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(54) Benævnelse: **KOMBINATION AF STOFFER TIL ANVENDELSE I REGENERATIV TERAPI TIL PATIENTER MED TYPE 1 DIABETES MELLITUS**

(56) Fremdragne publikationer:
WO-A2-2006/000567
US-A1- 2014 322 213
LIU WENJUAN ET AL: "Combined Oral Administration of GABA and DPP-4 Inhibitor Prevents Beta Cell Damage and Promotes Beta Cell Regeneration in Mice", FRONTIERS IN PHARMACOLOGY, vol. 8, 20 June 2017 (2017-06-20),

DESCRIPTION

Field of the Invention

[0001] This invention relates to the field of medicine, namely to endocrinology, and can be used to treat type 1 diabetes.

Background Art

[0002] Diabetes mellitus type 1 (DM1, insulin-dependent diabetes, juvenile diabetes) is an autoimmune disease of the endocrine pancreas. Its main diagnostic sign is chronic hyperglycemia (high blood sugar), polyuria (frequent urination), and as a direct result: thirst, weight loss, excessive or decreased appetite; severe general fatigue of the body. Additionally, a prolonged manifestation of the disease and the absence of diagnosis can lead to the poisoning of the body by the by-products of fat decomposition - often expressed as acetone body production and specific odour coming from the skin or the mouth.

[0003] Until 1921, when insulin treatment was discovered, this disease was regarded as fatal. Patients died from malnutrition and coma resulting from ketoacidosis (blood acidification and the production of acetone).

[0004] At the heart of the pathogenetic mechanism of type 1 diabetes development is the insufficient production of insulin by endocrine cells (β-cells of the islets of Langerhans in the pancreas). Type 1 diabetes constitutes 5%-10% of all diabetes cases, it is more likely to appear in childhood or adolescence and can be hereditary. Out of about 400,000,000 diabetic patients living in the world today, up to 40,000,000 are DM1 patients.

[0005] This type of diabetes is characterized by an early manifestation of symptoms that progress quickly over time.

[0006] Due to insulin deficiency, insulin-dependent tissues (liver, fat, and muscle) lose the ability to absorb blood glucose and, as a result, blood glucose level increases (hyperglycemia) - thus being the main diagnostic sign of diabetes mellitus. Insulin deficiency in adipose tissue causes fat breakdown, leading to an increased concentration of Free Fatty Acids (FFA) in the blood, while in the muscle tissue it leads to the disintegration of proteins, which creates increased levels of amino acids in the bloodstream. Substrates from the catabolism of fats and proteins are transformed into ketone bodies by the liver; these ketones are then used by insulin-independent tissues (mainly the brain) to maintain an energy balance against the backdrop of insulin deficiency.

[0007] The exact cause of the disease is unknown. All over the world, it is considered to be an

utterly incurable, disabling disease.

[0008] There are six stages of development of type 1 diabetes mellitus (DM1):

- Genetic predisposition to diabetes, associated with the HLA system.
- Hypothetical starting point: β-cells damage by various diabetogenic factors and by the stimulation of immune processes. Patients already have antibodies against the islet cells in a small titer, but insulin secretion does not yet appear to suffer.
- Active autoimmune insulitis - inflammation of the endocrine part of the pancreas. The antibody titer is high, the number of β-cells decreases, with the secretion of insulin decreasing as well.
- Decreased insulin secretion. In stressful situations, it is possible to identify impaired glucose tolerance (IGT) in the patient, as well as impaired fasting glucose (IFG).
- Clinical manifestation of diabetes, including a possible episode of the "honeymoon phase." The secretion of insulin is sharply reduced since more than 90% of β-cells have died.
- Complete destruction of β-cells, total cessation of insulin secretion.

[0009] Treatment of type 1 diabetes involves lifelong injections of insulin. Without this treatment, the disease progresses rapidly and leads to severe complications such as diabetic cardiomyopathy, stroke, kidney failure, diabetic retinopathy, diabetic foot ulcers, ketoacidosis, and diabetic coma, all of which may lead to disability or result in the patient's death.

[0010] However, a constant intake of insulin can often lead to an overdose of insulin, which can give rise to several complications. The risk of hypoglycemia, which contributes to the development of atherosclerosis and arterial hypertension, is particularly high. Therefore, modern methods of treating type 1 diabetes are aimed at finding new drugs that can save the patient from the daily administration of insulin by preserving the β-cells and even regenerating β-cell - pool.

[0011] There are known the proton pump inhibitors (US4786505, EP2201952). The proton pump inhibitor is administered orally at a daily dose of 10 to 40 mg, depending on the body weight. Proton pump inhibitors can be selected, for example, from omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole.

[0012] There is known gamma-aminobutyric acid (GABA), as well as other gamma-aminobutyric acid receptor agonists.

[0013] The drug Sitagliptin (Januvia) has been registered in many countries in the world. Sitagliptin may serve as a classic representative of a family of DPP - 4 inhibitors. Sitagliptin increases the concentration of two known hormones of the incretin family: GLP-1 and glucose-dependent insulinotropic peptide (GIP). Hormones of the family of incretins are secreted in the intestine during the day, with levels rising in response to food intake. Incretins are part of the

internal physiological system of regulation of glucose homeostasis. At normal or elevated blood glucose levels, the hormones of the incretin family promote an increase in insulin synthesis, as well as its secretion by beta cells of the pancreas, due to the intracellular signaling mechanisms associated with cyclic AMP. A double-blind, randomized, cross-over, 8-week, preliminary study in adult patients with type 1 diabetes showed that the drug had significantly reduced blood glucose levels despite a reduced total and lunch dose of insulin (DiabetMed. 2011 Oct; 28 (10): 1176-81 Effect of Sitagliptin on glucose control in an adult patient with Type 1 diabetes: a pilot, double-blind, randomized, crossover trial Ellis SL, Moser EG, Snell-Bergeon JK, Rodionova AS, Hazenfield RM, Garg SK.). This drug is now being considered for introduction into the clinical practice of type 1 diabetes treatment.

[0014] In addition, attempts have been made to create combined medications based on Sitagliptin and other DPP-4 inhibitors for the treatment of diabetes, taking into account the fact that insulin deficiency in the body develops due to its insufficient secretion by the β-cells of the islets of Langerhans in the pancreas.

[0015] In particular, in an article by Griffin KJ, Thompson PA, Gottschalk M, Kyllo JH, Rabinovitch A. Combination therapy with Sitagliptin and lansoprazole in patients with recent-onset type 1 diabetes (REPAIR-T1D): 12-month results of a multicentre, randomized, placebo-controlled, phase 2 trial. // Lancet Diabetes Endocrinol.2014 Sep; 2 (9): 710-8, it is postulated that Sitagliptin and lansoprazole will maintain the beta-cell function in patients with type 1 diabetes. However, in the analysis, it was noted that not all participants were able to increase their glucagon-like peptide 1 and gastrin concentrations.

[0016] International application WO2006000567 discloses the use of a GLP-1 receptor agonist and/or a DPP-4 inhibitor and a proton pump inhibitor such as omeprazole or esomeprazole, in the manufacture of a medicament for the treatment of type 1 diabetes. This combination does not allow a significant reduction of the insulin dose.

[0017] The US Patent No. 9463174 discloses a method for treating type 1 diabetes (T1D), including administering a therapeutically effective amount of gamma-aminobutyric acid (GABA) and an effective amount of a DPP-4 inhibitor, for example, Sitagliptin, to a T1D patient. GABA and the DPP-4 inhibitor are used in a single-dosage form or separate-dosage forms. The dosage includes GABA in 0.002 to 2 mg/kg of body weight. This combination does not lead to a significant recovery of beta cells of the pancreas.

[0018] Liu Wenjuan et.al. disclose combined oral administration of GABA and DPP-4 inhibitor to prevent beta cell damage and promote of beta cell regeneration in mice (Frontiers in Pharmacology, vol. 8, 20 June 2017).

Disclosure of the Invention

[0019] The goal of this invention is to provide a combination of substances that leads to a long-

lasting anti-hyperglycemic effect, is safe, and has a favourable side effects profile.

[0020] This objective is achieved by using a combination consisting of a dipeptipidipeptidase-4 inhibitor (DPP-4), a proton pump inhibitor (PPI) and gamma-aminobutyric acid or gamma-aminobutyric acid receptor agonist as further set out in the appended set of claims. This unique combination leads to a regeneration (recovery) of the β-cells of the pancreas and is intended for the treatment of type 1 diabetes.

[0021] The references to methods of treatment in the subsequent paragraphs of this description are to be interpreted as references to the compounds, pharmaceutical compositions and medicaments of the present invention for use in a method for treatment of the human (or animal) body by therapy (or for diagnosis).

Brief description of the figures

[0022]

Fig. 1- shows graph of continuous glucose monitoring (CGM) data of the patient in Example 1, before starting triple therapy;

Fig. 2- shows graph of continuous glucose monitoring (CGM) data during the triple therapy, accompanied by dramatic insulin requirement reduction, of the patient in Example 1; in April, 2018 his C-peptide became detectable;

Fig. 3 - CGM data of the patient in Example 2, before starting treatment;

Fig. 4 - CGM data of the patientin Example 2, two months on triple therapy and total Insulin discontinuation

Fig. 5- CGM data of the patient in Example 2, eight months on the triple therapy and total Insulin discontinuation.

[0023] The administration of the three-drug combination according to the present invention as set out in the appended claims, is proposed for the treatment of Type 1 Diabetes (T1DM). More particularly, according to the present invention the inventors propose a combination of substances for use in regenerative therapy in patients with type 1 diabetes mellitus, namely, for recovery of the β-cells of the pancreas.

[0024] The first drug of the proposed combination belongs to the group of DPP-4 inhibitors (DPP4i). The DPP-4 inhibitor is administered orally at a daily dose of 25 to 100 mg, depending on the body weight. Examples of drugs of this group, which are suitable to be used in this invention, are DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin. The use of sitagliptin (Sitagliptin) in particular is preferable in the practice of this invention. These

can be, for example, pills of sitagliptin manufactured by various companies.

[0025] The second drug of the proposed combination belongs to the PPI group. The proton pump inhibitor is administered orally at a daily dose of 10 to 40 mg, depending on the body weight. Proton pump inhibitors can be selected, for example, from omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole. Omeprazole is preferred in the practice of this invention, for example in the form of pills or capsules.

[0026] The third drug of the proposed combination is gamma-aminobutyric acid (GABA), as well as other gamma-aminobutyric acid receptor agonists. The drug is given in a daily dose of 125 to 500 mg three times a day, depending on the body weight. Capsules of GABA, gelatine or cellulose (US5698155) or tablets (aminalone) can be used. GABA agonists, such as baclofen, phenibut, pantogam, and anti-epileptic medications such as Valproic acid, Depalept, Topamax, Carbamazepine, and medical cannabis, can also be used instead of GABA.

[0027] Oral forms include any pharmaceutically acceptable dosage forms, powders, granules, capsules, tablets, microcapsule suspensions, and the like. The medications can be used alone or in a single dosage form, for example in the form of capsules.

[0028] The technical result of the invention lies in the fact that the administration of the drugs in this combination allows for a significant reduction in the need for insulin, and in some cases, it is even possible to stop insulin injections completely.

[0029] Drugs of the DPP-4i group (e.g., Sitagliptin, Vildagliptin, Saxagliptin) help in the regeneration of β-cells. This is due in particular to the fact that medications of the DPP-4i family are capable of modulating the immune response by limiting autoimmune activity, reducing the inflammatory component (insulitis) and ultimately achieving the regeneration of the β cells of the pancreas.

[0030] DPP-4 inhibitors (DPP-4i) block the activity of the DPP-4 enzyme, which leads to an increase in both concentration and the duration of action of GLP-1 and GIP. They are taken orally and provide a healthy physiological level of incretins in the blood.

[0031] A critically important feature of the effect of GLP-1 on the function of β and α cells is its glucose-dependent nature. This means that the GLP-1 stimulates insulin secretion and, on the other hand, suppresses the production of glucagon only under conditions of hyperglycemia. Once plasma glucose drops to a regular level, the effects above of GLP-1 subside, making it a reliable physiological mechanism for preventing the development of a hypoglycemic state.

[0032] GABA (Gamma Amino Butyric Acid) affects both β and α-cells, their functions and the viability of the pancreas as a whole. This substance is widely used as a food supplement. In α-cells, GABA induces hyperpolarization of the membrane and suppresses glucagon, whereas in β-cells it induces membrane depolarization and increases insulin secretion. Also, GABA has a multi-directional positive effect on β-cells, which includes the stimulation of cell proliferation and

anti-apoptosis, thus making it an attractive option for complex treatment of diabetes.

[0033] Proton pump inhibitors inhibit Na+/K+-ATPase (proton pump) on the apical membrane of parietal cells of the gastric mucosa and ensure the achievement of clinical, endoscopic remission in all acid-dependent diseases, including those requiring prolonged or continuous therapy. For an extended period during the day, they maintain pH values in the stomach within limits favorable for the healing of stomach or duodenal ulcers. The general effect of the pharmacological action of the drugs of this group is the increase of gastrin in the blood and the pancreatic tissue. Gastrin is a natural stimulant for the recovery (regeneration) of pancreatic cells.

[0034] In the light of the above, the use of triple therapy (DPP-4i + GABA + PPi) appears to be promising for maintaining pancreatic function and for controlling type 1 diabetes in human patients.

[0035] The above-mentioned triple combination showed unexpectedly good results. The possibility of carrying out the invention can be illustrated by the following examples presented below.

Example 1

[0036] An 82-year-old patient, with 35 years of type 1 diabetes. For the last ten years, has been taking 30 units of Insulin Lantus per day, and 10 units of Apidra daily with each meal. Glucophage 850 mg/day. Analysis: retinopathy, BMI = 27, frequent night hypoglycemia, hypothyroidism, HBalC = 10.5%; A/GAD (antibodies against glutamate decarboxylase) = 3.8 (nearly a fourfold increase); Undetectable C- peptide.

[0037] The results of the CGM study are shown in Fig. 1. The patient was prescribed with an orally-administered combination in accordance with the invention. The combination included sitagliptin at 25 mg per day, omeprazole at 20 mg per day, and GABA at 400 mg three times a day. Fig. 2 shows the changes during the treatment. The patient's need for insulin is reduced to 24.3 units a day. 7% of the time, the patient is in a hypoglycemic state: blood sugar below 70 mg/dL, glycated hemoglobin-HBalC = 6.6%.

Example 2

[0038] 19.5-year-old patient, diagnosed with type 1 diabetes since September 2015. Prior to his admission to the clinic, he has been treated with insulin Lantus (glargine) 26 units in the morning, and with insulin Actrapid three times a day during meals: 16-14-12 units. Analysis: unremarkable anamnesis, ketoacidosis, HBalC = 12.8%. The results of the CGM study are shown in Fig. 3.

[0039] The patient was prescribed with an orally-administered combination in accordance with the invention. The combination included sitagliptin at 50 mg per day, pantoprazole at 10 mg per day, and GABA at 300 mgthree times a day. Fig. 4 and Fig.5 demonstrate an absence of the need for insulin. HBalC = 5.1%. The patient did not require any insulin for almost 1.5 years.

[0040] A total of 46 people took part in the research. More than 50% of the patients were able to significantly reduce their insulin doses, with five patients stopping insulin injections completely for long - term period (months and even years). Also, the data demonstrate that the pancreas has regenerated its function. Patients in this category can be very different. In particular, as can be seen from Example 1, even severe forms of diabetes in patients of advanced age are responsive to treatment. The combination can be used even in children.

[0041] These studies conducted in humans demonstrate not only surprisingly good results but also the unexpectedly low toxicity of this therapy, with virtually no side effects.

[0042] Thus, significant results have indeed been obtained. That is, not only does this invention lead to a substantial decrease in the need for insulin injections - which in itself is outstanding and proves the restoration and regeneration of pancreatic function - but it also allows for the possibility of a complete long-term insulin discontinuation, although it is universally believed that Type 1 diabetes (T1D) is an irreversible disease.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US4786505A **[0011]**
- EP2201952A **[0011]**
- WO2006000567A **[0016]**
- US9463174B **[0017]**
- US5698155A **[0026]**

Non-patent literature cited in the description

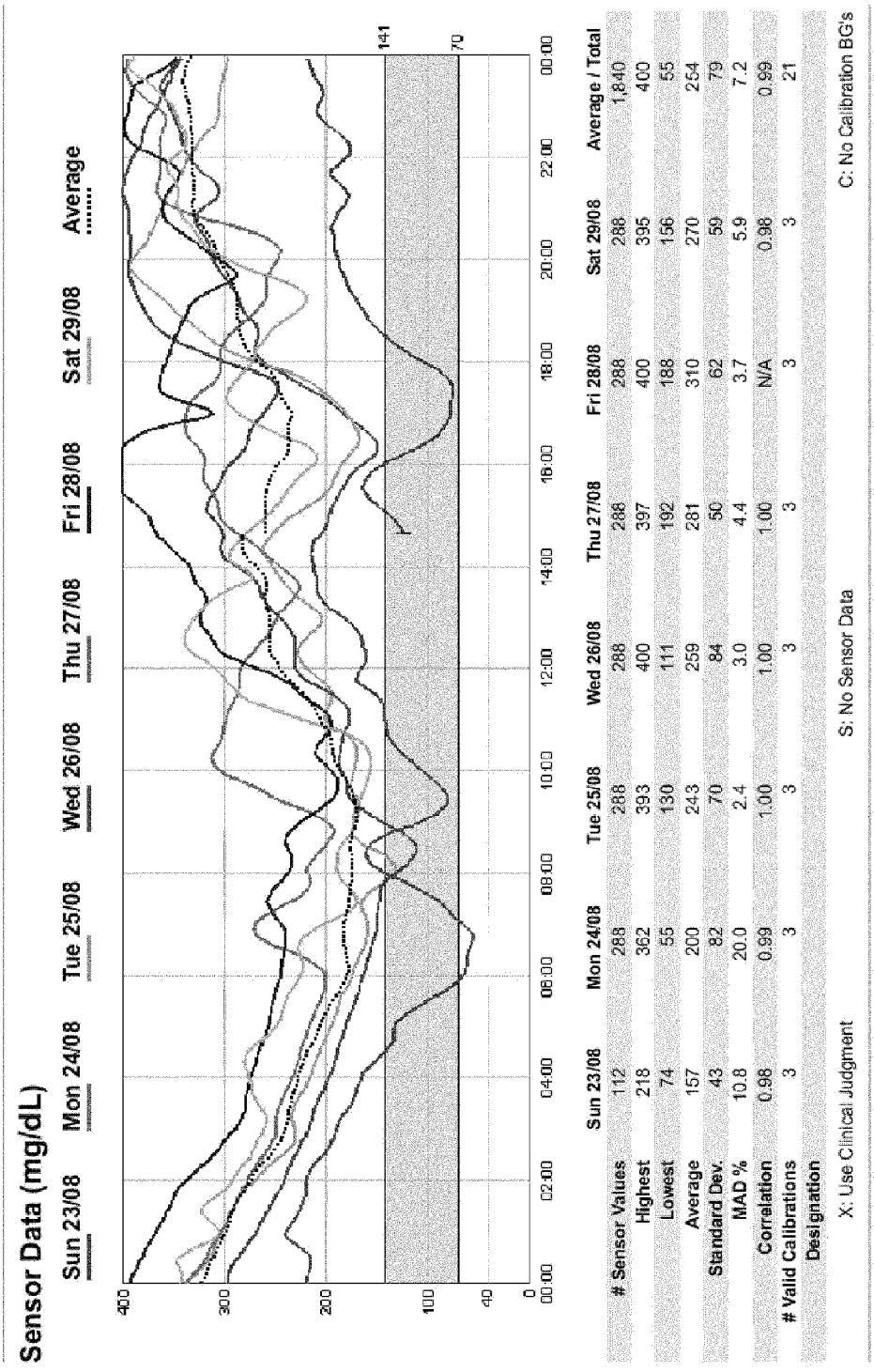
- DiabetMed., 2011, vol. 28, 101176-81 [0013]
- **GRIFFIN KJTHOMPSON PAGOTTSCHALK MKYLLO JHRABINOVITCH A**Combination therapy with Sitagliptin and lansoprazole in patients with recent-onset type 1 diabetes (REPAIR-T1D): 12-month results of a multicentre, randomized, placebo-controlled, phase 2 trial.Lancet Diabetes Endocrinol., 2014, vol. 2, 9710-8 [0015]
- Frontiers in Pharmacology, 2017, vol. 8, [0018]

Patentkrav

1. Oralt indgivet kombination til anvendelse i regenerativ terapi til patienter med type 1 diabetes mellitus, det vil sige, til bedring af β-celler af bugspytkirtlen, **kendetegnet ved, at** den består af: et medikament tilhørende gruppen af dipeptidylpeptidase- (DPP-4) inhibitorer og indeholder en terapeutisk effektiv mængde af DPP-4-inhibitor, som udgør op til 25 til 100 mg/dag; et medikament af protonpumpeinhibitorgruppen (PPI) som indeholder en terapeutisk effektiv mængde af PPI, omfattende 10 til 40 mg/dag; og terapeutisk effektiv daglig dosis af gamma-aminosmørsyre-præparat (GABA) eller gamma-aminosmørsyre-receptoragonist på 375 til 1500 mg/dag.

2. Kombination til anvendelse ifølge krav 1, **kendetegnet ved, at** medikamentet fra DPP-4-inhibitorgruppen er sitagliptin, hvor medikamentet fra PPI-gruppen er omeprazol.

DRAWINGS



	Sun 23/08	Mon 24/08	Tue 25/08	Wed 26/08	Thu 27/08	Fri 28/08	Sat 29/08	Average / Total
# Sensor Values	112	288	288	288	288	288	288	1,840
Highest	218	362	393	400	397	400	395	400
Lowest	74	55	130	111	192	188	156	55
Average	157	200	243	259	281	310	270	254
Standard Dev.	43	82	70	84	50	62	59	79
MAD %	10.8	20.0	2.4	3.0	4.4	3.7	5.9	7.2
Correlation	0.98	0.99	1.00	1.00	1.00	N/A	0.98	0.99
# Valid Calibrations	3	3	3	3	3	3	3	21
Designation								

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

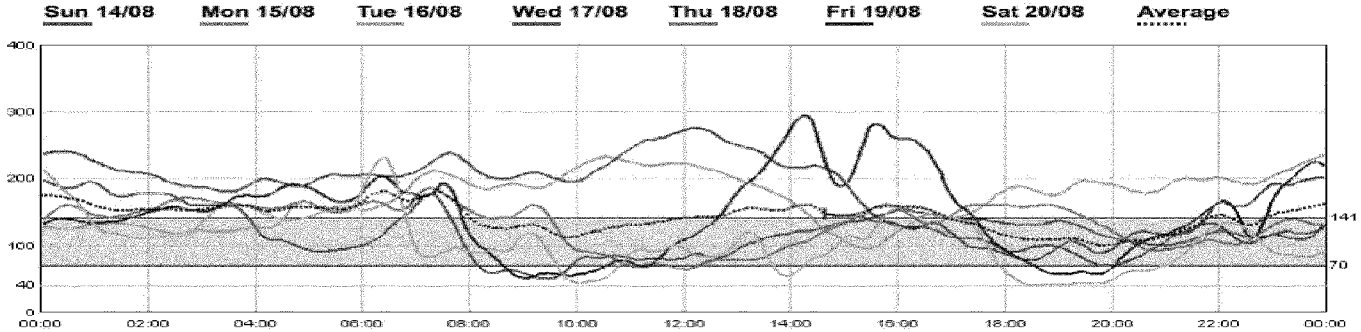
Fig. 1

Medtronic

14/08 - 20/08/2016

(7 days) Medtronic iPro2 Recorder #3034021

Sensor Data (mg/dL)



	Sun 14/08	Mon 15/08	Tue 16/08	Wed 17/08	Thu 18/08	Fri 19/08	Sat 20/08	Average / Total
# Sensor Values	113	288	288	288	288	288	288	1,841
Highest	201	198	235	275	185	294	232	294
Lowest	78	52	95	70	64	52	41	41
Average	129	121	171	177	133	148	107	142
Standard Dev.	34	35	37	57	32	61	42	51
MAD %	19.5	3.9	5.3	6.5	14.2	7.6	10.3	9.5
Correlation	1.00	N/A	N/A	0.96	N/A	1.00	N/A	0.97
# Valid Calibrations	3	3	3	4	3	3	3	22
Designation								

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

Excursion Summary (mg/dL/day)

	Sun 14/08	Mon 15/08	Tue 16/08	Wed 17/08	Thu 18/08	Fri 19/08	Sat 20/08	Average / Total
# Excursions	2	3	2	1	5	7	6	26
# High Excursions	2	2	2	1	3	4	3	17
# Low Excursions	0	1	0	0	2	3	3	9
AUC Above Limit	9.4	6.6	35.4	48.2	8.9	28.3	5.6	21.4
AUC Below Limit	0.0	0.8	0.0	0.0	0.1	1.6	3.6	1.0

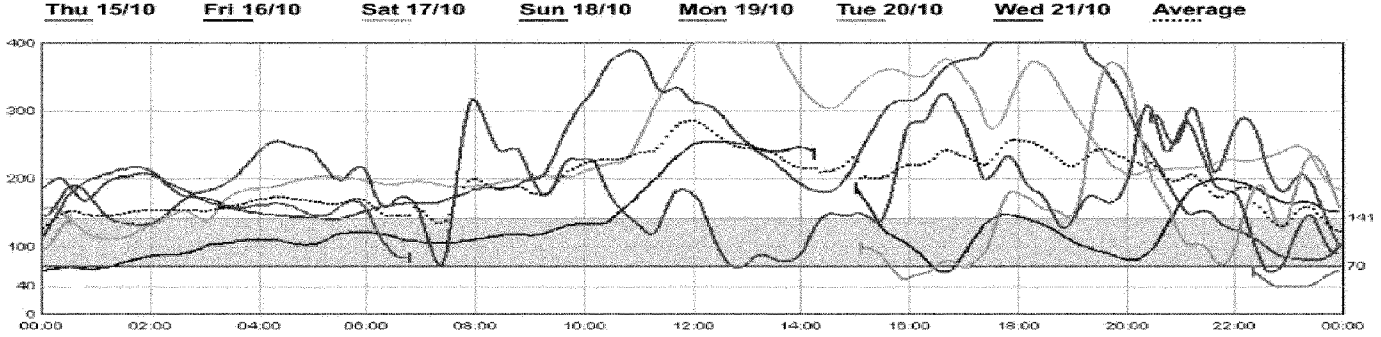
Duration Distribution (hh:mm)

Above 141	3:00	32%	6:15	26%	17:25	73%	15:35	65%	12:40	53%	12:50	53%	5:30	23%	73:15	48%
Within (70 - 141)	6:25	68%	16:00	67%	6:35	27%	8:25	35%	10:40	44%	7:45	33%	13:45	57%	69:35	45%
Below 70	0:00	0%	1:45	7%	0:00	0%	0:00	0%	0:40	3%	3:25	14%	4:45	20%	10:35	7%

Fig. 2

DK/EP 3520786 T3

Sensor Data (mg/dL)



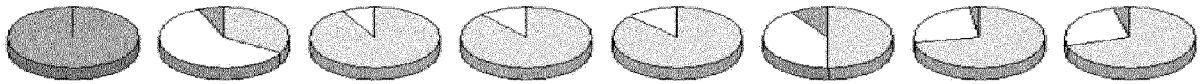
	Thu 15/10	Fri 16/10	Sat 17/10	Sun 18/10	Mon 19/10	Tue 20/10	Wed 21/10	Average / Total
# Sensor Values	20	280	288	286	125	114	288	1,403
Highest	64	254	400	400	305	371	325	400
Lowest	40	62	110	79	82	52	62	40
Average	48	135	246	231	187	152	180	191
Standard Dev.	9	53	82	94	51	79	62	85
MAD %	56.9	55.9	11.1	2.5	26.1	18.3	15.9	23.6
Correlation	N/A	0.89	N/A	1.00	N/A	N/A	N/A	0.85
# Valid Calibrations	1	3	3	3	2	2	3	17
Designation	X	X			X	X		

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

Excursion Summary (mg/dL/day)

	Thu 15/10	Fri 16/10	Sat 17/10	Sun 18/10	Mon 19/10	Tue 20/10	Wed 21/10	Average / Total
# Excursions	1	4	1	1	2	4	7	20
# High Excursions	0	3	1	1	2	2	5	14
# Low Excursions	1	1	0	0	0	2	2	6
AUC Above Limit	0.0	19.2	106.2	93.8	49.7	35.3	48.3	62.1
AUC Below Limit	21.8	0.2	0.0	0.0	0.0	1.0	0.1	0.5

Duration Distribution (hh:mm)



Above 141	0:00	0%	7:50	34%	22:00	92%	21:10	88%	9:05	87%	4:45	50%	17:20	72%	82:10	70%
Within (70 - 141)	0:00	0%	13:55	59%	2:00	8%	2:50	12%	1:20	13%	3:50	40%	6:10	26%	30:05	26%
Below 70	1:40	100%	1:35	7%	0:00	0%	0:00	0%	0:00	0%	0:55	10%	0:30	2%	4:40	4%

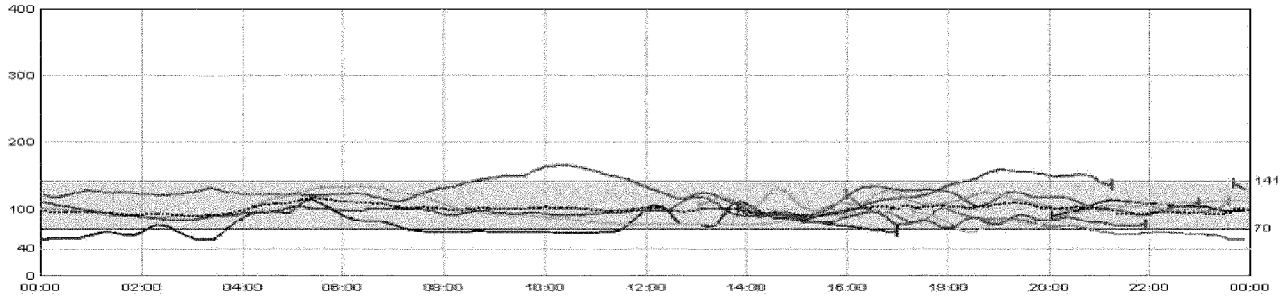
Fig. 3

10/12 - 16/12/2015

(7 days) Medtronic iPro2 Recorder #3070630

Sensor Data (mg/dL)

Thu 10/12 Fri 11/12 Sat 12/12 Sun 13/12 Mon 14/12 Tue 15/12 Wed 16/12 Average



	Thu 10/12	Fri 11/12	Sat 12/12	Sun 13/12	Mon 14/12	Tue 15/12	Wed 16/12	Average / Total
# Sensor Values	96	252	284	260	277	127	98	1,394
Highest	122	114	134	158	165	131	101	165
Lowest	54	54	66	63	88	92	71	54
Average	77	81	95	106	121	108	83	99
Standard Dev.	15	17	17	21	16	9	6	23
MAD %	15.2	15.4	4.4	11.6	5.4	2.8	8.5	8.9
Correlation	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
# Valid Calibrations	1	3	3	3	2	2	2	16
Designation	X				X	X	X	

X: Use Clinical Judgment S: No Sensor Data C: No Calibration BG's

Excursion Summary (mg/dL/day)

	Thu 10/12	Fri 11/12	Sat 12/12	Sun 13/12	Mon 14/12	Tue 15/12	Wed 16/12	Average / Total
# Excursions	1	3	1	1	1	0	0	7
# High Excursions	0	0	0	1	1	0	0	2
# Low Excursions	1	3	1	0	0	0	0	5
AUC Above Limit	0.0	0.0	0.0	1.3	1.8	0.0	0.0	0.6
AUC Below Limit	3.1	2.5	0.0	0.0	0.0	0.0	0.0	0.7

Duration Distribution (hh:mm)

Above 141	0:00	0%	0:00	0%	0:00	0%	2:40	12%	3:10	14%	0:00	0%	0:00	0%	5:50	5%
Within (70 - 141)	4:50	60%	12:55	62%	23:15	98%	19:00	88%	19:55	86%	10:35	100%	8:10	100%	98:40	85%
Below 70	3:10	40%	8:05	38%	0:25	2%	0:00	0%	0:00	0%	0:00	0%	0:00	0%	11:40	10%

Fig. 4

(7 days) Medtronic iPro2 Recorder #3080973

Avg SG: **102 mg/dL**

previous avg SG 104 mg/dL on 17/04/2016

Estimated A1C[1]: **5.2%** calculated from SG values

OBSERVED PATTERNS & SOME POSSIBLE CAUSES[2]

Time in range: **1% Above 141 mg/dL**

98% in target range

1% Below 70 mg/dL

1

Low SG
Overnight 23:00 - 06:00

5 out of 7 days excursions observed:

5 day(s) **50 - 101** mg/dL

0 day(s) **< 50** mg/dL

- Oral medication(s) too high or incorrectly timed?
- Basal insulin injection in evening(s) too high?
- Insulin to carbohydrate ratio not optimal in prior evening(s)?
- Less food intake in prior evening(s)?
- More exercise in prior evening(s)?
- Alcohol consumed in prior evening(s)?

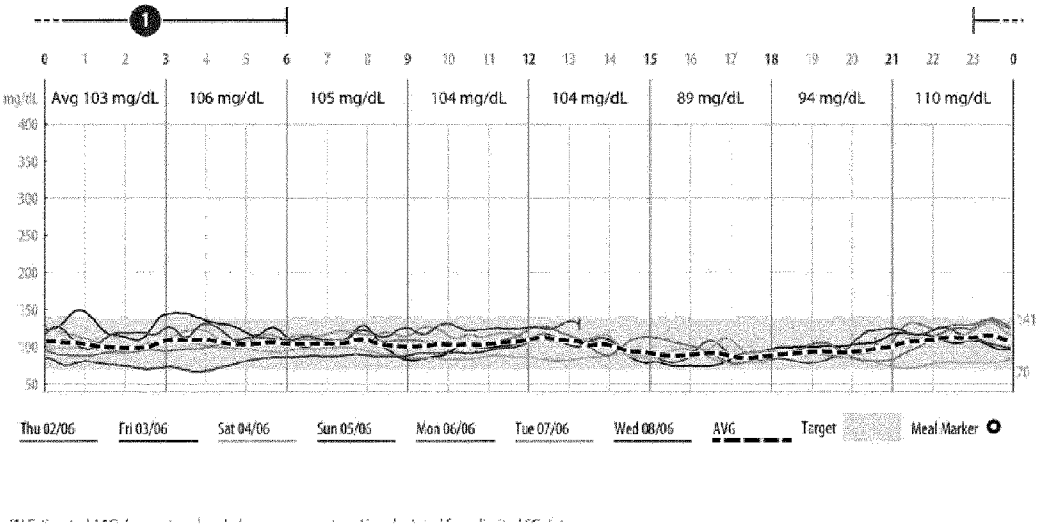


Fig. 5