END REPORT

MC CP TAN2012-60 XX-1

The DIAMOND® for the Treatment of Type 2 Diabetes: Can blood Triglycerides level be the predictor for therapy efficiency? A Multicentre, Prospective, Semi-randomized Study

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First patient recruited 21 Oct 2013
First patient implanted: 6 Nov 2013
Last patient implanted 17 Jun 2016
Last patient completed 17 June 2018

Release date: October 17, 2018

Attachment I: End Report Signature Page

Principal Investigator Signature

I have read and understand the contents of the End Report for the protocol MC CP TAN2012-60-DE-1

Investigator Name (print)	Signature	Date

Protocol Synopsis

Document Number	**MC CP TAN2012-60 DE-1 (V01, 15-Mar-2013)**
Title	The DIAMOND® for the Treatment of Type 2 Diabetes: Effect of blood Triglycerides level on therapy efficiency A Prospective, Semi-randomized Study
Investigational Device	DIAMOND Implantable Pulse Generator (IPG) with Charge Coil; UltraFlex leads; DIAMOND Charger, Programmer
Study Period	May 2013 to May 2018
Development phase	Phase III
Study aims	The main objectives of this study were: (1) to evaluate the efficacy of gastric stimulation (GCM) using the DIAMOND System in the improvement of glycemic control measured by changes in HbA1c. (2) Examine the relationship between blood TG levels and the GCM efficacy for mechanistic purpose. (3) The effects of GCM on weight loss and associated co-morbid conditions.
Methodology	Prospective, semi-randomized, study
Number of Subjects	59 patients were implanted
Indication/ main inclusion criteria	Adult overweight and obese Type 2 diabetic subjects with a body mass index (BMI) of 30 to 45 (kg/m^2) and poor glycemic control defined as HbA1c ≥ 7.3% and ≤ 9.5% and fasting blood glucose (FBG) between 120-350 mg/dL.
Duration of Treatment:	The study duration was one year of study and one year of post study follow up.
Evaluations	<u>Primary endpoints</u>

of safety and device functionality	Comparison of the differences in HbA1c levels between baseline before the implantation and 12 months post-implant for: - Low blood TG (Triglyceride) patients - High blood TG patients - High blood TG patients treated with blood TG lowering therapy concomitant with GCM therapy <u>Secondary endpoints:</u> • Trends in weight loss compared the reduction in weight during treatment in 3 patient groups • Trends in Meal Tolerance Test profile between baseline and 12 months post-implant for 3 patient groups • Trends in improvement in metabolic parameters such as waist circumference, blood pressure and lipids 3 patient groups Safety: An evaluation of the type, frequency and severity of device and/or procedure related adverse events. Device functionality was assessed by means of parameters and physiologic recordings obtained from device interrogations.
Statistical Methods:	The analysis compared ends of period measurements, specifically, the null hypothesis that there is no difference in HbA1c between baseline and 12 months post implant will be tested by a two-sided 0.05 level test using a t-statistic.
Results	<u>Enrollment and System Efficacy</u>. • The failure rate for enrollment reached 45%, higher than initially forecasted, with a total of 59 subjects implanted in 9 European clinical sites. • HbA1c decreased from baseline (average of first 3 visits prior implant) to last visit by -0.78% (p=0.005) in the Fibrate group, by -0.6% (p=0.039) in the Normal TG group and were

	negligible in the Placebo group (-0.33%, p=0.2). These results support the hindering effect of high TG in the long term effects of GCM. • Upon Fenofibrate clearance, TG decreased by -70±93 mg/dL in the Fibrate group (p=0.0021) and had a significant linear correlation with the improvement of HbA1c in this group, (regression coefficient F=0.0078), with TG explaining 57.6% of the change in HbA1c. This correlation was absent in the Placebo group. • Changes in body weight were significant in all groups, with the averages of: -4.9 kg in the Fibrate group, -3.9 kg in the normal TG and -2.7 kg in the Placebo. Waist circumference was significant only in the Fibrate and Normal TG groups (-5.2 cm and -3.1 cm, respectively). The change in weight was significantly associated with HbA1c only in the Fibrate group, explaining approximately 59% of the glycemic changes. Furthermore, systolic BP was associated with weight changes only in the Fibrate group. A responder analysis was done with cut off of -0.6% HbA1c in all groups. In the Fibrate group the resulting 13 responders out of 20 subjects had an average glycemic improvement of -1.6%; in the Normal TG, 9 responders out of 17 subjects, had an average change of -1.6% in HbA1c, and in the Placebo group 12 responders out of 20 subjects had a -1.3% HbA1c change. Regression analysis of all 34 responders showed a significant inverse relationship with TG, explaining about 53% of the improvement of HbA1c. <u>Device Functionality</u> Device statistics of accumulated eating detections and GCM trains delivered during the study showed no cumulative

	difference collected by the implanted device Safety Only 10 adverse events were considered to be have some relationship with the procedure, with 9 involving wound or pocket pain of mild to moderate severity in the post op period. There was one pocket infection (severe) and one wound producing seroma (mild). There were no serious adverse events.
Conclusions	In regards to safety, it can be concluded the Diamond system was well tolerated and its functionality did not cause adverse events. The system functionality was no different between the groups, suggesting differences between the groups could not be attributed to uneven GCM dose delivery. There remain issues of patient compliance with weekly charging of the battery, which may become challenging as the clinic visit intervals are extended. Mechanistically, a mediator role for Triglycerides in the action of GCM treatment can be inferred. Obese diabetics with normal TG and fibrate-treated high TG patients showed after one year treatment clear improvements in glycemia, body weight and waist circumference. Changes in these variables were minor or absent in a parallel group of obese-diabetics with untreated high TG. Changes in metabolic status may be attributed in part to central effects of the DIAMOND in early satiety and long term satiation. The latter would be associated with long term reduction in weight, waist circumference and concomitant glycemic improvement. Peripheral effects of GCM, such as increased sensitivity to insulin, improvement in glucose metabolism and in the indices of beta cell function comparing acute challenges at baseline and after 12 months,

	appear to be independent of TG. These are thought to reflect immediate GCM dependent efferent and vago-vagal signaling to abdominal organs such as the liver, intestine and pancreas improving their function and eliciting significant reductions in circulating glucose with similar initial insulin levels. Overall, improvement in diabetes type II can result from non-excitatory vagal stimulation via enhanced contractility of antrum smooth muscle contractility in selected obese-diabetic subjects. Clinical significance however, may be deemed moderate and require additional behavioral changes, as it remains dependent in patient compliance, ultimately preventing the realization of a relevant and convincing product.

1.1 ETHICS

Independent Ethics Committee (IEC) or Institutional Review Board (IR)

This trial was originally designed as a multi-center, prospective treatment study of minimum 45 obese-diabetic patients implanted with the Diamond I and

followed for 52 weeks post-operatively, with a second year of post study monitoring.

Before the study was initiated, the protocol and patient informed consent were submitted and approved by the Ethics Committee (EC) in (chronologically):

- Poland (Independent Public Clinical Hospital Witold Orłowski, CMKP in Warsaw, issued on 29-May-2013),
- Greece. Sc Eugeneudio, Athens issued on 7 Nov 2013.
- Serbia Clinical Center of Serbia, Clinic for Digestive Surgery, Belgrade and Institute for Pulmonary Diseases of Vojvodina (issued in 17 and 22 July 2014 respectively). Ministry of Health confirmation obtained on 24 Sep 2014.
- Italy (Catholic University, Rome, issued on 29-Jan-2015)

The formal written approval by the EC and all relevant correspondence pertaining to this submission have been filed in the Trial Master Files.
Slight revisions to the protocol addressed guiding Ethics Committee requests as new sites were incorporated. These changes maintained however, the same endpoints, enrollment criteria and methods:

- A revision Rev 02a, dated 10 November 2014 was approved for the Italian sites, allowing the study to run between March 2013 and July 2015. 65 subjects were expected to be enrolled. This version described in detail the secondary endpoints regarding trends in weight reduction, changes in the hormone profile at the Meal Tolerance Test between baseline and 12 months and trends in metabolic parameters such as weight circumference, blood pressure and lipid panel in the 3 groups.

- A second revision Rev 02c, dated 5 May 2015 was approved to reflect newly appointed sites in Australia (no patient was eventually

enrolled). This version allowed the study period to start in March 2015 and continuing until successful enrollment of 65 patients with a 30% dropout. The version had additional information on risks associated with Fenofibrate, the drug used to lower Triglycerides in High TG patients randomized to Triglyceride (lowering) treatment group.

- A Ver 01 of the protocol was released the 1st April 2016, changing the name to MC CP TAN2016 – 60. The Rev 1 version allowed the study to run from April 2016 to April 2018, changed the amount of implanted subjects to at least 40. It also added references to recent studies with the DIAMOND system, and allowed for potential use of the DIAMOND II device (not implemented eventually). This version widened the scope of the Triglyceride effect on the DIAMOND treatment through the randomization into treatment and placebo controlled data on patients enrolled to the high TG group.

This report was written in accordance with the latest version; and describes the 59 diabetic patients successfully implanted for this protocol and completed 1 year follow up.

1.2 ETHICAL CONDUCT OF THE STUDY

This study was performed in accordance with the protocol, GCP and the applicable national (ISO 14155) and local regulatory requirements. The principal investigators at the centers were responsible for the conduct and administration of the study and for collecting, recording, and reporting the data accurately and properly.

1.3 PATIENT INFORMATION AND INFORMED CONSENT

Written informed consent was obtained from each patient before any procedures or assessments were done and after the aims, methods, anticipated benefits and potential risks were explained. It was also made clear to study participants that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written and oral information about the study was given in a language that was understandable to all patients and the investigator kept the original form that was signed and dated by the patient.

1.4 Investigational Team and Study Administrative Structure

1.4.1 Participating Centers and Key personnel

Sites participating were chosen based on the qualifications of the Investigator, their availability of sufficient resources to carry out the required study procedures, and their ability to recruit subjects into the study.

Key Personnel	Site Number	Name
Principal Investigator	05	Prof. Wieslaw Tarnowski General and GI Tract Surgery Dept and Dept of Endocrinology, Centre for Postgraduate Medical Education (CMKP) Ul. Czerniakowska 2311090 Warsaw, Poland
Co-Investigator, medical team	01	Prof. Syrenicz Anhelli, Andrysiak Mamos Elzbieta MD, PhD Endocrinology and Internal Disease Dept. Pomeranian Medical University in Szczecin , ul. Unii Lubelskiej 1, Poland
	02	

Co-Investigator, medical team		Prof. MD PhD Roman Junik, MD, PhD Agata Bronisz Endocrinology and Diabetology Dept, Medical University in Bydgoszcz , Poland
Co-Investigator, medical team	03	MD, PhD Irena Szykowna Centre for Diabetes and Obesity Treatment „DIABETA-CARE" of Lubin, Poland
Co-Investigator, medical team	04	Prof. Maria Gorska Endocrinology, Dabetology and Internal Disease Dept., Medical University of Bialystok Ul. Marii, Poland
Principal Investigator	70	Dr Miloš Bjelović (Surgery) Dr. Snezana Polovina (Endocrinolgy, Diabetology), Belgrade, Serbia
Principal Investigator	71	Prof. dr Miroslav Ilić (Surgery), Novi Sad, Serbia
Principal Investigator	09	Prof. George Chroussos (Endocrinology), Athens, Greece
Principal Investigator	40	Prof. Geltrude Mingrone (Diabetes & Nutritional Science), Rome, Italy

1.4.2 KEY PERSONNEL AT METACURE

Project Manager	Dr. Ricardo Aviv
Field Clinical Engineers	Dr. Hakim Tafer
Medical Associates	Dr. Lech Rogoski
Medical Consultants	Stefan Tucholski Czarek Jagoszewski

1.4.3 CRA/CRO/associates.

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Statistics Data Management	Tseela Schwartz , Ayelet Goldwasser	GCP Clinical Studies Ltd. Phone: + 972 3 9002022 www.gcp.co.il

Important contributors to the design and execution of the clinical trial are Dr. Mateus Zelevski, Dr. Irit Yaniv and Prof. Harold Lebovitz. We thank Ayelet and Tseela for their continuous support.

1.5 Name and Intended Use of Device

The DIAMOND System was previously known as TANTALUS II; it is an implantable system capable of delivering gastric stimulation signals. The device is intended to induce weight loss and improve glycemic control in overweight and obese type II diabetic patients. In this study, the DIAMOND System employed the rechargeable implantable pulse generator (DIAMOND IPG) with automatic eating detection.

1.6 Study Objectives

The main objectives of this study are to evaluate the efficacy of gastric stimulation (GCM) using the DIAMOND System in the improvement of glycemic

control measured by changes in HbA1c. Relationship between blood TG level and the GCM efficacy will be evaluated. The effects of GCM on weight loss and associated co-morbid conditions will also be evaluated.

1.7 DURATION OF THE STUDY

It was expected that it will take up to eight (8) months to enroll up to forty five (45) subjects into the study. However, it required almost 32 months to recruit and imlant the 59 patients.

1.8 STUDY ENDPOINTS

1.8.1 Primary Endpoints

Comparison of the differences in HbA1c levels between baseline before the implantation and 12 months post-implant for:

- Low blood TG patients
- High blood TG patients
- High blood TG patients treated with blood TG lowering therapy concomitant with GCM therapy

1.8.2 Secondary Endpoints

- Trends in weight loss will be of a reduction in weight during treatment in 3 patient groups
- Trends in Meal Tolerance Test profile between baseline and 12 months post-implant for 3 patient groups

1.9 STUDY DESIGN

This was a multicenter, semi- randomized study.

All subjects underwent baseline evaluation (Visit 1 -3) during which the stability of their glycemic parameters, medical treatment and medical condition was assessed. Subjects meeting inclusion/exclusion criteria were implanted. Prior to their implantation, subjects were seen for 'pre-implant' medical evaluation (Visit 4). One week after implant (Visit 6, Week 1) subjects were assigned into one of two groups (LTG and HTG).

"Group LTG" subjects with baseline blood triglyceride level ≤ 1.7 mmol/l had their device programmed to deliver GCM signal including the setting of automatic eating detection parameters for a 48 weeks period.

"Group HTG" subjects with baseline blood triglyceride level > 1.7 mmol/l were randomized into two arms:

HTG + FENOFIBRATE had their device programmed to deliver GCM signal including the setting of automatic eating detection parameters for a 48 weeks period and will receive fenofibrate at the dose of 160mg per day

HTG + PLACEBO had their device programmed to deliver GCM signal including the setting of automatic eating detection parameters for a 48 weeks period and received placebo of fenofibrate administered in the same schedule as the drug.

At the end of the 48th week, all subjects were offered to keep the device active for another one year – a monitoring period/ follow up, section 10.7). Subjects were offered the opportunity to keep the device turned 'ON', and were issued a new device warranty and turned over to their investigator to monitor as appropriate for their diabetes.

The study design is summarized in figure 1.

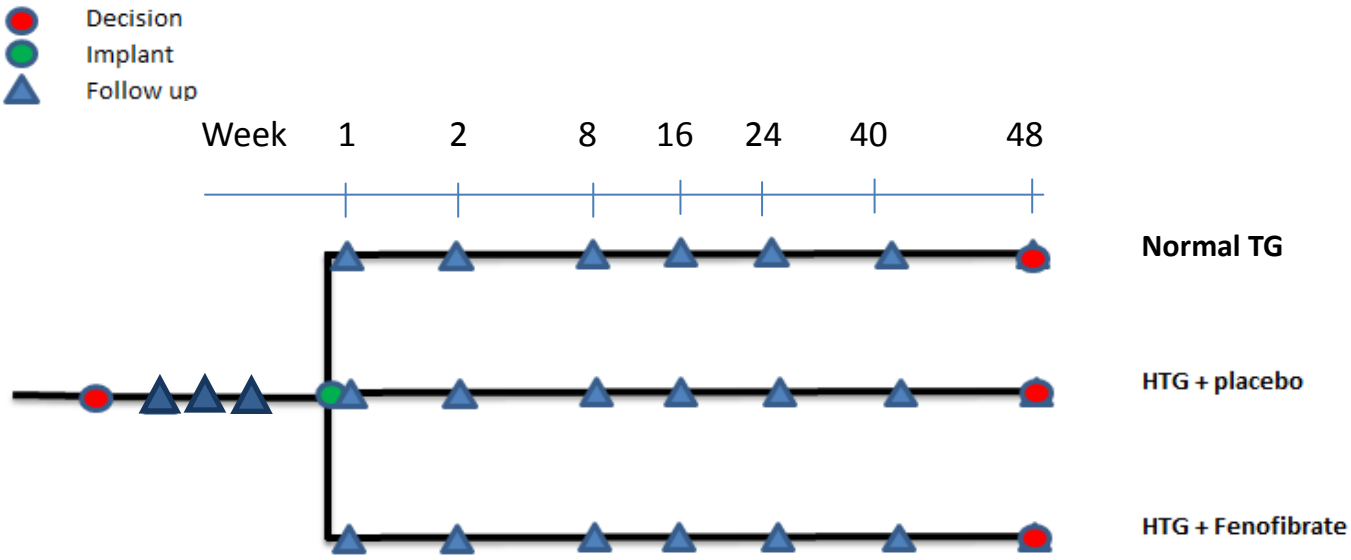

Fig 1. Study design. Patients are randomized to Fibrate treated group or Placebo if their TG is above ≤ 1.7 mmol/l. Patients enrolled with < 1.7 mmol/l participate in the Normal TG group

Type 2 Diabetes Mellitus (T2DM) remains a metabolic disorder characterized by a combination of insulin resistance and insulin secretory deficiency. These defects result in inappropriate glucose metabolism. During the last several years, we have evaluated effects of neuromodulation on metabolic regulation in patients with type 2 diabetes. This is a novel type of gastric electrical non-excitatory stimulation (GCM, Gastric Contractility Modulation) designed to influence gut-central nervous pathways thereby improving metabolism. Gastric electrical stimulation with the DIAMOND® device was shown to improve glycemia, associated reductions in body weight and systolic blood pressure. The same patient population, - obese patients with type 2 diabetes inadequately controlled by oral antidiabetic medications— was addressed throughout several open studies. [1-4]. Results from 12 month duration trails suggested the importance of TG (Triglyceride) levels on the glycemic effect of the DIAMOND® [1]. The major HbA1c reductions were observed in the subpopulation of patients with normal or

low fasting plasma triglyceride levels. These observations led us to incorporate to our working hypothesis that nutrient status -specifically fasting plasma triglycerides-- may modulate responses to gastric electrical non-excitatory stimulation in humans. Furthermore, initial experiments in animals showing GCM enhancement of afferent vagal signals support the view of a forward action of enhanced contractility on vagal targets, thus possible hypothalamic responses to GCM could in principle diverge under the influence of TG levels. [5].

Our current hypothesis states that GCM neuro-stimulation activates neural pathways involved in the regulation of metabolic homeostasis leading to satiation, and glycemia, see fig 2.

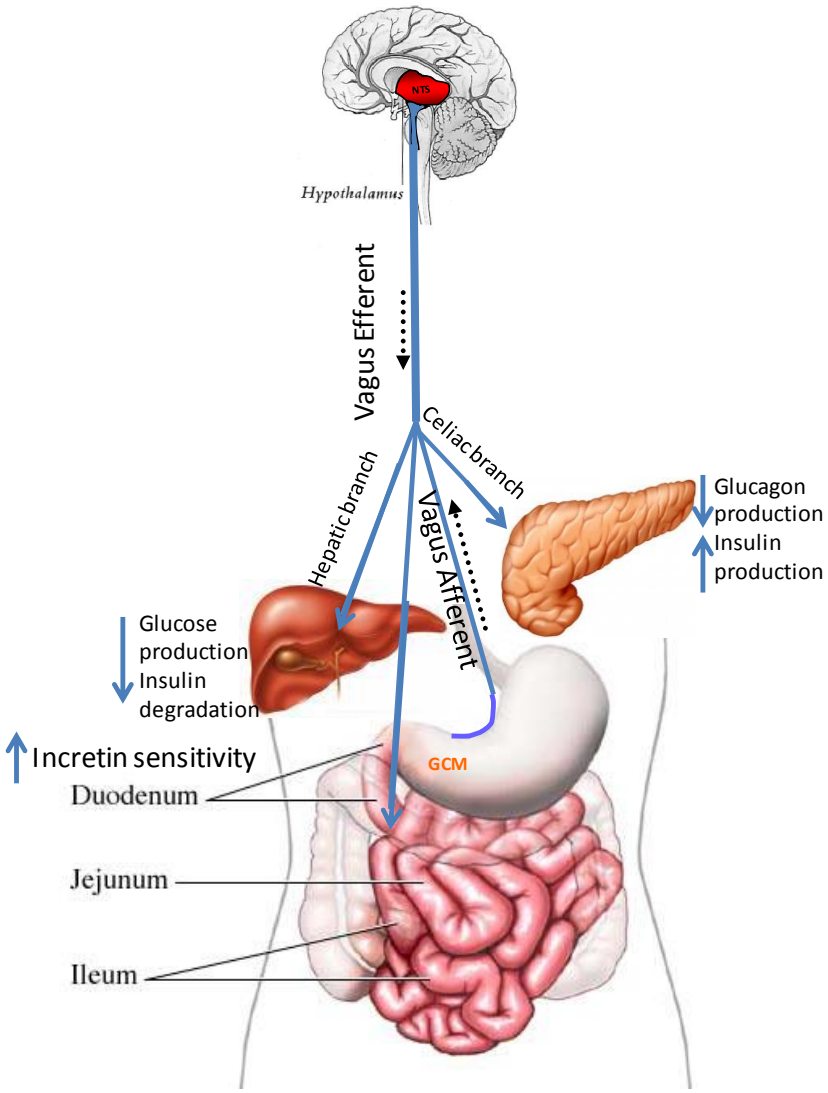

Fig 2. Current understanding of the mechanism of action of GCM. Persistent stretch of the stomach with food intake elicits afferent vagal firing. Individual antrum afferent fibers discharge directly into the NTS Nucleus Tractus Solitarius) during and after meals in a process enhanced by GCM. Enhanced NTS signaling is thought to integrate peripheral and sensorial information initiating the perception of satiety during ingestion, inhibiting further ingestion, and in the long term may sustain satiation. In parallel, local myenteric circuits respond to GCM sustained changes in smooth muscle contractility, improving gastric emptying in the post-prandial period, and fasting motility in the late-post prandial period. Further changes in the stomach excitability are though to propagate to neighboring organs resulting in improved insulin sensitivity and glycemic responses.

2.1 STUDY OUTLINE

The current protocol asks whether fasting plasma TG have a marker or a mediator role in the term magnitude and durability of the DIAMOND® metabolic effects. That is, if high TG subjects treated with fenofibrate to reduce TG levels show after one year reductions in HbA1c while these remain absent or are blunted in a parallel group of untreated high TG. Both high TG groups are further compared to a normal TG group where DIAMOND effects on glycemia are indeed expected. Figure 3 shows a diagram of the hypothesis.

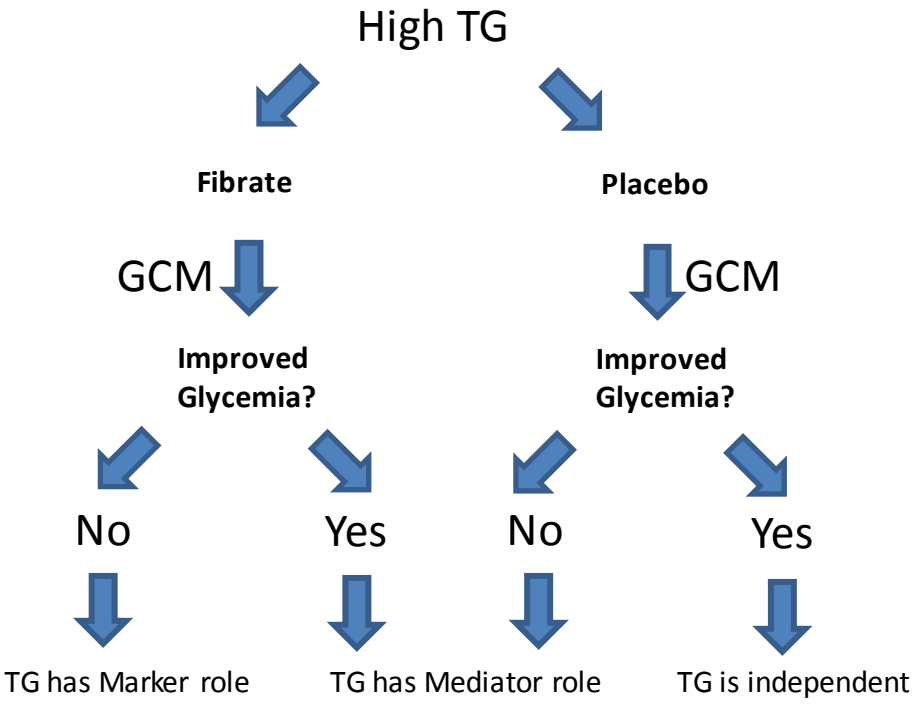

Fig 3. Evaluation of TG effect on GCM treatment. For a mediator role, low TG are required. The Normal TG group functions as the control for both the Fibrate and Placebo groups. The Normal TG group is expected to be comparable to the Fenofibrate treated high TG group, not shown on the diagram.

3 RESULTS

3.1 ENROLLMENT

The protocol had initially forecasted up to 30% screening failures, although a failure rate of 45% was observed. A total of 59 subjects were implanted, with mean age 52±8 y.o. Table 2 shows the enrollment per site.

Site	Enrolled	Implanted	Screening failure
01	5	4	20%
02	13	4	69%
03	10	3	60%
04	13	9	31%
05	13	7	46%
70	33	21	36%
71	10	5	50%
09	1	1	0%
40	8	5	38%
Totals	**105**	**59**	**Mean 45%**

Table 1. Enrollment per site. 27 subjects were implanted in 5 sites throughout Poland, 26 in two sites in Serbia, 5 subjects were implanted in one site in Italy, and one patient was implanted in Greece.

Basic characteristics of the implanted subjects are seen in Table 3. While the amount of participants was similar in the three groups, body weight was significantly lower in the Normal TG group when

compared to both High TG groups. Glycemic index HbA1c and FBG were significantly higher in the High TG-F vs. the Normal TG group as well. Waist circumference was significantly lower in the Normal TG group vs the High TG groups, while Blood Pressure were not different among the subjects.

Table 2 shows initial baseline characteristics for the three groups.

	Normal TG	**High TG Placebo**	**High TG Fenofibrate**	**t-test**
Number of subjects	21	17	21	
Female	13 (62%)	7 (41%)	13 (62%)	p=N.S.
Weight	101.8±16.7	112.2+19.1	111.2±16.5	p=0.044*, p=0.037**
HbA1c (%)	8.0±0.6	8.5±0.7	8.1± 0.7	p=0.011*
FBG (mg/dL)	154.5±69.0	206.5±49.3	164.2±28.3	p=0.008*
TG (mg/dL)	120.7±28.6	303.4±188.1	239.0±105.6	p<0.001*, **
Waist Circumference (cm)	114.3±11.5	121.6±14.2	121.0±10.4	p=0.043*, p=0.026**
Systolic BP (mmHg)	137.2±18.0	135.0±13.7	135.7±18.9	p=N.S.
Diastolic BP (mmHg)	84.5±11.1	84.4±9.9	85.4±9.5	p=N.S.

Table 2. Baseline values of the three groups. *, t-test between Normal

TG and High TG placebo, **, t-test between Normal TG and High TG Fenofibrate.

3.2 EFFICACY.

In order to evaluate the effect of neuromodulation on obese-T2DM we reviewed the data analysis in three iterations:

(1) normal and log data distribution. Only WC data was normally distributed. All other data variables were log transformed for further analysis. Baseline for all analysis was calculated as the average of the 3 reading values V1 to V3. Baseline was compared to V12 where available with paired t-tests. When the V12 value was missing, the last value available was carried forward, limited to V9, to prevent placebo effects.

(2) Temporal analysis, to reveal trends throughout the study. Relations between the variables were evaluated by assessing their degree of association with linear regressions.

(3) Responder analysis was used to evaluate the impact of the GCM treatment in the three groups.

3.3 GLYCEMIC STATUS

Plots of log(HbA1c) with time showed significant linear regression coefficients and significant reduction in the Fibrate and Normal TG, see fig 3. Decrease in HbA1c appeared to reach a minimum in the period of 8-20 weeks after the implant, and reverse thereafter. Paired t-tests between BL and Week 48 showed statistical significance on HbA1c Fibrate group, with reductions (on the 19 subjects with V12 data); where glycemic index improved from 8.1$\pm$0.7% to 7.4$\pm$1.4%, p=0.0109, whereas the Normal TG group showed a significant change (in the 19 subjects with visit 12) from 8.0$\pm$0.6% to 7.4$\pm$1.4%, p=

0.048, see fig 4. The Placebo showed only minor changes, from 8.4±0.5% to 8.1±1.8% (p=N.S.) These results suggest high circulating TG is detrimental to the GCM effects.

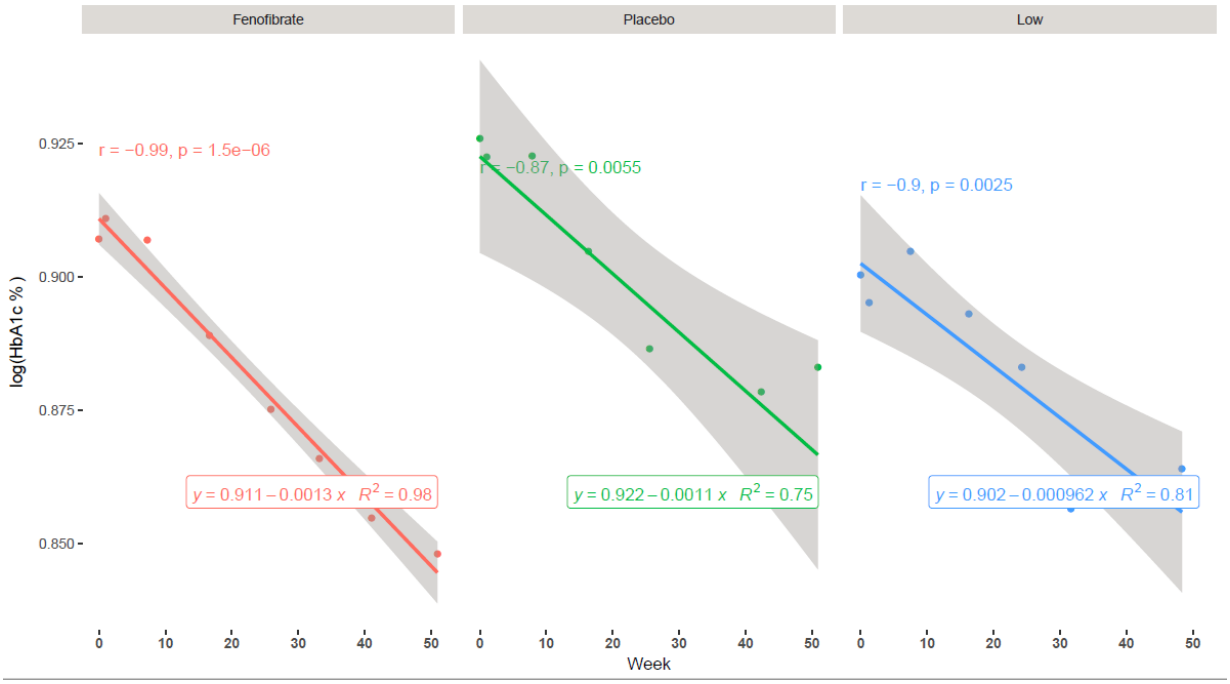

Fig 4. Temporal variation of HbA1c in the 3 groups. Plots show log conversion of the mean and standard deviation of HbA1c throughout the study. Linear regressions are significant for the three groups.

3.4 FBG

The log(FBG) distribution did not reach statistical significance in none of the groups. Apparent initial drops in FBG was gradually lost with mid-term minimum at 16-30 weeks after the implant, see fig 5. When differential changes are taken into account it becomes clear the changes respect to V5 (beginning of the GCM treatment) are variable and smaller with time, resulting in upward trends, although none of the linear regressions were significant, not shown. Accordingly, none

of the paired t-tests between BL and V12 reached statistical significance.

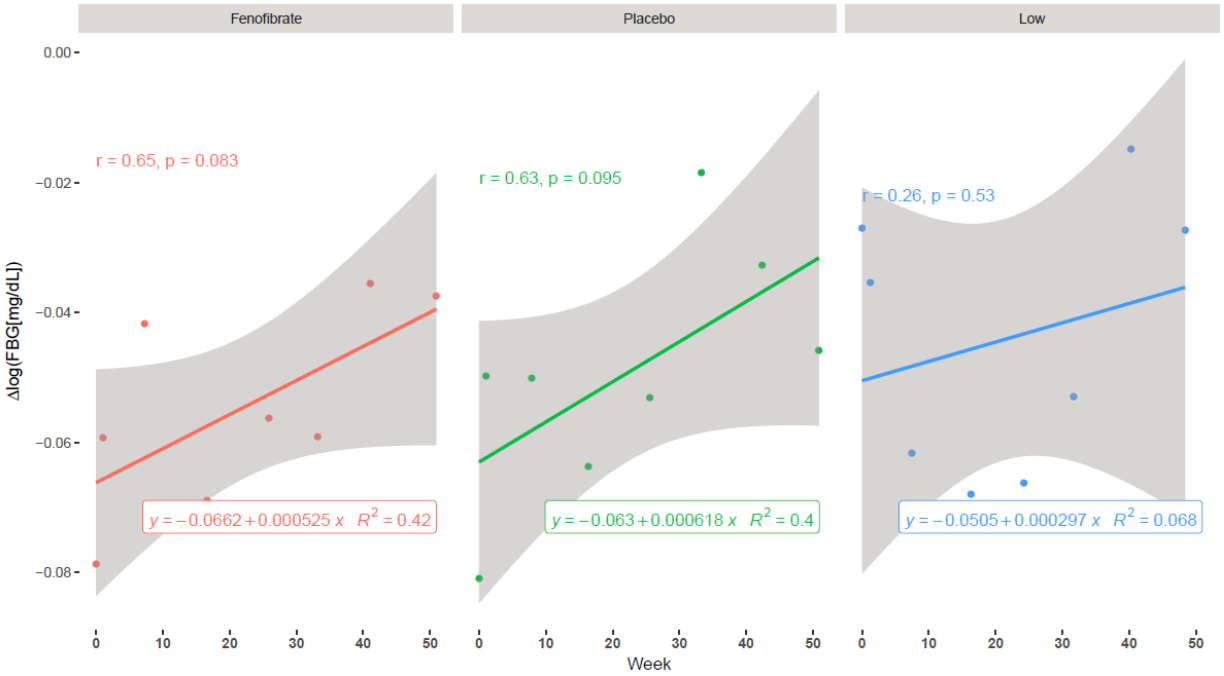

Fig 5. Linear regression of FBG distributions in the three groups showed upward trends, especially Fibrate and Placebo groups, although none did not reach statistical significance.

3.5 TRIGLYCERIDES

The distribution of TG in the three groups was dissimilar. The Fibrate group average showed a linear and statistically significant reduction, indicating a positive effect of the intended TG clearance in these subjects, see fig 6. Paired t-tests with the 19 subjects having data at visit 12, showed significant reduction in the Fibrate group, reducing the average BL 239±69 to 176.5±69.7 mg/dL at visit 12. Although the group average remained above the threshold seven subjects reached

Normal TG levels (<150 mg/dL), see responder analysis below.

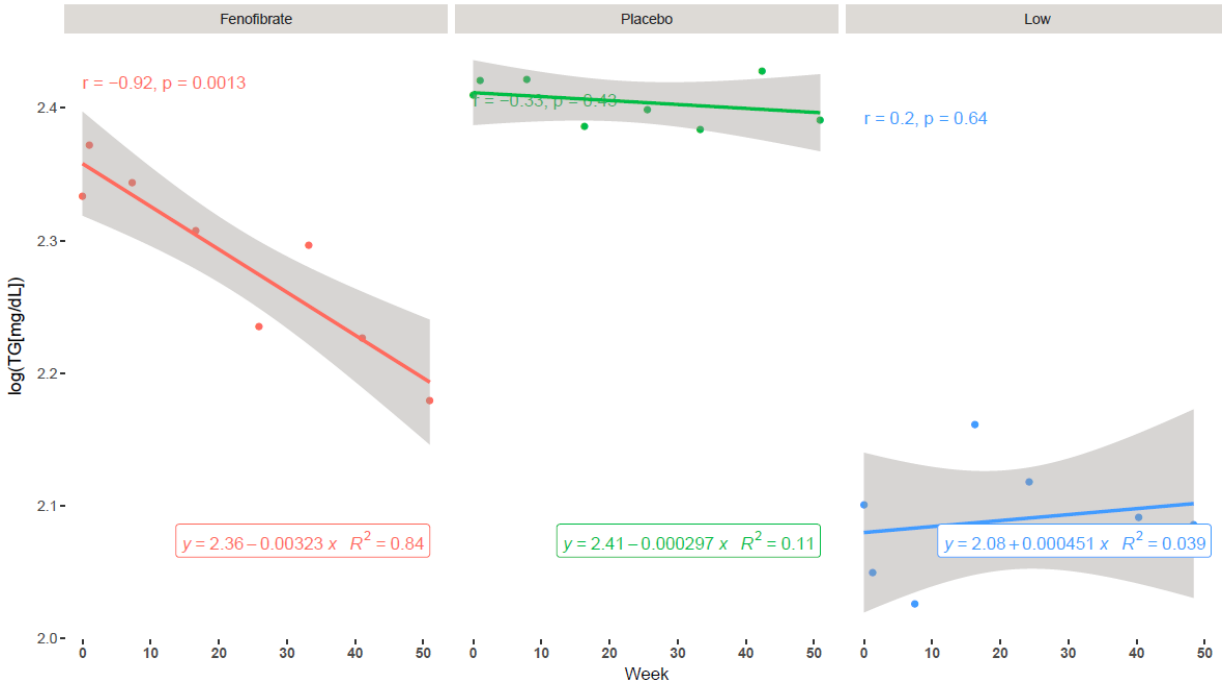

Fig 6. Log(TG) time course of mean and standard deviation in the three groups. Plots show the effect of fenofibrate in lowering Log(TG). Linear regression of the time course for the three groups shows significance only for the fibrate group.

3.6 TRIGLYCERIDES AND GLYCEMIA

To further assess whether GCM had an effect dependent on TG clearance from the circulation, linear regression between TG means at every visit vs HbA1c means were obtained. It is clear from fig 6 that TG lowering elicited an effect on HbA1c which was absent in the placebo group. Furthermore, whereas TG decreased in average 64±93 mg/dL in the fibrate group (p=0.0122) the placebo group had a non-significant change of -13±83 mg/dL.

While the difference in initial BL values between the high TG groups was not significant (p=0.09), it is likely that a process of sequential

randomization in blocks of small number of subjects, would have generated probably more homogenous groups at onset.

3.7 RELATIONSHIP BETWEEN TRIGLYCERIDES AND GLYCEMIA

Fig 7 shows linear regressions between changes in TG and HbA1c for all visits. A clear relationship in the Fibrate group is visible. These results support further the hypothesis that high TG hinder GCM action.

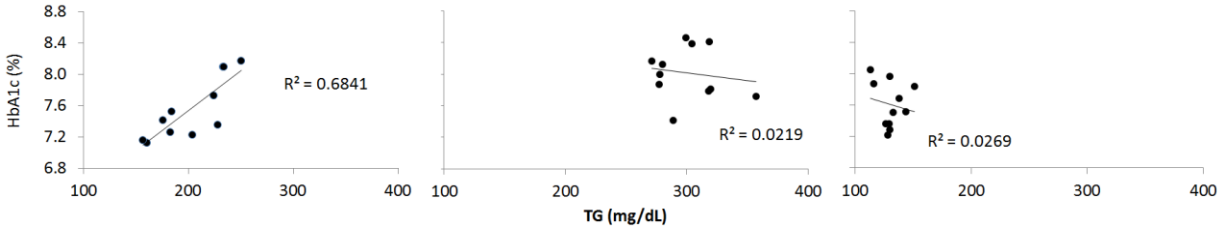

Fig 7. Linear regression between mean TG and mean HbA1c throughout trial visits. (Left, Fibrate group, R =0.827, p= 0.0061; middle, Placebo p=N.S; right, Normal TG p=N.S).

3.8 WEIGHT AND WAIST CIRCUMFERENCE

Changes in body weight and waist circumference were mild and in line with previous studies with the Diamond (1-4). Linear regression of the evolution of weight in the three groups showed significance for the Fibrate and the Normal TG groups ($p<0.05$), and a reduction trend in the Placebo group, see fig 8. These observations are in line with the glycemic dependence on TG and support the working hypothesis that high TG may hinder GCM effects on glycemia and weight. Paired t-tests showed that Fibrate and Normal TG had significant body weight changes, from 111.9±16.7kg to 107.0±16.9kg($p<0.01$, $n=19$) and from

99.6±17.7kg to 95.7±17.0kg (p<0.01, n=17), respectively. The Placebo group had also significant weight reductions albeit minor, from 112.1±19.1 to 109.4±18.7 kg, p<0.01, n=17. Changes in weight were more sustained in the Fibrate group, whereas after a rapid reduction at the beginning of the trial, weight changes were mild in the Placebo and in the Normal groups.

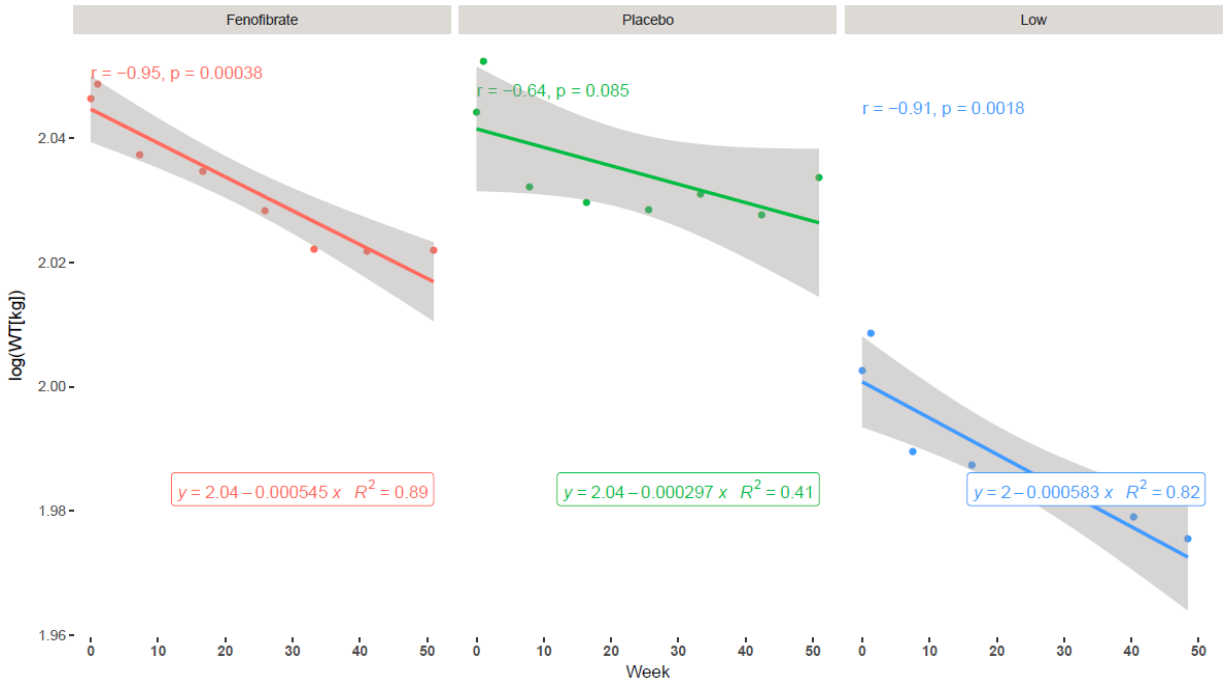

Fig 8. Mean weight changes with time. Log(kg) transformation of mean weight visit values.

WC changes accompanied weight changes with sustained and significant reductions throughout the trial. Linear regression of the progression of WC in the three groups showed significant changes for the all groups (p<0.05), see fig 9. As with weight, the variation in WC was more pronounced in the Fibrate and in the Normal TG group backing the working hypothesis that high TG may adversely affects

GCM secondary effects on WC as well. Paired t-tests showed that Fibrate and Normal TG had visible WC changes, from 121.5±10.0 cm to 116.3±8.8 cm (p<0.01, n=19) and from 112.3±11.5 cm to 109.2±12.2 cm (p < 0.01, n=17), respectively. The Placebo group showed non-significant changes in WC, from 120.7±14.2 cm to 119.5±14.5 cm, (p=0.084), n=16.

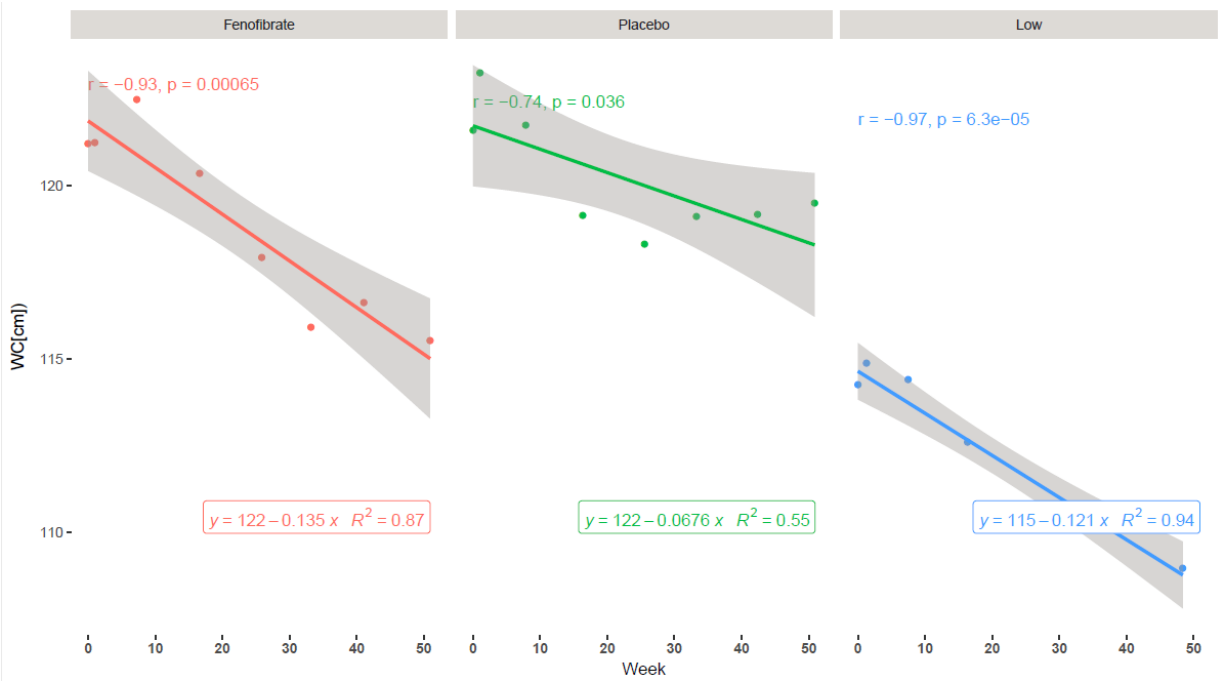

Fig 9. WC changes in the three groups, showed statistical significant linear regression values (upper panel).

Moreover, when the means of weight were plotted vs the means of WC, all three groups showed statistical significance, see fig 10. Changes in body weight and WC are often correlated in obese [6, 7]. In the present cohort, weight and waist circumference were highly associated in the Normal TG group (R=0.92, p<0.001), followed by the Placebo (R=0.89, p<0.01) and Fibrate group (R=0.78, p<0.01).

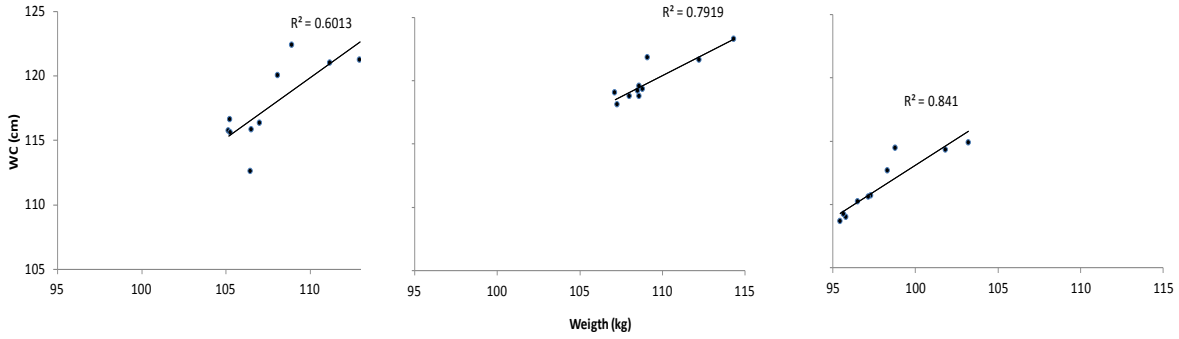

Fig 10. Relationship between Weight and WC. Means of weight and WC were significantly associated throughout the study. (Left, Fibrate group p= 0.0085; middle, Placebo p=0.0006; right, Normal TG p=0.0002).

3.9 ASSOCIATION BETWEEN WEIGHT AND HBA1C

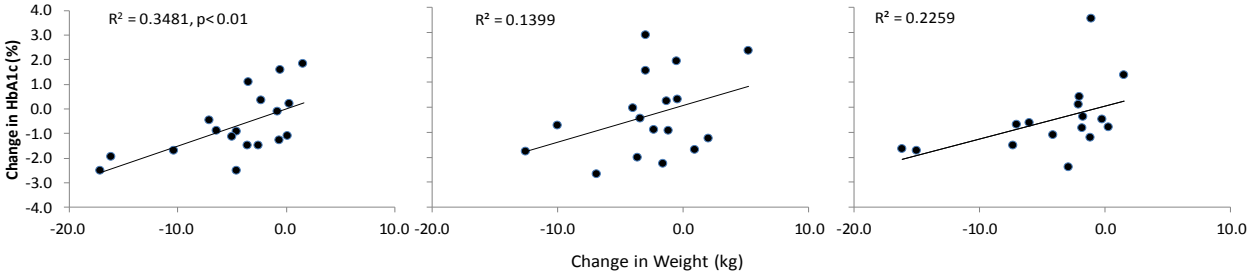

Fig 11. Association between Weight and HbA1c changes. Change in HbA1c and Weight per visit showed a statistically significant association only for the Fibrate group. (Left, Fibrate; middle, Placebo; right, Normal TG).

Changes in weight were as well significantly associated with changes in HbA1c in the Fibrate group but not in the other two groups, with weight explaining approximately 59% of the change in HbA1c. This

group had in average 5.9Kg reduction with 3 patients loosing 10 or more kg, which may explain the significance in this group. No correlations were obtained in WC changes with HbA1c or FBG.

When HbA1c means were plotted against the means of weight throughout the trial significant linear regressions for all groups were obtained, see fig 12. These results support the view of weight change as a major factor in the improvement of the glycemia. When weight decreases, reduced caloric intake, more exercise or a combination of both are often involved, leading to lower rises in blood glucose and improvement in glucose metabolism in the long term [8].

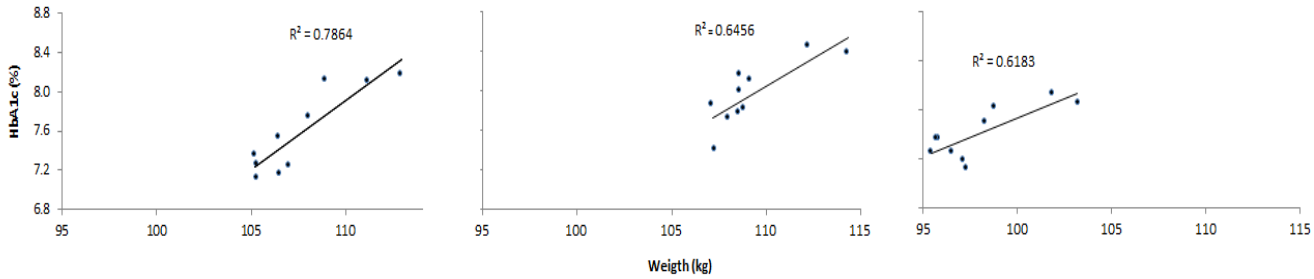

Fig 12, Linear regression showing association between HbA1c and weight. (Left, Fibrate group p= 0.0006; middle, Placebo p=0.0051; right, Normal TG p=0.0072).

3.10 BLOOD PRESSURE

Paired t-test between BL and Visit 12 of Systolic and diastolic BP showed no significance changes between time points. A trend for reduction in SBP was apparent in the Fibrate group temporal changes (p=0.088, decreasing from 136.21±17.5 to 129.7±14.5 mmHg). When the means throughout the visits were plotted against mean changes in weight, the variables aligned linearly with statistical significance (p=0.008) for the Fibrate group, see fig 13. No similar relationships were found with diastolic pressures.

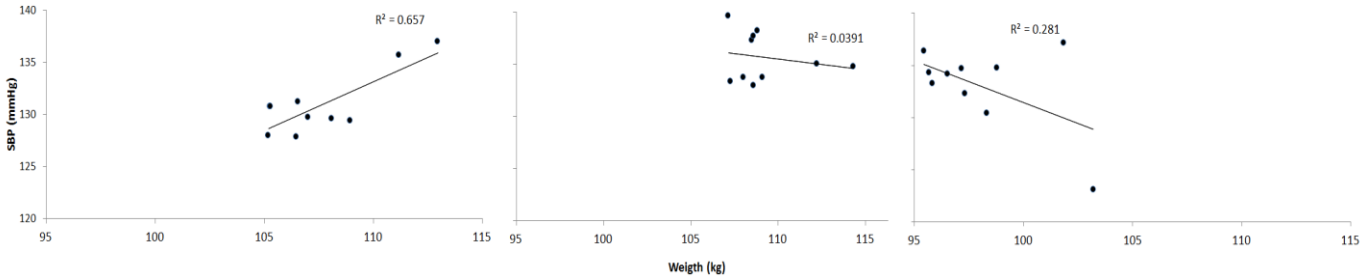

Fig 12. Association between weight and SBP in the three groups (left, Fibrate; middle, Placebo; right, Normal TG). The linear regression was statistically significant only for the fibrate group, (R=0.810, p<0.05).

3.11 RESPONDER ANALYSIS

A responder analysis was done to evaluate whether the treatment with GCM had a positive effects beyond glycemia on the subject groups. For this analysis individual subject data was plotted as the change from BL (average V1-V3) to visit 12. When visit 12 data was absent, the last value was carried forward, with a minimum of visit 8 data present to minimize placebo effects (otherwise the subject data were not included).

3.11.1 HBA1C

Responders were considered subjects who had a negative change of $\geq$0.6% of HbA1c. This value has been considered of clinical significance in previous studies [8,9]. Fig 14 shows the distribution of HbA1c values for responders and non-responders in each group: Fibrate had 65%, Placebo had 52% and Normal TG had 55% responders.

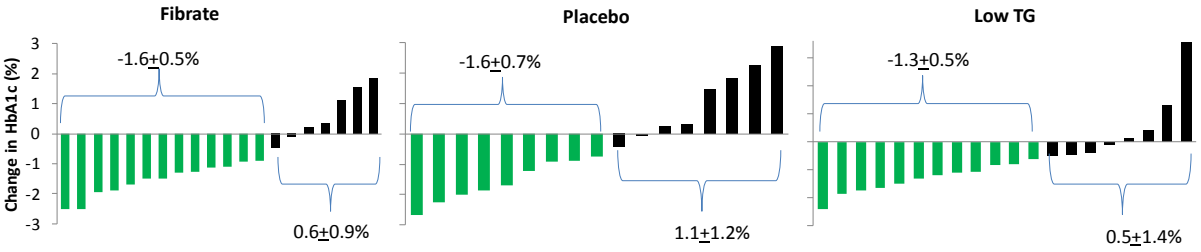

Fig 14. Distribution of individual HbA1c changes into responder (subjects with 0.6%≤HbA1c between BL and last visit, green bars) and non-responder (black bars) subjects.

3.11.2 BODY WEIGHT

Fig 15 shows the distribution of individual weight changes with the glycemic responder criterion. Glycemic responders in the Fibrate and Normal TG subgroups had considerably more weight loss than the Placebo.

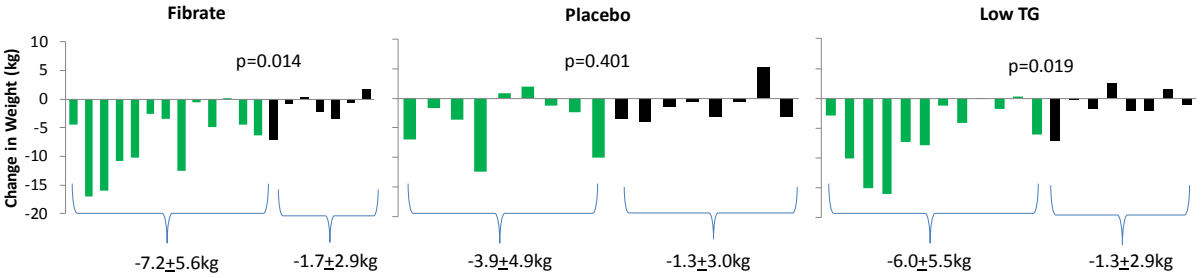

Fig 15. Distribution of individual weight loss in responder (green bars) and non-responder (black bars) subjects with the glycemic criteria (≥0.6%). P values show statistical significance for the Fibrate and Normal TG subgroups.

3.11.3 TRIGLYCERIDES AND GLYCEMIA

In order to assess the degree treatment with Fenofibrate was effective on this subgroups, (responder) distributions for the three groups were plotted together between BL and V12. The results show different spreads depending on drug treatment and the initial level. More subjects in the Fibrate group showed responses to the drug with reductions in TG levels than subjects in the Placebo. These observations are supported by statistically significant changes in the TG levels of the Fibrate and not on the Placebo group, see fig 6. TG changes were not significant in the Normal TG group.

Because all patients remained in anti-diabetic treatment with GCM, responder subjects from the three groups were pulled together for the evaluation of changes in TG (dietary and drug induced TG lowering) vs changes in HbA1c. Fig 13 shows the HbA1c changes as a function of the distribution of TG changes for the 34 responders. Subjects from the three groups are visualized by the different marker fill. Those from the Normal TG group distribute around the zero level TG change as expected. The spreading of values from subjects originally randomized to the High TG has left skewed distributions for both groups. One out of 8 showed reductions in HbA1c with lowered TG in the High TG-P and 10 out of 13 subjects in the High TG-F. Despite similar covariance in both groups (0.404 and 0.397 respectively) only linear regression on the High TG-F responders resulted in a significant $p < 0.001$, with lowered TG explaining more approximately 64% of the HbA1c change for this subgroup. Separated regressions in the High TG-P and Normal TG did not result in evidence of significant association between changes in TG levels and HbA1c changes for responder subjects.

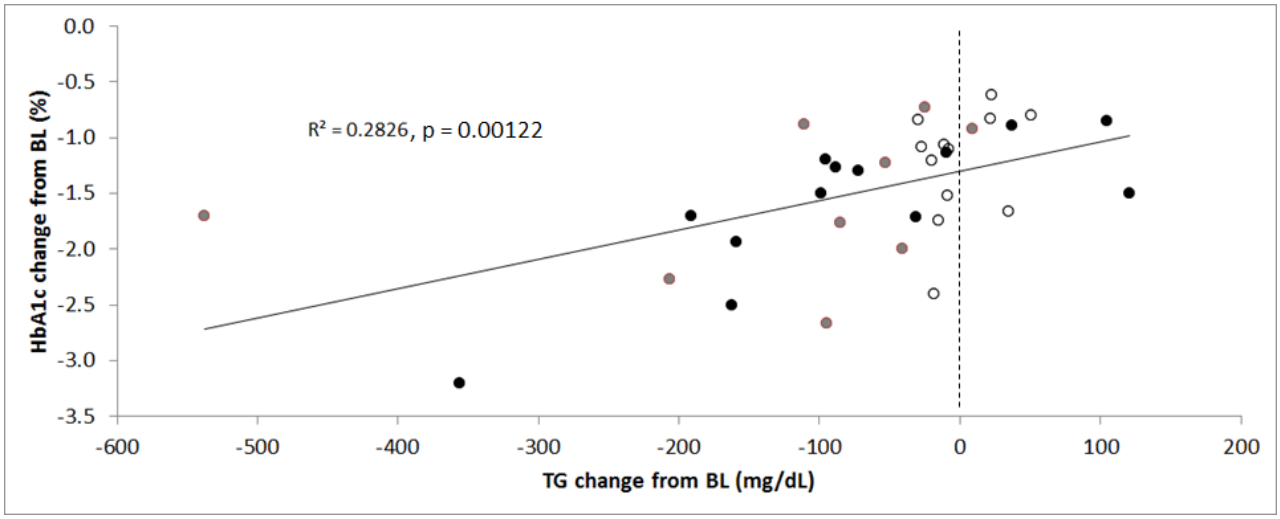

Fig 16. Linear association between changes in TG with changes in Hb1c in responder subjects. Normal TG, Open circles; Placebo, grey circles; Fibrates, closed circles. Regression values corresponds with the 34 responder subgroup. A clear trend for glycemic improvement with reduced TG is visible, this change explaining up to 53.2% of the change in HbA1c.

These results are important in two aspects: (1) in responders, the range of GCM glycemic effect is similar in most subjects, with -1.5% in average. (2) There is a definitive blunted effect of high TG levels on GCM. This becomes apparent as the linear regression shows the alignment of subjects in all groups with less glycemic effect the smaller the TG change, and support the view that high circulating TG levels blunt metabolic responses to GCM.

3.12 DEVICE FUNCTIONALITY

Device functionality was assessed to verify all groups received similar doses of GCM. The delivery of GCM with eating detection was programmed to entail one GCM per slow wave detected from the moment of therapy onset. The treatment was divided in 4 phases: an initial phase of 15 min, followed by 3 periods of 10 min, separated by 3 pauses of 10 min each, approximately 135 GCM trains per meal detection. Meal detections were adjusted to individual changes of gastric motility and fundus volume in test meals during selected follow ups. An optimal range of 3 to 5 detectable meals was allowed per day by programming the eating detector algorithm with parameters so that this range of daily meals could be detected. Each detection was followed by a refractory period in which the device could not start treatment, typically 2 hrs (immediately after a meal for example) which was made shorter or longer depending in the frequency of meals between visits.

Additional small adjustments to the refractory periods of individual GCM trains were also programmed. The time in seconds, in which the IPG was not allowed to detect slow waves, in cases when GCM could to change the intrinsic pace of the slow waves. These changes in rhythm were attributed to local tissue excitability, which in turn could influence the total train number for the daily dose.

Depending on the dietary regime of the subjects small variations in the number of meals were therefore possible. However, the average between groups showed no cumulative difference, see fig 17.

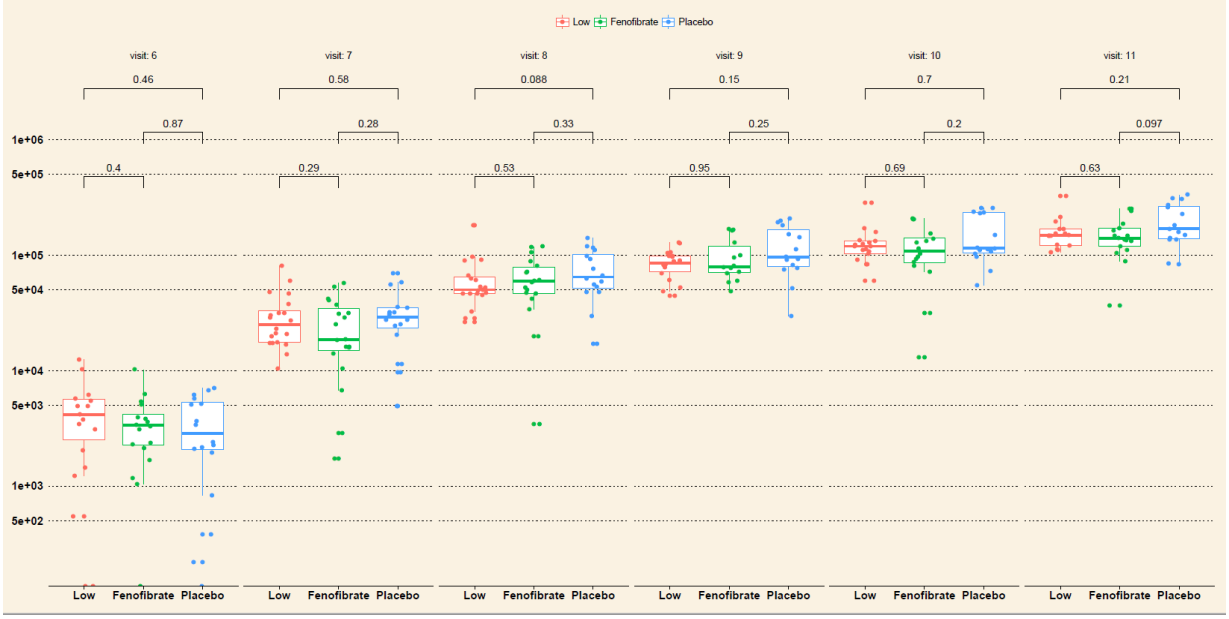

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Fig 17. Cumulative GCM dose count between the groups. T-test between the groups showed no difference in the GCM dose.

3.13 SAFETY

A total of 68 Adverse Events were recorded in 28 subjects during the trial. 58 AE (85.2%) were considered unrelated to device function or implant procedure and included 2 SAE, 3 events of documented hypoglycemia, 3 events of suspected hypoglycemia and one hyperglycemic event. The 2 SAE involved intracerebral hemorrhage occurring 2 month after the implant and a hospitalization following suspicion of breast cancer. One patient had a fatal car accident. 3 subjects had in 39.7% of the AE (7, 9 and 11 AE each); all other subjects reporting AE had a frequency of 1 event in 13 subjects, 2 events in 7 subjects, 3 events in 2 subjects and 4 events in 2 subjects.

Out of the 10 (14.7%) AE considered having some relationship to

device or procedure, 9 were anticipated, in the early or late post op period involving wound or pocket pain (N=6) of mild to moderate severity. There was one pocket infection/bleeding (severe) and one wound producing seroma (mild). There was an event considered to have a remote relationship with the procedure involving pneumonia (moderate severity) occurring two months after the procedure.

Overall it can be concluded the Diamond system was well tolerated and its functionality did not cause adverse events.

3.14 ADDITIONAL TESTS:

The Meal Tolerance Test has been recognized as a good alternative to study post-prandial responses to standard meals among patients with T2DM, generating indices of Beta cell function and insulin resistance. Insulin secretion and insulin sensitivity are associated through a negative feedback loop whereby pancreatic insulin compensates for changes in insulin sensitivity through proportionate and reciprocal changes in insulin secretion (10). The model postulates that a hepatic-beta cell feedback loop exists whereby elevated fasting glucose reflects a compensatory mechanism maintaining insulin levels despite diminished secretory capacity, and that elevated fasting insulin reflects diminished insulin sensitivity (11-13).

The protocol prescribed a MTT at baseline (visit 2) and after 12 month of GCM treatment on V12. Not all hormone samples were available at the compilation of this report, so analysis focuses on glucose and insulin levels as reported by the local labs. When baseline values were missing, the insulin value obtained from the blood test of the same visit was used. The MTT was performed by administration of a liquid meal “Sustacal” (35 g carbohydrate, 8.3 g fat, 8.8 g protein in 240ml) at V2 (BL) and V12 (12 Month of GCM treatment). Only complete data sets were used for the present analysis (BL and 12 month of glucose and insulin), with available data as follows: 12 pairs

in the Fibrate, 11 pairs on the Placebo and 17 pairs on the Normal group. The time course of the MTT is shown on fig 18.

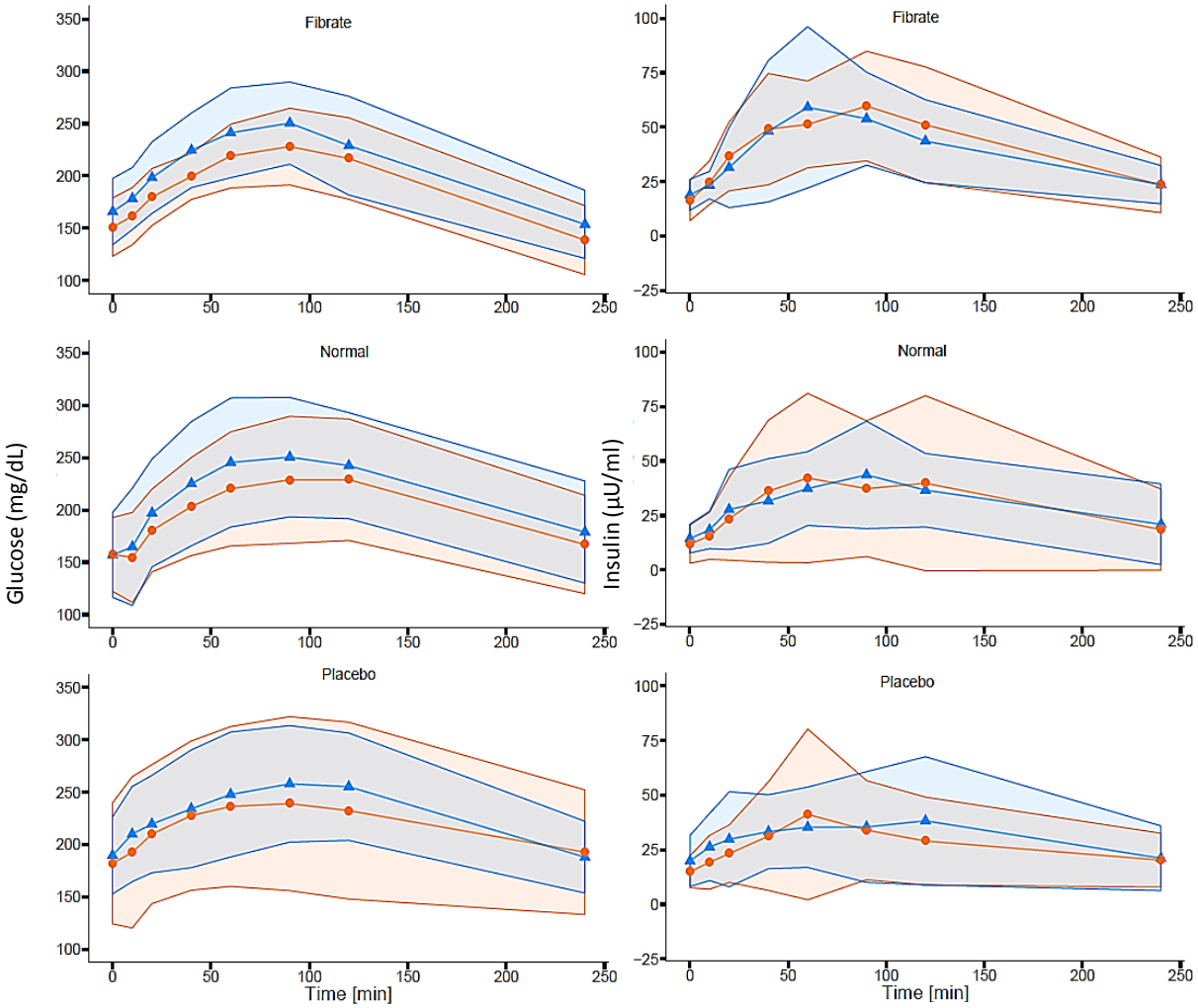

Fig 18. Glucose and insulin time course along the MTT. Mean and standard deviation of the blood values for BL glucose and insulin (triangles, blue) and 12 Month GCM (circles, orange).

3.14.1 ANALYSIS OF MEANS

BL means of glucose and insulin for the MTT test were compared between the groups. The mean glucose and insulin were not different among the three groups. This suggests that the three groups had comparable blood glucose at baseline. Whereas a small but significant reduction in blood glucose was achieved in the three groups, insulin showed only small changes, reaching significance only in the placebo group, see Table 3.

	Glucose (mg/dL)			**Insulin pU/ml**		
	BL	**Month 12**	**p value**	**BL**	**Month 12**	**p value**
Fibrate	205.1	186.7	**>0.0001**	37.7	38.9	0.2519
Normal	207.7	192.6	**0.0006**	28.8	28.1	0.3233
Placebo	225.3	214.1	**0.0041**	29.9	26.6	**0.0457**

Table 3. Analysis of means, BL vs 12 Month GCM. Blood glucose decreased in the 3 groups in average, whereas changes in insulin were negligible, except for the placebo.

Whereas the analysis of means evaluates the whole glucose and insulin change during the 2 hr challenge, the results on Table 4 focus on a relatively earlier insulin response obtained by averaging the results of the 20 and 40 min. Although not the standard early secretion measure -usually done at 10 min from the challenge start--, it still addresses the early prandial response to the meal when GCM driven satiety was expected. The early insulin response was calculated as ($Ins_{30'}$-$Ins_{0'}$/$Gluc_{30'}$-$Gluc_{0'}$) and the disposition index was obtained by dividing the early insulin response by $ins_{0'}$. The latter index increases all

groups, reaching significance in the Fibrate and Normal groups indicating a reduction in the insulin resistance and a lowering risk of diabetes (14, 15).

	30 min insulin response			30 min Disposition Index		
	BL	**Month 12**	**p value**	**BL**	**Month 12**	**p value**
Fibrate	0.44	0.64	**0.0250**	0.023	0.049	**0.0043**
Normal	1.25	1.79	**0.0265**	0.037	0.070	**0.0136**
Placebo	0.84	2.53	0.1908	0.023	0.038	0.1705

Table 4. Early insulin response and disposition index show increased insulin availability for all three groups, reaching significance for the Fibrate and Normal groups.

3.14.2 INSULIN SENSITIVITY

The HOMA values were obtained with the calculator at www.dtu.ox.ac.uk/homa which represents the iterative structural model simulating physiological processes of glucose and insulin levels to derive estimates of beta cell function (HOMA_%B) and insulin sensitivity (HOMA_%S).

The widely-used formulae available for HOMA1 provide only linear approximations of HOMA_%B and HOMA_IR, the inverse of HOMA_%S.

These are:

HOMA1_IR = (FPI x FPG)/22.5

HOMA1_%B = (20 x FPI)/(FPG - 3.5)

HOMA1_%B	**Fibrate**	**Normal**	**Placebo**
BL	60.77	62.94	48.47
12 Month	57.86	52.17	44.14
p value	0.3560	**0.0322**	0.3349
HOMA_%S			
BL	38.77	61.24	51.83
12 Month	60.52	84.86	71.8
p value	**0.0443**	**0.0100**	**0.0040**
HOMA_IR			
BL	2.88	1.96	2.88
12 Month	2.32	1.57	1.85
p value	**0.0393**	**0.0194**	**0.0463**

Table 4. MTT derived insulin sensitivity between BL and 12 Mo. for the three groups. HOMA values were obtained for BL and 12 month of each patient; the resulting p values arise from paired comparisons.

Insulin sensitivity augmented throughout the year in the three groups reaching statistical significance. HOMA indices suggest better improved Beta cell sensitivity to glucose at the pancreas for the normal group, whereas insulin resistance was reduced in all groups, with the largest improvements in sensitivity seen in the Fibrate and Normal groups, closely followed by the Placebo. These results indicate that peripheral improvement of sensitivity to insulin is a possible mechanism of GCM, and further, that is independent of TG. Although the major components of altered insulin sensitivity were not targeted individually, glucose metabolism as a whole appeared to improve. GCM mechanisms may involve the reversal of major sources of impaired insulin sensitivity in peripheral tissues: (i)

decreased insulin-stimulated glucose uptake into skeletal muscle, (ii) impaired insulin-mediated inhibition of hepatic glucose production in liver, and (iii) reduced ability of insulin to inhibit lipolysis in adipose tissue. Oral glucose tolerance tests done in the same population in the past showed that GCM was associated with a decreased first pass hepatic degradation (3). Those results were extended in the present study, whereby through the acute challenge, mean glucose decreased significantly in all groups with no change or reduced insulin from BL. The early insulin response and the disposition index were increased in all groups reaching statistical significance for the Fibrate and normal TG groups. Furthermore insulin resistance significantly decreased in all groups. Taken together, the acute test performance had markedly improved when compared to BL; and support the view of peripheral GCM effects that appear largely independent of circulating TG.

4 DISCUSSION

In recent years, device based treatments for obesity, inflammation and T2DM have been tested as a potential alternatives to oral medications and better compliance, exploiting their ability to influence central pathways to improve metabolic syndrome and hypertension (16-17). Neuromodulation of hunger and satiety as well as of hypertension and inflammation have common neural targets on hypothalamic subnuclei, as these regulate energy stores, biological rhythms, endocrine and autonomic responses, and reflex behaviors as aggression and fear and the flight or fight response.

In normal physiological conditions, absorption and transport of nutrients into the circulation is expected to occur with input from the CNS, with gastro-intestinal, liver and pancreatic autonomic nerves and hormonal discharges regularly coping with catabolic and anabolic fluctuations. Central pathways monitor, control and change flow in one or other direction, fine-tuning metabolic function to perceived

or actual demand (for example, hunger and emotions may affect each other in the same or opposite direction, despite satiety or actual need for nutrients). Several modalities of regulation have been widely established such as altered sensitivity, neuro-humoral signaling, and direct neural input to increase absorption and secretion (18-21).

To frame the DIAMOND as a neuromodulator eliciting reduced food intake we need to address normal physiological responses of brain circuits with the current understanding of satiation (ending a meal) and satiety (the interval between meals).

4.1 POSSIBLE ROLE OF GCM IN EARLY SATIATION

Hindbrain neurons in the Area Postrema (AP) and Nucleus Tractus Solitarius (NTS) are among the first hypothalamic subnuclei receiving neural information throughout feeding on the GI events processing intake and eliciting satiation. Early with food intake, the stomach initiates afferent signaling to the NTS following sensing of chemical, osmotic and volumetric properties of the ingested nutrients involving interaction of enteroendocrine, vagal and spinal afferents. The As a non-excitatory signal, GCM delivered to the antrum does not initiate new slow waves followed by contractions, but it increases the force of occurring contractions. Each GCM train also determines to some extent the excitability of the antrum tissue to the next slow wave, thus effectively influencing the setting of the gastric pacemakers. The modulated contractility is then transduced by local mechano-receptors into afferent neural input. Tension and stretch are transduced by glutamatergic transmission while gastric distension is mediated by serotonergic transmission, both reaching the NTS (22). Hypothalamic circuits (NTS to PVN) receive multiple visceral signals involved in ending a meal. These are conveyed directly via vagal afferent fibers; in part are mediated by glutamatergic into NTS neurons. Additional satiation signals run through afferent vagal neurons from proximal and distal intestine and colon. Circulating peptides (such as ghrelin, CCK, insulin and leptin, etc) elicit neural responses in

hypothalamic structures associated with hunger and satiety (23-27). Vagal neurons with cell bodies in the nodose ganglion, have receptors for these peptides, which are the recipients for paracrine activation and modulate forward activity in hypothalamic neurons (28-29). Furthermore, activities of these peptides, either after crossing the BBB or locally produced can change the sensitivity to these signals at the hunger, satiety and reward systems. Current views of the development of satiety model its process as a waves flowing from the NTS, proceeding into the arcuate nucleus and then into more complex structures associated with reward system sensitivity (30-31). GCM is expected to add to the efferent side of these satiety waves, reaching across hypothalamic subnuclei involved in energy balance, managing hunger to establish satiation. As the stomach distends with the meal, stretching of sensitive mechanoreceptors adjacent to the electrodes were shown to generate higher firing rates when GCM was ON (5). Indeed, a higher vagal afferent firing rate was observed on individual selected mechanoreceptors in anesthetized rats instrumented with a balloon to simulate meal distension. The extent of excitation changes generated by GCM in hypothalamic neurons associated with hunger and satiety remains however currently unknown. Self-reporting questionnaire data from the current (not shown) and previous studies has revealed hunger and disinhibition were reduced, with accompanying cognitive feeding restrain (3). These observations suggest GCM effects beyond the hindbrain, into rostral and limbic nuclei associated with the sustention of satiation and behaviors in line with intake inhibition. We speculate that changes in the electrical properties of vagal neurons, such as modulated excitabilities and increased firing rates may add to long term responses of myenteric neurons activated in the post-prandial period by GLP-1 and CCK, which ultimately send secondary and tertiary waves to the hypothalamus to mediate satiation (the ending of a meal) and longer satiety (longer periods between meals). GLP-1 is known for its effects from the area postrema into Lateral hypothalamus, Paraventricular nucleus and the Nucleus Accumbens, where it is believed to mediate reduction in food intake and satiation and increase in the reward feeling. The anorectic effects of GLP-1 are not only

elicited through vagal neurons firing into the hindbrain, but may as well be modulated by several local and peripheral peptides ghrelin, leptin and CCK (23, 26). Furthermore, evidence of GCM induced satiety was obtained indirectly by studies evaluating the length and functionality of the Motor Migratory Complex in obese and T2DM subjects where the length of Phase II intervals were longer after GCM treatment (32). Gastric MMC has been previously studied with the DIAMOND (33). This motility pattern has been often viewed with a 'home keeping' role, distally moving debris and fluid. It occurs only during established fasting; therefore the presence of more and longer fasting intervals with GCM suggests long term effect in satiation (32).

4.2 GCM IN THE HIGH TG GROUPS

Results of multiple studies with the DIAMOND System showed that glycemic improvement was positively correlated with lower TG levels (34-35). These observations raised the hypothesis that prospective lowering of TG would result in improved glycemia with GCM treatment. High TG were found to be associated with metabolic syndrome, obesity, insulin resistance, inhibition of satiety, with reversibility to some extent (36-39). TG clearance would be expected to elicit better glycemic response than that observed in an equivalent group not subjected to Fenofibrate. This was confirmed with the present results, where HbA1c on the Fibrate group decreased significantly more than the placebo group.

In order to formulate an hypothesis that can explain both the glycemic effects of GCM in the Fibrate and Normal TG groups we need to take in account the circumstances in which TG may rise in normal conditions and explore the possibility that abnormally high TG in the proximity of satiety and hunger hypothalamic areas may represent one of the early signals involved in the unrelenting shift from overweight to obese and to insulin resistance in an high caloric diet (40-41).

In normal physiology, TG-rich lipoproteins transport TG to peripheral organs to be hydrolyzed by lipase activity in adipose tissue and muscle. Continuous TG availability of hepatic and intestinal origin elicits a flexible storage in adipose tissue. Adipose tissue is densely innervated by the sympathetic system and can readily deliver its content for energy or heat demand. Adrenergic stimulation for hepatic production of TG is important in the fasting state when lipids become an important source for energy, as in a sustained fight or flight response (43-44).

The involvement of the lateral hypothalamus (LH) in hyperphagia in a TG rich environment has been shown. The overeating is thought to be mediated by orexigenic peptides released in the presence of high TG (45-46). Discharges of catecholamine in the LH and in the hypothalamic PVN neurons are essential for over-feeding and for downstream secretion of the corticotropic releasing hormone respectively. Studies have demonstrated the HPA axis and the sympathetic nervous system may be activated also by mental processes such as frustration and anticipatory anxiety, -for example, when an expected reward is withdrawn (47-48). Further studies have shown that TG levels in the CSF rapidly equilibrate with circulating TG and promote leptin and insulin resistance eventually impairing hunger control and dietary TG intake. TG have been proposed to constitute a survival related starvation signal with its leptin resistance at the basis of feeding seeking behavior (49). Thus, repeated TG intake may have a role in promoting metabolic syndrome by adding into obesity and diabetes. Abnormalities in TG metabolism are important features of T2DM eliciting enhanced TG secretion due to insulin resistance (50-52). Genetic, epigenetic and behavioral factors such as sedentary lifestyle, alcohol abuse, poor dietary habits, etc. can exacerbate these conditions and further promote cardiovascular disease and hypertension (53-58).

The DIAMOND effects in glycemia and weight were maximal in the Fibrate group, both in extent of change and in percent of subjects exhibiting an improvement. The results thus support the concept of reducing TG to enhance central satiation with GCM, leading to further improvements in weight and glycemia. The actions of GCM were thus favored by an environment of lowered

TG. The placebo group represented an appropriate control for these variables. Furthermore, in the presence of dyslipedima, the Placebo group exhibited modest reductions in glycemia and weight, that support action of GCM treatment independent of the TG levels. These actions will be discussed below.

4.3 GCM IN THE NORMAL TG GROUP.

GCM treatment in the Normal TG group resulted in a modest but significant weight loss of approximately 4 kg, a reduction of 4.7 cm in WC, an improvement in HbA1c of -0.6%, in line with previous DIAMOND studies (3-4). The reduction in weight and HbA1c were rapid in the initial weeks of the study and slower thereafter. Placebo and surgical effects may play an important role in first weeks after implant whereby changes in the blood supply to abdominal fat would have increased insulin sensitivity by favoring dyslipidemia and abdominal adiposity towards catabolic processes. In the long term however, possible GCM action in satiation in the absence of high TG, accompanied by improved peripheral insulin sensitivity would be necessary to differentiate this group from placebo. Indeed, changes in the Fibrate group were comparable, with HbA1c of -0.7%, weight loss of -4.9 kg and -5.5 cm in WC. In line with the previous argument, satiety originated in areas past the NTS regions presumably un-hindered by high TG, would allow GCM to power active afferent gut signals, such as glucose, CCK, leptin, GLP-1 and others. It is then possible that lowered and normal TG allowed a reversal of impaired insulin sensitivity in peripheral tissues such as skeletal tissue, greater inhibition of hepatic glucose production in liver and an increased ability of insulin to inhibit lipolysis in adipose tissue.

5 CONCLUSIONS

In regards to safety, it can be concluded the Diamond system was well tolerated and its functionality did not cause adverse events. The system functionality was no different between the groups, suggesting differences between the groups could not be attributed to uneven GCM dose delivery. There remain issues of

patient compliance with weekly charging of the battery, which may become challenging as the clinic visit intervals are extended.

Mechanistically, a mediator role for Triglycerides in the action of GCM treatment can be inferred. Obese diabetics with normal TG and fibrate-treated high TG patients showed after one year treatment clear improvements in glycemia, body weight and waist circumference. Changes in these variables were minor or absent in a parallel group of obese-diabetics with untreated high TG. Changes in metabolic status may be attributed in part to central effects of the DIAMOND in early satiety and long term satiation. The latter would be associated with long term reduction in weight, waist circumference and concomitant glycemic improvement. Peripheral effects of GCM, such as increased sensitivity to insulin, improvement in glucose metabolism and in the indices of beta cell function comparing acute challenges at baseline and after 12 months, appear to be independent of TG. These are thought to reflect immediate GCM dependent efferent and vago-vagal signaling to abdominal organs such as the liver, intestine and pancreas improving their function and eliciting significant reductions in circulating glucose with similar initial insulin levels.

Overall, improvement in diabetes type II can result from non-excitatory vagal stimulation via enhanced contractility of antrum smooth muscle contractility in selected obese-diabetic subjects. Clinical significance however, may be deemed moderate and require additional behavioral changes, as it remains dependent in patient compliance, ultimately preventing the realization of a relevant and convincing product.

6 LITERATURE

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7.1 Appendix 1. Patient Raw data comparison of BL to average of visits V9-V12.

Fibrate				
Pt ID	**HbA1c (%) V1-V3 Ave**	**HbA1c (%) V9-V12 Ave**	**Difference**	**P Value**
HES70-21	8.3	7.7	-0.6	
HES01-04	8.9	7.8	-1.2	
HES02-04	7.6		NA	
HES02-08	7.7	7.8	0.12	
HES03-09	8.1	7.1	-1	
HES04-03	7.5	8.0	0.52	
HES04-04	8.6	8.7	0	
HES04-12	7.8	9.7	1.9	
HES05-02	8.0	6.5	-1.5	
HES05-22	8.6	9.0	0.4	
HES40-01	7.4	6.4	-1	
HES70-02	7.8	7.0	-0.8	
HES70-07	8.9	9.5	0.6	
HES70-10	9.5	6.6	-2.9	
HES70-12	8.5	7.9	-0.6	
HES70-28	7.4	5.8	-1.6	
HES70-30	8.3	6.3	-2	
HES70-32	9.6	6.5	-3.1	
HES71-03	7.4	5.9	-1.5	
HES71-04	7.5	5.4	-2.1	
HES71-05	7.4	5.7	-1.7	
Mean	**8.15**	**7.24**	**-0.9**	**0.0021**
Pt ID	**FPG (mmol/L) V1-V3 Ave**	**FPG (mmol/L) V9-V12 Ave**	**Difference**	**P Value**
HES70-21	9.4	8.0	-1.5	
HES01-04	9.7	7.0	-2.7	

HES02-04	8.6		NA	
HES02-08	9.8	9.3	-0.5	
HES03-09	8.9	8.8	-0.1	
HES04-03	8.4	8.4	0.0	
HES04-04	8.6	10.5	1.9	
HES04-12	8.3	12.3	4.0	
HES05-02	8.8	7.3	-1.5	
HES05-22	8.2	10.8	2.5	
HES40-01	7.7	5.3	-2.4	
HES70-02	9.3	7.8	-1.5	
HES70-07	8.0	11.9	3.9	
HES70-10	10.3	7.1	-3.2	
HES70-12	10.5	9.2	-1.4	
HES70-28	8.5	8.0	-0.6	
HES70-30	8.4	8.3	-0.2	
HES70-32	13.8	8.6	-5.2	
HES71-03	7.4	6.0	-1.4	
HES71-04	7.4	5.7	-1.6	
HES71-05	6.5	5.4	-1.2	
Mean	**8.9**	**8.3**	**-1.5**	0.1176
Pt ID	**Insulin (mIU/L) V1-V3 Ave**	**Insulin (mIU/L) V9-V12 Ave**	**Difference**	**P Value**
HES70-21	185.2	109.8	-75.4	
HES01-04	39.6	21.4	-18.2	
HES02-04	20.4		NA	
HES02-08	42.2	18.3	-23.9	
HES03-09	22.2	13.6	-8.5	
HES04-03	14.4	18.1	3.7	
HES04-04	37.6	38.7	1.1	
HES04-12	24.7	15.4	-9.3	
HES05-02	24.5	26.3	1.9	
HES05-22	41.1		NA	
HES40-01	29.7	19.6	-10.2	
HES70-02	64.4	115.9	51.5	
HES70-07	79.2	103.2	24.0	
HES70-10	234.5	110.9	-123.6	
HES70-12	273.7	230.0	-43.7	
HES70-28	153.2	138.9	-14.3	
HES70-30	100.1	224.0	123.9	
HES70-32	121.3	140.1	18.9	
HES71-03	24.6	20.0	-4.6	
HES71-04	25.5	23.2	-2.3	

HES71-05	33.8	14.4	-19.4	
Mean	**80.5**	**73.78**	**-6.8**	0.2765
Pt ID	**TG (mmo/L) V1-V3 Ave**	**TG (mmo/L) V9-V12 Ave**	**Difference**	**P Value**
HES70-21	2.2	1.3	-1.0	
HES01-04	2.2	3.2	1.0	
HES02-04	2.2		NA	
HES02-08	3.8	3.6	-0.2	
HES03-09	1.8	2.0	0.2	
HES04-03	2.3	1.9	-0.5	
HES04-04	2.8	2.5	-0.3	
HES04-12	3.1	2.0	-1.2	
HES05-02	2.3	1.6	-0.7	
HES05-22	1.9	2.1	0.2	
HES40-01	2.2	1.5	-0.7	
HES70-02	1.7	0.9	-0.8	
HES70-07	1.9	1.5	-0.3	
HES70-10	4.7	2.5	-2.3	
HES70-12	2.0	2.0	0.0	
HES70-28	2.5	1.5	-1.0	
HES70-30	2.0	1.4	-0.6	
HES70-32	6.3	2.0	-4.2	
HES71-03	3.1	1.7	-1.4	
HES71-04	3.4	2.0	-1.5	
HES71-05	2.3	1.4	-0.9	
Mean	**2.7**	**1.9**	**-0.8**	**0.0017**
Pt ID	**Weight (kg) V1-V3 Ave**	**Weight (kg) V9-V12 Ave**	**Difference**	**P Value**
HES70-21	104.0	100.1	-3.9	
HES01-04	81.8	77.4	-4.4	
HES02-04	113.6		NA	
HES02-08	125.4	123.6	-1.8	
HES03-09	111.0	104.3	-6.7	
HES04-03	103.1	100.0	-3.1	
HES04-04	101.5	101.0	-0.4	
HES04-12	114.1	115.3	1.2	
HES05-02	87.8	85.3	-2.5	
HES05-22	93.9	93.8	-0.1	
HES40-01	103.0	96.8	-6.3	
HES70-02	124.9	116.0	-8.9	
HES70-07	100.5	96.5	-4.0	
HES70-10	129.2	130.5	1.3	

HES70-12	120.5	118.4	-2.1	
HES70-28	138.9	137.1	-1.8	
HES70-30	92.5	81.8	-10.8	
HES70-32	115.9	103.0	-12.9	
HES71-03	100.0	84.7	-15.3	
HES71-04	127.4	115.3	-12.1	
HES71-05	140.1	123.9	-16.2	
Mean	**110.8**	**105.2**	**-5.5**	**0.0001**
Normal TG				
Pt ID	**HbA1c (%) V1-V3 Ave**	**HbA1c (%) V9-V12 Ave**	**Difference**	**P Value**
HES 01-02	8.6	7.7	-0.9	
HES 01-03	7.4	7.2	-0.2	
HES 01-05	8.1	8.0	-0.1	
HES 03-01	7.4	7.6	0.2	
HES 03-02	8.2	7.6	-0.6	
HES 04-02	7.9	8.0	0.2	
HES 04-06	7.5	5.8	-1.8	
HES 04-10	7.9	6.9	-1.0	
HES 05-08	7.8	6.6	-1.2	
HES 05-11	7.8	7.0	-0.8	
HES 05-19	7.9	9.8	1.8	
HES 09-01	7.9		NA	
HES 40-02	8.6	6.3	-2.3	
HES 40-05	7.5	6.9	-0.7	
HES 40-06	7.3	6.7	-0.7	
HES 70-01	7.9			
HES 70-09	7.6	7.0	-0.6	
HES 70-13	9.3	7.5	-1.8	
HES 70-23	8.1	7.4	-0.7	
HES 70-26	9.0	10.1	1.1	
Mean	**8.0**	**7.4**	**-0.6**	**0.0143**
Pt ID	**FPG (mmol/L) V1-V3 Ave**	**FPG (mmol/L) V9-V12 Ave**	**Difference**	**P Value**
HES 01-02	11.1	10.2	-0.9	
HES 01-03	10.6	10.5	-0.1	
HES 01-05	10.0	9.9	0.0	
HES 03-01	7.5	8.6	1.0	
HES 03-02	10.2	8.2	-2.0	
HES 04-02	5.8	8.6	2.8	
HES 04-06	8.8	6.3	-2.5	

HES 04-10	9.0	7.0	-1.9	
HES 05-08	7.6	6.2	-1.4	
HES 05-11	9.9	8.4	-1.5	
HES 05-19	8.5	10.9	2.4	
HES 09-01	14.4		NA	
HES 40-02	5.3	5.8	0.5	
HES 40-05	7.0	5.4	-1.6	
HES 40-06	6.6	4.8	-1.8	
HES 70-01	10.3			
HES 70-09	9.1	7.9	-1.2	
HES 70-13	14.1	9.9	-4.2	
HES 70-23	6.3	6.8	0.4	
HES 70-26	10.5	12.1	1.5	
Mean	**8.8**	**8.2**	**-0.6**	0.2279
Pt ID	**Insulin (mIU/L) V1-V3 Ave**	**Insulin (mIU/L) V9-V12 Ave**	**Difference**	**P Value**
HES 01-02	13.2	13.1	-0.1	
HES 01-03	15.7	15.8	0.1	
HES 01-05	21.5	18.9	-2.6	
HES 03-01	27.5	23.8	-3.8	
HES 03-02	7.7	13.3	5.7	
HES 04-02	12.8	10.9	-2.0	
HES 04-06	8.6	6.9	-1.7	
HES 04-10	14.3	9.3	-5.0	
HES 05-08	13.1	11.0	-2.1	
HES 05-11	13.5	12.7	-0.8	
HES 05-19	15.2	16.3	1.1	
HES 09-01	25.3		NA	
HES 40-02	15.0	16.0	0.9	
HES 40-05	57.1	9.5	-47.6	
HES 40-06	15.1	15.5	0.4	
HES 70-01	10.6		NA	
HES 70-09	80.1	92.7	12.6	
HES 70-13	68.9	85.0	16.1	
HES 70-23	233.0	269.0	35.9	
HES 70-26	169.9	98.6	-71.3	
Mean	**44.6**	**41.0**	**-3.6**	0.2592
Pt ID	**TG (mmo/L) V1-V3 Ave**	**TG (mmo/L) V9-V12 Ave**	**Difference**	**P Value**
HES 01-02	1.6	1.4	-0.2	
HES 01-03	1.9	1.8	-0.1	
HES 01-05	0.9	0.7	-0.2	
HES 03-01	1.3	1.4	0.0	

HES 03-02	2.0	1.9	-0.1	
HES 04-02	1.2	1.2	0.0	
HES 04-06	1.0	0.8	-0.1	
HES 04-10	1.2	1.4	0.2	
HES 05-08	1.3	1.3	0.0	
HES 05-11	1.5	1.5	0.0	
HES 05-19	1.2	1.5	0.2	
HES 09-01	1.2		-1.2	
HES 40-02	1.7	2.0	0.3	
HES 40-05	1.0	0.9	-0.1	
HES 40-06	1.7	1.5	-0.2	
HES 70-01	1.0		-1.0	
HES 70-09	1.8	2.0	0.3	
HES 70-13	1.1	1.1	0.0	
HES 70-23	1.4	2.2	0.8	
HES 70-26	1.5	2.5	1.0	
Mean	**1.4**	**1.5**	**0.1**	0.1001
Pt ID	**Weight (kg) V1-V3 Ave**	**Weight (kg) V9-V12 Ave**	**Difference**	**P Value**
HES 01-02	75.8	73.9	-1.9	
HES 01-03	97.5	96.1	-1.4	
HES 01-05	87.6	86.6	-1.1	
HES 03-01	96.5	94.0	-2.5	
HES 03-02	89.4	89.5	0.2	
HES 04-02	101.5	101.2	-0.2	
HES 04-06	79.4	65.7	-13.7	
HES 04-10	107.8	97.8	-10.0	
HES 05-08	110.9	104.6	-6.3	
HES 05-11	85.7	81.8	-3.9	
HES 05-19	88.3	87.2	-1.1	
HES 09-01	119.0		NA	
HES 40-02	101.5	98.8	-2.7	
HES 40-05	101.0	94.8	-6.3	
HES 40-06	102.0	94.0	-8.0	
HES 70-01	103.6		NA	
HES 70-09	93.3	91.3	-2.0	
HES 70-13	145.0	128.2	-16.8	
HES 70-23	133.8	134.8	1.0	
HES 70-26	104.0	103.8	-0.2	
Mean	**100.0**	**95.8**	**-4.3**	**0.0011**
Placebo				

Pt ID	HbA1c (%) V1-V3 Ave	HbA1c (%) V9-V12 Ave	Difference	P Value
HES 02-02	8.0	7.5	-0.5	
HES 02-09	7.7	7.8	0.2	
HES 04-07	8.0	7.7	-0.4	
HES 04-08	8.4	7.7	-0.8	
HES 04-13	7.8	6.9	-1.0	
HES 05-17	8.5	7.5	-1.0	
HES 40-03	7.5	6.4	-1.2	
HES 70-03	9.0	6.4	-2.6	
HES 70-06	8.7	6.8	-1.9	
HES 70-08	8.8	8.5	-0.4	
HES 70-11	9.6	11.1	1.4	
HES 70-22	9.0	10.4	1.4	
HES 70-27	7.9	9.1	1.2	
HES 70-29	8.3	11.1	2.8	
HES 70-31	8.1	6.2	-1.9	
HES 71-02	8.7	7.0	-1.8	
HES 71-09	8.8	6.6	-2.2	
Mean	**8.4**	**7.9**	**-0.5**	0.0931
Pt ID	**FPG (mmol/L) V1-V3 Ave**	**FPG (mmol/L) V9-V12 Ave**	**Difference**	**P Value**
HES 02-02	9.1	9.1	-0.1	
HES 02-09	8.1	9.5	1.4	
HES 04-07	14.7	12.8	-1.9	
HES 04-08	11.5	10.8	-0.6	
HES 04-13	9.7	8.2	-1.4	
HES 05-17	10.9	8.1	-2.9	
HES 40-03	9.4	9.0	-0.5	
HES 70-03	10.7	8.3	-2.5	
HES 70-06	9.2	8.0	-1.2	
HES 70-08	11.0	9.9	-1.1	
HES 70-11	13.0	17.6	4.5	
HES 70-22	14.7	14.2	-0.5	
HES 70-27	11.2	10.9	-0.3	
HES 70-29	10.7	15.0	4.3	
HES 70-31	7.4	7.7	0.3	
HES 71-02	16.4	8.6	-7.9	
HES 71-09	8.3	6.9	-1.3	
Mean	**10.9**	**10.3**	**-0.7**	**0.1580**
Pt ID	**Insulin (mIU/L) V1-V3 Ave**	**Insulin (mIU/L) V9-V12 Ave**	**Difference**	**P Value**

HES 02-02	14.4	17.3	2.9	
HES 02-09	22.0	21.6	-0.4	
HES 04-07	5.0	8.4	3.3	
HES 04-08	11.9	9.7	-2.2	
HES 04-13	52.1	38.0	-14.2	
HES 05-17	15.1	18.5	3.5	
HES 40-03	18.4	61.3	42.9	
HES 70-03	26.1	88.7	62.7	
HES 70-06	19.2	145.7	126.5	
HES 70-08	69.0	100.5	31.5	
HES 70-11	265.4	218.3	-47.1	
HES 70-22	94.7	57.3	-37.4	
HES 70-27	81.8	71.9	-9.9	
HES 70-29	76.4	109.1	32.7	
HES 70-31	94.0	109.8	15.8	
HES 71-02	11.5	11.4	-0.1	
HES 71-09	19.0	15.7	-3.3	
Mean	**52.7**	**64.9**	**12.2**	0.11
Pt ID	**TG (mmo/L) V1-V3 Ave**	**TG (mmo/L) V9-V12 Ave**	**Difference**	**P Value**
HES 02-02	2.6	2.1	-0.5	
HES 02-09	1.6	1.5	-0.1	
HES 04-07	3.9	4.6	0.7	
HES 04-08	4.0	3.0	-0.9	
HES 04-13	2.1	2.0	-0.2	
HES 05-17	4.0	3.4	-0.6	
HES 40-03	2.0	1.9	-0.1	
HES 70-03	2.0	1.7	-0.3	
HES 70-06	2.6	2.5	-0.1	
HES 70-08	1.7	1.7	0.0	
HES 70-11	4.1	8.8	4.7	
HES 70-22	3.1	2.9	-0.2	
HES 70-27	4.4	6.0	1.6	
HES 70-29	1.5	2.6	1.1	
HES 70-31	2.9	2.3	-0.6	
HES 71-02	10.5	4.9	-5.6	
HES 71-09	5.1	3.7	-1.4	
Mean	**3.4**	**3.3**	-0.2	0.3741
Pt ID	**Weight (kg) V1-V3 Ave**	**Weight (kg) V9-V12 Ave**	**Difference**	**P Value**
HES 02-02	91.3	88.7	-2.6	
HES 02-09	130.2	129.9	-0.3	

HES 04-07	100.4	98.9	-1.5	
HES 04-08	103.8	105.0	1.3	
HES 04-13	108.8	107.9	-0.9	
HES 05-17	97.9	94.0	-3.9	
HES 40-03	125.0	113.5	-11.5	
HES 70-03	153.0	139.6	-13.3	
HES 70-06	120.0	115.3	-4.8	
HES 70-08	87.0	81.7	-5.3	
HES 70-11	136.8	140.8	4.0	
HES 70-22	121.5	117.8	-3.7	
HES 70-27	98.5	67.9	-30.6	
HES 70-29	109.0	107.0	-2.0	
HES 70-31	118.5	108.5	-10.1	
HES 71-02	80.1	81.8	1.7	
HES 71-09	124.5	120.8	-3.7	
Mean	**112.1**	**107.0**	**-5.1**	**0.0089**

Table 6: Comparison of BL (averages of first 3 visits) to end of study (average of 4 last visits). This analysis was meant to prevent effects of placebo and implant procedures deemed to last up to 6 month. P values reflect analysis of available data pairs.

7.2 APPENDIX 2 PROTOCOL DEVIATIONS TABLE FOR ALL PATIENTS

Main deviations were categorized in 4 groups Out of window (28 in Poland, 14 in Italy and 21 in Serbia), lab value problematic or missing (43 in Poland, 2 in Italy and 42 in Serbia), Eligibility criteria problematic (16 in Poland and 2 in Serbia) or missing of other data or missing visit (32 in Poland, 3 in Italy and 42 in Serbia).

Deviation Table (I) Poland

Patient ID	**Deviation type**	**Deviation description/Comment**
01-001	Lab Out of Window Visit	*MTT test not performed during baseline visit* *V1, V2. V3 date unknown*

01-002	Lab Out of Window Visit	*MTT test not performed during baseline visit* *V1, V2,V3,V6,V8,V9*
	Eligibility Missing data Missing Visit Missing data Eligibility	*patient had stopped Lipanthyl treatment two weeks after the screening visit* *V2-height, weight, waist Circumference assessment are missing* *Patient didn't come for V13 and V14 although she was invited by Dr. Rogowski – in both cases she stated that this was not suitable time for her but she is willing to come for next visit* *V9 (17.06.2014)- blood test and patients questioners (chemistry hematology and lipid panel) not performed although were performed during unscheduled Visit performed on 8.05.2014)* *eligibility criteria concerns stable HbA1c, cannot be confirmed as the results of HbA1c assessment recorded within 3 months before study enrolment are not available*
01-003	Lab Out of Window Visit Missing data Out of Window Visit Eligibility Lab Lab Lab	*MTT test not performed during baseline visit* *V1, V2,V3,V6,V7,V9* *V10 HbA1c was not assessed* *V13 (3 months late)* *eligibility criteria concerns stable HbA1c, cannot be confirmed as the results of HbA1c assessment recorded within 3 months before study enrolment are not available* *V2 was performed twice as during first V2 blood assessment was forgotten* *V2 performed (9.01.2014) CRP was not assessed (although accessed on second V2 (B) performed 17.02.2014)* *V2 B –performed on 17.02.2014- height, weight, waist Circumference assessment are missing - although assessed during first V2 (9.01.2014)*
01-004	Out of Window Visit Lab Lab Missing data	*V1, V2,V9, V12* *MTT test performed on 19.02.2015 although procedure had place in January* *TG were not assessed on V13* *During MV it was detected that on Visit Summary Sheet provided by Dr. Mamos after each visit – one medication (Atoris) was missing*
01-005	Out of Window Visit Lab	*V1, V2,V9, V12* *V2- HbA1c not assessed*

		Obesity Questioner recorded later than visit took place
	Lab	*MTT test performed on 19.02.2015 although procedure had place in January*
	Lab	*Insulin level and HbA1c were not assessed during V12*
	Lab	*TG were not assessed on V13*
		SAE not reported on time
02-002	Out of Window Visit	*V1, V2,V6,V8- V10*
	Missing data	*missing data on V2*
	Lab	*HBA1c was not assessed during V3 but on the day of V4*
	Lab	*MTT not performed during V12*
02-004	Out of Window Visit	*V2, V6 and V7*
	Eligibility	*Problematic interpretation of confirmation HbA1c stability*
	Lab	*Lab assessments missing during V3*
	Missing data	*missing data on V2*
02-008	Out of Window Visit	*V1-V3*
	Eligibility	*Problematic interpretation of confirmation HbA1c stability*
03-001	Lab	*MTT test not performed during baseline visit.*
	Out of Window Visit	*V1, V2- unknown, V3, V6, V7.*
03-002	Lab	*MTT test not performed during baseline visit*
	Out of Window Visit	*V1, V2- unknown, V3, V6, V8. V10*
	Lab	*V2- HbA1c - not done*
	Lab	*V6&9 - chloride, magnesium, phosphates, direct bilirubin, amylase, uric acid, bun, albumin, total protein, LDH - not done*
	Lab	*V12 blood sample for chemistry assessment and lipid panel were not collected*
	Eligibility	*Although required by protocol copy of previous patient's documentation from 6 months prior to the study enrolment were not available and data collected only based on patient's statement.*
	Missing data	*Page 26(patient's questioner) was forgotten to be completed by patient*
03-003	Lab	*blood chemistry parameters were missing*
03-009	Eligibility	*HbA1c could not be confirmed as stable within 3 months to enrolment as there was no previous HbA1c results available. Only HbA1c assessment performed during V1 could be transferred to CRF.*

	Eligibility	*Insulin assessment was done after procedure (properly should be checked during V3)*
	Lab	*V2 and V6- pregnancy test and some chemistry parameters not assessed*
	Out of Window Visit	*V6*
	Lab	*V8 – pregnancy test not performed*
	Lab	*V9 – direct bilirubin assessment has not been performed by local lab.*
04-002	Out of Window Visit	*V12 one week out of expected visit time window*
	Out of Window Visit	*V1-V3 and V7*
	Lab	*Creatinine level was not assessed by local lab*
04-003	Out of Window Visit	*V1-V3, V13*
04-004	Out of Window Visit	*V1-V3 and V8*
04-006	Out of Window Visit	*V9 – one day out of expected visit time window*
04-007	Lab	*V9- ALAT, ASPAT, total protein Not done*
04-008	Out of Window Visit	*V1-V3; V6 out of expected visit time window*
	Missing data	*V6 - Missing device assessment caused by device disorder*
04-010	Out of Window Visit	*V1-V3 and V5*
04-012	Eligibility	*patient was included without records concerning most resent HbA1c before V1. This means eligibility criteria concerning stable HbA1c could not be confirmed in this case*
	Lab	*V12-urea and BUN missing*
04-013	Out of Window Visit	*V1-V3*
	Lab	*V12-urea and BUN missing*
05-002	Out of Window Visit	*V6, V7, V8*
	Lab	*HBA1c was not assessed during V3 but available on next visit*
	Eligibility	*Eligibility criteria were confirmed in source data as meet although they were verified based on information collected from patient. Corresponding Note to File was prepared.*
	Eligibility	*Previous to the Diamond study Patient's documentation not available , all collected information from the past based on patients statements*
	Missing data	*V2 missing data was found for blood reassure, height, weight, BMI, waist circ. – this was cost by changing procedure during the study (previous CRF did not requested*

		those data)
	Lab	*HbA1c not assessed during V2*
	Lab	*V6: HbA1c, blood chemistry, hematology and lipid panel assessments missing*
	Missing data	*V9 – patient did not complete the questionnaire*
	Missing data	*V7 and V10 – TG level not assessed*
	Eligibility	*Between 15.062014 and 15.08.2014 used herbal treatment (RUTIDIL) for lowering body weight not allowed by protocol*
05-008	Out of Window Visit Missing Visit Missing data	*V1, V2, and V8,* V6 is missing, *V2 – vital signs not assessed*
05-011	Out of Window Visit Lab Missing Visit Lab Lab	*V1, V2 and V8* *HbA1c not assessed during V2* *V6 not performed* *V9: sodium and potassium assessment missing* *MTT not done on V12*
05-014	Eligibility	*did not have HbA1c assessed before V1*
05-017	Lab Lab Eligibility Out of Window Visit Lab Missing data	*HBA1c, TG, and fasting glucose test was not assessed during V5* *V2 - blood reassure, height, weight, BMI, waist circ. - not done* *Diabetic treatment was not stabile between v1 and V3* *V6, V9, V10* *MTT not done on V12* *Some Concomitant Diseases recorded on Czerniakowska were missing at Bielany documentation (epilepsy, hiperuricemia)*
05-019	Out of Window Visit Missing data Lab Lab Lab Lab	V1, V2 and V3 V2 - missing height, weight, BMI, waist circ V6 – assessments of Cholesterol , TG, HDL. LDL are missing *MTT not done on V12* *V12 - phosphates assessment missing* *V10 - TG assessment missing*
05-022	Eligibility Missing data Out of Window Visit Missing Visit Lab	*Eligibility criteria were confirmed based of patients statement recorded as medical history* *BP, height, weight, BMI - missing from V2* *V9,10,11* *V10 not performed* *V11-Hba1c and Insulin test not done*

	Out of Window Visit	*V12 – visit was performed 26.04.2017 but Investigator followed procedures from V11, On CRA request Patient was asked to returned to the site and complete all missing tests so Lab test and Questionnaires were completed with the delay on 2.05.017*
	Lab	*MTT of V12 not done*

Deviation Table (II) Italy

Patient Number	**Deviation type**	**Deviation description/Comment**
040-001	Out of Window Visit	The visit 7 performed on the 22nd July, instead on the 4th August because on August the department was closed. The patient took the drug intermittently from 22nd July to 29th September because there was an adverse event. On the 09th October the patient stopped Fenofibrate/Placebo because reported again the increase of the GGT value.
	Out of Window Visit	The visit 8 performed on the 9th october, instead on the 29th September because the patient could not reach the hospital. She had problems with her car.
	Out of Window Visit	The patient performed the visit 11 on the 9th March instead on the 15th March because she couldn't.
	Out of Window Visit	The patient performed the visit 11 on the 9th March instead on the 15th March because she couldn't.
	Out of Window Visit	The patient did not yet performed the visit 12 scheduled on the 10th May 2016 because she reported by phone to the Investigator a cervicobrachialgie. She performed the visit on the 16/Jun/2016.
040-002	Out of Window Visit	Visit 4 should performed on the 24th November but there were some organization problems and the surgery room was not available. The implantation will take place on 1st December.
	Out of Window Visit	The patient performed the visit 11 on 13/Sep/2016 instead 06/Sep/2016.
040-003	Out of Window Visit	The patient 040-003 performed the visit 9 on the 30/Jun/2016 instead on the 12/Jul/2016 because she reported personal problems.
	Out of Window Visit	The patient performed the visit 10 on 22/Sep/2016 instead 06/Sep/2016 and visit 11 on 30/Nov/2016 instead 01/Nov/2016.
	Out of Window Visit	Patient performed the visit 12 on 10/Jan/2017 instead 27/Dec/2016.
	Missing data	patient refused to complete visit 13, only "System Status Assessment" section was completed
040-005	Out of Window Visit	The patient performed the visit 9 on 06/Sep/2016 instead 30/Aug/2016.

	Missing data	Visit 9. The question 22 of the RAND-36 Quality of life questionnaire is not filled
	Missing data	At visit 12, the patient did not filled all pages of the questionnaires.
	Out of Window Visit	Patient performed the visit 10 on 13/Dec/2016 instead 20/Dec/2016 and visit 12 on 02/Feb/2017 instead 14/Feb/2017.
040-006	Out of Window Visit	The patient performed the visit 8 on 06/Sep/2016 instead 30/Aug/2016.

Deviations Table (III) Serbia

Patient Number	**Deviation type**	**Deviation description/Comment**
070-001	Lab	*At visit 6: blood chemistry – direct bilirubin result is missing*
070-002	Lab	*At visit 6: blood chemistry – direct bilirubin result is missing*
	Out of Window Visit	Visit 13 was scheduled by SI after 2 months of V12 as that was an agreement with patient.
070-003	Lab	*At visit 1: laboratory, psychological evaluation – fasting insulin result is missing*
	Lab	*At visit 2: laboratory, pregnancy Test - fasting insulin result is missing*
	Lab	*At visit 2: Hematology, lipid panel – result of Neutrophils, Lymphocytes, Eosinophils, Basophils and Monocytes are missing*
	Out of Window Visit	Visit 12 rescheduled, fiber drink not available for MTT
	Out of Window Visit	Visit 13 was scheduled by SI after 2 months of V12 as that was an agreement with patient.
	Out of Window Visit	Visit 14 was scheduled by SI after 2 months of V14 as patient was not able to come for the visit later in April, May and Jun.
070-006	Missing Visit	*patient missed V9*
	Lab	At visit 12 result of direct bilirubin is missing,
	Missing data	*IPG assessment was not performed (no internet on site)*
	Missing Visit	*V15*
	Out of Window Visit	Visit 13 was scheduled by SI after 2 months of V12 as that was an agreement with patient
070-007	Out of Window Visit	*V8*
	Lab	At visit 9 results for Magnesium were not done

	Missing Visit	Patient did not come for Visit 14 that was scheduled for the 22nd of Sep 2016
	Missing Visit	Patient did not come for Visit 14 that was scheduled for the 22nd of Sep 2016
	Out of Window Visit	V14, 15
	Missing data	At visit 16 IPG reading was not performed
	Missing data	On the visit 13 (20-Jun-2016) device interrogation was not performed
070-008	Lab	At visit 2: blood chemistry – direct bilirubin result is missing
	Out of Window Visit	V9, V10
	Missing data	*IPG assessment was not performed (no internet on site)*
	Lab	At visit 12 result of direct bilirubin is missing,
070-009	Lab	at visit 2: Blood Chemistry – Magnesium, total bilirubin, direct bilirubin, potassium, lactic dehydr. values are missing
	Out of Window Visit	V8
	Lab	Visit 15, test of fasting insulin not performed
070-010	Out of Window Visit	V8, V13, V15
	Lab	At visit 12 results of direct bilirubin and lactic dehydrogenase are missing. ALT value had hemolysis
070-012	Out of Window Visit	V8, V10
	Lab	V12 - result of direct bilirubin is missing
	Missing data	At Visit 12, IPG reading not performed as patient was 4 days late for visit
070-013	Out of Window Visit	V8
	Lab	V12 - result of direct bilirubin is missing
	Missing data	Device assessment and lab tests were not performed at Visit 16
070-021	Out of Window Visit	V7
	Lab	V12 - result of direct bilirubin is missing
	Missing data	MTT and device interrogation were not performed at this visit. Questionnaires were not completed.
070-022	Out of Window Visit	V7
	Lab	V12 - result of direct bilirubin is missing
	Missing data	MTT and device interrogation were not performed at this visit. Questionnaires were not completed.

070-023	Out of Window Visit Missing data	V13 Device assessment and lab tests were not performed at Visit 16
070-026	Lab Out of Window Visit Out of Window Visit	At visit 2 result of direct bilirubin is missing V10 – patient was late for the visit Period between Visit 11 and 12 shorter than required by protocol. MTT was performed even before the visit.
070-027	Out of Window Visit Lab Out of Window Visit Out of Window Visit Lab Missing Visit	Visit 2 rescheduled, fiber drink not available for MTT At visit 6 result of direct bilirubin is missing V9 - patient was late for the visit, V10 – already late for the visit V9, V10 At visit 12, MTT was not performed. Lab results of albumin, total protein, lactic dehydrogenase and LDL are missing. V13
070-028	Lab Out of Window Visit Out of Window Visit Missing data	At visit 6 result of direct bilirubin is missing Patient was late for visit 8 Patient was too early for Visit 12 and MTT Device assessment and lab tests were not performed at Visit 13
070-029	Lab Eligibility Lab	At visit 6 result of direct bilirubin is missing Patient was randomized into HTG group even though average values of triglyceride at all three baseline visits was below 1,7 mmol/L. Lactic dehydrogenase analyses were not done at Visit 12
070-030	Lab Lab	At visit 2 results of direct bilirubin and lactic dehydrogenase are missing. Potassium value could not be calculated as serum had hemolysis. V8 - result of direct bilirubin is missing
070-031	Lab	At visit 12 MTT was not performed, lab analyses for ALT, AST, alkaline phosphatase and amylase are missing.
070-032	Lab	At visit 2 result of direct bilirubin is missing.
071-002	Lab Lab	At visit 2: Laboratory, Pregnancy Test CRP not done Randomization No 71502 instead of 71501 At visit 2: Lipid Panel LDL value is missing

	Lab	At visit 6: LDL value is missing
071-003	Lab	At visit 2: Blood Chemistry Amylase, Alkaline phosphatase not done Randomization No 71101 instead of 71502
071-004	Lab Lab	At visit 1: Medical History-Diabetes serum insulin value is not available At Visit 16 lab result of triglyceride is missing Randomization No 71104 instead of 71101
071-005	Lab Lab	At visit 1: Medical History-Diabetes serum insulin value is not available At Visit 16 lab result of triglyceride is missing Randomization No 71106 instead of 71102
071-009	Other	Randomization procedure was not adequately followed. Subject randomization envelope was not triggered in correct order.

Table 7 Protocol deviation during the study.