activated calcium channel subunit expression in a genetic model of absence epilepsy in the rat. Brain Res Mol Brain Res 75:159-165; Broicher T et al. (2008) Correlation of T-channel coding gene expression, IT, and the low threshold Ca2+ spike in the thalamus of a rat model of absence epilepsy. Mol Cell Neurosci 39:384-399; Powell KL et al. (2009) A $Ca_v3.2$ T-type calcium channel point mutation has splice-variant-specific effects on function and segregates with seizure expression in a polygenic rat model of absence epilepsy. J Neurosci 29:371-380). Acquired channelopathies involving long-term alterations in thalamic $Ca_v3.2$ channels have also been described for a mouse model of temporal lobe epilepsy (Graef JD et al. (2009) An acquired channelopathy involving thalamic T-type Ca2+ channels after status epilepticus. J Neurosci 29:4430-4441).

Several lines of evidence link mutations in the $Ca_v3.1$ subtype with epilepsy in humans and in rodent animal models. Genetic variants have been detected in patients with juvenile myoclonic epilepsy, another form of IGE (Lory P et al. (2010) Calcium channelopathies in inherited neurological disorders: Relevance to drug screening for aquired channel disorders. IDrugs 13:467-471). Overexpression of $Ca_v3.1$ channels in mice leads to frequent bilateral cortical seizures (Ernst WL et al. (2009) Genetic enhancement of thalamocortical network activity by elevating alpha 1g-mediated low-voltage-activated calcium current induces pure absence epilepsy. J Neurosci 29:1615-1625) and $Ca_v3.1$ knockout mice are protected from absence seizures (Kim D et al. (2001) Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking alpha (1G) T-type Ca(2+) channels. Neuron 31:35-45; Song I et al. (2004) Role of the alpha1G T-type calcium channel in spontaneous absence seizures in mutant mice. J Neurosci 24:5249-5257).

It was surprisingly found that N-[1-(5-Cyano-pyridin-2-ylmethyl)-1H-pyrazol-3-yl]-2-[4-(1-trifluoromethyl-cyclopropyl)-phenyl]-acetamide showed a synergistic effect in a mouse model of generalized tonic-clonic seizures when administered together with existing AEDs.

Summary

In one aspect, there is provided a pharmaceutical combination comprising a first active ingredient which is N-[1-(5-Cyano-pyridin-2-ylmethyl)-1H-pyrazol-3-yl]-2-[4-(1-trifluoromethyl-cyclopropyl)-phenyl]-acetamide or a pharmaceutically acceptable salt thereof and a second active ingredient which has an anti-epileptic effect, or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a pharmaceutical combination as described herein for use as a medicament.

In yet another aspect, there is provided a pharmaceutical composition containing, as active principle, N-[1-(5-Cyano-pyridin-2-ylmethyl)-1H-pyrazol-3-yl]-2-[4-(1-trifluoromethyl-cyclopropyl)-phenyl]-acetamide, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient, wherein the pharmaceutical composition is to be administered in combination with a second pharmaceutical composition containing, as active principle, 5*H*-dibenzo[*b,f*]azepine-5-carboxamide, (*RS*)-3-ethyl-3-methyl-pyrrolidine-2,5-dione, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, (*S*)-2-(2-oxopyrrolidin-1-yl)butanamide, 10,11-dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide, 2-propylpentanoic acid, *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide, (2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide, 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione, 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one, (*S*)-10-acetoxy-10,11-dihydro-5*H*-dibenz[b,f]azepine-5-carboxamide, (3-carbamoyloxy-2-phenylpropyl) carbamate, 1-(aminomethyl)cyclohexaneacetic acid, (*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide, 5'-(2-cyanophenyl)-1'-phenyl-2,3'-bipyridinyl-6'(1'H)-one, 5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione, 5,5-diphenylimidazolidine-2,4-dione, 2-(2-oxopyrrolidin-1-yl)acetamide, (3*S*)-3-(aminomethyl)-5-methylhexanoic acid, 5-ethyl-5-phenyl-1,3-diazinane-4,6-dione, ethyl (2-amino-4-((4-fluorobenzyl)amino)phenyl)carbamate, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, (*RS*)-(*E*)-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol, (3*R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-buten-1-yl]-3-piperidinecarboxylic acid, 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, (*RS*)-4-aminohex-5-enoic acid, or benzo[d]isoxazol-3-ylmethanesulfonamide, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

In another aspect, there is provided a pharmaceutical composition containing, as active principle, 5*H*-dibenzo[*b,f*]azepine-5-carboxamide, (*RS*)-3-ethyl-3-methyl-pyrrolidine-2,5-dione, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, (*S*)-2-(2-oxopyrrolidin-1-yl)butanamide, 10,11-dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide, 2-propylpentanoic acid, *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide, (2*S*)-2-[(4*R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide, 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione, 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one, (*S*)-10-acetoxy-10,11-dihydro-5*H*-dibenz[b,f]azepine-5-carboxamide, (3-carbamoyloxy-2-phenylpropyl) carbamate, 1-(aminomethyl)cyclohexaneacetic acid, (*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide, 5'-(2-cyanophenyl)-1'-phenyl-2,3'-bipyridinyl-6'(1'H)-one, 5-ethyl-5-

phenyl-1,3-diazinane-2,4,6-trione, 5,5-diphenylimidazolidine-2,4-dione, 2-(2-oxopyrrolidin-1-yl)acetamide, (*3S*)-3-(aminomethyl)-5-methylhexanoic acid, 5-ethyl-5-phenyl-1,3-diazinane-4,6-dione, ethyl (2-amino-4-((4-fluorobenzyl)amino)phenyl)carbamate, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, (*RS*)-(*E*)-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol, (*3R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-buten-1-yl]-3-piperidinecarboxylic acid, 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, (*RS*)-4-aminohex-5-enoic acid, or benzo[d]isoxazol-3-ylmethanesulfonamide, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient, wherein the pharmaceutical composition is to be administered in combination with a second pharmaceutical composition containing, as active principle, N-[1-(5-Cyano-pyridin-2-ylmethyl)-1H-pyrazol-3-yl]-2-[4-(1-trifluoromethyl-cyclopropyl)-phenyl]-acetamide, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

In another aspect, there is provided a kit of parts comprising a first pharmaceutical composition containing, as active principle, N-[1-(5-Cyano-pyridin-2-ylmethyl)-1H-pyrazol-3-yl]-2-[4-(1-trifluoromethyl-cyclopropyl)-phenyl]-acetamide, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient; and a second pharmaceutical composition containing, as active principle, 5*H*-dibenzo[*b,f*]azepine-5-carboxamide, (*RS*)-3-ethyl-3-methyl-pyrrolidine-2,5-dione, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, (*S*)-2-(2-oxopyrrolidin-1-yl)butanamide, 10,11-dihydro-10-oxo-5*H*-dibenz[b,f]azepine-5-carboxamide, 2-propylpentanoic acid, *N*-(5-sulfamoyl-1,3,4-thiadiazol-2-yl)acetamide, (*2S*)-2-[(*4R*)-2-oxo-4-propylpyrrolidin-1-yl]butanamide, 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione, 5-(2-chlorophenyl)-7-nitro-1,3-dihydro-1,4-benzodiazepin-2-one, (*S*)-10-acetoxy-10,11-dihydro-5*H*-dibenz[b,f]azepine-5-carboxamide, (3-carbamoyloxy-2-phenylpropyl) carbamate, 1-(aminomethyl)cyclohexaneacetic acid, (*R*)-2-acetamido-*N*-benzyl-3-methoxypropanamide, 5'-(2-cyanophenyl)-1'-phenyl-2,3'-bipyridinyl-6'(1'H)-one, 5-ethyl-5-phenyl-1,3-diazinane-2,4,6-trione, 5,5-diphenylimidazolidine-2,4-dione, 2-(2-oxopyrrolidin-1-yl)acetamide, (*3S*)-3-(aminomethyl)-5-methylhexanoic acid, 5-ethyl-5-phenyl-1,3-diazinane-4,6-dione, ethyl (2-amino-4-((4-fluorobenzyl)amino)phenyl)carbamate, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide, (*RS*)-(*E*)-4,4-dimethyl-1-[3,4(methylenedioxy)-phenyl]-1-penten-3-ol, (*3R*)-1-[4,4-bis(3-methyl-2-thienyl)-3-buten-1-yl]-3-piperidinecarboxylic acid, 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, (*RS*)-4-aminohex-5-enoic acid, or benzo[d]isoxazol-3-ylmethanesulfonamide, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.

Description of the invention:

1) In a first embodiment the present invention relates to a pharmaceutical combination comprising a first active ingredient which is N-[1-(5-Cyano-pyridin-2-ylmethyl)-1H-pyrazol-3-yl]-2-[4-(1-trifluoromethyl-cyclopropyl)-phenyl]-acetamide (hereinafter also referred to as "COMPOUND 1") or a pharmaceutically acceptable salt thereof and a second active ingredient which has an anti-epileptic effect, or a pharmaceutically acceptable salt thereof.

COMPOUND 1 is a selective and orally available triple T-type calcium channel blocker, i.e. COMPOUND 1 blocks the three T-type calcium channel subtypes $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$. COMPOUND 1 has been described to be useful in the prevention/prophylaxis