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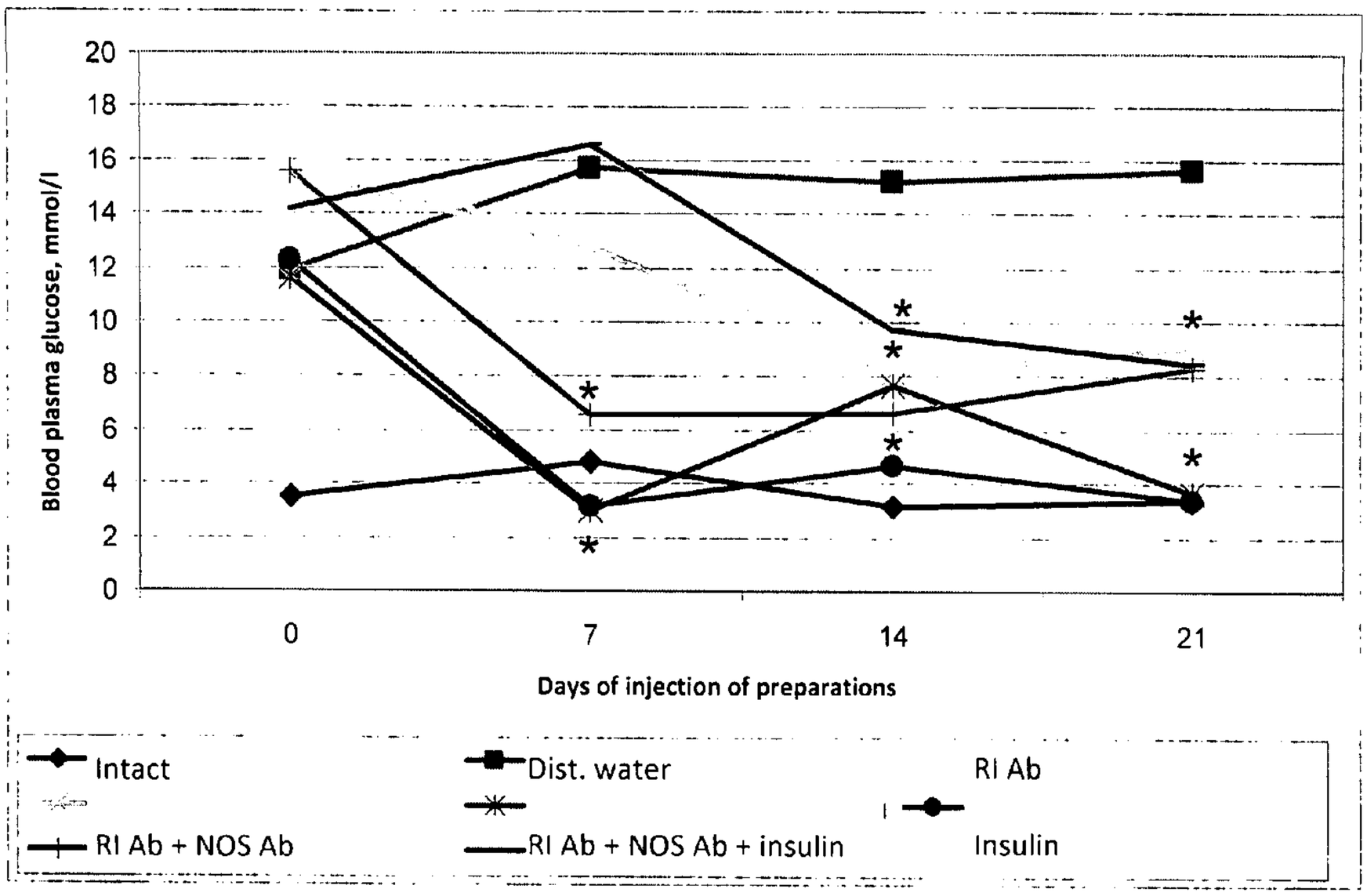
(54) Title: A COMBINATION PHARMACEUTICAL COMPOSITION AND METHODS OF TREATING DIABETES AND METABOLIC DISORDERS



* differencesare statistically significant relative to control (distilled water), p<0.05

(57) Abrégé/Abstract:
The present application provides a pharmaceutical composition for administration to a patient suffering from diabetes and other metabolic disorders, the composition comprises a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

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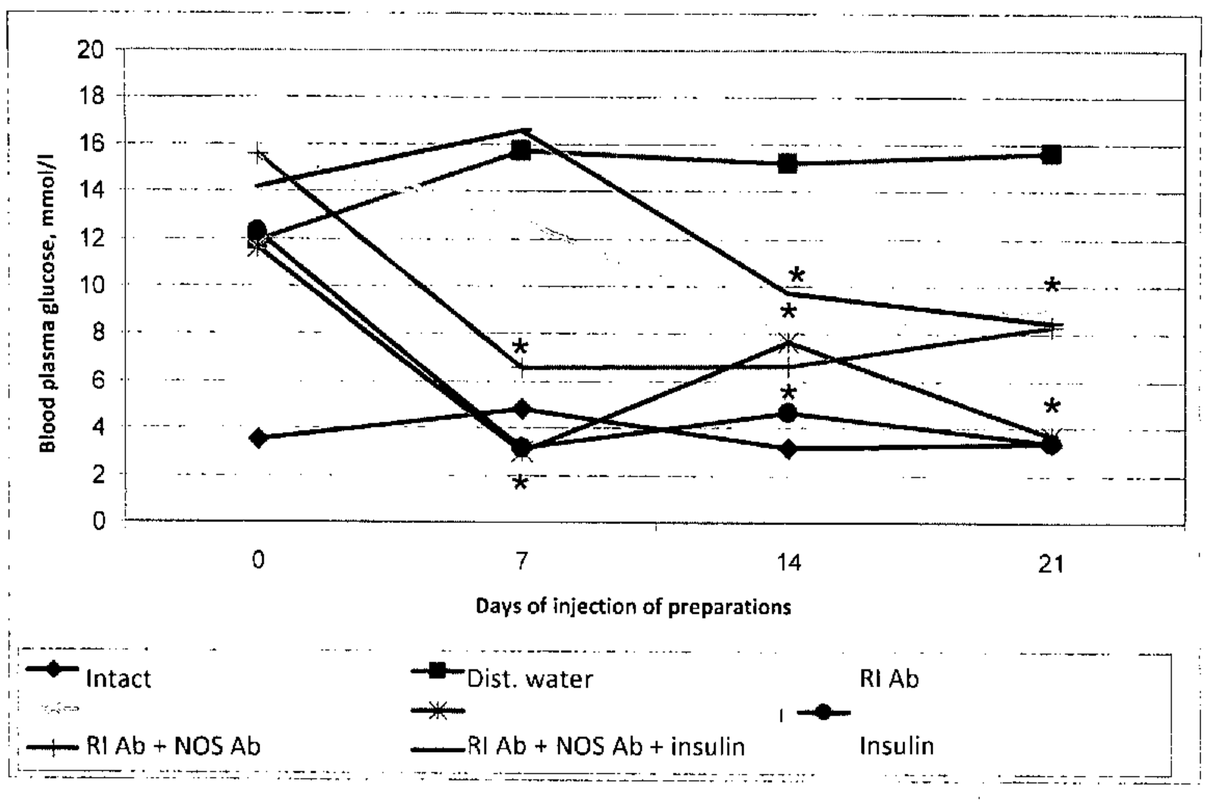

FIG. 1

(57) Abstract: The present application provides a pharmaceutical composition for administration to a patient suffering from diabetes and other metabolic disorders, the composition comprises a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

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A COMBINATION PHARMACEUTICAL COMPOSITION AND METHODS OF TREATING DIABETES AND METABOLIC DISORDERS

FIELD

The present invention relates to the field of medicine and can be used for the treatment and prevention of diseases of the diabetes and other metabolic disorders.

BACKGROUND

Diabetes Mellitus is a chronic condition characterized as hyperglycemia (high levels of sugar in blood). Continuing increments of blood glucose levels increase the risk of diabetes-related complications such as kidney damage, vision loss, heart disease, and foot ulcers.

There are two major types of diabetes: type 1 diabetes and type 2 diabetes. With type 1 diabetes, hyperglycemia develops because the pancreas cannot produce insulin. This type of diabetes usually appears in childhood or young adulthood. In type 2 diabetes, the pancreas is capable of producing insulin, but it cannot adequately meet the body's demands. The problem is that the body does not respond to the insulin appropriately, which in turn leads to less glucose being absorbed by the cells and results in abnormally elevated blood glucose levels. After overworking the pancreas for a number of years, the pancreas may eventually fail and exhaust its ability to produce insulin, which at this point a person with type 2 diabetes may require insulin therapy.

Insulin, a natural hormone produced by the pancreas, transports glucose from the bloodstream to the inside of the cells. Thus, the main job of insulin is to regulate the glucose transport into the cells thereby lowering the level of blood glucose.

The actions of insulin are controlled through the activation of a heterotetrameric receptor which is found in the plasma membrane. The insulin receptor is a glycoprotein composed of two extracellular alpha-subunits and two transmembrane beta-subunits linked by disulfide bonds. Ullrich et al., Nature, 313:756-61, 1985. The alpha-subunits contain the insulin-binding domain, and the intracellular portion of the beta-subunit

contains the insulin-regulated tyrosine protein kinase (the enzyme that catalyzes the transfer of a high-energy group from a donor (usually ATP) to an acceptor).

When an insulin molecule is released by the beta cells of the pancreas and arrives at a cell, it binds onto the insulin receptor on the surface of most cells. Once insulin binds, the intrinsic phosphotransferase function of the insulin receptor beta-subunit is activated, resulting in the tyrosine phosphorylation of a number of intracellular proteins. Once the insulin receptor has been activated, the phosphorylation event leads to an increase in glucose storage and consequently a decrease in blood glucose levels.

Effective control of glucose level is difficult to achieve for prolonged periods even with the most meticulous mode of insulin therapy in the most motivated patients. Thus, there is a continuing need for new drug products with desired therapeutic efficacy for treatment of diseases and metabolic disorders.

Nitric oxide (NO) is a gaseous molecule that has been shown to acts in the signaling of different biological processes. Endothelium-derived NO is a key molecule in regulation of vascular tone and its association with vascular disease has long been recognized. NO inhibits many processes known to be involved in the formation of atherosclerotic plaque, including monocyte adhesion, platelet aggregation and vascular smooth muscle cell proliferation. Another important role of endothelial NO is the protection of the vascular wall from the oxidative stress induced by its own metabolic products and by the oxidation products of lipids and lipoproteins. Endothelial dysfunction occurs at very early stages of atherosclerosis. It is therefore possible that deficiency in local NO availability could be a final common pathway that accelerates atherogenesis in humans. In addition to its role in the vascular endothelium, NO availability has been shown to modulate metabolism of lipoproteins. Negative correlation has been reported between plasma concentrations of NO metabolic products and plasma total and Low Density Lipoprotein [LDL] cholesterol levels while High Density Lipoprotein [HDL] improves vascular function in hypercholesterolaemic subjects. The loss of NO has considerable effect on the development of the disease. Diabetes mellitus is associated with increased rates of morbidity and mortality caused primarily by the accelerated development of atherosclerotic disease. Moreover, reports

show that diabetics have impaired lung functions. It has been proposed that insulin resistance leads to airway inflammation. Habib et al., *Nitric Oxide Measurement From Blood To Lungs, Is There A Link?* Pak J Physiol 2007;3(1).

Nitric oxide is synthesized by the endothelium from L-arginine by nitric oxide synthase (NO synthase). NO synthase occurs in different isoforms, including a constitutive form (cNOS) and an inducible form (iNOS). The constitutive form is present in normal endothelial cells, neurons and some other tissues.

The therapeutic effect of an extremely diluted (or ultra-low) form of antibodies potentized by homeopathic technology has been discovered by the inventor of the present patent application, Dr. Oleg I. Epshtein. U.S. Patent No. 7,582,294 discloses a medicament for treating Benign Prostatic Hyperplasia or prostatitis by administration of a homeopathically activated form of antibodies to prostate specific antigen (PSA). U.S. Patent No. 7,700,096 discloses a homeopathically potentized form of antibodies to endothelial NO-synthase. The homeopathically potentized form of antibodies to endothelial NO-synthase is marketed in the Russian Federation and other countries under the name Impaza®.

SUMMARY

In one aspect, the invention provides a pharmaceutical composition for administration to a patient suffering from diseases of diabetes and other metabolic disorders, the composition comprises a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In one aspect, the invention provides a pharmaceutical composition for administration to a patient suffering from diseases of diabetes and other metabolic disorders, the composition comprises a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In one variant, the pharmaceutical composition of this aspect of the invention comprises a) an activated-potentiated form of an antibody to human insulin receptor, and

b) an activated-potentiated form of an antibody to endothelial NO-synthase, wherein the insulin receptor molecule comprises at least one alpha subunit and at least one beta subunit.

In one variant, the pharmaceutical composition of this aspect of the invention includes activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor or the activated-potentiated form of an antibody to human insulin receptor in the form of a mixture of C12, C30, and C200 homeopathic dilutions impregnated onto a solid carrier. The activated-potentiated form of an antibody to endothelial NO-synthase in the form of mixture of C12, C30, and C200 homeopathic dilutions may be subsequently impregnated onto the solid carrier.

In another variant, the pharmaceutical composition of this aspect of the invention includes the activated-potentiated form of an antibody to endothelial NO-synthase is in the form of mixture of C12, C30, and C200 homeopathic dilutions impregnated onto a solid carrier. The activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor or the activated-potentiated form of an antibody to human insulin receptor is in the form of mixture of C12, C30, and C200 homeopathic dilutions may be subsequently impregnated onto the solid carrier.

Preferably, the activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor or the activated-potentiated form of an antibody to human insulin receptor is a monoclonal, polyclonal or natural antibody, more preferably, a polyclonal antibody. In one variant of this aspect of the invention, the activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor or the activated-potentiated form of an antibody to human insulin receptor is prepared by successive centesimal dilutions coupled with shaking of every dilution.

Preferably, the activated-potentiated form of an antibody to endothelial NO-synthase is a monoclonal, polyclonal or natural antibody, more preferably, a polyclonal antibody. In one variant of this aspect of the invention, the activated-potentiated form of an antibody to endothelial NO-synthase is prepared by successive centesimal dilutions coupled with shaking of every dilution.

In another aspect, the invention provides a method of treating a patient suffering from Type I, diabetes, the method comprising administering to the patient a combination of a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In another aspect, the invention provides a method of treating a patient suffering from Type I diabetes, the method comprising administering to the patient a combination of a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In another aspect, the invention provides a method of treating a patient suffering from Type II, diabetes, the method comprising administering to the patient a combination of a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In another aspect, the invention provides a method of treating a patient suffering from Type II diabetes, the method comprising administering to the patient a combination of a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In another aspect, the invention provides a method of reducing blood glucose level in a mammal, the method comprising administering to the mammal a combination of a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In another aspect, the invention provides a method of reducing blood glucose level in a mammal, the method comprising administering to the mammal a combination of a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In another aspect, the invention provides a method of treating insulin resistance in a mammal, the method comprising administering to the mammal a combination of a) an

activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In another aspect, the invention provides a method of treating insulin resistance in a mammal, the method comprising administering to the mammal a combination of a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In one variant of this aspect of the invention, there is provided administration of from one to two unit dosage forms of the activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor or an activated-potentiated form of an antibody to human insulin receptor, and from one to two unit dosage forms of the activated-potentiated form of an antibody to endothelial NO-synthase, each of the dosage form being administered from once daily to four times daily. Preferably, the one to two unit dosage forms of each of the activated-potentiated forms of antibodies is administered twice daily.

DESCRIPTION OF THE FIGURES

Figure 1 - Illustrates the effect of tested preparations on blood plasma glucose level of rats with streptozotocin-induced diabetes mellitus

Figure 2 - Illustrates the effect of tested preparations on day 14 of injection on indicators of area under concentration-time curve (AUC) in the glucose tolerance test in rats with streptozotocin-induced diabetes mellitus.

Figure 3 - Illustrates the effect of tested preparations on blood plasma glucose level of rats with spontaneous non-insulin-dependent diabetes mellitus.

Figure 4 - Illustrates the effect of tested preparations on day 28 of injection on indicators of area under concentration-time curve (AUC) in glucose tolerance test in rats with spontaneous non-insulin-dependent diabetes mellitus.

Figure 5 – Illustrates the dynamics of glucose and glycolated hemoglobin levels in patients with type 1 diabetes mellitus against background of taking IR Ab + NOS Ab preparation.

Figure 6 - Illustrates the dynamics of glucose and glycolated hemoglobin levels in patients with type 2 diabetes mellitus against background of taking IR Ab + NOS Ab preparation.

DETAILED DESCRIPTION

The invention is defined with reference to the appended claims. With respect to the claims, the glossary that follows provides the relevant definitions.

The term "antibody" as used herein shall mean an immunoglobulin that specifically binds to, and is thereby defined as complementary with, a particular spatial and polar organization of another molecule. Antibodies as recited in the claims may include a complete immunoglobulin or fragment thereof, may be natural, polyclonal or monoclonal, and may include various classes and isotypes, such as IgA, IgD, IgE, IgG1, IgG2a, IgG2b and IgG3, IgM, etc. Fragments thereof may include Fab, Fv and F(ab')2, Fab', and the like. The singular "antibody" includes plural "antibodies."

The term "activated-potentiated form" or "potentiated form" respectively, with respect to antibodies recited herein is used to denote a product of homeopathic potentization of any initial solution of antibodies. "Homeopathic potentization" denotes the use of methods of homeopathy to impart homeopathic potency to an initial solution of relevant substance. Although not so limited, 'homeopathic potentization" may involve, for example, repeated consecutive dilutions combined with external treatment, particularly (mechanical) shaking. In other words, an initial solution of antibody is subjected to consecutive repeated dilution and multiple vertical shaking of each obtained solution in accordance with homeopathic technology. The preferred concentration of the initial solution of antibody in the solvent, preferably water or a water-ethyl alcohol mixture, ranges from about 0.5 to about 5.0 mg/ml. The preferred procedure for preparing each component, i.e. antibody solution, is the use of the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution (mother tincture) of antibodies diluted 100^{12}, 100^{30} and 100^{200} times, respectively, which is equivalent to centesimal homeopathic dilutions (C12, C30, and C200) or the use of the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution of

antibodies diluted 100^{12}, 100^{30} and 100^{50} times, respectively, which is equivalent to centesimal homeopathic dilutions (C12, C30 and C50). Examples of homeopathic potentization are described in U.S. Patent. Nos. 7,572,441 and 7,582,294, which are incorporated herein by reference in their entirety and for the purpose stated. . While the term “activated-potentiated form” is used in the claims, the term “ultra-low doses” is used in the examples. The term “ultra-low doses” became a term of art in the field of art created by study and use of homeopathically diluted and potentized form of substance. The term “ultra-low dose” or “ultra-low doses” is meant as fully supportive and primarily synonymous with the term ‘activated-potentiated” form used in the claims.

In other words, an antibody is in the “activated-potentiated” form when three factors are present. First, the “activated-potentiated” form of the antibody is a product of a preparation process well accepted in the homeopathic art. Second, the “activated-potentiated” form of antibody must have biological activity determined by methods well accepted in modern pharmacology. And third, the biological activity exhibited by the “activated potentiated” form of the antibody cannot be explained by the presence of the molecular form of the antibody in the final product of the homeopathic process.

For example, the activated potentiated form of antibodies may be prepared by subjecting an initial, isolated antibody in a molecular form to consecutive multiple dilutions coupled with an external impact, such as mechanical shaking. The external treatment in the course of concentration reduction may also be accomplished, for example, by exposure to ultrasonic, electromagnetic, or other physical factors. V. Schwabe "Homeopathic medicines", M., 1967, U.S. Patents Nos. 7,229,648 and 4,311,897, which are incorporated by reference in their entirety and for the purpose stated, describe such processes that are well accepted methods of homeopathic potentiation in the homeopathic art. This procedure gives rise to a uniform decrease in molecular concentration of the initial molecular form of the antibody. This procedure is repeated until the desired homeopathic potency is obtained. For the individual antibody, the required homeopathic potency can be determined by subjecting the intermediate dilutions to biological testing in the desired pharmacological model. Although not so limited, ‘homeopathic potentization” may involve, for example, repeated consecutive dilutions combined with external treatment, particularly vertical

(mechanical) shaking. In other words, an initial solution of antibody is subjected to consecutive repeated dilution and multiple vertical shaking of each obtained solution in accordance with homeopathic technology. The preferred concentration of the initial solution of antibody in the solvent, preferably, water or a water-ethyl alcohol mixture, ranges from about 0.5 to about 5.0 mg/ml. The preferred procedure for preparing each component, i.e. antibody solution, is the use of the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution (mother tincture) of antibodies diluted 100^{12}, 100^{30} and 100^{200} times, respectively, which is equivalent to centesimal homeopathic dilutions C12, C30 and C200 or the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution (mother tincture) of antibodies diluted 100^{12}, 100^{30} and 100^{50} times, respectively, which is equivalent to centesimal homeopathic dilutions C12, C30 and C50. Examples of how to obtain the desired potency are also provided, for example, in U.S. Patent Nos. 7,229,648 and 4,311,897, which are incorporated by reference for the purpose stated. The procedure applicable to the "activated potentiated" form of the antibodies described herein is described in more detail below.

There has been a considerable amount of controversy regarding homeopathic treatment of human subjects. While the present invention relies on accepted homeopathic processes to obtain the "activated-potentiated" form of antibodies, it does not rely solely on homeopathy in human subjects for evidence of activity. It has been surprisingly discovered by the inventor of the present application and amply demonstrated in the accepted pharmacological models that the solvent ultimately obtained from consecutive multiple dilution of a starting molecular form of an antibody has definitive activity unrelated to the presence of the traces of the molecular form of the antibody in the target dilution. The "activated-potentiated" form of the antibody provided herein are tested for biological activity in well accepted pharmacological models of activity, either in appropriate in vitro experiments, or in vivo in suitable animal models. The experiments provided further below provide evidence of biological activity in such models. The human clinical studies, also provided herein below, are evidence, inter alia, that the activity observed in the animal model are well translated to human therapy. The human study also provide evidence of availability of the "activated potentiated" forms described herein to treat specified human diseases or disorders well accepted as pathological conditions in the medical science.

Also, the claimed "activated-potentiated" form of antibody encompass only solutions or solid preparations the biological activity of which cannot be explained by the presence of the molecular form of the antibody remaining from the initial, starting solution. In other words, while it is contemplated that the "activated-potentiated" form of the antibody may contain traces of the initial molecular form of the antibody, one skilled in the art could not attribute the observed biological activity in the accepted pharmacological models to the remaining molecular form of the antibody with any degree of plausibility due to the extremely low concentrations of the molecular form of the antibody remaining after the consecutive dilutions. While the invention is not limited by any specific theory, the biological activity of the "activated-potentiated' form of the antibodies of the present invention is not attributable to the initial molecular form of the antibody. Preferred is the "activated-potentiated" form of antibody in liquid or solid form in which the concentration of the initial molecular form of the antibody is below the limit of detection of the accepted analytical techniques, such as capillary electrophoresis and High Performance Liquid Chromatography. Particularly preferred is the "activated-potentiated" form of antibody in liquid or solid form in which the concentration of the initial molecular form of the antibody is below the Avogadro number. In pharmacology of molecular forms of therapeutic substances, it is common practice to create a dose-response curve in which the level of pharmacological response is plotted against the concentration of the active drug administered to the subject or tested in vitro. The minimal level of the drug which produces any detectable response is known as a threshold dose. It is specifically contemplated and preferred that the "activated-potentiated" form of the antibodies contains molecular antibody, if any, at a concentration below the threshold dose for the molecular form of the antibody in the given biological model.

The present invention provides a pharmaceutical composition for administration to a patient suffering from diseases of diabetes and other metabolic disorders, comprising a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor or an activated-potentiated form of an antibody to human insulin receptor and b) an activated-potentiated form of an antibody to endothelial NO-synthase. As set forth herein above, each of the individual components of the combination is generally known for its own individual medical uses. However, the inventors of the present patent application surprisingly discovered that administration of

the combination is useful in treating a patient with diabetes and insulin resistance and further reduces blood glucose levels. While applicant is not bound by this theory, the "accelerator" hypothesis assumes that type I diabetes mellitus (DM) and type II diabetes mellitus are the same disease characterized by insulin resistance, whose development into type I DM and type II DM is determined by the patient's genotype. This hypothesis does not deny the role of autoimmune processes; however, it casts doubt on its primary role. The "accelerator" hypothesis divides type I and type II diabetes mellitus according to the speed of progression: in with type I diabetes, rapid development of pathologic changes determines the earlier onset of the manifestations of clinical disease symptoms. The hypothesis was proposed for the first time in 2001 and at present is confirmed by the results of 6 independent clinical trials (see Wilkin, T.J. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type [I] as well as type II diabetes. // International Journal for Obesity. 2009: Vol. 33 - p. 716-726.). A key role in the pathogenesis of both types of diabetes is played by insulin resistance, which decrease leads to alleviation of the clinical course of both type I diabetes and type II diabetes (see Cellular mechanisms of insulin resistance. World Congress on Insulin Resistance Syndrome, 2009, Diabetes Care. 2010: Vol. 33, N8, pp. 103-108.). The role of the insulin receptor beta subunit in the insulin signal path is known. After insulin binding with the receptor and beta subunit activation, the path can go into two different directions: phosphatidylinositol 3-kinase (PI 3- K) or MAP kinase (MAP- K). The first path appears to be necessary for realization of the majority of the metabolic and antiapoptotic effects of insulin, and the alternate path is connected with its non-metabolic, proliferative and mitogenic effects. In insulin resistance, it has been shown that only metabolic insulin resistance, linked with the beta subunit activation along the P13-K pathway, plays an important role in determining the development of diabetes mellitus. (See Muntoni, S, Muntoni, S. *Insulin Resistance: Pathophysiology and Rationale for Treatment,* Ann. Nutr. Metab. 2011: Vol. 58, N1, pp. 25-36). The claimed pharmaceutical composition ensures an effect on metabolic insulin resistance.

The pharmaceutical composition in accordance with this aspect of the invention may be in the liquid form or in solid form. Each of the activated potentiated forms of the

antibodies included in the pharmaceutical composition is prepared from an initial molecular form of the antibody via a process accepted in homeopathic art. The starting antibodies may be monoclonal, or polyclonal antibodies prepared in accordance with known processes, for example, as described in *Immunotechniques*, G. Frimel, M., "Meditsyna", 1987, p. 9-33; "*Hum. Antibodies. Monoclonal and recombinant antibodies, 30 years after*" by Laffly E., Sodoyer R. – 2005 – Vol. 14. – N 1-2. P.33-55, both incorporated herein by reference.

Monoclonal antibodies may be obtained, e.g., by means of hybridoma technology. The initial stage of the process includes immunization based on the principles already developed in course of polyclonal antisera preparation. Further stages of work involve production of hybrid cells generating clones of antibodies with identical specificity. Their separate isolation is performed using the same methods as in case of polyclonal antisera preparation.

Polyclonal antibodies may be obtained via active immunization of animals. For this purpose, for example, suitable animals (e.g. rabbits) receive a series of injections of the appropriate antigen, either endothelial NO-synthase and C-terminal fragment of the beta subunit of human insulin receptor or endothelial NO-synthase and human insulin receptor. The animals' immune system generates corresponding antibodies, which are collected from the animals in a known manner. This procedure enables preparation of a monospecific antibody-rich serum. If desired, the serum containing antibodies may be purified, e.g., using affine chromatography, fractionation by salt precipitation, or ion-exchange chromatography. The resulting purified, antibody-enriched serum may be used as a starting material for preparation of the activated-potentiated form of the antibodies. The preferred concentration of the resulting initial solution of antibody in the solvent, preferably, water or water-ethyl alcohol mixture, ranges from about 0.5 to about 5.0 mg/ml.

The preferred procedure for preparing each component is the use of the mixture of three aqueous-alcohol dilutions of the primary matrix solution of antibodies diluted 100^{12}, 100^{30} and 100^{200} times, respectively, which is equivalent to centesimal homeopathic dilutions C12, C30 and C200. To prepare a solid dosage form, a solid

carrier is treated with the desired dilution obtained via the homeopathic process. To obtain a solid unit dosage form of the combination of the invention, the carrier mass is impregnated with each of the dilutions. Both orders of impregnation are suitable to prepare the desired combination dosage form.

In the preferred embodiment, the starting material for the preparation of the activated potentiated form that comprise the combination of the invention is polyclonal, animal-raised antibody to the corresponding antigen, namely, C-terminal fragment of beta subunit of human insulin receptor or human insulin receptor and endothelial NO-synthase. To obtain the activated-potentiated form of polyclonal antibodies to C-terminal fragment of beta subunit of human insulin receptor, the desired antigen may be injected as immunogen into a laboratory animal, preferably, rabbits'. Peptides of particular interest may include at least about 3 amino acids, usually at least about 10 on either side of the sequence, preferably having at least 3 amino acids at the C-terminal side. The following sequences of human insulin receptor are specifically contemplated as suitable antigens:

Entire alpha-subunit of human insulin receptor:

SEQ ID NO: 1

```
                                                          His Leu Tyr

                                                           28      30
Pro Gly Glu Val Cys Pro Gly Met Asp Ile Arg Asn Asn Leu Thr

 31                  35                  40                  45
Arg Leu His Glu Leu Glu Asn Cys Ser Val Ile Glu Gly His Leu

 46                  50                  55                  60
Gln Ile Leu Leu Met Phe Lys Thr Arg Pro Glu Asp Phe Arg Asp

 61                  65                  70                  75
Leu Ser Phe Pro Lys Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu

 76                  80                  85                  90
Phe Arg Val Tyr Gly Leu Glu Ser Leu Lys Asp Leu Phe Pro Asn

 91                  95                 100                 105
Leu Thr Val Ile Arg Gly Ser Arg Leu Phe Phe Asn Tyr Ala Leu

106                 110                 115                 120
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Val Ile Phe Glu Met Val His Leu Lys Glu Leu Gly Leu Tyr Asn

121                 125                 130                 135
Leu Met Asn Ile Thr Arg Gly Ser Val Arg Ile Glu Lys Asn Asn

136                 140                 145                 150
Glu Leu Cys Tyr Leu Ala Thr Ile Asp Trp Ser Arg Ile Leu Asp

151                 155                 160                 165
Ser Val Glu Asp Asn Tyr Ile Val Leu Asn Lys Asp Asp Asn Glu

166                 170                 175                 180
Glu Cys Gly Asp Ile Cys Pro Gly Thr Ala Lys Gly Lys Thr Asn

181                 185                 190                 195
Cys Pro Ala Thr Val Ile Asn Gly Gln Phe Val Glu Arg Cys Trp

196                 200                 205                 210
Thr His Ser His Cys Gln Lys Val Cys Pro Thr Ile Cys Lys Ser

211                 215                 220                 225
His Gly Cys Thr Ala Glu Gly Leu Cys Cys His Ser Glu Cys Leu

226                 230                 235                 240
Gly Asn Cys Ser Gln Pro Asp Asp Pro Thr Lys Cys Val Ala Cys

241                 245                 250                 255
Arg Asn Phe Tyr Leu Asp Gly Arg Cys Val Glu Thr Cys Pro Pro

256                 260                 265                 270
Pro Tyr Tyr His Phe Gln Asp Trp Arg Cys Val Asn Phe Ser Phe

271                 275                 280                 285
Cys Gln Asp Leu His His Lys Cys Lys Asn Ser Arg Arg Gln Gly

286                 290                 295                 300
Cys His Gln Tyr Val Ile His Asn Asn Lys Cys Ile Pro Glu Cys

301                 305                 310                 315
Pro Ser Gly Tyr Thr Met Asn Ser Ser Asn Leu Leu Cys Thr Pro

316                 320                 325                 330
Cys Leu Gly Pro Cys Pro Lys Val Cys His Leu Leu Glu Gly Glu

331                 335                 340                 345
Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Glu Leu Arg Gly Cys

346                 350                 355                 360
```

```
Thr Val Ile Asn Gly Ser Leu Ile Ile Asn Ile Arg Gly Gly Asn

361                 365                 370                 375
Asn Leu Ala Ala Glu Leu Glu Ala Asn Leu Gly Leu Ile Glu Glu

376                 380                 385                 390
Ile Ser Gly Tyr Leu Lys Ile Arg Arg Ser Tyr Ala Leu Val Ser

391                 395                 400                 405
Leu Ser Phe Phe Arg Lys Leu Arg Leu Ile Arg Gly Glu Thr Leu

406                 410                 415                 420
Glu Ile Gly Asn Tyr Ser Phe Tyr Ala Leu Asp Asn Gln Asn Leu

421                 425                 430                 435
Arg Gln Leu Trp Asp Trp Ser Lys His Asn Leu Thr Ile Thr Gln

436                 440                 445                 450
Gly Lys Leu Phe Phe His Tyr Asn Pro Lys Leu Cys Leu Ser Glu

451                 455                 460                 465
Ile His Lys Met Glu Glu Val Ser Gly Thr Lys Gly Arg Gln Glu

466                 470                 475                 480
Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Gln Ala Ser Cys

481                 485                 490                 495
Glu Asn Glu Leu Leu Lys Phe Ser Tyr Ile Arg Thr Ser Phe Asp

496                 500                 505                 510
Lys Ile Leu Leu Arg Trp Glu Pro Tyr Trp Pro Pro Asp Phe Arg

511                 515                 510                 525
Asp Leu Leu Gly Phe Met Leu Phe Tyr Lys Glu Ala Pro Tyr Gln

526                 530                 535                 540
Asn Val Thr Glu Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser

541                 545                 550                 555
Trp Thr Val Val Asp Ile Asp Pro Pro Leu Arg Ser Asn Asp Pro

556                 560                 565                 570
Lys Ser Gln Asn His Pro Gly Trp Leu Met Arg Gly Leu Lys Pro

571                 575                 580                 585
Trp Thr Gln Tyr Ala Ile Phe Val Lys Thr Leu Val Thr Phe Ser
```

586 590 595 600
Asp Glu Arg Arg Thr Tyr Gly Ala Lys Ser Asp Ile Ile Tyr Val

601 605 610 615
Gln Thr Asp Ala Thr Asn Pro Ser Val Pro Leu Asp Pro Ile Ser

616 620 625 630
Val Ser Asn Ser Ser Ser Gln Ile Ile Leu Lys Trp Lys Pro Pro

631 635 640 645
Ser Asp Pro Asn Gly Asn Ile Thr His Tyr Leu Val Phe Trp Glu

646 650 655 660
Arg Gln Ala Glu Asp Ser Glu Leu Phe Glu Leu Asp Tyr Cys Leu

661 665 670 675
Lys Gly Leu Lys Leu Pro Ser Arg Thr Trp Ser Pro Pro Phe Glu

676 680 685 690
Ser Glu Asp Ser Gln Lys His Asn Gln Ser Glu Tyr Glu Asp Ser

691 695 700 705
Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp Ser Gln Ile Leu

706 710 715 720
Lys Glu Leu Glu Glu Ser Ser Phe Arg Lys Thr Phe Glu Asp Tyr

721 725 730 735
Leu His Asn Val Val Phe Val Pro Arg Lys Thr Ser Ser Gly Thr

736 740 745 750
Gly Ala Glu Asp Pro Arg Pro Ser Arg Lys Arg Arg

751 755 760 762

Fragments of alpha-subunit of human insulin receptor:

SEQ ID NO: 2

Leu Gly Leu Tyr Asn
131 135
Leu Met Asn Ile Thr Arg Gly Ser Val

136 140 144

SEQ ID NO: 3

Lys Gly Lys Thr Asn
191 195

Cys Pro Ala Thr Val Ile Asn Gly
196 200 203

SEQ ID NO: 4

Trp Ser Lys His Asn Leu Thr Ile Thr Gln
441 445 450

Gly Lys Leu
451 453

SEQ ID NO: 5

Asn Val Thr Glu Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser
541 545 550 555

Trp Thr Val Val Asp
556 560

SEQ ID NO: 6

Asp Ile Ile Tyr Val
611 615

Gln Thr Asp Ala Thr
616 620

SEQ ID NO: 7

```
                                                        Tyr Glu Asp Ser
                                                        702         705
Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp Ser Gln Ile
706                 710                 715             719
```

Entire beta subunit of human insulin receptor:

SEQ ID NO: 8

```
                                                              Ser Leu Gly
                                                              763     765
Asp Val Gly Asn Val Thr Val Ala Val Pro Thr Val Ala Ala Phe
766                 770                 775                 780
Pro Asn Thr Ser Ser Thr Ser Val Pro Thr Ser Pro Glu Glu His
781                 785                 790                 795
Arg Pro Phe Glu Lys Val Val Asn Lys Glu Ser Leu Val Ile Ser
796                 800                 805                 810
Gly Leu Arg His Phe Thr Gly Tyr Arg Ile Glu Leu Gln Ala Cys
811                 815                 820                 825
Asn Gln Asp Thr Pro Glu Glu Arg Cys Ser Val Ala Ala Tyr Val
826                 830                 835                 840
Ser Ala Arg Thr Met Pro Glu Ala Lys Ala Asp Asp Ile Val Gly
841                 845                 850                 855
Pro Val Thr His Glu Ile Phe Glu Asn Asn Val Val His Leu Met
856                 860                 865                 870
Trp Gln Glu Pro Lys Glu Pro Asn Gly Leu Ile Val Leu Tyr Glu
871                 875                 880                 885
Val Ser Tyr Arg Arg Tyr Gly Asp Glu Glu Leu His Leu Cys Val
886                 890                 895                 900
Ser Arg Lys His Phe Ala Leu Glu Arg Gly Cys Arg Leu Arg Gly
901                 905                 910                 915
Leu Ser Pro Gly Asn Tyr Ser Val Arg Ile Arg Ala Thr Ser Leu
```

916 920 925 930
Ala Gly Asn Gly Ser Trp Thr Glu Pro Thr Tyr Phe Tyr Val Thr

931 935 940 945
Asp Tyr Leu Asp Val Pro Ser Asn Ile Ala Lys Ile Ile Ile Gly

946 950 955 960
Pro Leu Ile Phe Val Phe Leu Phe Ser Val Val Ile Gly Ser Ile

961 965 970 975
Tyr Leu Phe Leu Arg Lys Arg Gln Pro Asp Gly Pro Leu Gly Pro

976 980 985 990
Leu Tyr Ala Ser Ser Asn Pro Glu Tyr Leu Ser Ala Ser Asp Val

991 995 1000 1005
Phe Pro Cys Ser Val Tyr Val Pro Asp Glu Trp Glu Val Ser Arg

1006 1010 1015 1020
Glu Lys Ile Thr Leu Leu Arg Glu Leu Gly Gln Gly Ser Phe Gly

1021 1025 1030 1035
Met Val Tyr Glu Gly Asn Ala Arg Asp Ile Ile Lys Gly Glu Ala

1036 1140 1145 1050
Glu Thr Arg Val Ala Val Lys Thr Val Asn Glu Ser Ala Ser Leu

1051 1155 1160 1065
Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser Val Met Lys Gly

1066 1170 1175 1080
Phe Thr Cys His His Val Val Arg Leu Leu Gly Val Val Ser Lys

1081 1185 1190 1095
Gly Gln Pro Thr Leu Val Val Met Glu Leu Met Ala His Gly Asp

1096 1100 1105 1110
Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Ala Glu Asn Asn

1111 1115 1120 1125
Pro Gly Arg Pro Pro Pro Thr Leu Gln Glu Met Ile Gln Met Ala

1126 1130 1135 1140
Ala Glu Ile Ala Asp Gly Met Ala Tyr Leu Asn Ala Lys Lys Phe

1141 1145 1150 1155
Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Val Ala His Asp

```
1156                1160                1165                1170
Phe Thr Val Lys Ile Gly Asp Phe Gly Met Thr Arg Asp Ile Tyr

1171                1175                1180                1185
Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys Gly Leu Leu Pro Val

1186                1190                1195                1200
Arg Trp Met Ala Pro Glu Ser Leu Lys Asp Gly Val Phe Thr Thr

1201                1205                1210                1215
Ser Ser Asp Met Trp Ser Phe Gly Val Val Leu Trp Glu Ile Thr

1216                1220                1225                1230
Ser Leu Ala Glu Gln Pro Tyr Gln Gly Leu Ser Asn Glu Gln Val

1231                1235                1240                1245
Leu Lys Phe Val Met Asp Gly Gly Tyr Leu Asp Gln Pro Asp Asn

1246                1250                1255                1260
Cys Pro Glu Arg Val Thr Asp Leu Met Arg Met Cys Trp Gln Phe

1261                1265                1270                1275

Asn Pro Lys Met Arg Pro Thr Phe Leu Glu Ile Val Asn Leu Leu

1276                1280                1285                1290
Lys Asp Asp Leu His Pro Ser Phe Pro Glu Val Ser Phe Phe His

1291                1295                1300                1305
Ser Glu Glu Asn Lys Ala Pro Glu Ser Glu Glu Leu Glu Met Glu

1306                1310                1315                1320
Phe Glu Asp Met Glu Asn Val Pro Leu Asp Arg Ser Ser His Cys

1321                1325                1330                1335
Gln Arg Glu Glu Ala Gly Gly Arg Asp Gly Gly Ser Ser Leu Gly

1336                1340                1345                1350
Phe Lys Arg Ser Tyr Glu Glu His Ile Pro Tyr Thr His Met Asn

1351                1355                1360                1365
Gly Gly Lys Lys Asn Gly Arg Ile Leu Thr Leu Pro Arg Ser Asn

1366                1370                1375                1380
Pro Ser

13811382
```

Fragments of C-terminal fragment of beta subunit of human insulin receptor:

SEQ ID NO: 9

Lys Lys Asn Gly Arg Ile Leu Thr Leu Pro

1368 1370 1375 1377

SEQ ID NO: 10

Arg Ile Leu Thr Leu Pro Arg Ser Asn

1372 1375 1380

Pro Ser

13811382

SEQ ID NO: 11

Lys Asn Gly Arg Ile Leu Thr

13691370 1375

SEQ ID NO: 12

Gly Gly Lys Lys Asn Gly Arg Ile Leu Thr Leu Pro Arg Ser Asn

1366 1370 1375 1380

Pro Ser

13811382

SEQ ID NO: 13

Asn

1365

Gly Gly Lys Lys Asn Gly Arg Ile Leu Thr Leu Pro Arg Ser Asn

1366 1370 1375 1380

Pro Ser

13811382

The use of human insulin receptor as antigen is also contemplated. The suitable sequence for such antigen is as follow:

SEQ ID NO: 14

```
Met Ala Thr Gly Gly Arg Arg Gly Ala Ala Ala Ala Pro Leu Leu
 1               5                  10                  15

Val Ala Val Ala Ala Leu Leu Leu Gly Ala Ala Gly His Leu Tyr

 16              20                  25                  30
Pro Gly Glu Val Cys Pro Gly Met Asp Ile Arg Asn Asn Leu Thr

 31              35                  40                  45
Arg Leu His Glu Leu Glu Asn Cys Ser Val Ile Glu Gly His Leu

 46              50                  55                  60
Gln Ile Leu Leu Met Phe Lys Thr Arg Pro Glu Asp Phe Arg Asp

 61              65                  70                  75
Leu Ser Phe Pro Lys Leu Ile Met Ile Thr Asp Tyr Leu Leu Leu

 76              80                  85                  90
Phe Arg Val Tyr Gly Leu Glu Ser Leu Lys Asp Leu Phe Pro Asn

 91              95                 100                 105
Leu Thr Val Ile Arg Gly Ser Arg Leu Phe Phe Asn Tyr Ala Leu

106             110                 115                 120

Val Ile Phe Glu Met Val His Leu Lys Glu Leu Gly Leu Tyr Asn

121             125                 130                 135
Leu Met Asn Ile Thr Arg Gly Ser Val Arg Ile Glu Lys Asn Asn

136             140                 145                 150
Glu Leu Cys Tyr Leu Ala Thr Ile Asp Trp Ser Arg Ile Leu Asp

151             155                 160                 165
Ser Val Glu Asp Asn Tyr Ile Val Leu Asn Lys Asp Asp Asn Glu

166             170                 175                 180
Glu Cys Gly Asp Ile Cys Pro Gly Thr Ala Lys Gly Lys Thr Asn

181             185                 190                 195
Cys Pro Ala Thr Val Ile Asn Gly Gln Phe Val Glu Arg Cys Trp
```

196 200 205 210
Thr His Ser His Cys Gln Lys Val Cys Pro Thr Ile Cys Lys Ser

211 215 220 225
His Gly Cys Thr Ala Glu Gly Leu Cys Cys His Ser Glu Cys Leu

226 230 235 240
Gly Asn Cys Ser Gln Pro Asp Asp Pro Thr Lys Cys Val Ala Cys

241 245 250 255
Arg Asn Phe Tyr Leu Asp Gly Arg Cys Val Glu Thr Cys Pro Pro

256 260 265 270
Pro Tyr Tyr His Phe Gln Asp Trp Arg Cys Val Asn Phe Ser Phe

271 275 280 285
Cys Gln Asp Leu His His Lys Cys Lys Asn Ser Arg Arg Gln Gly

286 290 295 300
Cys His Gln Tyr Val Ile His Asn Asn Lys Cys Ile Pro Glu Cys

301 305 310 315
Pro Ser Gly Tyr Thr Met Asn Ser Ser Asn Leu Leu Cys Thr Pro

316 320 325 330
Cys Leu Gly Pro Cys Pro Lys Val Cys His Leu Leu Glu Gly Glu

331 335 340 345
Lys Thr Ile Asp Ser Val Thr Ser Ala Gln Glu Leu Arg Gly Cys

346 350 355 360
Thr Val Ile Asn Gly Ser Leu Ile Ile Asn Ile Arg Gly Gly Asn

361 365 370 375
Asn Leu Ala Ala Glu Leu Glu Ala Asn Leu Gly Leu Ile Glu Glu

376 380 385 390
Ile Ser Gly Tyr Leu Lys Ile Arg Arg Ser Tyr Ala Leu Val Ser

391 395 400 405
Leu Ser Phe Phe Arg Lys Leu Arg Leu Ile Arg Gly Glu Thr Leu

406 410 415 420
Glu Ile Gly Asn Tyr Ser Phe Tyr Ala Leu Asp Asn Gln Asn Leu

421 425 430 435
Arg Gln Leu Trp Asp Trp Ser Lys His Asn Leu Thr Ile Thr Gln

436 440 445 450
Gly Lys Leu Phe Phe His Tyr Asn Pro Lys Leu Cys Leu Ser Glu

451 455 460 465
Ile His Lys Met Glu Glu Val Ser Gly Thr Lys Gly Arg Gln Glu

466 470 475 480
Arg Asn Asp Ile Ala Leu Lys Thr Asn Gly Asp Gln Ala Ser Cys

481 485 490 495
Glu Asn Glu Leu Leu Lys Phe Ser Tyr Ile Arg Thr Ser Phe Asp

496 500 505 510
Lys Ile Leu Leu Arg Trp Glu Pro Tyr Trp Pro Pro Asp Phe Arg

511 515 510 525
Asp Leu Leu Gly Phe Met Leu Phe Tyr Lys Glu Ala Pro Tyr Gln

526 530 535 540
Asn Val Thr Glu Phe Asp Gly Gln Asp Ala Cys Gly Ser Asn Ser

541 545 550 555
Trp Thr Val Val Asp Ile Asp Pro Pro Leu Arg Ser Asn Asp Pro

556 560 565 570
Lys Ser Gln Asn His Pro Gly Trp Leu Met Arg Gly Leu Lys Pro

571 575 580 585
Trp Thr Gln Tyr Ala Ile Phe Val Lys Thr Leu Val Thr Phe Ser

586 590 595 600
Asp Glu Arg Arg Thr Tyr Gly Ala Lys Ser Asp Ile Ile Tyr Val

601 605 610 615
Gln Thr Asp Ala Thr Asn Pro Ser Val Pro Leu Asp Pro Ile Ser

616 620 625 630
Val Ser Asn Ser Ser Ser Gln Ile Ile Leu Lys Trp Lys Pro Pro

631 635 640 645
Ser Asp Pro Asn Gly Asn Ile Thr His Tyr Leu Val Phe Trp Glu

646 650 655 660
Arg Gln Ala Glu Asp Ser Glu Leu Phe Glu Leu Asp Tyr Cys Leu

661 665 670 675
Lys Gly Leu Lys Leu Pro Ser Arg Thr Trp Ser Pro Pro Phe Glu

676 680 685 690
Ser Glu Asp Ser Gln Lys His Asn Gln Ser Glu Tyr Glu Asp Ser

691 695 700 705
Ala Gly Glu Cys Cys Ser Cys Pro Lys Thr Asp Ser Gln Ile Leu

706 710 715 720
Lys Glu Leu Glu Glu Ser Ser Phe Arg Lys Thr Phe Glu Asp Tyr

721 725 730 735
Leu His Asn Val Val Phe Val Pro Arg Lys Thr Ser Ser Gly Thr

736 740 745 750
Gly Ala Glu Asp Pro Arg Pro Ser Arg Lys Arg Arg Ser Leu Gly

751 755 760 765
Asp Val Gly Asn Val Thr Val Ala Val Pro Thr Val Ala Ala Phe

766 770 775 780
Pro Asn Thr Ser Ser Thr Ser Val Pro Thr Ser Pro Glu Glu His

781 785 790 795
Arg Pro Phe Glu Lys Val Val Asn Lys Glu Ser Leu Val Ile Ser

796 800 805 810
Gly Leu Arg His Phe Thr Gly Tyr Arg Ile Glu Leu Gln Ala Cys

811 815 820 825
Asn Gln Asp Thr Pro Glu Glu Arg Cys Ser Val Ala Ala Tyr Val

826 830 835 840
Ser Ala Arg Thr Met Pro Glu Ala Lys Ala Asp Asp Ile Val Gly

841 845 850 855
Pro Val Thr His Glu Ile Phe Glu Asn Asn Val Val His Leu Met

856 860 865 870
Trp Gln Glu Pro Lys Glu Pro Asn Gly Leu Ile Val Leu Tyr Glu

871 875 880 885
Val Ser Tyr Arg Arg Tyr Gly Asp Glu Glu Leu His Leu Cys Val

886 890 895 900
Ser Arg Lys His Phe Ala Leu Glu Arg Gly Cys Arg Leu Arg Gly

901 905 910 915
Leu Ser Pro Gly Asn Tyr Ser Val Arg Ile Arg Ala Thr Ser Leu

916 920 925 930
Ala Gly Asn Gly Ser Trp Thr Glu Pro Thr Tyr Phe Tyr Val Thr

931 935 940 945
Asp Tyr Leu Asp Val Pro Ser Asn Ile Ala Lys Ile Ile Ile Gly

946 950 955 960
Pro Leu Ile Phe Val Phe Leu Phe Ser Val Val Ile Gly Ser Ile

961 965 970 975
Tyr Leu Phe Leu Arg Lys Arg Gln Pro Asp Gly Pro Leu Gly Pro

976 980 985 990
Leu Tyr Ala Ser Ser Asn Pro Glu Tyr Leu Ser Ala Ser Asp Val

991 995 1000 1005
Phe Pro Cys Ser Val Tyr Val Pro Asp Glu Trp Glu Val Ser Arg

1006 1010 1015 1020
Glu Lys Ile Thr Leu Leu Arg Glu Leu Gly Gln Gly Ser Phe Gly

1021 1025 1030 1035
Met Val Tyr Glu Gly Asn Ala Arg Asp Ile Ile Lys Gly Glu Ala

1036 1140 1145 1050
Glu Thr Arg Val Ala Val Lys Thr Val Asn Glu Ser Ala Ser Leu

1051 1155 1160 1065
Arg Glu Arg Ile Glu Phe Leu Asn Glu Ala Ser Val Met Lys Gly

1066 1170 1175 1080
Phe Thr Cys His His Val Val Arg Leu Leu Gly Val Val Ser Lys

1081 1185 1190 1095
Gly Gln Pro Thr Leu Val Val Met Glu Leu Met Ala His Gly Asp

1096 1100 1105 1110
Leu Lys Ser Tyr Leu Arg Ser Leu Arg Pro Glu Ala Glu Asn Asn

1111 1115 1120 1125
Pro Gly Arg Pro Pro Pro Thr Leu Gln Glu Met Ile Gln Met Ala

1126 1130 1135 1140
Ala Glu Ile Ala Asp Gly Met Ala Tyr Leu Asn Ala Lys Lys Phe

1141 1145 1150 1155
Val His Arg Asp Leu Ala Ala Arg Asn Cys Met Val Ala His Asp

1156 1160 1165 1170
Phe Thr Val Lys Ile Gly Asp Phe Gly Met Thr Arg Asp Ile Tyr

1171 1175 1180 1185
Glu Thr Asp Tyr Tyr Arg Lys Gly Gly Lys Gly Leu Leu Pro Val

1186 1190 1195 1200
Arg Trp Met Ala Pro Glu Ser Leu Lys Asp Gly Val Phe Thr Thr

1201 1205 1210 1215
Ser Ser Asp Met Trp Ser Phe Gly Val Val Leu Trp Glu Ile Thr

1216 1220 1225 1230
Ser Leu Ala Glu Gln Pro Tyr Gln Gly Leu Ser Asn Glu Gln Val

1231 1235 1240 1245
Leu Lys Phe Val Met Asp Gly Gly Tyr Leu Asp Gln Pro Asp Asn

1246 1250 1255 1260
Cys Pro Glu Arg Val Thr Asp Leu Met Arg Met Cys Trp Gln Phe

1261 1265 1270 1275

Asn Pro Lys Met Arg Pro Thr Phe Leu Glu Ile Val Asn Leu Leu

1276 1280 1285 1290
Lys Asp Asp Leu His Pro Ser Phe Pro Glu Val Ser Phe Phe His

1291 1295 1300 1305
Ser Glu Glu Asn Lys Ala Pro Glu Ser Glu Glu Leu Glu Met Glu

1306 1310 1315 1320
Phe Glu Asp Met Glu Asn Val Pro Leu Asp Arg Ser Ser His Cys

1321 1325 1330 1335
Gln Arg Glu Glu Ala Gly Gly Arg Asp Gly Gly Ser Ser Leu Gly

1336 1340 1345 1350
Phe Lys Arg Ser Tyr Glu Glu His Ile Pro Tyr Thr His Met Asn

1351 1355 1360 1365
Gly Gly Lys Lys Asn Gly Arg Ile Leu Thr Leu Pro Arg Ser Asn

1366 1370 1375 1380
Pro Ser

13811382

The exemplary procedure for preparation of the starting polyclonal antibodies to C-terminal fragment of beta subunit of human insulin receptor may be described as follows. In 7-9 days before blood sampling, 1-3 intravenous injections of the desired antigen are made to the rabbits to increase the level of polyclonal antibodies in the rabbit blood stream. Upon immunization, blood samples are taken to test the antibody level. Typically, the maximum level of immune reaction of the soluble antigen is achieved within 40 to 60 days after the first injection of the antigen. Upon completion of the first immunization cycle, rabbits have a 30-day rehabilitation period, after which re-immunization is performed with another 1-3 intravenous injections.

To obtain antiserum containing the desired antibodies, the immunized rabbits' blood is collected from rabbits and placed in 50ml centrifuge tube. Product clots formed on the tube sides are removed with a wooden spatula, and a rod is placed into the clot in the tube center. The blood is then placed in a refrigerator for one night at the temperature of about 40°C. On the following day, the clot on the spatula is removed, and the remaining liquid is centrifuged for 10 min at 13,000 rotations. Supernatant fluid is the target antiserum. The obtained antiserum is typically yellow. 20% of NaN_3 (weight concentration) is added in the antiserum to the final concentration of 0.02% and stored before use in frozen state at the temperature of -20°C (or without NaN_3 at the temperature of -70°C). To separate the target antibodies to C-terminal fragment of beta subunit of human insulin-receptor from the antiserum, the following solid phase absorption sequence is suitable:

10 ml of the antiserum of rabbits is diluted twofold with 0.15 M NaCl, after which 6.26g Na_2SO_4 is added, mixed and incubated for 12-16 hours at 4°C. The sediment is removed by centrifugation, diluted in 10ml of phosphate buffer and dialyzed against the same buffer during one night at ambient temperature. After the sediment is removed, the solution is applied to DEAE-cellulose column balanced by phosphate buffer. The antibody fraction is determined by measuring the optical density of eluate at 280 Nm.

The isolated crude antibodies are purified using the affine chromatography method by attaching the obtained antibodies to a C-terminal fragment of beta subunit of

human insulin receptor located on the insoluble matrix of the chromatography media, with subsequent elution by concentrated aqueous salt solutions.

The resulting buffer solution is used as the initial solution for the homeopathic dilution process used to prepare the activated potentiated form of the antibodies. The preferred concentration of the initial matrix solution of the antigen-purified polyclonal rabbit antibodies to C-terminal fragment of beta subunit of human insulin-receptor is 0.5 to 5.0 mg/ml, preferably, 2.0 to 3.0 mg/ml.

The polyclonal antibodies to endothelial NO-synthase are obtained by a similar methodology using the adjuvant. In order to obtain polyclonal antibodies to endothelial NO-synthase, it is possible to use the entire molecule of bovine endothelial NO-synthase of the below-described sequence as immunogen (antigen):

SEQ ID NO: 15

```
Met Gly Asn Leu Lys Ser Val Gly Gln Glu Pro Gly Pro Pro Cys
 1               5                  10                  15
Gly Leu Gly Leu Gly Leu Gly Leu Gly Leu Cys Gly Lys Gln Gly
 16              20                  25                  30
Pro Ala Ser Pro Ala Pro Glu Pro Ser Arg Ala Pro Ala Pro Ala
 31              35                  40                  45
Thr Pro His Ala Pro Asp His Ser Pro Ala Pro Asn Ser Pro Thr
 46              50                  55                  60
Leu Thr Arg Pro Pro Glu Gly Pro Lys Phe Pro Arg Val Lys Asn
 61              65                  70                  75
Trp Glu Leu GLys er Ile Thr Tyr Asp Thr Leu Cys Ala Gln Ser
 76              80                  85                  90
Gln Gln Asp Gly Pro Cys Thr Pro Arg Cys Cys Leu GLys er Leu
 91              95                 100                 105
Val Leu Pro Arg Lys Leu Gln Thr Arg Pro Ser Pro Gly Pro Pro
106             110                 115                 120
Pro Ala Glu Gln Leu Leu Ser Gln Ala Arg Asp Phe Ile Asn Gln
121             125                 130                 135
Tyr Tyr Ser Ser Ile Lys Arg Ser GLys er Gln Ala His Glu Glu
136             140                 145                 150
Arg Leu Gln Glu Val Glu Ala Glu Val Ala Ser Thr Gly Thr Tyr
151             155                 160                 165
His Leu Arg Glu Ser Glu Leu Val Phe Gly Ala Lys Gln Ala Trp
166             170                 175                 180
Arg Asn Ala Pro Arg Cys Val Gly Arg Ile Gln Trp Gly Lys Leu
181             185                 190                 195
```

Gln Val Phe Asp Ala Arg Asp Cys Ser Ser Ala Gln Glu Met Phe
196 200 205 210
Thr Tyr Ile Cys Asn His Ile Lys Tyr Ala Thr Asn Arg Gly Asn
211 215 220 225
Leu Arg Ser Ala Ile Thr Val Phe Pro Gln Arg Ala Pro Gly Arg
226 230 235 240
Gly Asp Phe Arg Ile Trp Asn Ser Gln Leu Val Arg Tyr Ala Gly
241 245 250 255
Tyr Arg Gln Gln Asp GLys er Val Arg Gly Asp Pro Ala Asn Val
256 260 265 270
Glu Ile Thr Glu Leu Cys Ile Gln His Gly Trp Thr Pro Gly Asn
271 275 280 285
Gly Arg Phe Asp Val Leu Pro Leu Leu Leu Gln Ala Pro Asp Glu
286 290 295 300
Ala Pro Glu Leu Phe Val Leu Pro Pro Glu Leu Val Leu Glu Val
301 305 310 315
Pro Leu Glu His Pro Thr Leu Glu Trp Phe Ala Ala Leu Gly Leu
316 320 325 330
Arg Trp Tyr Ala Leu Pro Ala Val Ser Asn Met Leu Leu Glu Ile
331 335 340 345
Gly Gly Leu Glu Phe Ser Ala Ala Pro Phe Ser Gly Trp Tyr Met
346 350 355 360
Ser Thr Glu Ile Gly Thr Arg Asn Leu Cys Asp Pro His Arg Tyr
361 365 370 375
Asn Ile Leu Glu Asp Val Ala Val Cys Met Asp Leu Asp Thr Arg
376 380 385 390
Thr Thr Ser Ser Leu Trp Lys Asp Lys Ala Ala Val Glu Ile Asn
391 395 400 405
Leu Ala Val Leu His Ser Phe Gln Leu Ala Lys Val Thr Ile Val
406 410 415 420
Asp His His Ala Ala Thr Val Ser Phe Met Lys His Leu Asp Asn
421 425 430 435
Glu Gln Lys Ala Arg Gly Gly Cys Pro Ala Asp Trp Ala Trp Ile
436 440 445 450
Val Pro Pro Ile Ser GLys er Leu Thr Pro Val Phe His Gln Glu
451 455 460 465
Met Val Asn Tyr Ile Leu Ser Pro Ala Phe Arg Tyr Gln Pro Asp
466 470 475 480
Pro Trp Lys GLy Ser Ala Thr Lys Gly Ala Gly Ile Thr Arg Lys
481 485 490 495
Lys Thr Phe Lys Glu Val Ala Asn Ala Val Lys Ile Ser Ala Ser
496 500 505 510
Leu Met Gly Thr Leu Met Ala Lys Arg Val Lys Ala Thr Ile Leu
511 515 510 525
Tyr Ala Ser Glu Thr Gly Arg Ala Gln Ser Tyr Ala Gln Gln Leu
526 530 535 540

Gly Arg Leu Phe Arg Lys Ala Phe Asp Pro Arg Val Leu Cys Met
541 545 550 555
Asp Glu Tyr Asp Val Val Ser Leu Glu His Glu Ala Leu Val Leu
556 560 565 570
Val Val Thr Ser Thr Phe Gly Asn Gly Asp Pro Pro Glu Asn Gly
571 575 580 585
Glu Ser Phe Ala Ala Ala Leu Met Glu Met Ser Gly Pro Tyr Asn
586 590 595 600
Ser Ser Pro Arg Pro Glu Gln His Lys Ser Tyr Lys Ile Arg Phe
601 605 610 615
Asn Ser Val Ser Cys Ser Asp Pro Leu Val Ser Ser Trp Arg Arg
616 620 625 630
Lys Arg Lys Glu Ser Ser Asn Thr Asp Ser Ala Gly Ala Leu Gly
631 635 640 645
Thr Leu Arg Phe Cys Val Phe Gly Leu GLy Ser Arg Ala Tyr Pro
646 650 655 660
His Phe Cys Ala Phe Ala Arg Ala Val Asp Thr Arg Leu Glu Glu
661 665 670 675
Leu Gly Gly Glu Arg Leu Leu Gln Leu Gly Gln Gly Asp Glu Leu
676 680 685 690
Cys Gly Gln Glu Glu Ala Phe Arg Gly Trp Ala Lys Ala Ala Phe
691 695 700 705
Gln Ala Ser Cys Glu Thr Phe Cys Val Gly Glu Glu Ala Lys Ala
706 710 715 720
Ala Ala Gln Asp Ile Phe Ser Pro Lys Arg Ser Trp Lys Arg Gln
721 725 730 735
Arg Tyr Arg Leu Ser Thr Gln Ala Glu Gly Leu Gln Leu Leu Pro
736 740 745 750
Gly Leu Ile His Val His Arg Arg Lys Met Phe Gln Ala Thr Val
751 755 760 765
Leu Ser Val Glu Asn Leu Gln Ser Ser Lys Ser Thr Arg Ala Thr
766 770 775 780
Ile Leu Val Arg Leu Asp Thr Ala Gly Gln Glu Gly Leu Gln Tyr
781 785 790 795
Gln Pro Gly Asp His Ile Gly Ile Cys Pro Pro Asn Arg Pro Gly
796 800 805 810
Leu Val Glu Ala Leu Leu Ser Arg Val Glu Asp Pro Pro Pro Pro
811 815 820 825
Thr Glu Ser Val Ala Val Glu Gln Leu Glu Lys GLys er Pro Gly
826 830 835 840
Gly Pro Pro Pro Ser Trp Val Arg Asp Pro Arg Leu Pro Pro Cys
841 845 850 855
Thr Leu Arg Gln Ala Leu Thr Phe Phe Leu Asp Ile Thr Ser Pro
856 860 865 870
Pro Ser Pro Arg Leu Leu Arg Leu Leu Ser Thr Leu Ala Glu Glu
871 875 880 885

Pro Ser Glu Gln Gln Glu Leu Glu Thr Leu Ser Gln Asp Pro Arg
886 890 895 900
Arg Tyr Glu Glu Trp Lys Trp Phe Arg Cys Pro Thr Leu Leu Glu
901 905 910 915
Val Leu Glu Gln Phe Pro Ser Val Ala Leu Pro Ala Pro Leu Leu
916 920 925 930
Leu Thr Gln Leu Pro Leu Leu Gln Pro Arg Tyr Tyr Ser Val Ser
931 935 940 945
Ser Ala Pro Asn Ala His Pro Gly Glu Val His Leu Thr Val Ala
946 950 955 960
Val Leu Ala Tyr Arg Thr Gln Asp Gly Leu Gly Pro Leu His Tyr
961 965 970 975
Gly Val Cys Ser Thr Trp Leu Ser Gln Leu Lys Thr Gly Asp Pro
976 980 985 990
Val Pro Cys Phe Ile Arg Gly Ala Pro Ser Phe Arg Leu Pro Pro
991 995 1000 1005
Asp Pro Tyr Val Pro Cys Ile Leu Val Gly Pro Gly Thr Gly Ile
1006 1010 1015 1020
Ala Pro Phe Arg Gly Phe Trp Gln Glu Arg Leu His Asp Ile Glu
1021 1025 1030 1035
Ser Lys Gly Leu Gln Pro Ala Pro Met Thr Leu Val Phe Gly Cys
1036 1040 1045 1050
Arg Cys Ser Gln Leu Asp His Leu Tyr Arg Asp Glu Val Gln Asp
1051 1055 1060 1065
Ala Gln Glu Arg Gly Val Phe Gly Arg Val Leu Thr Ala Phe Ser
1066 1070 1075 1080
Arg Glu Pro Asp Ser Pro Lys Thr Tyr Val Gln Asp Ile Leu Arg
1081 1085 1090 1095
Thr Glu Leu Ala Ala Glu Val His Arg Val Leu Cys Leu Glu Arg
1096 1100 1105 1110
Gly His Met Phe Val Cys Gly Asp Val Thr Met Ala Thr Ser Val
1111 1115 1120 1125
Leu Gln Thr Val Gln Arg Ile Leu Ala Thr Glu Gly Asp Met Glu
1126 1130 1135 1140
Leu Asp Glu Ala Gly Asp Val Ile Gly Val Leu Arg Asp Gln Gln
1141 1145 1150 1155
Arg Tyr His Glu Asp Ile Phe Gly Leu Thr Leu Arg Thr Gln Glu
1156 1160 1165 1170
Val Thr Ser Arg Ile Arg Thr Gln Ser Phe Ser Leu Gln Glu Arg
1171 1175 1180 1185
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Pro
1186 1190 1195 1200
Asp Thr Pro Gly Pro
1201 1205

Polyclonal antibodies to NO synthase may be obtained using the whole molecule of human NO synthase of the following sequence:

SEQ ID NO:16

Met Gly Asn Leu Lys Ser Val Ala Gln Glu Pro Gly Pro Pro Cys

1 5 10 15

Gly Leu Gly Leu Gly Leu Gly Leu Gly Leu Cys Gly Lys Gln Gly

16 20 25 30

Pro Ala Thr Pro Ala Pro Glu Pro Ser Arg Ala Pro Ala Ser Leu

31 35 40 45

Leu Pro Pro Ala Pro Glu His Ser Pro Pro Ser Ser Pro Leu Thr

46 50 55 60

Gln Pro Pro Glu Gly Pro Lys Phe Pro Arg Val Lys Asn Trp Glu

61 65 70 75

Val GLys er Ile Thr Tyr Asp Thr Leu Ser Ala Gln Ala Gln Gln

76 80 85 90

Asp Gly Pro Cys Thr Pro Arg Arg Cys Leu GLys er Leu Val Phe

91 95 100 105

Pro Arg Lys Leu Gln Gly Arg Pro Ser Pro Gly Pro Pro Ala Pro

106 110 115 120

Glu Gln Leu Leu Ser Gln Ala Arg Asp Phe Ile Asn Gln Tyr Tyr

121 125 130 135

Ser Ser Ile Lys Arg Ser GLys er Gln Ala His Glu Gln Arg Leu

136 140 145 150

Gln Glu Val Glu Ala Glu Val Ala Ala Thr Gly Thr Tyr Gln Leu

151 155 160 165

Arg Glu Ser Glu Leu Val Phe Gly Ala Lys Gln Ala Trp Arg Asn
166 170 175 180
Ala Pro Arg Cys Val Gly Arg Ile Gln Trp Gly Lys Leu Gln Val
181 185 190 195
Phe Asp Ala Arg Asp Cys Arg Ser Ala Gln Glu Met Phe Thr Tyr
196 200 205 210
Ile Cys Asn His Ile Lys Tyr Ala Thr Asn Arg Gly Asn Leu Arg
211 215 220 225
Ser Ala Ile Thr Val Phe Pro Gln Arg Cys Pro Gly Arg Gly Asp
226 230 235 240
Phe Arg Ile Trp Asn Ser Gln Leu Val Arg Tyr Ala Gly Tyr Arg
241 245 250 255
Gln Gln Asp GLy Ser Val Arg Gly Asp Pro Ala Asn Val Glu Ile
256 260 265 270
Thr Glu Leu Cys Ile Gln His Gly Trp Thr Pro Gly Asn Gly Arg
271 275 280 285
Phe Asp Val Leu Pro Leu Leu Leu Gln Ala Pro Asp Glu Pro Pro
286 290 295 300
Glu Leu Phe Leu Leu Pro Pro Glu Leu Val Leu Glu Val Pro Leu
301 305 310 315
Glu His Pro Thr Leu Glu Trp Phe Ala Ala Leu Gly Leu Arg Trp
316 320 325 330
Tyr Ala Leu Pro Ala Val Ser Asn Met Leu Leu Glu Ile Gly Gly
331 335 340 345
Leu Glu Phe Pro Ala Ala Pro Phe Ser Gly Trp Tyr Met Ser Thr

346 350 355 360

Glu Ile Gly Thr Arg Asn Leu Cys Asp Pro His Arg Tyr Asn Ile

361 365 370 375

Leu Glu Asp Val Ala Val Cys Met Asp Leu Asp Thr Arg Thr Thr

376 380 385 390

Ser Ser Leu Trp Lys Asp Lys Ala Ala Val Glu Ile Asn Val Ala

391 395 400 405

Val Leu His Ser Tyr Gln Leu Ala Lys Val Thr Ile Val Asp His

406 410 415 420

His Ala Ala Thr Ala Ser Phe Met Lys His Leu Glu Asn Glu Gln

421 425 430 435

Lys Ala Arg Gly Gly Cys Pro Ala Asp Trp Ala Trp Ile Val Pro

436 440 445 450

Pro Ile Ser GLys er Leu Thr Pro Val Phe His Gln Glu Met Val

451 455 460 465

Asn Tyr Phe Leu Ser Pro Ala Phe Arg Tyr Gln Pro Asp Pro Trp

466 470 475 480

Lys Gly Ser Ala Ala Lys Gly Thr Gly Ile Thr Arg Lys Lys Thr

481 485 490 495

Phe Lys Glu Val Ala Asn Ala Val Lys Ile Ser Ala Ser Leu Met

496 500 505 510

Gly Thr Val Met Ala Lys Arg Val Lys Ala Thr Ile Leu Tyr Gly

511 515 510 525

Ser Glu Thr Gly Arg Ala Gln Ser Tyr Ala Gln Gln Leu Gly Arg

526 530 535 540

Leu Phe Arg Lys Ala Phe Asp Pro Arg Val Leu Cys Met Asp Glu
541 545 550 555
Tyr Asp Val Val Ser Leu Glu His Glu Thr Leu Val Leu Val Val
556 560 565 570
Thr Ser Thr Phe Gly Asn Gly Asp Pro Pro Glu Asn Gly Glu Ser
571 575 580 585
Phe Ala Ala Ala Leu Met Glu Met Ser Gly Pro Tyr Asn Ser Ser
586 590 595 600
Pro Arg Pro Glu Gln His Lys Ser Tyr Lys Ile Arg Phe Asn Ser
601 605 610 615
Ile Ser Cys Ser Asp Pro Leu Val Ser Ser Trp Arg Arg Lys Arg
616 620 625 630
Lys Glu Ser Ser Asn Thr Asp Ser Ala Gly Ala Leu Gly Thr Leu
631 635 640 645
Arg Phe Cys Val Phe Gly Leu GLys er Arg Ala Tyr Pro His Phe
646 650 655 660
Cys Ala Phe Ala Arg Ala Val Asp Thr Arg Leu Glu Glu Leu Gly
661 665 670 675
Gly Glu Arg Leu Leu Gln Leu Gly Gln Gly Asp Glu Leu Cys Gly
676 680 685 690
Gln Glu Glu Ala Phe Arg Gly Trp Ala Gln Ala Ala Phe Gln Ala
691 695 700 705
Ala Cys Glu Thr Phe Cys Val Gly Glu Asp Ala Lys Ala Ala Ala
706 710 715 720
Arg Asp Ile Phe Ser Pro Lys Arg Ser Trp Lys Arg Gln Arg Tyr

721 725 730 735

Arg Leu Ser Ala Gln Ala Glu Gly Leu Gln Leu Leu Pro Gly Leu

736 740 745 750

Ile His Val His Arg Arg Lys Met Phe Gln Ala Thr Ile Arg Ser

751 755 760 765

Val Glu Asn Leu Gln Ser Ser Lys Ser Thr Arg Ala Thr Ile Leu

766 770 775 780

Val Arg Leu Asp Thr Gly Gly Gln Glu Gly Leu Gln Tyr Gln Pro

781 785 790 795

Gly Asp His Ile Gly Val Cys Pro Pro Asn Arg Pro Gly Leu Val

796 800 805 810

Glu Ala Leu Leu Ser Arg Val Glu Asp Pro Pro Ala Pro Thr Glu

811 815 820 825

Pro Val Ala Val Glu Gln Leu Glu Lys Gly Ser Pro Gly Gly Pro

826 830 835 840

Pro Pro Gly Trp Val Arg Asp Pro Arg Leu Pro Pro Cys Thr Leu

841 845 850 855

Arg Gln Ala Leu Thr Phe Phe Leu Asp Ile Thr Ser Pro Pro Ser

856 860 865 870

Pro Gln Leu Leu Arg Leu Leu Ser Thr Leu Ala Glu Glu Pro Arg

871 875 880 885

Glu Gln Gln Glu Leu Glu Ala Leu Ser Gln Asp Pro Arg Arg Tyr

886 890 895 900

Glu Glu Trp Lys Trp Phe Arg Cys Pro Thr Leu Leu Glu Val Leu

901 905 910 915

Glu Gln Phe Pro Ser Val Ala Leu Pro Ala Pro Leu Leu Leu Thr
916 920 925 930
Gln Leu Pro Leu Leu Gln Pro Arg Tyr Tyr Ser Val Ser Ser Ala
931 935 940 945
Pro Ser Thr His Pro Gly Glu Ile His Leu Thr Val Ala Val Leu
946 950 955 960
Ala Tyr Arg Thr Gln Asp Gly Leu Gly Pro Leu His Tyr Gly Val
961 965 970 975
Cys Ser Thr Trp Leu Ser Gln Leu Lys Pro Gly Asp Pro Val Pro
976 980 985 990
Cys Phe Ile Arg Gly Ala Pro Ser Phe Arg Leu Pro Pro Asp Pro
991 995 1000 1005
Ser Leu Pro Cys Ile Leu Val Gly Pro Gly Thr Gly Ile Ala Pro
1006 1010 1015 1020
Phe Arg Gly Phe Trp Gln Glu Arg Leu His Asp Ile Glu Ser Lys
1021 1025 1030 1035
Gly Leu Gln Pro Thr Pro Met Thr Leu Val Phe Gly Cys Arg Cys
1036 1040 1045 1050
Ser Gln Leu Asp His Leu Tyr Arg Asp Glu Val Gln Asn Ala Gln
1051 1055 1060 1065
Gln Arg Gly Val Phe Gly Arg Val Leu Thr Ala Phe Ser Arg Glu
1066 1070 1075 1080
Pro Asp Asn Pro Lys Thr Tyr Val Gln Asp Ile Leu Arg Thr Glu
1081 1085 1090 1095
Leu Ala Ala Glu Val His Arg Val Leu Cys Leu Glu Arg Gly His

1096 1100 1105 1110

Met Phe Val Cys Gly Asp Val Thr Met Ala Thr Asn Val Leu Gln

1111 1115 1120 1125

Thr Val Gln Arg Ile Leu Ala Thr Glu Gly Asp Met Glu Leu Asp

1126 1130 1135 1140

Glu Ala Gly Asp Val Ile Gly Val Leu Arg Asp Gln Gln Arg Tyr

1141 1145 1150 1155

His Glu Asp Ile Phe Gly Leu Thr Leu Arg Thr Gln Glu Val Thr

1156 1160 1165 1170

Ser Arg Ile Arg Thr Gln Ser Phe Ser Leu Gln Glu Arg Gln Leu

1171 1175 1180 1185

Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Ser Asp Thr

1186 1190 1195 1200

Asn Ser Pro

1201 1203

The following sequences of the endothelial NO-synthase fragment is specifically contemplated as suitable antigens:

SEQ ID NO: 17

Pro Trp Ala Phe

1192 1195

SEQ ID NO: 18

Gly Ala Val Pro

1189 1192

SEQ ID NO: 19

```
                                                                  Arg
                                                                 1185
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Pro
1186            1190                1195                1200
Asp Thr Pro Gly Pro
1201            1205
```

SEQ ID NO: 20

```
                                    Ala Phe Asp Pro Pro Gly Pro
                                    11941195                1200
Asp Thr Pro Gly Pro
1201            1205
```

SEQ ID NO: 21

```
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp
1186            1190                11951196
```

SEQ ID NO: 22

```
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Pro
1186            1190                1195                1200
Asp Thr Pro Gly Pro
1201            1205
```

The activated potentiated form of each component of the combination may be prepared from initial solution by homeopathic potentization, preferably using the method of proportional concentration decrease by serial dilution of 1 part of each preceding solution (beginning with the initial solution) in 9 parts (for decimal dilution), or in 99 parts (for centesimal dilution), or in 999 parts (for millesimal dilution) of a neutral solvent, coupled with external impact. Preferably, the external impact involves multiple vertical shaking (dynamization) of each dilution. Preferably, separate containers are used for each subsequent dilution up to the required potency level, or the dilution factor. This

method is well-accepted in the homeopathic art. See, e.g. V. Schwabe "*Homeopathic medicines*", M., 1967, p. 14-29, incorporated herein by reference for the purpose stated.

For example, to prepare a 12-centesimal dilution (denoted C12), one part of the initial matrix solution of antibodies to C-terminal fragment of beta subunit of human insulin receptor with the concentration of 3.0 mg/ml is diluted in 99 parts of neutral aqueous or aqueous-alcohol solvent (preferably, 15%-ethyl alcohol) and then vertically shaken many times (10 and more) to create the 1st centesimal dilution (denoted as C1). The 2nd centesimal dilution (C2) is prepared from the 1st centesimal dilution C1. This procedure is repeated 11 times to prepare the 12th centesimal dilution C12. Thus, the 12th centesimal dilution C12 represents a solution obtained by 12 serial dilutions of one part of the initial matrix solution of antibodies to C-terminal fragment of beta subunit of human insulin-receptor with the concentration of 3.0 mg/ml in 99 parts of a neutral solvent in different containers, which is equivalent to the centesimal homeopathic dilution C12. Similar procedures with the relevant dilution factor are performed to obtain dilutions C30 and C 200.The intermediate dilutions may be tested in a desired biological model to check activity. The preferred activated potentiated forms for both antibodies comprising the combination of the invention are a mixture of C12, C30, and C200 dilutions. When using the mixture of various homeopathic dilutions (primarily centesimal) of the active substance as biologically active liquid component, each component of the composition (e.g., C12, C30, C200) is prepared separately according to the above-described procedure until the next-to-last dilution is obtained (e.g., until C11, C29, and C199 respectively), and then one part of each component is added in one container according to the mixture composition and mixed with the required quantity of the solvent (e.g. with 97 parts for centesimal dilution).

It is possible to use the active substance as mixture of various homeopathic dilutions, e.g. decimal and/or centesimal (D 20, C 30, C100 or C12, C30, C50 etc.), the efficiency of which is determined experimentally by testing the dilution in a suitable biological model, for example, in models described in the examples herein.

In course of potentiation and concentration decrease, the vertical shaking may be substituted for external exposure to ultrasound, electromagnetic field or any similar external impact procedure accepted in the homeopathic art.

Preferably, the pharmaceutical composition of the invention may be in the form of a liquid or in the solid unit dosage form. The preferred liquid form of the pharmaceutical composition is a mixture, preferably, at a 1:1 ratio of the activated potentiated form of antibodies to C-terminal fragment of beta subunit of human insulin-receptor and the activated potentiated form of antibodies to endothelial NO-synthase. The preferred liquid carrier is water or water-ethyl alcohol mixture.

The solid unit dosage form of the pharmaceutical composition of the invention may be prepared by using impregnating a solid, pharmaceutically acceptable carrier with the mixture of the activated potentiated form aqueous or aqueous-alcohol solutions of active components are mixed, primarily in 1:1 ratio and used in liquid dosage form. Alternatively, the carrier may be impregnated consecutively with each requisite dilution. Both orders of impregnation are acceptable.

Preferably, the pharmaceutical composition in the solid unit dosage form is prepared from granules of the pharmaceutically acceptable carrier which was previously saturated with the aqueous or aqueous-alcoholic dilutions of the activated potentiated form of antibodies to C-terminal fragment of beta subunit of human insulin-receptor and the activated potentiated form of antibodies to endothelial NO-synthase. The solid dosage form may be in any form known in the pharmaceutical art, including a tablet, a capsule, a lozenge, and others. As an inactive pharmaceutical ingredients one can use glucose, sucrose, maltose, amylum, isomaltose, isomalt and other mono- olygo- and polysaccharides used in manufacturing of pharmaceuticals as well as technological mixtures of the above mentioned inactive pharmaceutical ingredients with other pharmaceutically acceptable excipients, for example isomalt, crospovidone, sodium cyclamate, sodium saccharine, anhydrous citric acid etc), including lubricants, disintegrants, binders and coloring agents. The preferred carriers are lactose and isomalt. The pharmaceutical dosage form may further include standard pharmaceutical excipients, for example, microcrystalline cellulose and magnesium stearate.

To prepare the solid oral form, 100-300 μm granules of lactose are impregnated with aqueous or aqueous-alcoholic solutions of the activated potentiated form of antibodies to histamine, activated-potentiated form of antibodies to C-terminal fragment of beta subunit of human insulin-receptor and the activated potentiated form of antibodies to endothelial NO-synthase in the ratio of 1 kg of antibody solution to 5 or 10 kg of lactose (1:5 to 1:10). To effect impregnation, the lactose granules are exposed to saturation irrigation in the fluidized boiling bed in a boiling bed plant (e.g. "Hüttlin Pilotlab" by Hüttlin GmbH) with subsequent drying via heated air flow at a temperature below 40˚C. The estimated quantity of the dried granules (10 to 34 weight parts) saturated with the activated potentiated form of antibodies is placed in the mixer, and mixed with 25 to 45 weight parts of “non-saturated” pure lactose (used for the purposes of cost reduction and simplification and acceleration of the technological process without decreasing the treatment efficiency), together with 0.1 to 1 weight parts of magnesium stearate, and 3 to 10 weight parts of microcrystalline cellulose. The obtained tablet mass is uniformly mixed, and tableted by direct dry pressing (e.g., in a Korsch – XL 400 tablet press) to form 150 to 500 mg round pills, preferably, 300 mg. After tableting, 300mg pills are obtained that are saturated with aqueous-alcohol solution (3.0-6.0 mg/pill) of the combination of the activated potentiated form of antibodies to C-terminal fragment of beta subunit of human insulin-receptor and the activated potentiated form of antibodies to endothelial NO-synthase. Each component of the combination used to impregnate the carrier is in the form of a mixture of centesimal homeopathic dilutions C12, C30, and C50 or a mixture of centesimal homeopathic dilutions C12, C30 and C200.

While the invention is not limited to any specific theory, it is believed that the activated potentiated form of the antibodies described herein do not contain the molecular form of the antibody in the amount sufficient to have biological activity attributed to such molecular form. The biological activity of the combination of the invention is amply demonstrated in the appended examples.

The pharmaceutical composition of the invention may be used for administration to patients having any type of diabetes.

The said pharmaceutical composition can be used in the treatment of Diabetes Mellitus as a monotherapy of hyperglycaemia and in the complex therapy as an add-on to insulin replacement therapy; and/or with oral hypoglycemic agents such as biguanides (metformin); sulfonylureas (glybenclamide, glipizide, gliclazide, glicvidone, glimepiride); thiazolidinediones (rosiglitazone); alpha-glucosidase inhibitors (acarbose) etc; as well as add-on to accompanying therapy of Diabetes Mellitus to prevent diabetic complications.

As shown in the appended examples, the administration of the combination of the invention to such patients improves blood glucose levels.

EXAMPLES

Example 1.

The two experimental studies investigated the effects of antibodies to the C-terminal fragment to the insulin receptor β-subunit affinity purified on antigen, in ultra-low dose, obtained by super dilution of the initial matrix solution 100^{12}, 100^{30}, 100^{200} times (ULD anti-IR), antibodies to endothelial NO-synthase affinity purified on antigen, in ultra-low dose, obtained by hyper-dilution of the initial matrix solution 100^{12}, 100^{30}, 100^{200} (ULD anti-ULD anti-eNOS), as well as the combination of ultra-low doses of antibodies to the C-terminal fragment to the insulin receptor β-subunit and ultra-low dose of antibodies to endothelial NO-synthase (ULD anti-IR + ULD anti-eNOS).

According to World Health Organization (WHO) criteria, diabetes mellitus (types I and II) is characterized by an increase in the blood glucose level (hyperglycemia) and by glucose tolerance disturbance. The latter can be caused by abnormal insulin secretion and/or by decreased insulin sensitivity of peripheral tissues. The glucose-tolerance test, based on dynamic evaluation of the ability of body tissues to utilize glucose, is a sensitive method of evaluating disturbance of body issue glucose tolerance.

Study 1.

In the study, 150 male Wistar were used (weight at beginning of study 250-300 g, age 3.5-4 months). 10 rats were intact. The rest were intravenously injected with streptozotocin at the dose of 50 mg/kg (experimental model of diabetes mellitus). 72 hours after injection of streptozotocin, rats with blood plasma glucose level not less than 12 mmol/l were selected, divided into 7 groups (20 rats in each), which over 21 days were given distilled water (5 ml/kg/day, once daily intragastrically), insulin® (8 units/kg/day, subcutaneously), Rosiglitazone® (8 mg/kg/day, twice daily intragastrically), ULD anti-IR (2.5 ml/kg/day in a volume of 5 ml/kg/day, once daily intragastrically), ULD anti-IR + ULD anti-eNOS (5 ml/kg/day, once daily intragastrically), and also Rosiglitazone® and insulin® together or ULD anti-IR + ULD anti-eNOS and insulin®, according to regimes corresponding to each preparation (as described above). Intact rats received distilled water in the same volume. On days 7, 14 and 21 of injection of preparations in rats, fasting blood plasma glucose level measured with enzymatic method (glucose oxidase method) with utilization of "glucose FKD" kits (Russia).

Oral glucose tolerance test (OGTT) was performed on day 14 of the study (day 14 of administration of preparation) according to standard method (Du Vigneaud and Karr, 1925). The rats were starving at water for 18 hours. 60 min before the test they were last given test substances. Intact rats received distilled water in the same volume. Glucose was administered per os 50% w/w water glucose solution (1 g/kg of rat weight). Serum glucose of blood sample from tail vein was measured by using "Glucose FKD" kit (OOO "Pharamaceutical and clinical diagnostics, Russia, www.fkd.ru) at 0, 30, 60, 90, 120 min. Mean area under the curve (AUC) concentration of blood glucose over time was calculated.

Injection of streptozotocin led to a substantial increase in blood plasma glucose of rats in comparison with intact animals (18 mmol/l versus 3.5 mmol/l, $p<0.05$). In the ULD anti-IR group, on day 7, 14 and 21 of injection of preparation, glucose level was lower than in the control group by 22-28% on average; however, differences did not reach a statistically significant level. The combination of ULD anti-IR and anti-eNOS was more efficacious; the decrease in glucose level on days 14 and 21 of the experiment were 47% and 42%, respectively ($p<0.05$ versus control). The reference

preparation, Rosiglitazone, also lowered glucose level by day 14 and 21 of the experiment; at that, the effect reached statistical significance on day 14 of the experiment only (36%, $p<0.05$ versus control).

Insulin, injected at ½ of the effective dose (selected in the preliminary study) most effectively lowered glucose level in all observation periods (down to the level of the intact control). (Figure 1). It should be taken into account that short-acting insulin was used in the study and blood plasma glucose was measured 1 hour after its injection, which also influenced the effect of the ½ insulin dose on blood glucose level. Against this background it was not possible to fully determine what the effect of the combined use of insulin and rosiglitazone or insulin and complex ULD anti-IR + anti-eNOS is.

Glucose tolerance disturbance (reduction in glucose utilization by the body) is one of the most important indicators in diagnostic and treatment of diabetes mellitus. In intact animals, in the oral glucose tolerance test (day 14 of injection of preparations), complex preparation ULD anti-IR + ULD anti-eNOS and insulin most effectively increased glucose tolerance when administered alone. Rosiglitazone also reduced the area under concentration over time curve (increased glucose tolerance); however, its efficacy was not statistically significant versus the control group (Figure 2).

Study 2.

In the study, 36 male Goto-Kakizaki rats were used (weight at beginning of study 250-280 g, age 10-12 weeks). Rats of this line are characterized by spontaneous development of non-insulin-dependent diabetes. The animals were divided into 3 groups (12 rats in each) and received either distilled water (5 ml/kg, once daily intragastrically), or ULD anti-IR (2.5 ml/kg once daily intragastrically), or ULD anti-IR + ULD anti-eNOS (5 ml/kg, once daily intragastrically) for 28 days. Blood plasma glucose level was measured with the help of a glucose analyzer (Beckman, Fullerton, California, USA) before beginning injection of preparations and on day 4, 8, 12, 16, 20, 24, 28 of injection of preparations. On day 28, a glucose tolerance test was carried out (glucose p.o., 1 g/kg).

Injection of ULD anti-IR led to a significant ($p<0.05$) drop in blood plasma glucose level of rats; however, the use of complex ULD anti-IR + ULD anti-eNOS was more efficacious ($p<0.001$ versus control) (Figure 3).

The results were confirmed by glucose tolerance test data carried out on day 28 of injection of preparations (Figure 4). Injection of ULD anti-IR led to an increase in glucose tolerance (statistically insignificant drop by 44% AUC versus control). At the same time, the reduction in this parameter (AUC) caused by injection of complex ULD anti-IR + ULD anti-eNOS was 62% and it was statistically significant versus control ($p<0.05$).

Example 2.

A clinical study of combination of ultra-low doses of antibodies to the beta subunit C-terminal fragment of the insulin receptor (ULD anti-IR) and ultra-low doses of antibodies to endothelial NO-synthase (ULD anti-eNOS), each in the form of water-alcohol mixture of homeopathic dilutions C12, C30, and C200 impregnated onto isomalt was carried in humans.

An open-label noncomparative study of the efficacy and safety of ULD anti-IR + ULD anti-eNOS in patients with type 1 diabetes mellitus (DM) included patients with a diagnosis of DM type 1 of mild to moderate severity without signs of serious macro- and microvascular pathology. After obtaining the patient's voluntary informed consent for participation in the clinical trial, an initial survey was conducted for the purpose of establishing whether the patient met inclusion/exclusion criteria. A 2-week "wash-out period" was provided before the beginning of the study, during which an examination of patients was carried out (complaints, fasting glycemia, glycated hemoglobin, daily glycemic profile and lipoproteinogram as well and efficacy and safety of current treatment were assessed). In a 12-week study, the key endpoints were measured in the "wash-out" weeks, then at weeks 6 and 12 of the treatment. In 4 patients, during the "wash-out" period and at the end of the study, continuous monitoring of glycemic level had been carried out with the help of the CGMS system. The continuous glucose monitoring system (CGMS) makes it possible to control the glucose level over three

days. The test results show how glucose level changes over 3 days, depending on insulin therapy and life style. This data helps to distinguish periods of high or low glucose level depending on diet, medications intake or physical load. The system in graphic form shows minimum glucose level of 2.2 mmol/L, maximum values up to 22.2 mmol/L, and also mean daily blood glucose level.

Patients with DM type 1, mild to moderate severity, at the decompensation stage, received standard insulin therapy before inclusion and during the study:

1. Long-acting insulins (Protaphane®, Lantus®) in average doses from 12 to 26 U/day.
2. Short-acting insulins (Apidra®, Novorapid®, Aktropid®) in the average doses:
   - morning 8-10 U/day
   - lunch 8-12 U/day
   - supper 8-13 U/day.

After confirming the patient's ability to participate, the patient was included in the study and, as an add-onn to standard therapy of DM type 1 received the ULD anti-IR + ULD anti-eNOS preparation; the administration regimen depended on the degree of severity and compensation of the DM type 1. Patients included in the study received therapy by ULD anti-IR + ULD anti-eNOS preparation in different dosages:

1. Four patients – 1 tablet 4 times a day at 8:00 AM, 12:00 PM, 6:00 PM, 10:00 PM.
2. Two patients – 1 tablet 2 times a day at 8:00 AM, 6:00 PM.

On weeks 3 and 8, the daily glycemic profile was also controlled (eight-point measurement) and patients were contacted by phone (telephone "visits"). Clinical examinations were done every week. As a total, the patients had been observed for 14 weeks.

Six patients were included in the study, five of whom completed according to the study protocol. Evaluation of glycemia was carried out by eight-point daily glucose profile at a baseline and after 3, 6 and 12 weeks of treatment. The level of glycated hemoglobin was determined at a baseline and after 12 weeks of therapy.

All DM type 1 patients included in the study noted that daily glycemia tended to fall after 6-week therapy with the study drugs. According to eight-point daily glucose profile, an average drop in glycemia of 20% was recorded in patients with DM type 1. After 12 weeks of therapy, glycated hemoglobin was on average 10-15% lower in comparison with the baseline value.

According to the results of continuous glucose monitoring with the CGMS system in all patients, 3-month therapy by ULD anti-IR + ULD anti-eNOS resulted in a reduction in mean daily glycemia and decreased oscillations of minimum and maximum glycemia of 15-20% of the baseline.

In patient No. 103 with DM type 1 at a decompensation stage, a significant drop in daily glycemia of 48% was unexpectedly observed (1 week – 8.0 mmol/L, 12 weeks – 4.8 mmol/L), which required a correction of insulin therapy (reduction in daily dose of short-acting insulin down to 8 U/d). The dynamics of the mean blood glucose level and glycated hemoglobin is shown in Fig. 5.

In the course of the study, no adverse events including serious adverse one were recorded, which evidences the safety of the preparation.

Example 3.

A clinical study of combination of ultra-low doses of antibodies to the beta subunit C-terminal fragment of the insulin receptor (ULD anti-IR) and ultra-low doses of antibodies to endothelial NO-synthase (ULD anti-eNOS), each in the form of water-alcohol mixture of homeopathic dilutions C12, C30, and C200 impregnated onto isomalt was carried in humans.

An open-label noncomparative study of the efficacy and safety of ULD anti-IR + ULD anti-eNOS in patients with type 2 diabetes mellitus (DM) included patients with a diagnosis of DM type 2 of mild to moderate severity without signs of serious macro- and microvascular pathology, who received average therapeutic doses of Metformin. After obtaining the patient's voluntary informed consent for participation in the clinical trial, an initial survey was conducted for the purpose of establishing whether the patient met inclusion/exclusion criteria. Upon confirmation of the possibility of participating in the

study, the patient received 1 tablet of Subbetta 4 times a day in addition to type 2 DM standard therapy. A 2-week “wash-out period” was provided before the beginning of the study, during which an examination of patients was carried out (complaints, fasting glycemia, glycated hemoglobin, daily glycemic profile and lipoproteinogram, insulin resistance index indicators (HOMA- IR) as well and efficacy and safety of current treatment were assessed). In a 12-week study, the key endpoints were measured in the “wash-out” weeks, then at weeks 6 and 12 of the treatment. In 4 patients, during the “wash-out” period and at the end of the study, continuous monitoring of glycemic level had been carried out with the help of the CGMS system. On weeks 3 and 8, eight-point glycemic profile was additionally controlled and telephone “visits” were conducted. Clinical condition was checked every week. On the whole, the patient was observed over 14 weeks.

Eleven patients with type 2 DM type 2 at decompensation stage were included in the study. One patient voluntary dropped out of the study. The remaining patients continue the treatment. In DM type 2 patients, according to eight-point daily profile data, an average drop in glycemia of 20% was registered by the week 6. On week 12, an average drop in glycated hemoglobin of 15-19% of the baseline value was noted.

In all patients in the course of 12 weeks, blood test parameters (erythrocytes, hemoglobin, leukocytes, thrombocytes, leukocyte formula, ESR), lipoproteinogram, EKG, assay of hepatic function (ALT, AST, bilirubin and its fractions) remained within normal limits. Insulin resistance, determined by HOMA-IR test, dropped on average by 17-19% of the baseline value.

In 12-week course of the study, no adverse events including serious adverse one were recorded, which evidences the safety of the preparation. No abnormalities in liver functional activity were also revealed.

The dynamics of the mean blood glucose level and glycated hemoglobin are shown in Fig. 6.

Example 4.

A patient X. (male, 74 years old) diagnosed with Diabetes type II has been receiving Maninil (Glibenclamide, Berlin – Chemie) at a dose of 5 mg twice a day. A deep necrotic foot ulcer at the calcaneal bone was appeared 3 years ago despite the treatment he was given. The patient was twice hospitalized on a surgical ward; however, the treatment did not result in significant improvement. A claimed pharmaceutical composition, a tablet of 250 mg, comprising activated potentiated form (ultra-low doses) of antibodies to C-terminal of insulin receptor beta subunit (Ab RI) and endothelial NO synthase (Ab NOS) impregnated on isomalt as a mixture of water-ethanol homeopathic dilutions C12, C30, C200 (Ab RI + Ab NOS) was added to the Maninil therapy. As a result of one-month treatment the dose of Maniil® was reduced to 5 mg daily (one tablet before sleep). Glucose blood level dropped to normal values (from 8-10 mmol/L to 5-6 mmol/L). The given therapy turned back development of the foot ulcer. The ulcer cleared of necrotic masses and cuticularised. On examination the ulcer has gone, there is round white area (3.5 cm in diameter) of peeling skin at the calcaneal bone.

What is claimed is:

1. A pharmaceutical composition comprising a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO synthase.

2. A pharmaceutical composition comprising a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

3. A pharmaceutical composition comprising a) an activated-potentiated form of an antibody to human insulin receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, wherein the insulin receptor molecule consist of one alpha subunit and one beta subunit.

4. A pharmaceutical composition comprising pharmaceutically acceptable solid carrier, and a) an activated-potentiated form of an antibody to a C-terminal fragment of the beta subunit of human insulin receptor in the form of a mixture of C12, C30, and C200 homeopathic dilutions impregnated onto said solid carrier, and b) activated-potentiated form of an antibody to endothelial NO-synthase in the form of mixture of C12, C30, and C200 homeopathic dilutions impregnated onto said solid carrier.

5. The pharmaceutical composition of claims 1, 2, 3, or 4, wherein said antibody to human insulin receptor is monoclonal, polyclonal or natural antibody.

6. The pharmaceutical composition of claim 5, wherein said antibody to human insulin receptor is a polyclonal antibody.

7. The pharmaceutical composition of claim 6, the activated-potentiated form of an antibody to a human insulin receptor is prepared by successive centesimal dilutions coupled with shaking of every dilution.

8. The pharmaceutical composition of claims 1, 2, 3, or 4, wherein said antibody to endothelial NO-synthase is monoclonal, polyclonal or natural antibody.

9. The pharmaceutical composition of claim 8, wherein said antibody to endothelial NO-synthase is a polyclonal antibody.

10. The pharmaceutical composition of claim 9, the activated-potentiated form of an antibody to endothelial NO-synthase is prepared by successive centesimal dilutions coupled with shaking of every dilution.

11. The pharmaceutical composition of claim 1, wherein said human insulin receptor consists of sequence selected from group consisting of in SEQ ID No: 1, SEQ ID No: 2, SEQ ID No: 3, SEQ ID No: 4, SEQ ID No: 5, SEQ ID No: 6, SEQ ID No: 7, SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ ID No: 14.

12. The pharmaceutical composition of claim 1, wherein said endothelial NO synthase consists of sequence provided in SEQ. ID No. 15, SEQ ID No: 16, SEQ ID No: 17, SEQ ID No: 18, SEQ ID No: 19, SEQ ID No: 20, SEQ ID No: 21, SEQ ID No: 22.

13. A method of treating Type I diabetes in a human patient, said method comprising administering the pharmaceutical composition of claims 1, 2, 3, or 4 to said patient.

14. The method of claim 13, wherein said pharmaceutical composition is administered to a patient in one solid dosage form per administration.

15. The method of claim 13, wherein said dosage form is a tablet.

16. The method of claim 15, wherein said tablet is obtained by direct compression.

17. The method of claim 15, wherein said tablet is administered from once daily to four times daily.

18. The method of claim 15, wherein said tablet is administered twice daily.

19. The method of claim 15, wherein said tablet is administered four times daily.

20. A method of treating Type II diabetes in a human patient, said method comprising administering the pharmaceutical composition of claims 1, 2, 3, or 4 to said patient.

21. The method of claim 20, wherein said pharmaceutical composition is administered to a patient in one solid dosage form per administration.

22. The method of claim 21, wherein said dosage form is a tablet.

23. The method of claim 22, wherein said tablet is obtained by direct compression.

24. The method of claim 22, wherein said tablet is administered from once daily to four times daily.

25. The method of claim 15, wherein said tablet is administered four times daily.

26. A method of reducing blood glucose level in a mammal, said method comprising administering the pharmaceutical composition of claims 1, 2, 3, or 4 to said mammal.

27. The method of claim 26, wherein said mammal is a human.

28. The method of claim 27, wherein said pharmaceutical composition is administered to a patient as one or two unit dosage forms.

29. The method of claim 28, wherein said dosage form(s) is/are administered from once daily to four times daily.

30. The method of claim 29, wherein said dosage form(s) is administered thrice daily.

31. A method of treating insulin resistance, said method comprising administering the pharmaceutical composition of claims 1, 2, 3, or 4 to saidmammal.

32. The method of claim 31, wherein said mammal is a human.

33. The method of claim 32, wherein said pharmaceutical composition is administered to a patient as one or two unit dosage forms.

34. The method of claim 33, wherein said dosage form(s) is/are administered from once daily to four times daily.

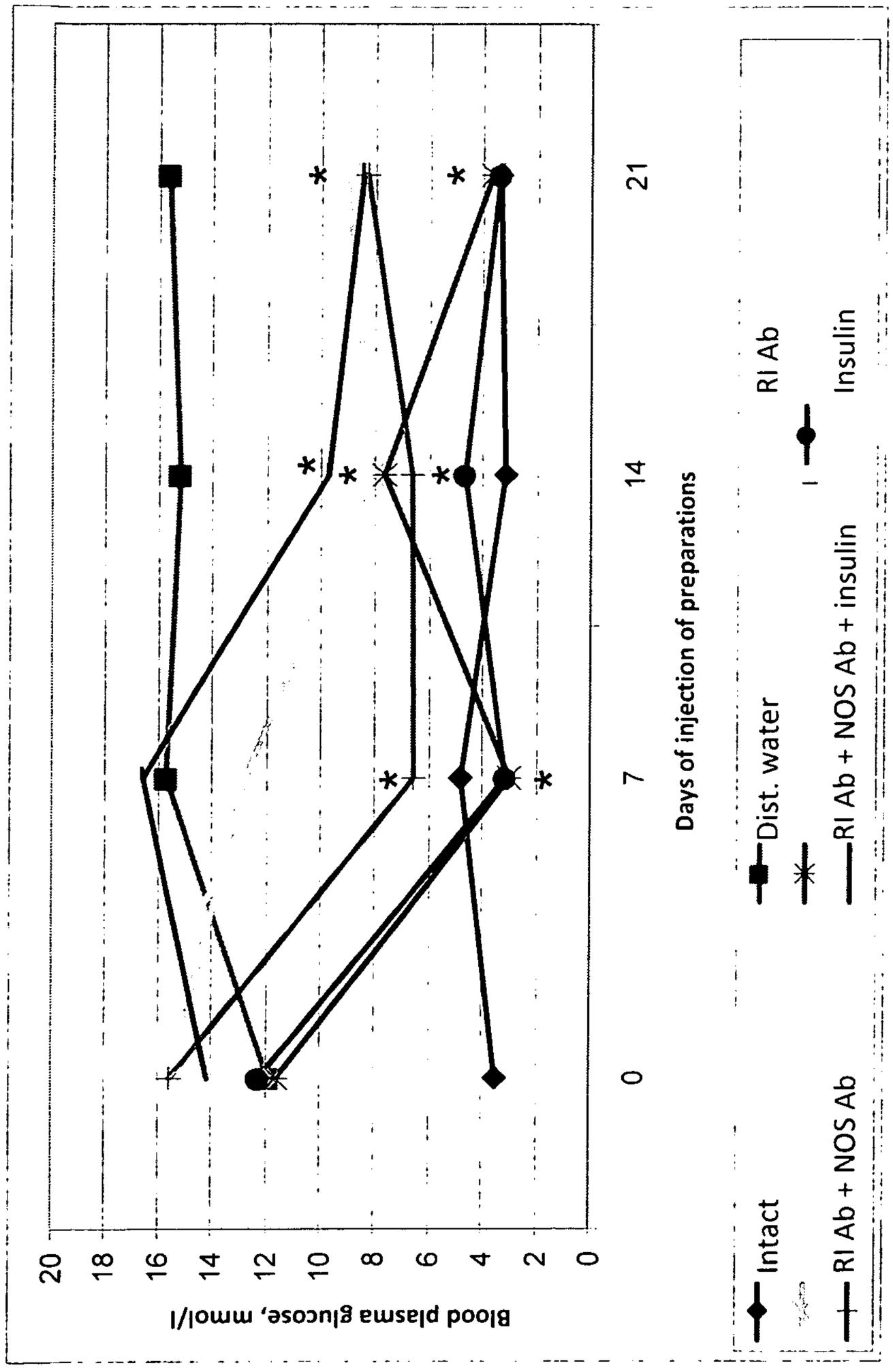
35. The method of claim 34, wherein said dosage form(s) is administered thrice daily.

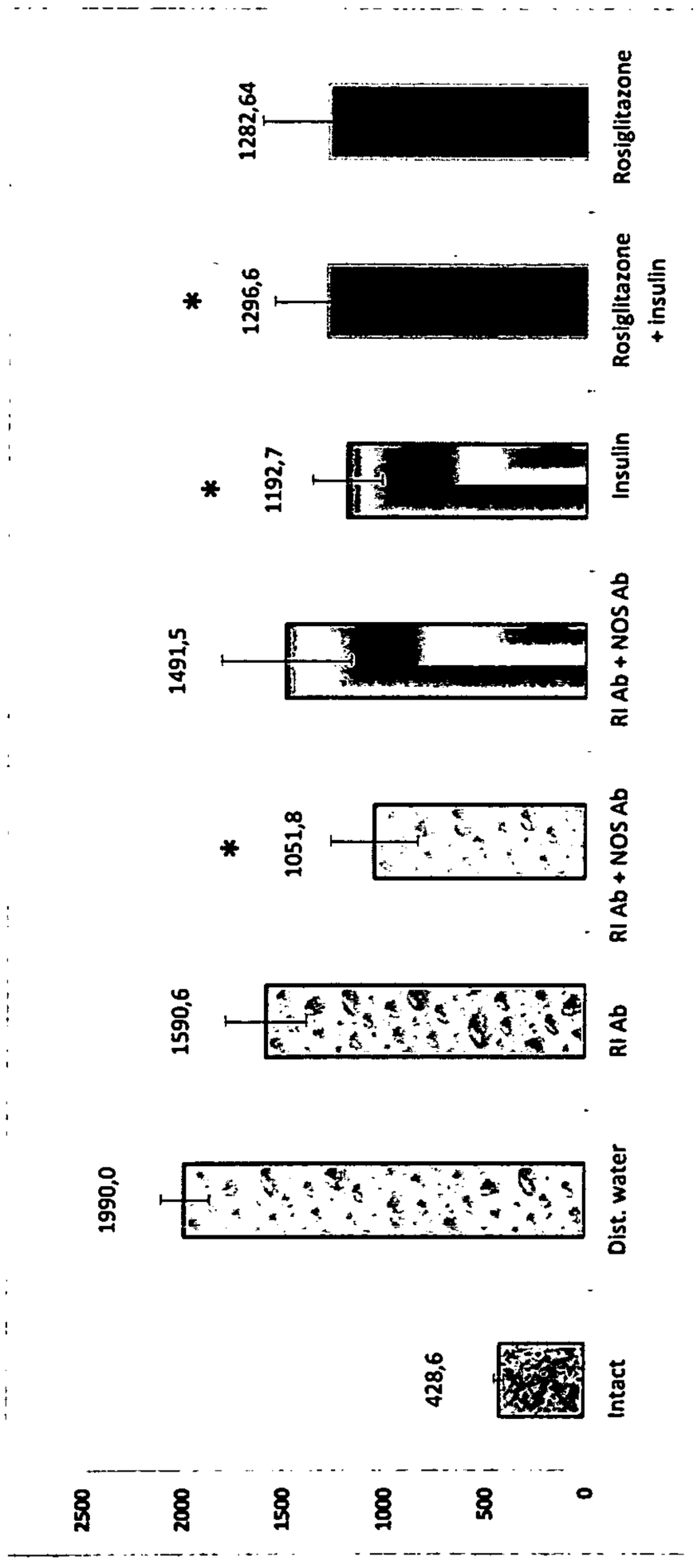
36. The method of claim 13, said method further comprising administering insulin or other additional pharmaceutical agents suitable for treating Type I diabetes.

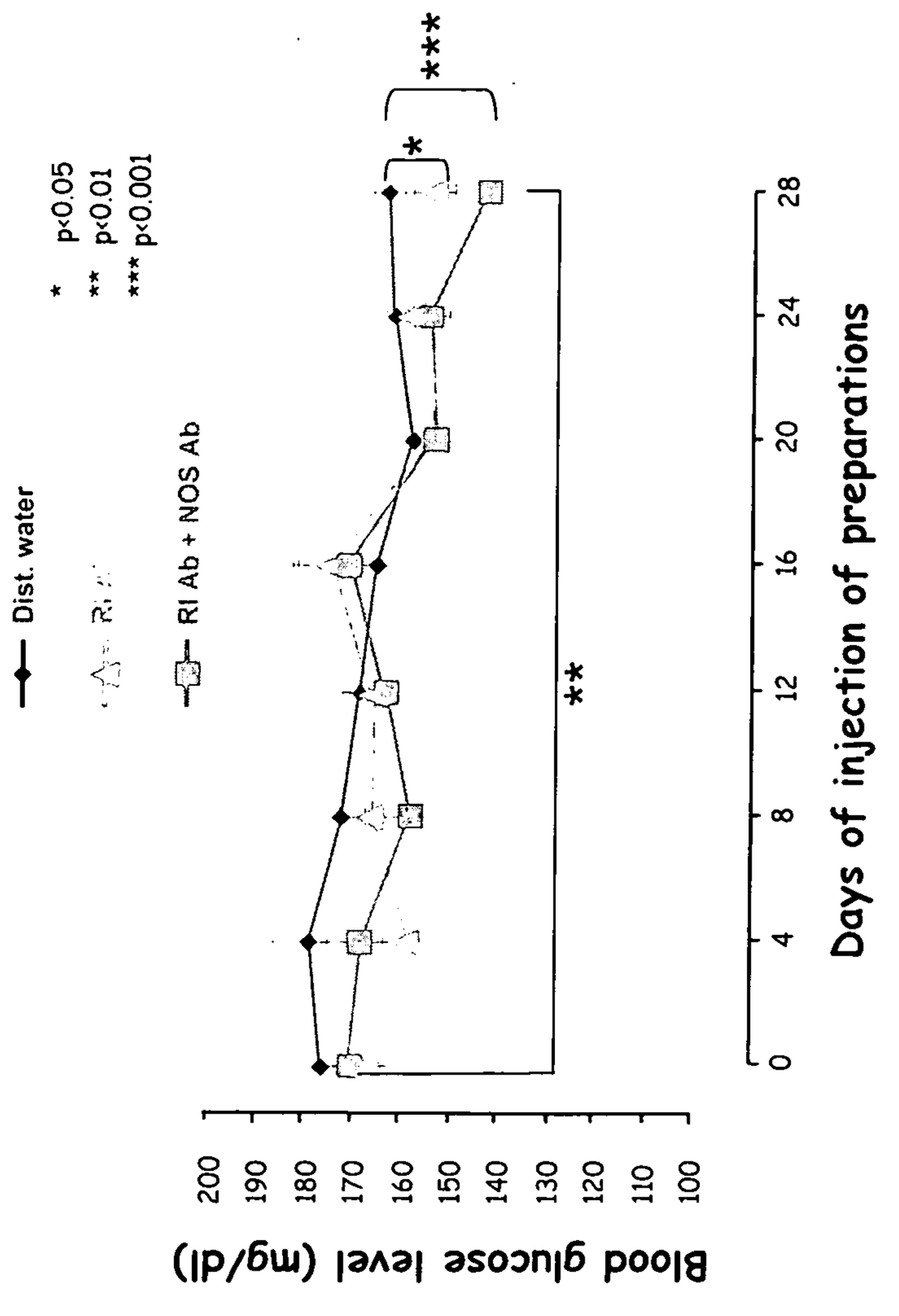
37. The method of claim 20, said method further comprising administering additional pharmaceutical agents suitable for treating Type II diabetes.

38. A pharmaceutical composition for use in treating a patient suffering from diabetes or other metabolic disorder, said composition having been obtained by providing a) an activated-potentiated form of an antibody to human insulin receptor and b) an activated-potentiated form of an antibody to endothelial NO-synthase, each prepared by consecutive repeated dilution and multiple shaking of each obtained solution in accordance with homeopathic technology, and then either combining the potentiated solutions by mixing them, or, alternatively, impregnating a carrier mass with said combined solution or with the solutions separately.

39. The pharmaceutical composition of claim 38, wherein said activated-potentiated form of an antibody to human insulin receptor is an activated-potentiated form of an antibody to a C-terminal fragment of human insulin receptor.


Blood plasma glucose, mmol/l
0
2
4
6
8
10
12
14
16
18
20
0
7
14
21
Days of injection of preparations
Intact
Dist. water
RI Ab + NOS Ab
RI Ab + NOS Ab + insulin
RI Ab
Insulin
* differencesare statistically significant relative to control (distilled water), p<0.05


2500
2000
1500
1000
500
0
1990,0
1590,6
1051,8
1491,5
428,6
1192,7
1296,6
1282,64
Dist. water
RI Ab
RI Ab + NOS Ab
RI Ab + NOS Ab
Intact
Insulin
Rosiglitazone + insulin
Rosiglitazone
*
*
* differences are statistically significant in reference to control (distilled water), p<0.05


Dist. water
RI Ab
RI Ab + NOS Ab
* p<0.05
** p<0.01
*** p<0.001
Blood glucose level (mg/dl)
200
190
180
170
160
150
140
130
120
110
100
0
4
8
12
16
20
24
28
Days of injection of preparations
*
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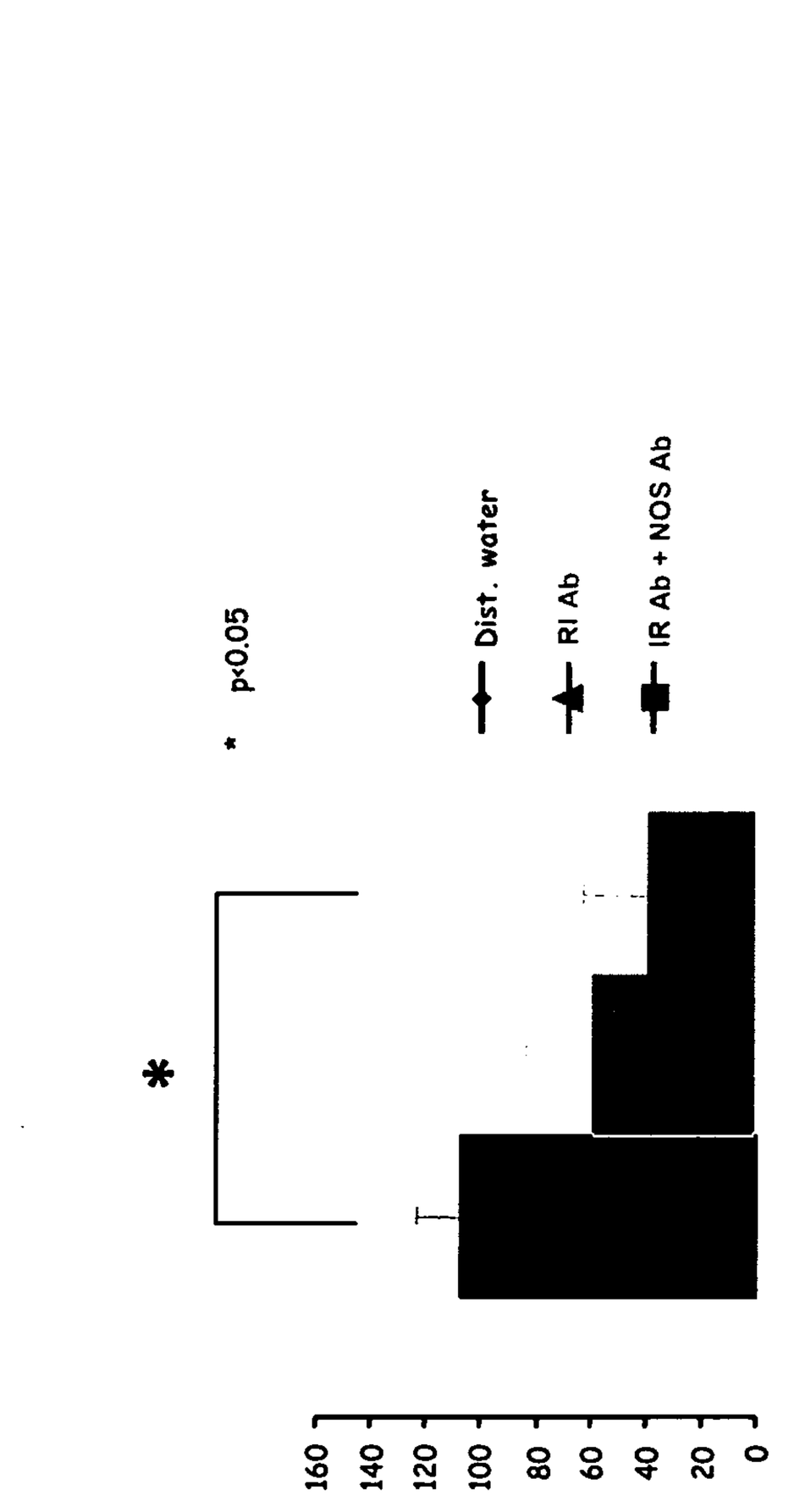
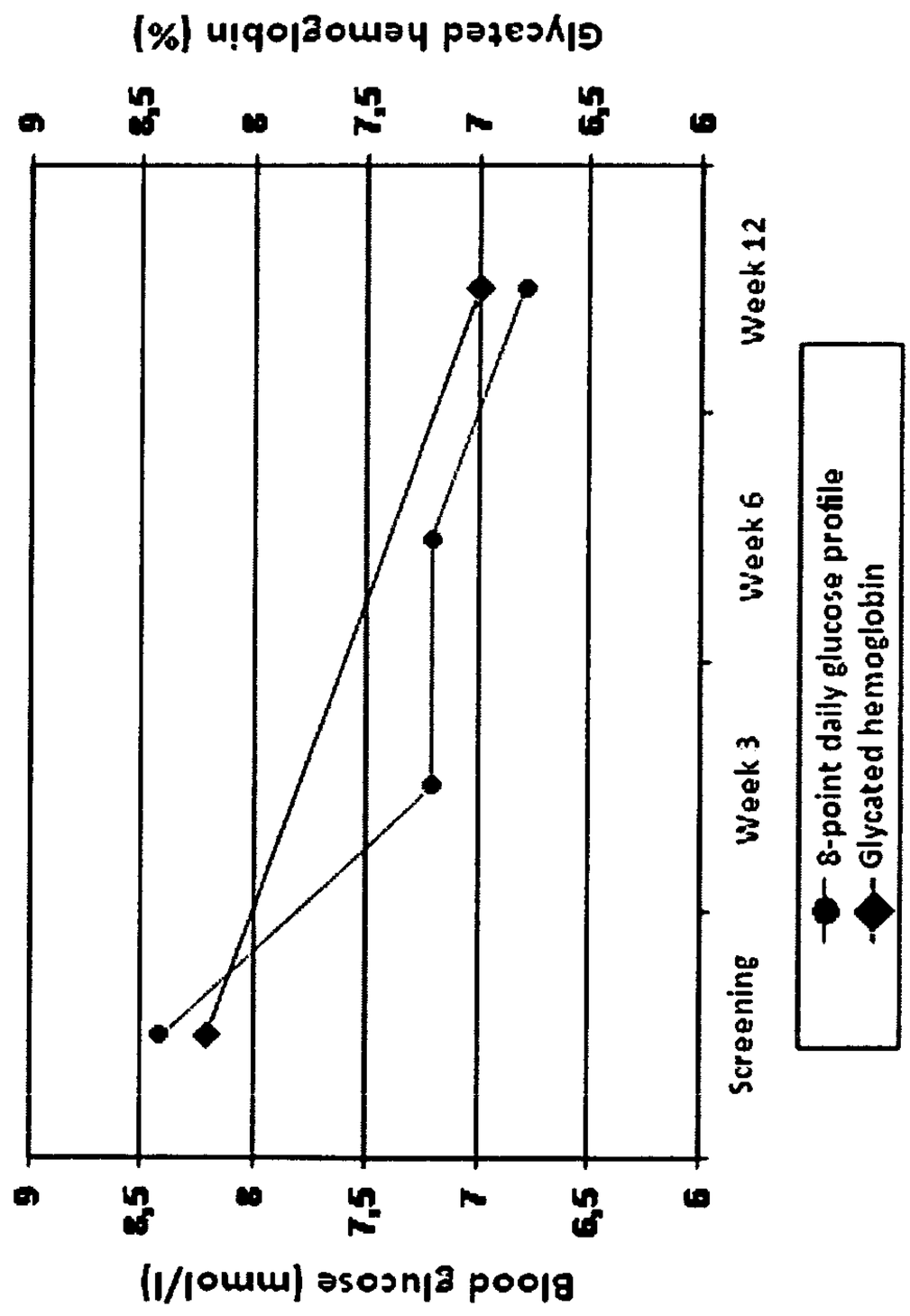
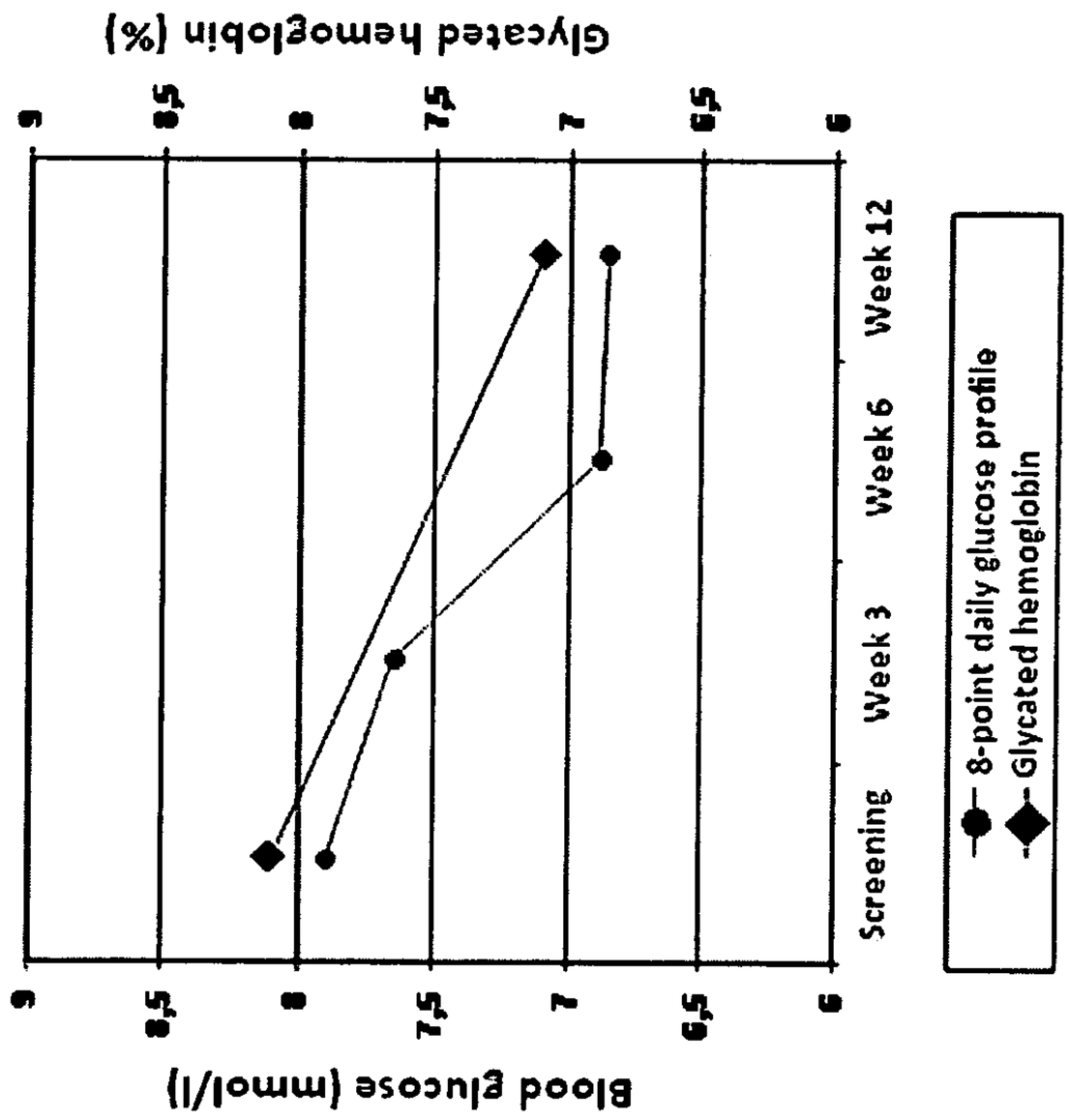

Dist. water
RI Ab
IR Ab + NOS Ab
p<0.05
*
160
140
120
100
80
60
40
20
0


Glycated hemoglobin (%)
9
8,5
8
7,5
7
6,5
6
Week 12
Screening
Week 3
Week 6
8-point daily glucose profile
Glycated hemoglobin
Blood glucose (mmol/l)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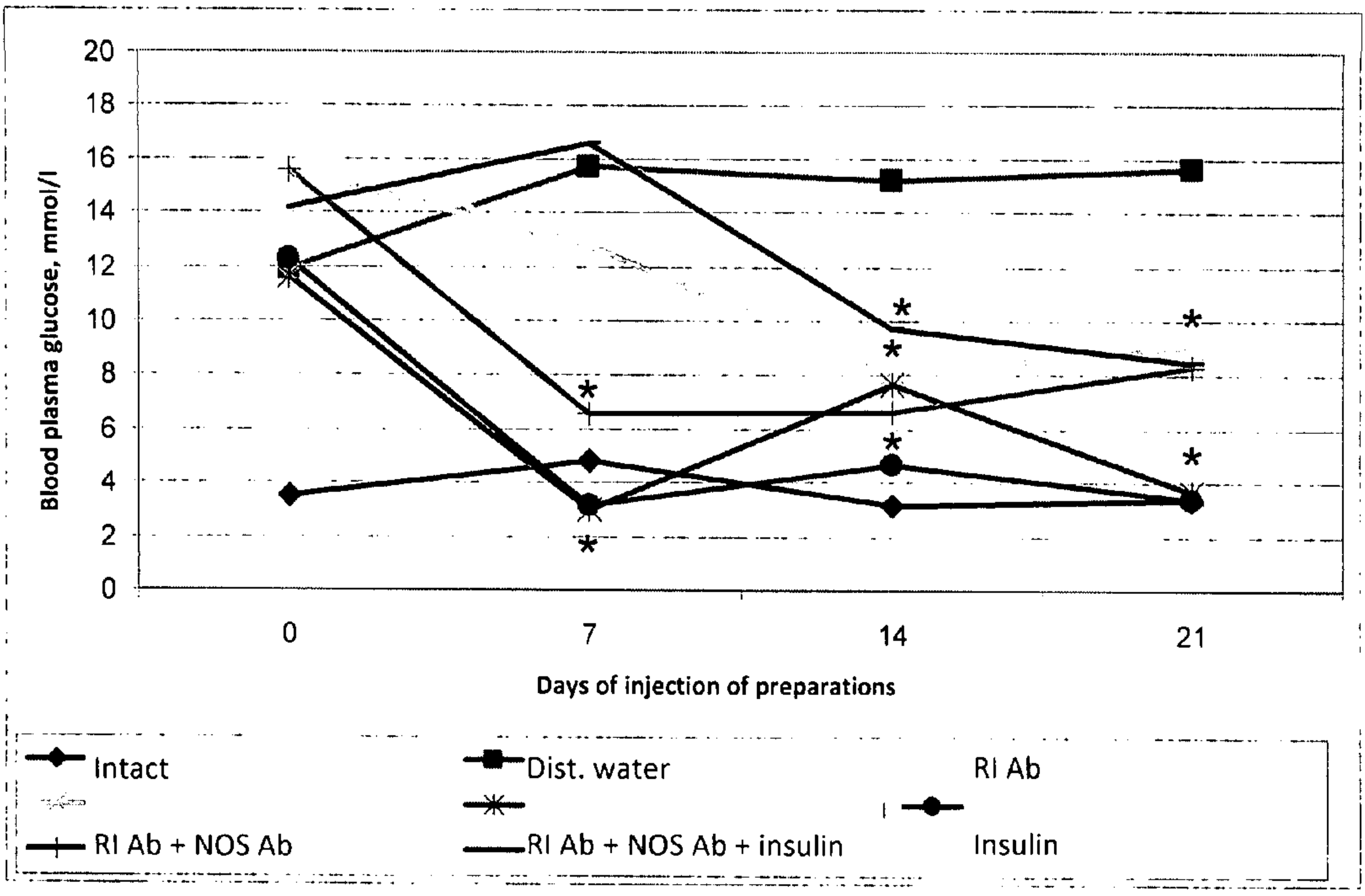
Glycated hemoglobin
Blood glucose (mmol/l)



* differencesare statistically significant relative to control (distilled water), $p<0.05$