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EndoBarrier™ in obese subjects with type 2 diabetes: Impact on pancreatic function, insulin resistance, gut peptides and gut permeability – a pilot study

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the sponsor, the investigator team, regulatory authorities and members of the Research Ethics Committee.

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LIST OF ABBREVIATIONS

13C-UBT	13C-Urease breath test
AIR	Acute Insulin Response
AUC	Area under Curve
BID	Twice a day
BMI	Body Mass Index
BS	Bariatric Surgery
CRF	Case Report Form
DEGS	Deutsche Erwachsenen Gesundheits-Survey
DEXA	Dual energy x-ray absorptiometry
DI	Disposition Index
DPP-4	Dipeptidyl-Peptidase Inhibitor - 4
EBWL	Excess body weight loss
ECG	Electrocardiography
EIR	Early Insulin Response
FFQ	Food Frequency Questionnaire
GCP	Good Clinical Practice
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide-1
HEC	Hyperinsulinemic-euglycaemic Clamp
ICH	International Conference on Harmonisation
IDF	International Diabetes Federation
IGI	Insulinogenic Index
IVGTT	Intravenous glucose tolerance test
MODY	Maturity Onset Diabetes of the Young
MTT	Meal Tolerance Test
NEMONIT	Nationales Ernährungsmonitoring
NSAID	Non-steroidal anti-inflammatory drug
OGTT	Oral Glucose Tolerance Test
T2DM	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study
WHO	World Health Organisation

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2. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

3. SYNOPSIS

Study Title	Duodenal-jejunal bypass liner (EndoBarrier™) in obese subjects with type 2 diabetes: Impact on pancreatic function, insulin resistance, gut peptides and gut permeability
Study Design	Open, single-centre, single-arm pilot study
Study Participants	Obese, adult, type 2 diabetic subjects with suboptimal glycaemic control and a BMI between 30 and 49 kg/m^2.
Number of Participants	12
Follow-up duration	15 months
Planned Duration	30 months
Primary Objective	The primary aim of the study is to explore short and long-term effects of the EndoBarrier™ implantation on insulin resistance and beta-cell function assessed by repeated Botnia clamps.
Secondary Objectives	In addition we will determine the changes in gut peptides and gut permeability after implantation of a removable duodeno-jejunal bypass device in obese subjects with sub-optimally controlled type 2 diabetes. Further we aim to investigate the changes in body weight, body composition, gut microbiota and the change in global cardiovascular risk from baseline to 9 months, estimated using the UKPDS risk engine.

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4. BACKGROUND AND RATIONALE

Obesity has reached epidemic proportions in the western world and has risen to the top of the public health policy agenda. The World Health Organisation (WHO) predicts that by 2015 approximately 2.3 billion adults will be overweight (BMI 25-29.9 kg/m²), and more than 700 million will be obese (BMI 30 kg/m² or more)(1).

In 2007, more than 40% of Austrian adults were either overweight or obese (11%) and the proportion of overweight people is projected to rise even further over the next 10 years (2).

The association between obesity and type 2 diabetes mellitus (T2DM) is well recognised. A higher body mass index (BMI) is a strong predictor of T2DM (3).

Currently, 285 million people suffer from type 2 diabetes, and this number is predicted to increase to 439 million by 2030 (4). T2DM raises the risk for cardiovascular events, heart failure, eye problems, and kidney diseases. The International Diabetes Federation (IDF) report 2012 predicts that diabetes will strike one in ten adults by 2030 (5). Previous research has demonstrated that the impact of diabetes on everyday life and the likelihood of costly and disabling complications can be minimized by more intensive management of glucose (6), blood pressure (7) and cholesterol (8).

Bariatric surgery (BS) has been established as a treatment option for morbidly obese patients or obese subjects with comorbidities such as T2DM. Bariatric surgery, besides reducing body weight, has been reported to improve glycaemic control in patients with T2DM and importantly to reduce cardiovascular events and overall mortality in obese subjects (9-12).

Interestingly, the degree of improvement in hyperglycaemia or reductions in rates of cardiovascular events or mortality do not appear to be directly associated with the amount of weight loss, suggesting a role for other mechanisms (11-13).

A crucial observation is that glycaemic improvement occurs rapidly, within the first weeks after BS, and cannot be explained by the relatively small weight loss seen during this short time period. These beneficial glycaemic changes after bypass procedures have been attributed to changes in incretin levels and other gut hormones (14). The more rapid stimulation of the distal ileum following operative exclusion of the duodenum and the proximal jejunum has been suggested as an explanation for the hormone changes observed (15). However, the definitive mechanisms leading to the rapid improvement in glycaemia or even remission of diabetes after BS have yet to be clarified.

Though, surgical interventions are irreversible and not free of complications. In some cases they require re-surgery or endoscopic procedures to correct problems such as fistulas etc. have to be performed (16). Additionally, operative therapies are not suitable for all obese patients or are not well accepted by all operative candidates.

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Recently a duodenal-jejunal bypass sleeve (EndoBarrier™ Gastrointestinal Liner; GI Dynamics, Inc., Lexington, MA, USA) has been introduced. The EndoBarrier™ is a 60 cm long impermeable fluoropolymer sleeve-like device that is placed endoscopically via the mouth and anchored in the duodenum to create a duodenal-jejunal bypass for up to 12 months. It allows transit of chyme from the stomach through to the jejunum without any contact with the duodenal wall. By not allowing mixing with bile and pancreatic exocrine secretions in the proximal jejunum, it mimics a duodenal-jejunal bypass and therefore induces weight loss.

A number of small studies have demonstrated the feasibility of implanting this device with subsequent weight reduction (17-19). In obese T2DM subjects a significant improvement in glycaemic parameters after EndoBarrier™ implantation has been observed (20) and a small randomised one-year study in 18 T2DM subjects with sham endoscopy as the comparator, demonstrated superiority of the liner in terms of glycaemic control compared to routine diabetes treatment (21). A recent small pilot study suggested that the implantation of the bypass device enhances secretion of incretin hormones such as glucagon-like peptide 1 (GLP-1), which might explain the improvement in glycaemic parameters observed. (22)

The potential advantages of the EndoBarrier™ are that it is minimally invasive, can be inserted and removed endoscopically as an out-patient procedure under conscious sedation, and the putative costs are lower than with BS. However, long-term efficacy and safety data on a large number of patients implanted with the EndoBarrier™ are lacking.

In addition, the detailed mechanisms of improved metabolic control induced by the EndoBarrier™ device as well as the impact on gut peptides or gut microbiota are largely unknown. As changes in gut microbiota have been suggested to be associated with changes in gut permeability, subsequent low-grade chronic inflammation and insulin resistance as well as glycaemia (23), the impact of this device on gut microbiome composition needs to be further elucidated, as it is very likely that it impacts gut microflora. Moreover, although an effect on glucose control and incretin levels was shown after the EndoBarrier™ implantation, data on sustainability of these effects after removal of the device are not yet available.

5. AIMS OF THE STUDY

The aim of the study is to explore short and longer-term effects of the EndoBarrier™ implantation on insulin resistance and beta-cell function assessed by repeated Botnia clamps. In addition we will determine the changes in gut peptides and gut permeability after implantation of a removable duodeno-jejunal bypass device in obese subjects with sub-optimally controlled type 2 diabetes. Further we aim to investigate the changes in body weight and body composition and the change in global cardiovascular risk from baseline to 9 months, estimated using the UKPDS risk engine.

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6. OBJECTIVES

6.1 Primary objective

Comparison of the changes in insulin sensitivity and beta-cell function following EndoBarrier™ implantation in patients with type 2 diabetes and suboptimal glycaemic control and a BMI between 30 and 49kg/m^2.

6.2 Secondary objectives

- To assess the beta cell insulin response to oral and intravenous glucose loads early (4 weeks) and 9 months after EndoBarrier™ implantation as well as 6 months after removal of the duodeno-jejunal bypass device.
- To assess changes in body weight from baseline to 9 and 15 months, respectively.
- To determine changes in gut permeability and gut microbiota from baseline to 9 and 15 months, respectively.
- To investigate changes in incretin hormone levels during the meal tolerance test (MTT) from baseline to 9 and 15 months, respectively.
- To evaluate changes in area under curve (AUC) of glucose from baseline to 9 and 15 months, respectively.
- To assess changes in body composition assessed by dual energy x-ray absorptiometry (DEXA) from baseline to 9 and 15 months, respectively.
- To evaluate correlations between MTT and Botnia clamp results regarding insulin sensitivity and beta-cell function
- To determine changes in cardiovascular risk as assessed by the UKPDS risk engine from baseline to 9 months and 15 months, respectively.

7. OUTCOMES

7.1 Primary outcome measures

- Acute insulin response to glucose during IVGTT will be used as a primary variable characterizing the beta cell function. Insulinogenic index (IGI), the early insulin response (EIR) and the ratio of AUC for C-peptide divided by AUC for glucose (AUC_{CP}/AUC_{GLU}) will be calculated.

7.2 Secondary outcome measures

- Plasma concentrations of incretins (GLP-1 and GIP) and its time profiles during MTT
- OGTT calculations and modelling describing beta cell response to oral glucose load; insulin and c-peptide areas under the curve during OGTT

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- Change in gut permeability (Lactulose/Mannitol Test)
- Weight loss will be reported as percentage of excess body weight loss (%EBWL) 4 and 36 weeks after EndoBarrier™ implantation as well as 6 months after removal of the EndoBarrier™
- Changes in cardiovascular risks (non-fatal and fatal coronary heart disease, fatal coronary disease, non-fatal and fatal stroke as well as fatal stroke)
- Changes in gut microbiota

8. STUDY DESIGN

This is an open, single-centre, prospective, single-arm pilot study evaluating the effect of EndoBarrier™ implantation on insulin sensitivity and beta-cell function in obese patients with type 2 diabetes. 12 subjects will be included in this pilot trial. The investigations will be performed at Medical University of Graz, Department of Internal Medicine, Division of Endocrinology and Metabolism and Division of Gastroenterology and Hepatology.

At baseline all subjects will undergo Dual-energy X-ray absorptiometry (DEXA) measurement, Botnia clamp, blood sampling as well as a meal tolerance test (MTT) and a Lactulose/Mannitol test to determine gut permeability. 4 Weeks, 36 weeks as well as 62 weeks after EndoBarrier™ implantation all subjects will undergo the above-named tests and investigations, again. Additionally at the baseline visit as well as after one year, tissue samples and intestinal content will be collected endoscopically. This pilot trial limited in size and scope will give us insight into the actions, efficacy and safety of the EndoBarrier™. The results of this pilot trial will help us in calculating the sample size for a further planned trial comparing the EndoBarrier™ against other established weight loss interventions.

8.1 Duration of Study

It is anticipated that the study will run for 30 months (from first patient first visit until last patient last visit).

8.2 Source Data

Source documents comprise the CRF and hospital records, laboratory records and correspondence.

All documents will be stored safely in a confidential manner. The subject will be referred to by a unique study subject number/code, their initials and date of birth on all study-specific documentations. The only exceptions will be the signed Consent Forms, Subject Identification log and subject clinical file, all of which will be stored securely by the clinical site.

Source data will be made available for internal and external audits or inspections by regulatory authorities to authorised personnel only.

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9. SELECTION AND WITHDRAWAL OF STUDY SUBJECTS

9.1 Subject Selection and Recruitment

The study population will consist of 12 subjects with type 2 diabetes mellitus and a BMI between 30 and 49kg/m^2. Patients will be identified from the outpatient clinic at the Department of Endocrinology and Metabolism, via Primary Care and adverts.

9.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or female, aged 18 - 70 years.
- Type 2 diabetes
- BMI 30-49 kg/m²
- HbA1c ≥ 6.5% (48 mmol/mol)
- Appropriate life style intervention measures have been tried but have failed to achieve or maintain adequate, clinically beneficial weight loss for at least 6 months
- Person is generally fit for intervention
- Person commits to the need for long-term follow-up

9.3 Exclusion Criteria

- Type 1 diabetes mellitus
- Maturity Onset Diabetes of the Young (MODY)
- Secondary diabetes due to a specific disease or glucocorticoid therapy
- Pregnancy or women of childbearing age without adequate contraception
- Women who are breast-feeding
- Hypothalamic cause of obesity, Cushing syndrome
- Major psychiatric disease including diagnosed eating disorders, history of drug or alcohol abuse
- History of bariatric surgery or complex abdominal surgery
- Inflammatory bowel disease
- Pancreatitis
- Cholelithiasis
- Uncontrolled gastroesophageal reflux
- Known upper GI bleeding conditions, e.g. gastric or esophageal varices
- Congenital or acquired abnormalities of the upper GI tract, e.g. stenosis

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- Subjects with or a history of coagulopathy, upper gastro-intestinal bleeding conditions such as esophageal or gastric varices, congenital or acquired intestinal telangiectasia
- Chronic non-steroidal anti-inflammatory drug (NSAID) or aspirin treatment (Subjects unable to discontinue NSAIDs (non-steroidal anti-inflammatory drugs) during the implant period)
- Previous GI surgery that could affect the ability to place the device or the function of the implant
- GLP-1 receptor agonist therapy
- Known ischaemic heart disease or heart failure
- History of stroke
- Active Helicobacter pylori (Note: Subjects may be enrolled if they had a prior history of Helicobacter Pylori and were successfully treated)
- Actual iron deficiency anemia
- Subjects or Family history of a known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder
- Known malignancy or any other multimorbid patient condition or circumstance, which, in the opinion of the investigator, would affect the patient's ability to participate in the protocol or would put the participant at an unjustified risk

9.4 Withdrawal/Drop out of subjects

Each subject has the right to withdraw from the study at any time without prejudice or compromise to future care.

The investigator may discontinue or withdraw the subjects under the following circumstances:

- Significant protocol deviation
- Significant non-compliance with treatment regime or study procedures
- An adverse event that requires discontinuation of the study medication or results in inability to continue to comply with study procedures. If a subject is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.
- Consent withdrawn
- Lost to follow up
- The study will be stopped prematurely if any information relating to the IMP or any other aspect of the study arises that may cause harm to the participant.
- Any other situation that may, in the opinion of the investigator, make it unsafe or inappropriate for the subject to continue in the trial

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9.5 Payment to subjects

Reimbursement of reasonable travel expenses will be considered.

9.6 End of study

The study end is defined as the last visit of the last patient. In the case of new data suggesting a significant safety concern of the device under investigation, the trial will be prematurely stopped.

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10 STUDY PROCEDURES

10.1 Schedule of study procedures

	Screening	Baseline			Follow-up					
	V1 (1-14day before V2)	**V2**	**V3** (up to 3 days after V2)	**V4** (up to 3 days after V2)	**V5** (4 weeks ± 2 week after V4)	**V6** (up to 3 days after V5)	**V7** (36 weeks ± 3 weeks)	**V8** (up to 1 week after V7)	**V9** (62 weeks ± 3 weeks)	**V10** (up to 1 week after V9)
Informed Consent	X									
Inclusion/exclusion criteria	X	X								
Demography, medical history	X									
Concomitant medication	X	X			X		X		X	
Vital signs	X	X			X		X		X	
Physical examination	X	X			X		X		X	
Pregnancy test (females with childbearing potential)	X	X			X		X		X	
Botnia clamp		X			X		X		X	
Blood sampling	X		X			X		X		X
Dual-energy X-ray absorptiometry (DEXA)		X			X		X		X	
Electrocardiography (ECG)	X									
Meal tolerance test (MTT)			X			X		X		X
^{13}C-Urea breath test	X									
Bypass liner insertion				X						
Bypass liner removal							X			
Food frequency questionnaire (FFQ)		X			X		X		X	
Biopsies				X			X			
Adverse Events			X	X	X		X		X	
Stool sampling			X			X		X		X
Lactulose/Mannitol Test			X			X		X		X
Gastroscopy Abdomen Sonography Liver Elastography		x								

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10.2 Visit Schedule

Visit 1 Screening (14 to 1 day(s) prior to potential enrolment)

Severely obese patients with T2DM are eligible to participate in our study. Those who accomplish the inclusion criteria and none of the exclusion criteria will be enrolled in the trial and submitted to the following investigation procedures in the screening visit, after signing the informed consent:

- Check inclusion and exclusion criteria
- Check for demographic data, medical and surgical history and concomitant medication
- Date of birth, gender, race, smoking status, alcohol consumption,
- Body weight and body height
- Vital signs: resting pulse and blood pressure
- Blood sample for HbA1c
- Baseline safety blood tests (fasting): Full blood cell count, renal function tests, liver function tests
- Physical examination
- Pregnancy test in female woman of childbearing age.
- ^{13}C-urea breath test

Visit 2 Baseline

In the morning of the second study visit (V2) the subjects will arrive at the Division of Endocrinology and Metabolism between 07:00 and 08:00 AM of the pre-scheduled day, after at least 8 hours fasting. During V2, the Botnia-Clamp (testing procedure combining intravenous glucose tolerance test [IVGTT] and hyperinsulinemic-euglycaemic clamp [HEC]) will be performed.

If blood recent blood values (within 6 weeks) are available to confirm the eligibility of a subject at the screening visit, visit 2 may also be performed together with the screening procedures.

As part of this visit the following procedures will be performed:

- Review inclusion and exclusion criteria
- Vital signs: resting pulse and blood pressure
- Body weight
- Physical examination
- Concomitant medication review
- Botnia clamp
- DEXA
- Urinary pregnancy test in female woman of childbearing age
- Gastroscopy
- Abdomen Sonography and Liver elastography
- Diet instructions.

Visit 3 Baseline (up to 3 days after V2)

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Study visit 3 will take place not later than 3 days after V2.

The subjects will arrive at the Division of Endocrinology and Metabolism after an overnight fast (at least 8 hours). Meal tolerance test (MTT) will be performed at V3.

Additionally, at Visit 3 subjects will be instructed by a qualified person to consume a liquid diet the first week after EndoBarrier™ placement, puree diet during the second week, and normal diet (1200 – 1500 kcal/day) combined with exercise and behaviour modification for the remainder of the implant duration. Participants will also be instructed to take a proton pump inhibitor (40mg BID omeprazole) starting 3 days before the implant through 2 weeks after explant. Daily multivitamin and iron supplements will be provided and recommended for use during the 52 weeks of the implant duration.

- Meal tolerance test
- Blood sampling
- Stool sampling
- Lactulose/Mannitol Test

Visit 4 (Implantation of EndoBarrier™)

Patient preparation

1. Patients must be fasting for 8 hours prior to the procedure.
2. Patients must be started on a Proton Pump Inhibitor (40mg twice a day) three days before the procedure and continue regimen until two weeks after the device is removed.
3. Spasmolytics may be used.

Sedation

4. The procedure will be performed under conscious sedation.

Procedural Step

5. Insertion will be performed according to manufacturer instructions

Visit 5 (week 4 ± 2 week)

Study visit 5 will take place not later than six weeks after the implantation of the EndoBarrier™.

- Physical examination
- Vital signs: resting pulse and blood pressure
- Body weight
- Concomitant medication review
- Botnia clamp
- DEXA
- Adverse events assessment

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- Pregnancy Test

Visit 6 (up to 3 days after V5)

Study visit 6 will take place not later than 3 days after V5.

- Meal tolerance test
- Stool sampling
- Blood sampling
- Lactulose/Mannitol Test

Visit 7 (36 weeks ± 3 weeks)

Study visit 5 will take place not later than 39 weeks after the implantation of the EndoBarrier™. At this visit the sleeve will be removed.

- Vital signs: resting pulse and blood pressure
- Body weight
- Concomitant medication review
- DEXA
- Adverse events assessment
- Biospies
- Botnia clamp

Visit 8 (up to 1 week after V7)

Study visit 8 will take place not later than 1 week after V7.

- Vital signs: resting pulse and blood pressure
- Body weight
- Concomitant medication review
- Adverse events assessment
- Meal tolerance test
- Stool sampling
- Blood sampling
- Lactulose/Mannitol Test

Visit 9 (62 weeks ± 3 weeks)

Study visit 9 will take place not later than 29 weeks after the removal of the EndoBarrier™.

- Physical examination

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- Vital signs: resting pulse and blood pressure
- Body weight
- Concomitant medication review
- Botnia clamp
- DEXA
- Adverse events assessment
- Pregnancy Test

Visit 10 (up to 1 week after V9)

Study visit 8 will take place not later than 1 week after V9.

- Meal tolerance test
- Stool sampling
- Blood sampling
- Lactulose/Mannitol Test
- Study end

Safety visits (after 12, 24 and 48 weeks)

12, 24 and 48 weeks after implantation safety visits will be carried out. As part of these visits blood samples (8ml) will be taken for safety measurements (including blood cell count, iron status, liver function). Additionally, the body weight will be recorded.

10.3 Laboratory results

All laboratory results will be reviewed and the reports signed by the study physician who will record whether it is normal, abnormal but not clinically significant, or abnormal and clinically significant. In the latter case, the eligibility of the subject will be reviewed.

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11 METHODS

11.1 Meal Tolerance Test (MTT)

The MTT will be performed after an overnight fast (apart from water). A standard gauge cannula will be placed into a subcutaneous vein for blood sampling. In order to prevent blood clotting in the cannula and to keep the cannula working it will be occasionally flushed with sterile normal saline. A pre-meal blood sample will be taken (- 5mins) and then all subjects will be asked to drink Fortimel compact (10 kcal/kg) over a period of 2-4 mins (time 0 mins). During the meal test further blood samples will be taken at 15, 30, 60, and 120 minutes. All samples will be used for determination of glucose and insulin. The blood at each time point will be placed into a fluoride oxalate tube (1ml) for plasma glucose and into a serum tube for insulin.

11.2 Botnia clamp (combined IVGTT and hyperinsulinaemic-euglycaemic clamp)

The Botnia clamp is a validated design for assessment of beta cell function and insulin sensitivity (24). After an overnight fast of at least 8 hours and after baseline samples have been obtained, 0.3 g/kg bodyweight of 20% glucose solution will be given at time 0 min. Blood samples for the measurement of plasma glucose, insulin and C-peptide will be obtained at -10, 0, 2, 4, 6, 8, 10, 20, 30, 40, 50 and 60min. At 60 min after the glucose bolus, hyperinsulinaemic-euglycaemic clamp will be started to evaluate insulin sensitivity. A priming dose insulin (3IU/m^2) followed by an infusion (40mU/m^2/min) of short-acting human insulin will be applied for 120 min. Blood glucose will be clamped at the concentration of 5.0 ± 0.5 mmol/l by a variable infusion of 20% glucose. Blood samples for measurement of plasma glucose concentrations will be obtained at 5 min interval, for measurement of insulin concentrations in 30 min intervals throughout the clamp. The mean amount of glucose infused during the last 60 min of euglycaemic clamp will be used to calculate the rate of whole-body glucose uptake.

11.3 Blood sampling

Glucose concentration in arterialized blood samples will be measured in duplicate, by using two Hitado Super GL (Hitado, Möhnesee, Germany). Insulin and C-peptide will be measured by using routinely available chemiluminescence on an ADVIA Centaur system (Siemens Healthcare Diagnostics, Eschborn, Germany). Routine parameters will be determined using a cobas analyzer (Roche Diagnostics, Mannheim, Germany). Plasma aliquots are prepared immediately after blood collection and stored at -80°C until batch analysis. 20 ml of serum and plasma respectively will be taken and stored at visits 3, 6, 8 and 10 for future biomarker analyses.

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11.4 GLP-1 and GIP analysis

Blood samples will be collected into pre-chilled tubes containing EDTA plus aprotoinin. After centrifugation plasma samples will be frozen at -80°C until analysis. For the determination of human active GIP a commercially available solid-phase sandwich ELISA Kit is used (GIP (active) ELISA; IBL International GmbH, Hamburg, Germany). The test is performed according the instructions provided by the distributor. Briefly, the coated plates are incubated with standards and samples. After that, incubation with labelled antibody is done followed by incubation with substrate solution. Reaction is stopped by addition of stop solution. After that, measurement is performed at 450nm in a Spectramax Plus 384 Microplate Spectrophotometer in combination with Spectramax Pro 4.6 software (Molecular devices, Ismaning, Germany).

11.5 Dual-energy X-ray absorptiometry (DEXA)

DEXA measurement will be performed with a GE Lunar iDEXA (GE Healthcare, Waukesha, WI, US) full size for the purpose of estimating percentage body fat according to the departmental Standard Operating Procedure. Body regions are defined using standard anatomical partitions. Scan areas are analysed to determine lean mass, fat mass, bone mineral content, and total body fluid percentage.

11.6 Gut microbiota analysis

Based on our previous studies the intestinal microbiota of the small intestine is not represented by the composition of the microbiota of stool samples. To study effects on the small intestine it is therefore mandatory to study samples obtained from the GI-tract.

Tissue samples and intestinal content will be collected endoscopically from the upper small intestine (duodenum) in addition to stool samples before and after implantation (at the time of removal) of the endoscopic duodenal-jejunal bypass liner. Samples will be analyzed for the small intestinal and the fecal microbiota using 16S rDNA based microbial community profiling by next-generation sequencing (NGS). Dependent on these results in a second step whole genome shot-gun sequencing for intestinal metagenome analysis would be possible. Furthermore the small intestinal mucosal immune system and enteroendocrine cells will be assessed by immuno-phenotyping of biopsies by means of immunohistochemistry (IHC) and FACS analyses.

11.7 Gut permeability (Lactulose/Mannitol Test)

The patient drinks a solution of 200 ml water containing 5 g lactulose and 1 g mannitol. Urine is collected over 5 hours while fasting is continued for 3 hours after study start. The urine volume collected at 5 hours is measured and 1-ml aliquots are frozen immediately at -80°C without preservative for subsequent analysis by high performance liquid chromatography. The mobile phase is

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degassed acetonitrile in distilled deionized water (70/30 by vol) at a flow rate of 1 ml/min. Detection is performed by a refractive index detector (LC 1240 R.I. Detector; GBC Scientific Equipment, Dandenong, Australia).

11.8 Food Frequency Questionnaire (FFQ)

A self-administered, semi-quantitative FFQ was developed to assess usual food consumption within the German Health Examination Survey for Adults 2008-2011 (DEGS) (25). The relative validity of this questionnaire was studied among participants of another nationwide survey, the German National Nutrition Monitoring (NEMONIT) (26). The FFQ includes questions about the frequency and the amount of 53 food items, consumed during the past four weeks. Frequency of consumption of food items was asked according to specified categories. In addition, the respondents had to indicate the portion size of the food items consumed in predefined answering categories. Pictures were used to aid the estimation of portion size for 33 food items. In total, 29 food groups will be presented by the food frequency questionnaire.

11.9 ^{13}C-urea breath test (13C-UBT)

The diagnosis of helicobacter pylori infection is currently established by histological, rapid urease, and culture tests using endoscopic biopsy specimens or by a 13C-UBT. The latter is a non-invasive approach based on the potent urease activity of helicobacter pylori and many reports evaluating its clinical utility have been published (27). The 13C-UBT is an excellent and non-invasive method for diagnosis of helicobacter pylori infection in the intact stomach and it is especially useful for judging the results of eradication therapy (28, 29).

11.10 Markers of insulin resistance

Serum-Aliquots will be used for untargeted analyses of signal peptides via Hot-MELT-MALDI technique (in co-operation with Prof. Makoto Sawada; University of Nagoya; Japan) to identify markers of insulin resistance.

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12 INVESTIGATIONAL MEDICINAL PRODUCT

12.1 Mechanism of action

The EndoBarrier™ works by creating a physical barrier between food and the intestinal wall. It is believed that this barrier alters the activation of hormonal signals that originate in the intestine. Food bypasses the duodenum and proximal jejunum as it does in a Roux-en-Y gastric bypass.

12.2 Therapeutical indications

The EndoBarrier™ System is indicated for the treatment of type 2 diabetes mellitus and/or obesity. Further, the EndoBarrier™ gastrointestinal liner is indicated for a maximum of 12 months.

12.3. Pre-procedural precautions

Patients must receive a Proton Pump Inhibitor (40 mg twice a day) 3 days prior to the procedure and should continue the medication until 2 weeks after the device is removed. To reduce the potential for infection, a single 2 gram dose of ceftriaxone should be administered intravenously 1-2 hours prior to device placement. Those individuals with known allergies or hypersensitivity to ceftriaxone, cephalosporins or penicillins should seek an equivalent, long acting, broad spectrum antibiotic.

12.4. Procedural precautions

A thorough gastroscopic examination of the stomach, pylorus and duodenum should be performed prior to device placement to ensure that the patient's alimentary canal is free of abnormalities which could interfere with the delivery, function and removal of the gastrointestinal liner. This should include observation of the papilla and other accessory ducts. This examination should be made to ensure that they are not located in the bulbous duodenum.

Placement and removal of the EndoBarrier™ requires the use of fluoroscopic guidance. Only water soluble contrast should be used. Gastrografin or equivalent is recommended. Do not use Barium. Caution should be used to protect the patient's reproductive organs from the effects of radiation.

An incorrectly positioned EndoBarrier™ may interfere with the bile duct or pylorus. Physicians should remove the incorrectly positioned device in these patients. Do not attempt to drag or push the device into position. Additionally, the EndoBarrier™ liner should be removed in any patient with clinical and/or chemical evidence of a biliary tract obstruction. Do not leave a device in place with a crossed tip. Crossed tips should be uncrossed by lifting them with endoscopic forceps.

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12.5. Post Procedural precautions

It is unknown if certain foods (such as grains and nuts) could interfere with the proper functioning of the gastrointestinal liner. Therefore, patients receiving the device will be placed on a diet regimen similar to that of a Roux-en-Y gastric bypass patient.

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13 ASSESSMENT OF SAFETY

Safety endpoints: All adverse events reported by the patients will be assessed and reported as outlaid below.

13.1. Definition

An Adverse Event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or clinical investigation subject administered a pharmaceutical product.

13.2. Potential Adverse Events

Potential complications during the placement procedure may include;

- GI tract laceration
- Oropharyngeal perforation
- Esophageal perforation
- Gastric perforation
- Bowel perforation
- Bleeding
- Aspiration
- Infection

Potential complications during the treatment period may include:

- Small bowel obstruction
- Implant migration
- Bezoar
- Erosion
- Bleeding
- Vitamin and mineral deficiency
- Dehydration
- Constipation
- Bloating
- Diarrhea
- Infection
- Hypoglycemia
- Hyperglycemia
- Flatulence

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- GERD
- Esophagitis
- Pseudopolyps
- Nausea/vomiting
- GI pain/cramping
- Peptic ulcer disease
- Duodenitis
- Gastric or bowel perforation
- Local inflammatory tissue reaction
- Flank/Back Pain
- Alopecia

Potential complications during and after device removal may include

- GI tract laceration
- Oropharyngeal perforation
- Esophageal perforation
- Gastric perforation
- Bowel perforation
- Bleeding
- Aspiration
- Adynamic ileus
- Infection
- Alopecia

Serious Adverse Event

A serious adverse event (SAE) is defined as any AE which:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered as serious, when base upon appropriate medical judgement that may jeopardise the patient/subject, and may require medical or surgical intervention to prevent one of the other seriousness criteria from occuring.

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Patients may be hospitalised for administrative or social reasons during the study (e.g. days on which infusion takes place, long distance from home to site). These and other hospitalisations planned at the beginning of the study do not need to be reported as a SAE in case they have been reported at screening visit in the source data and have been performed as planned

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information as documented above.

According to ICH E2A all SUSARs should be reported in an expedited manner to Competent Authorities, Ethics Committees and investigators concerned on an individual basis within timelines.

Regulatory timelines which have to be met are as follows:

- Fatal and life-threatening AEs: 7 calendar days after receipt
- Remaining serious AEs: 15 calendar days after receipt

The Intensity/Severity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated

Moderate: Enough discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship of adverse event

Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, dechallenge or rechallenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in case report forms.

13.2 Reporting Procedure for all Adverse Events

All Adverse events, serious and non-serious, will be collected, documented and reported on the appropriate CRFs/SAE reporting forms once informed consent has been signed and will end 28 days after completing the trial.

The following information will be recorded:

- participant details
- adverse event description
- start date of event

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- end date of event
- outcome of event
- severity of event
- treatment required
- relationship to study device (i.e. causality/relatedness)
- assessment of relatedness to other suspect drug or device
- action taken with study device
- whether subject withdrawn due to adverse event
- whether the event is serious
- Follow up information will be recorded as necessary

AEs considered to be related to study medication as judged by a medically qualified investigator will be followed until resolution or the event is considered stable. All related AEs that result in a subject's withdrawal from the study or are present at the end of the study will be followed up until a satisfactory resolution occurs.

14 STATISTICAL CONSIDERATIONS

14.1 Calculations

The combination of MTT and IVGTT will allow a comprehensive assessment of different aspects of beta cell function along with reliable measures of insulin sensitivity assessed during the euglycaemic clamp procedure (30).

From MTT data, the following empirical indices of beta cell function will be derived: a) insulinogenic index (IGI) calculated as (30 min insulin – basal insulin)/(30min glucose – basal glucose); b) the early insulin response (EIR) calculated using formula (30 min insulin – basal insulin)/(30 min glucose)(31) or c) ratio of AUC for C-peptide divided by AUC for glucose (AUC_{CP}/AUC_{GLU}). AUCs are determined by trapezoidal method. Additionally, we intend to implement the established mathematical modeling to describe distinct features of beta cell function (30, 32-34). The model describes the relationship between insulin secretion and glucose concentration coupled with a model of C-peptide kinetics. It provides not only basal insulin secretion rate and total insulin secretion during OGTT, but also three important indices of dynamic properties of beta cell function: beta cell sensitivity to glucose (glucose sensitivity), beta cell sensitivity to the rate of change of glucose (rate sensitivity) and a potentiation factor (representing relative potentiation of insulin secretion throughout the OGTT).

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Based on IVGTT measurements, the incremental trapezoidal area of insulin and C-peptide during the first 10 min after glucose administration represents the first-phase insulin response or acute insulin response (AIR). AIR will be also measured as the sum of insulin and C-peptide concentrations during the first 10 min after the glucose challenge. The incremental insulin/C-peptide secretion during the last 50 min of IVGTT represents the second-phase insulin secretion. The C-peptide deconvolution will be applied to reconstruct insulin secretory rates independently of insulin clearance.

It has been proved that rate sensitivity derived from OGTT is correlated to AIR calculated from IVGTT and it is therefore a valuable marker of first phase insulin secretion (34). AIR and rate sensitivity as well as insulin secretion rates are intended to be used for evaluation of beta cell insulin response to oral vs. intravenous glucose load.

Insulin sensitivity will be assessed as the mean glucose uptake, calculated from the glucose infusion rates during the last 60 min of euglycaemic clamp (M-value) and as the ratio of glucose infusion rates during the last 60 min of clamp and the mean steady state insulin levels during the same interval (M/I = S_I Index).

14.2 Statistical analysis

All data will be checked for distribution normality. Changes in beta cell function and other variables after EndoBarrier™ implantation will be assessed by analysis of variance (ANOVA) with repeated measures.

Additionally, the results of this pilot will be compared to already available results from a trial with comparable patients after bariatric surgery.

14.3 Sample size

This study is planned as a pilot trial to gain first data about the parameter outlined in the primary and secondary parameter section. Currently there is not sufficient data available which would allow to calculate the sample size needed. However, previous pilot trials investigating measurements of glucose metabolism with EndoBarrier have used 10-16 subjects to demonstrate improvements.[21,22] These data will then serve as a basis to perform adequately powered more definitive trials with this device in the future.

15 STUDY MONITORING

A risk-based approach will be taken to determine the frequency of study monitoring for the study which will be agreed with the Principal Investigator. Monitoring will be undertaken according to ICH

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GCP and the study monitoring plan. The study monitor will be suitably trained, qualified and experienced to perform this task. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents.

16 ETHICS

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, GCP-ICH and according to the protocol and the requirements of the concerned regulatory authorities.

The EndoBarrier™ is indicated for the treatment of type 2 diabetes and/or obesity. The EndoBarrier™ gastrointestinal liner is indicated for a maximum of 12 months.

The product is a thin tubular liner that isolates food from the digestive juices of the upper intestine. Although it avoids a surgical incision as required in conventional gastric by-pass surgery, an endoscopic procedure under sedation in hospital is still necessary to pass the liner, and later on to remove it. Although mostly well tolerated, patients may experience nausea, vomiting and upper abdominal pain. Other risks include infection and bleeding. It is contra-indicated in pregnancy. It is not a permanent treatment, and has to be removed after some months (mostly after 1 year). In that time it is anticipated that lifestyle changes will extend the duration of the improvement.

16.1 Informed Consent

1. Informed consent will be obtained for all participants in the study by the study physician.
2. Written versions of the subject information and Informed consent will be presented to the subjects detailing:
    - The exact nature of the study
    - The implications and constraints of the protocol
    - The known side effects and any risks involved in taking part.
3. It will be clearly stated that the subject is free to discontinue their participation in the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.
4. The subject will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their usual care provider or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of subject dated signature and dated signature of the person who presented and obtained the informed consent.

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5. A copy of the signed Informed Consent will be given to the subjects. The original signed form will be retained at the study site.

16.2 Ethical and Regulatory Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Ethics Committee of the Medical University of Graz, Austria.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

17. FINANCE

A research grant application has been submitted to the Austrian Nationalbank.

18. INSURANCE

Participant insurance according to legal requirements will be contracted.

19. RESPONSIBILITIES

The Principal Investigator is accountable for the conduct of the study. If any responsibilities are delegated, the Principal Investigator should maintain a list of appropriately qualified persons to whom he/she delegated specified significant study-related duties.

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