A PHARMACEUTICAL COMBINATION COMPRISING EITHER (S)-2-ETHOXY-3-[4-(2-{4-METHANESULFONYLOXYPHENYL}ETHOXY)PHENYL]PROPANOIC ACID or 3-{4-[2-(4-TERT-BUTOXYCARBONYLAMINOPHENYL)ETHOXY]PHENYL}-(S)-2-ETHOXY PROPANOIC ACID AND INSULIN

The present invention relates to the use of a combination of certain propanoic acid derivatives which act as peroxisome proliferator activated receptor (PPAR) agonists and insulin, which is useful in the treatment of states of insulin resistance, including type 2 diabetes mellitus and associated conditions. Novel pharmaceutical combination compositions are also defined, together with methods of their production.

Traditionally, therapeutic intervention in type 2 diabetes has had a 'glucocentric focus' dominated by the use of insulin secretogogues e.g. the sulfonylureas and the measurement of glycated haemoglobin (HbA1c) or fasting blood sugar level (FPG) as indices of diabetic control. In the USA, patients with type 2 diabetes are usually treated with diet and, when needed, a sulfonylurea compound. However, it is estimated that approximately 30% of patients initially treated with sulfonylurea agents have a poor response and in the remaining 70%, the subsequent failure rate is approximately 4-5% per annum. Other estimates put failure rates higher with few patients responding after 10 years therapy. A treatment-related increase in body weight is also experienced with these agents. Prior to the FDA approval of metformin in 1995, the only therapeutic option for type 2 diabetic patients, in whom sulfonylurea therapy had failed, was insulin.

Despite the introduction of newer agents both the incidence and prevalence of type 2 diabetes continues to increase on a global basis. Approximately 16 million people in the USA have diabetes mellitus, 90-95% of whom have type 2 disease. This represents an enormous healthcare burden; estimated in 1998 to be some $98 billion per annum in direct and indirect healthcare costs. Recently, both the ADA and WHO have revised guidelines for the diagnosis of diabetes and classified diabetes more according to aetiology. The threshold for diagnosis (FPG > 126mg/dl) has been lowered and the term 'type 2' is now used to describe mature onset diabetics. After the ADA implemented these new criteria in 1997, the prevalence of the type 2 disease sector increased by nearly 6 million people in the seven major pharmaceutical markets (France, Germany, Italy, Japan, Spain, UK and USA).

Apart from often mild acute symptoms, type 2 diabetics are also at a considerable risk of developing long term complications of the disease. These include a 4-5 fold higher risk, (compared with non-diabetics), of developing macrovascular disease including CHD and PVD and microvascular complications including retinopathy, nephropathy and neuropathy. In many individuals, overt type 2 diabetes is preceded by a period of reduced insulin sensitivity (insulin resistance), accompanied by a cluster of other cardiovascular risk factors, collectively termed as insulin resistance syndrome (IRS).

It has been estimated that approximately 80% of type 2 diabetics are obese and other co-morbidities of the IRS include: dyslipidemia, hyperinsulinemia, raised arterial blood pressure, uricemia and a reduced fibrinolysis. Given the increased global prevalence and incidence of type 2 diabetes and the very high costs of treating the long term complications of the disease there is tremendous interest in the development of agents that delay or prevent the onset of type 2 diabetes and in those that reduce the risk of cardiovascular complications associated with IRS. These activities have lead to the introduction of the thiazolidinedione (TZD) class of insulin sensitisers that improved the dyslipidemia and thus restored the insulin sensitivity leading to improved glycemic control and lower HbA1c levels.

Although the complex interplay between lipids and carbohydrates as metabolic fuels has been recognised for many decades it is only recently, that researchers and clinicians have begun to focus on the importance of dyslipidemia seen in type 2 diabetes. Much has been made of the relative sensitivities of muscle, liver and adipose tissues to insulin and a case for the primacy of insulin resistance in adipose tissue leading to the IRS has been debated. A typical dyslipidemic atherogenic lipoprotein phenotype (referred to as type B) is seen in IRS including frequently in type 2 diabetics, characterised by a modestly raised LDL-C, a more significant increase in VLDL-TG and reduced HDL. Apparently, changes in the physicochemical properties of VLDL-TG particles result in slower plasma clearance rates and in the generation of small dense LDL particles. The latter permeate the vascular endothelium more readily and are more prone to oxidation and glycation and are considered to play a critical role in atherogenesis in large vessels. Although more difficult to measure, improved free fatty acid (IFFA) flux is increasingly considered to play an

important role in the IRS affecting metabolic events in muscle, liver, adipose tissue and pancreas.

The first generation TZDs e.g. troglitazone, pioglitazone, rosiglitazone were in clinical development before the putative mechanism of action was discovered and published in 1995 (PPARγ activation). It is clear from experience with these first generation agents that it is difficult to predict from animal pharmacology the safety and efficacy profile these agents will have in the clinic. Thus, knowledge of the putative mechanism of action of this class coupled with concerns regarding safety, offers the opportunity to identify non-TZD activators of PPAR for the treatment of type 2 diabetes and is the subject of this invention. Furthermore, we recognise that agents with a dual action at both α and γ PPAR may have additional benefits in reducing diabetic co-morbidities, particularly raised triglycerides. Such agents may be useful in the treatment of type 2 diabetes, the IRS, dyslipidemia and in reducing risk of cardiovascular disease.

Two compounds which have both PPARα and PPARγ agonistic activity are, (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl] propanoic acid and 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and any solvates of either thereof. We believe these compounds may synergistic properties when used in combination therapy with insulin.

Specific synergistic effects will be in a more efficient reduction in fasting glucose levels and HbA1c levels in the plasma and an overall positive effect on underlying dyslipidemia. By the use of the term synergistic we mean that more than an additive effect is produced by the drug combination in either efficacy or reduction in side effects. It will be appreciated that as a consequence of synergy lower dosages of one or both active agents may be used when used in combination.

Therefore we present as a feature of the invention a pharmaceutical combination comprising either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-

ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and any solvates of either thereof and insulin.

Any biologically active form or derivative of insulin may be used in the present invention. For example bovine, porcine, or biosynthetic or semisynthetic human insulin, or a biologically active derivative of human insulin ("modified insulin"), for example having certain amino acid substitutions as taught by Brange et al in "Diabetes Care" 13:923, 1990, may be used. Modified insulins are developed in order to improve various properties, for example to improve stability or give an improved pharmokinetic profile (i.e. improved profile of absorption through the epithelial membranes). The insulin may be given by injection or by inhalation for example by using the formulations described in WO95/00127, WO95/00128, WO96/19197, WO 96/19207 and WO 96/19198 which are incorporated herein by reference.

It will be apparent that the combination of the invention may be used alongside other additional existing therapies for the treatment of type 2 diabetes and its associated complications, these include oral antihyperglycemics (these are divided into three classes of drug -. biguanides, prandial glucose regulators and alpha-glucosidase inhibitors). An example of a biguanide is metformin. Examples of an alpha-glucosidase inhibitors are acarbose, voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide. In addition the combination of the invention may be used in conjunction with another PPAR modulating agent. PPAR modulating agents include but are not limited to thiazolidine-2,4-diones for example troglitazone, ciglitazone, rosiglitazone and pioglitazone. In addition the combination of the invention may be used in combination with a sulfonylurea for example one or more of the following: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcylamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. Therefore the present invention includes administration of a combination of the present invention in conjunction with one, two or more existing therapies described in this paragraph. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those

known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination.

Accordingly, further independent aspects of the present invention include the following:

(1) a pharmaceutical combination comprising (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or a pharmaceutically-acceptable salt thereof or solvates of either and insulin;

(2) a pharmaceutical combination comprising or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid or a pharmaceutically-acceptable salt thereof or solvates of either and insulin.

The 'pharmaceutical combination' may be achieved by dosing each component drug of the combination to the patient separately in individual dosage forms administered together or sequentially. Alternatively the 'pharmaceutical combination' may be together in the same unit dosage form.

Therefore, as a further aspect of the invention we represent a pharmaceutical composition comprising a pharmaceutical combination as described hereinabove together with a pharmaceutically acceptable carrier and/or diluent.

As used hereafter the term propionic acid means either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid or a pharmaceutically-acceptable salt thereof or solvates of either.

The compositions of the propionic acid may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by

inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the propionic acid may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with

partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent

compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The size of the dose for therapeutic or prophylactic purposes of the pharmaceutical combinations will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

For guidance it is suggested that a dose of 0.5 to 25 mg per day , preferably 1 to 10 mg per day, for example 1mg, 2 mg, 3mg, 4mg or 5mg, is used for (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and any solvates of either thereof . Insulin is administered in U, and the dose can vary between 10-500, preferably 10-200U/d and more preferably at least 20 U/d.

In particular, the pharmaceutical combinations and compositions containing them will be used in the treatment of diabetes. Thus in yet a further aspect, the invention provides a method of treating or preventing diabetes which comprises administering to a patient in need thereof an effective amount of a pharmaceutical combination as defined above. The invention provides a method of treating insulin resistance syndrome which comprises administering to a patient in need thereof an effective amount of a pharmaceutical combination as defined above.

A further aspect of the present invention relates to a kit of parts comprising:

(i) a vessel containing either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-

butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and

(ii) a vessel containing insulin

and instructions for the sequential, separate or simultaneous administration of one of the propanoic acids and insulin to a patient for which such administration is necessary or advantageous.

Another aspect of the invention relates to a kit of parts comprising:

(i) a pharmaceutical formulation containing either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and

(ii) a pharmaceutical formulation containing insulin, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;

wherein the propanoic acids and the insulin are each provided in a form that is suitable for administration in conjunction with the other.

By "administration in conjunction with", we include that respective formulations comprising either propanoic acid and the sulfonylurea are administered, simultaneously, separately or sequentially, over the course of treatment of the relevant condition, which condition may be acute or chronic. Particularly, the term includes that the two formulations are administered (optionally repeatedly) sufficiently closely in time, for there to be a beneficial effect for the patient, that is greater, over the course of the treatment of the relevant condition, than if either of the two formulations are administered (optionally repeatedly) alone, in the absence of the other formulation, over the same course of treatment. Preferably the two formulations are administered simultaneously or sequentially, for example in the range of 15 minutes to 12 hours apart, preferably in the range 1 to 8 hours apart.

There is further provided:

(1) a pharmaceutical formulation including either (S)-2-ethoxy-3-[4-(2-{4-methane-sulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonyl-aminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and insulin, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier (which formulation is hereinafter referred to as a "combined preparation"); and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including either (S)-2-ethoxy-3-[4-(2-{4-methane-sulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonyl-aminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including insulin in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

According to a further aspect of the invention, there is provided a method of making a kit of parts as defined above, which method comprises bringing a component (a), as defined above, into association with a component (b), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

By bringing the two components "into association with" each other, we include that components (a) and (b) of the kit of parts may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or

(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Thus, there is further provided a kit of parts comprising:

(I) one of components (a) and (b) as defined herein; together with

(II) instructions to use that component in conjunction with the other of the two components.

The kits of parts described herein may comprise more than one formulation including either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof, and/or more than one formulation including an appropriate quantity/dose of insulin (1) in order to provide for repeat dosing. If more than one formulation (comprising either active compound) is present, such formulations may be the same, or may be different in terms of the dose of either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof or insulin, chemical composition and/or physical form.

Specifically claimed herein are specific fixed dose combinations where any dose stated for a test compound is combined with any dose stated of insulin, including the doses stated as limits for the ranges described earlier.

The invention will now be particularly described by way of example. A test compound as used hereafter means either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)-phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid.

The advantages of the present invention are demonstrable by administering a) control b) a test compound c) insulin and d) a combination of a test compound and insulin; to

genetically obese and diabetic animals, for example Male Wistar rats, fa/fa Zucker rats or ob/ob mice, and measuring plasma glucose levels or another physiological indicator of the insulin resistance syndrome for example glycemic parameters (fasting plasma glucose (FPG), insulin, proinsulin, C-peptide; lipid parameters (triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, total/HDL-cholesterol ratio. LDL/HDL-cholesterol ratio, Apo A1, Apo B, Apo B/Apo A1 ratio, free fatty acids); thrombosis/vascular markers (PAI-1, fibrinogen, urinary albumin/creatinine ratio). A statistical analysis of the results obtained for each compound separately compared to those obtained from the combination may show a synergistic effect.

Alternatively a 26-Week Randomized , Double-Blind, Multicenter, Placebo-Controlled Study is carried out to Evaluate the Efficacy of a test compound when added to the therapy of patients with Type 2 Diabetes Mellitus poorly controlled on insulin alone.

Three doses of test compound are compared to placebo in patients with type 2 diabetes mellitus who remain poorly controlled (i.e., Fasting Plasma Glucose Levels (FPG) 126-240 mg/dL) on insulin monotherapy plus diet/exercise during the placebo run-in period. The study will consist of a screening period (≥ 2 weeks), an insulin titration period (≤ 4 weeks), a placebo plus insulin run-in period (4 weeks, single-blind, insulin plus placebo plus diet and exercise), a treatment period (26 weeks, double blind), and a follow-up period (3 weeks). All oral antidiabetic medications are required to be discontinued at the initial screening visit. During the insulin titration period, patients will be titrated to optimal effect, taking into account fasting plasma glucose and safety/tolerability. However, in order to be eligible to continue in the study, patients must be on at least 30U insulin/day. After being on insulin monotherapy for a minimum of 14 days, patients well enter the placebo run-in period; patients with FPG ≥ 126 mg/dL and ≤ 240 mg/dL during the placebo run-in are eligible to enter the treatment period. Patients will be stratified according to gender and BMI. Randomization will be performed separately for each of these strata. Patients will be counseled on dietary modification, with reinforcement throughout the treatment period. Any patient with FPG > 270 mg/dL at consecutive visits will be required to be withdrawn from the study. At the end of the treatment period, eligible patients may enter a long-term open-label extension study.

Inclusion criteria

Patients may be included in the study if they satisfy the following criteria:

Have been diagnosed with type 2 diabetes mellitus (fasting plasma glucose ≥ 126 mg/dL) and are currently being treated with insulin for at least 3 months. Patients are eligible if they have also been treated with a single or multiple oral agents; however, patients are required to discontinue all oral antidiabetic medications at the screening visit. Patients are required to have a fasting plasma glucose level of ≥ 126 mg/dL and ≤ 240 mg/dL during the placebo run-in period.

Men or women who are 30 to 80 years of age at the screening visit.

Female patients must be post-menopausal (i.e., ≥ 6 months without a menstrual period), surgically sterile, or using hormonal contraceptives or intrauterine devices. Female patients taking hormonal contraceptives must also be using an additional barrier method of birth control. Endogenous insulin production as demonstrated by a fasting C-peptide level of ≥ 0.8 ng/mL at the screening and placebo run-in visits.

Fasting triglyceride concentrations at placebo run-in visits must be within 40 percent of each other, using the higher value as the denominator in the calculation (low/high > 0.6).

Sign the informed consent to participate.

Exclusion Criteria

Patients are excluded from the study if they satisfy one or more of the following criteria:

Be a diabetic patient treated with a thiazolidinedione (TZD; glitazone) within 6 months of screening. Patients treated with metformin, a sulfonylurea, a meglitinide, or an alpha glucosidase inhibitor are eligible for entrollment; however, their oral antidiabetic medications must be discontinued at the screening visit.

Have fasting triglycerides > 600 mg/dL or LDL-C > 250 mg/dL at any visit during the screening and placebo run-in period.

Have uncontrolled hypertension (mean systolic blood pressure ≥ 170 mm Hg or mean diastolic blood pressure ≥ 100 mm Hg). Patients on antihypertensive treatment with a

thiazide diuretic, an alpha-adrenergic blocking agent, or a beta-adrenergic blocking agent should be on a constant dose of that medication for at least one month prior to study enrollment and must remain on a constant dose throughout the study, unless medically indicated.

Be treated with fibrates or other lipid lowering agents within 1 month of the screening visit. HMG-CoA reductase inhibitors are allowed, provided that therapy was initiated at least 3 months prior to the screening visit and the dose has remained unchanged for ≥ 3 months prior to the screening visit.

Have a body mass index (BMI) > 40 kg/m^2 at screening.

Have active arterial disease such as unstable angina, myocardial infarction, transient ischemic attack (TIA), cerebrovascular accident (CVA), coronary artery bypass graft (CABG) surgery, or angioplasty within 3 months of the screening visit.

Have New York Heart Association Class III or IV heart failure.

Have active liver disease or hepatic dysfunction defined by ALT or AST elevations of ≥ 1.5 times the upper limit of normal at any time during the screening or placebo run-in period.

Have experienced previous liver enzyme elevations (> 2.5 times the upper limit of normal) or liver dysfunction while taking troglitazone, pioglitazone, or rosiglitazone.

Have renal impairment defined as a serum creatinine level > 1.8 mg/dL at any time during the screening or placebo run-in period.

Have a hemoglobinopathy or anemia defined as Hgb < 11 g/dL for males and < 10 g/dL for females at any time during the screening or placebo run-in period.

Have a history of malignancy within the last 5 years, excluding successful treatment of basal or squamous cell skin carcinoma.

Pregnancy or lactation.

Have serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the trial.

Have any clinically significant abnormality identified on the screening physical examination, laboratory tests, or electrocardiogram, which in the judgment of the investigator would preclude safe completion of the study.

Have a history of alcohol or drug abuse within the last 5 years.

Have an unstable weight as indicated by a > 3 kg change over the 3 months prior to screening.

Results

The effect of the test compound in combination with insulin on glycemic control, as determined by the mean change from baseline in HbA1c compared to insulin plus placebo.

In addition the mean change from baseline in the insulin + test compound groups with the insulin + placebo groups in the following parameters:

glycemic parameters (fasting plasma glucose (FPG), insulin, proinsulin, C-peptide; lipid parameters (triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol, total/HDL-cholesterol ratio. LDL/HDL-cholesterol ratio, Apo A1, Apo B, Apo B/Apo A1 ratio, free fatty acids); thrombosis/vascular markers (PAI-1, fibrinogen, urinary albumin/creatinine ratio).

In addition, the following will be evaluated:

responder analyses for HbA1c (proportion of patients with reductions from baseline of at least 0.7% and 1%); FPG (proportion of patients with reductions from baseline of at least 30 mg/dL), and TG (proportion of patients with reductions from baseline of at least 20% and 40%);

proportion of patients reaching target goals for HbA1c (≤ 8% and ≤ 7%); FPG (≤ 126 mg/dL); and TG (≤ 200 and ≤ 150 mg/dL);

HOMA: percentage change from baseline in insulin sensitivity and β-cell function.

Clinical safety and tolerability, as assessed by changes in physical examinations, vital signs, body weight, clinical laboratory tests adverse experiences, and electrocardiograms.

Dose

Three doses of test compound will be used: two top doses and one starting dose, given as a single daily dose for a duration of 26 weeks. If any safety concerns are raised with the highest dose during the 6-month trials, then the second top dose will be available for continued development. In addition, a placebo will be used as a comparator. Insulin will be administered in an open-label fashion.

Analysis of the results is expected to demonstrate one or more of the following:
significant improvement in glycemic control compared to baseline and placebo for a combination of the test compound with insulin;
improvement in lipid profile compared to baseline and compared to placebo for a combination of the test compound with insulin;
most patients are "responders" for glycemic and triglyceride control in combination with insulin;
most patients will achieve target goals for glycemic and lipid control in combination with insulin;
for the test compound in combination with insulin, effective glycemic and lipid control regardless of baseline BMI, age, gender, race, or severity of disease; no clinically relevant increases in weight.

It is also expected that statistical analysis of the above results will demonstrate that the combination of the test compound and insulin has a synergistic effect on one or more of the physiological responses measured.

CLAIMS

1. A pharmaceutical combination comprising either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and any solvates of either thereof and insulin.

2. A pharmaceutical combination comprising (S)-2-ethoxy-3-[4-(2-{4-methane-sulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or a pharmaceutically-acceptable salt thereof or a solvates of either thereof and insulin.

3. A pharmaceutical combination comprising or 3-{4-[2-(4-*tert*-butoxycarbonylamino-phenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid or a pharmaceutically-acceptable salt thereof or a solvates of either thereof and insulin.

4. A method of treating or preventing diabetes which comprises administering to a patient in need thereof an effective amount of a pharmaceutical combination as defined in any one of claims 1, 2 or 3.

5. A method of treating insulin resistance syndrome which comprises administering to a patient in need thereof an effective amount of a pharmaceutical combination as defined in any one of claims 1, 2 or 3.

6. A kit of parts comprising:
(i) a vessel containing either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}-ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and
(ii) a vessel containing insulin
and instructions for the sequential, separate or simultaneous administration of one of the propanoic acids and insulin to a patient for which such administration is necessary or advantageous.

7. A kit of parts comprising:

(i) a pharmaceutical formulation containing either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and

(ii) a pharmaceutical formulation containing insulin, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;

wherein the propanoic acids and the insulin are each provided in a form that is suitable for administration in conjunction with the other.

8. A combination product comprising:

(1) a pharmaceutical formulation including either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof and insulin, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxyphenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including insulin in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

9. A method of making a combination product as defined above, which method comprises bringing a component (a), as defined above, into association with a component (b), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

10. A method according to claim 9 wherein (a) and (b) of the kit of parts may be:
(i) provided as separate formulations independently of one another, which are subsequently brought together for use in conjunction with each other in combination therapy; or
(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

11. A kit of parts comprising:
(I) one of components (a) and (b) as defined herein; together with
(II) instructions to use that component in conjunction with the other of the two components.

12. A kit of parts according to any one of claims 6, 7 or 11 which comprises more than one formulation including either (S)-2-ethoxy-3-[4-(2-{4-methanesulfonyloxy-phenyl}ethoxy)phenyl] propanoic acid or 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-(S)-2-ethoxy propanoic acid, or a pharmaceutically-acceptable salt thereof, and/or more than one formulation including an appropriate quantity/dose of insulin in order to provide for repeat dosing.

13. A pharmaceutical combination according to any one of claims 1, 2 or 3 or a method according to any one of claims 4, 5, 9 or 10 or a kit of parts according to any one of claims 6, 7, 11 or 12 or a combination product according to claim 8 which further comprises one or more additional existing therapies for the treatment of type 2 diabetes and its associated complications.