Abstract:

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Title: AGENT FOR IBD TREATMENT

Abstract: Use of an mTOR inhibitor as - an agent for treating or preventing inflammatory bowel disease - a disease modifier in the treatment of inflammatory bowel diseases, - as a disease modifier in the progression of inflammatory bowel disease-mediated events, - as a modifier in inflammatory bowel disease-initiation events, - an agent for the delay of the onset of inflammatory bowel disease, optionally in combination with a second drug substance.
Agent for IBD treatment

The present invention relates to agents for IBD treatment, more specifically to the use of mTOR inhibitors for IBD treatment.

5 Inflammatory bowel disease (IBD), is the general name for diseases that cause inflammation in the intestines and includes e.g. Crohn's disease, ulcerative colitis, ulcerative proctitis. Crohn's disease (CD) is an inflammatory process that can affect any portion of the digestive tract, but is most commonly seen in the last part of the small intestine otherwise called the (terminal) ileum and cecum. Altogether this area is also known as the ileocecal region. Other cases may affect one or more of: the colon only, the small bowel only (duodenum, jejunum and/or ileum), the anus, stomach or esophagus. In contrast with ulcerative colitis, CD usually doesn't affect the rectum, but frequently affects the anus instead. The inflammation extends deep into the lining of the affected organ. The inflammation can cause pain and can make the intestines empty frequently, resulting in diarrhea. Crohn's disease may also be called enteritis. Granulomatous colitis is another name for Crohn's disease that affects the colon. Ileitis is CD of the ileum which is the third part of the small intestine. Crohn's colitis is CD affecting part or all of the colon.

10 Ulcerative colitis (UC) is an inflammatory disease of the large intestine, commonly called the colon. UC causes inflammation and ulceration of the inner lining of the colon and rectum.

15 The inflammation of UC is usually most severe in the rectal area with severity diminishing (at a rate that varies from patient to patient) toward the cecum, where the large and small intestine join. Inflammation of the rectum is called proctitis. Inflammation of the sigmoid colon (located just above the rectum) is called sigmoiditis. Inflammation involving the entire colon is termed pan-colitis. The inflammation causes the colon to empty frequently resulting in diarrhea. As the lining of the colon is destroyed ulcers form releasing mucus, pus and blood. Ulcerative proctitis is a form of UC that affects only the rectum.

Inflammatory bowel disease (IBD) as used herein e.g. includes disorders that cause inflammation in the intestines, e.g. including Crohn's disease, e.g. enteritis, granulomatous colitis, ileitis, Crohn's colitis; e.g. sigmoiditis, pan-colitis; ulcerative proctitis; and includes manifestations of inflammatory bowel disease, such as pain, diarrhea. Disorders includes diseases.
An mTOR inhibitor as used herein is a compound which targets intracellular mTOR ("mammalian Target of rapamycin"). mTOR is a family member of phosphatidylinositol 3-kinase (P13-kinase) related kinase. The compound rapamycin and other mTOR inhibitors inhibit the mTOR pathway via a complex with its intracellular receptor FKBP12 (FK506-binding protein 12). mTOR modulates translation of specific mRNAs via the regulation of the phosphorylation state of several different translation proteins, mainly 4E-PB1, P70S6K (p70S6 kinase 1) and eEF2. mTOR inhibitors as used herein include rapamycin and rapamycin derivatives.

Rapamycin is a known macrolide antibiotic produced by Streptomyces hygroscopicus and is a compound of formula

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Rapamycin derivatives, e.g. include
- 40-O-alkyl-rapamycin derivatives, such as 40-O-hydroxyalkyl-rapamycin derivatives, e.g. 40-O-(2-hydroxy)-ethyl-rapamycin (everolimus),
- 32-deoxo-rapamycin derivatives and 32-hydroxy-rapamycin derivatives, such as 32-deoxorapamycin,
- 16-0-substituted rapamycin derivatives such as 16-pent-2-ynyl-32-deoxorapamycin, 16-pent-2-ynyl-32(S or R)-dihydro-rapamycin, 16-pent-2-ynyl-32(S or R)-dihydro-40-O-(2-hydroxy)-ethyl-rapamycin,
- rapamycin derivatives which are acylated at the oxygen group in position 40, e.g. 40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-rapamycin (also known as CCI779 or temsirolimus),
- rapamycin derivatives which are substituted in 40 position by heterocyclyl, e.g. 40-epi-(tetrazolyl)-rapamycin (also known as ABT578, zotarolimus, Zomaxx),
- the so-called rapalogs, e.g. as disclosed in WO9802441 or WO01 14387, e.g. such as 40-O-dimethylphosphinyl-rapamycin, including AP23573,
- compounds disclosed under the name biolimus (biolimus, biolimus A9), including 40-O-(2-ethoxy)-ethyl-rapamycin,
- compounds disclosed under the name TFA-93, AP23464, AP23675 or AP23841;
- compounds as disclosed in WO2004101583, WO9205179, WO9402136, WO9402385 or WO9613273.

A preferred compound is e.g. 40-0- (2-hydroxyethyl)-rapamycin disclosed in Example 8 in WO9409010 (referred hereinafter as Compound A).

Another preferred compound is 32-deoxorapamycin.

Another preferred compound is 16-pent-2-ynyloxy-32 (S)-dihydro-rapamycin as disclosed in WO9641807.

Other preferred compounds e.g. include compounds as disclosed in WO9516691.

Preferred mTOR inhibitors include
rapamycin, and/or
40-O-(2-hydroxy)-ethyl-rapamycin, and/or
32-deoxorapamycin, and/or
16-pent-2-ynyloxy-32-deoxorapamycin, and/or
16-pent-2-ynyloxy-32 (S or R)-dihydro-rapamycin, and/or
16-pent-2-ynyloxy-32 (S or R)-dihydro-40-O- (2-hydroxyethyl)-rapamycin, and/or
40- [3-hydroxy-2- (hydroxy- methyl)-2-methylpropanoate]-rapamycin (also known as CCI779) and/or
40-epi-(tetrazolyl)-rapamycin (also known as ABT578), and/or
the so-called rapalogs, e.g. as disclosed in WO9802441, WO01 14387 and WO0364383, such as AP23573, AP23464, AP23675 or AP23841 from Ariad, e.g. AP23573, and/or
compounds disclosed under the name TFA-93 or biolimus (A9).

mTOR inhibitors, on the basis of observed activity, have been found to be useful e.g. as immunosuppressant, e.g. in the treatment of acute allograft rejection and have additionally
potent antiproliferative properties which make them useful for cancer chemotherapy, particularly for the treatment of solid tumors, especially of advanced solid tumors.

It was now found that mTOR inhibitors may establish surprising activities when treating inflammatory bowel disease (IBD) and IBD-mediated diseases. It was not only found that mTOR inhibitors, e.g. compound A, may protect against disease development established in IBD-model SCID mice, but even more surprisingly, that oral treatment with Compound A at for only the first 7 days causes significant disease abrogating effects, e.g. when mice are examined at 28 days. Longer treatment, 14 and 21 days, causes a greater reduction in disease parameters. The half-life of Compound A in the mouse is not long enough to account for these effects. It is therefore concluded that an mTOR inhibitor in IBD treatment
- is acting as an inflammatory bowel disease-modifier, e.g. by fundamental changing the disease parameters,
- is acting beyond the half-life of the specific mTOR inhibitor used,
- is delaying the (renewed) onset of IBD, e.g. beyond the half-life of the specific mTOR inhibitor used.

The present invention provides in several aspects:

1.1 The use of an mTOR inhibitor for the prevention or treatment of inflammatory bowel diseases.

1.2 The use of an mTOR inhibitor for the prevention of inflammatory bowel diseases.

2.1 The use of an mTOR inhibitor as an inflammatory bowel disease-modifier, e.g. the use of an mTOR inhibitor as a modifier of the manifestations of inflammatory bowel disease.

2.2 The use of an mTOR inhibitor as an inflammatory bowel disease-modifier in the treatment, e.g. in the long term treatment, of inflammatory bowel diseases.

2.3 The use of an mTOR inhibitor as an inflammatory bowel disease-modifier in the progression of inflammatory bowel disease-mediated events.
2.4 The use of an mTOR inhibitor as an inflammatory bowel disease modifier in inflammatory bowel disease-initiation events.

2.5 The use of an mTOR inhibitor as an inflammatory bowel disease modifier for the delay of the onset of inflammatory bowel diseases.

3.1 The use of an mTOR inhibitor for the preparation of a medicament for any use as referred to in 1.1, 1.2 and 2.1 to 2.5.

3.2 The use of an mTOR inhibitor for the preparation of a medicament for the prevention of inflammatory bowel diseases.

4.1 A method of treating or preventing inflammatory bowel diseases, e.g. in a mammal, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.

4.2 A method of preventing inflammatory bowel disease, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.

4.3 A method of modifying inflammatory bowel disease, e.g. a method for modifying manifestations of inflammatory bowel disease, e.g. in a mammal, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.

4.4 A method of modifying the progression of inflammatory bowel disease-mediated events, e.g. in a mammal, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.

4.5 A method of modifying inflammatory bowel disease-mediated initiation events, e.g. in a mammal, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.
4.6 A method for delaying the onset of inflammatory bowel disease, e.g. in a mammal, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.

5.1 The use or a method as set out under any of 1.1 to 4.6 above, wherein the inflammatory bowel disease is ulcerative colitis.

5.2 The use or a method as set out under any of 1.1 to 4.6 above, wherein the inflammatory bowel disease is Crohn's disease.

5.3 The use or a method as set out under any of 1.1 to 4.6 above, wherein the inflammatory bowel disease is ulcerative proctitis.

6.1 The use or a method as set out under 1.1 to 5.3 above, wherein the mTOR inhibitor is rapamycin, and/or 40-O-(2-hydroxy)-ethyl-rapamycin, and/or 32-deoxorapamycin, and/or 16-pent-2ynyloxy-32-deoxorapamycin, and/or 16-pent-2ynyloxy-32 (S or R)-dihydro-rapamycin, and/or 16-pent-2ynyloxy-32 (S or R)-dihydro-40-0-(2-hydroxyethyl)-rapamycin, and/or 40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-rapamycin (also known as CCI779) and/or 40-epi-(tetrazolyl)-rapamycin (also known as ABT578), and/or a so-called rapalogs, e.g. as disclosed in WO9802441, WO01 14387 and WO0364383, such as AP23573, AP23464, AP23675 or AP23841, e.g. AP23573, and/or compounds disclosed under the name TAFA-93 or biolimus.

6.2 The use or a method as set out under 6.1 above, wherein the mTOR inhibitor is selected from the group consisting of rapamycin, 40-O-(2-hydroxy)-ethyl-rapamycin, 32-deoxorapamycin, 40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-rapamycin, ABT578 and AP23573.
6.3 The use or a method as set out under 6.2 above, wherein the mTOR inhibitor is 40-O-(2hydroxy)-ethyl-rapamycin.

For any use or method as set out in 1.1 to 6.3 above calcineurin inhibition is to be kept constant, e.g. no combined treatment of an mTOR inhibitor with a calcineurin inhibitor is recommended in any of a method or use as set out in any of 1.1 to 6.3 above.

For the use or in a method as indicated under any of 1.1 to 6.3, an mTOR inhibitor may be in the form of a pharmaceutical composition.

In another aspect the present invention provides the use or a method of any of 1.1 to 6.3 wherein the mTOR inhibitor is in the form of a pharmaceutical composition, e.g. which pharmaceutical composition comprising an mTOR inhibitor in association with at least one pharmaceutically acceptable excipient, e.g. appropriate carrier and/or diluent, e.g. including fillers, binders, disintegrants, flow conditioners, lubricants, sugars or sweeteners, fragrances, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers.

Such pharmaceutical composition includes a solid, a liquid or a semiliquid composition, such as emulsions, microemulsions, emulsion preconcentrates or microemulsion preconcentrates, e.g. water-in-oil microemulsion preconcentrates or oil-in-water microemulsions, or solid dispersions of an mTOR inhibitor, e.g. such as commercially available.

Rapamycin and other rapamycin derivatives for the use or in a method of the present invention may be administered as appropriate, e.g. in dosages which are similar to such which are known for rapamycin or rapamycin derivatives, e.g. everolimus (Certican®) may be administered, e.g. orally, in dosages from 0.1 mg up to 15 mg, such as 0.1 mg to 10 mg, e.g. 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 2.5 mg, 5 mg, or 10 mg, e.g. in the form of (dispersible) tablets; e.g. a weekly dosage may include up to 70 mg, e.g. 30 mg to 70 mg, such as 30 mg to 50 mg; depending on the severity of the disease being treated.

Temsirolimus or rapamycin (sold under the trade name Rapammune®) may be e.g. administered parenterally, e.g. in liquid formulation, e.g. by injection; e.g. in similar dosage ranges as everolimus. Other rapamycin derivatives may be administered similarly, e.g. in similar dosage ranges than everolimus.
For the use or in a method as indicated under any of 1.1 to 6.3 above, one mTOR inhibitor or a combination of two or more mTOR inhibitors may be used; preferably one mTOR inhibitor is used.

For the use or in a method as indicated under any of 1.1 to 6.3 above an mTOR inhibitor may be used as the sole active ingredient or an mTOR inhibitor may be combined with a second drug substance, e.g. wherein a second drug substance includes one or more other drugs, e.g. and wherein a calcineurin inhibitor as a second drug substance is excluded.

In another aspect the present invention provides the use or a method as indicated under any of 1.1 to 6.3 above, comprising, beside an mTOR inhibitor a second drug substance, e.g. in the form of a combination, such as a pharmaceutical combination, e.g. a pharmaceutical composition, wherein a calcineurin inhibitor as a second drug substance is excluded.

Combinations include fixed combinations, in which an mTOR inhibitor and at least one second drug substance are in the same formulation; kits, in which an mTOR inhibitor and at least one second drug substance in separate formulations are provided in the same package, e.g. with instruction for co-administration; and free combinations in which an mTOR inhibitor and at least one second drug substance are packaged separately, but instruction for concomitant or sequential administration are given.

In another aspect the present invention provides
- A pharmaceutical package comprising a first drug substance which is an mTOR inhibitor and at least one second drug substance, beside instructions for combined administration;
- A pharmaceutical package comprising an mTOR inhibitor beside instructions for combined administration with at least one second drug substance;
- A pharmaceutical package comprising at least one second drug substance beside instructions for combined administration with an mTOR inhibitor;
for any use or any method as indicated under any of 1.1 to 6.3 above; wherein a calcineurin inhibitor as a second drug substance is excluded.

Treatment with combinations according to the present invention may provide improvements compared with single treatment.

In another aspect the present invention provides
- A pharmaceutical combination comprising an amount of an mTOR inhibitor and an amount of a second drug substance, wherein the amounts are appropriate to produce a synergistic therapeutic effect; wherein a calcineurin inhibitor as a second drug substance is excluded;

- A method for improving the therapeutic utility of an mTOR inhibitor, comprising co-administering, e.g. concomitantly or in sequence, of a therapeutically effective amount of an mTOR inhibitor and a second drug substance, wherein a calcineurin inhibitor as a second drug substance is excluded.;

- A method for improving the therapeutic utility of a second drug substance comprising co-administering, e.g. concomitantly or in sequence, a therapeutically effective amount of an mTOR inhibitor and a second drug substance, wherein a calcineurin inhibitor as a second drug substance is excluded.;

for any use or any method as indicated under any of 1.1 to 6.3 above.

Treatment of disorders (diseases) as described and used herein includes prophylaxis (prevention).

For such treatment, the appropriate dosage will, of course, vary depending upon, for example, the chemical nature and the pharmacokinetic data of an mTOR inhibitor and/or of a second drug substance used, the individual host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage for mTOR inhibitors is as described above; and for a second drug substance includes a range

- from about 0.0001 g to about 1.5 g, such as 0.001 g to 1.5 g;
- such as from about 0.001 mg/kg body weight to about 20 mg/kg body weight, such as 0.01 mg/kg body weight to 20 mg/kg body weight,

for example administered in divided doses up to four times a day,

e.g. dosages in ranges as known and described for a specific second drug substance, e.g. or even below such dosage ranges, e.g. in case of a synergistic combination.

A combination of an mTOR inhibitor and a second drug substance as a combination partner for any use or any method as indicated under any of 1.1 to 6.3 above, may be administered by any conventional route, for example as set out above for mTOR inhibitors and a second drug substance may be administered in dosages as appropriate, e.g. in dosage ranges which are similar to those used for single treatment, or, e.g. in case of synergy, even below conventional dosage ranges.
A pharmaceutical composition according to the present invention may be manufactured according, e.g. analogously, to a method as conventional, e.g. by mixing, granulating, coating, dissolving or lyophilizing processes. Unit dosage forms may contain, for example, from about 0.1 mg to about 1500 mg, such as 1 mg to about 1000 mg. Pharmaceutical compositions comprising a combination of an mTOR inhibitor and pharmaceutical compositions comprising a second drug substance as described herein, may be provided as appropriate, e.g. according, e.g. analogously, to a method as conventional, or as described herein for a pharmaceutical composition comprising an mTOR inhibitor.

A second drug substance as used herein may be administered by any conventional route, for example enterally, e.g. including nasal, buccal, rectal, oral, administration; parenterally, e.g. including intravenous, intraarterial, intramuscular, intracardiac, subcutaneous, intraosseous infusion, transdermal (diffusion through the intact skin), transmucosal (diffusion through a mucous membrane), inhalational administration; topically; e.g. including epicutaneous, intranasal, intratracheal administration; intraperitoneal (infusion or injection into the peritoneal cavity); epidural (peridural) (injection or infusion into the epidural space); intrathecal (injection or infusion into the cerebrospinal fluid); intravitreal (administration via the eye); or via medical devices, e.g. for local delivery, e.g. stents; e.g. in form of coated or uncoated tablets, capsules, (injectable) solutions, infusion solutions, solid solutions, suspensions, dispersions, solid dispersions; e.g. in the form of ampoules, vials, in the form of creams, gels, pastes, inhaler powder, foams, tinctures, lip sticks, drops, sprays, or in the form of suppositories.

A second drug substance as used herein is meant to include any drug substance other than an mTOR inhibitor, e.g. in free form, in the form of a salt, and/or in the form of a solvate, e.g. in any stereoisomeric form or stereoisomeric mixture, which may have beneficial effects in a use or a method as indicated under any of 1.1 to 6.3 above, e.g. including an anti-inflammatory and/or an immunomodulatory drug substance, e.g. including a drug substance which is active in IBD prevention or treatment and/or which is active in treating manifestations of IBD, e.g. IBD symptoms, such as anesthetic drug or an antidiarrheal drugs, but excluding a calcineurin inhibitor.
Anti-inflammatory and/or immunomodulatory drugs which are prone to be useful as a combination partner with an mTOR inhibitor in a use or method according to 1.1 to 6.3 above, include e.g.

- ascomycins having immuno-suppressive properties, e.g. ABT-281; ASM981;
- corticosteroids; cyclophosphamide; azathioprene; leflunomide; mizoribine; 6-mercaptopurine, methotrexate;
- mycophenolic acid or salt; e.g. mycophenolate sodium, mycophenolate mofetil;
- 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof;
- mediators, e.g. inhibitors, of bcr-abl tyrosine kinase activity;
- mediators, e.g. inhibitors, of c-kit receptor tyrosine kinase activity;
- mediators, e.g. inhibitors, of PDGF receptor tyrosine kinase activity, e.g. Gleevec (imatinib);
- mediators, e.g. inhibitors, of p38 MAP kinase activity,
- mediators, e.g. inhibitors, of VEGF receptor tyrosine kinase activity,
- mediators, e.g. inhibitors, of PKC activity, e.g. as disclosed in WO0238561 or WO0382859, e.g. the compound of Example 56 or 70;
- mediators, e.g. inhibitors, of JAK3 kinase activity, e.g. N-benzyl-3,4-dihydroxy-benzylidene-cyanoacetamide α-cyano-(3,4-dihydroxy)-]N-benzylcinnamamide (Tyrphostin AG 490), prodigiosin 25-C (PNU 156804), [4-(4'-hydroxyphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P131), [4-(3'-bromo-4'-hydroxylphenyl)-amino-6,7-dimethoxyquinazoline] (WHI-P154), [4-(3''-dibromo^''-hydroxylphenyO-amino-ej-dimethoxyquinazoline WHI-P97, KRX-21 1, 3-(3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d][pyrimidin-4-yl]-amino]-piperidin-1-yl]-3-oxo-propionitrile, in free form or in a pharmaceutically acceptable salt form, e.g. mono-citrate (also called CP-690,550), or a compound as disclosed in WO2004052359 or WO2005066156;
- mediators, e.g. agonists or modulators of S1P receptor activity, e.g. FTY720 optionally phosphorylated or an analog thereof, e.g. 2-amino-2-[4-(3-benzoxypyphenylthio)-2-chlorophenyl]ethyl-1 ,3-propanediol optionally phosphorylated or 1-[4-{1-(4-cyclohexyl-3-trifluoromethyl-benzoxymino)-ethyl]-2-ethyl-benzyl]-azetidine-3-carboxylic acid or its pharmaceutically acceptable salts;
- immunosuppressive monoclonal antibodies, e.g., monoclonal antibodies to leukocyte receptors, e.g., Blys/BAFF receptor, MHC, CD2, CD3, CD4, CD7, CD8, CD25, CD28, CD40, CD45, CD52, CD58, CD80, CD86, IL-12 receptor, IL-17 receptor, IL-23 receptor or their ligands;
- other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4lg (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y;
- mediators, e.g. inhibitors of adhesion molecule activities, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists,
- mediators, e.g. antagonists of CCR9 activity,
- mediators, e.g. inhibitors, of MIF activity,
- 5-aminosalicylate (5-ASA) agents, such as sulfasalazine, Azulfidine®, Asacol®, Dipentum®, Pentasa®, Rowasa®, Canasa®, Colazal®, e.g. drugs containing mesalamine; e.g. mesalazine in combination with heparin;
- mediators, e.g. inhibitors, of TNF-alpha activity, e.g. including antibodies which bind to TNF-alpha, e.g. infliximab (Remicade®), thalidomide, lenalidomide,
- nitric oxide releasing non-steroidal anti-inflammatory drugs (NSAIDs), e.g. including COX-inhibiting NO-donating drugs (CINOD);
- phosphodiesterase, e.g. mediators, such as inhibitors of PDE4B activity,
- mediators, e.g. inhibitors, of caspase activity,
- mediators, e.g. agonists, of the G protein coupled receptor GPBAR1,
- mediators, e.g. inhibitors, of ceramide kinase activity,
- 'multi-functional anti-inflammatory' 1 drugs (MFAIDs), e.g. cytosolic phospholipase A2 (cPLA2) inhibitors, such as membrane-anchored phospholipase A2 inhibitors linked to glycosaminoglycans;
- antibiotics, such as penicillins, cephalosporins, erythromycins, tetracyclines, sulfonamides, such as sulfadiazine, sulfisoxazole; sulfones, such as dapsone; pleuromutilins, fluoroquinolones, e.g. metronidazole, quinolones such as ciprofloxacin; levofloxacin; probiotics and commensal bacteria e.g. Lactobacillus, Lactobacillus reuteri;
- antiviral drugs, such as ribavirin, vidarabine, acyclovir, ganciclovir, zanamivir, oseltamivir phosphate, famciclovir, atazanavir, amantadine, didanosine, efavirenz, foscamet, indinavir, lamivudine, nelfinavir, ritonavir, saquinavir, stavudine, valacyclovir, valganciclovir, zidovudine.

Anti-inflammatory drugs which are prone to be useful as a combination partner with an mTOR inhibitor in a use or method according to 1.1 to 6.3 above include e.g. non-steroidal
antiinflammatory agents (NSAIDs) such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, and tioxaprofen), acetic acid derivatives, e.g. indomethacin, acemetacin, alclofenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac, tolmetin, zidometacin, and zomepirac, fenamic acid derivatives, e.g. flufenamic acid, meclofenamic acid, mefenamic acid, niflumic acid and tolfenamic acid, biphenylcarboxylic acid derivatives, e.g. diflunisal and flufenisal, oxicams, e.g. isoxicam, piroxicam, sudoxicam and tenoxican, salicylates, e.g. acetyl salicylic acid, sulfasalazine, and the pyrazolones, e.g. apazone, bezpiperylon, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone; aminosalicylates, e.g. 5-aminosalicylic acid and prodrugs thereof, cyclooxygenase-2 (COX-2) inhibitors such as celecoxib; inhibitors of phosphodiesterase type IV (PDE-IV); antagonists of the chemokine receptors, especially CCR-1, CCR-2, and CCR-3 antagonists; cholesterol lowering agents such as HMG-CoA reductase inhibitors, e.g. lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and other statins, sequestrants, e.g. cholestyramine, colestipol, nicotinic acid, fenofibric acid derivatives, such as gemfibrozil, clofibrat, fenofibrate, benzafibrate, probucol; anticholinergic agents such as muscarinic antagonists (ipratropium bromide); other compounds such as theophylline, antirheumatics.

Anesthetic drugs which are prone to be useful as a combination partner with an mTOR inhibitor in a use or method according to 1.1 to 6.3 above e.g. include ethanol, bupivacaine, chloroprocaine, levobupivacaine, lidocaine, mepivacaine, procaine, ropivacaine, tetracaine, desflurane, isoflurane, ketamine, propofol, sevoflurane, codeine, fentanyl, hydromorphone, marcaine, meperidine, methadone, morphine, oxycodone, remifentanil, sufentanil, butorphanol, nalbuphine, tramadol, benzocaine, dibucaine, ethyl chloride, xylocaine, and phenazopyridine.

Antidiarrheal drugs which are prone to be useful as a combination partner with an mTOR inhibitor in a use or method according to 1.1 to 6.3 above , e.g. include diphenoxylate, loperamide, codeine.

According to the present invention it was found that mTOR inhibitors, e.g. Compound A, both, protects against development of disease and can halt and reverse established severe
inflammation in the SCID mouse model of IBD induced by transfer of naïve T cells (Gut 2005,54(suppl.VII);A61). Calcineurin inhibition via FK506 protects against disease onset but only at doses with associated toxicity.

5 METHODS
SCID mice are reconstituted with naïve (CD4+CD45RbHi) T cells and treated with 1 mg/kg/d of Compound A or 10 mg/kg/d compound FK506 for 7 or 21 days. Mice are euthanized on day 29, serum haptoglobin measured by ELISA, colitis is evaluated histologically and lymphocyte numbers in blood, spleen and mesenteric lymph nodes (MLN) are measured by FACS analysis. Body weight (BW) is measured throughout and a score for diarrhea made at the end.

RESULTS
In 2 similar studies with n=8 mice per group placebo-treated mice lost a mean % BW of 23.1±2.6 whilst mice treated with Compound A lost only 8.8±5.3 relative to non-transferred controls. In a third study, BW loss is the same in FK506 or placebo-treated mice. Colitis severity in the placebo-treated groups is 7 and 7.4 (out of 8) whilst treatment with Compound A for only the first 7 days results in reduced mean scores of 5.0 and 4.2, respectively. Treatment with Compound A for 21 days results in significantly (p<0.01) reduced mean scores of 2.3 and 0.1, respectively. In contrast, no FK506-treated mice are protected against colitis. Serum haptoglobin in the 7 day treated mice by Compound A is reduced by 72 and 56%, respectively whilst FK506 treatment, even for 21 days, fails to reduce this acute phase protein. However, a significant reduction of 75.9±4.9 is measured when this dose of FK506 is given continuously for the entire 28 days. There is no significant reduction in lymphocyte numbers in blood, spleen or MLN after treatment with Compound A. Diarrhea scores are also lower in 7 days treated mice by Compound A with scores of 4 and 4.8 (out of 8) whilst placebo-treated mice scores 5.9 and 6, respectively.

CONCLUSION
Since the half-life of Compound A in the mouse is measured in hours these data suggest that Compound A is modifying the early events of disease progression without preventing T cell expansion. Calcineurin inhibition clearly needs to be kept constant for any protective benefit.
Patent Claims

1. The use of an mTOR inhibitor for the prevention or treatment of inflammatory bowel disease.

2. The use of an mTOR inhibitor for the prevention of inflammatory bowel disease.

3. The use of an mTOR inhibitor as an inflammatory bowel disease-modifier.

4. The use of an mTOR inhibitor as an inflammatory bowel disease-modifier in the progression of inflammatory bowel disease-mediated events.

5. The use of an mTOR inhibitor as an inflammatory bowel disease-modifier for the delay of the onset of inflammatory bowel diseases.

6. The use of an mTOR inhibitor for the preparation of a medicament for any use as claimed in any one of claims 1 to 5.

7. A method of treating or preventing inflammatory bowel disease, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.

8. A method of modifying inflammatory bowel disease in a mammal, comprising administering to a subject in need of such treatment an effective amount of an mTOR inhibitor.

9. The use or a method according to any one of claims 1 to 8, wherein the mTOR inhibitor is selected from the group consisting of rapamycin, 40-O-(2-hydroxy)-ethyl-rapamycin, 32-deoxorapamycin, 40-[3-hydroxy-2-(hydroxy-methyl)-2-methylpropanoate]-rapamycin, ABT578 and AP23573.

10. The use or a method as set out under 6.2 above, wherein the mTOR inhibitor is 40-O-(2-hydroxy)-ethyl-rapamycin.
11. The use or a method according to any preceding claim wherein the mTOR inhibitor is used in combination with a second drug substance, wherein a combination with a calcineurin inhibitor as a second drug substance is excluded.