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(54) Title: USE OF AN ANTI-GM-CSF ANTAGONIST IN THE TREATMENT OF AN INFECTIOUS DISEASE

(57) Abstract: The present invention relates to anti-GM-CSF antagonists in the treatment and prevention of infections caused by agents inducing hemorrhagic fever, such as Ebola viruses. The invention also relates to pharmaceutical compositions comprising such antagonists, which are preferably anti-GM-CSF antibodies.

Use of an anti-GM-CSF antagonist in the treatment of an infectious disease

Field of the invention

The present invention relates to the treatment and/or prevention of infectious diseases in individuals, e.g. humans, for example, those caused by agents inducing hemorrhagic fever, using agents antagonizing GM-CSF. Preferably, the antagonists are neutralizing antibodies against primate GM-CSF. These antagonists can be used alone or in combination with other drugs in the treatment and/or prevention of infections caused, e.g., by Ebola virus, and/or in modulating the cellular or immune response of an individual infected with or exposed to Ebola virus or any other agent causing hemorrhagic fever.

Technical background

Ebola virus disease (EVD) is caused by a negative single-stranded RNA filovirus. There have been self-contained and relatively few previous epidemics due to this virus [Feldmann H, 2014 and 2011] but the current epidemic, which began almost a year ago in the Republic of Guinea [Gatherer D, 2014], has taken the world by surprise because of its rapid spread over other Western African countries (Liberia, Sierra Leone, Nigeria, Senegal and Mali), reaching even global proportions when few exported cases were reported and treated in other continents. The main reason for the magnitude of the current epidemic is that the present epidemic was located in an urban populated setting from its very beginning, engulfing the Guinean capital, Conakry [Ibrahima E et al, 2014], unlike other previous epidemics which stayed in bush areas of Africa.

The fatality rate in EVD is very high, up to 90% in some outbreaks, and the current epidemic has around a 70% mortality rate [Schieffelin JS et al, 2014], though the rate may be slightly lower (~60%) if the patients are hospitalised and have access to standard medical supportive and critical care facilities [WHO Ebola Response Team, 2014].

On the basis of this high fatality rate, the CDC has classified the filoviruses as category A potential bioterrorism agents [CDC, website]. Indeed, in addition to the immediate need for new medicines and vaccines to alleviate the suffering of the affected populations, this current

epidemic has also made even clearer the necessity for stock-piling new drugs in preparation for future epidemics. Currently, the virus is not air-borne, and this is determined epidemiologically by the fact that all cases can be traced to a single (or multiple) known infected contact(s).

The virus is transmitted through body fluid (blood, sweat, vomit, diarrhea etc), and likely spread originally from consumption of wild animals such as bats, which are known reservoirs of the virus [Feldmann H et al, 2011]. The incubation of EVD is between 3- 21 days, though the median is only 11 days [WHO Ebola response team, 2014], and therefore the majority of patients develop symptoms around 11 days after contact with an infected patient.

The symptoms occur brutally as flu-like non-specific symptoms (fever, malaise, fatigue, body aches) and progress typically after 3 days through successive phases of the illness. The next phase is characterised by gastrointestinal symptoms for about 7 days with epigastric pain, nausea, vomiting and diarrhea. This phase is followed by either shock and usually death or recovery and the median time from the onset of symptoms to death is 8 days. [Chertow DS et al, 2014]. Clinically significant hemorrhage from the lower or upper GI tract occurs in about 5 % of cases [Chertow DS et al, 2014], though the total number of patients with any bleeding episode is close to 20% [WHO Ebola response team, 2014]. In relation to formal diagnosis, RT-PCR and viral antigen detection by ELISA are the primary assays and can be positive as soon as the onset of symptoms, but usually 2-3 days after onset [Feldmann H et al, 2011][Towner JS et al, 2004].

Currently there is no cure or vaccine against Ebola. The treatment is supportive care such as intravenous fluids replacement (IV crystalloid) and rehydration, electrolyte balance and nutrition, as well as anti-microbial, anti-malarial and symptomatic treatment for pain, GI and neurological symptoms [Sprecher A, 2014][Kreuels B et al, 2014][Ibrahima E et al, 2014].

There is a global effort to develop vaccines against the disease. In addition to vaccines, new drug therapies are under investigation for EVD and include direct antiviral drugs (targeting viral components involved with virus cellular entry, virus replication, and virus exit from host cells) and immunostimulation (to boost the immune response to the virus, such as promoting interferon response) [Clark P. 2014][Bausch DG et al, 2008].

The present invention relates to what is sometimes called "indirect anti-viral" therapy, which targets the virus host cells. This approach is based on the unique biology of the virus, which uses monocyte/macrophage/dendritic cells (DC) as key mediators of its infection. Infection of these cells is the main cellular tropism of the virus in approximately the first 3 symptomatic days. In addition, monocyte/macrophage/DC activation triggers an unregulated cytokine cascade, critical for endothelial cell dysfunction, a hallmark of the disease. Viral proteins re-program the host's anti-viral response at the level of JAK/STAT, IRF, and dsRNA sensors and dysregulate monocyte/macrophage/DC homeostasis, and hijack the infected monocytes as a vehicle to disseminate the virus throughout the body [Sullivan N et al. 2003][Martinez O et al., 2013][Wong G et al, 2014][Ansari AA, 2014]. The herein disclosed GM-CSF antagonists target different aspects of the monocytes/macrophage maturation, and by doing so slow down and minimize the virus dissemination and related symptoms.

Description of the invention

The present invention provides anti-GM-CSF antagonists for use in the treatment and/or prevention and/or modulation of the cellular or immune response of an individual infected with or exposed to an agent causing hemorrhagic fever.

As used herein anti- GM-CSF antagonists comprise antibodies or fragments thereof, preferably antibodies or fragments having the capability of neutralizing GM-CSF, peptidomimetics, polypeptides, small molecules or nucleic acids.

Further, the present invention provides anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, and/or the modulation of the cellular or immune response of an individual infected with or exposed to Ebola virus or any other agent causing hemorrhagic fever, wherein the treatment and/or prevention comprises modulating the cellular and/or immune response of an individual.

The individual treated by the method of the present invention includes a primate, wherein the primate is a human, or a non-human primate. Non-human primates include chimpanzee, gorilla, orangutan, monkey, Rhesus Macaque. Preferred is the treatment of humans.

The present invention also provides anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, wherein the treatment and/or prevention disrupts said agent's mechanism of infection, slows down disease progression, and/or provides time for the individual's immune system to raise a response.

The present invention also provides anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, wherein the treatment comprises modulating the cellular and/or immune response of an individual, wherein the modulation comprises at least one of the following features:

i. Suppression of expression of receptors on target cells comprising viral receptors;
ii. Inhibition of egression of monocytes from the bone marrow;
iii. Inhibition of transfer of monocytes from blood to tissue;
iv. Inhibition of maturation and/or differentiation of monocytes to tissue macrophages and/or dendritic cells;
v. Inhibition of activation of monocytes, macrophages, dendritic cells and neutrophils;
vi. Inhibition of agent-induced cytokine cascade comprising release of monocyte-derived, macrophage-derived, dendritic cell-derived, immune cell-derived, endothelial cell-derived cytokines;
vii. Regulating the homeostasis of cells of the myeloid lineage comprising monocytes, macrophages, dendritic cells and neutrophils;
viii. Reducing the number of target cells for infection with the agent causing hemorrhagic fever;
ix. Inhibition of endothelial cell dysfunction;
x. Inhibition of viral protein-induced reprogramming of the individual's JAK/STAT, IRF, and/or dsRNA sensors;
xi. Inhibition, slowing down or minimization of dissemination of the agent throughout the individual's body;
xii. Inhibition, slowing down or minimization of hemorrhagia in said individual; and/or
xiii. Inhibition, slowing down or minimization of clinical symptoms in said individual comprising symptoms selected from hypotonia, loss of body fluids, fever, blood loss, diarrhea, sore throat, muscle pain and headaches.

The present invention also provides an anti-GM-CSF antagonist for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, wherein the treatment increases the survival rate of the individual at least by 5%, at least by 10 %, at least by 15% , at least by 20%, at least by 25% or at least by 30%, or at least by up to 50% as compared to no treatment, based on a current survival rate of 40%. The survival rate is determined at day 7, or at day 14, or at day 21, or at day 28 from onset of symptoms.

In a further embodiment of the invention, the use or method of treatment reduces the severity of the following symptoms comprising fever, headache, respiratory and heart rates, diarrhoea, vomiting, compared to time of randomisation, reduces the survival rate at day 21 or day 28 from onset of symptoms, inhibits the progression to a later phase of the disease, decreases the incidence of organ failure, decreases the time to hospital discharge, the time to return to pre-morbid state, decreases the virus load and available laboratory assessments such as immune response at 2 weeks, and 4 weeks for survivors (IgG and IgM specific Ebola).

The present invention also provides anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, wherein the agent causing hemorrhagic fever is selected from the group comprising filoviridae, flaviviridae, arenaviridae, togaviridae and bunyaviridae (hantavirus). Arenaviridae comprise, e.g., Lassa virus, Junin virus and Machupo virus as representative agents inducing hemorrhagic fever. Togaviridae comprises e.g., Chikungunya virus as representative agent causing hemorrhagic fever. Flaviviridae comprises, e.g., Dengue viruses (all four known serotypes) as representative agent inducing hemorrhagic fever. The family of bunyaviridae comprises the genus Hantavirus as representative agent inducing hemorrhagic fever comprising as representative viruses, e.g. Hantaan river virus, Seoul virus, Puumula virus, Dobrava-Belgrade virus. According to the present invention, the herein described anti-GM-CSF antagonists can be used also in the treatment of infections and diseases caused by the above viruses.

The present invention provides further anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, wherein the agent causing hemorrhagic fever selected from filoviridae comprises the genera Ebola virus and Marburg virus. In embodiments of the invention, the Ebola virus is selected from the group comprising the strains Zaire Ebola virus (ZEBOV), Tai Forrest Ebola virus (TEBOV), Sudan Ebola virus (SEBOV), Reston Ebola virus (REBOV), Bundibugyo Ebola virus (BEBOV).

In some preferred embodiments of the above anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever said anti-GM-CSF antagonists are neutralizing antibodies or a fragment thereof. The neutralizing anti-GM-CSF antagonists for use in the treatment and/or prevention with an agent causing hemorrhagic fever may comprise in its heavy chain variable region a CDR 3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-13 or 56. Further, the neutralizing anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever may comprise a heavy chain variable region CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-13 or 56 in combination with a heavy chain variable region CDR1 having an amino acid sequence set out in SEQ ID NO: 14 and a heavy chain variable region CDR2 having an amino acid sequence set out in SEQ ID NO: 15. Still further, the neutralizing anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever may comprise a light chain variable region CDR1 having an amino acid sequence set out in SEQ ID NO: 16, a CDR2 having an amino acid sequence set out in SEQ ID NO: 17 and a CDR3 having an amino acid sequence set out in SEQ ID NO: 18. In further embodiments, the neutralizing anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever may comprise a light chain variable region CDR1 having an amino acid sequence as set out in SEQ ID NO: 16, a CDR2 having an amino acid sequence set out in SEQ ID NO: 17 and a CDR3 having an amino acid sequence set out in SEQ ID NO: 18 and comprising a heavy chain variable region CDR1 having an amino acid sequence set out in SEQ ID NO: 14, a CDR2 having an amino acid sequence set out in SEQ ID NO: 15 and a CDR3 having an amino acid sequence set out in SEQ ID NO: 2. In still further embodiments, the neutralizing anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever may comprise a light chain variable region sequence set out in SEQ ID NO: 19 and/or a heavy chain variable region sequence set out in SEQ ID NO: 21. In still further embodiments, the neutralizing anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, may comprise a light chain sequence set out in SEQ ID NO: 34 and/or a heavy chain sequence set out in SEQ ID NO: 35. The neutralizing anti-GM-CSF antagonist for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, wherein said neutralizing antibody or fragment thereof comprises at least one amino acid sequence having at least 70%, at least

80%, at least 90% or at least 95% identity to the amino acid sequence of any of SEQ ID NO: 1-48 and/or 52-56. It is clear that the above values of percentage identity comprise any value between, e.g., 70% and 80%, such as 71, 72, 73, 74, 75, 76, 77, 78, and 79%, and the same applies also to values between, e.g., 80% and 90%, values between, e.g., 90% and 95%, and between 95% and 100%.

Other neutralizing anti-GM-CSF antibodies are known. For example, Li el al., (2006) PNAS 103(10):3557-3562 describes the human E10 antibody and human G9 antibody. E10 and G9 are IgG class antibodies. E10 has an 870 pM binding affinity for GM-CSF and G9 has a 14 pM affinity for GM-CSF. Both antibodies are specific for binding to human GM-CSF and show strong neutralizing activity as assessed with a TF-1 cell proliferation assay. Further examples of human anti-GM-CSF antibodies as disclosed in WO2006/122797.

GM-CSF antagonists or neutralizers that are anti-GM-CSF receptor antibodies can also be employed in the present invention. Such GM-CSF antagonists include antibodies to the GM-CSF receptor alpha chain or beta chain. An anti-GM-CSF receptor antibody employed in the invention can be in any antibody form as explained above, e.g., intact, chimeric, monoclonal, polyclonal, antibody fragment or derivative, single-chain, humanized, humaneered, and the like. Examples of anti-GM-CSF receptor antibodies, e.g., neutralizing high-affinity antibodies, suitable for use in the invention are known in the art (see e.g., US Patent 5,747,032 and Nicola et al., Blood 82:15 1724, 1993).

Further, sequences for suitable antibodies are provided in applications and are incorporated by reference in their entirety. Anti-GM-CSF antibodies are provided in WO2006/122797, WO2007/049472, WO2007/092939, WO2009/134805, WO2009/064399, WO2009/038760. Antibodies against the GM-CSF receptor are provided in WO2007/110631.

In some embodiments, the anti-GM-CSF antagonist for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever as defined in any of the preceding sections is an scFv, a single domain antibody, an Fv, a VHH antibody, a diabody, a tandem antibody, a Fab, a Fab' or a $F(ab)_2$. As mentioned above, the anti-GM-CSF antagonist for use according to the present invention preferably neutralizes GM-CSF.

The present invention also relates to anti-GM-CSF antagonists for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever as defined in the preceding sections, wherein said antagonist specifically binds primate GM-CSF, e.g. human GM-CSF and non-human primate GM-CSF. As mentioned above, said antagonist is preferably a neutralizing antagonist, e.g. a neutralizing antibody or fragment thereof.

Further, the present invention relates to anti-GM-CSF antagonists as defined above for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever as defined in the preceding sections, wherein said antagonist is used in combination with drugs for use in the treatment and/or prevention of an infection with an agent causing hemorrhagic fever, e.g., a filovirus, such as Ebola virus, wherein said drug is selected from a group comprising antibodies, comprising, inter alia, the antibody ZMAPP, vaccines against agents causing hemorrhagic fever, medicaments for the treatment of fever, inflammation, infectious diseases, diarrhea, pain, vomiting, bleeding, hypotonia, virus infections, or any other symptoms associated with hemorrhagic fever.

In particular, the herein disclosed anti-GM-CSF antagonists may be used in combination with vaccines and/or therapeutics against agents causing hemorrhagic fever, e.g. Ebola virus. Antiviral agents may comprise (i) compounds directly targeting the virus, e.g. the viral polymerase, and/or (ii) compounds that target the host-viral life-cycle interaction (e.g. the budding, vesicle fusion, trafficking, sorting, packaging, etc.). Vaccines and/or therapeutics comprise Vesicular Stomatitis Virus (VSV) comprising and expressing Ebola-derived antigens (e.g. VSV-EBOV manufactured by NewLink Genetics Corp., BioProtection Corp., or VesiculoVax Ebola and Marburg virus developed by Profectus Biosciences Inc.), modified adenoviruses comprising and expressing Ebola antigens (e.g. cAd3-EBO developed by Glaxo-Smith-Kline), Vaccinia virus (e.g. MVA)-derived vaccines comprising and expressing Ebola antigens (e.g. MVA-BN Filo manufactured by Bavarian Nordic A/S), synthetic vaccines (e.g. SynCon Ebola and Marburg virus developed by Inovio Pharmaceuticals Inc.), siRNA molecules blocking virus replication (e.g. TKM-Ebola manufactured by Tekmira Pharmaceuticals Corp.), RNA-antisense molecules inhibiting VP24 gene expression (e.g. AVI-7537 manufactured by Sarepta Therapeutics Inc.), inhibitors of viral RNA polymerase (e.g. Favipiravir T-705 manufactured by Fujifilm Holdings Corp./MediVector Inc.), nucleosides as inhibitors of the viral RNA polymerase (e.g. BCX4430 developed by Biocryst Pharmaceuticals Inc.). Further antiviral agents comprise retrovirus protease inhibitor, optionally selected from the group comprising darunavir, atazanavir, indinavir, lopinavir,

ritonavir, and saquinavir. Also contemplated is the use of semicarbazone proteasome inhibitors, structural and/or functional analogue or a derivative thereof, dipeptidyl-boronic acid derivatives, or a pharmaceutically acceptable salt of either, optionally selected from the group comprising the semicarbazone S-2209 ([l-[l-{l-[(2,4-Dioxo- imidazo lidin-1-ylimino)-methyl] -2-phenyl-ethylcarbamoyl}-2-(1H-indo 1-3-yl)- ethylcarbamoyl]-2-(lH-indol)]). This list of antiviral agents is not considered limiting. Any additional presently existing antiviral agents that alleviate, ameliorate, prevent and/or cure infections with the herein disclosed viruses are explicitly contemplated for combined treatments with the disclosed antagonists of GM-CSF.

In other embodiments of the present invention the herein disclosed antagonists of GM-CSF, e.g. neutralizing antibodies or fragments thereof, are administered alone, i.e. without additional presently existing antiviral agents.

In other embodiments, the present invention relates to methods of treatment and/or prevention of an infection with an agent causing hemorrhagic fever as defined in the preceding sections, wherein the anti-GM-CSF antagonist (e.g. a neutralizing antibody or fragment) that is used

a. disrupts said agent's mechanism of infection; and/or
b. slows down disease progression; and/or
c. provides time for the individual's immune system to raise a response.

In other embodiments, the present invention relates to methods of treatment and/or prevention of an infection with an agent causing hemorrhagic fever as defined in the preceding sections, wherein the anti-GM-CSF antagonist (e.g. a neutralizing antibody or fragment) that is used modulates the cellular and/or immune response of an individual, wherein the modulation comprises at least one of the following features:

i. Suppression of expression of receptors on target cells comprising viral receptors;
ii. Inhibition of egression of monocytes from the bone marrow;
iii. Inhibition of transfer of monocytes from blood to tissue;
iv. Inhibition of maturation and/or differentiation of monocytes to tissue macrophages and/or dendritic cells;
v. Inhibition of activation of monocytes, macrophages, dendritic cells and neutrophils;

vi. Inhibition of agent-induced cytokine cascade comprising release of monocyte-derived, macrophage-derived, dendritic cell-derived, immune cell-derived, endothelial cell-derived cytokines;
vii. Regulating the homeostasis of cells of the myeloid lineage comprising monocytes, macrophages, dendritic cells and neutrophils;
viii. Limiting the number of target cells for infection with the agent causing hemorrhagic fever;
ix. Inhibition of endothelial cell dysfunction;
x. Inhibition of viral protein-induced reprogramming of the individual's JAK/STAT, IRF, and/or dsRNA sensors;
xi. Inhibition, slowing down or minimization of dissemination of the agent throughout the individual's body;
xii. Inhibition, slowing down or minimization of hemorrhagia in said individual;
xiii. Inhibition, slowing down or minimization of clinical symptoms in said individual comprising symptoms selected from hypotonia, loss of body fluids, fever, blood loss, diarrhea, sore throat, muscle pain and headaches.

In preferred embodiments, the present invention relates to methods of treatment and/or prevention of an infection with an agent causing hemorrhagic fever as defined in the preceding sections, wherein the individual treated is a human or a non-human primate.

Throughout this disclosure, the term "anti-GM-CSF antagonist" is frequently used, which means that compounds, e.g. antibodies, are meant that antagonize GM-CSF. It is clear that the term does not relate to antagonists of compounds antagonizing GM-CSF.

In the context of the present invention, the term "antibody" or its grammatically related variations relate to full length antibodies, human antibodies, humanized antibodies, fully human antibodies, genetically engineered antibodies (e.g. monoclonal antibodies, polyclonal antibodies, chimeric antibodies, recombinant antibodies) and multispecific antibodies, as well as to fragments of such antibodies retaining the characteristic binding properties of the full length antibody. In one specific embodiment, the antibody used in the present invention is a human antibody, in particular a human monoclonal antibody.

It is particularly difficult to prepare human antibodies which are monoclonal. In contrast to fusions of murine B cells with immortalized cell lines, fusions of human B cells with

immortalized cell lines are not viable. Thus, the human monoclonal antibody of the invention is the result of overcoming significant technical hurdles generally acknowledged to exist in the field of antibody technology. The monoclonal nature of the antibody makes it particularly well suited for use as a therapeutic agent, since such antibody will exist as a single, homogeneous molecular species which can be well-characterized and reproducibly made and purified. These factors result in a product whose biological activity can be predicted with a high level of precision. This is very important if such a molecule is going to gain regulatory approval for therapeutic administration in humans.

It is especially desirable that the monoclonal antibody (or the corresponding fragment) according to the invention be a human antibody (or the corresponding fragment). In contemplating an antibody agent intended for therapeutic administration to humans, it is advantageous if this antibody is of human origin. Following administration to a human patient, a human antibody or fragment thereof will most probably not elicit a strong immunogenic response by the patient's immune system, i.e. will not be recognized as being a "foreign", that is a non-human protein. This means that no patient antibodies will be generated against the therapeutic antibody which would otherwise block the therapeutic antibody's activity and/or accelerate the therapeutic antibody's elimination from the body of the patient, thus preventing it from exerting its desired therapeutic effect.

The term "human" antibody as used herein is to be understood as meaning that the antibody of the invention, or its fragment, comprises (an) amino acid sequence(s) contained in the human germ line antibody repertoire. For the purposes of definition herein, an antibody, or its fragment, may therefore be considered human if it consists of such (a) human germ line amino acid sequence(s), i.e. if the amino acid sequence(s) of the antibody in question or fragment thereof is (are) identical to (an) expressed human germ line amino acid sequence(s). An antibody or fragment thereof may also be regarded as human if it consists of (a) sequence(s) that deviate(s) from its (their) closest human germ line sequence(s) by no more than would be expected due to the imprint of somatic hyper mutation. Additionally, the antibodies of many non-human mammals, for example rodents such as mice and rats, comprise VH CDR3 amino acid sequences which one may expect to exist in the expressed human antibody repertoire as well. Any such sequence(s) of human or non-human origin which may be expected to exist in the expressed human repertoire would also be considered "human" for the purposes of the present invention.

According to a further embodiment of the invention, the human monoclonal antibody may be an IgG antibody. According to the present invention "IgG antibody" relates to a therapeutically useful antibody or fragment thereof falling within the IgG class (isotype) of antibodies and having a gamma-type (γ) heavy chain. This includes an antibody of any subtype of the IgG class known in the art, i.e. IgG1, IgG2, IgG3 or IgG4. As is well known in the art, an IgG antibody comprises not only the variable antibody regions responsible for the highly discriminative antigen recognition and binding, but also the constant regions of the heavy and light antibody polypeptide chains normally present in endogenously produced antibodies and, in some cases, even decoration at one or more sites with carbohydrates. Such glycosylation is generally a hallmark of the IgG format, and portions of these constant regions make up the so-called Fc region of a full antibody which is known to elicit various effector functions *in vivo*. In addition, the Fc region mediates binding of IgG to Fc receptor, hence prolonging half-life *in vivo* as well as facilitating homing of the IgG to locations with increased Fc receptor presence. Particularly, the IgG antibody is an IgG1 antibody or an IgG4 antibody, formats which are particularly desirable in the context of the present invention since their mechanism of action *in vivo* is particularly well understood and characterized. This is especially the case for IgG1 antibodies. Hence, in one specific embodiment, the antibody according to the present invention is an IgG1 antibody.

The terms "antibody fragment" or "fragment thereof" or its grammatically related variations relate to a part of a full length antibody specifically binding with the same antigen, i.e. primate GM-CSF as the full length antibody. In particular, it relates to a pharmaceutically active fragment of an antibody, i.e. having the same pharmaceutical effects as the full length anti-GM-CSF antibody. This part of a full length antibody may be at least the antigen binding portion or at least the variable region thereof. Genetically engineered proteins acting like an antibody are also included within the meaning of antibody fragment as used herein. Such genetically engineered antibodies may be scFv, i.e. fusion proteins of a heavy and a light chain variable region connected by a peptide linker. Further exemplary antibody fragments according to the present invention are Fab, Fab', $F(ab')_2$, VHH antibodies, diabodies, tandem antibodies, single domain antibodies and Fv.

These formats may generally be divided into two subclasses, namely those which consist of a single polypeptide chain, and those which comprise at least two polypeptide chains. Members

of the former subclass include a scFv (comprising one VH region and one VL region joined into a single polypeptide chain via a polypeptide linker); a single domain antibody (comprising a single antibody variable region) such as a VHH antibody (comprising a single VH region). Members of the latter subclass include an Fv (comprising one VH region and one VL region as separate polypeptide chains which are non-covalently associated with one another); a diabody (comprising two non-covalently associated polypeptide chains, each of which comprises two antibody variable regions - normally one VH and one VL per polypeptide chain - the two polypeptide chains being arranged in a head-to-tail conformation so that a bivalent antibody molecule results); a tandem diabody (bispecific single-chain Fv antibodies comprising four covalently linked immunoglobulin variable - VH and VL -regions of two different specificities, forming a homodimer that is twice as large as the diabody described above); a Fab (comprising as one polypeptide chain an entire antibody light chain, itself comprising a VL region and the entire light chain constant region and, as another polypeptide chain, a part of an antibody heavy chain comprising a complete VH region and part of the heavy chain constant region, said two polypeptide chains being intermolecularly connected via an interchain disulfide bond); a Fab' (as a Fab, above, except with additional reduced disulfide bonds comprised on the antibody heavy chain); and a $F(ab)_2$ (comprising two Fab' molecules, each Fab' molecule being linked to the respective other Fab' molecule via interchain disulfide bonds). In general, antibody fragments of the type described herein allow great flexibility in tailoring, for example, the pharmacokinetic properties of an antibody desired for therapeutic administration to the particular exigencies at hand. For example, it may be desirable to reduce the size of the antibody administered in order to increase the degree of tissue penetration when treating tissues known to be poorly vascularized (for example, joints). Under some circumstances, it may also be desirable to increase the rate at which the therapeutic antibody is eliminated from the body, said rate generally being accelerable by decreasing the size of the antibody administered.

The antibody according to the present invention or the fragment thereof neutralizes the activity of primate GM-CSF. As used herein, "neutralization," "neutralizer," "neutralizing" and grammatically related variants thereof refer to partial or complete attenuation of the biological effect(s) of GM-CSF. Such partial or complete attenuation of the biological effect(s) of GM-CSF results from modification, interruption and/or abrogation of GM-CSF-mediated signal transduction, as manifested, for example, in altering activation of cells, e.g. neurons, in particular nociceptive neurons, intracellular signaling, cellular proliferation or

release of soluble substances, up- or down-regulation of intracellular gene activation, for example that resulting in expression of surface receptors for ligands other than GM-CSF. As one of skill in the art understands, there exist multiple modes of determining whether an agent, for example an antibody in question or a fragment thereof is to be classified as a neutralizer. As an example, this may be accomplished by a standard *in vitro* test performed generally as follows: In a first proliferation experiment, a cell line, the degree of proliferation of which is known to depend on the activity of GM-CSF, is incubated in a series of samples with varying concentrations of GM-CSF, following which incubation the degree of proliferation of the cell line is measured. From this measurement, the concentration of GM-CSF allowing half-maximal proliferation of the cells is determined. A second proliferation experiment is then performed employing in each of a series of samples the same number of cells as used in the first proliferation experiment, the above-determined concentration of GM-CSF and, this time, varying concentrations of an antibody or fragment thereof suspected of being a neutralizer of GM-CSF. Cell proliferation is again measured to determine the concentration of antibody or fragment thereof sufficient to effect half-maximal growth inhibition. If the resulting graph of growth inhibition vs. concentration of antibody (or fragment thereof) is sigmoid in shape, resulting in decreased cell proliferation with increasing concentration of antibody (or fragment thereof), then some degree of antibody-dependent growth inhibition has been effected, i.e. the activity of GM-CSF has been neutralized to some extent. In such a case, the antibody or fragment thereof may be considered a "neutralizer" in the sense of the present invention. One example of a cell line, the degree of proliferation of which is known to depend on the activity of GM-CSF, is the TF-1 cell line, as described in Kitamura, T. *et al.* (1989). J Cell Physiol 140, 323-34. As one of ordinary skill in the art understands, the degree of cellular proliferation is not the only parameter by which neutralizing capacity may be established. For example, measurement of the level of signaling molecules (e.g. cytokines), the level of secretion of which depends on GM-CSF, may be used to identify a suspected GM-CSF neutralizer. Other examples of cell lines which can be used to determine whether an antibody in question or fragment thereof is a neutralizer of primate GM-CSF activity include AML-193 (Lange, B. *et al.* (1987). Blood 70, 192-9); GF-D8 (Rambaldi, A. *et al.* (1993). Blood 81, 1376-83); GM/SO (Oez, S. *et al.* (1990). Experimental Hematology 18, 1108-11); M07E (Avanzi, G. C. *et al.* (1990). Journal of Cellular Physiology 145, 458-64); TALL-103 (Valtieri, M. *et al.* (1987). Journal of Immunology 138, 4042-50); UT-7 (Komatsu, N. *et al.* (1991). Cancer Research 51, 341-8).

It is understood that "binds specifically" or "specifically binding" or grammatically related variations thereof relate to an antibody having a binding affinity to primate GM-CSF as defined herein of $\leq 10^{-9}$ mol/l. In one embodiment of the invention, the antibody or a fragment thereof bind to primate GM-CSF with extremely high affinity. K_D values of from about 4 x 10^{-9} M down to as low as about 0.04 x 10^{-9} M, the latter corresponding to about 40 pM, have been observed for molecules of this class. Since the kinetic on-rate of such molecules in aqueous media is largely diffusion controlled and therefore cannot be improved beyond what the local diffusion conditions will allow under physiological conditions, the low K_D arises primarily as a result of the kinetic off-rate, k_{off}, which for the highest affinity antibody binder is approximately 10^{-5} $^{-s}$. This means that once the complex between a human monoclonal antibody or fragment thereof according to the invention on the one hand and primate GM-CSF on the other hand is formed, it does not readily, or at least does not quickly separate. For binding molecules intended as neutralizers of biological activity, these characteristics are highly desirable since the neutralizing effect will normally last only as long as the molecule, the biological activity of which is to be neutralized (here primate GM-CSF) remains bound by the neutralizing binding molecule. So a neutralizing molecule which remains bound to its intended target for a long time will continue to neutralize for a correspondingly long time.

The high binding affinity of human monoclonal antibodies or fragments thereof to primate GM-CSF has an additional advantage. Normally, antibodies or fragments thereof will be eliminated from the bloodstream of a patient in a size-dependent fashion, with smaller molecules being excreted and eliminated before larger ones. Since the complex of the two polypeptides - antibody or antibody fragment and bound GM-CSF - is obviously larger than the antibody alone, the low k_{off} mentioned above has the effect that therapeutic neutralizer is excreted and eliminated from the patient's body more slowly than would be the case, were it not bound to GM-CSF. Thus, not only the magnitude of the neutralizing activity but also its duration *in vivo* is increased.

According to one embodiment of the invention, the primate GM-CSF to which the antibody or fragment thereof specifically binds is human GM-CSF (*Homo sapiens*, SEQ ID NO: 49) or non-human primate GM-CSF. Especially preferred variants of non-human primate GM-CSF include gibbon monkey GM-CSF (*Nomascus concolor*, also known as the western black crested gibbon, SEQ ID NO: 51) and GM-CSF of monkeys of the macaca family (SEQ ID NO: 50), for example rhesus monkey (*Macaca mulatta*) GM-CSF and cynomolgous monkey

GM-CSF (*Macaca fascicularis*). According to one embodiment of the invention, the human monoclonal antibody or fragment thereof exhibits cross reactivity between both human and at least one of the monkey species mentioned above. This is especially desirable for an antibody molecule which is intended for therapeutic administration in human subjects, since such an antibody will normally have to proceed through a multitude of tests prior to regulatory approval, of which certain early tests involve non-human animal species. In performing such tests, it is generally desirable to use as a non-human species a species bearing a high degree of genetic similarity to humans, since the results so obtained will generally be highly predictive of corresponding results which may be expected when administering the same molecule to humans. However, such predictive power based on animal tests depends at least partially on the comparability of the molecule, and is very high when, due to cross-species reactivity, the same therapeutic molecule may be administered to humans and animal models. As in this embodiment of the invention, when an antibody molecule is cross reactive for the same antigen in humans as in another closely related species, tests may be performed using the same antibody molecule in humans as in this closely related species, for example in one of the monkey species mentioned above. This increases both the efficiency of the tests themselves as well as predictive power allowed by such tests regarding the behavior of such antibodies in humans, the ultimate species of interest from a therapeutic standpoint.

According to a further embodiment of the invention, the human monoclonal antibody or fragment thereof specifically binds to an epitope, in particular to a discontinuous epitope, of human or non-human primate GM-CSF comprising amino acids 23-27 (RRLLN) and/or amino acids 65-77 (GLR/QGSLTKLKGPL).

The variability at position 67 within the amino acid sequence stretch 65-77 depicted above reflects the heterogeneity in this portion of primate GM-CSF between, on the one hand, human and gibbon GM-CSF (in which position 67 is R) and, on the other hand, monkeys of the macaca family, for example cynomolgous and rhesus monkeys (in which position 67 is Q).

As used herein, the numbering of human and non-human primate GM-CSF refers to that of mature GM-CSF, i.e. GM-CSF without its 17 amino acid signal sequence (the total length of mature GM-CSF in both human and non-human primate species described above is 127 amino acids). The sequence of human GM-CSF and gibbon GM-CSF is as follows:

APARSPSPST QPWEHVNAIQ EA**RRLLN***LSR D*TAAEMNETV EVISEMFDLQ EPTCLQTRLE LYKQ**GLRGSL TKLKGPL**TMM ASHYKQHCPP TPETSCATQI ITFESFKENL KDFLLVIPFD CWEPVQE. (SEQ ID NO: 49)

The sequence of GM-CSF in certain members of the macaca monkey family such as for example rhesus monkey and cynomolgous monkey is as follows:

APARSPSPGT QPWEHVNAIQ EA**RRLLN***LSR D*TAAEMNKTV EVVSEMFDLQ EPSCLQTRLE LYKQ**GLQGSL TKLKGPL**TMM ASHYKQHCPP TPETSCATQI ITFQSFKENL KDFLLVIPFD CWEPVQE. (SEQ ID NO: 50)

The minimum epitope, advantageously a discontinuous epitope, bound by the human monoclonal antibody of the invention (or fragment thereof) as described herein is indicated in the above GM-CSF sequence in boldface. As used herein, the term "discontinuous epitope" is to be understood as at least two non-adjacent amino acid sequence stretches within a given polypeptide chain, here mature human and non-human primate GM-CSF, which are simultaneously and specifically (as defined above) bound by an antibody. According to this definition, such simultaneous specific binding may be of the GM-CSF polypeptide in linear form. Here, one may imagine the mature GM-CSF polypeptide forming an extended loop, in one region of which the two sequences indicated in boldface above line up, for example more or less in parallel and in proximity of one another. In this state they are specifically and simultaneously bound by the antibody fragment of the invention. According to this definition, simultaneous specific binding of the two sequence stretches of mature GM-CSF indicated above may also take the form of antibody binding to a conformational epitope. Here, mature GM-CSF has already formed its tertiary conformation as it normally exists *in vivo* (Sun, H. W., J. Bernhagen, *et al.* (1996). Proc Natl Acad Sci USA 93, 5191-6). In this tertiary conformation, the polypeptide chain of mature GM-CSF is folded in such a manner as to bring the two sequence stretches indicated above into spatial proximity, for example on the outer surface of a particular region of mature, folded GM-CSF, where they are then recognized by virtue of their three-dimensional conformation in the context of the surrounding polypeptide sequences.

In one embodiment, the above (discontinuous) epitope to which the antibody or the fragment thereof specifically binds further comprises amino acids 28-31 (LSRD), italicized in the above sequences of human and non-human primate GM-CSF. In a specific embodiment, either of

the above (discontinuous) epitopes further comprises amino acids 32-33 (TA) and/or amino acids 21-22 (EA), each of which stretch is underlined in the above sequences of human and non-human primate GM-CSF.

According to a further embodiment of the invention, the human monoclonal antibody or fragment thereof, or compositions or medicaments according to the invention comprising such antibodies or fragments, comprise in its heavy chain variable region (VH) a CDR3 having an amino acid sequence chosen from the group consisting of those set out in any of the SEQ ID NOs: 1-13 or 56, preferably SEQ ID NO: 2.

One embodiment relates to a human monoclonal antibody or fragment thereof comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 1; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 2; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 3; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 4; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 5; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 6; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 7; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 8; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2

sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 9; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 10; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 11; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 12; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 13; or comprising a heavy chain variable region CDR1 sequence as set out in SEQ ID NO: 14, a heavy chain variable region CDR2 sequence as set out in SEQ ID NO: 15 and a heavy chain variable region CDR3 sequence as set out in SEQ ID NO: 56.

In another embodiment of the invention, any of the above 14 combinations of CDR1, CDR2 and CDR3 sequences exists in a human monoclonal antibody or fragment thereof further comprising in its light chain variable region a CDR1 having the amino acid sequence set out in SEQ ID NO: 16, a CDR2 having the amino acid sequence set out in SEQ ID NO: 17, and a CDR3 having the amino acid sequence set out in SEQ ID NO: 18.

According to a further embodiment, the human monoclonal antibody or fragment thereof may be derivatized, for example with an organic polymer, for example with one or more molecules of polyethylene glycol ("PEG") and/or polyvinyl pyrrolidone ("PVP"). As is known in the art, such derivatization can be advantageous in modulating the pharmacodynamic properties of antibodies or fragments thereof. Especially preferred are PEG molecules derivatized as PEG-maleimide, enabling conjugation with the antibody or fragment thereof in a site-specific manner via the sulfhydryl group of a cysteine amino acid. Of these, especially preferred are 20 kD and/or 40 kD PEG-maleimide, in either branched or straight-chain form. It may be especially desirable to increase the effective molecular weight of smaller human anti-primate GM-CSF antibody fragments such as scFv fragments by coupling the latter to one or more molecules of PEG, especially PEG-maleimide.

The production of the anti-GM-CSF antibodies and fragments may be conducted through any method known in the art and is disclosed in detail in WO2006/111353, the contents of which are incorporated herein in their entirety.

Another aspect of the present invention relates to a pharmaceutical composition for use in the treatment and/or prevention of any of the conditions according to the appending claims, comprising the antibody or a fragment thereof specifically binding (primate) GM-CSF.

In one embodiment, the pharmaceutical composition for use according to the present invention may further comprise at least one pharmaceutically acceptable carrier.

In the context of the present invention "pharmaceutically acceptable" relates to any compound which may be used in a pharmaceutical composition without causing any undesired effects (such as negative side effects) in a patient to which the composition is administered.

Pharmaceutically acceptable carriers may be those well known in the art such as phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions, liposomes, etc.. It is to be understood that the pharmaceutical composition for use according to the present invention may further include any compound considered suitable by the person skilled in the art, selected e.g. depending from the mode of administration for which the pharmaceutical composition is prepared. Preparations for parenteral administration include e.g. sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers (such as those based on Ringer's dextrose), and the like. Preservatives and other additives may also be present in the composition of the present invention such as, for example, antimicrobials, anti-oxidants, chelating agents, inert gases and the like. In addition, the pharmaceutical composition of the present invention might comprise proteinaceous carriers, like, e.g., serum albumin or immunoglobulin, preferably of human origin.

The antagonists, neutralizing antibodies and/or functional fragments thereof or the pharmaceutical composition comprising the same should provide sufficient stability upon storage. It is possible to produce a wide variety of proteins for therapeutic applications. After their production, protein pharmaceuticals are usually stored prior to their use. Due to the fact that proteins are generally larger and more complex than "traditional" pharmaceuticals, formulation and processing of protein pharmaceuticals that are suitable for storage can be particularly challenging. For reviews of protein pharmaceutical formulation and process design, see Carpenter *et al.* (1997), Pharm. Res. 14: 969-975; Wang (2000), Int. J. Pharmaceutics 203: 1 -60; and Tang and Pikal (2004), Pharm. Res. 21: 191-200. Several factors can be considered in designing formulations and processes for protein pharmaceutical production. Of primary concern is the stability of the protein through any or all steps of manufacture, shipping, and handling steps, which may include preparation of the composition, freezing, lyophilizing, drying, storage, shipping, reconstitution, freeze/thaw cycles, and post-reconstitution storage by the end user. Other potential considerations include ease and economy of manufacture, handling, and distribution, composition of the final product for patient administration, and ease of use by the end user, including solubility of the lyophilized formulation upon reconstitution.

Stable formulation comprising the anti-GM-CSF antagonist, neutralizing anti-GM-CSF antibody or fragments thereof according to the present invention may be an aqueous solution, wherein the antibody or fragments thereof are directly dissolved and/or dispersed therein. One embodiment of the present invention is a liquid formulation containing the antagonist, antibody or fragments thereof which is stable and does not undergo the formation of conjugates/aggregates or fragments/degradation products when stored for a long period, and which formulation is suitable for subcutaneous administration.

Specifically, the antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof could be stabilized if a tonicity modifier is added to the solution which is to be stored. Examples for tonicity modifiers include, but are not limited to, sugars and sugar alcohols. Simple sugars are called monosaccharides and include glucose, fructose, galactose, xylose, ribose, mannose, lactulose, allose, altrose, gulose, idose, talose, arabinose and lyxose. According to the present invention disaccharides which include for example sucrose, maltose, lactose, isomaltose, trehalose and cellubiose may be used. Sugar alcohols include sorbitol, mannitol, glycerin, erythritol, maltitol, xylitol, polyglycitol. In one embodiment, the sugar is

a non-reducing sugar such as sucrose or trehalose. Non-reducing sugars are characterized by the absence of an open chain structure, so they are not susceptible to oxidation-reduction reactions. Therefore one or more of non-reducing sugars, such as sucrose or trehalose, or one or more of sugar alcohols, such as mannitol or sorbitol could be added to the formulation comprising a neutralizing antibody or a fragment thereof as described herein. Also combinations of non-reducing sugars and sugar alcohols could be added to the solution, such as sucrose and mannitol, sucrose and sorbitol, trehalose and mannitol, or trehalose and sorbitol. In one embodiment, the sugar alcohols mannitol and/or sorbitol are added, optionally in their D-form, more specifically sorbitol is added to the solution. The concentration of the tonicity modifier, optionally sorbitol, is between about 1% and about 15% (w/v), optionally between about 2% and about 10% (w/v), specifically between about 3% and about 7% (w/v), more specifically between about 4% and about 6% (w/v) and most preferably about 5% (w/v).

Another substance to stabilize the antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof at a high concentration with regard to long-term storage is a buffer system with a pH of between about 4 and about 10, optionally between about 4 and about 7, specifically between about 4 and about 6 or between about 5 and about 7, more specifically between about 5.5 and about 6.5, or with a pH of about 5.8. The buffer may be selected from a histidine buffer, an acetate buffer and a citrate buffer. When referred herein, an amino acid is meant to be an L-amino acid or D-amino acid, wherein L-amino is preferred. In one embodiment, histidine or a salt thereof is used for the buffer system. In a specific embodiment, the salt is a chloride, phosphate, acetate or sulphate, optionally the salt is a chloride. The pH of the histidine buffer system is between about 5 and about 7, optionally between about 5.5 and about 6.5, specifically the pH is about or exactly 5.8. The pH may be adjusted by the use of conventionally used bases and acids, optionally NaOH. The concentration of the buffer system, optionally the histidine buffer system, is between about 10 mM and about 50 mM, optionally between about 20 mM and about 40 mM, specifically about 30mM.

According to one embodiment, a combination of the buffer system, optionally the histidine buffer, and the tonicity modifier, optionally the sugar alcohol, specifically mannitol or sorbitol, is used to stabilize the antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof in the solution, in order to prevent aggregation and to render the formulation sufficiently stable for long-term storage and/or for one or more freeze/thaw

cycles. It was shown that it is preferable in terms of stability to have about 6% (w/v) and higher of sugar alcohol, optionally sorbitol, in the formulation. However, the upper limit for osmolality of the formulation is set to be about 470mOsm/kg which is still hyperosmotic. In one embodiment, the concentration of sugar alcohol, optionally sorbitol, is therefore between about 3% and about 7% (w/v), optionally between about 4% and about 6% (w/v) and specifically about 5% (w/v). In some embodiments of the present invention, the formulations or compositions of the invention comprising the neutralizing anti-GM-CSF antibody or fragments thereof do not require further excipients in addition to those disclosed above (i.e., a buffer and a tonicity modifier), such as, for example, surfactants and amino acids, which are used in traditional formulations to stabilize proteins in solution. In addition, the formulations described herein are preferred over standard formulations because they have decreased immunogenicity due to the lack of additional agents commonly needed for protein stabilization. It is known that amino acids are useful to stabilize proteins at a high concentration by, *inter alia*, mediating protein solubility and/or inhibiting protein aggregation. Although threonine (e.g. at 250mM) indicates a minor stabilizing effect, the liquid formulation comprising the antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof is optionally free from further amino acids.

Furthermore, in one embodiment, the present formulation is free or essentially free of sodium chloride. By "essentially free" is meant that the concentration of sodium chloride is at or very near to 0 (zero) mM, e.g. less than about 50 mM, optionally less than about 20 mM, less than about 10 mM, less than about 5 mM, less than about 2 mM or even less than about 1 mM.

In biopharmaceutical products, the addition of surfactants can be useful to reduce protein degradation during storage. The polysorbates 20 and 80 (Tween 20 and Tween 80) are well established excipients for this purpose.

In a more preferred embodiment the polysorbate 20 to protein ratio is between about 0.01:1 to about 3:1, preferably between about 0.05:1 to about 2:1, more preferably between about 0.1:1 and about 1.5:1, even more preferably between about 0.1:1 to about 0.8:1, and most preferably between about 0.1:1 to about 0.2:1. For a protein concentration of 80 mg/mL, the polysorbate 20 concentration is between about 0.001% (w/v) and about 0.2% (w/v), preferably between about 0.005% (w/v) and about 0.15% (w/v), more preferably between about 0.007% (w/v) and about 0.1% (w/v), even more preferably between about 0.007% (w/v)

and about 0.06% (w/v) and most preferably about 0.01% (w/v). For a protein concentration of 150 mg/mL, the polysorbate 20 concentration is between about 0.001% (w/v) and about 0.4% (w/v), preferably between about 0.006% (w/v) and about 0.25% (w/v), more preferably between about 0.01% (w/v) and about 0.18% (w/v), even more preferably between about 0.01% (w/v) and about 0.1% (w/v) and most preferably about 0.02% (w/v).

In another more preferred embodiment, the polysorbate 80 to protein ratio is between about 0.01:1 to about 3:1, preferably between about 0.05:1 to about 2:1, more preferably between about 0.1:1 and about 1.5:1, even more preferably between about 0.1:1 to about 0.6:1, and most preferably from about 0.3:1 to about 0.6:1. For a protein concentration of 80 mg/mL, the polysorbate 80 concentration is between about 0.001% (w/v) and about 0.2% (w/v), preferably between about 0.004% (w/v) and about 0.14% (w/v), more preferably between about 0.007% (w/v) and about 0.1% (w/v), even more preferably between about 0.007% (w/v) and about 0.05% (w/v), and most preferably about 0.04% (w/v). For a protein concentration of 150 mg/mL, the polysorbate 80 concentration is between about 0.001% (w/v) and about 0.4% (w/v), preferably between about 0.007% (w/v) and about 0.26% (w/v), more preferably between about 0.01% (w/v) and about 0.2% (w/v), even more preferably between about 0.01% (w/v) and about 0.08% (w/v), most preferably about 0.04% (w/v).

The concentration of the antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof used is at least about 20 mg/ml, at least about 50 mg/ml or at least about 100 mg/ml in the liquid formulation which is to be stored, freeze/thawed and/or ready to use.

Concentrations of about 20 mg/ml to about 200mg/mg, about 50 mg/ml to about 200 mg/ml, about 100 mg/ml to about 180 mg/ml, about 130 mg/ml to about 170 mg/ml, about 135 mg/ml to about 165 mg/ml or about 150 mg/ml of the neutralizing antibody or a fragment thereof may be used in the present invention.

Another preferred concentration of the neutralizing anti-GM-CSF antibody or functional fragments thereof used is about 80 mg/ml.

Furthermore, in one embodiment, the present formulation of the neutralizing anti-GM-CSF antibody or functional fragments thereof comprises from about 80 mg/ml to about 150 mg/ml of the neutralizing antibody, about 5% (w/v) sorbitol, about 30 mM L-histidine, and from

about 0.01% to about 0.08% (w/v) polysorbate 80 and has a pH of about 5.8.

Furthermore, in one embodiment, the present formulation of the anti-GM-CSF antibody or a fragment thereof comprises from about 135 mg/ml to about 165 mg/ml of the neutralizing antibody, about 5% (w/v) sorbitol, about 30 mM L-histidine and has a pH of about 5.8.

Furthermore, in one embodiment, the present formulation of the anti-GM-CSF antibody or a fragment thereof comprises 150 mg/ml of the neutralizing antibody, about 5% (w/v) sorbitol, about 30 mM L-histidine and has a pH of about 5.8.

Furthermore, in one embodiment, the present formulation of the neutralizing anti-GM-CSF antibody or functional fragments thereof comprises about 80 mg/ml of the neutralizing antibody, about 5% (w/v) sorbitol, about 30 mM L-histidine, about 0.04% (w/v) polysorbate 80 and has a pH of about 5.8.

Furthermore, in one embodiment, the present formulation of the neutralizing anti-GM-CSF antibody or functional fragments thereof comprises about 150 mg/ml of the neutralizing antibody, about 5% (w/v) sorbitol, about 30mM L-histidine, about 0.04% (w/v) polysorbate 80 and has a pH of about 5.8.

The shelf life of the produced formulation may have a minimum requirement of 24 months at 2 to 8°C, 36 months at 2 to 8°C, 48 months at 2 to 8°C or at least 28 days at ambient temperature (25°C ± 2°C).

The antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof may be provided in a stable formulation, optionally a stable liquid formulation that allows for long-term storage of compounds neutralizing GM-CSF. This formulation is useful, in part, because it is more convenient to use for the patient, as the neutralizing anti-GM-CSF antibody or fragments thereof of this formulation are highly concentrated so as to reduce side effects like pain due to high volume injection.

Accordingly, the formulations comprising the antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof according to the invention comprise a buffer system optionally selected from a histidine buffer, an acetate buffer and/or a citrate buffer with a preferred pH of

between 5 and 7, and a tonicity modifier optionally selected from non-reducing sugars, such as sucrose or trehalose, or sugar alcohols, such as mannitol or sorbitol are rendered sufficiently stable for long-term storage and/or freeze/thaw cycles. The formulation of the invention has many advantages over standard buffered formulations. In one aspect, the formulation shows minimal aggregation behaviour upon long-term storage without deleterious effects that might be expected with high protein formulations. Other advantages of the formulation according to the invention are: minimal fragmentation of neutralizing anti-GM-CSF antibody or fragments thereof and no significant impact on bioactivity of the antagonist, the neutralizing anti-GM-CSF antibody or fragments thereof over long-term storage, and low viscosity of the composition. Finally, in one embodiment, the formulation is free of further excipients such as surfactants, additional amino acids and/or sodium chloride.

In some embodiments of the present invention, individuals to whom the herein described antagonists of GM-CSF are administered, e.g. neutralizing antibodies or fragments thereof, or pharmaceutical compositions comprising the same are selected from the following group of individuals:

a) Individuals, e.g. humans, receiving pre-/post-exposure prophylaxis. These individuals receive an early administration/treatment before onset of symptoms. Such individuals may be selected from the group comprising relief workers, family members exposed to infected individuals, etc. Such individuals are usually still negative in qPCR (quantitative real-time polymerase chain reaction or reverse transcription quantitative polymerase chain reaction) analysis for respective infectious agents, e.g. for Ebola virus for which a qPCR-based test is available, e.g. the WHO approved test manufactured by Altona Diagnositcs, Hamburg, Germany (RealStar® Filovirus Screen RT-PCR Kit 1.0). Similarly, individuals exposed to or in danger to become exposed to other agents causing hemorrhagic fever may also be treated with the inventive anti-GM-CSF-agonists or compositions comprising the same. Respective qPCR assays are available from various diagnostic companies (e.g. form Altona Diagnostics, Vela Diagnostics, etc. for Dengue virus, Chikungunya virus) and for Lassa virus and Hantavirus infections specialized laboratories exist, e.g. in clinical institutions in various countries;
b) Individuals with early onset clinical symptoms, e.g. those with detectable clinical symptoms correlating with a positive qPCR test for viral load;
c) Individuals suffering from hemorrhagic and diarrhea complications, fever, etc. that are in later stages of infections with the herein described agents.

For all of the preceding embodiments of the present invention, the use of neutralizing anti-GM-CSF antibodies or fragments or derivatives thereof is particularly preferred.

With respect to the dosing of anti-GM-CSF antibodies or fragments thereof it is contemplated to administer the same via any route of administration suitable for formulations comprising therapeutic antibodies. In some embodiments the antibody is administered subcutaneously (sc), in other embodiments, the antibody is administered intravenously (iv) For individuals receiving pre-/post-exposure prophylaxis, e.g. individuals exposed to or in danger to become exposed to other agents causing hemorrhagic fever that are still negative in qPCR analysis for respective infectious agents, e.g. for Ebola virus, the administration route may be subcutaneously. For individuals with early onset clinical symptoms, e.g. those with detectable clinical symptoms correlating with a positive qPCR test for viral load, as well as individuals suffering from hemorrhagic and diarrhea complications, fever, etc. that are in later stages of infections with the herein described agents the antibody may be administered intravenously.

In some embodiments, the antibody dose is selected from a range of 0.5 mg/kg up to about 10 mg/kg, e.g. the dose may be 0.5 mg/kg or 2 mg/kg, or it may be between 3-5 mg/kg, or it may be between 5-8 mg/kg.

In some embodiments of dosing schemes of the invention, it is preferred to administer initially a high dose (a loading dose), e.g. a dose of about 250-750 mg/day, e.g. about 300 mg/day or about 560 mg/day (corresponding to 8 mg/kg for an individual with a weight of 70 kg). Following the administration of the loading dose, it is possible to administer, e.g. a dose of about 100 mg/day to about 200 mg/day, preferably about 150 mg/day after about 7 days, optionally after about 14 days and further optionally (depending on the severity of the clinical symptoms) after about 28 days.

Further, when a loading dose is not administered, it is possible to initially administer from 0.5 mg/kg to about 8.0 mg/kg of the inventive antibody (i.e. between 35 mg/body weight to about 560 mg/body weight for an individual with a body weight of 70 kg).

In some embodiments is contemplated to administer from 0.5 mg/kg, about 2.0 mg/kg, about 3.0 mg/kg, about 5 mg/kg, about 8 mg/kg on day 0 and on day 14 (optionally also on day 7).

Administration of at least two doses is preferred, but a third or further administration may be contemplated depending on the clinical symptoms. For example, it is possible to administer from 0.5 mg/kg to 3.0 mg/kg on days 0 and 14 (optionally also on days 7 and 28).

Still further, when a loading dose is not administered, it is possible to initially administer from 3.0 mg/kg to about 5.0 mg/kg of the inventive antibody formulation on day 0 and from 3.0 mg/kg to about 5.0 mg/kg on day 14 (optionally also from 3.0 mg/kg to about 5.0 mg/kg on day 7). It is also possible to administer from 5.0 mg/kg to 8.0 mg/kg on days 0 and 14 (optionally also on days 7 and 28).

The formulations of antibodies referred to above may comprise a concentration of 150 mg/ml in vials for distribution.

The above described doses and dosing regimen may be administered to the

a. Individuals, e.g. humans, receiving pre-/post-exposure prophylaxis. These individuals receive an early administration/treatment before onset of symptoms. Administrations occurs from about two weeks, from about 1 week, form about 1 day prior to exposure and continues to about 1 week, to about 2 weeks, or to about 3 weeks after exposure.
b. Individuals with early onset clinical symptoms and with oral rehydration only (usually day 0-3 from onset of symptoms), e.g. those with detectable clinical symptoms correlating with a positive qPCR test for viral load for increasing the survival rate and other symptoms as described above.
   Administration occurs from day 0, from day 2, from day 3 of onset of symptoms and continues with the above described dosing regimen.
c. Individuals who are in the second phase of disease (confirmed cases with second phase-symptoms (mainly gastro-intestinal 3-10 days) requiring oral or IV rehydration) and suffering from hemorrhagic and/or diarrhea complications, fever, etc. that are in later stages of infections.
   Administration occurs from day 0, from day 1, from day 2, from day 3 diagnosis of symptoms and continues with the above described dosing regimen.

Experiments

1. Proof of concept study in Primates.

A single non-human primate study is performed to assess the efficacy of the neutralizing anti-GM-CSF antibody. Animals are to be dosed according to established dosing regimens in humans and observed for changes in disease severity relative to control animals (dosed with formulation buffer only), including, but not limited to, a decrease in morbidity and/or mortality, delay in time to death, or decreased viral burden.

A) Brief Study Design:

Twelve Non-Human Primates (Rhesus Macaques) are randomized into 2 groups of 3 animals each. The groups consist of 1) Formulation buffer only, 2) antibody against GM-CSF. The antibody against GM-CSF used in the example is a human monoclonal IgG1 antibody that binds to and neutralizes with high affinity and specificity human GM-CSF and that is described in WO2006/111353. Its generation is described in Example 2 of WO 2006/111353. More specifically, the antibody comprises the light chain and heavy chain CDR sequences as depicted in SEQ ID NOs: 16, 17, 18, 14, 15 and 2. These CDR sequences are comprised in the heavy and light chain variable domain, respectively, that are shown in SEQ ID Nos: 34 and 35, respectively. Animals are infected intramuscularly with 100 PFU of Ebola Zaire on study day 0. The first treatment occurs on day -1, with a dose of either 30mg/kg, or 10 mg/kg or 3 mg/kg of antibody in a concentration of e.g. 150 mg/ml. The antibody may be formulated according to one of the formulations provided in the description. Optionally a second dose is provided on study day 4. Samples are being collected every other day (if the animal weights and blood volume allow) for hematology, chemistries, viral load (by PCR), flow cytometry, and Bio-Plex analysis. Animals are monitored daily for signs of clinical disease and evaluated for euthanasia. The endpoints of the study are death/euthanasia or survival past study day 28. All animals have a full necropsy after death/euthanasia. Histology is performed on inguinal, tracheobronchial, mediastinal, and mandibular lymph nodes as well as liver, kidney, pancreas, lung, and spleen. Immunohistochemistry for viral antigen and appropriate macrophage cell markers is performed on the same tissues.

B) Brief Study Design for Acute treatment:

Twelve Non-Human Primates (Rhesus Macaques) are randomized into 2 groups of 3 animals each. The groups consist of 1) Formulation buffer only, 2) neutralizing antibody against GM-CSF. The antibody against GM-CSF used in the example is a human

monoclonal IgG1 antibody that binds to and neutralizes with high affinity and specificity human GM-CSF and that is described in WO2006/111353. Its generation is described in Example 2 of WO2006/111353. More specifically, the antibody comprises the light chain and heavy chain CDR sequences as depicted in SEQ ID NOs: 16, 17, 18, 14, 15 and 2. These CDR sequences are comprised in the heavy and light chain variable domain, respectively, that are shown in SEQ ID NOs: 34 and 35, respectively.
Animals are infected intramuscularly with 100 PFU of Ebola Zaire on study day 0. The animals are tested daily with qPCR for viral antigen load. As soon as the viral antigen is detectable, the first treatment occurs with a dose of either 30mg/kg, or 10 mg/kg or 3 mg/kg of antibody in a concentration of e.g. 150 mg/ml. The antibody may be formulated according to one of the formulations provided in the description. Optionally a second dose is administered on day 4. Samples are being collected every other day (if the animal weights and blood volume allow) for hematology, chemistries, viral load (by PCR), flow cytometry, and Bio-Plex analysis. Animals are monitored daily for signs of clinical disease and evaluated for euthanasia. The endpoints of the study are death/euthanasia or survival past study day 28. All animals have a full necropsy after death/euthanasia. Histology is performed on inguinal, tracheobronchial, mediastinal, and mandibular lymph nodes as well as liver, kidney, pancreas, lung, and spleen. Immunohistochemistry for viral antigen and appropriate macrophage cell markers is performed on the same tissues.

2. Proof of concept study in Humans

A phase 2, single or multicenter, open labeled, single arm, two patient cohorts, proof of concept, phase 2 human clinical study to evaluate the efficacy and safety of 1 to 3 doses of intravenous or subcutaneous administration of an anti-GM-CSF antibody for the treatment of confirmed Ebola virus disease (EVD). The antibody against GM-CSF used in the example is a human monoclonal IgG1 antibody that binds to and neutralizes with high affinity and specificity human GM-CSF and that is described in WO2006/111353. Its generation is described in Example 2 of WO2006/111353. More specifically, the antibody comprises the light chain and heavy chain CDR sequences as depicted in SEQ ID NOs: 16, 17, 18, 14, 15 and 2. These CDR sequences are comprised in the heavy and light chain variable domain, respectively, that are shown in SEQ ID NOs: 34 and 35, respectively.

The antibody is used at doses of 150 mg, 300 mg or 450 mg or higher as described below, and administered subcutaneously or intravenously to subjects with EBV either in the first phase of

disease (i.e. suspected or confirmed Ebola case patients with early-defined symptoms and with oral rehydration only (usually day 0-3 from onset of symptoms), or who are in the second phase of disease (confirmed cases with second phase-symptoms (mainly gastro-intestinal 3-10 days) requiring oral or IV rehydration).
The dose for the anti-GM-CSF antibody is 350 mg on day zero and then 150 mg on day 7, though the dose can be modulated up to 8 mg/kg if thought necessary, or decrease down to 1 mg/kg if necessary.

The effects of the subcutaneous or IV administration of the anti-GM CSF antibodies on EVD manifestation is assessed on survival, symptoms, progression of disease and safety and tolerability (see end-points).

Study population:
The study population is following a Simon-2 design with step-wise enrolment supervised by a data safety monitoring committee provided with live available data. A total of 42 patients are necessary for each cohorts to prove a decrease of 20% in mortality (increase in survival by 20%), this is on the basis of a current survival rate of 40% and an alpha error of 0.05 and a 80% power.

Study duration:
The study comprises three different periods, i.e.
a) a very brief screening period to confirm RT-PCR positivity, informed consent and then first drug administration (ideally less than 24 hours),
b) the isolation/intensive care field/hospital treatment lasting usually 15-20 days, and
c) the follow-up period lasting about 90 days (if possible in the field) The total trial duration being 90 days for survivors.

Endpoint:
The primary end-point is survival at day 14 from onset of symptoms. Secondary end-points are over the time frame of 4 weeks from onset of symptoms reduction in symptoms severity (fever, headache, respiratory & heart rates, diarrhea and vomiting, chemistry) compared to time of randomisation, survival at other time points, progression to later phase of the disease, incidence of organ failure, time to hospital discharge, time to return to pre-morbid state, virus load and available laboratory assessments such as immune response at 2weeks, and 4 weeks for survivors (IgG and IgM specific Ebola), in addition to assessing safety and tolerability

Screening period:

During the screening period which is preferably less than 24 hours, eligibility of the subjects for the study is assessed and the eligibility criteria include

- informed written consent
- clinically sign of EVD
- Confirmed diagnosis of EVD by RT-PCR or anti-Ebola IgM present
- age > 16 years
- adequate contraception throughout the duration of the study, relevant for the period of recovery up to 90 days after PCR negativity.

Treatment period:

Eligible subjects are hospitalised in isolation in the Ebola response care emergency facilities or in appropriate isolated treatment rooms in hospital. The subject is given the antibody intravenously or if not possible subcutaneously.

Evaluation of all viral signs, sign of complications and progression of the disease are monitored in this isolation hospitalisation setting. In addition, if available in the field, biochemistry and full blood count are also collected at regular intervals, ideally daily during the first 7-10 days, as well samples to monitor immune response (IgG and IgM specific to Ebola) to the Ebola virus

Follow-up period:

If the patient survives, the subject is followed-up for at least 30 days after discharge, though it is acknowledged than some subjects will be lost because they live in remote places far from the hospital. However, strong advice will be given to adhere strictly to appropriate method of contraception, and on a case-by case basis appropriate method of contraception will be provided free-of-charge to the subject.

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CLAIMS

1. Anti-GM-CSF antagonist for use in the treatment and/or prevention of an infection of an individual with an agent causing hemorrhagic fever.

2. The anti-GM-CSF antagonist for use according to claim 1, wherein the treatment and/or prevention comprises modulating the cellular and/or immune response of an individual.

3. The anti-GM-CSF antagonist for use according to claim 1 or claim 2, wherein the treatment and/or prevention
   a) disrupts said agent's mechanism of infection;
   b) slows down disease progression; and/or
   c) provides time for the individual's immune system to raise a response.

4. The anti-GM-CSF antagonist for use according to any one of claims 1 to 3, wherein the treatment comprises modulating the cellular and/or immune response of an individual, wherein the modulation comprises at least one of the following features:
   i. Suppression of expression of receptors on target cells comprising viral receptors;
   ii. Inhibition of egression of monocytes from the bone marrow;
   iii. Inhibition of transfer of monocytes from blood to tissue;
   iv. Inhibition of maturation and/or differentiation of monocytes to tissue macrophages and/or dendritic cells;
   v. Inhibition of activation of monocytes, macrophages, dendritic cells and neutrophils;
   vi. Inhibition of agent-induced cytokine cascade comprising release of monocyte-derived, macrophage-derived, dendritic cell-derived, immune cell-derived, endothelial cell-derived cytokines;
   vii. Regulating the homeostasis of cells of the myeloid lineage comprising monocytes, macrophages, dendritic cells and neutrophils;
   viii. Reducing the number of target cells for infection with the agent causing hemorrhagic fever;
   ix. Inhibition of endothelial cell dysfunction;

x. Inhibition of viral protein-induced reprogramming of the individual's JAK/STAT, IRF, and/or dsRNA sensors;

xi. Inhibition, slowing down or minimization of dissemination of the agent throughout the individual's body;

xii. Inhibition, slowing down or minimization of hemorrhagia in said individual; and/or

xiii. Inhibition, slowing down or minimization of clinical symptoms in said individual comprising symptoms selected from hypotonia, loss of body fluids, fever, blood loss, diarrhea, sore throat, muscle pain and headaches.

5. The anti-GM-CSF antagonist for use according to any one of claims 1 to 4, wherein the agent causing hemorrhagic fever is selected from the group comprising filoviridae, togaviridae, flaviviridae, arenaviridae, and bunyaviridae.

6. The anti-GM-CSF antagonist for use according to any one of claims 1 to 5, wherein the agent causing hemorrhagic fever selected from filoviridae comprises the genera Ebola virus and Marburg virus.

7. The anti-GM-CSF antagonist for use according to any one of claims 1 to 6, wherein the Ebola virus is selected from the group comprising the strains Zaire Ebola virus (ZEBOV), Tai Forrest Ebola virus (TEBOV), Sudan Ebola virus (SEBOV), Reston Ebola virus (REBOV), Bundibugyo Ebola virus (BEBOV).

8. The anti-GM-CSF antagonist for use according to any one of claims 1 to 7, wherein said anti-GM-CSF antagonist is a neutralizing antibody or a fragment thereof.

9. The anti-GM-CSF antagonist for use according to any one of claims 1 to 8, wherein said antibody or fragment thereof comprises in its heavy chain variable region a CDR 3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-13 or 56.

10. The anti-GM-CSF antagonist for use according to any one of claims 1 to 9, wherein said antibody or a fragment thereof comprises a heavy chain variable region CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-13 or 56 in combination with a heavy chain variable region CDR1 having an amino

acid sequence set out in SEQ ID NO: 14 and a heavy chain variable region CDR2 having an amino acid sequence set out in SEQ ID NO: 15.

11. The anti-GM-CSF antagonist for use according to any one of claims 1 to 10, wherein said antibody or a fragment thereof comprises a light chain variable region CDR1 having an amino acid sequence set out in SEQ ID NO: 16, a CDR2 having an amino acid sequence set out in SEQ ID NO: 17 and a CDR3 having an amino acid sequence set out in SEQ ID NO: 18.

12. The anti-GM-CSF antagonist for use according to any one of claims 1 to 11, wherein said antibody or fragment thereof comprises a light chain variable region CDR1 having an amino acid sequence as set out in SEQ ID NO: 16, a CDR2 having an amino acid sequence set out in SEQ ID NO: 17 and a CDR3 having an amino acid sequence set out in SEQ ID NO: 18 and comprising a heavy chain variable region CDR1 having an amino acid sequence set out in SEQ ID NO: 14, a CDR2 having an amino acid sequence set out in SEQ ID NO: 15 and a CDR3 having an amino acid sequence set out in SEQ ID NO: 2.

13. The anti-GM-CSF antagonist for use according to any one of claims 1 to 12, wherein said antibody or fragment thereof comprises a light chain variable region sequence set out in SEQ ID NO: 19 and/or a heavy chain variable region sequence set out in SEQ ID NO: 21.

14. The anti-GM-CSF antagonist for use according to any one of claims 1 to 13, wherein said antibody or a fragment thereof comprises a light chain sequence set out in SEQ ID NO: 34 and/or a heavy chain sequence set out in SEQ ID NO: 35.

15. The anti-GM-CSF antagonist for use according to any one of claims 1 to 14, wherein said neutralizing antibody or fragment thereof comprises at least one amino acid sequence having at least 70%, at least 80%, at least 90% or at least 95% identity to the amino acid sequence of any of SEQ ID NO: 1-48 and/or 52-56.

16. The anti-GM-CSF antagonist for use according to any one of claims 1 to 15 is an scFv, a single domain antibody, an Fv, a VHH antibody, a diabody, a tandem antibody, a Fab, a Fab' or a $F(ab)_2$.

17. The anti-GM-CSF antagonist for use according to any one of claims 1 to 16, wherein said antagonist specifically binds primate GM-CSF.

18. The anti-GM-CSF antagonist for use according to any one of the preceding claims, wherein said antagonist is used in combination with drugs for use in the treatment and/or prevention and/or modulation of the cellular or immune response of an individual infected with or exposed to an agent causing hemorrhagic fever, optionally a filovirus, further optionally Ebola virus, wherein said drug is selected from a group comprising antibodies, the antibody ZMAPP, vaccines against agents causing hemorrhagic fever, medicaments for the treatment of fever, inflammation, infectious diseases, diarrhea, pain, vomiting, bleeding, hypotonia, virus infections, or any other symptoms associated with hemorrhagic fever.

19. The anti-GM-CSF antagonist for use according to any one of the preceding claims, wherein the drugs and vaccines against agents causing hemorrhagic fever, infectious diseases, and/or virus infections are selected from the group comprising vaccines and/or therapeutics against viruses comprising
(i) compounds directly targeting the virus, e.g. the viral polymerase, and/or
(ii) compounds that target the host-viral life-cycle interaction (e.g. the budding, vesicle fusion, trafficking, sorting, packaging, and/or
(iii) vaccines and/or therapeutics against Ebola virus, such as Vesicular Stomatitis Virus (VSV) comprising and expressing Ebola-derived antigens, modified adenoviruses comprising and expressing Ebola antigens, Vaccinia virus-derived vaccines comprising and expressing Ebola antigens, synthetic vaccines, siRNA molecules blocking virus replication, RNA-antisense molecules inhibiting VP24 gene expression, inhibitors of viral RNA polymerase, and/or
(iv) nucleosides as inhibitors of the viral RNA polymerase, semicarbazone proteasome inhibitors or structural and/or functional analogue or a derivative thereof, dipeptidyl-boronic acid derivatives, or a pharmaceutically acceptable salt of either, optionally selected from the group comprising the semicarbazone S-2209 ([l-[l-{l-[(2,4-Dioxo-imidazo lidin-1-ylimino)-methyl] -2-phenyl-ethylcarbamoyl}-2-(1H-indo 1-3-yl)-ethylcarbamoyl]-2-(lH-indol)]) and [(1R)-3-methyl-1-({(2S)-3-phenyl-2-[(pyrazin-2-yl carbonyl) amino] propanoyl} amino) butyl] boronic acid.

20. A method of treatment and/or prevention and/or modulating the cellular or immune response of an individual infected with or exposed to Ebola virus or any other agent causing hemorrhagic fever, said method comprising administering an anti-GM-CSF antagonist as defined in any one of claims 1 to 17, optionally in combination with drugs as defined in claims 18 and 19.

21. The method according to claim 20, wherein the administration of said anti-GM-CSF antagonist
    a. disrupts said agent's mechanism of infection; and/or
    b. slows down disease progression; and/or
    c. provides time for the individual's immune system to raise a response.

22. The method according to claim 20 or 21, wherein the administration of said anti-GM-CSF antagonist modulates the cellular and/or immune response of an individual, wherein the modulation comprises at least one of the following features:
    i. Suppression of expression of receptors on target cells comprising viral receptors;
    ii. Inhibition of egression of monocytes from the bone marrow;
    iii. Inhibition of transfer of monocytes from blood to tissue;
    iv. Inhibition of maturation and/or differentiation of monocytes to tissue macrophages and/or dendritic cells;
    v. Inhibition of activation of monocytes, macrophages, dendritic cells and neutrophils;
    vi. Inhibition of agent-induced cytokine cascade comprising release of monocyte-derived, macrophage-derived, dendritic cell-derived, immune cell-derived, endothelial cell-derived cytokines;
    vii. Regulating the homeostasis of cells of the myeloid lineage comprising monocytes, macrophages, dendritic cells and neutrophils;
    viii. Limiting the number of target cells for infection with the agent causing hemorrhagic fever;
    ix. Inhibition of endothelial cell dysfunction;
    x. Inhibition of viral protein-induced reprogramming of the individual's JAK/STAT, IRF, and/or dsRNA sensors;

xi. Inhibition, slowing down or minimization of dissemination of the agent throughout the individual's body;

xii. Inhibition, slowing down or minimization of hemorrhagia in said individual;

xiii. Inhibition, slowing down or minimization of clinical symptoms in said individual comprising symptoms selected from hypotonia, loss of body fluids, fever, blood loss, diarrhea, sore throat, muscle pain and headaches.

23. The anti-GM-CSF antagonist for use according to any of claims 1 to 18, or the method according to any one of claims 19 to 22, wherein said antagonist is administered to individuals selected from:

- those pre-/post-exposure with an Ebola virus or any other agent causing hemorrhagic fever comprising relief workers and family members exposed to infected individuals or those suspected to be infected with or exposed to Ebola virus or any other agent causing hemorrhagic fever;
- those with early onset of detectable clinical symptoms comprising those with a positive virus test, optionally comprising a qPCR test for viral load,
- those with hemorrhagies and/or diarrhea.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/077175

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/24 A61K39/395
ADD. A61K39/00

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)
C07K A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/124163 A2 (THERACLONE SCIENCES INC [US]; CHAN-HUI PO-YING [US]; FREY STEVEN [US];) 28 October 2010 (2010-10-28) abstract page 6, paragraph 0128 -----	1-23
A	AU 2013 201 228 A1 (MORPHOTEK INC) 21 March 2013 (2013-03-21) page 10, paragraph 0041 - page 11 -----	1-23
A	WO 2006/111353 A2 (MICROMET AG [DE]; RAUM TOBIAS [DE]; HEPP NEE HENCKEL JULIA [CH]; KRINN) 26 October 2006 (2006-10-26) cited in the application sequences 34, 35 claims 20-21 -----	1-23

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 January 2016	05/02/2016

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1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/077175

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/038760 A2 (AMGEN INC [US]; KIRCHNER JACQUELINE A [US]; BRASEL KENNETH A [US]; OLS) 26 March 2009 (2009-03-26) page 75, paragraph 00283	1-23
A	BRAY M ET AL: "Ebola virus: The role of macrophages and dendritic cells in the pathogenesis of Ebola hemorrhagic fever", INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, PERGAMON, GB, vol. 37, no. 8, 1 August 2005 (2005-08-01) , pages 1560-1566, XP027742031, ISSN: 1357-2725 [retrieved on 2005-08-01] the whole document	1-23

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/077175

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010124163 A2	28-10-2010	CA 2759506 A1	28-10-2010
		CN 102459340 A	16-05-2012
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