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(54) **Title**: TREATMENT OF DIABETES MELLITUS WITH CARVEDILOL

(57) **Abstract**: Methods of treating diabetes mellitus by administering carvedilol in patients with diabetes mellitus are disclosed herein. The disclosed methods may eliminate the need for insulin and other blood sugar controlling agents in hypertensive patients with Type II diabetes mellitus, and may significantly reduce the required dosage of insulin and eliminate the need for other blood controlling agents in patients with Type I diabetes mellitus. The methods may also delay and/or prevent the progression of non-insulin dependent Type II diabetes mellitus to insulin-dependent Type II diabetes mellitus. Moreover, the methods have been shown to improve insulin receptor sensitivity such that a patient's HbAic level reaches and is maintained at or near 7% or less.

USE OF CARVEDILOL FOR TREATMENT OF DIABETES MELLITUS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Patent Appl. No. 13/547,047, filed on July 12, 2012, the disclosure of which is incorporated herein in its entirety by reference.

BACKGROUND

Field of the Invention

The present disclosure is generally directed to a method of treating diabetes mellitus by administering carvedilol in an effective amount to a patient with diabetes mellitus.

Description of the Related Art

Diabetes mellitus is one of the most common metabolic disorders in humans today. Nearly 26 million people have been diagnosed with the disease in the United States alone, corresponding to approximately 8.3% of the population. Type I diabetes mellitus typically appears in childhood or early adulthood. Type II diabetes mellitus, which has both insulin-dependent and non-insulin-dependent types, typically appears later in a person's life as a result of improper diet, lack of exercise, or a combination thereof. Both forms of diabetes mellitus alter the body's ability to convert blood glucose into energy, leading to elevated levels of blood glucose. Chronically high levels of blood glucose may increase the risk for long-term vascular complications such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy (loss of sensation, especially in the feet), gangrene, and gastroparesis (slowed emptying of the stomach). Improper blood

glucose control also increases the risk of short-term complications after surgery, such as poor wound healing.

Diabetes mellitus is a metabolic disease that is brought about by either the insufficient production of insulin or the inability of the body to properly respond to insulin. Insulin is produced by the pancreas and is the principal hormone that regulates the uptake of glucose from the blood into cells. The insulin receptor is a transmembrane receptor and belongs to the large class of tyrosine kinase receptors. Insulin insensitivity—a decrease in insulin receptor signaling—diminishes the ability of cells to take in glucose, resulting in an increase in circulating glucose (hyperglycemia) and leading to Type II diabetes mellitus.

Insulin deficiencies, the insensitivity of insulin receptors, or a combination of both play a central role in both forms of diabetes mellitus. Type I diabetes mellitus is caused by a decrease in the number of insulin-producing cells in the islets of Langerhans in the pancreas. Type II diabetes mellitus is generally characterized by the body's resistance to insulin, caused by the loss or diminished function of insulin receptors that mediate the entrance of insulin into the body's cells.

Diabetes mellitus is a chronic disease with no known cure. Management of the disease typically focuses on keeping blood sugar levels as close to normal ("euglycemia") as possible, without causing hypoglycemia. This is accomplished through the combination of proper diet and exercise and the use of appropriate medications (insulin for Type I diabetes, and oral medications with or without accompanying insulin for Type II diabetes).

Synthetic insulin is readily available to patients, but the high cost and inconvenience of its administration often leads to insufficient or improper use by patients. It is not uncommon for patients to be charged several hundred dollars monthly for their insulin prescriptions. Likewise, the proper regulation of diabetes mellitus requires patients to monitor their blood glucose levels at regular intervals each day. To successfully monitor

blood glucose levels patients are forced to retrieve and test small blood samples several times daily. Because monitoring diabetes mellitus can be very difficult and expensive, many patients do not do so properly and thus it remains responsible for many deaths. Even with proper dosages of insulin and other appropriate medications, patients with either form of diabetes mellitus may still suffer eye damage, delayed wound healing, and other serious consequences.

Because of the cost and inconvenience of conventional methods of treating diabetes mellitus, there remains a need for a safe, effective, and convenient method of treating both forms of diabetes mellitus.

SUMMARY

The present disclosure is directed to methods of treating patients with Type I diabetes mellitus or Type II diabetes mellitus by administering carvedilol. (±)-1-(carbazol-4-yloxy-3-[[2-(*o*-methoxyphenoxy)ethyl]amino]-2-propanol, commonly known as carvedilol, is a nonselective β-adrenergic blocking agent with α-1-blocking activity, that is used to treat hypertension and heart failure. Carvedilol is claimed in U.S. Patent No. 4,503,067. Methods of preparing carvedilol and related crystalline solids of carvedilol, processes for the manufacture thereof, and pharmaceutical compositions thereof are claimed in U.S. Patent Nos. 6,699,997, 6,710,184, 7,056,942, and 7,126,008, all of which are incorporated in their entireties by reference herein.

The disclosed methods reduce or eliminate the need for insulin and other blood sugar controlling agents in patients with Type II diabetes mellitus, significantly reduce the required dosage of insulin in patients with Type I diabetes mellitus, and delay and/or prevent the progression of non-insulin dependent Type II diabetes mellitus to insulin-dependent Type II diabetes mellitus by improving insulin receptor sensitivity through the administration of

carvedilol. Improved insulin receptor sensitivity allows diabetic patients to naturally regulate their blood glucose levels. Glycated hemoglobin (HbA_{1c}) is an accurate measure of a patient's average blood glucose concentration. HbA_{1c} testing is the preferred method of monitoring blood sugar control in patients with diabetes mellitus. Patients with diabetes mellitus have high amounts of HbA_{1c}, indicating poor control of blood glucose. The International Diabetes Federation and American College of Endocrinology recommend HbA_{1c} be below 48 mmol/mol (6.5%), while the American Diabetes Association recommends HbA_{1c} be below 53 mmol/mol (7.0%) for most patients. The administration of carvedilol improves insulin receptor sensitivity such that a diabetic patient's HbA_{1c} level reaches and is maintained at or near 7%.

The ability of carvedilol to improve insulin receptor sensitivity provides a novel method of treating patients with diabetes mellitus. Physicians can use carvedilol to enhance a diabetic patient's natural ability to respond to rising levels of blood glucose. This reduces the need for other treatments, enhances the effectiveness of other treatments (especially peripherally administered insulin), and delays or prevents progression of the disease. Carvedilol will even, in some instances, improve insulin receptor sensitivity to the extent that no other treatment is needed.

By reducing or eliminating the need for insulin or other treatments, the disclosed methods minimize the costs and difficulties of conventional treatments of diabetes mellitus. By increasing insulin receptor sensitivity, the disclosed methods may reduce or eliminate the hyperglycemia and/or hypoglycemia associated with conventional methods of treatment of diabetes mellitus. The disclosed methods may also reduce or eliminate some, if not all, of the long-term vascular complications of diabetes mellitus, such as coronary disease, heart attack, stroke, heart failure, kidney failure, blindness, erectile dysfunction, neuropathy (loss of sensation, especially in the feet), gangrene, and gastroparesis (slowed emptying of the

stomach). Additionally, the disclosed methods may reduce or eliminate the hyperinsulinemia associated with the peripheral administration (e.g., subcutaneous, intrapulmonary, intranasal, buccal mucosal) of insulin.

Various objects, features, aspects, and advantages of the disclosed methods will become more apparent from the following detailed description of preferred embodiments.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In some preferred embodiments, a physician prescribes carvedilol to a patient under a ramping up period until the amount of carvedilol administered to the patient reaches an effective amount. The initial dosage may preferably be 6.25 mg administered twice daily. That amount may preferably be doubled after the first week and doubled again every other week until the patient's HbA_{1c} level is maintained within a healthy range. The carvedilol dosage that maintains the patient's HbA_{1c} level within a healthy range is the effective dose. The patient then continues taking the effective dose. The effective dose of carvedilol may preferably be between 25 mg given twice daily and 50 mg given twice daily, but effective doses outside this range are possible. The effective dose may depend at least in part on the patient's body weight. For example, most patients weighing in excess of 85 kg require 50 mg carvedilol twice daily while most patients weighing less than 85 kg only require 25 mg carvedilol twice daily. When the carvedilol dosage is too low, HbA_{1c} levels generally will not fall within the normal range of 7.0% or lower. When the carvedilol dosage is too high, its side effects may become more prevalent. The physician may require quarterly visits to monitor the patient's success.

In some preferred embodiments, administration of carvedilol provides a method for replacing insulin and other blood sugar controlling agents in patients with Type II diabetes mellitus. Carvedilol may at first be administered in combination with a patient's existing

diabetes treatments. As blood glucose and HbA_{1c} levels decrease to normal ranges, the patient may preferably discontinue the use of peripherally administered insulin and other diabetes medications. Preferably within four to six weeks, and more preferably within two to three weeks, the patient may continue taking an effective amount of carvedilol alone in the absence of the previously required peripherally administered insulin. The effective amount may be sufficient to increase insulin receptor sensitivity such that the patient's body will be able to naturally maintain glucose homeostasis.

In other preferred embodiments, the administration of carvedilol reduces the insulin needs of patients with Type I diabetes mellitus. Carvedilol may at first be administered in combination with a patient's existing insulin requirements. The increased insulin receptor sensitivity resulting from treatment with carvedilol will naturally lower blood glucose and HbA_{1c} levels. As the patient's insulin receptors regain sensitivity to insulin, the response to peripherally administered insulin will correspondingly increase such that lower dosages of insulin will yield the same or better results. This may allow the patient to discontinue use of other anti-diabetic medications, if any. Preferably within four to six weeks, and more preferably within two to three weeks, the patient will continue taking an effective amount of carvedilol in conjunction with a now-lessened requirement of peripherally administered insulin. The effective amount of carvedilol will be sufficient to increase insulin receptor sensitivity such that the patient's body will require less peripherally administered insulin to be able to maintain glucose homeostasis indefinitely. Due to the nature of the disease, patients who suffer from Type I diabetes mellitus will never be able to fully withdraw from peripherally administered insulin, but the disclosed methods will allow said patients to dramatically decrease their peripherally administered insulin requirements.

In other preferred embodiments, the administration of carvedilol delays and/or prevents the progression of non-insulin dependent Type II diabetes mellitus to insulin

dependent Type II diabetes mellitus. Patients in early stages of Type II diabetes mellitus are able to regulate their blood sugar without the use of insulin through diet, exercise, anti-diabetic medications, or some combination thereof. These patients are able to use an effective amount of carvedilol to improve insulin receptor sensitivity. By doing so, they are able to continue managing their blood sugar without peripherally administered insulin for longer periods, or indefinitely. These results are achieved by administering carvedilol, preferably at first in combination with the patient's existing diabetes medications. As blood glucose and HbA_{1c} levels decrease the patient may preferably discontinue the use of other diabetes medications. Preferably within four to six weeks, and more preferably within two to three weeks, the patient may continue taking an effective amount of carvedilol alone in conjunction with the previously required diabetes medications. The effective amount may be sufficient to increase insulin receptor sensitivity such that the patient's body will be able to naturally maintain glucose homeostasis.

In some preferred embodiments, administration of an effective amount of carvedilol controls a rise in glucose typically associated with ingesting a meal (i.e., the post-prandial rise in glucose). The post-prandial rise in glucose may be partially or completely controlled by disclosed methods since insulin receptor function is improved such that the body will naturally release insulin to combat rising levels of blood glucose.

In some preferred embodiments, carvedilol may preferably be administered at appropriate dosages and frequencies so as to achieve and/or maintain homeostatic function of insulin receptors such that glucose homeostasis is maintained in patients with Type II diabetes mellitus. Carvedilol may also be preferably administered at appropriate dosages ·and frequencies so as to improve function of insulin receptors so as to maintain glucose homeostasis with limited dosages of peripherally administered insulin in patients with Type I diabetes mellitus.

In other preferred embodiments, carvedilol may be orally administered in an effective amount to a patient with diabetes mellitus in combination with an effective amount of an insulin drug to the patient. The use of peripherally administered insulin is only required in patients with Type I diabetes mellitus since carvedilol alone may eliminate the need for peripherally administered insulin in patients with Type II diabetes mellitus. In patients with Type I diabetes mellitus the preferred method of administration of insulin is performed by subcutaneous insulin injection, as will be understood by those skilled in the art. It is also known, however, that an oral insulin pill may be developed and administered in lieu of a subcutaneous injection, still in combination with an effective amount of carvedilol.

While use of oral medication has been described herein, those skilled in the art will understand that the use of carvedilol in other forms is also possible. Similarly, those skilled in the art will know to use the active ingredient, carvedilol, in combination with inactive ingredients that may alleviate or combat the various side effects of carvedilol, such as skin rash, itching, wheezing, swelling and weight gain, difficulty breathing, chest pain, dizziness, sweating, and confusion. It should also be readily apparent to those skilled in the art that carvedilol may be used in either a short- or long-acting capsule to achieve the desired results. For example, the oral administration of two pills per day to achieve the effective amount of carvedilol in a patient's bloodstream has been described above, but using a long-acting version of carvedilol whereby a single oral administration generates the same effective amount of carvedilol as two short-acting pills is also possible. All appropriate methods of delivering carvedilol are contemplated.

Examples

Data has been collected utilizing the various methods described herein and included for purposes of showing results and further exemplifying the preferred embodiments. A

study was performed on two groups: Group 1 and Group 2. Both groups included patients with diabetes mellitus and a history of uncontrolled blood sugar. Each group consisted of patients between the ages of 40 and 85, both males and females and of various ethnicities. Group I consisted of patients that were already taking insulin and who were unable to control their blood sugar. Group 2 consisted of patients taking oral medications who were unable to control their blood sugar, and needed insulin to regulate their disease.

Normal blood sugar levels were considered to be l20 mg % (mg % is milligram per l00 cc blood), which is equivalent to 6.0 HbA_{1c}, before meals or while fasting. After the first visit and examination, the patients' blood sugar and HbA_{1c} levels were reviewed. The patients were prescribed carvediol and advised to follow a diet routine suggested by the American Diabetes Association. The patients were requested to report their blood sugar weekly. Eventually, as their blood sugar was controlled, patients were taken off insulin completely. HbA_{1c} levels were checked approximately 2 to 3 months after controlling the blood sugar.

Group 1

Group 1 data is presented below for patients with Type II diabetes mellitus who were already taking insulin and were unable to control their blood sugar. The data includes blood sugar and HbA_{1c} levels before and after taking carvedilol.

1. JBM-65-M was first seen in January 2012. His HbA_{1c} was more than 9.0 and fasting plasma glucose was 282 mg %. He was taking 35 units of Lente insulin at night and regular insulin before each meal at a dosage of 10-30 units, on a sliding scale. He began taking an effective dose of carvedilol with a diet in February 2012. The patient was taken off insulin completely by April 2012; his HbA_{1c} came down to 5.5 and fasting plasma glucose was 122 mg %.

2. BS-81-F was taking 36 units of Humulin N twice per day in February 2012. Her HbA_{1c} was 7.6 and mean plasma glucose was 171 mg %. She began taking an effective dosage of carvedilol immediately. In April 2012 her HbA_{1c} was 6.5 and her mean plasma glucose was 140 mg %. The patient had been taken off of insulin completely by this time.

3. BD-63-M is a Type I diabetic with two episodes of myocardial infarction and four stents post percutaneous transluminal coronary angioplasty (PTCA). In January 2012 his HbA_{1c} was 8.2 with a mean plamsa glucose of 203 mg %. He was taking 400 units of Novolog mix 70/30 in two divided doses. After carvedilol administration and an improved diet, the dose of insulin has been reduced to a total of 90 units a day in two divided doses. His HbA_{1c} is the same but his recent blood sugar was 134 mg %.

4. MO-55-M was first seen in December 2011 with an HbA_{1c} of 11.4 and mean plasma blood glucose of 280 mg %. He was taking Novolog 70/30, 40 units twice per day. He was started on carvedilol along with an improved diet. The patient came off of insulin and subsequently reported an HbA_{1c} of 8.6 with a plasma blood glucose of 200 mg % in April 2012. Currently he is reporting a plasma blood glucose below 120 mg %.

5. DK-51-F suffered from renal failure and had an HbA_{1c} of 10.3 and mean plasma glucose of 249 mg % when first seen. She was taking Novolog 70/30, 20 units twice per day. After five weeks on carvedilol, she was taken off insulin and reported a plasma glucose of less than 120 mg %, which corresponds to an HbA_{1c} level of 6.0.

Group 2

Group 2 consisted of Type II diabetes mellitus patients who could not control their blood sugar on diet or oral medication and would need to start insulin. Carvedilol was used in place of insulin and other medications to control blood sugar.

1. AA-70-M had a blood sugar of 200 mg % and was intolerant to all oral diabetes medications except sitagliptin. Sitagliptin did not fully control his blood sugar, therefore carvedilol was prescribed. Taking both of these medications resulted in the patient experiencing hypoglycemia. Sitagliptin was then discontinued and the hypoglycemia subsequently disappeared. Carvedilol has controlled the patient's blood sugar. The patient's last recorded HbA_{1c} was 6.8.

2. LF-54-M had poorly controlled blood sugar but managed an HbA_{1c} of 8.0 and mean fasting glucose of 183 mg %. She was taking three oral medications: metformin 1000 mg BID, sitagliptin 100 mg daily, and sulfonylurea. She was started on carvedilol and her blood sugar came down to 90 mg %. She then discontinued use of sitagliptin. Her HbA_{1c} level is now 6.5.

3. HA-46-F had an HbA_{1c} of 8.5 and fasting plasma glucose of 197 mg %. She was prescribed metformin and Glyburide Micro. She was also given Byetta. Still, her blood sugar remained uncontrolled. She started on carvedilol recently and her blood sugar has reached normal levels. Her HbA_{1c} level is 8.4.

4. JF-65-F had a long standing history of poorly controlled blood sugar due to serious noncompliance. The patient also suffered from severe peripheral neuritis. Her HbA_{1c} was 10.2 in December 2011. The patient was taking metformin 1000 mg twice per day, sitagliptin 100 mg daily, and Glyburide Micro 6 mg twice per day. The patient was started on carvedilol in February 2012. Her HbA_{1c} in late March 2012 was down to 8.2 with a mean plasma glucose of 189 mg %. More recently she has reported her blood sugar as 95 mg % and has stopped taking Glyburide Micro. Her HbA_{1c} is now 7.8.

5. FL-76-M had an HbA_{1c} of 8.3 and mean plasma glucose of 163 mg %. He has been on Janumet 50/10 twice per day and glymepiride, the latter which was changed to Glyburide Micro 3 mg twice daily. He received a cortisone shot in his right knee which

caused his blood sugar to rise to 273 mg %. Carvedilol was added to his regimen and his blood sugar was recently reported at 81 mg %. The patient was able to stop Glyburide Micro. His HbA_{1c} level is now 7.1.

The examples above are intended as illustrative and are not intended to limit or otherwise restrict the invention. All references cited herein are expressly incorporated by reference.

What is claimed is:

1. A method of treating Type I diabetes mellitus in a patient comprising administering an amount of carvedilol to the patient to improve insulin receptor sensitivity, wherein said amount is sufficient to delay or prevent the progression of Type I diabetes mellitus.

2. The method of claim 1 wherein the amount of carvedilol administered is sufficient to reduce the need for other treatments of Type I diabetes mellitus.

3. The method of claim 1 wherein the amount of carvedilol administered is sufficient to reduce the patient's need for peripherally administered insulin.

4. The method of claim 1 wherein the amount of carvedilol administered is sufficient to enhance the effectiveness of peripherally administered insulin.

5. The method of claim 3 wherein the amount of carvedilol administered is an amount sufficient to reach and maintain healthy blood glucose control.

6. The method of claim 3 wherein the amount of carvedilol administered is an amount sufficient to reach and maintain HbA1c levels near 7% or less.

7. The method of claim 3 wherein insulin receptor sensitivity is improved sufficiently to reduce the need for other treatments of the Type I diabetes mellitus.

8. The method of claim 3 wherein insulin receptor sensitivity is improved sufficiently to enhance the effectiveness of peripherally administered insulin.

9. A method of treating diabetes mellitus in a patient being administered an amount of peripherally administered insulin comprising:

administering a starting dosage of carvedilol to a patient;

continuing to administer carvedilol, while increasing the amount administered until it is sufficient to improve insulin receptor sensitivity in the patient; and

reducing or eliminating the amount of peripherally administered insulin.

10. The method of claim 9 wherein the amount of carvedilol administered is sufficient to improve insulin receptor sensitivity in the patient when the patient reaches and maintains HbA_{1c} levels near 7%.

11. The method of claim 9 further comprising reducing or eliminating the use of other treatments of diabetes mellitus.

12. A method of treating Type II diabetes mellitus in a patient comprising administering an amount of carvedilol to the patient to improve insulin receptor sensitivity, wherein said amount is sufficient to delay or prevent the progression of non-insulin dependent Type II diabetes mellitus to insulin dependent Type II diabetes mellitus.

13. The method of claim 12 wherein said amount is sufficient to allow reduction or discontinuation of the use of peripherally administered insulin for the treatment of said patient.

14. The method of claim 13 wherein insulin receptor sensitivity is improved sufficiently to allow the patient's body to manage the post-prandial rise in blood glucose without administering insulin.

15. The method of claim 12 wherein the amount of carvedilol administered is sufficient to reduce the need for other treatments of the Type II diabetes mellitus.

16. The method of claim 12 wherein the amount of carvedilol administered is sufficient to enhance the effectiveness of peripherally administered insulin.

17. The method of claim 12 wherein the amount of carvedilol administered is an amount sufficient to reach and maintain healthy blood glucose control.

18. The method of claim 12 wherein the amount of carvedilol administered is an amount sufficient to reach and maintain HbA_{1c} levels near 7% or less.

INTERNATIONAL SEARCH REPORT

PCT/US13/50410

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/40, 31/505; A61P 9/12 (2013.01)

USPC - 514/274, 303, 411

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/40, 31/505; A61P 9/12 (2013.01)
USPC - 514/274, 303, 411

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MicroPatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A); Google Scholar; PubMed; IP.com; carvedilol, diabetes, insulin receptor, Type I diabetes, Type II diabetes, blood glucose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2005/0009897 A1 (ANDERSON, K et al.) January 13, 2005; paragraphs [0006], [0010], [0014]-[0015]	1-18
A	US 2006/0154959 A1 (CORNETT, GVB et al.) July 13, 2006; paragraphs [0001], [0017]	1-11
A	US 2003/0073729 A1 (KITAHARA, Y et al.) April 17, 2003; paragraphs [0010], [0035]-[0036]	1-18
A	WO 2011/161161 A1 (KLEIN, T et al.) December 29, 2011; page 47, lines 11-27; page 49, lines 2-9; page 53, lines 11-12	9-11
A	KVEIBORG, B et al. 'Metoprolol compared to carvedilol deteriorates insulin-stimulated endothelial function in patients with type 2 diabetes - a randomized study.' Cardovascular Diabetiology, Vol. 9, No. 21, 2010, pp. 1-11; column 1, paragraph 1 to column 2, paragraphs 2	1-8, 12-18
A	US 4,503,067 A (WIEDEMANN, F et al.) March 5, 1985; entire document	1, 9, 12
A	US 6,699,997 B2 (HILDESHEIM, J et al.) March 2, 2004; entire document	1, 9, 12
A	US 7,056,942 B2 (HILDESHEIM, J et al.) June 6, 2006; entire document	1, 9, 12
A	US 7,126,008 B2 (HILDESHEIM, J et al.) October 24, 2006; entire document	1, 9, 12
A	US 7,268,156 B2 (BROOK, CS et al.) September 11, 2007; entire document	1, 9, 12
A	CN 101417132 B (ZHIQUAN, Z) December 29, 2010; see machine translation; entire document	1, 9, 12
A	US 2007/0208073 A1 (BRYSON, IBD) September 6, 2007; entire document	1, 9, 12

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 November 2013 (30.11.2013)	09 DEC 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774