larger injection areas, and reusing needles less frequently are good approaches to avoid the development of lipodystrophy. (31,45)

2.7 Inpatient diabetes management

The number of people with diabetes is globally rising every year, so naturally, the number of inpatients with hyperglycemia is rising, too. This is also because acute infection, high levels of stress, or surgeries can all result in elevated blood glucose as a form of imbalance in glucose metabolism. Hormonal, metabolic, and inflammatory dysregulation are key factors in the management of hospitalized patients, with the prevalence of hyperglycemia in these patients stepping in at around 20-40%, even up to 70% in intensive care units. (7)
It is essential to keep blood glucose levels in adequate control since high blood glucose is a risk factor for both mortality and adverse effects like infections or postoperative complications. Every 40 mg/dl over the level of normoglycemia (<110 mg/dl) raises the risk for postoperative infections by 30%. (43)
Patients with hyperglycemia increase treatment cost and are at risk of having extended hospital stays. Acute and long-term complications can also factor into this, seeing as hyperglycemic coma or iatrogenic hypoglycemia, as well as micro- and macrovascular complications, can all be reasons for hospital admissions. (6,7,43)

Studies have shown that it is most beneficial for the patients to keep the blood glucose levels between 140 – 180 mg/dl and to start administering insulin in case of prolonged hyperglycemia during the hospital stay. (6,7)
A test to check HbA_{1c} levels should be performed in patients with preexisting diabetes or new-onset hyperglycemia unless a test result within the last 3 months is available. (6)
To avoid hypo- or hyperglycemic periods, blood glucose should be measured much more frequently than in the home setting. The glycemic targets strongly depend on the patient and factors like their comorbidities, the reason for their hospitalization, their weight, and the medication they take. Insulin therapy in hospitalized patients is often quite a challenge, especially for medical staff. It requires frequent blood glucose measurements, adequate insulin dose calculation, and correct timing of the injection in relation to meals. (7)
As intravenous (i.v.) insulin is easier to control due to its short half-life (<15 minutes) it is the preferred way to control blood glucose levels in critically ill patients treated at intensive care units (ICU). Critically ill patients often require an array of different medications and monitoring, which makes the flexibility of i.v. insulin a necessity, although the downside of this is the high demand for nursing support. As for general non-critically ill patients, subcutaneous injection of basal insulin coupled with prandial insulin at mealtimes is the most effective and safe treatment. In patients with regular adequate oral intake, this basal-bolus insulin therapy is preferred, seeing as it improves glycemic control and reduces the number of postoperative complications, especially wound infections. In patients with reduced or lack of oral intake due to acute illness, lack of appetite, medical procedures, or surgical interventions, the preferred treatment is basal insulin to cover basal insulin requirements with rapid-acting insulin administered as correction doses or with meals. In general, insulin therapy is favored in a hospital setting since there is only limited data available on oral antihyperglycemic agents and their safety and efficacy. Insulin however does not have drug interactions, which makes it safe to use in patients with preexisting medication or with medications rapidly being added, changed, or discontinued. (43,44)
One big challenge remains hypoglycemia and the management of it. It occurs in around 30% of hospitalized patients and is a common complication of insulin therapy. Insulin therapy requires individual customization, monitoring of the

patient, and dose titration, which is why hyper- and hypoglycemia are fairly common in inpatients. (43,46)
Until recently, blood glucose monitoring has been manual labor, with data written into patient charts to keep track of everything. Nowadays, electronic systems have been introduced to hospital life. This simplifies diabetes therapy and prevents mistakes. In Europe, GlucoTab® is the software used specifically for this reason (see 3.1.1). (4)

3 Clinical Study

This study was conducted to evaluate the efficacy of the GlucoTab® system in combination with a new ultra-long-acting insulin degludec in non-critically ill patients with type 2 diabetes or newly diagnosed hyperglycemia requiring subcutaneous insulin therapy. A log file was created to keep track of the insulin pens that were used, as well as the patients they were used on, the date and time. A signature of the person allocating the pen to the patient was required.

3.1 Material

3.1.1 Product of investigation GlucoTab®

GlucoTab® is a diabetes management system with a decision support component for subcutaneous insulin therapy in inpatients with type 2 diabetes. It is a mobile computerized system that provides help in two major categories: for one, it offers automated workflow support that assists healthcare professionals in treatment workflow organization. This includes a display for open tasks, providing visual proof of blood glucose levels and documentation thereof, as well as of nutrition and insulin doses. The other main objective of the GlucoTab® system is to provide two standardized recommendations for the total daily insulin dose, which are based on a basal-bolus insulin titration protocol that the leading physician has prescribed. This works via a basal-bolus insulin dosing algorithm that is set to achieve fasting blood glucose values of less than 140 mg/dl, which are determined by age, body weight, and renal function. (1,2)

GlucoTab® also suggests doses for individual insulin administrations before meals, at bedtime, and immediately after blood glucose measurements, if required. After these suggestions are confirmed, authorized personnel administer the insulin subcutaneously. The system also comes with safety features that consider if the patient ate anything, the amount of bolus insulin that is still active in the patient's system from a previous dose ("insulin on-board"), as well as a reduction of bolus insulin if the previous administration of it was delayed. However, healthcare professionals do have the final say in treatment and can override the system anytime. (1)
The algorithm for the dose has been tested in a clinical trial ClinDiab-02 (NCT01407289), a modification of it has also been tested in the ClinDiab-03 trial (NCT01766752), as well as the safety, efficacy, and usability of the GlucoTab® system in type 2 diabetes patients in the ClinDiab-04 trial (NCT01932775).
As for now, the only basal insulins that can be used with GlucoTab® are insulin glargine and insulin glargine U300. With this study, the main objective was to use insulin degludec as the basal insulin, which has not been approved for dose titration with GlucoTab® yet. Because of the qualities that insulin degludec has shown in extensive clinical studies (longer duration of action with less variability in plasma insulin exposure, as well as fewer hypoglycemic episodes), it could improve glycemic management even further. (47,48)

3.1.2 Insulin degludec (Tresiba®)

Insulin degludec is an analogue of ultra-long-acting human insulin which is used to establish glycemic control diabetes mellitus in patients 1 year of age or older. It should be injected once a day at any time of day, the time of the day thereafter should remain approximately the same (± 4 hours). Dose adjustments may be needed depending on physical activity, changes in meal intake, changes in renal/hepatic functions, or in phases of acute illness. (49)
Insulin degludec provides continuous and stable insulin replacement with a flat curve with only one injection over a period of 24 hours. This is possible due to prolonged and stable insulin absorption in the body, which results in an ultra-long lasting and flat glucose-lowering profile. (50)

The half-life of insulin degludec exceeds 25h as compared to around 12h for insulin glargine, reaching a steady state within 3 days of administration. The duration of action exceeds 42h, making it an ultra-long-acting basal insulin, on top of being more stable in glucose-lowering effect than insulin glargine. (37)
The reason why Insulin degludec was chosen to be used in this study is that compared to insulin glargine U100, which was previously used with the GlucoTab® system, it showed a reduced rate of symptomatic hypoglycemic events. (51)
Compared to insulin glargine U300, the rates of hypoglycemia were not significantly lower with insulin degludec U200, however, there was a lower rate of nocturnal symptomatic hypoglycemia, as well as general severe hypoglycemia with degludec U200 vs. glargine U300. (52)
Therefore, insulin degludec may be an alternative for patients who are prone to hypoglycemia using insulin glargine. (53)
This is a relevant reason to use insulin degludec within this study since severe hypoglycemia is linked to higher subsequent all-cause mortality. (42,54)

3.1.3 Insulin aspart (NovoRapid®)

Insulin aspart is a rapid-acting insulin analogue. It is used for the treatment of diabetes mellitus in adults, adolescents, and children over the age of one. It is usually used in combination with an intermediate- or long-acting insulin, while measuring the blood glucose levels frequently to adjust the dose of insulin to assure optimal glycemic control. Because of the relatively fast onset of insulin action of insulin aspart, it should be injected right before having a meal. Additionally, it can be used to correct elevated blood glucose levels throughout the day whenever required. (55)

3.1.4 Non-investigational medical devices

3.1.4.1 FreeStyle Libre Pro Flash Glucose Monitoring System

The FreeStyle Libre Pro Flash Glucose Monitoring System by Abbott Diabetes Care (California, USA) was the non-investigational product used for blinded continuous glucose monitoring (CGM). It is CE-certified and marketed and registered for the use of measuring and recording glucose values in patients with diabetes or hyperglycemia. The sensor of the FreeStyle Libre Pro was inserted at the beginning of the treatment period, changed after a maximum of 14 days, and removed and reinserted if patients required medical imaging (X-rays, CTs or MRIs). In case of accidental removal, the sensor was replaced as well. The continuous glucose data were analyzed retrospectively, and no treatment was based on the data. (56)

3.1.4.2 Accu-Chek® Inform II

The Accu-Chek Inform II is a blood glucose monitoring system produced by Roche Diagnostics (Switzerland) and was used in this study to quantitatively measure blood glucose. Capillary blood was used on test strips with this point of care-device, the measurements were performed by the nurse on duty. Capillary glucose measurements were performed 4-times daily (pre-meal and bedtime). Additional measurements could be performed by the nurse on duty if deemed necessary. (57)

3.2 Methods

3.2.1 Use of GlucoTab® with insulin degludec

The goal of this study was to evaluate the efficacy and safety of the GlucoTab® system in combination with the newer ultra-long-acting basal insulin degludec. This was performed on patients with type 2 diabetes or with newly diagnosed hyperglycemia requiring subcutaneous insulin therapy in a hospital setting. Insulin aspart was used as rapid-acting insulin analogue. (2)

In order to be able to use the GlucoTab® system with insulin degludec, it had to be proven that this was a safe and efficient combination that could benefit patients. Patients that were discharged from the hospital or that ended their participation in the study were adjusted back to their pre-existing diabetes medication or potentially received an adjusted treatment plan according to their treating physicians. After the end of the trial, there were no further consequences for the patients regarding the study or their therapy.

3.3 Study Objectives and Endpoints

3.3.1 Primary Objective

The main objective of this study was to evaluate the efficacy of the GlucoTab® system for glycemic management using insulin degludec in non-critically ill patients with type 2 diabetes at the general ward.

3.3.2 Secondary Objective

- To investigate safety, usability, and further efficacy parameters of the GlucoTab system using insulin degludec
- Hypoglycemia rates
- Time in target (100-140mg/dl)
- Glucose variability as assessed by continuous glucose monitoring
- Insulin doses (total, basal, bolus)

3.3.3 Primary Endpoint

The primary endpoint of the study was to calculate the mean percentage of blood glucose measurements in the target range of 70 - 140 mg/dl, as calculated by all premeal and bedtime glucose values measured ≥ 24 hours after start of therapy.

3.3.4 Secondary Endpoints

Safety

- Number of hypoglycemic episodes requiring third party help
- Number of blood glucose measurements per day
- Number of missed blood glucose measurements per day
- Number of additionally required blood glucose measurements
- Insulin dose - basal, bolus and corrective insulin dose per day
- Number of insulin injections per day
- Number and reasons for non-performance of insulin injections per day
- Relevant concomitant medication (corticosteroids, parenteral nutrition, oral hypoglycemic agents)

Usability

- Adherence to the insulin dose suggestion of the GlucoTab® system

Efficacy

- Mean daily blood glucose as calculated by premeal and bedtime blood glucose values: Overall and per treatment day
- Mean pre-breakfast blood glucose, mean pre-lunch blood glucose, mean pre-dinner blood glucose, mean bedtime blood glucose
- Mean pre-enrolment blood glucose
- Number and percentage of the following ranges:
    - 0 – <40 mg/dl
    - 40 - <70 mg/dl
    - 70 - <100 mg/dl
    - 100 - <140 mg/dl
    - >140 - <180 mg/dl
    - 180 - <300 mg/dl
    - ≥ 300 mg/dl
- Time of glucose measurements (Abbott FreeStyle Libre Pro Flash Glucose Monitoring System) in the following ranges:
    - 0 – <40 mg/dl

- 40 - <70 mg/dl
- 70 - <100 mg/dl
- 100 - <140 mg/dl
- >140 - <180 mg/dl
- 180 - <300 mg/dl
- ≥ 300 mg/dl

Based on the secondary endpoints, it can be determined whether the GlucoTab® system is safe to use for patients and other users, if the system is easily usable, and if the system is able to bring the blood glucose levels back to an acceptable range.

3.4 Study Population

The study recruited both male and female patients suffering from type 2 diabetes or with newly diagnosed hyperglycemia that requires subcutaneous insulin therapy, regardless of the diagnosis that led to the hospital admission. A total of 30 patients were planned to be included in the study.

3.4.1 Inclusion criteria

The following criteria had to be fulfilled to be eligible for study participation.

- Informed consent given by the patients after being informed of the nature and progression of the study
- Patients aged 18 years or older, regardless of gender
- A diagnosis of type 2 diabetes (previously treated with diet and/or lifestyle changes, oral anti-diabetic drugs, non-insulin injected anti-diabetic medication, insulin therapy or any combination of the four) or newly diagnosed hyperglycemia requiring subcutaneous insulin therapy

3.4.2 Exclusion criteria

If any of these criteria were met, the patients were excluded from study participation.

- Type 1 diabetes or gestational diabetes
- Any disease or condition that could potentially interfere with the study trial or the safety of the patient, as judged by the investigator or treating physician
- Continuous subcutaneous insulin infusion
- Extreme hyperglycemic episodes (ketoacidosis, hyperosmolar state) that would require intravenous insulin therapy
- Pregnancy
- Mental conditions that lead to incapability of the patient to give consent
- Potential or confirmed allergy to insulin degludec or insulin aspart
- Continuous parenteral nutrition
- Participation in another trial which could potentially influence the software algorithm

3.5 Study Design

This study was conducted as an open non-controlled, single-center, single-arm prospective pilot study. It included a total of 30 eligible patients that were hospitalized at the general ward of the Division of Endocrinology and Diabetology at the Medical University of Graz who required subcutaneous insulin therapy regardless of their primary medical conditions and who consented to participate. The investigational treatment was using the GlucoTab® system with insulin degludec as the long-acting basal insulin and insulin aspart as bolus insulin postprandially and to correct elevated blood glucose levels.

3.6 Study Procedures

3.6.1 Screening

For every potential admitted patient, a physician went and explained the nature, purpose and risks of the study and provided the patient with a copy of the patient information sheet. After informed consent had been obtained and the inclusion and exclusion criteria have been evaluated, screening information has been obtained. A patient number was assigned to the patient in ascending order at the ward. Demography (date of birth, sex, ethnicity), admission diagnosis, medical history, diabetes history, and diabetes therapy were assessed. Body measurements (body weight, height, and body mass index (calculated as $\frac{body\ weight}{height^2}$), vital signs (diastolic and systolic blood pressure, pulse, body temperature), renal function parameters and routine laboratory parameters (HbA_{1c}, creatinine level, blood glucose) as recorded in the patient file were documented. A urine pregnancy test in female participants of childbearing potential was also performed. Patients who complied with all the inclusion and exclusion criteria were included in the study, while screened patients who did not comply with all inclusion and exclusion criteria were not.

3.6.2 Treatment Period

The use of certain OHAs (glinides, sulfonylureas, and glitazones) were stopped, while metformin, SGLT2-inhibitors, GLP-1 analogues, and DPP-4-inhibitors were continued under the discretion of the treating physician. Insulin therapy was adjusted according to the GlucoTab® system with the incorporated software algorithm. Participants were treated with the GlucoTab® and its integrated algorithm for basal bolus therapy using insulin degludec and insulin aspart. The algorithm has been tested previously using insulin glargine and glargine U300 and has shown to safely establish glycemic control. (1,2)
Insulin therapy prescription for the next 24 hours is suggested once daily by the GlucoTab® system by taking previous insulin doses, glucose readings, patient age, renal function, and insulin sensitivity into account. The goal of the GlucoTab® system is to maintain fasting and pre-meal glucose concentrations between 70 –

140 mg/dl. According to GlucoTab®, insulin therapy was initiated at a daily dose of 0.5 units/kg. Half of this dose was administered as long acting insulin once daily (degludec) and the other half as short acting insulin (aspart) before meals. A bedtime glucose >180 mg/dl was not corrected by GlucoTab®. The initial total daily dose was reduced to 0.3 units/kg in patients ≥70 years of age and/or with serum creatinine ≥ 2.0 mg/dl. If the patient was already on insulin therapy, it was possible to pre-set the doses manually. The glucose measurements were performed-prandially and at bedtime by nursing staff. If a patient did not eat, the proposal for short acting insulin dosage was adapted and only a recommendation for correctional insulin (if necessary) was offered by the algorithm.

Treatment duration per patient:

The patients will be treated for the length of their hospital stay or a maximum of 21 days after admission. To get usable data however, it is necessary that the minimum time of stay at the general ward is 48h after initiation of therapy with the study insulin. Nurses and physicians at the ward are well trained in the use of the GlucoTab® system to guarantee safe implementation. Blood glucose measurements and insulin dosing were performed and documented by the nurse on duty. The suggested insulin dose could be overruled by the treating physician at any time and/or an additional glucose measurement could be taken. Trial related activities were not supposed to interfere with regular patient care. When the patients were discharged, they returned to their previous anti-diabetic treatment, unless further insulin therapy was indicated by the treating physician. Blinded continuous subcutaneous glucose monitoring (Abbott FreeStyle Libre Pro Flash Glucose Monitoring System) was performed throughout the study to better understand glycemic excursions over time.

Table 4: Trial Flow Chart

Visit No.	**1**	**2**	**3**
Visit Name	**Screening**	**Study Treatment**	**Discharge**
Informed consent	X		
In/Exclusion criteria	X		
Demography	X		
Admission diagnosis	X		
Diagnosis of diabetes	X		
Concomitant diagnosis	X		
Withdrawal criteria		X	
Body measurements (body weight, height, BMI)	X		
Vital signs	X		
Pregnancy test	X		
Rout. laboratory assessment (creatinine, HbA_{1c})	X		
Blood glucose (capillary)	X	X	
Glucose sensor insertion		X	
Continuous glucose monitoring		X	
Glucose sensor removal			X
Adverse events		X	
Concomitant medication		X	
Diabetes therapy	X	X	X
Usability parameters	X	X	X
End of trial			X

3.6.3 Withdrawal of individual patients

In accordance with the Declaration of Helsinki and other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. The patient will receive the same medical care than before their entrance in the

study. Patients who drop out will be replaced until a total of 30 evaluable patients is achieved.

Specific criteria for withdrawal:

Patients may be removed from the study if any of the following events occur

- Significant protocol violation or non-compliance
- Refusal of the patient to continue treatment and/or observations
- Decision by the investigator or treating physician that termination is in the patient's best medical interest

3.7 Assessments

3.7.1 Blood glucose measurements

Capillary blood glucose was analyzed using a point of care device (AccuChek® Inform, Roche Diabetes Care). No extra training for the use of the bedside blood glucose analyzers was needed since those were already in use at the study site. The measurement was taken by the nurse on duty. Blood glucose was analyzed four times a day (pre-meal and bedtime). If a patient did not eat, the suggestion for bolus insulin dosage was adapted and only a recommendation for correctional insulin (if necessary) was offered by the algorithm.

3.7.2 Insulin dose

The insulin dose was derived from the individual insulin need, was determined by the GlucoTab® system, and was documented in the system and on the source data form of the patient.

3.7.3 Vital Signs

The following vital signs were measured routinely and documented at the ward

- Diastolic and systolic blood pressure (mmHg)
- Heart rate (beats per min) and body temperature (°C).

3.7.4 Laboratory Screening and Safety Parameters

Routine measurement of HbA_{1c} and creatinine were taken as standard procedure at the local laboratory and were also recorded. All hypoglycemic episodes (defined as blood glucose level ≤60 mg/dl), and possible accompanying clinical symptoms (e.g., convulsions) were documented. All adverse events were recorded.

3.7.5 Concomitant medication

The use of relevant concomitant medication (steroids, parenteral bolus nutrition, concomitant antihyperglycemic medication) was recorded.

3.7.6 Source Documents

Table 5: Source Documents

Variable	Source
Patient Information/Consent	Informed consent file
Inclusion/Exclusion Criteria	Source data form
Demographic data, History, Weight, Height	GlucoTab® system, source data form
Routine Laboratory, Pregnancy test	Print out
Glucose values	GlucoTab® system, hospital information system
Insulin dose	GlucoTab® system, medical chart
Relevant concomitant medication	Medical chart
Hypoglycemic events	GlucoTab® system, hospital information system
Record of adverse events	Source data form, medical chart

4 Safety Reporting

4.1 Adverse events / Adverse device effects

Hypoglycemic episodes without third party help that occur during the observation were not recorded as adverse events since they were corrected as part of the study procedures. Adverse events (AEs) are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the method under investigation. An adverse device effect (ADE) is an AE that is (possibly or probably) related to the use of a medical device. All AEs / ADEs reported spontaneously by the subject or observed by the investigator or their staff were recorded. Hyperglycemic episodes were documented in the CRF, but not in the adverse events section.

4.2 Serious adverse events / Serious adverse device effects

A serious adverse event (SAE) is any unwanted medical occurrence or effect that

- results in death regardless of the dose
- is life threatening (at the time of the event)
- requires hospitalization or prolongation of existing inpatients' hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction.

A serious adverse device effect (SADE) is an ADE that

- shows a (possible or probable) relationship to the investigational device *AND*
- has resulted in one or more criteria characteristic of a SAE *OR*
- might have led to one or more criteria characteristic of a SAE
    - if suitable action had not been taken *OR*
    - if intervention had been made *OR*
    - if circumstances had been less fortunate.

All SAEs and SADEs had to be reported, all adverse events were followed up on throughout the course of the clinical trial.

4.3 Data Management

The investigator had to ensure the accuracy, completeness, legibility, and timeliness of data reported in the GlucoTab® system, the eCRF and all required reports. Any change or correction had to be dated, initialed, and explained (if necessary), while leaving the original entry unobscured (for both written and electronic changes). Data reported on the eCRF that are derived from source documents had to be consistent with the source documents, in case of any discrepancies, they had to be explained. The eCRF within the application Phoenix Clinical Trial Management Software (www. phoenixctms.org), which was developed at the Medical University of Graz, was used.

All data management procedures were detailed in a separate specifically identified document known as the Data Management Plan (DMP).

4.3.1 Data Collection

The investigator had to maintain required records for all study subjects. Data for this study was recorded in the GlucoTab® system, the subject's source data form and on electronic Case Report Forms (eCRFs). Data in the eCRF were documented anonymously to protect personal data.

Allocation of subject numbers:
Division of Endocrinology and Diabetology: E-201, E-202, etc.

4.3.2 Source documentation

Investigators had to keep accurate separate records of all subjects' visits, making sure to include all pertinent study related information. A statement was issued indicating that the subjects have been enrolled in this clinical study and have provided written Informed Consent. Any adverse events were thoroughly documented.

4.4 Quality Control and Quality Assurance

4.4.1 Personnel training

4.4.1.1 Study-related training

Prior to enrolling any participants, an initiation visit was conducted. Key personnel such as the study coordinator, investigators or other applicable personnel attended this visit. During this meeting, participants were briefed about the protocol, study specific procedures, source data forms and eCRF. Additionally, all study related staff documented in the “Log-of-staff” sheet were trained in all study related procedures by the study coordinator. All clinical staff must provide certified knowledge in GCP. The study training has been recorded as part of the Trial Master File. The study was performed according to Good Clinical Practice and the Declaration of Helsinki.

4.4.1.2 Investigational product related training

The intended workflow of the GlucoTab system was presented to the end users, including the main operation functions and how to use the GlucoTab® system to perform blood glucose management.

4.4.2 Recruitment and consent

It was the responsibility of the investigator to obtain oral and written informed consent. In obtaining and documenting informed consent, the investigator had to

comply with applicable regulatory documents and adhere to the ICH- GCP guidelines and to the requirements in the Declaration of Helsinki. The investigator had to fully inform (orally and written) the participants of all aspects of the observation study.
All patients had to be fully informed about the study, in language and terms they were able to understand. Prior to a patient's participation, the written informed consent form had to be signed and personally dated by the patient and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form was provided to the patient.

4.4.3 Insurance

Insurance for all patients included in the study was contracted.

5 Statistical Analysis

5.1 Analysis principles

- All analyses were conducted on an intention-to-treat basis.
- Missing values were not put in unless specified otherwise.
- P-values were not adjusted for multiplicativity

5.2 Study Hypothesis

We expected the mean percentage of blood glucose measurements in the target range 70 to 140 mg/dl to be greater than the criterion value of 42%.

Results of a current clinical trial showed that the percentages of glucose readings within the target range between 70 and 140 mg/dL were achieved in 42% of the BG measurements using a basal-bolus algorithm. (58)

5.3 Statistical Methods

The statistical analysis was performed after all the completed, corrected and amended case report forms and data from the GlucoTab® system are available. For numerical parameters, means ± standard deviations or medians and interquartile ranges were used to describe the outcome data. For categorical data, proportions were used to describe the outcome data. Results were presented graphically when it was possible.

Primary analysis:

For the primary analysis, let p_i denote the percentage that, for the i-th subject, a premeal or bedtime blood glucose value measured ≥ 24 hours after start of therapy is in the target range 70 to 140 mg/dl. Furthermore, let us assume a population mean p and a standard deviation σ such that $p_i \sim N(p,\sigma)$. Then the above test problem can be stated as: H_0: $p \leq 42$; H_1: $p > 42$.

The unknown parameter p_i can be estimated as $\hat{p}_i = n_i / N_i * 100$, where:

- n_i is the number of blood glucose (BG) values of the i-th subject in the target range 70 to 140 mg/dl (restricted to BG measurements ≥ 24 hours after start of therapy)
- N_i is the total number of BG values of the i-th subject (restricted to measurements ≥ 24 hours after start of therapy).

To estimate the population mean p, we computed a weighted mean with the total number of BG measurements N_i as weights: $\hat{p} = 1/N * \sum \hat{p}_i N_i = 1/N \sum n_i$, with $N=N1+\ldots+N_I$. Therefore, to test whether the population mean p exceeds the criterion value 42, we applied a one-sample t-test, weighted by the total number of BG measurements per subject. The level of significance was set to 5%.

Explorative analyses:

All secondary parameters will be analyzed by descriptive statistical methods. Exploratory statistical analyses will be performed. The level of significance will be set to 5% in all explorative analyses. A detailed description of the statistical

analysis will be presented in the statistical analysis plan (SAP), which will be finalized prior to data analysis.

5.4 Sample size calculations

The sample size calculation is based on results of the ClinDiab-04 trial (NCT01932775), where the GlucoTab system was used to guide the glycemic management process on four different general wards in the Departments of Internal Medicine and Surgery. For patients at the Division of Endocrinology and Metabolism, the mean percentage of blood glucose measurements in the target range 70 to 140 mg/dl was equal to 52.3 ± 20.7. (1)
As opposed to the ClinDiab-04 trial (where insulin glargine was used as basal insulin), the novel ultra-long-acting basal insulin degludec was used. It was assumed that insulin degludec leads to comparable glycemic control with reduced rates of hypoglycemia. Thus, for sample size calculation, we assumed that the weighted estimate of the population mean p is equal to 52.3 ± 20.7.
A one-tailed one-sample t-test, weighted by the total number of BG measurements per subject, with a significance of 5% and a power of 80% would require a total of 27 patients to appropriately test the study hypothesis.
It is important to note here that, in calculating the primary endpoint, only the blood glucose measurements were considered that were taken ≥ 24 hours after the initiation of therapy. To make sure that the calculation of the primary endpoint was based on the blood glucose data of at least 27 patients, the total number of patients was increased to 30.
Sample size calculation was performed by using SAS 9.2

6 Results

6.1 General Information

6.1.1 Timeline

Table 6: Study Milestones

Milestones	**Date**
FPFV (first patient first visit)	15.01.2020
LPLV (last patient last visit)	24.03.2020
Study paused	Not applicable
Study canceled	Not applicable

6.1.2 Study participants

The data of the patients recruited for the study is compiled in the following tables.

Table 7: Overview of patient recruitment

	Number of patients at the Division of Endocrinology and Diabetology
FPFV	15.01.2020
Screening	30
Patients included	30
Study concluded Normal End Canceled Patients	 30 (100%) -
LPLV	24.03.2020

6.1.3 Demographic data

Table 8: Overview of demographic data

Parameters	**Value**
n (number of participants)	30
Sex (f/m)	18/12
Age (in years)	74.1 ± 10.9
BMI (kg/m^2)	28.6 ± 5.6
Body weight (kg)	80.3 ± 19.1
Ethnicity	100% Caucasian
Serum creatinine levels (mg/dl)	1.5 ± 1.2
HbA_{1c} (mmol/mol)	72.4 ± 22.3
Duration of diabetes disease (in years)	13.2 ± 11.6
Heartrate (beats per minute)	81.7 ± 18.7
Blood pressure systolic/diastolic (mmHg)	143.1 ± 33.6 / 75.7 ± 13.8
Body temperature (°C)	36.6 ± 0.5
Length of study participation (days)	8.2 ± 3.6
Way of admission spontaneous planned	 29 (96.7%) 1 (3.3%)

Table 9: Diabetes therapy at admission and discharge

Therapy	Admission: N	Admission: %	Discharge: N	Discharge: %
Diet only	-	-	-	-
OHA only	11	39.3	5	18.5
GLP1 only	-	-	-	-
Insulin only	4	14.3	1	3.7
OHA + GLP1	-	-	1	3.7
OHA + Insulin	13	46.4	16	59.3
GLP1 + Insulin	-	-	1	3.7
OHA + GLP1 + Insulin	-	-	3	11.1

Table 10: Summary of admission diagnoses

Reason of admission	N	%
Hematologic disorder	0	0
Gastrointestinal disorder	0	0
Endocrinological disorder	8	23.5
Lung disorder	0	0
Cardiovascular disorder	9	26.5
Neurologic disorder	0	0
Psychiatric disorder	0	0
Infectious disorder	16	47.1
Kidney disorder	0	0
Urogenital disorder	0	0
Dermatological disorder	0	0
Musculoskeletal disorder	1	2.9
Injuries	0	0
Neoplasm	0	0
Ears- Nose- Throat- Disorder	0	0
Other	0	0

Table 11: Summary of concomitant diagnoses

Concomitant diagnoses	N	%
Hematologic disorder	2	1.6
Gastrointestinal disorder	6	4.8
Endocrinological disorder	29	23.0
Lung disorder	11	8.7
Cardiovascular disorder	27	21.4
Neurological disorder	5	4.0
Psychiatric disorder	2	1.6
Infectious disorder	0	0
Kidney disorder	19	15.1
Urogenital disorder	5	4.0
Dermatological disorder	2	1.6
Musculoskeletal disorder	15	11.9
Injuries	0	0
Neoplasm	1	0.8
Ears- Nose- Throat- Disorder	2	1.6
Other	0	0

6.1.4 Deviation from Clinical Investigation Plan

There was no deviation from the clinical investigation plan.

6.2 Summary of adverse events

Table 12 shows the adverse events that happened during the run of the study. None of them were device related and none of them caused participants to drop-out of the study.

Table 12: Overview of Adverse Events

AE Nr.	Participant ID	Date of Event	Diagnosis	Severity	Device Related	ADE	SADE	Recovery	Therapy	Measures
1	E-201	16.01.2020	Pneumonia	moderate	unlikely	unlikely	no	cured	antibiotic therapy	not excluded from study
2	E-202	20.01.2020	Pneumonia	moderate	unlikely	unlikely	no	in recovery	antibiotic therapy	not excluded from study
3	E-203	24.01.2020	Urinary Tract Infection	moderate	unlikely	unlikely	no	cured	antibiotic therapy	not excluded from study
4	E-205	04.02.2020	Osteoporosis	moderate	unlikely	unlikely	no	not cured	recommendation for osteoporosis therapy	not excluded from study
5	E-213	14.02.2020	Thoracic pain	low	unlikely	unlikely	no	cured	myocardial perfusion imaging and 24-h-ECG unremarkable	not excluded from study
6	E-214	19.02.2020	Intertriginous bilateral inguinal dermatitis	low	unlikely	unlikely	no	in recovery	antifungal + anti-inflammatory topical drug, dermatological consultation initiated	not excluded from study
7	E-217	24.02.2020	Acute Cholecystitis	moderate	unlikely	unlikely	no	cured	as per surgical consultation conservative therapy	not excluded from study
8	E-217	25.02.2020	Atrial Flutter, Dyspnea, Tachycardia (in ECG)	moderate	unlikely	unlikely	no	cured	no thrombi in transthoracic echocardiography, cardioversion with following sinus rhythm	not excluded from study
9	E-218	27.02.2020	Superficial vein thrombosis (V. saphena parva dextra)	low	unlikely	unlikely	no	in recovery	no specific therapy	not excluded from study

10	E-219	28.02.2020	Vitamin D deficiency	low	unlikely	unlikely	no	in recovery	Vitamin D supplements	not excluded from study
12	E-220	03.03.2020	Hyperlipidemia	low	unlikely	unlikely	no	in recovery	therapy with lipid-lowering agents (statins) initiated	not excluded from study
11	E-220	06.03.2020	Pain in left arm-suspected psoriatic arthritis	low	unlikely	unlikely	no	in recovery	pain therapy	not excluded from study
14	E-221	04.03.2020	Urinary Tract Infection	low	unlikely	unlikely	no	cured	antibiotic therapy	not excluded from study
15	E-225	04.03.2020	Anisocoria dextra	low	unlikely	unlikely	no	cured	iatrogenic anisocoria (because of ophthalmologic examination)	not excluded from study
16	E-227	17.03.2020	Infection of unknown origin (elevated CRP)	moderate	unlikely	unlikely	no	in recovery	urine and thoracic x-rays unremarkable; change of antibiotic therapy initiated; no clinical symptoms	not excluded from study

6.2.1 Summary of serious adverse (device) events

No SAEs or SADEs were reported.

6.2.2 Summary of system malfunctions and anomalies

There were no system malfunctions during the duration of the study.

6.3 Efficacy

6.3.1 Primary Endpoint

The mean percentage of blood glucose levels in the target range (70 – 140 mg/dl) 24 hours after start of GlucoTab® assistance was 52.2 ± 10.2%. For this evaluation, the initiation phase (the first 24 hours of GlucoTab® therapy) was excluded, so it would more accurately reflect the true treatment with the help of the GlucoTab® algorithm.

6.3.2 Secondary Endpoint

6.3.2.1 Mean blood glucose levels per daytime

Table 13: Overview of mean blood glucose levels (mean ± standard deviation)

Time	Patient number	Blood Glucose (mg/dl)
Pre-enrolment BG	30	215.1 ± 78.5
Daily BG	30	150.5 ± 26.9
Pre-breakfast BG	30	130.5 ± 39.6
Pre-lunch BG	30	166.2 ± 47.2
Pre-dinner BG	30	161.9 ± 31.9
Bedtime BG	30	143.7 ± 36.7

During the duration of the study, daily mean blood glucose levels were at average at 150.5 ± 26.9 mg/dl.

6.3.2.2 Mean glucose levels per treatment day

After four days the mean blood glucose levels were in the target range of 140 mg/dl, after which they remained in that area. In general, pre-breakfast and bedtime blood glucose levels were slightly lower than the mean, while pre-lunch and pre-dinner blood glucose was slightly higher.

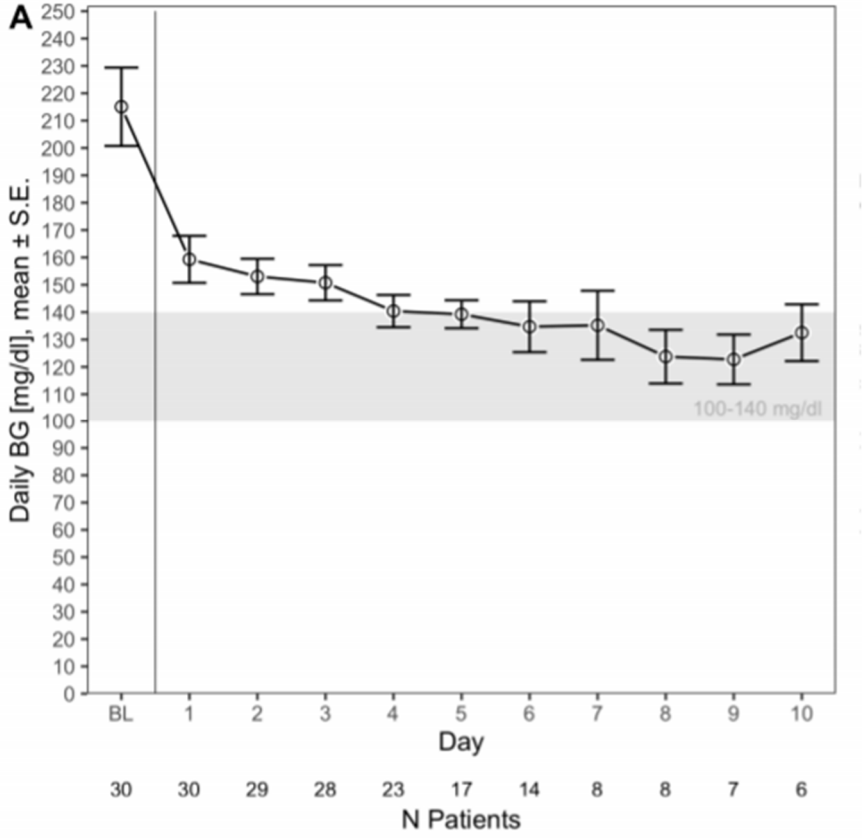

Figure 1: Blood Glucose per treatment day

6.3.2.3 Blood glucose levels in different ranges

The following table shows that for around 74.5% of the time the patients were treated with the help of the GlucoTab® system, their blood glucose levels stayed in the range of 70 - <180 mg/dl. The target range for the study of 70 – 140 mg/dl was achieved with around 52.2% of BG levels falling into that bracket during the treatment period, which falls in line with the primary endpoint results (Figure 2).

Table 14: Overview of blood glucose measurements in different ranges

Range	Number of measurements (N)	%
>0 mg/dl	722	100
<40 mg/dl	0	0.0
<54 mg/dl	2	0.3
<70 mg/dl	9	1.3
40 - <54 mg/dl	2	0.3
40 - <70 mg/dl	9	1.3
54 - <70 mg/dl	7	1.0
70 - <100 mg/dl	138	19.1
70 - <110 mg/dl	193	26.7
70 - 140 mg/dl	377	52.2
70 - <180 mg/dl	538	74.5
100 - 140 mg/dl	239	33.1
110 - 140 mg/dl	184	25.5
>140 - <180 mg/dl	161	22.3
180 - <250 mg/dl	142	19.7
180 - <300 mg/dl	169	23.4
250 - <300 mg/dl	27	3.7
≥180 mg/dl	175	24.2
≥250 mg/dl	33	4.6
≥300 mg/dl	6	0.8

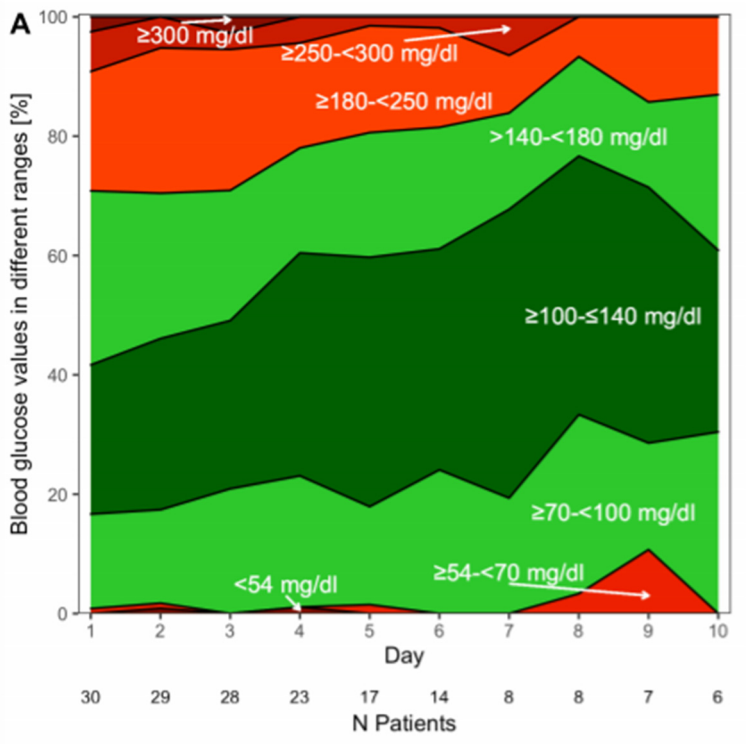

Figure 2: Time in ranges per treatment day

6.3.2.4 Blood glucose measurements in different ranges – first vs. last full treatment day

Table 15: Blood glucose measurements in different ranges - first vs. last day

Range	N (first)	% (first)	N (last)	% (last)
>0 mg/dl	120	100	117	100
<40 mg/dl	0	0.0	0	0.0
<54 mg/dl	0	0.0	0	0.0
<70 mg/dl	1	0.8	2	1.7
40 - <54 mg/dl	0	0.0	0	0.0
40 - <70 mg/dl	1	0.8	2	1.7
54 - <70 mg/dl	1	0.8	2	1.7
70 - <100 mg/dl	19	15.8	25	21.4
70 - <110 mg/dl	25	20.8	36	30.8
70 - 140 mg/dl	49	40.8	62	53.0
70 - <180 mg/dl	84	70.0	90	76.9
100 - 140 mg/dl	30	25.0	37	31.6

110 - 140 mg/dl	24	20.0	26	22.2
>140 - <180 mg/dl	35	29.2	28	23.9
180 - <250 mg/dl	24	20.0	19	16.2
180 - <300 mg/dl	32	26.7	25	21.4
250 - <300 mg/dl	8	6.7	6	5.1
≥180 mg/dl	35	29.2	25	21.4
≥250 mg/dl	11	9.2	6	5.1
≥300 mg/dl	3	2.5	0	0.0

As evident both in Table 15 and in Figure 4 & 5, the blood glucose values on the first day of the study differed from the blood glucose values on the last day. On the last day, the blood glucose values had improved and were in the target range in more cases, which indicates improved glycemic control.

6.3.2.5 CGM-based 24-hour profiles

Continuous glucose monitoring (CGM) was implemented next to traditional blood glucose measurements.
With the help of CGM, accurate blood glucose data was collected over the span of the study. Data shows that in 52.2% of the time, the CGM-based glucose values were in the target range of 70 – 140 mg/dl (Figure 3).

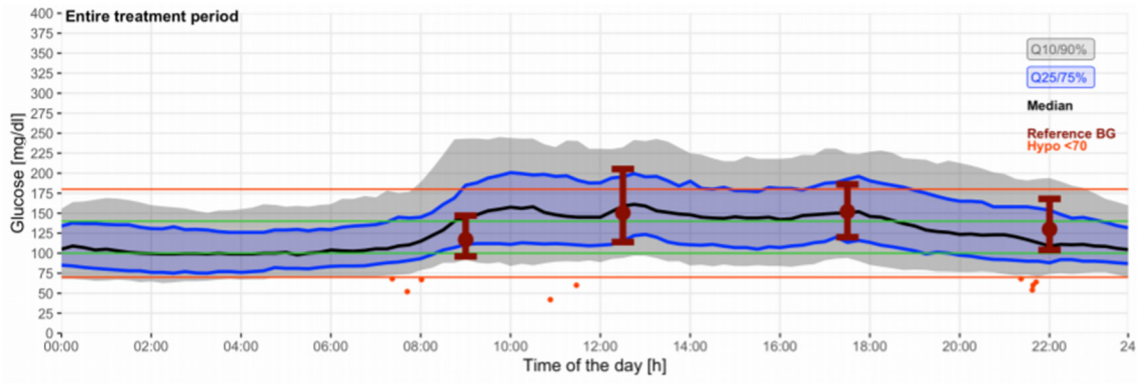

Figure 3: Median CGM values throughout the entire treatment period

Interquartile range (blue): Q 25/75%
10th and 90th percentile (grey): Q 10/90 %

On the first full day of the study, 49.1% of the time the CGM-based glucose measurements were in that target range, whereas the number increased to 56.2% on the final full day of the study. Furthermore, there were fewer outliers in the hyperglycemic ranges and there was less glucose variability (Figures 4 & 5).

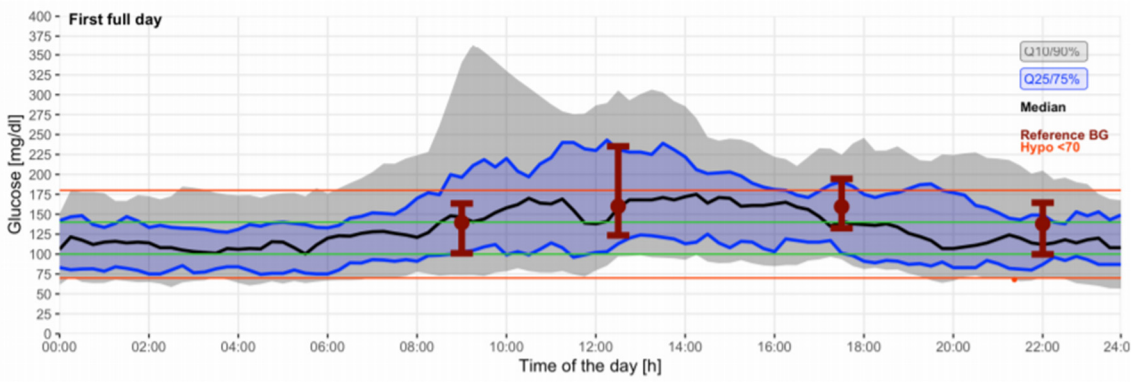

Figure 4: Median CGM values on the first full day

Interquartile range (blue): Q 25/75%
10th and 90th percentile (grey): Q 10/90 %

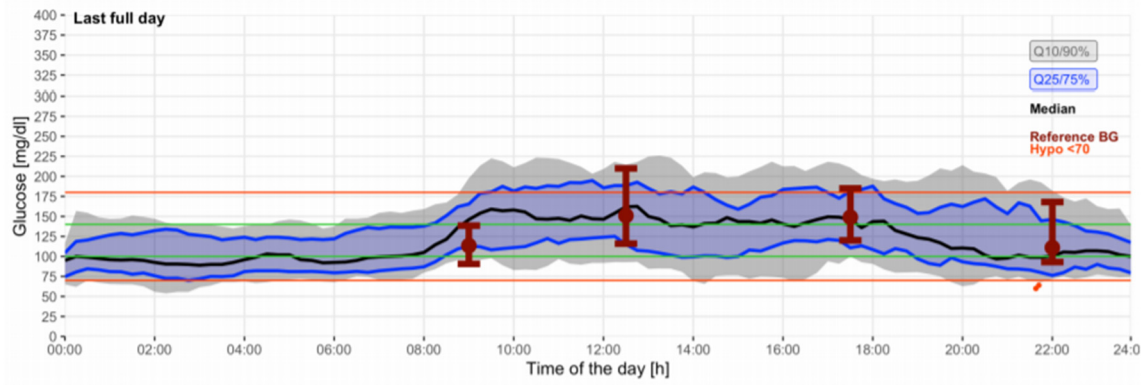

Figure 5: Median CGM values on the last full day

Interquartile range (blue): Q 25/75%
10th and 90th percentile (grey): Q 10/90 %

6.4 Safety

6.4.1 Hypoglycemic episodes

No severe hypoglycemic episodes <40 mg/dl requiring third-party help occurred. Nine episodes of hypoglycemia <70 mg/dl (1.25%) and two episodes <54 mg/dl (0.28%) were documented from a total of 722 blood glucose measurements (100%).

6.4.2 Blood glucose measurements overall

During the entire treatment period, the GlucoTab® system scheduled 735 blood glucose measurements, of which 722 were performed. An additional 28 unscheduled measurements were performed. Thirteen of the scheduled BG measurements were missed. The total percentage for blood glucose measurements that took place as scheduled was 98.2%.

6.4.3 Insulin therapy

During the study, the GlucoTab® system made suggestions for insulin doses, which are explained as follows.

Suggested insulin dose: the dose of insulin that the GlucoTab® algorithm suggests initially before any corrections take place.

Corrected insulin dose: insulin dose that gets added or subtracted to the primarily suggested dose at the second step of the algorithm

Calculated insulin dose: the final dose of insulin that the algorithm calculated

The difference between the calculated insulin dose that the algorithm produced and the actual dose that was administered (injected insulin dose) is qualified as the corrected dose through the user.

Table 16: Mean values of daily BG measurements, insulin administrations and doses

Parameters	Mean ± SD
Number of performed scheduled BG measurements	3.9 ± 0.3
Number of missed scheduled blood glucose measurements	1.1 ± 0.3
Number of performed unscheduled blood glucose measurements	3.9 ± 0.3
Number of basal insulin administrations	1.0 ± 0.1
Number of total bolus insulin administrations	3.2 ± 0.7
Number of mealtime bolus insulin administrations	2.7 ± 0.6
Number of corrected bolus insulin administrations	0.5 ± 0.6
Administered bolus insulin dose (U)	19.8 ± 13.3
Calculated bolus insulin dose (U)	20.6 ± 12.9
User- corrected bolus insulin dose (U)	-0.8 ±1.7
Administered basal insulin dose (U)	15.8 ± 7.7
Calculated basal insulin dose (U)	15.8 ± 7.7
User- corrected basal insulin dose (U)	0.0 ± 0.2

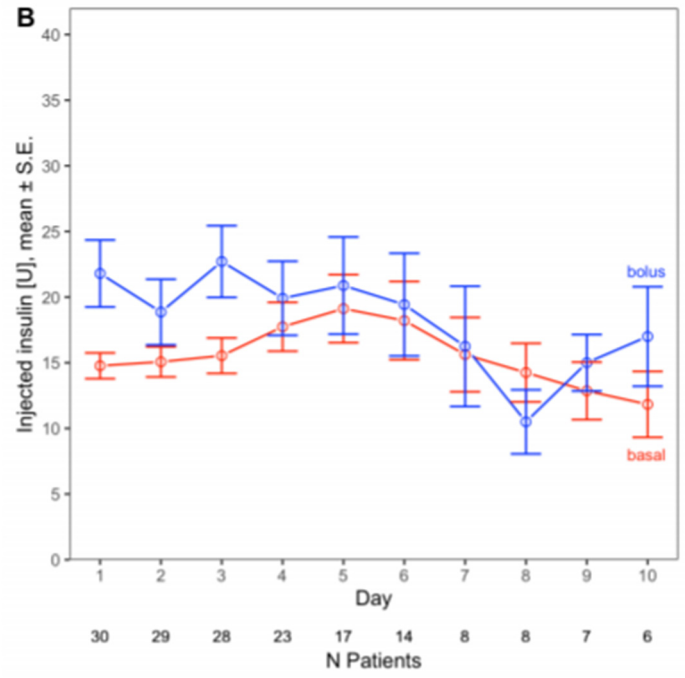

Figure 6: Mean administered insulin dose per treatment day

Table 16 shows the mean number of insulin doses/units administered throughout the study, while Figure 6 is a visual representation of the mean injected basal and bolus insulin doses that were administered.

6.5 Usability

6.5.1 Adherence to the GlucoTab® suggestions

The adherence to the insulin dose suggestion of the GlucoTab® system was high, with 93.6% of all suggested total daily doses being adhered to from study start, and 94.2% of all suggestions starting from the first full day of the study.
From the first full day of the study, the GlucoTab® system suggested 185 doses for basal insulin, of which 184 were administered, marking an adherence of 99.5%.
For bolus insulin from the first full study day, the GlucoTab® system suggested an insulin dose 586 times, while 500 doses were administered as suggested, setting the adherence at 85.0%.

6.5.2 Corrections of doses

The lowest percentage for adherence was on the day the study started (with an adherence of 76.3%). The first and last day of the study have to be taken into consideration as the users were unsure of previous or continued patient treatment and thus were more careful in administering insulin.
As for basal insulin doses, only 2.3% of suggested doses were not administrated as suggested by the algorithm over the whole study period, even less than that with 0.5% from the first full day of the study.
Of all suggested bolus insulin doses, 16.3% were adjusted by the user over the whole study period, while 14.97% were corrected from the first full day of the study. Adherence was lowest for bedtime suggestions. This was mostly because the suggested doses were low (approximately 1U of insulin) that the nurse on duty cancelled the recommended administration.
Throughout the study, the number of adjustments was highest on the first study day (with a total of 28.6%).

Table 17: Total dose corrections by user

Parameters	Calculations	Corrections	%
Total daily insulin dose corrections from study start	248	15	6.1%
Total daily insulin dose corrections from first full day	224	13	5.8%
Basal insulin corrections from study start	215	5	2.3%
Basal insulin corrections from first full day	185	1	0.5%
Bolus insulin corrections from study start	649	104	16.0%
Bolus insulin corrections from first full day	586	86	14.7%
Bolus morning corrections	174	19	10.9%
Bolus noon corrections from study start	383	32	8.4%
Bolus noon corrections from first full day	353	26	7.4%
Bolus evening corrections from study start	233	41	17.6%
Bolus evening corrections from first full day	186	29	15.6%
Bolus bedtime corrections from study start	74	17	23.0%
Bolus bedtime corrections from first full day	58	13	22.4%

Table 17 shows that the highest number of dose adjustments were performed at bedtime.

7 Conclusion

In total, the data indicates that the use of the GlucoTab® system for workflow and decision-making support results in good glycemic control with a low number of hypoglycemic events. With the GlucoTab® system being readily available in a clinical setting, as well as the high adherence of clinical staff towards dose suggestions, it is a useful tool to help manage patients with diabetes and new-onset hyperglycemia, especially on wards where staff is not as familiar with the management.

7.1 Potential positive effects of the GlucoTab® system

Studies have shown that using a computerized decision support system improves inpatient diabetes care, with better blood glucose in target ranges and lower mean blood glucose levels without causing an increase in hypoglycemia. (1,2)

The GlucoTab® system used in this study provides suggestions for basal and bolus insulin doses. It has shown good usability and its suggestions were well accepted by users (see 6.5) while maintaining safety during use (see 6.4).

7.1.1 Improved glycemic control with reduced risk for hypoglycemia

Inadequate glycemic control is associated with bad clinical outcome, including risk of infections, higher all-cause morbidity and mortality. The ideal target range for premeal blood glucose for hospitalized patients was set at 140 – 180 mg/dl by the ADA, with a more stringent goal of 110 – 140 mg/dl for selected patients if this goal can be achieved without significant hypoglycemia. (6)

In this study 52.2 ± 10.2% of measured blood glucose values were in the range of 70 – 140 mg/dl. In 74.5% of the time that patients were treated with the support of the GlucoTab® algorithm, the measured blood glucose levels stayed in the range of 70 - <180 mg/dl, in 33.1% they even fell in the tighter range of 100-140 mg/dl.

When comparing the first full treatment day of the study to the last, it becomes evident that blood glucose values improved by using the algorithm (see 6.3.2.4 and 6.3.2.5). On the first day, 49.1% of the CGM values landed in the target range of 70 – 140 mg/dl, while the number increased to 56.2% on the last day.

7.2 Potential risks of the GlucoTab® system

7.2.1 Hypoglycemic events

Nine episodes of hypoglycemia <70 mg/dl occurred during this study, which makes up 1.25% of all blood glucose measurements. Two episodes of glucose <54 mg/dl were recorded, which accounts for 0.28% of the measurements. No hypoglycemic event <40 mg/dl or hypoglycemic episode that required third party assistance occurred (see 6.4.1) The number of hypoglycemic events were comparable to similar studies or even lower. (1–3,58–60)

7.2.2 Hyperglycemic events

Only 0.8% of all blood glucose measurements were ≥300 mg/dl, which is less than a recent study conducted with the GlucoTab® system and insulin glargine U300, where 1.7% of blood glucose measurements were ≥300 mg/dl. (2)

It can be said that the rate of hyperglycemic events was not higher than in comparable studies, like Neubauer et. al. [2015] where 2.7% of blood glucose values were at ≥300 mg/dl, or Aberer et. al. [2019] with 1.7% at that range. (1,2)

During the duration of the study, daily mean blood glucose levels were on average at 150.5 ± 26.9 mg/dl. Furthermore, comparing the mean blood glucose values (see 63.2.4) as well as the CGM measurements (see 6.3.2.5) from the first day of the study to the last, it is obvious that glycemic control improved during the study.

7.2.3 Adherence to GlucoTab® suggestions

The medical staff worked well with the GlucoTab® system and accepted the suggested insulin doses in most cases (see 6.5). Of all suggested total daily insulin doses, 93.6% were adhered to from study start. The first and final day of the study were the ones with the lowest adherence (of 76.3%). Most of the corrections on those days took place because the users were unsure about the specifics of medication the patients had already taken or insulin injections that had been performed before the study, as well as being careful on the last day as to not negatively affect the patients for when they return home.
As for suggested doses that were not administered, this mostly occurred at bedtime where the suggested dose was as low as 1U, which medical staff decided to skip as the benefits did not outweigh the burden of insulin injection.
The mean user-corrected doses were low: with -0.8 ±1.7 U for bolus insulin and 0.0 ± 0.2 U for basal insulin. Once again, this finding is comparable to similar studies. (1–3)
The GlucoTab® system scheduled 735 blood glucose measurements throughout the treatment period, of which 722 were performed. In addition to that, 28 unscheduled measurements were performed, whereas thirteen scheduled measurements were missed. In total, the percentage of blood glucose measurements that were performed as scheduled was 98.2%, which shows high adherence to the suggestions of the algorithm.
The adherence for basal insulin administration was 99.5%, for bolus insulin it was 85.0% (both excluding the first study day). Adherence to bolus insulin was similar to studies like Neubauer et. al. [2015] and Aberer et. al. [2019], although adherence to bolus insulin was slightly lower in this study. (1,2)

There were no technical problems, system malfunctions or anomalies. In addition to that, there were no adverse events related to the device (see 6.2) and no serious adverse events or serious adverse device effects.

These numbers tell us that the GlucoTab® system offers good assistance in a clinical setting and that it was made use of frequently. The blood glucose measurements as well as the insulin injections were largely performed and

documented as suggested by the GlucoTab® system, which falls in line with previously conducted studies. (1–3)
Therefore, it is safe to say that the GlucoTab® system was incorporated well into the daily hospital routine and was accepted well by medical staff.

8 Bibliography

1. Neubauer KM, Mader JK, Höll B, Aberer F, Donsa K, Augustin T, et al. Standardized Glycemic Management with a Computerized Workflow and Decision Support System for Hospitalized Patients with Type 2 Diabetes on Different Wards. In: Diabetes Technology and Therapeutics. Mary Ann Liebert Inc.; 2015. p. 685–92.
2. Aberer F, Lichtenegger KM, Smajic E, Donsa K, Malle O, Samonigg J, et al. GlucoTab-guided insulin therapy using insulin glargine U300 enables glycaemic control with low risk of hypoglycaemia in hospitalized patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2019 Mar 1;21(3):584–91.
3. Spat S, Donsa K, Beck P, Höll B, Mader JK, Schaupp L, et al. A Mobile Computerized Decision Support System to Prevent Hypoglycemia in Hospitalized Patients with Type 2 Diabetes Mellitus. Journal of Diabetes Science and Technology. 2017 Jan 1;11(1):20–8.
4. Schmutterer I, Delcour J, Griebler R (Hrsg.), Wien: Bundesministerium für Gesundheit und Frauen. Österreichischer Diabetesbericht 2017 [Internet]. Available from: www.bmgf.gv.at
5. Bilous R, Donnelly R. Handbook of Diabetes, Fourth Edition. 2019.
6. Diabetes care in the hospital: Standards of medical care in diabetes-2021. Diabetes Care. 2021 Jan 1;44:S211–20.
7. Mader JK, Brix J, Aberer F, Vonbank A, Resl M, Pieber TR, et al. Hospital diabetes management (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:200–11.
8. Arasteh K, Baenkler H, Bieber C et al. Hrsg 4. , überarbeitete Auflage. Duale Reihe Innere Medizin. Stuttgart: Thieme; 2018. 691–718.
9. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. [Internet]. [cited 2021 May 26]. Available from: https://www.diabetesatlas.org
10. Herold Gerd. Innere Medizin 2020. Walter de Gruyter GmbH & Co KG. 2020;722–50.

11. Kasper DL, Fauci AS, Hauser SL, Longo DL 1., Jameson JL, Loscalzo J. Harrison’s principles of internal medicine, 19e. Vol. 1. No. 2. McGraw Hill Education, 2015. :2850–83.
12. Hien P, Böhm B, Böhm B, Claudi-Böhm S, Krämer C, Kohlhas K. Diabetes-Handbuch. Diabetes-Handbuch. Springer Berlin Heidelberg; 2013. 82–83.
13. Silbernagl S, Lang F. Taschenatlas Pathophysiologie. Taschenatlas Pathophysiologie. Georg Thieme Verlag; 2019. 324–329.
14. Jingi AM, Tankeu AT, Ateba NA, Noubiap JJ. Mechanism of worsening diabetic retinopathy with rapid lowering of blood glucose: The synergistic hypothesis. BMC Endocrine Disorders. 2017 Oct 10;17(1).
15. Radda S, Bolz M, Egger S, Gasser-Steiner V, Kralinger M, Mennel S, et al. Diagnosis, treatment and monitoring of diabetic eye disease (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:164–8.
16. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. The Lancet [Internet]. 2010;376:124–36. Available from: www.thelancet.com
17. Lechleitner M, Abrahamian H, Francesconi C, Kofler M, Sturm W, Köhler G. Diabetic neuropathy and diabetic foot syndrome (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:141–50.
18. Qi C, Mao X, Zhang Z, Wu H. Classification and differential diagnosis of diabetic nephropathy. Vol. 2017, Journal of Diabetes Research. Hindawi Limited; 2017.
19. Sourij H, Edlinger R, Prischl FC, Auinger M, Kaser S, Horn S, et al. Diabetic kidney disease (Update 2019): Position paper of the Austrian Diabetes Association and the Austrian Society for Nephrology. Wiener Klinische Wochenschrift. 2019 May 1;131:151–63.
20. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021 Jan 1;44:S15–33.
21. Harreiter J, Roden M. Diabetes mellitus—Definition, classification, diagnosis, screening and prevention (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:6–15.
22. Renz-Polster H, Steffen Krautzig, Jörg Braun. Basislehrbuch Innere Medizin: kompakt-greifbar-verständlich. Elsevier Health Sciences Germany. 2012. S732-769

23. Toplak H, Leitner DR, Harreiter J, Hoppichler F, Wascher TC, Schindler K, et al. “Diabesity”—Obesity and type 2 diabetes (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:71–6.
24. Glycemic targets: Standards of medical care in diabetes−2021. Diabetes Care. 2021 Jan 1;44:S73–84.
25. Francesconi C, Niebauer J, Haber P, Weitgasser R, Lackinger C. Lifestyle: physical activity and training as prevetion and therapy of type 2 diabetes mellitus (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:61–6.
26. Clodi M, Abrahamian H, Brath H, Brix J, Drexel H, Fasching P, et al. Antihyperglycemic treatment guidelines for diabetes mellitus type 2 (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:27–38.
27. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021 Jan 1;44:S111–24.
28. Lechleitner M, Clodi M, Abrahamian H, Brath H, Brix J, Drexel H, et al. Insulin therapy of type 2 diabetes mellitus (Update 2019). Wiener Klinische Wochenschrift. 2019 May 1;131:39–46.
29. Krentz AJ. Drug Therapy for Type 2 Diabetes Pocket Reference. S32-47
30. Hofmann F, Editorial Board Beavo MJ, Ganten WD, J-A Karlsson B, Michel SM, Page AC, et al. Handbook of Experimental Pharmacology- Diabetes-Perspectives in Drug Therapy [Internet]. Available from: http://www.springer.com/series/164
31. Pozzuoli GM, Laudato M, Barone M, Crisci F, Pozzuoli B. Errors in insulin treatment management and risk of lipohypertrophy. Acta Diabetologica. 2018 Jan 1;55(1):67–73.
32. American Diabetes Association- Insulin Basics [Internet]. [cited 2021 Jun 30]. Available from: https://www.diabetes.org/healthy-living/medication-treatments/insulin-other-injectables/insulin-basics
33. Crasto W, Jarvis J, Davies MJ. Handbook of Insulin Therapies. 2016.
34. Avgerinos I, Papanastasiou G, Karagiannis T, Michailidis T, Liakos A, Mainou M, et al. Ultra-rapid-acting insulins for adults with diabetes: A systematic review and meta-analysis. 2021;

35. Owens DR, Bolli GB. The continuing quest for better subcutaneously administered prandial insulins: a review of recent developments and potential clinical implications. Vol. 22, Diabetes, Obesity and Metabolism. Blackwell Publishing Ltd; 2020. p. 743–54.
36. Niswender KD. Basal insulin: Physiology, pharmacology, and clinical implications. Postgraduate Medicine. 2011 Jul;123(4):17–26.
37. Haahr H, Heise T. A Review of the Pharmacological Properties of Insulin Degludec and Their Clinical Relevance. Vol. 53, Clinical Pharmacokinetics. Springer International Publishing; 2014. p. 787–800.
38. CHMP. NovoMix, INN-insulin aspart [Internet]. Available from: www.ema.europa.eu/contact
39. CHMP. Ryzodeg; INN-insulin degludec / insulin aspart [Internet]. Available from: www.ema.europa.eu/contact
40. Belinda P. Childs AMC, Nathaniel G. Clark MMR, Daniel J. Cox P, Philip E. Cryer M (chair), Stephen N. Davis M, Monica M. DiNardo MCC, et al. Defining and Reporting Hypoglycemia in Diabetes- A report from the American Diabetes Association Workgroup on Hypoglycemia. 2005.
41. Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, Katabi A, McCoy RG. Hypoglycemia Among Patients with Type 2 Diabetes: Epidemiology, Risk Factors, and Prevention Strategies. Vol. 18, Current Diabetes Reports. Current Medicine Group LLC 1; 2018.
42. Pieber TR, Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, et al. DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality. Diabetologia. 2018 Jan 1;61(1):58–65.
43. Lansang MC, Umpierrez GE. Inpatient hyperglycemia management: A practical review for primary medical and surgical teams. Vol. 83, Cleveland Clinic journal of medicine. 2016. p. S34–43.
44. Gupta T, Hudson M. Update on glucose management among noncritically ill patients hospitalized on medical and surgical wards. Journal of the Endocrine Society. 2017;1(4):247–59.
45. Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes and Metabolism. 2013 Oct;39(5):445–53.

46. Gerard SO, Ritchie J. Challenges of inpatient glycemic control. Journal of Nursing Care Quality. 2017;32(3):267–71.
47. Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, et al. Efficacy and Safety of IDegLira Versus Basal-Bolus Insulin Therapy in Patients With Type 2 Diabetes Uncontrolled on Metformin and Basal Insulin; DUAL VII Randomized Clinical Trial. Diabetes Care. 2018 Feb 26;dc171114.
48. Marso SP, McGuire DK, Zinman B, Poulter NR, Emerson SS, Pieber TR, et al. Efficacy and Safety of Degludec versus Glargine in Type 2 Diabetes. New England Journal of Medicine. 2017 Aug 24;377(8):723–32.
49. Tresiba® - Novo Nordisk Prescribing information [Internet]. 2019 [cited 2021 Jun 16]. Available from: https://www.novonordiskmedical.com/our-products/tresiba.html
50. Heise T, Nosek L, Bøttcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes, Obesity and Metabolism. 2012;14(10):944–50.
51. Wysham C, Bhargava A, Chaykin L, de La Rosa R, Handelsman Y, Troelsen LN, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes the SWITCH 2 randomized clinical trial. JAMA - Journal of the American Medical Association. 2017 Jul 4;318(1):45–56.
52. Philis-Tsimikas A, Klonoff DC, Khunti K, Bajaj HS, Leiter LA, Hansen M v, et al. Risk of hypoglycaemia with insulin degludec versus insulin glargine U300 in insulin-treated patients with type 2 diabetes: the randomised, head-to-head CONCLUDE trial. [cited 2021 May 25]; Available from: https://doi.org/10.1007/s00125-019-05080-9
53. Jinxin WZ, Xiaodong T, Chen ZH. Insulin Degludec, a Novel Ultra-Long-Acting Basal Insulin versus Insulin Glargine for the Management of Type 2 Diabetes: A Systematic Review and Meta-Analysis. Diabetes Therapy [Internet]. Available from: https://doi.org/10.6084/
54. Yun JS, Park YM, Han K, Cha SA, Ahn YB, Ko SH. Severe hypoglycemia and the risk of cardiovascular disease and mortality in type 2 diabetes: A nationwide population-based cohort study. Cardiovascular Diabetology. 2019 Aug 14;18(1).

55. NovoRapid® - Novo Nordisk Pro Prescribing information [Internet]. 2020 [cited 2021 Jun 15]. Available from: https://www.novonordiskpro.de/content/dam/Germany/AFFILIATE/www-novonordiskpro-de/de_de/diabetes/fi/FI_NovoRapid.pdf
56. FreeStyle Libre by Abbott [Internet]. [cited 2021 Jun 28]. Available from: https://www.freestyle.abbott/in-en/home.html
57. ACCU-CHEK ® Inform II BLOOD GLUCOSE MONITORING SYSTEM Operator's Manual.
58. Umpierrez GE, Smiley D, Hermayer K, Khan A, Olson DE, Newton C, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: Basal plus trial. Diabetes Care. 2013;36(8):2169–74.
59. Umpierrez GE, Smiley D, Jacobs S, Peng L, Temponi A, Mulligan P, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care. 2011 Feb;34(2):256–61.
60. Umpierrez GE, Smiley D, Zisman A, Prieto LM, Palacio A, Ceron M, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes (RABBIT 2 Trial). Diabetes Care. 2007 Sep;30(9):2181–6.