Abstract:

A method or treatment with a combination of a cholinesterase inhibitor and a thiazolidinedione derivative.

Title: COMBINED TREATMENT WITH A CHOLINESTERASE INHIBITOR AND A THIADIAZOLIDINEDIONE DERIVATIVE

(57) Abstract: A combination of a cholinesterase inhibitor and a thiazolidinedione derivative; a pharmaceutical composition comprising a cholinesterase inhibitor and a thiazolidinedione derivative; a medical kit useful for administering in combination a cholinesterase inhibitor and a thiazolidinedione derivative; a method or treatment with a combination of a cholinesterase inhibitor and a thiazolidinedione derivative.
COMBINED TREATMENT WITH A CHOLINESTERASE INHIBITOR AND A THIADIAZOLIDINEDIONE DERIVATIVE

FIELD OF THE INVENTION

The present invention is related to a combination of a cholinesterase inhibitor and a thia diazolidinedione derivative; to a pharmaceutical composition comprising a cholinesterase inhibitor and a thia diazolidinedione derivative; a medical kit useful for administering in combination a cholinesterase inhibitor and a thia diazolidinedione derivative; and a method or treatment with a combination of a cholinesterase inhibitor and a thia diazolidinedione derivative.

BACKGROUND OF THE INVENTION

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized clinically by memory and cognitive dysfunction. The neuropathology of AD is characterized by two types of lesions, senile plaques and neurofibrillary tangles (NFTs), composed respectively of β-amyloid (Aβ), a cleavage product of the amyloid precursor protein (APP), and aberrantly phosphorylated tau, a microtubule-associated protein (for a review of AD pathology, see J Clin Invest., 1999, 104(9), 1169-70.


Although sporadic AD is rare in individuals younger than 60 years of age, the incidence steadily increases with age, affecting up to 40% of those who are more than 85 years old. In 2006, there were more than 26 million cases of AD in the world and it is expected that by the year 2050 the worldwide prevalence of AD will grow fourfold to almost 107 million [Alzheimer's & Dementia, 2007, 3(3), 186-191. Forecasting the global burden of Alzheimer's disease. Brookmeyer, R. et al.]

Cholinesterase inhibition as a treatment of AD

There is evidence from preclinical studies, and some studies in humans, that cholinesterase inhibition affects basic processes that have been implicated in AD
pathogenesis. For example, acetylcholinesterase (AChE) inhibition may influence expression of AChE isoforms and increase expression of nicotinic receptors, both of which correlate with cognitive improvements in AD patients. It has also been shown that AChE inhibition influences amyloid precursor protein (APP) processing and attenuates Aβ-induced toxicity via mechanisms including interruption of the production of Aβ, alteration of the levels of Aβ1-40 and Aβ1-42, and formation of the soluble form of amyloid precursor protein.

Therefore currently, cholinesterase inhibitors (ChEI) represent the treatment of choice for Alzheimer’s disease (AD) therapy. Following the introduction in the late eighties of a first generation of drugs, represented by phystostigmine and tacrine, a second generation of more suitable compounds were developed in the nineties. Three of them have reached the market: donepezil, rivastigmine and galantamine. The symptomatic effects of ChEIs (due to increases in cholinergic neurotransmission) have been demonstrated in a number of large, randomized controlled trials.

The brain of mammals contains two major forms of cholinesterases: acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) are involved in the breakdown of acetylcholine in the brain and inhibition of these enzymes may produce symptomatic effects in numerous pathologies [CNS Drugs, 1999, 12(4), 307-23].

Selectivity of cholinesterase inhibition. Clinical implications for the treatment of Alzheimer’s disease. Weinstock, M.J. Hence, Cholinesterases as used herein comprise AChE and BuChE.

Marketed Cholinesterase Inhibitors

Currently, three cholinesterase inhibitors are marketed worldwide for the treatment of Alzheimer’s disease, namely donepezil, galantamine and rivastigmine.

Donepezil (1-Benzyl-4-[(5,6-dimethoxy-1-indanon)-2-yl]-methyl-piperidine) (formula 1) is a reversible inhibitor of acetylcholinesterase (AChE) developed by Eisai for the treatment of Alzheimer’s disease (AD). The drug has been launched in over 60 countries worldwide for the once-daily treatment of mild-to-moderate AD, and is approved for the treatment of severe AD in the US. Additionally, donepezil is marketed for the treatment of vascular dementia. Donepezil is also undergoing late stage clinical development for the treatment of paediatric attention impairment following cancer treatment, dementia associated with Parkinson’s disease, Lewy body dementia and for
the prevention of migraine. Clinical trials were also initiated for mild cognitive impairment and post-stroke aphasia.

![Donepezil](image)

**Formula 1**

Donepezil hydrochloride is available in conventional 5 and 10 mg tablets (o.d.), in rapid disintegration tablet formulations (o.d.), in a 23 mg sustained release tablet formulation (o.d.), in a oral jelly (3, 5 and 10 mg., o.d.) and in an oral liquid solution (5 mg./ml.). Transdermal patch formulations of donepezil are also being developed in the US.

The most common adverse events of donepezil, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. See Table 1 for a comparison of the most common adverse events following one and six week titration regimens.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No titration (n=315)</th>
<th>One week titration (n=315)</th>
<th>Six week titration (n=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>5%</td>
<td>19%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>6%</td>
<td>14%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3%</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>3%</td>
<td>8%</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>2%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2%</td>
<td>3%</td>
<td>7%</td>
</tr>
</tbody>
</table>

The adverse events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical
practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Results regarding adverse events reported in controlled clinical trials in at least 2% of patients receiving donepezil (Aricept®) and at a higher frequency than placebo-treated patients, confirm that the most common adverse events related with donepezil are gastrointestinal disorders, i.e. nausea (11% vs. 6%) and diarrhea (10% vs. 5%) [for additional information in connection with adverse events, see "Physicians’ Desk Reference. Ed. Thomson PDR. 60th edition. 2006"; herewith incorporated by specifical reference].


Galantamine ([4aS-(4aa, 6β, 8aR’)]-4a, 5, 9, 10, 11, 12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a, 3, 2-et] [2] benzazepin-6-ol) (formula 2), an alkaloid isolated from the snowdrop Galanthus nivalis, is a highly selective, reversible and competitive inhibitor of acetylcholinesterase. Galantamine has been launched in more than 30 countries for the treatment of mild-to-moderate AD and clinical trials were also started for delirium, mild cognitive impairment, vascular dementia, chronic fatigue syndrome and fibromyalgia.
Galantamine hydrobromide is available in conventional tablets (4 mg., 8 mg. and 12 mg. bid), in extended release capsules (8 mg., 16 mg. and 24 mg. o.d.) and in an oral solution formulation (4mg./ml., bid).

The most frequent adverse events of galantamine, defined as those occurring at a frequency of at least 5% and at least twice the rate on placebo with the recommended maintenance dose of either 16 or 24 mg/day of galantamine (Razadyne®) under conditions of every 4-week dose-escalation for each dose increment of 8 mg/day, are shown in Table 2.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n=286)</th>
<th>Galantamine (Razadyne®) 16 mg/day (n=279)</th>
<th>Galantamine (Razadyne®) 24 mg/day (n=273)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5%</td>
<td>13%</td>
<td>17%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6%</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>1%</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

The most common adverse events (adverse events occurring with an incidence of at least 2% with galantamine (Razadyne®) treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of galantamine (Razadyne®) were confirmed to be gastrointestinal disorders, i.e. nausea (24% vs. 9%) and vomiting (13% vs. 4%) [for additional information in connection with adverse events, see "Physicians’ Desk Reference. Ed. Thomson PDR. 60th edition. 2006"; herewith incorporated by specifical reference].

Galantamine was firstly disclosed in US 4,663,318 and EP 0236684 and, subsequently, it has been included in additional patents, such as US 7,160,559, EP 1140105, US 6,099,863 or US 6,358,527, US 6,358,941, US 7,307,162, US 7,297,691 or EP 0449247. The content of the above patent publications is herewith incorporated by specifical reference.

**Rivastigmine** ((S)-N-ethyl-3-[1-(dimethylamino)ethyl]-N-methyl-phenyl-carbama-te) (formula 3), is a reversible, noncompetitive inhibitor of acetylcholinesterase and butyrylcholinesterase with preferential action at central sites, for the treatment of mild-to-moderately severe AD. Rivastigmine oral capsules were initially approved in
Switzerland for AD in 1997, and have since been cleared for marketing in over 70 countries worldwide, including the US, Canada and all of Europe. Furthermore, rivastigmine has been launched for dementia in the UK and is being developed for vascular dementia.

![Rivastigmine](image)

Formula 3

Rivastigmine tartrate is available in conventional tablets (1.5 mg., 3 mg., 4.5 mg. and 6 mg., bid), in an oral liquid solution (2 mg./ml.) and in a transdermal patch formulation as a more convenient alternative to the oral capsule formulation. The product is available in two sizes and dosage strengths, i.e. 5 cm² (4.6 mg/day) and 10 cm² (9.5 mg/day) containing 9 and 18 mg. of rivastigmine, respectively. The rivastigmine transdermal patch is available to date in the US, Canada and the UK, and has been approved in the EU.

The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are significant gastrointestinal events including nausea, vomiting, anorexia and weight loss. Furthermore, table 3 lists treatment emergent signs and symptoms that were reported in placebo-controlled clinical trials in at least 2% of patients and for which the rate of occurrence was greater for patients receiving rivastigmine (Exelon®) (6-12 mg/day) than for those treated with placebo. [for additional information in connection with adverse events, see *Physicians’ Desk Reference. Ed. Thomson PDR. 60th edition. 2006*; herewith incorporated by specific reference].
Table 3.- Most frequent adverse events of rivastigmine.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo n=888</th>
<th>Rivastigmine (Exelon®) 6-12 mg/day n=1,189</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12%</td>
<td>47%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>31%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3%</td>
<td>17%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11%</td>
<td>21%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4%</td>
<td>9%</td>
</tr>
</tbody>
</table>


**Other cholinesterase inhibitors in clinical or preclinical development**

Clinical and/or preclinical trials have also been performed for other cholinesterase inhibitors, namely for tacrine hydrochloride (CI-970, THA.HCl), huperzine A, acotiamide, dimebolin, DEBIO 9902, EN 101, phenserine tartrate, R-phenserine, stacofylline hydrochloride (S-9977, S-9977-2), NP-61, bisnorcymserine, COL-204, SPH 1371, SPH 1373, SPH 1375, SP 04, CM 2433, metrifonate, 7-methoxytacrine (7 MEOTA), P 11149, Arisugacin, FR 152558, HUP 13, isovanihuperzine A (IVHA), MHP 133, NP 7557, P 10358, P 11012, physostigmine salicylate, velnacrine maleate (HP-029, P83-6029A), epastigmine tartrate (L-693487), ipidacrine, zanapezil, ganstigmine, icopezil maleate (CP-1 18954, CP-1 18954-1 1), KW 5092, quilstigmine (HP-290, NXX-066), SM 10888, T 82, TAK 802, zifrosilone MDL-73745), BGC 201259, CHF 2060, CI 1002, E 2030, ER 127528, ET 142, F 3796, huprine X, MF 247, MF 268 bitartrate, MF 8615, P 26, PD 142012, RO 465934, SS 20, thiatolserine, tolserine tartrate, UR 1827.

(Source: ADIS R&D Insight, on 25/02/2010; herewith incorporated by specifical reference)
For the above indicated cholinesterase inhibitors not only clinical and/or preclinical trials for AD have been performed, but also for other disorders or diseases, namely cognitive disorders and neurodegenerative diseases such as dementia, vascular dementia, Huntington's disease, Parkinson's disease or condition, progressive supranuclear palsy, amyotrophic lateral sclerosis, mild cognitive impairment, drug-induced dyskinesia, and other pathologies such as pain, neuropathic pain, myasthenia gravis, poisoning, hypersomnia, smoking withdrawal, HIV infections, inflammatory bowel disease, schistomatosis, urinary incontinence or xerostomia. (Source: ADIS R&D Insight, on 25/02/2010; herewith incorporated by specific reference)

**Other cholinesterase inhibitors**

Additional compounds have been described to inhibit cholinesterases, for example edrophonium, demecarium, ambenonium, neostigmine bromide, dehydroevodiamine chloride, eseroline, imperatorin, scopoletin (SCT), huperzine A (Hup A), heptylstigmine tartrate (MF-201), suronacrine maleate (HP-128), UCB-1 1056, berberine iodide, norpyridostigmine, quilostigmine (HP-290, NXX-066), THB-013, PD-142676, terestigmine tartrate (CHF-2060), thiacymserine, MF-8615, MF-268 bitartrate, anseculin hydrochloride (KA-672.HCl), ensaculin hydrochloride, icopezil maleate (CP-118954), eserine salicylate, physostigmine salicylate, JWS-USC-75IX, P1467, P10358, bis(7)-taocrine, HMR-2420, CP-126998, TV-3279, MSF, THA-C8, subergorgic acid, suberogorgin, SPH-1286, huperzine B (Hup B), pyridostigmine bromide (Ro-1-5130), huprine Y, coronaridine, RS-1233, kobophenol A, bis(12)-huperine, RS-1259, ITH-4012, TK-19, T-81, TH-171, TH-185, distigmine bromide (BC-51), (-)-9-dehydrogalanthaminium bromide, memoquin, phlorofucofuroeckol A (PFF), phlorofucofuroeckol A, (-)-3-O-acetylspectaline hydrochloride and rhaphiasaponin 1, or salts, free bases, racemates or enantiomers thereof.

**Diseases related to a deregulation in the expression or activity of cholinesterase**

As indicated above, the first indication for ChEI has been AD. However, with time this indication has been expanded to include other types of dementia and CNS disorders such as dementia [CMAJ, 2008, 179(10), 1019-26. Diagnosis and treatment
of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate
dementia. Hogan DB et al., vascular & cerebrovascular dementia [Lancet Neurol,
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memantine in vascular dementia: a metaanalysis of randomised controlled trials.
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impairment [Gender Med 2009, 6, 345-55. Treatment response to rivastigmine in mild
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brain injury: a critical review. Writer BW & Schillerstrom JE.], migraine [Headache,
2002, 42(7), 596-602. Central cholinergic challenging of migraine by testing second-
generation anticholinesterase drugs. Nicolodi M et al.,] systemic amyloidosis or
irreversible acetylcholinesterase inhibitors cause changes in neuronal amyloid
precursor protein processing and protein kinase C level in vitro. Pakaski M, Rakonczay

For further details regarding AChE inhibitors and their use as potential treatments for these pathologies, please see Pharmacological Research 2004, 50, 433-440; Current Medical Research & Opinion 2009, 25(10), 2439-2446; Current Alzheimer Research 2009, 6(2), 86-96.

Glycogen synthase kinase-3 (GSK-3)


Diseases related to a Glycogen synthase kinase-3 (GSK3) deregulation


In addition to its possible relevance to prevent neurodegeneration, GSK3 inhibitors may also be useful to foster other forms of neuronal repair, including axon regeneration [J. Neurosci., 2008, 28, 8914-28. Inactivation of glycogen synthase kinase 3 promotes axonal growth and recovery in the CNS. Dill, J. et al.,].


10 **GSK-3 inhibitors**


35 **Thiaiazolidinediones**
Small heterocyclic thiadiazolidinediones, the first ATP non-competitive GSK-3 inhibitors reported to date, have been proposed as new disease-modifying agents for the effective treatment of Alzheimer's disease and other pathologies. These compounds have great interest since they may be disease modifying agents in AD.

Some thiadiazolidinediones were firstly disclosed as GSK-3 inhibitors in the International Patent Application WO 01/85685. Subsequently, additional thiadiazolidinediones have been disclosed for example in J. Med. Chem. 2002, 45, 1292-1299 and WO 05/971 17.

The above documents are herewith incorporated by reference, specifically in what regards the preparation of thiadiazolidinedione derivatives.

**SUMMARY OF THE INVENTION**

It has been found that the combined treatment with a cholinesterase inhibitor and a thiadiazolidinedione derivative shows important advantages with respect to the treatment with cholinesterase inhibitors alone, increasing the efficacy of the cholinesterase inhibitor treatment, and reducing the adverse effects in most System-Organ Classes.

Therefore, according to a first aspect, the present invention provides a combination of at least one thiadiazolidinedione derivative of formula (I) and a therapeutically effective amount of at least one cholinesterase inhibitor, or a pharmaceutically acceptable salt or solvate thereof, wherein the cholinesterase inhibitor may form part of a separate medicament or the same medicament, and wherein formula (I) is:

![Formula (I)](image)

wherein:

R<sup>a</sup> and R<sup>b</sup> are independently selected from hydrogen, substituted or unsubstituted C1-C6 alkyl, cycloalkyl, aryl, -(Z)<sub>a</sub>-aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted benzo-fused heterocyclic ring system having 2 or 3 rings, -OR', -C(0)R\ \ -C(0)OR',-(Z)\, C(0)OR' and -S(0), -
is independently selected from \(-C(R')(R'')-\), \(-C(O)-\), \(-0-\), \(-C(=NR>)-\), \(-S(0)\_\) and \(-N(R')\); 
n is zero, one or two; 
t is zero, one, two or three; 
R' and R" are independently selected from hydrogen, alkyl, aryl and heterocyclic or may together form a C=0 group;

According to a further aspect, the present invention is related to a pharmaceutical composition comprising a therapeutically effective amount of at least one thiazolidinedione derivative of formula (I) as defined above or a pharmaceutically acceptable salt or solvate thereof, a therapeutically effective amount of a cholinesterase inhibitor or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutical carrier, adjuvant and/or vehicle.

Another aspect of the present invention is a medical kit comprising (i) a supply of thiazolidinedione derivative of formula (I) as defined above, or a pharmaceutically acceptable salt or solvate thereof, in dosage units, wherein each of said dosage units contains a therapeutically effective amount of said thiazolidinedione derivative or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, adjuvant and/or vehicle, and (ii) instructions for administering said thiazolidinedione derivative in combination with a cholinesterase inhibitor, or a pharmaceutically acceptable salt or solvate thereof.

An additional aspect of the present invention is a thiazolidinedione derivative of formula (I) as defined above, for use in the reduction of side effects caused by the treatment with a cholinesterase inhibitor.

An additional aspect of the present invention is a combination or a composition or a kit for use as a medicament.

According to another aspect, the present invention refers to the use of at least one thiazolidinedione derivative of formula (I) as defined above, in the preparation of a medicament for the treatment of a human patient affected by a cholinesterase or GSK-3 mediated disease by combination therapy, involving the administration of a therapeutically effective amount of at least one thiazolidinedione derivative if formula
(I) or a pharmaceutically acceptable salt or solvate thereof, and a therapeutically effective amount of at least one cholinesterase inhibitor or a pharmaceutically acceptable salt or solvate thereof, wherein the cholinesterase inhibitor may form part of a separate medicament or the same medicament.

A further aspect of the present invention is a method of treating a GSK3 or cholinesterase mediated disease, comprising administering to a patient in need of such treatment a therapeutically effective amount of a thiadiazolidinedione derivative of formula (I) as defined above, or a pharmaceutically acceptable salt or solvate thereof, and a therapeutically effective amount of a cholinesterase inhibitor, or a pharmaceutically acceptable salt or solvate thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a graphical representation of the evolution of MMSE (Mini Mental State Examination) score from baseline to the end of the study, split by placebo and active in those patients who were escalated up to 1,000 mg of thiadiazolidine derivative once daily, and thus completed the study.

Figure 2 is a graphical representation of the evolution of Alzheimer’s Disease assessment Scale (ADAS-cog+) score, from baseline to the end of the study, split by placebo and active in those patients who were escalated up to 1,000 mg of thiadiazolidine derivative once daily, and thus completed the study.

Figure 3 is a graphical representation of the Global Clinical Assessment of changes observed at the end of the study, split by placebo and active. Figure 4 is a table detailing the incidence of adverse effects (absolute number and percentage) during the study, classified by Organ-System Class, split by placebo and active.

DEFINITIONS

In the present application the following terms have the meaning as indicated:

"GSK3 or cholinesterase mediated disease" refers to any disease or condition wherein a modulation of the expression or activity of GSK3 or cholinesterase may be of benefit for patients suffering said disease or condition. This includes, but is not limited to, those diseases or conditions implying a deregulation in the expression or activity of GSK3 or cholinesterase.

The term "carrier, adjuvant and/or vehicle" refers to molecular entities or substances with which the active ingredients are administered. Such pharmaceutical
carriers, adjuvants or vehicles can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like, excipients, disgregants, wetting agents or diluents. Suitable pharmaceutical carriers, adjuvants and/or vehicles are described in

"Remington's Pharmaceutical Sciences" by E.W. Martin.

"C1-C6 Alkyl" refers to a straight or branched hydrocarbon chain radical, said chain consisting of 1 to 6 carbon and hydrogen atoms, preferably, 1 to 3 carbon atoms, containing no saturation, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, t-pentyl, etc. Alkyl radicals may be optionally substituted by one or more substituents such as halo, hydroxy, alkoxy, carboxy, cyano, carbonyl, acyl, alkoxy carbonyl, amino, nitro, mercapto and alkylthio.

"Alkenyl" means a monovalent, unbranched or branched hydrocarbon chain having one or more double bonds therein, said chain consisting of 2 to 6 carbon atoms, preferably from 2 to 4 carbon atoms. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted with one or two suitable substituents.

"Alkoxy" refers to a radical of the formula -OR where R is an alkyl radical as defined above, e.g., methoxy, ethoxy, propoxy, etc.

"Aryl" refers to an aromatic ring system. According to one embodiment, aryl groups comprise 6 to 14 carbon atoms, more particularly 6 to 10, even more particularly 6 carbon atoms. According to an embodiment, aryl is a phenyl, naphthyl, indenyl, fenanthryl or anthracyl radical, preferably phenyl or naphthyl radical. Said aryl radical may be optionally substituted by one or more substituents such as hydroxy, mercapto, halo, alkyl, phenyl, alkoxy, haloalkyl, nitro, cyano, dialkylamino, aminoalkyl, acyl and alkoxy carbonyl, as defined herein.

"Benzo-fused heterocyclic ring system" refers to a phenyl ring, fused to one or two further rings, at least one of them being a heterocycle or heteroaryl, especially an oxygen containing heterocycle or heteroaryl, e.g. benzo[1,3]dioxol, benzoimidazol, benzofurane, etc.

"Cycloalkyl" refers to a stable 3-to 10-membered monocyclic or bicyclic radical which is saturated or partially saturated, and which consist solely of carbon and
hydrogen atoms, preferably, 3 to 8 carbon atoms, more preferably 5, 6 or 7 carbon atoms. Unless otherwise stated specifically in the specification, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more such as alkyl, halo, hydroxy, amino, cyano, nitro, alkoxy, carboxy and alkoxy carbonyl.

"Halo" refers to bromo, chloro, iodo or fluoro.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, e.g., trifluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

The term "heteroaryl" means a monocyclic- or polycyclic aromatic ring comprising carbon atoms, hydrogen atoms, and one or more heteroatoms, preferably, 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. In an embodiment of the invention, the heteroaryl group has 3 to 15 members. In a particular embodiment it has 4 to 8 members. Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, phenyl, isoxazolyl, and oxazolyl. A heteroaryl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, a heteroaryl group is a monocyclic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms.

"Heterocycle" refers to a heterocyclyl radical. The heterocycle refers to a stable 3-to-15 membered ring which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, preferably a 4-to-8-membered ring with one or more heteroatoms, more preferably a 5- or 6-membered ring with one or more heteroatoms. For the purposes of this invention, the heterocycle may be a monocyclic, bicyclic or tricyclic ring system, which may include fused ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidised; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated or aromatic. Examples of such heterocycles include, but are not limited to, azepines, benzimidazole, benzothiazole, furan, isothiazole, imidazole, indole, piperidine, piperazine, purine, quinoline, thiaziazole, tetrahydrofuran.

References herein to substituted groups in the compounds of the present invention refer to the specified moiety that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C1-6 alkanoyl group such as
acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonil linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl or naphthyl and aralkyl such as benzyl. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

**DETAILED DESCRIPTION OF THE INVENTION**

We have made clinical studies comparing the treatment with cholinesterase inhibitors alone with the combination of cholinesterase inhibitors and a thiazolidinedione derivative.

Unexpectedly and surprisingly, it has been found that the combined treatment with a thiazolidinedione derivative and a cholinesterase inhibitor causes a reduction of the incidence of adverse effects, when classified by System-Organ Classes (further details are given in the EXAMPLES), than the treatment only with a cholinesterase inhibitor. Especially unexpected is the reduction in gastrointestinal adverse effects, which are typical and frequent side effects of the treatment with cholinesterase inhibitors. The results show that the adverse effects occurring during the treatment with cholinesterase inhibitors are reduced by co-administering the thiazolidinedione derivative, without significantly adding adverse effects, when classified by System-Organ Classes. These statements will be further detailed and supported in the EXAMPLES.

Further, the efficacy of the cholinesterase inhibitor in the treatment of the corresponding disease is improved by co-administering the thiazolidinedione derivative.
Therefore, the combined treatment with a cholinesterase inhibitor and a thiadiazolidinedione derivative shows important advantages with respect to the treatment with cholinesterase inhibitors alone, increasing the efficacy of the cholinesterase inhibitor treatment, and reducing the adverse effects, in most System-Organ Classes.

As detailed above, the present invention refers to the following aspects:

- a combination of at least one thiadiazolidinedione derivative of formula (I) and at least one cholinesterase inhibitor;

- a pharmaceutical composition comprising a therapeutically effective amount of at least one thiadiazolidinedione derivative of formula (I) a therapeutically effective amount of a cholinesterase inhibitor, and at least one pharmaceutical carrier, adjuvant and/or vehicle;

- a medical kit comprising (i) a supply of thiadiazolidinedione derivative of formula (I) and a pharmaceutically acceptable carrier, adjuvant and/or vehicle, and (ii) instructions for administering the thiadiazolidinedione derivative in combination with a cholinesterase inhibitor;

- a combination or a composition or a kit for use as a medicament;

- a thiadiazolidinedione derivative as defined above, for use in the reduction of side effects caused by the treatment with a cholinesterase inhibition;

- the use of at least one thiadiazolidinedione derivative of formula (I) as defined above, in the preparation of a medicament for the treatment of a human patient affected by a cholinesterase or GSK-3 mediated disease by combination therapy involving the co-administration of at least one cholinesterase inhibitor;

- a method of treating a GSK3 or cholinesterase mediated disease, comprising administering to a patient in need of such treatment a therapeutically effective amount of a thiadiazolidinedione derivative of formula (I) and a therapeutically effective amount of a cholinesterase inhibitor.

In all of the above aspects, according to a preferred embodiment, the thiadiazolidinedione derivative has formula (II):
wherein:

- \( R^a \) is an organic group comprising at least one aromatic ring and having at least 8 atoms selected from C or O;
- \( R^c \), \( R^d \) are independently selected from hydrogen and alkyl, or \( R^c \) and \( R^d \) together can form a group =0;
- \( R_i, R_2, R_3, R_4, R_5 \) are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, -COR, -C(0)OR, -C(0)N R_7 R_8, -C=N R_7, -CN, -OR, -OC(0)R, -S(0) R, -NR_7 R_8, -NR_7 C(0)R, -NO2, -N=CR R_8 or halogen,
- \( t \) is zero, one, two or three,
- \( R_7 \) and \( R_8 \) are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, halogen;
- or a pharmaceutically acceptable salt or solvate thereof.

Preferably, in the above aspects the thiazolidinedione derivative is selected from the following compounds:

- 4-benzyl-2-phenethyl-[1,2,4]thiazolidine-3,5-dione,
- 4-benzyl-2-diphenylmethyl-1,2,4-thiazolidine-3,5-dione,
- 4-benzyl-2-naphthalen-1-yl-[1,2,4]thiazolidine-3,5-dione,
- 4-benzyl-2-(4-methoxy-phenyl)-[1,2,4]thiazolidine-3,5-dione,
- 4-benzyl-2-(4-phenoxy-phenyl)-[1,2,4]thiazolidine-3,5-dione,
4-benzyl-2-(2-tert-butyl-6-methyl-phenyl)-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-(4-methyl-benzyl)-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-(2-benzyl-phenyl)-[1,2,4]thiadiazolidine-3,5-dione,
2-benzo[1,3]dioxol-5-yl-4-benzyl-[1,2,4]thiadiazolidine-3,5-dione, and
4-benzyl-2-methyl-1,2,4-thiadiazolidine-3,5-dione,
or a pharmaceutically acceptable salt or solvate thereof.

More preferably, the thiadiazolidinedione derivative is 4-benzyl-2-naphtalen-1-yl-1,2,4-thiadiazolidine-3,5-dione.

Further preferred embodiments are the compounds and general formulas disclosed in WO 01/85685 and WO 05/97117, which are herewith incorporated by reference.

The above defined aspects may either comprise one thiadiazolidinedione derivative or a pharmaceutically acceptable salt or solvate thereof, or more than one of such thiadiazolidinedione derivatives.

The above defined aspects may either comprise one cholinesterase inhibitor or a pharmaceutically acceptable salt, or more than one such cholinesterase inhibitors.

Preferably, the above aspects comprise one thiadiazolidinedione derivative and one cholinesterase inhibitor.

The above aspects may comprise, additionally to the thiadiazolidinedione derivative and the cholinesterase inhibitor, other pharmaceutically active compounds.

According to a further preferred embodiment, the cholinesterase inhibitor derivative is selected from the group consisting of Donepezil, Galantamine, Rivastigmine, tacrine hydrochloride, huperzine A, acotiamide, dimebolin, DEBIO 9902, EN 101, phenserine tartrate, R-phenserine, stacofylline hydrochloride (S-9977, S-9977-2), NP-61, bisnorcymserine, COL-204, SPH 1371, SPH 1373, SPH 1375, SP 04, CM 2433, metrifonate, 7-methoxytacrine (7 MEOTA), P 11149, Arisugacin, FR 152558, HUP 13, isovanihuperzine A (IVHA), MHP 133, NP 7557, P 10358, P 11012, physostigmine salicylate, velnacrine maleate (HP-029, P83-6029A), epastigmine tartrate (L-693487), ipidacrine, zanapezil, ganstigmine, icopezil maleate (CP-118954, CP-118954-11), KW 5092, quilostigmine (HP-290, NXX-066), SM 10888, T 82, TAK 802, zifrosilone MDL-73745), BGC 201259, CHF 2060, CI 1002, E 2030, ER 127528, ET 142, F 3796, huprine X, MF 247, MF 268 bitartrate, MF 8615, P 26, PD 142012, RO 465934, SS 20, thiatolserine, tolserine tartrate, UR 1827, edrophonium, demecarium, ambenonium, neostigmine bromide, dehydroevodiamine chloride, eseroline, imperatorin, scopoletin (SCT), huperizine A (Hup A), heptylstigmine tartrate (MF-201).
suronacrine maleate (HP-128), UCB-1 1056, berberine iodide, norpyridostigmine, quilostigmine (HP-290, NXX-066), THB-013, PD-142676, terestigmine tartrate (CHF-2060), thiacymserine, MF-8615, MF-268 bitartrate, anseculin hydrochloride (KA-672.HCI), ensaculin hydrochloride, icopezil maleate (CP-118954), eserine salicylate, phyostigmine salicylate, JWS-USC-75IX, P11467, P-10358, bis(7)-tacrine, HMR-2420, CP-126998, TV-3279, MSF, THA-C8, subergorgic acid, suberogorgin, SPH-1286, huperzine B (Hup B), pyridostigmine bromide (Ro-1-5130), huprine Y, coronaridine, RS-1233, kobophenol A, bis(12)-huperine, RS-1259, ITH-4012, TK-19, T-81, TH-171, TH-185, distigmine bromide (BC-51), (-)-9-dehydrogalanthaminium bromide, memoquin, scopolentin 7-O-beta-D-glucopyranoside (NSC-404560), scopolin (SCN), scopolosin, BW-284c51, withaferin A (NSC-101088), withaferine (NSC-273757), (+)-corynoline, corynoline, (S)-(-)-oxypeucedanin, oxypeucedanin, (-)-voacangine, carbomethoxyibogaine, voacangine, dieckol, phlorofucofuroeckol (PFF), phlorofucofuroeckol A, (-)-3-0-acetylspectaline hydrochloride and rhaphiasaponin 1, or pharmaceutically acceptable salts, free bases, racemates or enantiomers thereof.

More preferably, the cholinesterase inhibitor is selected from the group consisting of Donepezil, Galantamine and Rivastigmine.

According to a preferred embodiment, the cholinesterase inhibitor and the thia diazolidinedione derivative form part of the same medicament.

According to a further preferred embodiment, the cholinesterase inhibitor and the thia diazolidinedione derivative are administered as separate medicaments. The separate medicament comprising the cholinesterase inhibitor may be administered at the same time as the medicament comprising the thia diazolidinedione derivative. Alternatively, the separate medicament comprising the cholinesterase inhibitor may be administered at a different time than the medicament comprising the thia diazolidinedione derivative.

In the above aspects, the GSK-3 mediated disease to be treated is selected from Alzheimer's disease, Parkinson's disease, frontotemporal dementia, Pick's disease, progressive supranuclear palsy, subacute panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, corticobasal degeneration, argyrophilic grain disease, familial frontotemporal dementia and parkinsonism linked to chromosome 17 due to mutations in the tau gene (FTDP-17-tau), AIDS associated dementia, Huntington's disease, Lewy body disease, bipolar disorder, depression, schizophrenia, epilepsy, mood disorders, autism, attention deficit hyperactivity disorder, Down's syndrome, ischemia/reperfusion and shock, brain
injury, multiple sclerosis, autoimmune and inflammatory diseases afflicting the CNS, spinocerebellar ataxia type 1, cerebral bleeding due to solitary cerebral amyloid angiopathy, amyotrophic lateral sclerosis, chronic inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease and psoriasis, arthritis, peritonitis, systemic inflammation, renal dysfunction and hepatotoxicity in endotoxemia, asthma, sepsis, colitis, inflammation-induced organ injury caused by hemorrhage and resuscitation, inflammatory injury in chronic renal allograft disease, lupus, heart disease, atherosclerosis, hypertension, restenosis, leukopenia, metabolic syndrome X, hair loss, severe acute respiratory syndrome coronavirus cocaine addiction, bone loss and glaucoma.

In the above aspects, the cholinesterase mediated disease is selected from cognitive disorders and neurodegenerative diseases, dementia, vascular dementia, Huntington's disease, Parkinson's disease or condition, progressive supranuclear palsy, amyotrophic lateral sclerosis, mild cognitive impairment, drug-induced dyskinesia, and other pathologies such as pain, neuropathic pain, nociceptive pain, myasthenia gravis, poisoning, hypersomnia, smoking withdrawal, HIV infections, inflammatory bowel disease, schistomatisis, urinary incontinence, xerostomia, cerebrovascular dementia, frontotemporal dementia, dementia with Lewy bodies, dementia with argyrophilic grains (AG), essential tremor and tardive dyskinesia, prion disease, attention deficit hyperactivity disorder (ADHD), Down syndrome, traumatic brain injury, migraine, systemic amyloidosis or condition, ataxia, cognitive impairment in multiple sclerosis, narcolepsy, hyperkinesia, Wernicke-Korsakoff disease (WKD), delirium, behavioural dysregulation, apathy, irritability, psychosis, depression, mania, tics, panic, personality disorders, anorexia nervosa, autism spectrum disorders (ASD), stimulant addiction, poststroke aphasia, poisoning, schistosomiasis and glaucoma.

Therefore, according to a further embodiment, the disease to be treated is selected from Alzheimer's disease, Parkinson's disease or condition, dementia, vascular dementia, cerebrovascular dementia, dementia with Lewy bodies, dementia with argyrophilic grains (AG), frontotemporal dementia, Pick's disease, progressive supranuclear palsy, subacute panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, corticobasal degeneration, argyrophilic grain disease, familial frontotemporal dementia and parkinsonism linked to chromosome 17 due to mutations in the tau gene (FTDP-17-tau), AIDS associated dementia, Huntington's disease, Lewy body disease, bipolar disorder, depression, schizophrenia, epilepsy, mood disorders, autism, attention deficit
hyperactivity disorder, Down's syndrome, ischemia/reperfusion and shock, brain injury, traumatic brain injury, multiple sclerosis, autoimmune and inflammatory diseases afflicting the CNS, ataxia, spinocerebellar ataxia type 1, cerebral bleeding due to solitary cerebral amyloid angiopathy, amyotrophic lateral sclerosis, chronic inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease and psoriasis, arthritis, peritonitis, systemic inflammation, renal dysfunction and hepatotoxicity in endotoxemia, asthma, sepsis, colitis, inflammation-induced organ injury caused by hemorrhage and resuscitation, inflammatory injury in chronic renal allograft disease, lupus, heart disease, atherosclerosis, hypertension, restenosis, leukopenia, metabolic syndrome X, hair loss, severe acute respiratory syndrome coronavirus, stimulant addiction, cocaine addiction, bone loss, glaucoma, mild cognitive impairment, drug-induced dyskinesia, pain, neuropathic pain, nociceptive pain, poisoning, hypersomnia, smoking withdrawal, HIV infections, schistomiasis, urinary incontinence, xerostomia, essential tremor and tardive dyskinesia, prion disease, migraine, systemic amyloidosis or condition, cognitive impairment in multiple sclerosis, narcolepsy, hyperkinesis, Wernicke-Korsakoff disease (WKD), delirium, behavioural dysregulation, apathy, irritability, psychosis, mania, tics, panic, personality disorders, anorexia nervosa, autism spectrum disorders (ASD), myasthenia gravis, poststroke aphasia or schistosomiasis.

According to a particularly preferred embodiment, the disease is selected from Alzheimer's Disease, Parkinson's disease, amyotrophic lateral sclerosis and progressive supranuclear palsy.

The effective amount of thiadiazolidine derivative is comprised between 400 and 1,000 mg, preferably between 400 and 800 mg/day, more preferably between 400 and 600 mg.

The therapeutically effective amount of cholinesterase derivative is the amount thereof commonly prescribed, preferably the minimum dose or even below, as efficacy is improved by the combination according to the present application.

For example, in the case of Donepezil, the therapeutically effective amount thereof is comprised between 3 and 10 mg/day, preferably between 3 and 5 mg, more preferably is 3 mg. The amount may also be comprised between 1 and 3 mg/day.

In the case of Galantamine, the effective amount is comprised between 4 and 24 mg, preferably between 4 and 16 mg, more preferably between 4 and 12 mg, even more preferably between 4 and 8 mg. The amount may also be comprised between 1 and 4 mg/day.
In the case of Rivastigmine, the effective amount is comprised between 1.5 and 12 mg/day, preferably between 1.5 and 9.5 mg, more preferably between 1.5 and 6 mg, even more preferably between 1.5 and 4.6 mg, and most preferably between 1.5 and 3 mg.

The effective amount of at least one thidiazolidinedione derivative or a pharmaceutically acceptable salt or solvate thereof and the effective amount of a cholinesterase inhibitor may be administered by oral administration, subcutaneous administration, including subcutaneous implants and injections, by intravenous administration, cutaneous administration (e.g. patches), intramuscular administration, intraperitoneal, sublingual or by nasal administration.

When the effective amounts of the thidiazolidinedione derivative and the cholinesterase inhibitor are comprised in the same medicament, the administration of both drugs will evidently be performed by the same route, which may be selected from the above detailed administration routes. For example, both drugs may be administered as an oral medicament; or both drugs may be administered as a subcutaneous medicament; etc.

When the effective amounts of the thidiazolidinedione derivative and the cholinesterase inhibitor are comprised in separate medicaments, the administration of each of them may be performed by the same or by different routes, which may be selected from the above detailed administration routes. For example, both the medicament comprising the thidiazolidinedione derivative and the medicament comprising the cholinesterase inhibitor may be administered orally. As another example, the medicament comprising the thidiazolidinedione derivative may be administered orally, while the medicament comprising the cholinesterase inhibitor is administered subcutaneously; etc. All possible combinations of routes of administration of the both medicaments and drugs are meant to be comprised within the present invention.

In the above defined medical kit, according to a preferred embodiment, said medical kit further comprises (iii) a supply of a cholinesterase inhibitor, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, adjuvant and/or vehicle.

In the following, the invention is further illustrated in the following examples.

They should in no case be interpreted as a limitation of the scope of the invention as defined in the claims.
EXAMPLES

An exploratory Phase IIa study with the thiazolidinedione derivative 4-benzyl-2-naphtalen-1-yl-1,2,4-thiazolidine-3,5-dione was performed, in order to evaluate the safety and tolerability of four escalated doses of the thiazolidinedione derivative. The study was performed with 30 patients, currently receiving a cholinesterase inhibitor treatment (particularly, Donepezil, Galantamine or Rivastigmine), on a stable and well tolerated dosage for at least 2 months prior to baseline evaluation; the cholinesterase inhibitor treatment was maintained constant during the duration of the study. The patients were administered either escalating doses from 400 mg to 1,000 mg during 20 weeks, once daily, of said thiazolidinedione derivative ("Active" group), or a matching placebo ("Placebo" group). That is, patients in the Placebo group received cholinesterase inhibitor treatment and a placebo, and patients in the Active group received cholinesterase inhibitor treatment and thiazolidinedione derivative treatment. Particularly, 20 patients were treated with Active, and another 10 patients with Placebo. All the patients had been diagnosed of mild to moderate Alzheimer's Disease; they were aged in the range of 55 to 84 years; 20 were women and 10 were men. Patients in Active and Placebo groups were well balanced for demographics, medical history, disease stage and duration, concomitant medication and anticholinesterasic treatment. Regarding the anticholinesterasic treatment, the following was the detailed distribution of the particular anticholinesterasic treatments among the patients:

<table>
<thead>
<tr>
<th>Anticholinesterasic treatment</th>
<th>Active (n=20)</th>
<th>Placebo (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Galantamine</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

The protocol established the following escalating regime for the thiazolidinedione derivative:
<table>
<thead>
<tr>
<th>Weeks No.</th>
<th>Once daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-4</td>
<td>400 mg</td>
</tr>
<tr>
<td>Weeks 5-8</td>
<td>600 mg</td>
</tr>
<tr>
<td>Weeks 9-14</td>
<td>800 mg</td>
</tr>
<tr>
<td>Weeks 15-20</td>
<td>1,000 mg</td>
</tr>
</tbody>
</table>

During the study, adverse events were monitored by the study staff. Further, efficacy endpoints related to the assessment of cognition and global functioning were monitored at baseline and regularly throughout the study. In addition, Global Clinical Assessment was performed at the end of the double-blind period.

The patients that were administered placebo worsened their state during the study in comparison with the baseline, according to several clinical instruments which will be further detailed hereinafter. It has been found that the state of the patients being administered Active was not only not worsened, but even improved, by the combined treatment with a thiazolidinedione derivative and a cholinesterase inhibitor, after a treatment of only 20 weeks. While patients only receiving treatment with cholinesterase inhibitors presented a detectable decline of their mental and physical state during this period of time, patients on the combined treatment not only did not further decline during this period, but even improved their mental and physical state. Further details are given in FIGURES.

The main efficacy determinations were:

1) **Mini-Mental State Examination (MMSE)**

   The MMSE is a frequently used screening instrument for AD drug studies. It evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, ability to create a sentence and ability to copy two intersecting polygons. A lower score indicates greater cognitive impairment. The highest possible (best) score is 30. For further detail, see for example *J. Psychiatr. Res. 1975, 12, 189*, which is herewith incorporated by reference.

2) **Alzheimer's Disease assessment Scale (ADAS-cog+)**

   Cognition was assessed using the modified ADAS-cog (ADAS-cog+), which is a composite questionnaire assessing memory, language, praxis functions, delayed word recall, concentration distractibility, digit cancellation and maze completion.
The total score is calculated from the ADAS-cog+ sub scale scores and ranges from 0 (No impairment) to 95 (Errors in all sub-tests). Therefore, higher scores are associated with greater cognitive impairment. For further detail, see for example *Alzheimer Dis Assoc Disord.* 2004, 18(4), 236-40, which is here with incorporated by reference.

3) **Global Clinical Assessment**

At the end of the study the investigator evaluated the overall clinical state of the patients, in comparison with their basal state at the start of the study, in a seven point scale: markedly better, much better, slightly better, similar, slightly worse, much worse, markedly worse.

**Efficacy**

**Example 1: Mini-Mental State Examination (MMSE)**

The MMSE score for each patient, both for the patients being administered Placebo or Active, was determined at the beginning of the Phase Ila study, before administrating neither Placebo nor Active, and at the end of the study, once the 20 weeks of study were completed and the last dose was administered. In **Figure 1**, the mean change in MMSE score from baseline (considered “0”), in absolute figures, for both Placebo and Active groups, are shown.

As may be observed, the patients being administered Placebo showed a decline in the MMSE score during the 20 weeks, specifically by a mean value of 1.13 points in the MMSE scale, according to the expected rate of around 2.5 points per year. That means, their neurodegenerative disease continued worsening during the study.

Meanwhile, the patients being administered Active, not only did not decline, maintaining the same MMSE score, but even experienced an improvement with respect to the baseline value, specifically a mean value of 0.56 points in the MMSE scale.

Therefore, a clear improvement in the MMSE score was detected in the patients receiving concurrently a cholinesterase inhibitor treatment and Active, in comparison with those being treated with a cholinesterase inhibitor and Placebo; i.e., the combined treatment of a cholinesterase inhibitor and the thiazolidinedione derivative has shown clearly more effective than the treatment with cholinesterase inhibitor alone, despite the Phase Ila study being a relatively short study, which was initially designed for proving safety and tolerability of the Active, and not for determining efficacy of the Active.
No significant differences in the results were detected with regard of the particular anticholinesterasic treatment of the patients (Donepezil, Galantamine or Rivastigmine).

**Example 2: Alzheimer’s Disease assessment Scale (ADAS-cog+)**

The ADAS-cog+ score for each patient, both for the patients being administered Placebo and Active, was determined several times along the phase Ila study (baseline, week 4, week 8, week 14 and week 20).

In **Figure 2**, the mean change in ADAS-cog+ score from baseline (considered "0"), in absolute figures, for both Placebo and Active groups, are shown.

As may be observed, the patients being administered Placebo suffered an increase in the ADAS-cog+ score during the 20 weeks, specifically by a mean value of 3.13 points in the ADAS-cog+ score, according to the expected rate of around 6 to 8 points per year, which means that their neurodegenerative disease continued worsening during the study.

Meanwhile, the patients being administered Active, not only did not worsen their state, maintaining the same MMSE score, but even experienced an improvement with respect to the baseline value, specifically a mean reduction of 1.60 points in the ADAS-cog+ score.

Therefore, a clear improvement in the ADAS-cog+ score was detected in the patients receiving concurrently a cholinesterase inhibitor treatment and Active, in comparison with those being treated with a cholinesterase inhibitor and Placebo; i.e., the combined treatment of a cholinesterase inhibitor and the thiazolidinedione derivative has shown clearly more effective than the treatment with cholinesterase inhibitor alone, despite the Phase Ila study being a relatively short study, which was initially designed for proving safety and tolerability of the Active, and not for determining efficacy of the Active.

No significant differences in the results were detected with regard of the particular anticholinesterasic treatment of the patients (Donepezil, Galantamine or Rivastigmine).

**Example 3: Global Clinical Assessment**

At the beginning and the end of the study the overall clinical state of the patients was evaluated, in order to establish a comparison between their basal state and final state, using a seven point scale. In **Figure 3**, the global results for all the patients that have participated in the study are shown.
As may be observed, the clinical state evolution in the Placebo group is comprised between *slightly better* and *much worse*, while in the Active group it is comprised between *slightly better* and *slightly worse*, the highest percentages being found at *similar* and *slightly better*. Therefore, evolution of the clinical state of the patients is clearly improved in the patients receiving a concurrent treatment with a cholinesterase inhibitors and the Active, in comparison with those patients being treated with a cholinesterase inhibitor alone, despite the relatively short duration of the study, i.e. 20 weeks.

No significant differences in the results were detected with regard of the particular anticholinesterasic treatment of the patients (Donepezil, Galantamine or Rivastigmine).

### ADVERSE EVENTS

**Example 4: Adverse Events by System-Organ Classes**

All the adverse events that occurred during the Phase Ila study were monitored, both in the placebo and the Compound population. The observed adverse events were classified in the following System-Organ Classes:

- Cardiac disorders
- Ear and labyrinth disorders
- Eye disorders
- Gastrointestinal disorders
- General and administration disorders
- Infections and infestations
- Injuries
- Investigations and laboratory results
- Metabolism and nutrition disorders
- Musculoskeletal disorders
- Psychiatric disorders
- Nervous System disorders
- Renal and urinary disorders
- Respiratory and thoracic disorders
- Skin disorders
- Vascular disorders

Particularly, the following particular adverse events were classified within the above classes:
Cardiac disorders:
- Bradycardia

Ear and labyrinth disorders:
- Vertigo

Eye disorders:
- Diplopia, eyelid oedema

Gastrointestinal disorders:
- Abdominal pain, constipation, diarrhoea, eructation, pale faeces, flatulence, frequent bowel movements, nausea

General and administration disorders
- Fatigue, inflammation, vessel puncture site haematoma

Infections and infestations
- Erysipelas, herpes virus infection

Injuries
- Excoriation, fall, skin laceration

Investigations and lab. Results
- Altered blood levels, blood pressure and weight; breath sounds

Metabolism and nutrition disorders
- Folate deficiency, vitamin B12 deficiency

Musculoskeletal disorders
- Arthralgia, limb discomfort, muscle spasms, temporomandibular joint syndrome

Psychiatric disorders
- Apathy

Nervous System disorders
- Aura, dizziness, headache, somnolence

Renal and urinary disorders
- Micturition urgency

Respiratory and thoracic disorders
- Cough

Skin disorders
- Acne, pruritus

Vascular disorders
- Haematoma, hypertension, orthostatic hypotension
The statistics of the observed adverse events are shown in Figure 4. Both the absolute number (n) of patients and the percentage within each of the administration groups, i.e. Active and Placebo, is indicated. In the right column, the group with highest percentage is indicated.

As may be observed, unexpectedly and surprisingly, in 12 out of 16 System-Organ Classes, the adverse events were higher in the Placebo group (being administered only cholinesterase inhibitors) than in the Active group (being administered both cholinesterase inhibitors and the thiaiazolidinedione derivative). Especially unexpected is the reduction in gastrointestinal adverse effects, which are typical and frequent side effects of the treatment with cholinesterase inhibitors. The results suggest that the adverse effects occurring during the treatment with cholinesterase inhibitors are reduced by co-administering the Compound, without significantly adding other adverse effects.

No significant differences in the results were detected with regard of the particular anticholinesterasic treatment of the patients (Donepezil, Galantamine or Rivastigmine).
CLAIMS

1) A combination of at least one thiadiazolidinedione derivative of formula (I):

\[
\begin{array}{c}
\text{O} \\
\text{S} \\
\text{N} \\
\text{R}^a \\
\text{R}^b \\
\text{N} \\
\text{O}
\end{array}
\]

wherein:

- R\(^a\) and R\(^b\) are independently selected from hydrogen, substituted or unsubstituted C1-C6 alkyl, cycloalkyl, aryl, -(Z)_n-aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted benzo-fused heterocyclic ring system having 2 or 3 rings, -OR, -C(0)R, -C(0)OR, -(Z)_n-C(0)OR and -S(0)\(^t\)
- Z is independently selected from -C(R')(R")-; -O-, -C(=NR')-, -S(0)\(^t\) and -N(R')-;
- n is zero, one or two;
- t is zero, one, two or three;
- R' and R" are independently selected from hydrogen, alkyl, aryl and heterocyclic or may together form a C=O group;

and a therapeutically effective amount of at least one cholinesterase inhibitor or a pharmaceutically acceptable salt or solvate thereof, wherein the cholinesterase inhibitor may form part of a separate medicament or the same medicament.

2) A combination according to claim 1, wherein the thiadiazolidinedione derivative has formula (II):
wherein:

5  \( R^a \) is an organic group comprising at least one aromatic ring and having at least 8 atoms selected from C or O;

\( R^c, R^d \) are independently selected from hydrogen and alkyl, or \( R^c \) and \( R^d \) together can form a group =0;

10 \( R_1, R_2, R_3, R_4, R_5 \) are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyi, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycyl, \(-\text{COR}_7, \text{-C(0)OR}_7, \text{-C(0)N}_R_7R_8, \text{-C}_N, \text{-OR}_7, \text{-OC(0)R}_7, \text{-S(0)}_R_7R_8, \text{-NR}_7C(0)R_8, \text{-NO}_2, \text{-N=CR}_7R_8 \) or halogen;

15 \( t \) is zero, one, two or three,

\( R_7 \) and \( R_8 \) are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyi, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocycyl, halogen;

20 or a pharmaceutically acceptable salt or solvate thereof.

3) The combination according claim 1, wherein the thiadiazolidinedione derivative of formula (I) is selected from:

4-benzyl-2-phenethyl-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-diphenylmethyl-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-naphthalen-1-yl-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-(4-methoxy-benzyl)-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-(4-phenoxy-phenyl)-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-(2-tert-butyl-6-methyl-phenyl)-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-(4-methyl-benzyl)-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-(2-benzyl-phenyl)-[1,2,4]thiadiazolidine-3,5-dione,
2-benzo[1,3]dioxol-5-yl-4-benzyl-[1,2,4]thiadiazolidine-3,5-dione,
4-benzyl-2-methyl-[1,2,4]thiadiazolidine-3,5-dione,
or a pharmaceutically acceptable salt or solvate thereof.

4) The combination according to claim 3, wherein the thia-
diazolidinedione derivative is 4-benzyl-2-naphthalen-1-yl-1,2,4-
thiadiazolidine-3,5-dione.

5) The combination according to any one of claims 1 to 4, wherein the
colinesterase inhibitor is selected from the group consisting of Donepezil, Galantamine,
Rivastigmine, tacrine hydrochloride, huperzine A, acotiamide, dimebolin, DEBIO 9902,
EN101, phenserine tartrate, R-phenserine, stacofylline hydrochloride (S-9977, S-9977-2),
NP-61, bisnorcymserine, COL-204, SPH 1371, SPH 1373, SPH 1375, SP 04, CM
2433, metrifonate, 7-methoxytacrine (7 MEOTA), P 11149, Arisugacin, FR 152558,
HUP 13, isovanihuperzine A (IVHA), MHP 133, NP 7557, P 10358, P 11012,
physostigmine salicylate, veclacrine maleate (HP-029, P83-6029A), epastigmine
tartrate (L-693487), ipidacrine, zanapezil, ganstigmine, icopezil maleate (CP-18954,
CP-18954-1 1), KW 5092, quistigmine (HP-290, NXX-066), SM 10888, T 82, TAK
802, zifrosilone MDL-73745), BGC 201259, CHF 2060, C1 1002, E 2030, ER 127528,
ET 142, F 3796, huprine X, MF 247, MF 268 bitartrate, MF 8615, P 26, PD 142012, RO
465934, SS 20, thiatolserine, tolserine tartrate, UR 1827, edrophonium, demecarium,
ambenonium, neostigmine bromide, dehydroevodiamine chloride, eseroline,
imperatorin, scopoletin (SCT), huperzine A (Hup A), heptylstigmine tartrate (MF-201 ),
suronacrine maleate (HP-128), UCB-1 1056, berberine iodide, norpyridostigmine,
quilostigmine (HP-290, NXX-066), THB-013, PD-1 42676, terestigmine tartrate (CHF-
2060), thiacymserine, MF-8615, MF-268 bitartrate, anseculin hydrochloride (KA-
672. HCI), ensaculin hydrochloride, icopezil maleate (CP-118954), eserine salicylate, physostigmine salicylate, JWS-USC-75IX, P 11467, P-10358, bis(7)-tacrine, HMR-2420, CP-126998, TV-3279, MSF, THA-C8, subergorgic acid, suberogorgin, SPH-1286, huperzine B (Hup B), pyridostigmine bromide (Ro-1-5130), huprine Y, coronaridine, RS-1233, kobophenol A, bis(12)-huperine, RS-1259, ITH-4012, TK-19, T-81, TH-171, TH-185, distigmine bromide (BC-51), (-)-9-dehydrogalanthaminium bromide, memoquin, scophotoin 7-O-beta-D-glucopyranoside (NSC-404560), scopolin (SCN), scopoloside, BW-284c51, withaferin A (NSC-101088), withaferine (NSC-273757), (+)-corynoline, corynoline, (S)-(−)-oxypeucedanin, oxypeucedanin, (−)-voacangine, carbomethoxyibogaine, voacangine, diekol, phlorofucofuroeckol (PFF), phlorofucofuroeckol A, (−)-3-0-acetylspectaline hydrochloride and rhaphiasaponin 1, or pharmaceutically acceptable salts or solvates thereof.

6) The combination according to claim 5, wherein the cholinesterase inhibitor is selected from the group consisting of Donepezil, Galantamine and Rivastigmine, or a pharmaceutically acceptable salt or solvate thereof.

7) A pharmaceutical composition comprising a therapeutically effective amount of at least one thiazolidinedione derivative of formula (I) as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, a therapeutically effective amount of a cholinesterase inhibitor, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutical carrier, adjuvant and/or vehicle.

8) A medical kit comprising (i) a supply of thiazolidinedione derivative as defined in any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, in dosage units, wherein each of said dosage units contains a therapeutically effective amount of said thiazolidinedione derivative or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, adjuvant and/or vehicle, and (ii) instructions for administering the thiazolidinedione derivative in combination with a cholinesterase inhibitor, or a pharmaceutically acceptable salt or solvate thereof.

9) A medical kit according to claim 8, further comprising (iii) a supply of a cholinesterase inhibitor, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier, adjuvant and/or vehicle.
10) A combination according to any one of claims 1 to 6 or a composition according to claim 7 or a kit according to any one of claims 8 or 9 for use as a medicament.

11) A combination according to any one of claims 1 to 6 or a composition according to claim 7 or a kit according to any one of claims 8 or 9 for use in the treatment of a GSK3 or cholinesterase mediated disease.

12) A combination or composition or kit according to claim 11, wherein the disease is selected from Alzheimer's disease, Parkinson's disease or condition, dementia, vascular dementia, cerebrovascular dementia, dementia with Lewy bodies, dementia with argyrophilic grains (AG), frontotemporal dementia, Pick's disease, progressive supranuclear palsy, subacute panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, guam parkinsonism-dementia complex, corticobasal degeneration, argyrophilic grain disease, familial frontotemporal dementia and parkinsonism linked to chromosome 17 due to mutations in the tau gene (FTDP-17-tau), AIDS associated dementia, Huntington's disease, Lewy body disease, bipolar disorder, depression, schizophrenia, epilepsy, mood disorders, autism, attention deficit hyperactivity disorder, Down's syndrome, ischemia/reperfusion and shock, brain injury, traumatic brain injury, multiple sclerosis, autoimmune and inflammatory diseases afflicting the CNS, ataxia, spinocerebellar ataxia type 1, cerebral bleeding due to solitary cerebral amyloid angiopathy, amyotrophic lateral sclerosis, chronic inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease and psoriasis, arthritis, peritonitis, systemic inflammation, renal dysfunction and hepatotoxicity in endotoxemia, asthma, sepsis, colitis, inflammation-induced organ injury caused by hemorrhage and resuscitation, inflammatory injury in chronic renal allograft disease, lupus, heart disease, atherosclerosis, hypertension, restenosis, leukopenia, metabolic syndrome X, hair loss, severe acute respiratory syndrome coronavirus, stimulant addiction, cocaine addiction, bone loss, glaucoma, mild cognitive impairment, drug-induced dyskinesia, pain, neuropathic pain, nociceptive pain, poisoning, hypersomnia, smoking withdrawal, HIV infections, schistosomiasis, urinary incontinence, xerostomia, essential tremor and tardive dyskinesia, prion disease, migraine, systemic amyloidosis or condition, cognitive impairment in multiple sclerosis, narcolepsy, hyperkinesia, Wernicke-Korsakoff disease (WKD), delirium, behavioural
dysregulation, apathy, irritability, psychosis, mania, tics, panic, personality disorders, anorexia nervosa, autism spectrum disorders (ASD), myasthenia gravis, poststroke aphasia or schistosomiasis.

13) A combination or composition or kit according to claim 11 for the treatment of Alzheimer's Disease.

14) A thiazolidinedione derivative as defined in any one of claims 1 to 4, for use in the reduction of side effects caused by the treatment with a cholinesterase inhibitor.
FIGURE 1

MMSE: mean change from baseline for patients who completed were escalated up to 1,000 mg

- - - Placebo

- - - Active

FIGURE 2

Mean Adas-cog scores: changes from baseline for patients who were escalated up to 1,000 mg

- - - Placebo

- - - Active
FIGURE 3
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FIGURE 4
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER


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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) A61K

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

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

EPO-Internal, BEI LSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>DE 44 20 522 Al (BAYER AG [DE]) 14 December 1995 (1995-12-14) page 3, lines 18-53 claims 1-8; table 1</td>
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<td>US 3 818 024 A (KRENZER J) 18 June 1974 (1974-06-18) column 5, line 16 - column 6, line 9 claims 1-6</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another invention

"O" document by another person for which the claimed invention is obvious, or which contains similar disclosenre or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

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

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

"A" document member of the same patent family

Date of the actual completion of the international search: 1 August 2011

Date of mailing of the international search report: 08/08/2011

Name and mailing address of the ISA:

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Renard, Delphine

Final text of the search report: The claims of the international application 08/08/2011 are considered individually. Each claim is considered for the relevance to the closest prior art. Additional claims may be made.

Form PCT/ISA/210 (second sheet) (April 2005)
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