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(54) Title: C5AR1 INHIBITORS FOR USE IN THE TREATMENT OF OCULAR MUCOUS MEMBRANE PEMPHIGOID AND/OR ORAL MUCOUS MEMBRANE PEMPHIGOID

(57) Abstract: The invention relates to C5aR1 inhibitors for use in the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid.

C5aR1 INHIBITORS FOR USE IN THE TREATMENT OF OCULAR MUCOUS MEMBRANE PEMPHIGOID AND/OR ORAL MUCOUS MEMBRANE PEMPHIGOID

TECHNICAL FIELD

The invention relates to C5aR1 inhibitors for use in the prevention and/or treatment of ocular mucous membrane pemphigoid (OcMMP) and/or oral mucous membrane pemphigoid.

BACKGROUND OF THE INVENTION

Mucous membrane pemphigoid (MMP) is a systemic cicatrizing autoimmune disease that primarily affects orificial mucous membranes, such as the conjunctiva, the nasal cavity, the oropharynx, and the genitalia.

About 75% of MMP patients generate antibodies against BP180 (type XVII collagen) and 25% of MMP patients against laminin 332. In less than 5% of MMP patients, antibodies against type VII collagen or α6β4 integrin are detected (Domloge-Hultsch, N., et al., J Clin Invest, 1992. 90(4): p. 1628-33; Oyama, N., et al., Br J Dermatol, 2006. 154(1): p. 90-8; Schmidt, E., et al., Br J Dermatol, 2001. 145(5): p. 778-83).

Ocular involvement occurs in about 70% of all MMP cases and ocular MMP is the leading cause of cicatrizing conjunctivitis in developed countries.

Linear immunoglobulin A disease, mucosal dominated epidermolysis bullosa acquisita, and anti-laminin 332/anti-epiligrin/anti-laminin 5 pemphigoid are encompassed by Ocular MMP (OcMMP).

The progressive inflammatory and scarring nature of ocular MMP leads to severe visual impairment in 30% of affected eyes and bilateral blindness in 20%.

Ocular MMP is often associated with oral mucosa lesions including desquamative gingivitis, vesicles, erosions covered by pseudomembranes and ulcers.

In some cases of MMP, only the oral mucosa is involved.

The underlying pathophysiological mechanism of the disease is a type 2 hypersensitivity reaction against the basal epithelial membrane of the conjunctiva.

In particular, conjunctival involvement is critical since the autoantibody-induced inflammation results in conjunctival scarring that may even progress after the inflammatory process has halted and leads to visual impairment and blindness.

Early diagnosis and appropriate treatment are of paramount importance to avoid inflammatory and infectious complications, as well as possible visual loss.

Several mechanisms have been proposed underlying the development of antibody-mediated MMP.

Ocular MMP management is aimed at controlling the immune-mediated inflammatory disease preventing fibrosis and progression of the disease.

Georgoudis, P. et al, "Ocular Mucous Membrane Pemphigoid: Current State of Pathophysiology, Diagnostics and Treatment", Ophthalmol. Ther. (2019) 8, 5–17, discloses that a stepladder approach is used to select immunosuppressive agents and to escalate treatment, depending on disease severity (mild, moderate, severe). The medications used are dapsone, sulphapyridine, sulphasalazine, azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), cyclophosphamide, and short courses of oral steroids.

CD20 monoclonal antibodies, TNFα inhibitors, and intravenous immunoglobulin (IVIg) are used to treat disease in patients non-responsive to conventional immunosuppressants.

The therapeutic mainstay are high-dose systemic corticosteroids supplemented with potentially corticosteroid sparing agents such as azathioprine, mycophenoles, dapsone, antibiotics with anti-inflammatory activity such as doxycycline, high-dose-intravenous immunoglobulins, and the anti-CD20 antibody rituximab.

The current treatment armamentarium is frequently not effective and associated with severe adverse events.

Thus, there is still a high need for effective and safe therapies.

Different C5aR1 inhibitors have been developed and are well known to the skilled person.

W02007/060215 discloses (R)-arylalkylamino derivatives and their use in the treatment of diseases that involve C5a induced human PMNs chemotaxis such as sepsis, psoriasis, bullous pemphigoid, rheumatoid arthritis, ulcerative colitis, acute respiratory distress syndrome, idiopathic fibrosis, cystic fibrosis, chronic obstructive pulmonary disease, glomerulonephritis and in the prevention and the treatment of injury caused by ischemia and reperfusion.

It is therefore the aim of the invention to provide an effective treatment of MMP, in particular ocular and oral MMP.

SUMMARY OF THE INVENTION

The invention is directed to C5aR1 inhibitors for use in the prevention and/or treatment of ocular mucous membrane pemphigoid (OcMMP) and/or oral mucous membrane pemphigoid in a subject.

The invention is also directed to pharmaceutical compositions comprising a C5aR1 inhibitor and at least one pharmaceutically acceptable excipient or carrier for use in the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid in a subject.

The invention is also directed to a method of preventing and/or treating ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid,

which comprises administering an effective amount of one or more C5aR1 inhibitor compounds of the invention to a subject in need thereof.

The invention is also directed to the use of the claimed C5aR1 inhibitors in the manufacture of a medicament for the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid in a subject.

BRIEF DESCRIPTION OF FIGURES

Figure 1 shows the effects of treatment with DF3966A, administered by topical ophthalmic application, or methylprednisolone (MP), administered by intraperitoneal injection, in an experimental MMP mouse model at day 12 after the initial anti-mLAMα3 IgG injection, compared to control treatment with vehicle, by topical ophthalmic administration (vehicle). In details:

Panel A shows the effect of DF3966A or MP on palpebral conjunctival split formation at day 12, expressed as conjunctiva score. Data are presented as means +/- standard deviation. On day 12 there is a statistically significant difference between the vehicle group and DF3966A (p=0.0016). Animals treated with IgG isolated from normal rabbit serum injected s.c. (NR IgG), were used as negative control.

Data are based on 12-14 mice per group, except for NR IgG (n=10). The asterisk indicates statistical significance (ANOVA with Holm Sidaks method for multiple comparisons).

Panel B shows semi-quantification of subepithelial inflammatory infiltrate based on hematoxylin and eosin (H&E) stained biopsies of the palpebral conjunctiva, in mice treated with DF3966A or MP. On day 12 there is a statistically significant difference between the vehicle group and MP group. Animals treated with IgG isolated from normal rabbit serum injected s.c. (NR IgG), were used as negative control.

Data are presented as means +/- standard deviation. Data are based on 7-10 mice per group, except for NR IgG (n=3). The asterisk indicates statistical significance (ANOVA with Holm Sidaks method for multiple comparisons).

Figure 2 shows representative clinical presentations of the eyes and H&E stained sections of the palpebral conjunctiva obtained 12 days after the initial anti-mLAMα3 IgG injection, in mice treated with DF3966A, by topical ophthalmic administration, or methylprednisolone (MP), by intraperitoneal injection.

Figure 3 shows the reduction of split formation in the palpebral conjunctiva in experimental MMP mice at day 28 after the initial anti-mLAMα3 IgG injection, treated with DF3966A, by topical ophthalmic administration, or methylprednisolone (MP), by intraperitoneal injection. In details:

Panel A shows the effect of treatment with DF3966A or MP on palpebral

conjunctival split formation on day 28, expressed as conjunctiva score, compared to vehicle. Animals treated with IgG isolated from normal rabbit serum injected s.c. (NR IgG) were used as negative control.

Data are presented as means +/- standard deviation. On day 28 there is a statistically significant difference between the vehicle group and DF3966A (p=0.0414). Data are based on 11-14 mice per group, except for NR IgG (n=9). The asterisk indicates statistical significance (ANOVA with Holm Sidaks method for multiple comparisons).

Panel B shows the semi-quantification of subepithelial inflammatory infiltrate based on hematoxylin and eosin (H&E) stained biopsies of the palpebral conjunctiva in mice treated with DF3966A or MP, compared to vehicle. Animals treated with IgG isolated from normal rabbit serum injected s.c. (NR IgG) were used as negative control. Data are presented as means +/- standard deviation. On day 28 there is a statistically significant difference between the vehicle group and DF3966A (p=0.0188). Data are based on 7-9 mice per group, except for NR IgG (n=5). The asterisk indicates statistical significance based on ANOVA with Dunnetts method for multiple comparisons.

Figure 4 shows representative clinical presentations of the eyes and H&E stained sections of the palpebral conjunctiva obtained 28 days after the initial anti-mLAMα3 IgG injection, in mice treated with DF3966A, by topical ophthalmic administration, or methylprednisolone (MP), by intraperitoneal injection.

Figure 5 shows the effect of DF3996A and MP treatment on severity of oral lesions on day 12, expressed as oral score. Data are presented as means +/- standard deviation. For day 12 there is a statistically significant difference between the vehicle group and DF3966A (p=0.0479). Data are based on 12-14 mice per group, except for NR IgG (n=10). The asterisk indicates statistical significance (ANOVA with Holm Sidaks method for multiple comparisons).

Figure 6 shows the effect of DF3996A and MP treatment on severity of oral lesions on day 28, expressed as oral score. Data are presented as means +/- standard deviation. For day 28 there is a statistically significant difference between the vehicle group and DF3966A (p=0.0372). MP treatment significantly increased the oral score (p=0.0136) compared to vehicle treated group. Data are based on 11-14 mice per group, except for NR IgG (n=9). The rhombus indicates statistical significance by ANOVA with uncorrected Fishers LSD method (no correction for multiple comparisons).

DETAILED DESCRIPTION OF THE INVENTION

It has been surprisingly found that the C5aR1 inhibitors are effective in the prevention and/or treatment of ocular mucous membrane pemphigoid (OcMMP) and/or oral mucous membrane pemphigoid in a subject.

The terms "treatment" and "prevention" as used herein refer to the eradication/amelioration or prevention/delay in onset, respectively, of the disorder being treated or of one or more of the symptoms associated thereof, notwithstanding the fact that the patient may still be afflicted with the underlying disorder.

Accordingly, the invention is directed to a C5aR1 inhibitor for use in the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid.

According to a preferred embodiment, the invention is directed to a C5aR1 inhibitor for use in the prevention and/or treatment of ocular mucous membrane pemphigoid.

According to a further preferred embodiment, the invention is directed to a C5aR1 inhibitor for use in the prevention and/or treatment of oral mucous membrane pemphigoid.

According to a further preferred embodiment, the invention is directed to a C5aR1 inhibitor for use in the prevention and/or treatment of ocular mucous membrane pemphigoid and oral mucous membrane pemphigoid.

The term "C5aR1 inhibitor" in accordance with the present invention means any compound that interacts with C5aR1 and prevents its binding to C5a or that blocks the signaling of C5aR1 upon binding of C5a.

Preferably, said C5aR1 inhibitor compound is selected from C5aR1 competitive antagonists, anti-C5aR1 antibodies able to block the C5a binding sites on the receptor and C5aR1 non-competitive allosteric inhibitors, more preferably said C5aR1 inhibitor compound is a non-competitive allosteric inhibitor.

"Noncompetitive allosteric inhibitor of C5a receptor" according to the present invention means a compound that interacts with C5a receptors in an allosteric site, located in the TM region, and inhibits intracellular signal transduction events activated by the agonist binding, without affecting any binding of endogen ligand C5a on its receptor.

According to one preferred embodiment, said C5aR1 competitive antagonists are selected from the group consisting of:

- (2R,3S)-2-[4-(Cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (Avacopan, Vynpenta®);
- N-Acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine-N-5.2-C-1.6-lactam (PMX-53);
- Acetylated phenylalanine-[ornithyl-proline-(D)cyclohexylalanine-tryptophyl-arginine];
- L-Alanyl-L-seryl-glycyl-L-alanyl-L-prolyl-L-alanyl-L-prolyl-glycyl-L-prolyl-L-alanyl-glycyl-L-prolyl-L-leucyl-L-arginyl-L-prolyl-L-methionyl-L-phenylalanine;

- N,N-Bis(1,3-benzodioxol-5-ylmethyl)-N-(1-butyl-2,4-diphenyl-1H-imidazol-5-ylmethyl)amine;
- N-[2-(4-Chlorophenyl)ethyl]-N-(1,4-dioxaspiro[4.5]dec-8-yl)-2-isobutylbenzamide;
- N-[2-(4-Chlorophenyl)ethyl]-N-(4-hydroxycyclohexyl)-1-benzothiophene-3-carboxamide;
- N-[2-(4-Chlorophenyl)ethyl]-N-(4-hydroxycyclohexyl)naphthalene-1-carboxamide;
- 2-(2-Ethyl-6-methylphenyl)-4-methoxy-N-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydroquinolin-5-amine;
- 2-(2,6-Diethylphenyl)-N-ethyl-4-methoxy-N-(1-naphthyl)-5,6,7,8-tetrahydroquinolin-5-amine;
- N-[2,6-Dioxohexahydropyrimidin-4(S)-ylcarbonyl]-L-phenylalanyl-L-ornithyl-L-prolyl-5-methyl-L-norleucyl-4-fluoro-L-phenylalanyl-L-phenylalaninamide (JPE-1375; JSM-1375);
- N-(3-Phenylpropionyl)-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine N-5.1-C-1.5-lactam (PMX-205);
- N,N'-Bis(4-amino-2-methylquinolin-6-yl)urea (NSC12155);
- N-[4-(Dimethylamino)benzyl]-N-(4-isopropylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide hydrochloride (W54011);
- L-Phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine N-5.2-C-1.6-cyclic peptide;
- (4aR,16aS)-6,18-Dihydroxy-23(S)-[2(S)-hydroxy-2-[2(R)-hydroxy-6(R)-methyl-5(R)-[2(S)-methylbutyl]tetrahydro-2H-pyran-2-yl]propionamido]-22(S)-isopropyl-7(S),19(R)-dimethyldocosahydro-13H,22H-dipyridazino[6,1-f:6',1'o][1,4,7,10,13,16]oxapentaazacyclononadecine-5,7,11,17,20,24-hexanone (L-156602).

Anti-C5aR1 antibodies are commercially available, for example they are sold by Abcam, ThermoFisher Scientific, Biocompare.

According to one preferred embodiment, the anti-C5aR1 antibodies or aptamers are selected from the group consisting of:

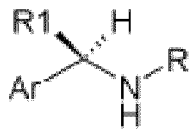
- Avdoralimab (IPH-5401)
- MOR-044254, also known as anti-C5aR monoclonal antibody TJ210;
- NOX-D20, a PEGylated biostable mirror-image mixed (L)RNA/DNA aptamer (Spiegelmer);
- Anti-C5aR1ab-C5-SiRNA conjugate, anti-C5aR1ab-protamine-C5siRNA conjugate;
- m20/70 mIgG2a.1;
- 3C5;

- 7F3.

According to one preferred embodiment, said non-competitive allosteric inhibitors are selected from:

- (2R)-2-[3-(furan-2-carbonyl)phenyl]-N-[4-(trifluoromethyl)-1,3-thiazol-2-yl]propenamide (DF2427);
- R(-)-2-[(4'-trifluoromethanesulfonyloxy)phenyl]-N-[3-(N'-pirrolidinyl)propyl] propionamide (DF2297X) or its chloride salt (DF2297A); and
- the compounds of formula (I) and (II) described hereinbelow.

According to a preferred embodiment, said non-competitive allosteric inhibitors are compounds having general formula (I):



(I)

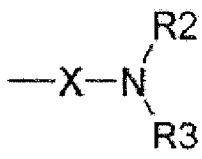
or a pharmaceutically acceptable salt thereof, wherein

R is selected from:

- 2-thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert-butyl or trifluoromethyl group;
- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,
- CORa, SORa, SO_2Ra, PORa, PO_2Ra,

wherein **Ra** is selected from:

- C_1-C_5-alkyl, C_3-C_6-cycloalkyl, C_2-C_5-alkenyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino;
- a heteroaryl group selected from pyridine, pyrimidine, pyrrole, thiophene, furane, indole, thiazole, oxazole, such heteroaryl being unsubstituted or substituted with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkoxy, hydroxy, C_1-C_4- acyloxy, phenoxy, cyano, nitro, amino;
- a α or β carboxyalkyl residue consisting of straight or branched C_1- C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, C_1-C_6-phenylalkyl, optionally substituted with a further carboxy (COOH) group;
- an ω-aminoalkylamino group of formula (II):



(II)

wherein in said formula (II) **X** is selected from:

- linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by:

a) a CO_2R4 group, wherein R4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group, or

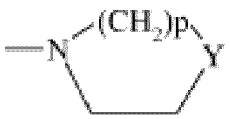
b) a CONHR5 group wherein R5 represents

- hydrogen, linear or branched C_2-C_6 alkyl or an OR4 group, R4 being defined as above;

- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R4 or CONHR5 group, as defined above, wherein B is an oxygen, or sulfur atom, or nitrogen atom optionally substituted by a C_1-C_4 alkyl group, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3; or B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;

R2 and **R3** are independently selected form hydrogen, linear or branched C_1-C_6 alkyl, optionally interrupted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group; or

R2 and **R3** together with the N atom to which they are bound, form a 3-7 membered nitrogen heterocyclic ring of formula (III)



(III)

wherein **Y** represents:

- a single bond, CH_2, O, S, or a N-R6 group, where R6 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4- alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, and p represents an integer from 0 to 3;

- a residue of formula SO_2R7 wherein R7 is C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, aryl and heteroaryl;

or

in said formula (II), **X** together with the nitrogen atom to which it is bound and with the **R2** group, forms a nitrogen containing 3-7 membered heterocyclic, monocyclic or polycyclic ring, and **R3** is selected from the group comprising hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4- acyloxy, phenoxy, cyano, nitro, amino;

R1 is linear or branched C_1-C_5 alkyl, C_3-C_5 cycloalkyl;
Ar is selected from:

-a phenyl group unsubstituted or substituted by one or more groups independently selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, C_1-C_4-acylamino, halo-C_1- C_3- alkyl, halo-C_1-C_3-alkoxy, benzoyl, heteroaryl carbonyl, heteroaryl, linear or branched C_1-C_8-alkanesulfonate, linear or branched C_1-C_8-alkanesulfonamides, linear or branched C_1-C_8 alkyl sulfonylmethyl; or

- a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan, indole.

Among the above compounds, particularly preferred are compounds of said formula (I) or pharmaceutically acceptable salts thereof, wherein:

R is selected from:

- 2-thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert-butyl or trifluoromethyl group,
- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,
- CORa, SORa or SO_2Ra,

wherein Ra is as defined above; and

Ar is selected from the group comprising:

3'-benzoylphenyl, 3'-(4-chloro-benzoyl)-phenyl, 3'-(4-methyl-benzoyl)-phenyl, 3'-acetyl-phenyl, 3'-propionyl-phenyl, 3'-isobutanoyl-phenyl, 4'-isobutyl-phenyl, 4'-trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 4'-trifluoromethanesulfonylamino-phenyl, 4'-benzenesulfonylamino-phenyl, 4'-benzenesulfonylmethyl-phenyl, 4'-acetoxyphenyl, 4'-propionyloxy-phenyl, 4'-benzoyloxy-phenyl, 4'-acetylamino-phenyl, 4'-propionylamino-phenyl, 4'- benzoylamino-phenyl, 3'-(furan-2-carbonyl)-phenyl, 3'-(benzofuran-2-carbonyl)-phenyl, 3'-(thiophen-2-carbonyl)-phenyl, 3'-(pyridine-2-carbonyl)-phenyl, 3 '-(thiazole-2-carbonyl)-phenyl, 3'-(oxazole-2-carbonyl)-phenyl, 3'-(2-furyl)-phenyl, 3'-(2-oxazolyl)- phenyl, 3'-(3-isoxazolyl)-phenyl, 3'-(2-benzoxazolyl)-phenyl, 3'-(3- benzoisoxazolyl)-phenyl, 3'-(2-thiazolyl)-phenyl, 3'-(2-pyridyl)-phenyl, 3'-(2- thiophenyl)-phenyl;

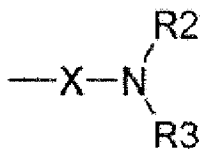
or **Ar** is a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan or indole.

According to a further embodiment, (R)-arylalkylamino derivatives are compounds of formula (I) as defined above, wherein:

R is

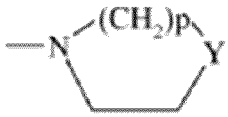
- 2-thiazolyl, unsubstituted or substituted by a group selected from methyl or trifluoromethyl;

- CORa, SO2Ra,
wherein Ra is selected from:
- C_1-C_5-alkyl, C_3-C_5-cycloalkyl;
- phenyl, 2-pyridyl, 2-furyl, 2-thiophenyl groups;
- a group of formula II,



(II)

wherein
X represents:
linear or branched C_1-C_6 alkylene,
R2 and R3 together with the N atom to which they are bound, form a 4-6 membered nitrogen containing heterocyclic ring of formula (III)



(III)

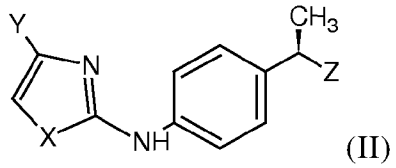
wherein Y represents CH_2 and p represents an integer from 0 to 2;
R1 is methyl;
Ar is selected from:
3'-benzoylphenyl, 3'-(4-chloro-benzoyl)-phenyl, 3'-(4-methyl-benzoyl)-phenyl,
4'-trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 3'-(furan-2-carbonyl)-phenyl.
Preferred compounds of formula (I) according to the invention are selected from:
- 4-{(1R)-1-[(phenylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]benzenesulfonamide;
- 4-{(1R)-1-[(pyridine-3-ylsulfonyl)amino]ethyl}phenyltrifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]methanesulfonamide;
- N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}thiophene-2-sulfonamide;
- N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}methanesulfonamide;
- 4-{(1R)-1-[(thien-2-ylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]thiophene-2-sulfonamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]-3-pyrrolidin-1-ylpropane-1-sulfonamide;

- methyl 5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoate;
- 5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoic acid;
- 4-{(1R)-2-methyl-1-[(methylsulfonyl)amino]propyl}phenyltrifluoromethanesulfonate;
- N-((1R)-1-{4-[1-methyl-1-(phenylsulfonyl)ethyl]phenyl}ethyl)methanesulfonamide;
- 4-[(1R)-1-(isobutyrylamino)ethyl]phenyltrifluoromethanesulfonate;
- 4-{[(1R)-1-(pyridine-3-ylcarbonyl)amino]ethyl]}phenyltrifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]benzamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]-2-furamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]cyclobutanecarboxamide;
- N-[(1R)-1-(4-trifluoromethanesulfonyloxy)phenylethyl]-4-piperidin-1-yl butanamide (DF2593Y);
- 4-{(1R)-1-[(4-pyrrolidin-1-ylbutanoyl)amino]ethyl]}phenyl trifluoromethanesulfonate;
- 3-{(1R)-1-[4-(4-trifluoromethyl-1,3-thiazol-2-yl)amino]ethyl}phenyl)(phenyl)methanone.

Particularly preferred compounds of formula (I) according to the invention are N-[(1R)-1-(4-trifluoromethanesulfonyloxy)phenylethyl]-4-piperidin-1-yl butanamide (DF2593Y) and pharmaceutically acceptable salts thereof, preferably its chloride salt (DF2593A).

Compounds of formula (I) are described in WO2007/060215, which also discloses their method of synthesis.

According to a further preferred embodiment, said non-competitive allosteric inhibitors are compounds having general formula (II):



(II)

or pharmaceutically acceptable salts thereof,

wherein

X is a heteroatom selected from S, O and N;

Y is H or a residue selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy, hydroxy, -COOH, C_1-C_4-acyloxy, phenoxy, cyano, nitro, -NH_2, C_1-C_4-acylamino, halo-C_1-C_3-alkyl, benzoyl, linear or branched C_1-C_8-alkanesulfonate, linear or branched C_1-C_8-alkanesulfonamides, linear or branched C_1-C_8-akyl sulfonylmethyl;

Z is an heteroaryl ring selected from the group consisting of unsubstituted tetrazole and triazole, pyrazole, oxazole, thiazole, isooxazole, isothiazole, thiadiazole and oxadiazole substituted by one hydroxy group and optionally

further substituted by one or more groups selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkylamino, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-acyloxy, cyano, nitro, NH_2, C_1-C_4-acylamino, halo-C_1-C_3-alkyl, halo-C_1-C_3-alkoxy, linear or branched C_1-C_8-alkanesulfonate and linear or branched C_1-C_8-alkanesulfonamides.

Among the above compounds of formula (II), preferred are compounds wherein:

X is a heteroatom selected from S and O;

Y is H or a residue selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl and halo-C_1-C_3-alkyl; preferably selected from the group consisting of trifluoromethyl, chlorine, methyl and tert-butyl;

Z is an heteroaryl ring selected from the group consisting of unsubstituted tetrazole and triazole, pyrazole, isooxazole, isothiazole, thiadiazole and oxadiazole substituted by one hydroxy group and optionally further substituted by one or more groups selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_1-C_4-alkylthio and halo-C_1-C_3-alkyl; preferably selected from the group consisting of methyl, trifluoromethyl and chlorine.

Particularly preferred compounds of formula (II) according to the invention are selected from:

- 5-[(1*R*)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]tetrazol-2-ide (DF3966Y) or its sodium salt (DF3966A);
- 4-methyl-N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;
- 4-tert-butyl-N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;
- N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;
- N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-4-(trifluoromethyl)-1,3-oxazol-2-amine;
- 4-methyl-N- {4-[(1R)-1-(1H tetrazol-5-yl)ethyl]phenyl}-1,3-oxazol-2-amine;
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H pyrazol-1-ol;
- 4-methyl-5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) ethyl]-1H-pyrazol-1-ol;
- 5-[(1R)-1-(4-([4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H-1,2,3-triazol-1-ol;
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl] isoxazol-3-ol;
- 4-methyl-5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) ethyl]isoxazol-3-ol;
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl] isothiazol-3-ol;
- 4-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-

1,2,5-oxadiazol-3-ol;

- 4-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1,2,5-thiadiazol-3-ol;

- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H 1,2,4-triazol-1-ol.

A particular preferred compound of formula (II) is 5-[(1*R*)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]tetrazol-2-ide (DF3966Y) or its sodium salt (DF3966A).

Compounds of formula (II) are described in WO2009/050258, which also discloses their method of synthesis.

Preferred C5aR1 inhibitors according to the invention are Avacopan, PMX-53, W54011, Avdoralimab, MOR-044254, PMX-205, DF2593A, DF2297A, DF2427 and DF3966A, more preferably the C5aR1 inhibitor is DF3966A.

Preferably, the C5aR1 inhibitor for use according to the present invention is administered topically to the surface of the eye of a subject. Preferably, the C5aR1 inhibitor for use according to the present invention is formulated in form of eyedrops.

As will be discussed in the experimental section, the present inventors have shown that topical application of a C5aR1 inhibitor to the surface of the eye results in amelioration of both ocular and oral MMP.

The invention is also directed to a pharmaceutical composition comprising a C5aR1 inhibitor, as above described, and at least one pharmaceutically acceptable excipient or carrier for use in the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid.

Preferably, the pharmaceutical composition is an ophthalmic composition suitable for topical application to the surface of the eye.

Accordingly, the invention is further directed to an ophthalmic composition comprising a therapeutically effective amount of a C5aR1 inhibitor, as above described, and at least one ophthalmologically acceptable excipient or carrier.

According to a preferred embodiment, the invention is further directed to an ophthalmic composition comprising a therapeutically effective amount of a C5aR1 inhibitor, as above described, and at least one ophthalmologically acceptable excipient or carrier for use in the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid.

An "ophthalmologically acceptable excipient" is an inert excipient which allows delivery of a medicament to the eye and/or eyelids, to treat an ocular disease or condition without deleterious effects on the eye.

According to an embodiment, said ophthalmic composition may be a liquid, eye drop composition for topical administration to the anterior segment of the eye.

Said liquid composition may be in form of a solution, emulsion, or suspension.
Said liquid composition may include micelles.
In one embodiment, the liquid composition is an aqueous composition.
Preferably, the liquid composition is an aqueous eye drop composition.
Preferably, said liquid composition comprises ophthalmologically acceptable excipients selected from ophthalmologically acceptable viscosity enhancers, penetration enhancers, buffering agents, osmolarity regulators, preservatives and surfactants.
Viscosity enhancers have the function to increase viscosity of the composition and to improve its retention in the conjunctival sac and are preferably selected from cellulose derivatives, preferably hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, methylcellulose; polyvinylpyrrolidone and gelling agents, preferably gellan, xanthan gum and carbopol-974.
Penetration enhancers have the function of enhancing drug permeability across ocular membranes and are preferably selected from cyclodextrins, chelating agent, crown ethers, bile acids and bile salts.
Buffering agents have the function of providing and maintaining the correct pH of the formulation to be compatible for use in the eye, preferably at a pH comprised between 6 and 8. The preferred buffer is phosphate buffer, but other buffers capable of maintaining the pH within the desired range, especially buffers suitable for ophthalmic use, are also included.
Osmolarity regulators are salts able to make the liquid composition isotonic with ocular fluids. The preferred salt is sodium chloride (NaCl) but other biologically acceptable salts may be used, such as for instance potassium chloride (KCl), calcium chloride ($CaCl_2$) and magnesium chloride ($MgCl_2$) and their admixtures.
Preservatives inhibit microbial activity. Suitable preservatives include for instance quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.
Surfactants have the function of making the composition stable and are preferably selected from polysorbates such as Tween 80, poloxamers such as Pluronics F68 or proteins such as serum albumin.
Said liquid, eye drop composition can be part of a kit comprising the composition, a container for holding the composition and a drop dispenser.
A “therapeutically effective amount” according to the present invention means an amount sufficient to achieve treatment or prevention of the disease. Determination of the effective amounts is well within the capability of those skilled in the art based upon the achievement of a desired effect. An effective amount will depend on factors including, but not limited to, the weight of a subject and/or the degree of the disease or unwanted condition from which a

subject suffers.

The invention relates also to the use of the above C5aR1 inhibitors in the manufacture of a medicament for the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid.

The invention is also directed to a method of preventing and/or treating ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid, which comprises administering an effective amount of one or more C5aR1 inhibitors of the invention to a subject in need thereof.

The invention is further illustrated by the following example.

EXAMPLE

A study was designed to investigate and show the effect of pharmacological inhibition of C5aR1 exerted by the compound DF3966A in a mouse model of MMP.

Materials and methods

Test compounds

- DF3966A Sodium Salt (Lot. LC446-81-1 GLB21001, Dompé S.p.A.)
- Vehicle (solvent, Dompé S.p.A.) - (positive control)
- Methylprednisolone (MP) (sourced by UKSH, Lübeck – Supplier Sanofi) - (reference treatment)

Animal model - Mice

Adult C57Bl/6 (B6) mice (male and female) aged at least 6 weeks old were used. Animals were maintained on a 12-h light–dark cycle at the animal facility of the University of Lübeck. Mice were held under SPF conditions and fed acidified drinking water and standard chow ad libitum. Protocols were approved by the Animal Rights Commission of the Ministry of Agriculture and Environment, Schleswig-Holstein.

Generation, isolation and characterization of anti-mLAMα3 IgG

For production of anti-mLAMα3 IgG, New Zealand White rabbits were immunized subcutaneously with 250µg of an equimolar mixture of the 2 purified recombinant proteins (aa1656-1985 and aa2756-3330 of murine Laminin alpha3 chain, produced in E. coli as disclosed by Heppe, E.N., et al., J Invest Dermatol, 2017, 137, 1709-1718) suspended in complete Freund's adjuvant. The animals were boosted twice with the same protein preparation in incomplete Freund's adjuvant. Immune sera were obtained at regular intervals and characterized by IF microscopy on cryosections of murine skin. IgG from rabbits immunized with recombinant fragments of murine mLAMα3 and from non-immunized rabbits was purified by affinity chromatography using protein G sepharose affinity chromatography (Amersham Biosciences, Heidelberg, Germany). Reactivity of IgG fractions was analyzed by IF microscopy on murine skin (Sitaru et al., *Induction of complement-fixing autoantibodies*

against type VII collagen results in subepidermal blistering in mice. J Immunol 2006, 177: 3461-8). In addition, each batch of anti-mLAMα3 IgG was characterized *in vivo* regarding its capability to induce experimental MMP in C57Bl/6 (B6) mice (WP1.1). From this experiment, the amount of antibodies that leads to moderate experimental MMP was determined; i.e. the amount needed to induce disease development with moderate involvement of the conjunctiva (i.e. score of 1-3 in a maximum of 50% of the animals on day 12) in the model of antibody transfer-induced MMP. For this purpose, the intensity of the separation of the conjunctiva is determined histologically. The body surface area affected should be between 3-8% at the concentration used. The conjunctiva score was set histologically post-mortem and was in a range of 0-4, depending on the intensity of the separation of the conjunctiva. The amount needed was determined to be 5 mg/injection of anti-mLAMα3 IgG.

Study design

Induction of experimental MMP by repetitive injections of anti-mLAMα3 IgG and treatment protocol

To test DF3966A at 0.05% effects on the severity of conjunctival involvement in experimental MMP, the disease was induced by repetitive subcutaneous (s.c.) injections of anti-mLAMα3 IgG (5mg/mouse) on alternating days (0, 2, (...) and 10) into adult B6 mice, which were treated throughout the entire experiment twice a day via eyedrops. Three eyedrops per eye were given twice daily. Mice treated with solvent via eyedrops or methylprednisolone (MP) via i.p. injections were used as treatment controls. Mice s.c. injected with IgG isolated from normal rabbit serum (NR IgG) served as negative control.

Evaluation of conjunctival lesions

The primary endpoint of this experiment was the extent of conjunctival lesions as determined by lesional histopathology (H&E stain) on day 12 and 28 following an established scoring system (Heppe, E.N., et al., J Invest Dermatol, 2017, 137, 1709-1718). In detail, biopsies from the palpebral conjunctiva were taken on day 12 and day 28 and paraffine embedded. 4.5µm thick sections from 3 different depths of the biopsies were cut in triplicate and H&E stained for further quantification. Among the H&E stained histologies those with a palpebral conjunctival-epithelium with more than 1000µm were used for quantification. For this score the length of the split formation (split = epithelia separation from the underlying dermal structures) is measured. The split length is categorized to a score of 0-4 with no split = 0, less than 100µm = 1, less than 200µm = 2, less than 300µm = 3, more or equal 300µm = 4. Splits that occurred at the end of the tissue were excluded, because they were most likely to be of artificial nature due to the cutting. The longest split out of 9 possible sections is decisive for the final score.

The endpoint was analyzed on day 12 in the following groups:
- normal rabbit IgG (n=10)
- Anti-mLAMα3 IgG + solvent (positive control) (n=14)
- Anti-mLAMα3 IgG + MP (reference treatment) (n=13)
- Anti-mLAMα3 IgG + DF3966A (n=12)

The endpoint was analyzed on day 28 in the following groups:
- normal rabbit IgG (n=9)
- Anti-mLAMα3 IgG + solvent (positive control) (n=11)
- Anti-mLAMα3 IgG + MP (reference treatment) (n=11)
- Anti-mLAMα3 IgG + DF3966A (n=12)

The experiments were performed at two independent time points for each day 12 and day 28, including 7 mice/group and 5 mice/normal rabbit IgG.

Evaluation of severity of oral lesions

The extent of oral lesions was determined by endoscopy (Videomed, München, Germany) at day 12 and 28, following an established scoring system (Heppe, E.N., et al., J Invest Dermatol, 2017, 137, 1709-1718). In detail, each affected mouth-quarter of the mouse is counted as one point if there are lesions/blisters/crusts/erosions. The quarters are defined as: left buccal mucosa, right buccal mucosa, hypopharynx, tongue. The maximum score is 4.

Statistical analysis

For statistical analysis GraphPad Prism (version 8.4.3) was used. For comparison of treatment effects in multiple groups ANOVA was used. To isolate the group or groups that differ from others, Dunnett's or Holm Sidaks multiple comparison were used when appropriate.

Results

1. Local application of DF3966A reduced split formation in the palpebral conjunctiva in experimental MMP

Injection of rabbit anti-mLAMα3 IgG into adult B6 mice persistently lead to induction of experimental MMP within 4-8 days after the first IgG injection. After 12 days of twice daily local application of the drug as eyedrops a significant reduction of the conjunctival split formation for the group treated with DF3966A was observed, compared to mice that received the sole vehicle (**figure 1A**). No statistically significant reduction was seen in the subepithelial inflammatory cell infiltrate by semi-quantification of H&E stained palpebral conjunctival biopsies taken on day 12 of mice treated with DF3966A compared to those biopsies of mice that received the vehicle (**figure 1B**). In mice injected with NR-IgG no conjunctival lesions were observed compared to the other groups on day 12 (**figure 2**).

Treatment over 28 days twice daily via eyedrops lead to a significant reduction of palpebral conjunctival split formation in mice receiving DF3966A (**figure**

3A). This is also reflected in a decreased subepithelial inflammatory infiltrate by semi-quantification of H&E stained biopsies of the palpebral conjunctiva (**figure 3B**). Mice that just received NR-IgG from healthy rabbits did not show conjunctival lesions compared to the other groups on day 28 (**figure 4**).

DF3966A reduced the conjunctival split formation on both 12 and 28 experimental days and decreased the inflammatory infiltrate after 28 days of treatment, compared to mice that received the solvent.

2. Local application of DF3966A reduces oral lesions in experimental MMP

Treatment with DF3966A decreased severity of oral involvement after 12 days (Figure 5) and 28 days (Figure 6) of eyedrops application, with a statistically significant difference between the vehicle group and DF3966A (day 12: p=0.0479; day 28: p=0.0372).

Conclusions

Overall, treatment with DF3966A twice daily via eyedrops reduced conjunctival split formation already on day 12 without reducing the underlying inflammation in these tissues. A longer lasting treatment until day 28 via eyedrops also decreased the inflammatory infiltrate in the palpebral conjunctiva. Furthermore, at both day 12 and 28 significant decrease in severity of oral lesions is observed.

CLAIMS

1. A C5aR1 inhibitor for use in the prevention and/or treatment of ocular mucous membrane pemphigoid and/or oral mucous membrane pemphigoid in a subject.

2. A C5aR1 inhibitor for use as claimed in claim 1, wherein said C5aR1 inhibitor is administered topically to the surface of the eye of the subject.

3. A C5aR1 inhibitor for use according to claim 1 or claim 2, wherein said C5aR1 inhibitor is selected from C5aR1 competitive antagonists, anti-C5aR1 antibodies and C5aR1 non-competitive allosteric inhibitors.

4. A C5aR1 inhibitor for use according to any one of claims 1 to 3, wherein said C5aR1 inhibitor is a C5aR1 competitive antagonist selected from the group consisting of:

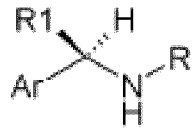
- (2R,3S)-2-[4-(Cyclopentylamino)phenyl]-1-(2-fluoro-6-methylbenzoyl)-N-[4-methyl-3-(trifluoromethyl)phenyl]piperidine-3-carboxamide (Avacopan, Vynpenta®);
- N-Acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine-N-5.2-C-1.6-lactam (PMX-53);
- Acetylated phenylalanine-[ornithyl-proline-(D)cyclohexylalanine-tryptophyl-arginine];
- L-Alanyl-L-seryl-glycyl-L-alanyl-L-prolyl-L-alanyl-L-prolyl-glycyl-L-prolyl-L-alanyl-glycyl-L-prolyl-L-leucyl-L-arginyl-L-prolyl-L-methionyl-L-phenylalanine;
- N,N-Bis(1,3-benzodioxol-5-ylmethyl)-N-(1-butyl-2,4-diphenyl-1H-imidazol-5-ylmethyl)amine;
- N-[2-(4-Chlorophenyl)ethyl]-N-(1,4-dioxaspiro[4.5]dec-8-yl)-2-isobutylbenzamide;
- N-[2-(4-Chlorophenyl)ethyl]-N-(4-hydroxycyclohexyl)-1-benzothiophene-3-carboxamide;
- N-[2-(4-Chlorophenyl)ethyl]-N-(4-hydroxycyclohexyl)naphthalene-1-carboxamide;
- 2-(2-Ethyl-6-methylphenyl)-4-methoxy-N-(5-methoxy-2-methylphenyl)-5,6,7,8-tetrahydroquinolin-5-amine;
- 2-(2,6-Diethylphenyl)-N-ethyl-4-methoxy-N-(1-naphthyl)-5,6,7,8-tetrahydroquinolin-5-amine;
- N-[2,6-Dioxohexahydropyrimidin-4(S)-ylcarbonyl]-L-phenylalanyl-L-ornithyl-L-prolyl-5-methyl-L-norleucyl-4-fluoro-L-phenylalanyl-L-phenylalaninamide (JPE-1375; JSM-1375);
- N-(3-Phenylpropionyl)-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine N-5.1-C-1.5-lactam (PMX-205);
- N,N'-Bis(4-amino-2-methylquinolin-6-yl)urea (NSC12155);

- N-[4-(Dimethylamino)benzyl]-N-(4-isopropylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene-1-carboxamide hydrochloride (W54011);
- L-Phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-L-arginine N-5.2-C-1.6-cyclic peptide;
- (4aR,16aS)-6,18-Dihydroxy-23(S)-[2(S)-hydroxy-2-[2(R)-hydroxy-6(R)-methyl-5(R)-[2(S)-methylbutyl]tetrahydro-2H-pyran-2-yl]propionamido]-22(S)-isopropyl-7(S),19(R)-dimethyldocosahydro-13H,22H-dipyridazino[6,1-f:6',1'o][1,4,7,10,13,16]oxapentaazacyclononadecine-5,7,11,17,20,24-hexanone (L-156602).

5. A C5aR1 inhibitor for use according to any one of claims 1 to 3, wherein said C5aR1 inhibitor is an anti-C5aR1 antibody or aptamer selected from the group consisting of:

- Avdoralimab;
- MOR-044254;
- NOX-D20;
- Anti-C5aR1ab-C5-SiRNA conjugate, anti-C5aR1ab-protamine-C5siRNA conjugate;
- m20/70 mlgG2a.1;
- 3C5;
- 7F3.

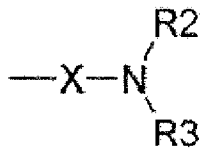
6. A C5aR1 inhibitor for use according to any one of claims 1 to 3, wherein said C5aR1 inhibitor is a C5aR1 non-competitive allosteric inhibitor selected from:
(2R)-2-[3-(furan-2-carbonyl)phenyl]-N-[4-(trifluoromethyl)-1,3-thiazol-2-yl]propenamide (DF2427);
R(-)-2-[(4'-trifluoromethanesulfonyloxy)phenyl]-N-[3-(N'-pirrolidinyl)propyl] propionamide (DF2297X) or its chloride salt (DF2297A);
a compound having general formula (I):



(I)

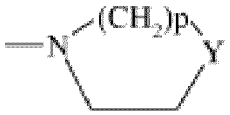
or a pharmaceutically acceptable salt thereof, wherein
R is selected from:
- 2-thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert-butyl or trifluoromethyl group;
- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,
- CORa, SORa, SO_2Ra, PORa, PO_2Ra,
wherein **Ra** is selected from:
- C_1-C_5-alkyl, C_3-C_6-cycloalkyl, C_2-C_5-alkenyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-

C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino;
- a heteroaryl group selected from pyridine, pyrimidine, pyrrole, thiophene, furane, indole, thiazole, oxazole, such heteroaryl being unsubstituted or substituted with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkoxy, hydroxy, C_1-C_4- acyloxy, phenoxy, cyano, nitro, amino;
- a α or β carboxyalkyl residue consisting of straight or branched C_1- C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, C_1-C_6-phenylalkyl, optionally substituted with a further carboxy (COOH) group;
- an ω-aminoalkylamino group of formula (II):



(II)

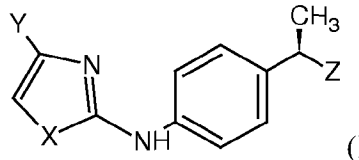
wherein in said formula (II) **X** is selected from:
- linear or branched C_1-C_6 alkylene, C_4-C_6 alkenylene, C_4-C_6 alkynylene, optionally substituted by:
a) a CO_2R4 group, wherein R4 represents hydrogen or a linear or branched C_1-C_6 alkyl group or a linear or branched C_2-C_6 alkenyl group, or
b) a CONHR5 group wherein R5 represents
- hydrogen, linear or branched C_2-C_6 alkyl or an OR4 group, R4 being defined as above;
- a $(CH_2)_m$-B-$(CH_2)_n$, group, optionally substituted by a CO_2R4 or CONHR5 group, as defined above, wherein B is an oxygen, or sulfur atom, or nitrogen atom optionally substituted by a C_1-C_4 alkyl group, m is zero or an integer from 2 to 3 and n is an integer from 2 to 3; or B is a CO, SO or CONH group, m is an integer from 1 to 3 and n is an integer from 2 to 3;
R2 and **R3** are independently selected form hydrogen, linear or branched C_1-C_6 alkyl, optionally interrupted by an oxygen or sulfur atom, a C_3-C_7 cycloalkyl, C_3-C_6 alkenyl, C_3-C_6-alkynyl, aryl-C_1-C_3-alkyl, hydroxy-C_2-C_3-alkyl group; or **R2** and **R3** together with the N atom to which they are bound, form a 3-7 membered nitrogen heterocyclic ring of formula (III)



(III)

wherein **Y** represents:
- a single bond, CH_2, O, S, or a N-R6 group, where R6 represents hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4- alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino,
and p represents an integer from 0 to 3;

- a residue of formula SO_2R7 wherein R7 is C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkenyl, aryl and heteroaryl;
or
in said formula (II), **X** together with the nitrogen atom to which it is bound and with the **R2** group, forms a nitrogen containing 3-7 membered heterocyclic, monocyclic or polycyclic ring, and **R3** is selected from the group comprising hydrogen, C_1-C_4 alkyl, C_1-C_4 acyl, unsubstituted or substituted phenyl with a group selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino;
R1 is linear or branched C_1-C_5 alkyl, C_3-C_5 cycloalkyl;
Ar is selected from:
-a phenyl group unsubstituted or substituted by one or more groups independently selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, hydroxy, C_1-C_4-acyloxy, phenoxy, cyano, nitro, amino, C_1-C_4-acylamino, halo-C_1- C_3- alkyl, halo-C_1-C_3-alkoxy, benzoyl, heteroaryl carbonyl, heteroaryl, linear or branched C_1-C_8-alkanesulfonate, linear or branched C_1-C_8-alkanesulfonamides, linear or branched C_1-C_8 alkyl sulfonylmethyl; or
- a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan, indole;
and a compound having general formula (II)



(II)

or pharmaceutically acceptable salts thereof,
wherein
X is a heteroatom selected from S, O and N;
Y is H or a residue selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkoxy, hydroxy, -COOH, C_1-C_4-acyloxy, phenoxy, cyano, nitro, $-NH_2$, C_1-C_4-acylamino, halo-C_1-C_3-alkyl, benzoyl, linear or branched C_1-C_8-alkanesulfonate, linear or branched C_1-C_8-alkanesulfonamides, linear or branched C_1-C_8-alkyl sulfonylmethyl;
Z is an heteroaryl ring selected from the group consisting of unsubstituted tetrazole and triazole, pyrazole, oxazole, thiazole, isooxazole, isothiazole, thiadiazole and oxadiazole substituted by one hydroxy group and optionally further substituted by one or more groups selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_2-C_4-alkenyl, C_1-C_4-alkylamino, C_1-C_4-alkoxy, C_1-C_4-alkylthio, C_1-C_4-acyloxy, cyano, nitro, NH_2, C_1-C_4-acylamino, halo-C_1-C_3-alkyl, halo-C_1-C_3-alkoxy, linear or branched C_1-C_8-alkanesulfonate and linear or branched C_1-C_8-alkanesulfonamides.

7. A C5aR1 inhibitor for use according to claim 6, wherein in said compound of formula (I)

R is selected from:
- 2-thiazolyl or 2-oxazolyl, unsubstituted or substituted by a group selected from methyl, tert-butyl or trifluoromethyl group,
- C(Ra)=N-W wherein W is linear or branched C_1-C_4 alkyl,
- CORa, SORa or SO_2Ra,

wherein Ra is as defined in claim 6; and

Ar is selected from the group comprising:
3'-benzoylphenyl, 3'-(4-chloro-benzoyl)-phenyl, 3'-(4-methyl-benzoyl)-phenyl, 3'-acetyl-phenyl, 3'-propionyl-phenyl, 3'-isobutanoyl-phenyl, 4'-isobutyl-phenyl, 4'-trifluoromethanesulfonyloxy-phenyl, 4'-benzenesulfonyloxy-phenyl, 4'-trifluoromethanesulfonylamino-phenyl, 4'-benzenesulfonylamino-phenyl, 4'-benzenesulfonylmethyl-phenyl, 4'-acetoxyphenyl, 4'-propionyloxy-phenyl, 4'-benzoyloxy-phenyl, 4'-acetylamino-phenyl, 4'-propionylamino-phenyl, 4'- benzoylamino-phenyl, 3'-(furan-2-carbonyl)-phenyl, 3'-(benzofuran-2-carbonyl)-phenyl, 3'-(thiophen-2-carbonyl)-phenyl, 3'-(pyridine-2-carbonyl)-phenyl, 3 '-(thiazole-2-carbonyl)-phenyl, 3'-(oxazole-2-carbonyl)-phenyl, 3'-(2-furyl)-phenyl, 3'-(2-oxazolyl)-phenyl, 3'-(3-isoxazolyl)-phenyl, 3'-(2-benzoxazolyl)-phenyl, 3'-(3-benzoisoxazolyl)-phenyl, 3'-(2-thiazolyl)-phenyl, 3'-(2-pyridyl)-phenyl, 3'-(2-thiophenyl)-phenyl;
or **Ar** is a heteroaryl ring selected from pyridine, pyrrole, thiophene, furan or indole.

8. A C5aR1 inhibitor for use according to claim 6 or 7, wherein said C5aR1 inhibitor is a compound of formula (I) selected from:
- 4-{(1R)-1-[(phenylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]benzenesulfonamide;
- 4-{(1R)-1-[(pyridine-3-ylsulfonyl)amino]ethyl}phenyltrifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]methanesulfonamide;
- N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}thiophene-2-sulfonamide;
- N-{(1R)-1-[3-(2-furoyl)phenyl]ethyl}methanesulfonamide;
- 4-{(1R)-1-[(thien-2-ylsulfonyl)amino]ethyl}phenyl trifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]thiophene-2-sulfonamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]-3-pyrrolidin-1-ylpropane-1-sulfonamide;
- methyl 5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoate;
- 5-({[(1R)-1-(3-benzoylphenyl)ethyl]amino}sulfonyl)-2-furoic acid;
- 4-{(1R)-2-methyl-1-[(methylsulfonyl)amino]propyl}phenyltrifluoromethanesulfonate;
- N-((1R)-1-{4-[1-methyl-1-

(phenylsulfonyl)ethyl]phenyl}ethyl)methanesulfonamide;
- 4-[(1R)-1-(isobutyrylamino)ethyl]phenyltrifluoromethanesulfonate;
- 4-{[(1R)-1-(pyridine-3-ylcarbonyl)amino]ethyl]}phenyltrifluoromethanesulfonate;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]benzamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]-2-furamide;
- N-[(1R)-1-(3-benzoylphenyl)ethyl]cyclobutanecarboxamide;
- N-[(1R)-1-(4-trifluoromethanesulfonyloxy)phenylethyl]-4-piperidin-1-yl butanamide (DF2593Y);
- 4-{(1R)-1-[(4-pyrrolidin-1-ylbutanoyl)amino]ethyl]}phenyl trifluoromethanesulfonate;
- 3-{(1R)-1-[4-(4-trifluoromethyl-1,3-thiazol-2-yl)amino]ethyl}phenyl) (phenyl)methanone.

9. A C5aR1 inhibitor for use according to claim 6, wherein in said compound of formula (II)

X is a heteroatom selected from S and O;

Y is H or a residue selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl and halo-C_1-C_3-alkyl; preferably selected from the group consisting of trifluoromethyl, chlorine, methyl and tert-butyl;

Z is an heteroaryl ring selected from the group consisting of unsubstituted tetrazole and triazole, pyrazole, isooxazole, isothiazole, thiadiazole and oxadiazole substituted by one hydroxy group and optionally further substituted by one or more groups selected from the group consisting of halogen, linear or branched C_1-C_4-alkyl, C_1-C_4-alkylthio and halo-C_1-C_3-alkyl; preferably selected from the group consisting of methyl, trifluoromethyl and chlorine.

10. A C5aR1 inhibitor for use according to claim 6 or 9, wherein said C5aR1 inhibitor is a compound of formula (II) selected from:
- 5-[(1*R*)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]tetrazol-2-ide (DF3966Y) or its sodium salt (DF3966A);
- 4-methyl-N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;
- 4-tert-butyl-N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;
- N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-1,3-thiazol-2-amine;
- N-{4-[(1R)-1-(1H-tetrazol-5-yl)ethyl]phenyl}-4-(trifluoromethyl)-1,3-oxazol-2-amine;
- 4-methyl-N- {4-[(1R)-1-(1H tetrazol-5-yl)ethyl]phenyl}-1,3-oxazol-2-amine;
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H pyrazol-1-ol;
- 4-methyl-5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) ethyl]-1H-pyrazol-1-ol;

- 5-[(1R)-1-(4-([4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H-1,2,3-triazol-1-ol;
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl] isoxazol-3-ol;
- 4-methyl-5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) ethyl]isoxazol-3-ol;
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl] isothiazol-3-ol;
- 4-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1,2,5-oxadiazol-3-ol;
- 4-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1,2,5-thiadiazol-3-ol;
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]-1H 1,2,4-triazol-1-ol.

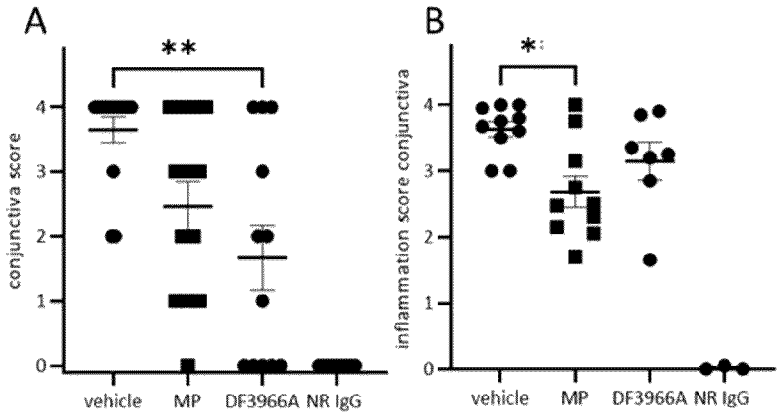
11. A C5aR1 inhibitor for use according to any one of claims 6 to 10, selected from:
- N-[(1R)-1-(4-trifluoromethanesulfonyloxy)phenylethyl]-4-piperidin-1-yl butanamide (DF2593Y) and pharmaceutically acceptable salts thereof, preferably its chloride salt (DF2593A),
- R(-)-2-[(4'-trifluoromethanesulfonyloxy)phenyl]-N-[3-(N'-pirrolidinyl)propyl] propionamide (DF2297X) or its chloride salt (DF2297A), and
- 5-[(1R)-1-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)ethyl]tetrazol-2-ide (DF3966Y) or its sodium salt (DF3966A).

12. A C5aR1 inhibitor for use according to claims 1-11, selected from: Avacopan, PMX-53, W54011, Avdoralimab, MOR-044254, PMX-205, DF2593A, DF2297A, DF2427 and DF3966A.

13. A C5aR1 inhibitor for use according to claims 6 to 12, which is DF3966A.

14. An ophthalmic composition comprising a therapeutically effective amount of a C5aR1 inhibitor as defined in claims 3-13 and at least one ophthalmologically acceptable excipient or carrier.

Figure 1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conjunctiva score
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1
2
3
4
vehicle
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B
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inflammation score conjunctiva
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MP
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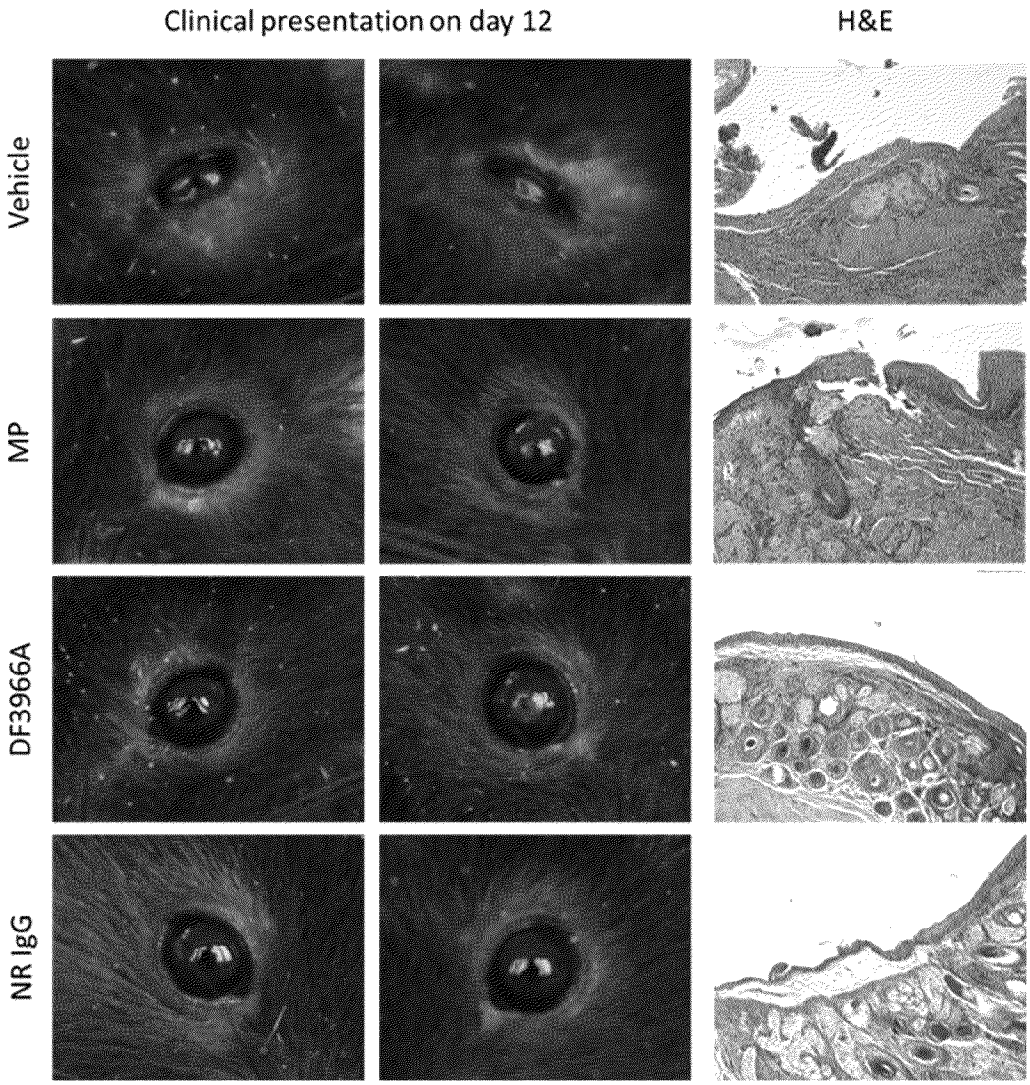
NR IgG

Figure 2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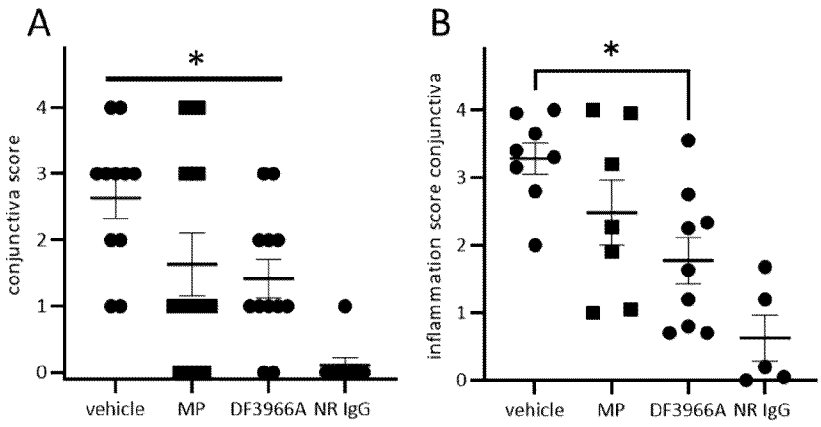
Vehicle
MP
DF3966A
NR IgG

Figure 3


A
*
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1
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3
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vehicle
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NR IgG
B
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inflammation score conjunctiva
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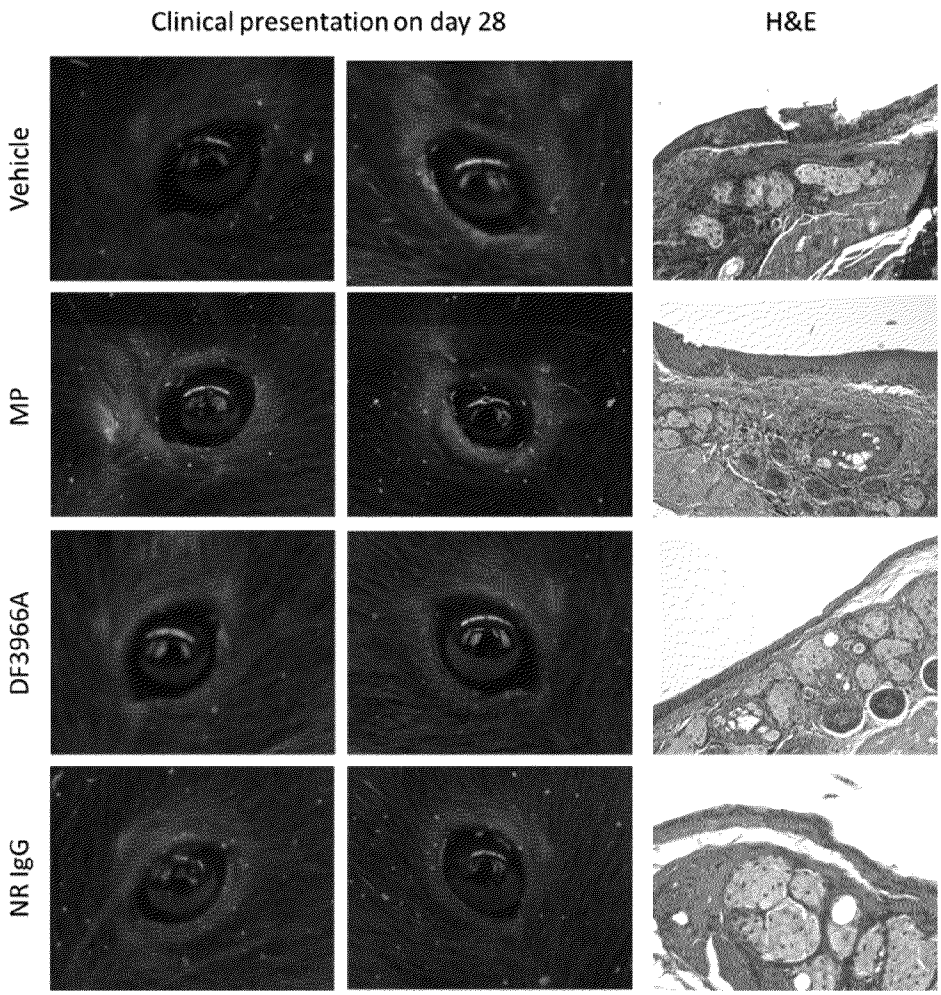
1
2
3
4
vehicle
MP
DF3966A
NR IgG

Figure 4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Vehicle
MP
DF3966A
NR IgG

Figure 5

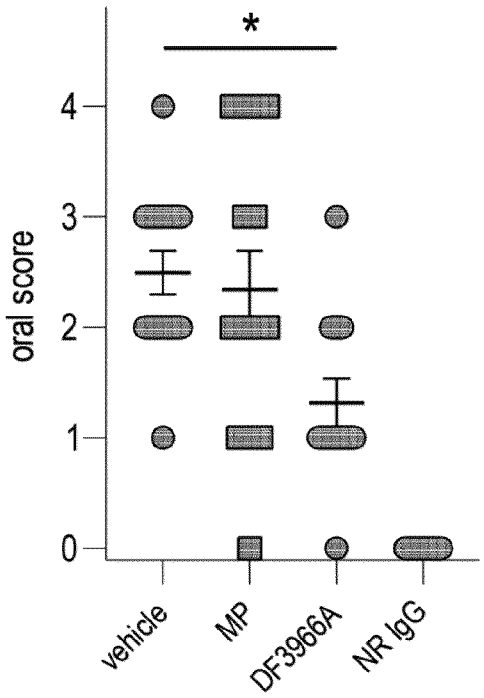
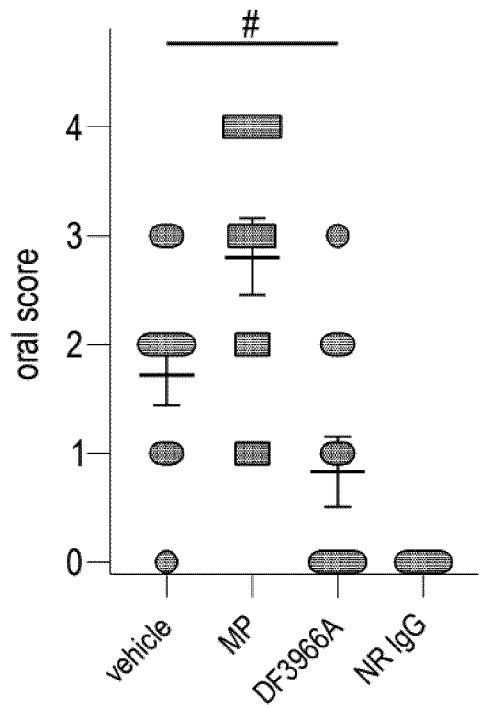


Figure 6



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/050158

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/426 A61K31/155 A61K31/166 A61K31/40 A61K31/445
A61P17/00 A61P27/02 A61P27/12 A61P37/00 A61K31/404
A61K31/4453 A61K39/395 A61K39/00 C07K16/28

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 A61P C07K

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 practicable, search terms used)
EPO-Internal, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HEPPE EVA NINA ET AL: "Experimental Laminin 332 Mucous Membrane Pemphigoid Critically Involves C5aR1 and Reflects Clinical and Immunopathological Characteristics of the Human Disease", JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 137, no. 8, 1 August 2017 (2017-08-01), pages 1709-1718, XP093036966, NL ISSN: 0022-202X, DOI: 10.1016/j.jid.2017.03.037 [retrieved on 2017-03-01] right column and abstract; page 1711, paragraph 2 figure 5 ----- -/--	1-13

[x] Further documents are listed in the continuation of Box C.

[x] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2024	16/04/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Healy, Cathal

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2022/033981 A1 (INNATE PHARMA [FR]) 17 February 2022 (2022-02-17) page 1, line 9 - line 12 page 11, line 24 - line 25	1-13
Y	EP 4 059 497 A1 (DOMPE FARM SPA [IT]) 21 September 2022 (2022-09-21) paragraph [0025] paragraph [0047]	1-13
A	CHRISTIAN D. SADIK ET AL: "The critical role of C5a as an initiator of neutrophil-mediated autoimmune inflammation of the joint and skin", SEMINARS IN IMMUNOLOGY, vol. 37, 1 June 2018 (2018-06-01), pages 21-29, XP055486276, US ISSN: 1044-5323, DOI: 10.1016/j.smim.2018.03.002 Section 5	1-14
A	Innate Pharma: "NCT04563923 : Treatment of Bullous Pemphigoid With Avdoralimab (IPH5401), an Anti-C5aR1 Monoclonal Antibody (IPH)", Clinical Trials . gov, 20 October 2020 (2020-10-20), XP055858398, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/history/NCT04563923?V_2=View#StudyPageTop [retrieved on 2023-05-20] Study Identification section	1-14
Y	"ICW - 2021 Virtual Workshop of the International Complement Society (ICS) - Abstracts; December 07 - 10, 2021 ED - Blank Ulrich; Pucillo Carlo E", MOLECULAR IMMUNOLOGY, PERGAMON, GB, vol. 141, 2 December 2021 (2021-12-02), pages 116-235, XP086921518, ISSN: 0161-5890, DOI: 10.1016/J.MOLIMM.2021.11.020 [retrieved on 2021-12-02] right column, section 187; page 223	1-13
A	US 2008/220003 A1 (SCHNATBAUM KARSTEN [DE] ET AL) 11 September 2008 (2008-09-11) paragraph [0274]	1-14
7 X	US 2019/218278 A1 (ALEXION PHARMA INC) 18 July 2019 (2019-07-18) Example 2 paragraph [0116] - paragraph [0135]	14
1	-/--	

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/050158

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2020/397725 A1 (BRANDOLINI LAURA [IT] ET AL) 24 December 2020 (2020-12-24) par.140-142, claim 11	1-13

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/050158

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2022033981 A1	17-02-2022	AU 2021324314 A1	25-05-2023
		CA 3194881 A1	17-02-2022
		CN 116615454 A	18-08-2023
		EP 4196501 A1	21-06-2023
		JP 2023537417 A	31-08-2023
		KR 20230045075 A	04-04-2023
		US 2023340140 A1	26-10-2023
		WO 2022033981 A1	17-02-2022
EP 4059497 A1	21-09-2022	NONE	
US 2008220003 A1	11-09-2008	AR 057041 A1	14-11-2007
		AU 2006254313 A1	07-12-2006
		BR PI0610875 A2	03-08-2010
		CA 2607862 A1	07-12-2006
		CN 101189209 A	28-05-2008
		EP 1739078 A1	03-01-2007
		EP 1885691 A1	13-02-2008
		JP 2008545727 A	18-12-2008
		KR 20080015401 A	19-02-2008
		TW 200716524 A	01-05-2007
		US 2008220003 A1	11-09-2008
		WO 2006128670 A1	07-12-2006
		ZA 200708824 B	30-07-2008
US 2019218278 A1	18-07-2019	EP 3359566 A1	15-08-2018
		JP 2018530574 A	18-10-2018
		US 2019218278 A1	18-07-2019
		WO 2017062649 A1	13-04-2017
US 2020397725 A1	24-12-2020	AU 2018385364 A1	09-07-2020
		BR 112020009972 A2	09-02-2021
		CA 3082762 A1	20-06-2019
		CN 111511363 A	07-08-2020
		EP 3498269 A1	19-06-2019
		EP 3723744 A2	21-10-2020
		IL 275132 A	30-07-2020
		JP 7430141 B2	09-02-2024
		JP 2021505647 A	18-02-2021
		JP 2024028984 A	05-03-2024
		KR 20200108839 A	21-09-2020
		MA 51128 A	24-03-2021
		RU 2020122678 A	13-01-2022
		SG 11202004322V A	29-07-2020
		US 2020397725 A1	24-12-2020
		WO 2019115493 A2	20-06-2019