CD19-selective T cell engaging molecule for treating autoimmune diseases / autoimmune conditions

The present invention relates to a method for the treatment, alleviation of symptoms, prevention of worsening of symptoms and disease progression of patients suffering from autoimmune diseases, for example, patients suffering from Systemic Lupus Erythematosus (SLE), Sclerosis, Myasthenia Gravis (MG), or Rheumatoid Arthritis (RA) amongst others, comprising the administration of molecule comprising a domain that binds CD19 and a domain and a domain that binds a molecule on the surface of an immune effector cell, e.g., a T cell or an NK cell. Specifically, the present invention relates to the use of multispecific, e.g., bispecific T cell engaging molecules for the treatment of, the alleviation of symptoms, prevention of worsening of symptoms and disease progression of patients suffering from autoimmune diseases. In particular embodiments of the invention, the T cell engaging molecule is blinatumomab.

Background of the invention

The treatment of autoimmune diseases aims to control the immune system's overactivity and manage symptoms. Often there is no cure for autoimmune diseases, but various treatment options are available to help alleviate symptoms and improve the quality of life for individuals with these conditions. Treatment approaches may vary depending on the specific autoimmune disease and its severity. Some common strategies are:

- Immunosuppressive medications: These drugs are designed to suppress the immune system's activity and reduce inflammation. Examples include corticosteroids (such as prednisone), immunosuppressants (like azathioprine, methotrexate, and cyclosporine), and biologics (such as adalimumab, etanercept, or rituximab).
- Nonsteroidal anti-inflammatory drugs (NSAIDs): These medications help reduce inflammation and alleviate pain. They are often used for conditions like rheumatoid arthritis and lupus.
- Disease-modifying antirheumatic drugs (DMARDs): These drugs aim to slow down the progression of autoimmune diseases, especially those affecting the joints. Examples include methotrexate, hydroxychloroquine, and sulfasalazine.

- Biologic therapies: Biologics are a type of medication that targets specific components of the immune system. They are often used in conditions like rheumatoid arthritis, psoriasis, and inflammatory bowel diseases.
- Corticosteroids: These are powerful anti-inflammatory medications that can provide rapid relief of symptoms. However, they are generally used for short-term management due to potential long-term side effects.
- Physical therapy: For autoimmune diseases affecting the musculoskeletal system, physical therapy can be beneficial in maintaining joint function, improving flexibility, and reducing pain.
- Lifestyle modifications: Adopting a healthy lifestyle can help manage symptoms and improve overall well-being. This includes regular exercise, a balanced diet, stress management, and adequate sleep.
- Symptomatic treatment: Depending on the specific autoimmune disease, additional medications may be prescribed to manage specific symptoms. For example, pain relievers, antimalarial drugs, or medications to control specific organ involvement.
- Intravenous immunoglobulin (IVIG): This treatment involves infusions of concentrated antibodies from healthy donors and is used in certain autoimmune disorders to modulate the immune response.
- Plasma exchange (plasmapheresis): This procedure involves removing blood plasma and replacing it with a substitute or donated plasma. It may be used in severe cases of certain autoimmune diseases to remove harmful antibodies.

Despite progress made in the past decades, there is still a need for new, alternative, or improved therapies that result in the improvement of at least one disease symptom, preferably of more than one symptom. Further, there is a need for new therapies that help patients with autoimmune diseases or autoimmune conditions that do not respond or no longer respond to standard of care (SOC) measure used for the respective disease/condition and are in need of an efficient, safe, well-tolerated therapy. The majority of SOC regimens can result in severe toxicities.

Methods of treatment or alleviation of disease symptoms not only depend on the types of diseases, symptoms, cell types involved, etc.. The present invention is based on the clinical findings that a molecule comprising a domain that binds CD19 and a domain that binds

CD3 is surprisingly effective in the treatment of autoimmune disease and the alleviation of symptoms associated with said diseases.

Mougiakakos et al. reported on a successful application of anti-CD19 chimeric antigen receptor (CAR) T-cells in a previously heavily pretreated 20-year-old female patient with severe and active SLE presenting with multiple complications, e.g., lupus nephritis, endocarditis Libmann-Sacks, pleuritis and pericarditis. Five weeks after the application of anti-CD19 CAR T-cells the level of double-stranded DNA (dsDNA) autoantibodies normalized from above 5000 U/ml to 4 U/ml followed by the normalization of previously low complement C3 and C4 levels. A clinical remission could be documented with decrease of proteinuria from above 2000 mg/gram of creatinine to 250 mg/gram of creatinine and decrease of the Systemic Lupus Erythematosus Disease Activity Index score (SELENA [Safety of Estrogens in Lupus National Assessment] modification) from 16 at baseline to 0 at follow-up demonstrating high efficacy of this approach.

Mackensen et al, reported on successful treatment of further five heavily pretreated patients with lupus nephritis with remissions achieved after three months in all patients, suggesting feasibility of CAR T approach. However, CAR T approaches also require costly patient-specific treatment, which is still difficult to perform in hospitals other than highly specialized institutions.

Irrespective of the above reports, the use of a compound that significantly impacts the immune system is always to be handled with the utmost caution. Consequently, it was surprising to note that an anti-leukemic immunotherapeutic compound, specifically a T cell engaging compound like Blinatumomab, can be used to treat and alleviate symptoms in patients with autoimmune diseases.

Bucci, L., et al, reported and confirmed the successful treatment of patients with refractory Rheumatoid Arthritis with Blinatumomab (Nat Med 2024 Jun;30(6):1593-1601, Epub 2024 Apr 26).

One of the reasons for the unexpected technical effect is that cytokine release and neurological reactions have not only been observed with monoclonal antibodies binding to the T cell receptor but also with a CD19xCD3 bispecific single chain T cell engager (TCE) binding to the CD3 part of the T cell receptor. Consequently, the surprising effects of using such compounds in the treatment of diseases with a serious imbalance of the immune

system, particularly in patients that have already been pre-treated albeit unsuccessfully with immunosuppressive drugs, were unexpectedly positive. Further, Blinatumomab is a well-established drug, which has been used in the clinic for more than a decade.

Detailed description

It must be noted that as used herein, the singular forms “a”, “an”, and “the”, include plural references unless the context clearly indicates otherwise. Thus, for example, reference to “a reagent” includes one or more of such different reagents and reference to “the method” includes reference to equivalent steps and methods known to those of ordinary skill in the art that could be modified or substituted for the methods described herein.

Unless otherwise indicated, the term "at least" preceding a series of elements is to be understood to refer to every element in the series. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the present invention.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word “comprise”, and variations such as “comprises” and “comprising”, will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integer or step. In each instance herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms.

Several documents are cited throughout the text of this specification. Nothing herein is to be construed as an admission that the invention is not entitled to antedate the disclosure of the publications and patents cited throughout the text of this specification (including all patents, patent applications, scientific publications, manufacturer’s specifications, instructions etc.). To the extent the cited material contradicts or is inconsistent with this specification, the specification will supersede any such material.

As pointed out above, Blinatumomab is currently the best-established bispecific T-cell engager (BiTE). Blinatumomab consists of a murine anti-human CD3 and anti-human CD19 single-chain antibody fragment and induces a T-lymphocyte response in an MHC-independent manner bypassing common escape mechanisms.

The short serum half-life of approximately two hours demonstrated the need for continuous administration of blinatumomab. Applied as a continuous intravenous infusion over a portable mini-pump port system, blinatumomab showed remarkable single-agent activity in patients with relapsed and/or refractory non-Hodgkin lymphoma and R/R B cell precursor acute lymphoblastic leukemia. The most common adverse events (AE) were flu-like symptoms such as fever, chills, headache, and fatigue. The most common laboratory AEs were lymphopenia and CRP increase. Most AEs were observed during the first 72 h of treatment and in most cases resolved upon continued application. The clinically most relevant (grade 3) and dose-limiting toxicities were side effects of the central nervous system (CNS) such as encephalopathy, aphasia, tremor, disorientation, and seizure.

The evidence of B cell depletion was observed already at doses of 5 µg/m2/day and occurred rapidly. On the other hand, the first objective clinical responses in patients with B-cell lymphomas were documented at a dose level of 15 µg/m2/day.

Blinatumomab monotherapy received FDA as well as EMA approval for the treatment of R/R B-precursor ALL as well as for treatment of ALL in complete hematological remission but positive measurable residual disease (MRD).

Blinatumomab is a B cell malignancy-directed, recombinant bispecific single-chain CD19xCD3 T cell engager that binds to CD19 on the surface of almost all B cells and B tumor cells and concomitantly can engage a T cell, thereby triggering the T-cell to kill the target B cell or B tumor cell. Blinatumomab consists of four immunoglobulin variable domains assembled into a single polypeptide chain. Two of the variable domains form the binding site for CD19, a cell surface antigen expressed on most B cells and B tumor cells. The other two variable domains form the binding site for the CD3 complex on T cells. Blinatumomab is designed to direct the body's cytotoxic, or cell-destroying, T cells against tumor cells, and is the first BiTE molecule that received market approval.

According to authorization details of the European Medical Agency (EMA) (https://www.ema.europa.eu/en/medicines/human/EPAR/blincyto), Blinatumomab is given by infusion (drip) into a vein using a pump device. For treatment of relapsed or refractory B-precursor ALL, Blinatumomab is infused continuously during a treatment cycle of four weeks. Each cycle is separated by a two-week treatment-free interval. Patients who have no signs of cancer after two cycles may be treated with up to three additional

cycles of Blinatumomab if the benefits outweigh the risks for the patient. For treatment of patients with minimal residual disease (MRD), the dose depends on the patient's bodyweight. Blinatumomab is infused continuously during a treatment cycle of four weeks. After receiving the first induction cycle patients may be treated for up to three additional treatment cycles, each one given after a two-week treatment-free interval.

According to the present invention, a molecule comprising a domain that binds CD19, e.g., a CD19-binding TCE, particularly Blinatumomab, is used in the treatment of a patient suffering from autoimmune disease and/or the alleviation of and/or prevention of worsening of symptoms associated with a given autoimmune disease.

Embodiments of the invention

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition.

As used herein, the terms autoimmune disease and autoimmune condition designate known autoimmune diseases as well as pathological conditions with an autoimmune component, e.g., conditions wherein autoaggressive immunoglobulins are produced, and/or autoimmune cells in a subject cause and/or contribute to pathological symptoms, in particular conditions that are the consequence of autoreactive activated B-lymphocytes. Treating these diseases, conditions and/or symptoms using the herein described molecules alleviates, mitigates, abolishes, prevents, or reduces the symptoms. As used herein, any form of treatment that improves a patient's overall health, e.g., alleviates pain, reduces swelling or rashes, or in any shape or form reduces pathological symptoms or overall improves the quality of life of such a patient can be regarded as treatment of an autoimmune disease or autoimmune condition.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein said molecule is a single chain polypeptide.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient

suffering from an autoimmune disease or autoimmune condition, wherein the first domain comprises the CDR 1, 2, and 3 sequences of a variable light chain depicted in SEQ ID NOs: 20, 21, and 22, and the CDR 1, 2, and 3 sequences of the variable heavy chain depicted in SEQ ID NOs: 17, 18, and 19.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the first domain comprises the sequence of the variable light chain depicted in SEQ ID NO: 5 and the sequence of the variable heavy chain depicted in SEQ ID NO: 3.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule comprises as sequence as depicted in SEQ ID NO: 1.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the disease is selected from the group comprising Acromegaly, Acquired aplastic anemia, Acquired hemophilia, Agammaglobulinemia, primary, Alopecia areata, Ankylosing spondylitis (AS), Anti-NMDA receptor encephalitis, Antiphospholipid syndrome (APS) | catastrophic antiphospholipid syndrome (CAPS) / Asherson's syndrome, Arteriosclerosis, Autoimmune Addison’s disease (AAD), Autoimmune autonomic ganglionopathy (AAG) / autoimmune dysautonomia | autoimmune gastrointestinal dysmotility (AGID), Autoimmune encephalitis | acute disseminated encephalomyelitis (ADEM), Autoimmune gastritis, Autoimmune hemolytic anemia (AIHA), Autoimmune hepatitis (AIH), Autoimmune hyperlipidemia, Autoimmune hypophysitis/lymphocytic hypophysitis, Autoimmune inner ear disease (AIED), Autoimmune lymphoproliferative syndrome (ALPS), Autoimmune myelofibrosis, Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis (AIP), Autoimmune polyglandular syndromes, types I, II, & III (APS type 1, APS type 2, APS type 3, APECED), Autoimmune progesterone dermatitis, Autoimmune retinopathy (AIR), Autoimmune sudden sensorineural hearing loss (SNHL), Balo disease, Behçet’s disease, Birdshot chorioretinopathy / birdshot uveitis, Bullous pemphigoid,

Castleman disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic autoimmune urticaria, Churg-Strauss syndrome / eosinophilic granulomatosis with polyangiitis (EGPA) , Cogan's syndrome, Cold agglutinin disease, CREST syndrome | limited cutaneous systemic sclerosis, Crohn's disease (CD), Cronkhite-Canada syndrome (CSS), Cryptogenic organizing pneumonia (COP), Dermatitis herpetiformis, Dermatomyositis, Diabetes, type 1, Discoid lupus, Dressler's syndrome / postmyocardial infarction / postpericardiotomy syndrome, Eczema/Atopic Dermatitis, Endometriosis, Eosinophilic esophagitis/eosinophilic gastroenteritis, Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibrosing alveolitis/Idiopathic pulmonary fibrosis (IPF), Giant cell arteritis / temporal arteritis / Horton's disease, Giant Cell Myocarditis, Glomerulonephritis, Goodpasture's syndrome / anti-GBM/anti-TBM disease, Granulomatosis with polyangiitis (GPA) / Wegener's granulomatosis, Graves' disease / thyroid eye disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis / chronic lymphocytic thyroiditis / autoimmune thyroiditis, Henoch-Schönlein purpura / IgA vasculitis, Hidradenitis suppurativa, Hurst's disease / acute hemorrhagic leukoencephalitis (AHLE), Hypogammaglobulinemia, IgA nephropathy / Berger's disease, Immune-mediated necrotizing myopathy (IMNM), Immune thrombocytopenia (ITP) / autoimmune thrombocytopenic purpura / autoimmune thrombocytopenia, Inclusion body myositis, IgG4-related sclerosing disease (ISD), Interstitial cystitis, Juvenile idiopathic arthritis / Adult-onset Still's disease, Juvenile polymyositis | Juvenile dermatomyositis | juvenile myositis, Kawasaki disease, Lambert-Eaton myasthenic syndrome (LEMS), Leukocytoclastic vasculitis, Lichen planus | Lichen planopilaris, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD) | linear IgA bullous dermatosis (LABD), Lupus nephritis, Lyme disease / chronic Lyme disease / post-treatment Lyme disease syndrome (PTLDS), Lymphocytic colitis/microscopic colitis, Lymphocytic hypophystitis/autoimmune hypophystitis, Ménière's disease, Microscopic polyangiitis (MPA)/ANCA-associated vasculitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal motor neuropathy, Multiple sclerosis (MS), Myalgic encephalomyelitis (ME)/ Chronic fatigue syndrome (CFS), Myasthenia gravis (MG), Narcolepsy, Neuromyelitis Optica/Devic's disease, Ocular cicatricial pemphigoid, Opsoclonus-myoclonus syndrome (OMS), Palindromic rheumatism, Paraneoplastic cerebellar degeneration, Paraneoplastic pemphigus, Parry-Romberg syndrome

(PRS)/Hemifacial atrophy (HFA)/Progressive facial hemiatrophy, Paroxysmal nocturnal hemoglobinuria (PNH), Peripheral uveitis/pars planitis, PANS/PANDAS, Parsonage-Turner syndrome, Pemphigus gestationis / herpes gestationis, Pemphigus foliaceus, Pemphigus vulgaris, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Postural orthostatic tachycardia syndrome (POTS), Primary biliary cirrhosis (PBC) / primary biliary cholangitis, Primary sclerosing cholangitis (PSC), Psoriasis, Palmoplantar Pustulosis, Psoriatic arthritis, Pulmonary fibrosis, idiopathic (IPF), Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Rasmussen's encephalitis, Raynaud's syndrome/phenomenon, Reactive arthritis / Reiter's syndrome, Reflex sympathetic dystrophy syndrome (RSD) / Complex regional pain syndrome (CRPS), Relapsing polychondritis, Restless leg syndrome (RLS) / Willis-Ekbom disease, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome / autoimmune polyendocrine syndrome type II / polyglandular autoimmune syndrome, type 2, Scleritis, Scleroderma, Sclerosing Mesenteritis / Mesenteric Panniculitis, Serpiginous choroidopathy, Sjögren's syndrome, Stiff person syndrome (SPS), Small fiber sensory neuropathy, s erythematosus (SLE), Subacute bacterial endocarditis (SBE), Subacute cutaneous lupus, Susac syndrome, Sydenham's chorea, Sympathetic ophthalmia, Takayasu's arteritis (vasculitis), Testicular autoimmunity (vasculitis, orchitis), Tolosa-Hunt syndrome, Transverse myelitis (TM), Tubulointerstitial nephritis uveitis syndrome (TINU), Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis anterior/intermediate/posterior, Vasculitis, VEXAS Syndrome, Vitiligo, Vogt-Koyanagi-Harada syndrome (VKH)

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the patient is non-responsive to standard of care (SOC) treatment, or not sufficiently responsive to standard of care treatment, suffers from side-effects associated with SOC treatment, or wherein the patient does not respond to at least one, two, or more standard immunosuppressive drugs. As used herein, the terms "non-responsive to standard of care", or "sufficiently responsive to standard of care" mean that the SOC is not effective or not sufficiently effective to reduce the symptoms of an autoimmune disease or autoimmune condition to benefit a treated patients' overall quality of life, e.g., reduce pain, reduce

swelling, rashes, fever, or any other symptom that causes the patient discomfort or participation in every days' activities, such as social activities, working, caring for family members, sexual activities, sports activities, etc. These symptoms also include psychological symptoms, such as anxiety, depression, or even suicidal thoughts.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for intravenous administration. As used herein, the term "formulated for" indicates that a formulation is suitable for a given route of administration, comprises excipients that are known in the art to administer such formulation to a patient in need thereof in a therapeutically effective manner and amount. Excipients of pharmaceutical formulations or pharmaceutical compositions can be found in well-known textbooks such as the European pharmacopeia (e.g., https://www.ema.europa.eu/en/glossary/european-pharmacopoeia).

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is sclerosis, e.g., systemic sclerosis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a pediatric patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is sclerosis, e.g., systemic sclerosis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is Rheumatoid arthritis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a pediatric patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is Rheumatoid arthritis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 (also referred to as CD19xCD3 T cell engager (TCE)) for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is refractory Rheumatoid arthritis. Refractory Rheumatoid arthritis is characterized by a lack of clinical response to several consecutive drugs with different modes of action and may exhibit significant progression of joint damage and irreversible disability.

There is no formal consensus definition of this category of patients, and they are referred as “difficult to treat” or “refractory” (Tan et al, 2022; Melville et al, 2020; Buch, 2019). As used herein, patients with “refractory RA” have moderate to severe active disease despite having received treatment with a conventional synthetic disease-modifying antirheumatic drug (csDMARD) and at least two biologic disease-modifying anti-rheumatic drug (bDMARD) is a type of medication that prevents joint damage by block bDMARDs of different mechanisms of action or one, preferably two, bDMARD and at least one targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD).

The treatment with the CD19 binding and CD3 binding molecule may be a treatment with Blinatumomab, which may be administered by continuous infusion, but in a preferred embodiment is performed by subcutaneous administration. In a further embodiment, the CD19xCD3 TCE, e.g., Blinatumomab, is for subcutaneous administration at a dose of at least 20 µg weekly, at least 30 µg weekly, at least 40 µg weekly, at least 50 µg weekly, at least 60 µg weekly, at least 70 µg weekly, at least 80 µg weekly, at least 90 µg weekly, at least 100 µg weekly, at least 120 µg weekly, at least 1500 µg weekly, at least 2000 µg weekly, at least 20 µg weekly, at least 250 µg weekly, at least 500 µg weekly, and at least 1000 µg weekly. In some of sub-embodiments, the molecule is administered at 40 µg weekly for at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, or longer. In one sub-embodiment, the molecule is administered at 40 µg subcutaneously for at least 12 weeks, or at 120 µg subcutaneously for at least 12 weeks, or at 250 µg subcutaneously for at least 12 weeks. Each administration cycle, e.g., 40 µg subcutaneously for at least 12 weeks, or at 120 µg subcutaneously for at least 12 weeks, or at 250 µg subcutaneously for at least 12 weeks may be repeated after a period of TCE administration-free interval. The treatment cycles may be repeated at least 2, 3, 4, and 5 times. Of course, it is also possible to treat RA patients that are not refractory to other anti-rheumatic drugs. In a recent study, 6 multidrug-resistant

patients with active and severe RA received blinatumomab (CD19xCD3 BiTE) under compassionate use (Bucci et al, 2024). A rapid improvement in RA clinical disease activity, improved synovitis as measured by ultrasound and FAPI-PET-CT and reduced autoantibody titers (RF and ACPA) were observed in all 6 participants. Activated memory B-cells were depleted and replaced by non-class-switched IgD-positive naïve B-cells. However, as subcutaneously administered Blinatumomab has never been tested in non-oncology settings, and it was entirely unclear how patients, particularly, immunosuppressed patients with heavily pretreated rRA would respond to this drug, it was difficult to find the most effective and safe treatment regimen.

Dexamethasone can be used as a premedication for CRS prophylaxis and prophylaxis of first dose effects such as skin rash and pruritus. Premedication with dexamethasone can also be used at the investigator's discretion prior to subsequent doses.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is Myasthenia gravis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a pediatric patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is Myasthenia gravis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is dermatomyositis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is juvenile dermatomyositis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient

suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is Guillain-Barré syndrome (GBS).

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is Hashimoto's thyroiditis.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is Neuromyelitis Optica/Devic's disease.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 5µg/m2 to about 112 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 5µg/m2 to about 56 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 5µg/ m2 to about 25 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 5µg/ m2 to about 20 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 5µg/ m2 to about 15 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 7 µg/ m2 to about 12 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 8 µg/ m2 to about 10 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 9 µg/ m2.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 9 µg/ m2 for at least 1 day, at least 3 days, at least 5 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, particularly for at least 5 days in a first administration cycle. The first administration cycle may be followed by at least one more administration cycle, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 9 µg/ m2 for at least 1 day, at least 3 days, at least 5 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, particularly for at least 5 days. The first administration cycle or a subsequent administration cycle, e.g., a third administration

cycle may be followed by at least one more administration cycle, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 28 µg/ m2 for at least 1 day, at least 3 days, at least 5 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, particularly for at least 5 days. In one embodiment, a fourth administration cycle comprises daily administrations of 28 µg for at least 7 days to 14 days, for example, for 10 days. After each administration cycle, the subject to be treated may be without treatment with the molecule for at least 1 week, for at least 2 weeks, for at least 3 weeks, or for at least 4 weeks, or longer.

In a further embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition in a pediatric patient (particularly pediatric patients having a body weight of up to 45 kg), wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 5 µg/ m2 for at least 1 day, at least 3 days, at least 5 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, particularly for at least 5 days in a first administration cycle. The first administration cycle may be followed by at least one more administration cycle, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 5 µg/ m2 for at least 1 day, at least 3 days, at least 5 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, particularly for at least 5 days. The first administration cycle or a subsequent administration cycle, e.g., a third administration cycle may be followed by at least one more administration cycle, wherein the molecule is formulated for continuous intravenous administration of a daily dose of about 15 µg/ m2 for at least 1 day, at least 3 days, at least 5 days, at least 7 days, at least 10 days, at least 14 days, at least 21 days, at least 28 days, at least 35 days, at least 42 days, particularly for at least 5 days. After each administration cycle, the subject to be treated may be without treatment with the molecule for at least 1 week, for at least 2 weeks, for at least 3 weeks, or for at least 4 weeks, or longer.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient

suffering from an autoimmune disease or autoimmune condition, wherein the molecule is formulated for subcutaneous administration.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the molecule is for administration over a period of at least 3 days, preferably at least 4 days, more preferably for at least 5 days, or longer as describe above, e.g. for up to 42 days, or for up to 40 days.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is SLE.

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a pediatric patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease is SLE.

In a further embodiment the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from Systemic lupus erythematosus, such as SLE with active and/or refractory SLE and/or Class III/IV glomerulonephritis. The molecule used in the treatment of these patients, particularly adult subjects, is administered subcutaneously in a suitable pharmaceutical formulation, i.e., as a suitable pharmaceutical composition comprising the molecule. In an embodiment, the molecule is blinatumomab. In another embodiment the patient experienced, prior to treatment with the herein disclosed molecule/pharmaceutical composition of the present invention, a failure to respond to previous standard therapies including immunosuppressive therapies and treatment with a biological agent. In an embodiment the patient is treated with blinatumomab at a weekly dose of at least 10 µg. In another embodiment the patient is treated with blinatumomab at a weekly dose of at least 25 µg. In still another embodiment the patient is treated with blinatumomab at a weekly dose of at least 40 µg. In still another embodiment the patient is treated with blinatumomab at a weekly dose of at least 100 µg. In still another embodiment the patient is treated with blinatumomab at a weekly dose of at least 120 µg. In still another embodiment the patient

is treated with blinatumomab at a weekly dose of at least 200 µg. In still another embodiment the patient is treated with blinatumomab at a weekly dose of at least 250 µg. In still another embodiment the patient is treated with blinatumomab at a weekly dose of at least 500 µg. In still another embodiment the patient is treated with blinatumomab at a weekly dose of at least 750 µg or even 1000 µg. The treatment period lasts for 6 weeks, followed by a treatment-free period. In another embodiment, the treatment period lasts for 9 weeks, followed by a treatment-free period. In another embodiment, the treatment period lasts for 12 weeks, followed by a treatment-free period.

The treatment of these patients results in at least one or more of the following improvements, e.g., as determined after a 12-week treatment cycle:

- 24-hour urine protein-creatinine ratio (UPCR) ≤0.5 mg/mg
- Remission in SLE as defined by (DORIS)
- Lupus Low Disease Activity State (LLDAS)
- Pain reduction, improved overall health (including mental health), reduction in number of antinuclear antibodies (ANA) below 1:80, reduction in number of anti-double deoxyribonucleic acid (anti-dsDNA) antibodies elevated, in number of anti-Smith antibodies, reduction of SLE Disease Activity Index 2000 (SLEDAI-2K) ≤ 8, reduction of active, biopsy-proven, proliferative lupus nephritis demonstrating Class III or Class IV with or without co-existing of Class V lupus nephritis according to 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria. Renal biopsy must have been performed within 6 months before enrollment. In embodiments of the invention, the patient, before treatment with CD19 x CD3, e.g., blinatumomab, showed and inadequate response, for lack of efficacy or intolerance after 6 months to at least one therapy at the maximally tolerated doses as recommended by the KDIGO guidelines in lupus nephritis.

In embodiments of invention, the subcutaneously treated patients are premedicated with corticosteroids (e.g., dexamethasone 20 mg IV) within 6 hours before the first subcutaneous injection of day 1. It is possible to concomitantly administer antiproteinuric agents (such as angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors and SGLT2 inhibitors if on stable dose 2 months prior treatment with blinatumomab), antihypertensive agents, immunomodulators, and further corticosteroids, e.g., prednisone (max. 40 mg/day).

In an embodiment, the present invention relates to a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a pediatric patient suffering from an autoimmune disease or autoimmune condition, wherein the autoimmune disease.

In an embodiment, the present invention relates to a pharmaceutical composition comprising the molecule as defined in any of the preceding embodiments for use in the treatment of a patient suffering from an autoimmune disease.

In an embodiment, the present invention relates to a nucleic acid molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein said molecule nucleic acid selected from the group comprising ribonucleic acid, deoxyribonucleic acid, or mixtures thereof. With the increasing use of nucleic acid-based drugs that can be administered to a patient in need thereof so that the patient produces the thereby encoded polypeptide, it is also contemplated to provide nucleic acids that encode the herein described molecules so that the patient's own cells produce the same. This reduces the frequency of treatments of a patient, the number of visits to a hospital, etc.

In an embodiment, the present invention relates to a nucleic acid molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein said nucleic acid is formulated for administration to said patient.

In an embodiment, the present invention relates to a pharmaceutical composition comprising the nucleic acid molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein said composition is suitable for parenteral or intravenous administration.

In an embodiment, the present invention relates to a molecule comprising a domain binding CD19 and a domain binding an immune effector cell (effector cells of the immune system as used herein comprise T cells, NK cells, and NKT cells), e.g. a T cell-binding domain for use in the treatment of a patient suffering from an autoimmune disease/condition. As used herein, molecules comprising a domain that binds CD19 are cell-free, isolated, soluble, non-transmembrane-spanning entities, which makes them different from, e.g., cell-bound

transmembrane receptor-type structures, which are found, e.g., on CAR T cells, or NK cells that have been modified to express proteins that target molecules on the cell surface of those cells that should be eliminated after being selectively recognized and bound by said CAR T cells, modified NK cells. Therefore, terms such as “isolated”, “cell-free”, and "soluble” can be used in accordance with the present invention and indicate that the herein disclosed and claimed molecules are not inserted into the membrane of effector cells. An example for such a molecule and compound is a BiTE molecule, for example, Blinatumomab.

In an embodiment, the present invention relates to a molecule comprising a domain that binds CD19 and a domain that binds to a molecule expressed by a T cell, an NK cell, or an NKT cell for use in the treatment of a patient suffering from an autoimmune disease/condition. The domain that binds to a molecule expressed by a T cell may bind to CD3. In another embodiment the domain binds the CD3 epsilon chain. In a further embodiment, the domain binds to a molecule expressed substantially by an NK cell, or an NKT cell, e.g., CD56 (neural cell adhesion molecule-1, NCAM1) and CD16 (low affinity Fc gamma receptor 3A, FCGR3A, FcγRIII), or to any molecule of engineered immune effector cells that express said molecule, but naturally do not express it.

As used in the embodiments of the present invention, which refer to autoimmune diseases or autoimmune conditions that can be treated or alleviated by the herein described molecules, as well as compositions comprising the same, and that have a relevant contribution of autoreactive antibodies that are produced by CD19-positive cells, which are the target of the molecules that are used in accordance with the herein disclosed embodiments, the following list of diseases and conditions is explained briefly below:

- Acromegaly: A hormonal disorder that results from excessive growth hormone (GH) production in the pituitary gland, leading to abnormal growth of bones and tissues, particularly in the hands, feet, and face.
- Acquired aplastic anemia: A rare condition where the bone marrow fails to produce enough blood cells, including red blood cells, white blood cells, and platelets, leading to fatigue, infections, and bleeding.

- Acquired hemophilia: A rare bleeding disorder where the body produces antibodies that attack clotting factors, particularly factor VIII, causing prolonged and spontaneous bleeding episodes.
- Agammaglobulinemia: A primary immunodeficiency disorder characterized by a lack of mature B cells, leading to decreased production of antibodies (immunoglobulins), increasing the risk of infections.
- Alopecia areata: An autoimmune condition causing hair loss in patches on the scalp or other parts of the body due to the immune system mistakenly attacking hair follicles.
- Ankylosing spondylitis (AS): A type of inflammatory arthritis primarily affecting the spine and sacroiliac joints, leading to stiffness, pain, and eventually fusion of the spine.
- Anti-NMDA receptor encephalitis: An autoimmune disorder where the body's immune system attacks NMDA receptors in the brain, resulting in a range of neurological symptoms, including psychosis, seizures, and movement disorders.
- Antiphospholipid syndrome (APS): An autoimmune disorder characterized by the presence of antiphospholipid antibodies, leading to blood clots in arteries and veins, recurrent miscarriages, and other complications.
- Catastrophic antiphospholipid syndrome (CAPS): A severe form of APS characterized by widespread blood clotting in multiple organs, leading to organ failure and life-threatening complications.
- Asherson's syndrome: A variant of antiphospholipid syndrome characterized by the triad of antiphospholipid antibodies, thrombosis, and multiorgan failure, often triggered by infections or medications.
- Arteriosclerosis: A condition where arteries become hardened and narrowed due to the buildup of plaque, leading to reduced blood flow and increased risk of heart attack, stroke, and other cardiovascular problems.
- Autoimmune Addison's disease (AAD): An autoimmune disorder where the adrenal glands are damaged, leading to insufficient production of cortisol and aldosterone hormones, resulting in symptoms like fatigue, weight loss, low blood pressure, and electrolyte imbalances.
- Autoimmune autonomic ganglionopathy (AAG): An autoimmune disorder where the body's immune system attacks the autonomic ganglia, leading to dysfunction of

the autonomic nervous system and symptoms such as orthostatic hypotension, gastrointestinal dysmotility, and sweating abnormalities.

- Autoimmune dysautonomia: A condition characterized by dysfunction of the autonomic nervous system due to autoimmune attack, leading to symptoms such as dizziness, fainting, abnormal heart rate, and gastrointestinal problems.
- Autoimmune gastrointestinal dysmotility (AGID): A disorder where the immune system attacks the nerves or muscles of the gastrointestinal tract, disrupting the normal movement of food and leading to symptoms such as bloating, nausea, vomiting, and constipation or diarrhea.
- Autoimmune encephalitis: A condition where the immune system attacks the brain, leading to inflammation and a range of neurological symptoms, including confusion, memory problems, seizures, and hallucinations.
- Acute disseminated encephalomyelitis (ADEM): An autoimmune disorder characterized by widespread inflammation of the brain and spinal cord, typically occurring after a viral infection or vaccination, leading to symptoms such as fever, headache, seizures, and neurological deficits.
- Autoimmune gastritis: An autoimmune disorder where the immune system attacks the stomach lining, leading to inflammation, decreased production of stomach acid and intrinsic factor, and potentially resulting in pernicious anemia and malabsorption of nutrients.
- Autoimmune hemolytic anemia (AIHA): A condition where the immune system mistakenly attacks and destroys red blood cells, leading to anemia and symptoms such as fatigue, weakness, pallor, and shortness of breath.
- Autoimmune hepatitis (AIH): A chronic liver disease where the immune system attacks liver cells, leading to inflammation and liver damage, potentially progressing to cirrhosis and liver failure if left untreated.
- Autoimmune hyperlipidemia: An autoimmune condition where the body attacks its own lipids, leading to abnormal levels of fats in the blood, which can increase the risk of cardiovascular diseases such as heart attack and stroke.
- Autoimmune hypophysitis/lymphocytic hypophysitis: An autoimmune disorder where the body's immune system attacks the pituitary gland, leading to inflammation and dysfunction of the gland, which can cause hormonal imbalances and symptoms such as fatigue, weight loss, and hormonal deficiencies.

- Autoimmune inner ear disease (AIED): An autoimmune condition where the immune system attacks the inner ear structures, leading to hearing loss, vertigo, and balance problems.
- Autoimmune lymphoproliferative syndrome (ALPS): A rare genetic disorder characterized by abnormal lymphocyte proliferation and impaired apoptosis (cell death), leading to lymphadenopathy (enlarged lymph nodes), splenomegaly (enlarged spleen), autoimmune cytopenias (low blood cell counts), and an increased risk of lymphoma.
- Autoimmune myelofibrosis: An autoimmune disorder characterized by fibrosis (scarring) of the bone marrow, leading to impaired blood cell production and symptoms such as anemia, fatigue, and an enlarged spleen.
- Autoimmune myocarditis: An autoimmune condition where the body's immune system attacks the myocardium (heart muscle), leading to inflammation and damage to the heart tissue, which can cause heart failure and arrhythmias.
- Autoimmune oophoritis: An autoimmune disorder where the body's immune system attacks the ovaries, leading to inflammation and dysfunction of the ovaries, which can cause hormonal imbalances and infertility.
- Autoimmune pancreatitis (AIP): An autoimmune condition where the immune system attacks the pancreas, leading to inflammation and fibrosis of the pancreatic tissue, which can cause abdominal pain, jaundice, and pancreatic dysfunction.
- Autoimmune polyglandular syndromes (APS): A group of rare autoimmune disorders characterized by the simultaneous or sequential dysfunction of multiple endocrine glands, leading to hormonal imbalances and symptoms such as fatigue, weight loss, and autoimmune manifestations in various organs.
- Autoimmune progesterone dermatitis: An autoimmune condition where the body's immune system attacks progesterone, leading to skin rashes, hives, and other allergic reactions during the luteal phase of the menstrual cycle.
- Autoimmune retinopathy (AIR): An autoimmune disorder where the immune system attacks proteins in the retina, leading to inflammation and damage to the retinal tissue, which can cause vision loss and blindness.

- Autoimmune sudden sensorineural hearing loss (SNHL): An autoimmune condition where the body's immune system attacks the inner ear structures involved in hearing, leading to sudden hearing loss without any apparent cause.
- Balo disease: Also known as Balo concentric sclerosis, it's a rare neurological disorder characterized by alternating bands of demyelination and normal-appearing white matter in the brain, often leading to neurological symptoms such as weakness, paralysis, and cognitive impairment.
- Behçet's disease: A chronic inflammatory disorder that affects multiple parts of the body, including the mouth, genitals, skin, eyes, and blood vessels. It's characterized by recurrent oral and genital ulcers, skin lesions, uveitis (eye inflammation), and vascular involvement.
- Birdshot chorioretinopathy / birdshot uveitis: A rare form of autoimmune uveitis (inflammation of the uvea in the eye) that primarily affects the retina and choroid. It presents with characteristic "birdshot" lesions in the retina and can lead to vision loss if left untreated.
- Bullous pemphigoid: An autoimmune skin disorder characterized by the formation of large, fluid-filled blisters (bullae) on the skin and mucous membranes. It occurs when the immune system attacks the proteins that help attach the epidermis (outer layer of skin) to the underlying dermis.
- Castleman disease: A group of rare lymphoproliferative disorders characterized by the abnormal growth of lymphatic cells in lymph nodes. It can be localized or systemic and presents with symptoms such as enlarged lymph nodes, fever, fatigue, and other systemic manifestations.
- Celiac disease: An autoimmune disorder triggered by the ingestion of gluten, a protein found in wheat, barley, and rye. It causes damage to the small intestine's lining, leading to malabsorption of nutrients and various gastrointestinal symptoms, including diarrhea, abdominal pain, and weight loss.
- Chagas disease: A tropical parasitic infection caused by the protozoan parasite Trypanosoma cruzi. It's transmitted to humans primarily through the bite of infected triatomine bugs. Chagas disease can lead to acute or chronic symptoms, including fever, fatigue, organ damage (heart, esophagus, colon), and in severe cases, heart failure.

- Chronic inflammatory demyelinating polyneuropathy (CIDP): An autoimmune disorder characterized by progressive weakness and sensory loss due to inflammation and damage to the peripheral nerves' myelin sheath. It often presents with symmetric limb weakness, sensory disturbances, and impaired reflexes.
- Chronic autoimmune urticaria: A chronic skin condition characterized by recurrent episodes of hives (urticaria) and/or angioedema (swelling beneath the skin). It occurs due to an autoimmune reaction that leads to the release of histamine and other inflammatory mediators, causing skin reactions.
- Churg-Strauss syndrome / eosinophilic granulomatosis with polyangiitis (EGPA): A rare autoimmune disorder characterized by inflammation of small and medium-sized blood vessels (vasculitis) and eosinophilic infiltration of various organs. It typically presents with asthma, allergic rhinitis, and systemic vasculitis affecting multiple organs.
- Cogan's syndrome: An autoimmune disorder characterized by inflammation of the cornea and inner ear structures, leading to symptoms such as vertigo, hearing loss, tinnitus, and eye inflammation. It can also affect blood vessels and other organs.
- Cold agglutinin disease: An autoimmune hemolytic anemia characterized by the presence of cold-reacting antibodies that cause red blood cells to clump together (agglutinate) at low temperatures, leading to their destruction and anemia.
- CREST syndrome | limited cutaneous systemic sclerosis: A subtype of systemic sclerosis (scleroderma) characterized by calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia. It primarily affects the skin, blood vessels, and gastrointestinal tract, causing fibrosis and vascular abnormalities.
- Crohn's disease (CD): A chronic inflammatory bowel disease characterized by inflammation of the digestive tract, most commonly affecting the small intestine and colon. It causes abdominal pain, diarrhea, weight loss, and fatigue, and can lead to complications such as strictures, fistulas, and abscesses.
- Cronkhite-Canada syndrome (CSS): A rare non-inherited disorder characterized by multiple polyps in the digestive tract, hair loss, nail abnormalities, skin pigmentation changes, diarrhea, and protein-losing enteropathy. The cause is unknown, but it's believed to involve autoimmune and inflammatory processes.

- Cryptogenic organizing pneumonia (COP): A rare lung condition characterized by inflammation and fibrosis of the small airways and air sacs (alveoli), leading to cough, shortness of breath, and flu-like symptoms. The cause is often unknown, but it's believed to involve autoimmune and inflammatory mechanisms.
- Dermatitis herpetiformis: A chronic skin condition characterized by intensely itchy, blistering rash, typically found on the elbows, knees, back, and buttocks. It is associated with gluten sensitivity and is considered a manifestation of celiac disease.
- Dermatomyositis: An inflammatory disease affecting the skin and muscles, characterized by muscle weakness, skin rash (often on the face, knuckles, elbows, or knees), and occasionally systemic symptoms such as fever and fatigue. It's considered an autoimmune disorder.
- Diabetes, type 1: A chronic condition where the pancreas produces little to no insulin, leading to high blood sugar levels. It is considered an autoimmune disease where the body's immune system attacks and destroys insulin-producing beta cells in the pancreas.
- Discoid lupus: A chronic skin condition that causes coin-shaped lesions on the skin, typically on the face, scalp, and ears. It is a form of lupus erythematosus that primarily affects the skin, causing inflammation and scarring.
- Dressler's syndrome / postmyocardial infarction / postpericardiotomy syndrome: An inflammatory condition involving the sac surrounding the heart (pericardium), which occurs weeks to months after a heart attack or heart surgery. It presents with chest pain, fever, and sometimes fluid accumulation around the heart.
- Eczema/Atopic Dermatitis: A chronic inflammatory skin condition characterized by red, itchy, and inflamed patches of skin. It often occurs in individuals with a personal or family history of allergic conditions such as asthma and hay fever.
- Endometriosis: A disorder in which tissue like the lining of the uterus (endometrium) grows outside the uterus, commonly causing pelvic pain, infertility, and irregular menstrual bleeding. The exact cause is unknown, but it's believed to involve hormonal and immune factors.
- Eosinophilic esophagitis/eosinophilic gastroenteritis: Conditions characterized by inflammation of the esophagus or gastrointestinal tract due to the accumulation of

eosinophils, a type of white blood cell. Symptoms may include difficulty swallowing, abdominal pain, vomiting, and diarrhea.

- Eosinophilic fasciitis: A rare disorder characterized by inflammation and thickening of the fascia (connective tissue) beneath the skin, typically affecting the arms, legs, and trunk. It causes pain, swelling, and stiffness in the affected areas.
- Erythema nodosum: A type of skin inflammation characterized by tender, red, and swollen nodules, usually on the shins. It is often associated with systemic conditions such as infections, inflammatory bowel disease, and autoimmune disorders.
- Essential mixed cryoglobulinemia: A condition characterized by the presence of abnormal proteins called cryoglobulins in the blood, which can lead to inflammation and damage to blood vessels, causing symptoms such as skin rash, joint pain, and organ damage.
- Evans syndrome: A rare autoimmune disorder characterized by the simultaneous or sequential destruction of red blood cells (hemolytic anemia) and platelets (thrombocytopenia) by the body's immune system, leading to anemia, bruising, and bleeding.
- Fibrosing alveolitis/Idiopathic pulmonary fibrosis (IPF): A progressive lung disease characterized by scarring (fibrosis) of the lung tissue, which makes it difficult to breathe. It is of unknown cause (idiopathic) and typically affects older adults, leading to worsening respiratory symptoms over time.
- Giant cell arteritis (Temporal arteritis): An inflammatory condition that affects the medium and large arteries, particularly those in the head, especially the temporal arteries. It presents with severe headache, scalp tenderness, jaw pain, and vision problems. If left untreated, it can lead to blindness or stroke.
- Horton's disease: Another name for giant cell arteritis, which is an inflammatory disease involving the arteries, particularly those in the head.
- Giant Cell Myocarditis: A rare form of myocarditis characterized by inflammation of the heart muscle (myocardium), typically involving multinucleated giant cells. It can lead to heart failure and sudden cardiac death.
- Glomerulonephritis: Inflammation of the glomeruli, the tiny filters in the kidneys responsible for filtering waste and excess fluids from the blood. It can be acute or chronic and may result from various causes, including autoimmune diseases, infections, and certain medications.

- Goodpasture's syndrome / anti-GBM/anti-TBM disease: An autoimmune disorder characterized by the production of autoantibodies targeting the glomerular basement membrane (GBM) in the kidneys and sometimes the basement membrane in the lungs. It leads to kidney damage (glomerulonephritis) and lung hemorrhage.
- Granulomatosis with polyangiitis (GPA) / Wegener's granulomatosis: A type of vasculitis characterized by inflammation of blood vessels, particularly small and medium-sized vessels. It commonly affects the respiratory tract and kidneys, causing symptoms such as sinusitis, lung nodules, and kidney damage.
- Graves' disease: An autoimmune disorder characterized by overactivity of the thyroid gland (hyperthyroidism), resulting in symptoms such as weight loss, rapid heartbeat, tremors, and eye problems (Graves' ophthalmopathy). Graves' ophthalmopathy or thyroid-associated orbitopathy, it is an autoimmune condition that affects the tissues around the eyes, causing inflammation, swelling, and sometimes protrusion of the eyes (exophthalmos).
- Guillain-Barré syndrome (GBS): A rare autoimmune disorder characterized by the immune system attacking the peripheral nerves, leading to muscle weakness, paralysis, and sometimes respiratory failure. It often follows a viral or bacterial infection.
- Hashimoto's thyroiditis / chronic lymphocytic thyroiditis / autoimmune thyroiditis: An autoimmune condition causing inflammation of the thyroid gland, leading to hypothyroidism (underactive thyroid). It is characterized by symptoms such as fatigue, weight gain, cold intolerance, and depression.
- Henoch-Schönlein purpura: A type of vasculitis characterized by inflammation of the small blood vessels, resulting in a rash (purpura), joint pain, abdominal pain, and kidney inflammation (nephritis). It commonly affects children but can occur in adults as well.
- IgA nephropathy (Berger's disease): A kidney disorder where an antibody called immunoglobulin A (IgA) builds up in the kidneys, causing inflammation that can lead to kidney damage and, in some cases, kidney failure.
- Immune-mediated necrotizing myopathy (IMNM): A rare autoimmune muscle disease characterized by muscle weakness and damage due to inflammation and necrosis (death of muscle cells).

- Immune thrombocytopenia (ITP) / autoimmune thrombocytopenic purpura / autoimmune thrombocytopenia: Conditions where the immune system mistakenly attacks and destroys platelets, which are necessary for blood clotting, leading to a low platelet count and an increased risk of bleeding.
- Inclusion body myositis: A progressive muscle disorder characterized by muscle weakness and atrophy, particularly in the muscles of the arms and legs. It is associated with the accumulation of abnormal proteins in muscle cells.
- IgG4-related sclerosing disease (ISD): A condition characterized by chronic inflammation and fibrosis (scar tissue formation) in various organs, such as the pancreas, salivary glands, and lymph nodes, due to an abnormal immune response involving immunoglobulin G4 (IgG4).
- Interstitial cystitis: Also known as painful bladder syndrome, it is a chronic condition characterized by bladder pain, urinary urgency, and frequency, often without an identifiable cause.
- Juvenile idiopathic arthritis (JIA): A chronic autoimmune inflammatory joint disease that begins before the age of 16 and persists for at least six weeks. It encompasses several subtypes of arthritis, including oligoarthritis, polyarthritis, systemic arthritis, and others.
- Adult-onset Still's disease: A rare systemic inflammatory disorder characterized by high spiking fevers, joint pain, rash, and inflammation of internal organs, such as the heart, lungs, and liver.
- Juvenile polymyositis / Juvenile dermatomyositis / juvenile myositis: Autoimmune diseases characterized by muscle weakness and inflammation, particularly affecting children and adolescents.
- Kawasaki disease: An acute febrile illness that primarily affects young children, causing inflammation of blood vessels throughout the body, leading to symptoms such as fever, rash, red eyes, swollen lymph nodes, and coronary artery abnormalities.
- Lambert-Eaton myasthenic syndrome (LEMS): A rare autoimmune disorder characterized by muscle weakness, particularly in the limbs, due to antibodies targeting voltage-gated calcium channels at the neuromuscular junction.

- Leukocytoclastic vasculitis: A type of vasculitis characterized by inflammation and damage to small blood vessels in the skin, resulting in the appearance of palpable purpura (small red or purple spots).
- Lichen planus: An inflammatory skin condition characterized by itchy, flat-topped bumps or lesions that can occur on the skin, mucous membranes, nails, or scalp.
- Lichen planopilaris: A variant of lichen planus that affects the scalp, leading to scarring hair loss (cicatricial alopecia).
- Lichen sclerosus: A chronic inflammatory skin disorder that primarily affects the genital and anal areas, causing white, patchy skin that may become thin and wrinkled.
- Ligneous conjunctivitis: A rare form of chronic conjunctivitis characterized by the formation of thick, woody-like pseudomembranes on the conjunctiva (the membrane covering the white part of the eye).
- Linear IgA disease (LAD) / linear IgA bullous dermatosis (LABD): A rare autoimmune blistering skin disorder characterized by the formation of blisters and erosions on the skin and mucous membranes due to the deposition of IgA antibodies along the basement membrane zone.
- Lupus nephritis: Inflammation of the kidneys caused by systemic lupus erythematosus (SLE), an autoimmune disease. It can lead to kidney damage and impaired kidney function.
- Lyme disease / chronic Lyme disease / post-treatment Lyme disease syndrome (PTLDS): An infectious disease caused by bacteria transmitted through the bite of infected ticks. Chronic Lyme disease and PTLDS refer to persistent symptoms that may occur after treatment, such as fatigue, joint pain, and cognitive difficulties.
- Lymphocytic colitis / microscopic colitis: Chronic inflammatory bowel diseases characterized by inflammation of the colon (large intestine) and persistent diarrhea, often with normal appearing colonoscopies. Lymphocytic colitis involves increased lymphocytes in the colon lining, while microscopic colitis includes both lymphocytic colitis and collagenous colitis.
- Lymphocytic hypophysitis / autoimmune hypophystitis: Inflammation of the pituitary gland (hypophysis) due to an autoimmune reaction, leading to hormonal imbalances and pituitary dysfunction.

- Ménière's disease: A disorder of the inner ear characterized by episodes of vertigo (spinning sensation), hearing loss, tinnitus (ringing in the ear), and a feeling of fullness or pressure in the ear.
- Microscopic polyangiitis (MPA): A type of vasculitis (inflammation of blood vessels) that primarily affects small blood vessels, leading to damage in various organs, including the kidneys, lungs, and nervous system.
- ANCA-associated vasculitis: A group of autoimmune diseases characterized by inflammation of blood vessels and the presence of anti-neutrophil cytoplasmic antibodies (ANCA). Examples include granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).
- Mixed connective tissue disease (MCTD): A rare autoimmune disorder characterized by features of several connective tissue diseases, including systemic lupus erythematosus (SLE), scleroderma, and polymyositis.
- Mooren's ulcer: A rare autoimmune disease affecting the cornea of the eye, characterized by progressive ulceration and inflammation that can lead to vision loss if not treated promptly.
- Mucha-Habermann disease: Also known as pityriasis lichenoides et varioliformis acuta (PLEVA), it is a rare skin disorder characterized by the sudden onset of red, scaly papules or plaques that may ulcerate and heal with scarring.
- Multifocal motor neuropathy: A rare autoimmune disorder characterized by weakness and wasting of muscles in the limbs, typically affecting one side of the body more than the other.
- Multiple sclerosis (MS): A chronic autoimmune disease of the central nervous system (brain and spinal cord) characterized by inflammation, demyelination (damage to the protective covering of nerve fibers), and the formation of scar tissue, leading to a wide range of neurological symptoms.
- Myalgic encephalomyelitis (ME) / Chronic fatigue syndrome (CFS): A complex disorder characterized by extreme fatigue that is not improved by rest and is often accompanied by other symptoms such as cognitive difficulties, sleep disturbances, and muscle pain.

- Myasthenia gravis (MG): An autoimmune neuromuscular disorder characterized by weakness and fatigue of voluntary muscles due to antibodies interfering with the communication between nerves and muscles.
- Narcolepsy: A chronic neurological disorder characterized by excessive daytime sleepiness, sudden loss of muscle tone (cataplexy), sleep paralysis, and hallucinations during sleep onset or upon awakening.
- Neuromyelitis Optica / Devic's disease: An autoimmune inflammatory disorder affecting the optic nerves and spinal cord, leading to episodes of optic neuritis (inflammation of the optic nerve) and myelitis (inflammation of the spinal cord).
- Ocular cicatricial pemphigoid: A rare autoimmune disorder characterized by chronic inflammation and scarring of the conjunctiva (the membrane covering the white part of the eye), leading to vision impairment or blindness if left untreated.
- Opsoclonus-myoclonus syndrome (OMS): A rare neurological disorder characterized by rapid, involuntary eye movements (opsoclonus), muscle jerks (myoclonus), ataxia (loss of coordination), irritability, and developmental regression, often associated with an underlying tumor or autoimmune process.
- Palindromic rheumatism: A rare form of inflammatory arthritis characterized by recurrent episodes of joint pain, swelling, and stiffness that resolve spontaneously within days to weeks, leaving no residual joint damage.
- Paraneoplastic cerebellar degeneration: A rare autoimmune disorder characterized by degeneration of the cerebellum (part of the brain responsible for coordination and balance), often associated with an underlying cancer.
- Paraneoplastic pemphigus: A rare autoimmune blistering disorder characterized by painful mucosal erosions and skin lesions, often associated with an underlying cancer.
- Parry-Romberg syndrome (PRS) / Hemifacial atrophy (HFA) / Progressive facial hemiatrophy: A rare disorder characterized by progressive shrinkage and degeneration of the tissues on one side of the face, leading to facial asymmetry and other complications.
- Paroxysmal nocturnal hemoglobinuria (PNH): A rare, acquired disorder of the blood characterized by the destruction of red blood cells, leading to episodes of hemolysis (breakdown of red blood cells) and symptoms such as fatigue, shortness of breath, and dark urine.

- Peripheral uveitis / pars planitis: Inflammation of the uvea (the middle layer of the eye) or the area around the pars plana (a part of the eye's ciliary body), leading to symptoms such as eye pain, redness, and vision changes.
- PANS / PANDAS: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) are conditions characterized by sudden onset neuropsychiatric symptoms such as obsessive-compulsive disorder (OCD) and tics, often following a streptococcal infection.
- Parsonage-Turner syndrome: Also known as brachial neuritis or neuralgic amyotrophy, it is a rare disorder characterized by sudden, severe shoulder pain followed by weakness and muscle wasting in the affected arm and shoulder.
- Pemphigus gestationis / herpes gestationis: A rare autoimmune blistering skin disorder that occurs during pregnancy or shortly after delivery, characterized by the formation of itchy, blistering skin lesions, often around the abdomen and trunk.
- Pemphigus foliaceus / Pemphigus vulgaris: Autoimmune blistering disorders characterized by the formation of painful blisters and erosions on the skin and mucous membranes.
- Pernicious anemia: A type of anemia caused by vitamin B12 deficiency due to the body's inability to absorb this vitamin, often resulting from autoimmune destruction of parietal cells in the stomach, which produce intrinsic factor necessary for B12 absorption.
- POEMS syndrome: A rare multisystem disorder characterized by polyneuropathy (nerve damage), organomegaly (enlargement of organs), endocrinopathy (hormonal abnormalities), monoclonal gammopathy (abnormal proteins in the blood), and skin changes.
- Polyarteritis nodosa: A type of vasculitis characterized by inflammation of medium-sized arteries, leading to damage in various organs, including the skin, nerves, kidneys, and gastrointestinal tract.
- Polymyalgia rheumatica: An inflammatory disorder characterized by pain and stiffness, primarily in the shoulders and hips, often accompanied by constitutional symptoms such as fatigue, fever, and weight loss.

- Polymyositis: An autoimmune inflammatory myopathy characterized by muscle weakness and inflammation, primarily affecting the proximal muscles (those close to the trunk), leading to difficulties with mobility and daily activities.
- Postural Orthostatic Tachycardia Syndrome (POTS): A disorder characterized by an abnormal increase in heart rate (tachycardia) when transitioning from lying down to standing up, often accompanied by symptoms such as dizziness, lightheadedness, fainting, fatigue, and palpitations.
- Primary Biliary Cirrhosis (PBC) / Primary Biliary Cholangitis: An autoimmune liver disease characterized by progressive destruction of the bile ducts within the liver, leading to impaired bile flow, liver inflammation, fibrosis, and eventually cirrhosis.
- Primary Sclerosing Cholangitis (PSC): A chronic liver disease characterized by inflammation and scarring (fibrosis) of the bile ducts, leading to obstruction of bile flow and eventually liver damage and cirrhosis.
- Psoriasis: A chronic autoimmune skin disorder characterized by the rapid proliferation of skin cells, resulting in the formation of thick, red, scaly patches (plaques) that may be itchy or painful. Psoriasis can affect any part of the body, including the scalp, elbows, knees, and lower back.
- Palmoplantar Pustulosis: A chronic skin condition characterized by the formation of sterile pustules (fluid-filled blisters) on the palms of the hands and/or the soles of the feet, often accompanied by redness, scaling, and pain.
- Psoriatic Arthritis: An inflammatory arthritis that occurs in some individuals with psoriasis, characterized by joint pain, swelling, and stiffness, typically affecting the fingers, toes, spine, and large joints such as the knees and ankles.
- Pulmonary Fibrosis, Idiopathic (IPF): A progressive lung disease characterized by the formation of scar tissue (fibrosis) in the lungs, leading to stiffening of the lung tissue, impaired gas exchange, and respiratory symptoms such as shortness of breath, cough, and fatigue. The cause of idiopathic pulmonary fibrosis is unknown.
- Pure Red Cell Aplasia (PRCA): A rare disorder characterized by a failure of the bone marrow to produce red blood cells, resulting in severe anemia. PRCA can be acquired or congenital and may be associated with underlying conditions or triggered by certain medications or infections.

- Pyoderma Gangrenosum: A rare inflammatory skin disorder characterized by the development of painful, rapidly progressing ulcers, typically on the legs. The ulcers may begin as small pustules or nodules that quickly enlarge and break down, leaving large, irregularly shaped wounds with undermined edges.
- Rasmussen's Encephalitis: A rare, progressive neurological disorder characterized by inflammation of one hemisphere of the brain, leading to seizures, cognitive decline, and neurological deficits, typically occurring in children.
- Raynaud's Syndrome/Phenomenon: A condition characterized by episodes of vasospasm in the small arteries of the fingers and toes, resulting in color changes (pallor, cyanosis, redness) and sensation of cold or numbness in response to cold temperatures or emotional stress.
- Reactive Arthritis/Reiter's Syndrome: An inflammatory arthritis that develops in response to an infection in another part of the body, typically the genitourinary or gastrointestinal tract. It is characterized by joint pain, swelling, and stiffness, along with symptoms such as urethritis, conjunctivitis, and skin lesions.
- Reflex Sympathetic Dystrophy Syndrome (RSD) / Complex Regional Pain Syndrome (CRPS): A chronic pain condition characterized by severe, continuous pain, often affecting one limb, accompanied by changes in skin color, temperature, and sensitivity, as well as abnormal sweating and swelling.
- Relapsing Polychondritis: An autoimmune disorder characterized by recurrent inflammation and destruction of cartilage throughout the body, leading to symptoms such as pain, swelling, and deformity of the ears, nose, joints, and respiratory tract.
- Restless Leg Syndrome (RLS) / Willis-Ekbom Disease: A neurological disorder characterized by an irresistible urge to move the legs, often accompanied by uncomfortable sensations such as crawling, tingling, or burning, typically worsening at night and interfering with sleep.
- Rheumatic Fever: An inflammatory condition that can develop following an untreated or inadequately treated streptococcal infection, characterized by fever, joint pain, skin rash, and inflammation of the heart, joints, and nervous system.
- Rheumatoid Arthritis: An autoimmune disorder characterized by chronic inflammation of the joints, leading to pain, swelling, stiffness, and progressive joint damage. Rheumatoid arthritis can also affect other organs and systems in the body.

- Sarcoidosis, Schmidt Syndrome/Autoimmune Polyendocrine Syndrome Type II (Polyglandular Autoimmune Syndrome, Type 2): A rare autoimmune disorder characterized by the formation of granulomas (inflammatory nodules) in various organs, particularly the lungs and lymph nodes. Schmidt syndrome specifically involves autoimmune thyroiditis, adrenal insufficiency, and type 1 diabetes mellitus.
- Scleritis: An inflammatory condition characterized by inflammation of the sclera (the white outer layer of the eye), leading to eye pain, redness, and decreased vision. Scleritis is often associated with autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus.
- Scleroderma: A chronic autoimmune disease characterized by excessive collagen production, leading to fibrosis and thickening of the skin, as well as involvement of internal organs such as the lungs, heart, kidneys, and gastrointestinal tract.
- Sclerosing Mesenteritis/Mesenteric Panniculitis: A rare inflammatory disorder affecting the mesentery (the tissue that attaches the intestines to the abdominal wall), characterized by inflammation, fibrosis, and fat necrosis, leading to abdominal pain, bloating, and bowel obstruction.
- Serpiginous Choroidopathy: An inflammatory eye condition affecting the choroid (the layer of blood vessels beneath the retina), characterized by the formation of serpentine-shaped lesions, leading to vision loss and distortion.
- Sjögren's Syndrome: An autoimmune disorder characterized by inflammation of the exocrine glands, particularly the salivary and lacrimal glands, leading to dry eyes and mouth, as well as systemic symptoms such as fatigue and joint pain.
- Stiff Person Syndrome (SPS): A rare neurological disorder characterized by progressive muscle stiffness and rigidity, particularly in the trunk and limbs, often triggered by stress or sudden movements.
- Small Fiber Sensory Neuropathy: A disorder affecting the small nerve fibers in the skin, characterized by symptoms such as burning pain, tingling, and numbness, typically in the hands and feet.
- Systemic Lupus Erythematosus (SLE): A chronic autoimmune disease characterized by inflammation and damage to multiple organs and systems in the body, including the skin, joints, kidneys, heart, lungs, and nervous system.

- Subacute Bacterial Endocarditis (SBE): An infection of the heart valves or inner lining of the heart chambers, typically caused by bacteria, leading to symptoms such as fever, fatigue, and heart murmurs, and potentially serious complications such as heart failure or stroke.
- Subacute Cutaneous Lupus: A form of lupus erythematosus characterized by skin lesions that develop in sun-exposed areas, typically as red, scaly patches or ring-shaped lesions, often accompanied by systemic symptoms such as fatigue and joint pain.
- Susac Syndrome: A rare autoimmune disorder characterized by inflammation and blockage of the small blood vessels in the brain, retina, and inner ear, leading to symptoms such as headache, visual disturbances, and hearing loss.
- Sydenham's Chorea: A neurological disorder that can occur as a complication of streptococcal infection, characterized by involuntary movements of the face, limbs, and trunk, as well as emotional lability and behavioral changes.
- Sympathetic Ophthalmia: An autoimmune inflammatory condition affecting the eyes, typically occurring after trauma or surgery to one eye, characterized by inflammation of both eyes and potentially leading to vision loss.
- Takayasu's Arteritis (Vasculitis): An autoimmune condition characterized by inflammation of the large arteries, particularly the aorta and its branches, leading to symptoms such as fatigue, limb pain, and pulselessness, and potentially serious complications such as arterial stenosis or aneurysm.
- Testicular Autoimmunity (Vasculitis, Orchitis): An autoimmune condition characterized by inflammation of the blood vessels in the testes (vasculitis) or inflammation of the testes themselves (orchitis), leading to symptoms such as testicular pain, swelling, and infertility.
- Tolosa-Hunt Syndrome: A rare neurological disorder characterized by severe, unilateral headaches, typically around the eye, caused by inflammation of the cavernous sinus or adjacent structures, often accompanied by eye pain, vision changes, and facial numbness.
- Transverse Myelitis (TM): An inflammatory disorder affecting the spinal cord, characterized by sudden onset of neurological symptoms such as weakness, sensory loss, and bowel/bladder dysfunction, typically occurring over hours to days.

- Tubulointerstitial Nephritis Uveitis Syndrome (TINU): An inflammatory disorder characterized by inflammation of the kidneys (tubulointerstitial nephritis) and the eyes (uveitis), leading to symptoms such as kidney dysfunction and eye pain, redness, and vision changes.
- Ulcerative Colitis (UC): A chronic inflammatory bowel disease characterized by inflammation and ulceration of the inner lining of the colon and rectum, leading to symptoms such as diarrhea, rectal bleeding, abdominal pain, and weight loss.
- Undifferentiated Connective Tissue Disease (UCTD): A condition characterized by symptoms and laboratory findings suggestive of a connective tissue disease (such as lupus or rheumatoid arthritis) but not meeting the criteria for a specific diagnosis.
- Uveitis (Anterior/Intermediate/Posterior): Inflammation of the uvea (the middle layer of the eye), which includes the iris, ciliary body, and choroid. Uveitis can affect different parts of the eye and is classified based on the part of the uvea involved.
- Vasculitis: A group of disorders characterized by inflammation of blood vessels, leading to symptoms such as fatigue, fever, rash, joint pain, and potentially serious complications such as organ damage or failure.
- VEXAS Syndrome: An autoinflammatory syndrome characterized by vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic mutations (VEXAS), leading to symptoms such as recurrent fevers, pulmonary infiltrates, and myelodysplastic syndrome (MDS).
- Vitiligo: A skin condition characterized by the loss of pigment-producing cells (melanocytes), leading to the development of white patches on the skin and hair.
- Vogt-Koyanagi-Harada Syndrome (VKH): A rare autoimmune disorder characterized by bilateral inflammation of the eyes, skin, and nervous system, leading to symptoms such as uveitis, vision changes, hearing loss, and skin pigmentation changes.

As used herein, Systemic lupus erythematosus is a severe chronic autoimmune disease of unknown etiology that can cause multiorgan inflammation and damage. Lupus nephritis is one of the most common and severe disease manifestations, occurring in approximately 31% to 60% of patients with lupus and is more prevalent in certain ethnic groups, such as

African Americans, Asians, and Hispanics (Borchers et al, 2010; Hanly et al, 2016; Mahajan et al, 2020; Anders et al, 2020). Despite recent and substantial progress in the treatment of SLE and LN high unmet needs remain. The production of autoantibodies indicates a principal role for B-cells in SLE pathogenesis.

Lupus nephritis is the most common major organ manifestation of SLE. It affects approximately 31% to 60% of lupus patients and is more prevalent in certain ethnic groups, such as African Americans, Asians, and Hispanics (Borchers et al, 2010; Hanly et al, 2016; Mahajan et al, 2020; Anders et al, 2020). Although renal outcomes have improved with the introduction of immunosuppressive treatment, LN still represents a major risk factor for the long-term outcome of patients with SLE and adversely affects the prognosis, as measured by patient and renal survival rates as well as quality of life and work disability (Furst et al, 2013; Li et al, 2009; Mok et al, 2013; Pelletier et al, 2009; Parikh et al, 2020). Renal survival rates (i.e., survival without dialysis) in recent studies ranged from 83% to 92% at 5 years of follow-up and from 74% to 84% at 10 years of follow-up (Mok et al, 2013). The risk of end stage renal disease (ESRD) is particularly high in patients with diffuse proliferative glomerulonephritis (Mok et al, 2013). Several studies have shown that the standardized mortality ratio of patients with LN is 6-9-fold higher compared to the general population and about 3-fold higher compared to patients with non-renal SLE (reviewed in Mok et al, 2013; Hanly et al, 2016). The mortality rate increases with accumulation of renal damage and is highest in LN patients with ESRD. The life expectancy of SLE patients with renal disease and those with renal damage is reduced by approximately 15 years and 23 years, respectively, compared to the general population (Mok et al, 2013). Lupus nephritis is also a major factor contributing to SLE related hospitalizations and overall health care costs (Furst et al, 2013; Li et al, 2009; Pelletier et al, 2009; Thompson et al, 2022). Proliferative Class III or IV Lupus Nephritis is an aggressive disease that requires prompt and effective therapy. The main goals in the treatment are achieving a prompt response within months, maintaining this response and avoiding flares, to preserve kidney function and reduce the morbidity and mortality associated with chronic kidney disease (CKD) and kidney failure, while minimizing medication-associated toxicities. The initial (induction) treatment may consist of one of the following options as recommended in the recent KDIGO guidelines (Kidney Disease:

Improving Global Outcomes [KDIGO] clinical practice guideline for the management of LN, Kidney Inter, 2024):

- mycophenolate mofetil (MMF 2–3 g/day or mycophenolic acid (MPA) at equivalent dose) or
- MMF in association with calcineurin inhibitor (CI; cvoclosporine or tacrolimus) or
- low-dose intravenous (IV) cyclophosphamide (500 mg × 6 biweekly doses), or
- combination of belimumab with either MMF or reduced dose of cyclophosphamide. They are combined with glucocorticoids (pulses of IV methylprednisolone, then oral prednisone (0.35 to 1 mg/kg/day without exceeding 80 mg/day) (KDIGO, 2024).

Subsequent long-term maintenance treatment follows the initial treatment and includes either MMF (or analogs) as first choice in combination with oral glucocorticoids (< 5 mg/day) or alternative immunosuppressive schemas including either CNIs, azathioprine (AZA), or belimumab as recommended in the KDIGO (KDIGO, 2024). The total duration of initial immunosuppression plus combination maintenance immunosuppression for proliferative LN should be at least 36 months (KDIGO, 2024).

Despite recent important advances in the management of LN a significant proportion of patients either do not respond to first-line immunosuppressive drugs or relapse after having achieved initial remission (Kalloo et al, 2013).

Refractory LN is commonly defined as “no response to standard treatment according to Joint European League Against Rheumatism and European Renal Association- European Dialysis and Transplant Association guidelines, i.e., failure to improve within 3 to 4 months, not achieving partial response after 6 to 12 months, or complete response to standard of care (SOC) therapy after 2 years of treatment (Arora et al, 2022).

This population is associated with high risk of poor outcome including ESRD. Overall 10-year survival rates and renal survival rates reported in patients with partial remission was 76% and 45%, respectively; 45% and 19%, respectively if no remission as opposed to (95% and 94%, respectively) in patients achieving a complete remission (Chen et al, 2008). Similarly, failure to achieve complete response at 6 months predicts relapse and ESRD in the long-term (So et al, 2011). There is an urgent need for developing specific treatment

strategies for refractory LN to limit the risks of poor outcome. Several therapeutic options for the management of these subjects are mentioned in the KDIGO guidelines (KDIGO, 2024). Off-label use of Rituximab has shown encouraging results in the treatment of refractory LN (Alshaiki et al, 2018; Weidenbusch et al, 2013). Other potential alternative therapies have been or are currently under investigation and include various biologics that target B-cells, T-cells or different cytokines (reviewed in Roccatello et al, 2023). Among these potential alternatives, a recent growing body of evidence is supporting the rationale of an anti-CD19 strategy in these cases as recently reported (Mougiakakos et al, 2021; Mackensen et al, 2022; Muller et al, 2024).

In an embodiment, the present invention relates to a molecule comprising a domain that binds CD19 and a domain that binds to a molecule expressed by a T cell (e.g., to CD3) for use in the treatment of a patient suffering from an autoimmune disease/condition, wherein the molecule is formulated for subcutaneous administration. One advantage of the administration of a subcutaneous formulation is the patient comfort and or patient compliance. Patients may not need to be hospitalized, or the hospitalization period may be shortened when compared with continuous intravenous administration of the T cell engaging molecule. In the case of Blinatumomab, the quantity of the present invention relates to a molecule comprising a domain that binds CD19 and a domain that binds to a molecule expressed by an immune effector cell, e.g. a T cell (e.g., to CD3) may be substantially higher than the amount administered via (continuous) intravenous administration.

In an embodiment, the present invention relates to a method of treatment of a patient suffering from an autoimmune disease/condition, wherein said method comprises the steps of administering to said patient a therapeutic dose of a molecule comprising a domain that binds CD19 and a domain that binds a molecule expressed on a T cell, wherein said domain that binds CD19 and the domain that binds to a molecule expressed on a T cell, said patient, and/or said therapeutic dose are as defined in any of the preceding embodiments. Another method comprises the step of selecting a patient suffering from an autoimmune disease or an autoimmune condition eligible for such treatment, particularly a patient who suffers from any or more of the above autoimmune diseases and who is refractory to standard-of-care treatment(s), particularly, wherein the disease is refractory to immunosuppressive treatment, CAR-T cell treatment, treatment by plasmapheresis, treatment for a respective

disease selected from the group comprising treatment with glucocorticoids, cyclophosphamide, azathioprine, rituximab baricitinib, hydroxychloroquine, and ruxolitinib.

Since the administration of a molecule comprising a domain that binds CD19 and a domain that binds a molecule expressed on a T cell may reduce the number of B-cells in a patient, it is suggested to surveil and adapt the treatment in accordance with commonly known measures to monitor, prevent and treat, e.g., infections, fever, and the like, for example, by co-administration or separate administration dependent on the developments of infections, fever, and the like, with antibiotics, fever-reducing medicaments, and the like.

Compound according to the present invention

The molecule according to the present invention bind the CD3 molecule, in separate embodiments, the molecule binds the CD3 epsilon chain on human or macaque lymphocytes. These lymphocytes may be T lymphocytes or cells that have been genetically modified to express CD3 or the CD3 epsilon chain.

The molecule is preferably Blinatumomab or an equivalent thereof, e.g., a molecule that binds selectively to CD19 and has the activity of engaging CD3 positive cells that exert effector functions resulting in selective destruction of the cell expressing CD19 and that is selectively bound by the molecule, for example a molecule that has identical CDR regions. The molecules of the present invention may selectively bind the CD3 epsilon chain. The molecules of the present invention may, in addition to CD19-selective and CD3 epsilon-selective binding domains, comprise an additional domain, e.g., a half-life extending domain as known in the art (e.g., Mandrup et al., Communications Biology volume 4, Article number: 310 (2021); Suurs et al., J Nucl Med. 2021 Dec; 62(12): 1797–1804.).

Methods of treatment

The present invention relates to a method of treating or ameliorating an autoimmune disease in a patient using a molecule as defined herein above and comprising the steps:

- Administering said molecule to said patient in a first treatment cycle;
- Wherein at least one or two individual doses of a first quantity of said molecule are administered in a first predetermined period;

- Optionally wherein at least two individual doses of a second quantity of said molecule are administered in a second predetermined period.

As used herein, the terms "first quantity", "second quantity", etc., define the individual amounts of a drug, e.g., Blinatumomab, that is administered at a given point in time. In other words, combined "quantities" of the drug will be administered over a period of time, which, for the sake of the present disclosure, is defined as a "predetermined period" preceded by a specific number. This means that the present inventors have identified respective periods in which it is beneficial to administer a medication and thereby provide "predetermined period(s)" that are applied in steps of the methods and the uses of the present invention. Consequently, a "treatment cycle" is composed of various "predetermined periods". As used herein, the first period may comprise one day to several weeks, e.g. 3 days, 5 days, 7 days. As used herein, the first quantity may be as described above, e.g., 9 µg day in adult patients or patients weighing at least 45 kg, or the first quantity may be 5 µg/m2/day in pediatric patients or patients or patients weighing less than 45 kg. As used herein, the second period may comprise one day to several weeks, e.g. 3 days, 5 days, 7 days. As used herein, the second quantity may be as described above, e.g., 9 µg day in adult patients or patients weighing at least 45 kg, or the first quantity may be 5 µg/m2/day in pediatric patients or patients or patients weighing less than 45 kg. As used herein, a subsequent period may comprise one day to several weeks, e.g. 3 days, 5 days, 7 days, but up to 45 days or more, e.g., 40 days. As used herein, the subsequently administered quantity may be as described above, e.g., 9 to 56, e.g., 28 µg day in adult patients or patients weighing at least 45 kg, or the first quantity may be 5 to 30, e.g., 15 µg/m2/day in pediatric patients or patients or patients weighing less than 45 kg. In one embodiment, blinatumomab is administered to patients in a fourth cycle for at least 7 days to 14 days, particularly for 10 days (particularly to patients with systemic sclerosis or SLE, or patients with Rheumatoid Arthritis).

Further, the present invention relates to a method according to any preceding embodiment, wherein said first treatment cycle is preceded by and/or followed by at least one additional treatment cycle. The additional treatment cycle may either precede the first treatment cycle or follow said cycle or both. In embodiments, the medication administered in the first treatment cycle is identical to the medication in the preceding and/or following cycles. The

medication in these cycles may be administered using a different or the same administration mode, i.e. the drug may be administered intravenously or per continuous intravenous infusion as in the first treatment cycle, or it may be administered, for example, intravenously. Further, the medication comprises the administration of a T cell engaging polypeptide construct, particularly a T cell engager such as Blinatumomab.

Further, the present invention relates to a method according to any of the preceding embodiments, wherein a third predetermined treatment-free period precedes and/or follows said first treatment cycle.

Further, the present invention relates to a method according to any of the preceding embodiments, wherein the patient has been subject to at least one of the following treatments preceding the administration of the TCE according to the present invention, wherein said preceding treatments is selected from the group comprising cIV administration of a T cell engaging polypeptide construct, particularly with a CD19-specific CAR T-cell therapy, and/or administration of a CD20-targeting agent, and/or administration of an corticosteroid and/or any form of chemotherapy and/or any other immune suppressive therapy

- Selecting a patient suffering from an autoimmune disease or autoimmune condition;
- Administering Blinatumomab to said patient in a first treatment cycle,

wherein said patient receives 5-20 μg of blinatumomab, preferably about 7-12, e.g., 9 μg daily.

Subsequently, in another treatment cycle the patient receives 5-20 μg of blinatumomab, preferably about 7-12, e.g., 9 μg daily.

Subsequently, in another treatment cycle the patient receives 15 to 112 μg of blinatumomab, preferably about 28 to 56, e.g., 28 μg daily.

Further, the present invention relates to a method according to any of the preceding embodiments, wherein a patient (e.g., a patient with systemic sclerosis, particularly with severe prior treatment resistant systemic sclerosis, wherein said patient is administered with, 28 μg daily of blinatumomab for about 7 to 14 days, preferably for about 10 days in

a fourth cycle following initial two cycles of administration of 9 µg daily for 5 days each, and a third cycle where the dose is increased to 28 µg daily for 5 days. In one embodiment blinatumomab is administered as single agent during these cycles.

Further, the present invention relates to a method according to any of the preceding embodiments, wherein the patient is a pediatric patient that has been subject to at least one of the following treatments preceding the administration of the TCE according to the present invention, wherein said preceding treatments is selected from the group comprising cIV administration of a T cell engaging polypeptide construct, particularly with a CD19-specific CAR T-cell therapy, and/or administration of a CD20-targeting agent, and/or administration of an corticosteroid and/or any form of chemotherapy and/or any other immune suppressive therapy

- Selecting a pediatric patient suffering from an autoimmune disease or autoimmune condition;
- Administering Blinatumomab to said patient in a first treatment cycle,

wherein said patient receives 3-15 µg of blinatumomab, preferably about 4-12, e.g., 5 µg/m2/daily.

Subsequently, in another treatment cycle the patient receives 5-20 µg of blinatumomab, preferably about 4-12, e.g., 5 µg/m2/daily.

Subsequently, in another treatment cycle the patient receives 15 to 112 µg of blinatumomab, preferably about 4-12, e.g., 15 µg/m2/daily.

Further, the treatment may be followed by at least one additional cycle, wherein said patient receives 5-20 µg of Blinatumomab, preferably about 7-12, e.g., 9 µg daily.

In further embodiments, the present invention relates to uses of the herein described B cell-depleting agents, particularly Blinatumumab, in the preparation of a medicament wherein said medicament is suitably adapted or prepared for administration to a patient in need thereof according to any of the above-mentioned methods / dosing regimen.

In still further embodiments, the present invention relates to apparatus that either comprising a containment device or that can be connected with such a containment device, wherein the containment device (e.g., a syringe, a vessel, etc.) comprises an of the herein described B cell-depleting agents, particularly Blinatumumab, suitably adapted or prepared for administration to a patient in need thereof according to any of the above-mentioned methods / dosing regimen.

Yet other embodiments of the invention relate to kits-of-parts that comprise dosage units suitably adapted or prepared for administration to a patient in need thereof according to any of the above-mentioned methods / dosing regimen. Such kits may comprise an injection device, e.g., a syringe, injection needles, vessels comprising liquids for reconstitution of freeze-dried active agents and/or additives, particularly for blinatumumab, or ready-prepared formulations in individual dosage units. Individual dosage units may be color-coded to select the appropriate dose to be administered at a given time-point of the inventive dosing regimen. Of course, kits may also comprise technical information in form of hard copies or in digitalized form.

The term “patient” includes all humans, including children and adults. When used herein, the term “subject” is used interchangeably with the term “patient”. What is disclosed with reference to a “patient” herein also applies to a group of patients, mutatis mutandis.

The uses and methods of the present invention involve administration of a (therapeutically effective amount of) molecule to a patient (or a group of patients).

In further embodiments, the molecule of the present invention, e.g., blinatumomab, is used for the preparation of a medicament for the treatment of an autoimmune disease / autoimmune condition as defined in any of the above embodiments.

It is noted that, instead of referring to a molecule binding CD19 and CD3, it is also contemplated in the herein described uses and methods to administer NK cell binding molecules, which activate NK cells to exert their cytolytic potential upon formation of a close enough contact between a target cell and an NK cell. In such a case, the polypeptide binds to a target antigen such as CD19 and to an NK cell-specific antigen establishing a proximity between target cell and effector cell that permits an activated NK cell to effectively lyse or otherwise kill the target cell.

The term "a molecule comprising a domain binding CD19 and a domain binding CD3", or related terms in accordance with the present invention mean molecules resulting from joining at least two antibody variable regions in a single polypeptide chain devoid of the constant and/or Fc portion(s) present in full immunoglobulins. A "linker" as used herein connects V domains of the same specificity, whereas a "spacer" as used herein connects V domains of different specificities. For example, a bispecific single chain T cell engager may be a construct with a total of two antibody variable regions, for example two VH regions, each capable of specifically binding to a separate antigen, and connected with one another through a short (usually less than 10 amino acids) synthetic polypeptide spacer such that the two antibody variable regions with their interposed spacer exist as a single contiguous polypeptide chain. Another example of a bispecific single chain T cell engager may be a single polypeptide chain with three antibody variable regions. Here, two antibody variable regions, for example one VH and one VL, may make up an scFv, wherein the two antibody variable regions are connected to one another via a synthetic polypeptide linker, the latter often being genetically engineered to be minimally immunogenic while remaining maximally resistant to proteolysis. This scFv is capable of specifically binding to a particular antigen, and is connected to a further antibody variable region, for example a VH region, capable of binding to a different antigen than that bound by the scFv. Yet another example of a bispecific single chain T cell engager may be a single polypeptide chain with four antibody variable regions. Here, the first two antibody variable regions, for example a VH region and a VL region, may form one scFv capable of binding to one antigen, whereas the second VH region and VL region may form a second scFv capable of binding to another antigen. Within a single contiguous polypeptide chain, individual antibody variable regions of one specificity may advantageously be separated by a synthetic polypeptide linker as described above, whereas the respective scFvs may advantageously be separated by a short polypeptide spacer as described above. Non-limiting examples of bispecific single chain T cell engagers as well as methods for producing them are shown in WO 99/54440, WO 2004/106381, Mack, J. Immunol. (1997), 158, 3965-70; Mack, PNAS, (1995), 92, 7021-5; Kufer, Cancer Immunol. Immunother., (1997), 45, 193-7; Löffler, Blood, (2000), 95, 6, 2098-103; Brühl, J. Immunol., (2001), 166, 2420-2426. As used herein, the above terms can also be extended to T cell engaging molecules that have more than one domain that binds to a tumor-associated antigen. This means that at least two domains can bind to at least two antigenic sides on the same or different tumor associated targets. Similarly, the T

cell engaging part of the respective molecule may bind to at least two antigens expressed by a T cell (or, as the case may be, an NK cell). These two antigens may be identical, e.g. two identical antigens on two identical cell surface proteins or two different antigens on either the same protein or on different proteins may be bound. It is noted that T cell engagers according to the present invention may comprise a half-life extending domain, such as disclosed, for example, in WO2017/134140, particularly those disclosed in the claims and in Figure 1, which explicitly refers to certain Fc constructs, and T cell engagers comprising a human serum albumin component.

As used herein, "human CD3" denotes an antigen that is expressed on human T cells as part of the multimolecular T cell receptor complex, the CD3 consisting of five different chains: CD3-epsilon, CD3-gamma, CD3-delta, CD3-eta and CD3 zeta. Clustering of CD3 on T cells e.g. by anti-CD3 antibodies leads to T cell activation similar to the binding of an antigen but independent from the clonal specificity of the T cell subset, as described above. Thus, the term "a molecule/bispecific single chain T cell engager polypeptide construct specifically binding with one of its domains the human CD3 antigen" as used herein relates to a CD3-specific construct capable of binding to the human CD3 complex expressed on human T cells and capable of inducing elimination/lysis of target cells, wherein such target cells carry/display an antigen which is bound by the other, non-CD3-binding portion of the bispecific single chain T cell engager. Binding of the CD3 complex by CD3-specific binders (e.g. a bispecific single chain T cell engager polypeptide construct as administered according to the pharmaceutical means and methods of the invention) leads to activation of T cells as known in the art; see e.g. WO 99/54440 or WO 2004/106381. Accordingly, a construct appropriate for the pharmaceutical means and methods of the invention is advantageously able to eliminate/lyse target cells in vivo and/or in vitro. Preferably, said second domain is human CD19 which has already been described in WO 99/54440 or WO 2004/106381. According to this embodiment, each antigen-specific portion of the bispecific single chain T cell engager comprises an antibody VH region and an antibody VL region. Advantageous variants of this bispecific single chain T cell engager are from N terminus to C terminus:

VL(CD19)-VH(CD19)-VH(CD3)-VL(CD3),

VH(CD19)-VL(CD19)-VH(CD3)-VL(CD3),

VH(CD3)-VL(CD3)-VH(CD19)-VL(CD19), or

VH(CD3)-VL(CD3)-VL(CD19)-VH(CD19).

More particularly, within the meaning of the invention, the term "binding" or related terms is/are to be understood as being characterized primarily by two parameters: a qualitative parameter (the binding epitope, or where an antibody or an inventive molecule binds) and a quantitative parameter (the binding affinity, or how strongly this molecule binds where it does). Which epitope is bound by an antibody can advantageously be determined by e.g. FACS methodology, ELISA, peptide-spot epitope mapping, or mass spectroscopy. The strength of an antibody or an inventive T cell engager binding to a particular epitope may advantageously be determined by e.g. known Biacore and/or ELISA methodologies. A combination of such techniques allows the calculation of a signal:noise ratio as a representative measure of binding specificity. In such a signal:noise ratio, the signal represents the strength of antibody or T cell engager binding to the epitope of interest, whereas the noise represents the strength of antibody or T cell engager binding to other, non-related epitopes differing from the epitope of interest. A signal:noise ratio of, for example at least 50, but preferably about 80 for a respective epitope of interest as determined e.g. by Biacore, ELISA or FACS may be taken as an indication that the antibody evaluated binds the epitope of interest in a specific manner, i.e. is a "specific binder". The term "binding to/interacting with" may also relate to a conformational epitope, a structural epitope or a discontinuous epitope consisting of two regions of the human target molecules or parts thereof. In context of this invention, a conformational epitope is defined by two or more discrete amino acid sequences separated in the primary sequence which come together on the surface of the molecule when the polypeptide folds to the native protein (Sela, (1969) Science 166, 1365 and Laver, (1990) Cell 61, 553-6). The term "discontinuous epitope" means in context of the invention non-linear epitopes that are assembled from residues from distant portions of the polypeptide chain. These residues come together on the surface of the molecule when the polypeptide chain folds into a three-dimensional structure to constitute a conformational/structural epitope.

According to the present invention the term "variable region" used in the context with Ig-derived antigen-interaction comprises fragments and derivatives of polypeptides which at least comprise one CDR derived from an antibody, antibody fragment or derivative thereof.

It is envisaged by the invention, that said at least one CDR is preferably a CDR3, more preferably the CDR3 of the heavy chain of an antibody (CDR-H3). However, other antibody derived CDRs are also particularly comprised by the term "variable region".

Molecule of the present invention binding CD19 and CD3

The uses and methods of the present invention involve administration of a (therapeutically effective amount of) molecule for use according to the present invention.

In general, any route of administration is conceivable depending, e.g., on the formulation, bioavailability and mechanism of action of the molecule for use according to the present invention. However, in the context of the present invention, the molecule for use according to the present invention can be administered intravenously, e.g., per continuous administration, or it can be administered parenterally, e.g., via subcutaneous administration.

By "therapeutically effective amount" is meant an amount of the molecule for use according to the present invention that elicits a desired therapeutic effect, e.g., alleviation or amelioration (complete or partial) of the symptoms or condition of the patient (or group of patients), or any other desired improvement in the patient's (or group of patients') symptoms, disease or condition. The exact amount dose may depend on, e.g., age, body weight, general health, gender, diet, drug interaction and the severity of the condition, as will be ascertainable with routine experimentation by those skilled in the art.

The term molecule for use according to the present invention, e.g., a polypeptide construct, includes agents that directly or indirectly destroy some or a therapeutically relevant number of B-cells, e.g. by induction of cell death signals, antibody dependent cell-mediated cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), or engagement of cytotoxic T-cells, and agents that block B cell activation or development. The term “B-cell” includes progenitor (or pre-pro) B cells, early pro (or pre-pre)-B cells, late pro (or pre-pre)-B cells, large pre-B cells, small pre-B cells, immature B cells and mature B cells. B cell depletion can be partial or complete, i.e. affect all B-cells or subpopulations of B-cells. Preferred T cell engaging polypeptide constructs for use in the methods of the invention can reduce (or maintain) the level of B-cells in the blood of a patient (or group of patients) within a predefined period of time to one B-cell/ml serum or less as ascertainable by the skilled person using routine experimentation as described herein. It is in particular

envisaged that T cell engaging polypeptide constructs used in the methods of the invention are capable of depleting peripheral CD19+ B-cells.

Without wishing to be bound by theory, it is thought that Blinatumomab transiently links CD19+ B cells to CD3+ T-cells, thereby inducing T-cell mediated serial lysis of B-cells and concomitant T-cell proliferation.

Blinatumomab comprises the

(a) anti-CD3 CDRs of the heavy chain shown as CD3 CDR-H1 in SEQ ID NO: 11 (GYTFTRYTMH), CD3 CDR-H2 in SEQ ID NO: 12 (YINPSRGYTNYNQKFKD) and CD3 CDR-H3 in SEQ ID NO: 13 (YYDDHYCLDY); and/or

(b) anti-CD3 CDRs of the light chain shown as CD3 CDR-L1 in SEQ ID NO: 14 (RASSSVSYMN), CD3 CDR-L2 in SEQ ID NO: 15 (DTSKVAS) and CD3 CDR-L3 in SEQ ID NO: 16 (QQWSSNPLT); and/or

(c) anti-CD19 CDRs of the heavy chain shown as CD19 CDR-H1 in SEQ ID NO: 17 (GYAFSSYWMN), CD19 CDR-H2 in SEQ ID NO: 18 (QIWPGDGDTNYNGKFKG) and CD19 CDR-H3 in SEQ ID NO: 19 (RETTTVGRYYYAMDY); and/or

(d) anti-CD19 CDRs of the light chain shown as CD19 CDR-L1 in SEQ ID NO: 20 (KASQSVDYDGDSYLN), CD19 CDR-L2 in SEQ ID NO: 21 (DASNLVS) and CD19 CDR-L3 in SEQ ID NO: 22 (QQSTEDPWT).

[0001] Further, Blinatumomab comprises the

(a) CD19 binding variable heavy chain shown in SEQ ID NO: 3 (nucleotide sequence is shown in SEQ ID NO: 4); and/or

(b) CD19 binding variable light chain shown in SEQ ID NO: 5 (nucleotide sequence is shown in SEQ ID NO: 6); and/or

(c) CD3 binding variable heavy chain shown in SEQ ID NO: 7 (nucleotide sequence is shown in SEQ ID NO: 8); and/or

(d) CD3 binding variable light chain shown in SEQ ID NO: 9 (nucleotide sequence is shown in SEQ ID NO: 10).

In a further alternative, the molecule for use according to the present invention comprises an amino acid sequence selected from the group consisting of

(a) an amino acid sequence as depicted in SEQ ID NO: 1;

(b) an amino acid sequence encoded by a nucleic acid sequence as shown in SEQ ID NO: 2;

(c) an amino acid sequence encoded by a nucleic acid sequence having at least 70%, 80%, 90%, 95% or 99% identity to a nucleic acid sequence of (b), wherein said amino acid sequence is capable of binding to CD3 and CD19; and

(d) an amino acid sequence encoded by a nucleic acid sequence which is degenerate as a result of the genetic code to a nucleotide sequence of (b), wherein said amino acid sequence is capable of binding to CD3 and CD19.

The CD3 binding domain of a CD3 x CD19 binding molecule as used herein may preferably comprise a VL region and a VH region selected from the group consisting of:

The CD19 binding domain of a CD19 x CD3 binding molecule as used herein is preferably characterized by the VH and/or VL regions or CDRs as described herein for Blinatumomab.

The molecule of the present invention may also comprise the herein described CDR regions in the context of a humanized construct. The molecule of the invention may also be modified to permit its binding of non-human primates, such as monkeys, for example cynomolgus monkeys.

It is envisaged that the number of B-cells in the blood of the patient (or group of patients) remains or falls below detection limit of one B cell/ml serum within the predefined period of time as defined herein.

In general, B-cell numbers can be evaluated through several techniques available in the art, e.g. using the white blood cell (WBC, or leukocytes) count and differential. White blood cells can be counted manually in hemocytometers (Neubauer chamber) or with automated counters. To determine the differential, a drop of blood can be thinly spread over a glass slide, air dried, and stained with a Romanofsky stain, most commonly the Wright or May-

Grunewald-Giemsa technique. Cells are then counted and classified using morphologic examination and/or histochemistry as described in Blumenreich MS. The White Blood Cell and Differential Count. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 153. Alternatively, leukocytes are isolated from a blood sample and stained with fluorescent-labeled antibodies against lymphocyte cell surface markers and subsequently analyzed by flow cytometry as described in the appended examples. Percentages of each type of lymphocyte are multiplied with absolute lymphocyte numbers to calculate absolute cell numbers for each lymphocyte subpopulation.

It is envisaged that the number of B-cells in the blood of the treated patient (or treated group of patients) remains or falls below one B-cell/ml serum within a predefined period of time after the initial treatment with said T cell engaging polypeptide construct. The initial treatment with the administered molecule as used herein preferably means a first treatment with said molecule, i.e. the patient (or group of patients) has not received the molecule before. Said patient (or group of patients) may, however, have received further treatments as described above. It is also conceivable that the patient (or group of patients) has received another CD19 and CD3 binding molecule before the initial treatment with the applied molecule for use according to the present invention. E.g., when a first molecule for use has no therapeutic effect, and/or fails to reduce (or maintain) the number of B-cells in the blood of a patient (or group of patients) to one B-cell/ml serum or less, a second molecule comprising domains binding to CD19 and CD3 may be used. The initial treatment with the second molecule will then start on the first day of treating the patient (or group of patients) with the second molecule. That is, it is conceivable to apply the methods of the invention repeatedly (i.e., in several cycles) with different molecules, the "initial treatment" starting at the day of first treatment with the molecule of the respective cycle. The term "different" molecule binding CD19 and CD3 also includes the same molecule as used in a preceding cycle, but in a different formulation, concentrations, or the like. It is also conceivable to repeat several cycles of treatment with the same molecule until the desired level of B-cells in the blood of the patient (or group of patients) is achieved.

The "predefined period of time" in which the number of B-cells remains or falls below one B-cell/ml serum is envisaged to be 15 days or less, i.e. 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3 days or less. The length of the predefined period of time is ascertainable by the skilled

person in the art and may depend on the molecule for use according to the present invention, its concentration, treatment regimen, the type of autoimmune disease to be treated, and the like. Without wishing to be bound by theory, it is thought that when the number of B-cells can be adjusted to the desired number below detection limit of one B-cell/ml serum or less within the predefined period of time, subsequent treatment is likely to be effective. A possible reason is the expansion of the T- and/or TEM-cell population in patients exhibiting a clearance of (peripheral) B cells, which may enhance the clinical activity of subsequent therapies employing the cytotoxic potential of the T-cell system. "Subsequent treatment" may comprise further treatment with the molecule for use according to the present invention applied in the inventive method, with another molecule for use according to the present invention, further treatment as described herein or combinations thereof after the B-cell numbers have been successfully reduced to (or maintained at) one B-cell per ml/serum or less within the predefined period of time. It is in general also conceivable that no subsequent treatment is necessary. In accordance with the foregoing, the methods of the invention therefore allow stratification of patients (or groups of patients), i.e. sorting patients (or groups of patients) into those who may or may benefit from subsequent therapy. Also, it is envisaged that patients (or groups of patients) in which the number of B-cells in the blood can be reduced to or maintained at one B-cell/ml serum or less within the predefined period of time are likely to benefit from subsequent therapy, while patients in which the number of B-cells in the blood exceeds one B-cell/ml serum within the predefined period of time, are not likely to benefit from subsequent therapy.

In the aforementioned method, the number of B-cells in the blood of a patient (or group of patients) having received a molecule for use according to the present invention is monitored/determined after a first predefined period of time after the initial treatment with said B cell depleting agent. Means and methods for determining/monitoring the number of B-cells in the blood of a patient (or group of patients) have been defined elsewhere herein. Notably, the first period of time is shorter than the predefined period of time as defined elsewhere herein, and is preferably between 2 and 14 days, i.e. 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days. Step (b) of the inventive method is useful in determining whether or not the patient is responsive to the administration of said molecule for use according to the present invention, i.e. in stratifying patients into those likely to benefit from subsequent treatment after the first predefined period of time and those who are not. If the number of

B-cells remains or falls below one B cell/ml serum within said first predefined period of time, then subsequent treatment is likely to be therapeutically effective.

If, however, the molecule for use according to the present invention, e.g., fails to reduce or maintain the number of B-cells at the desired level of one B-cell/ml serum or less within the first predefined period of time, then the molecule for use according to the present invention can be adjusted such that the number of B-cells in the blood of the patient (or group of patients) remains or falls below one B cell/ml serum within a predefined period of time of preferably 15 days or less after the initial treatment with said B cell depleting agent, i.e., the molecule for use according to the present invention.

In general, the first predefined period of time and the predefined period of time can be of any length, as long as the first predefined period of time is shorter than the predefined period of time. Both periods of time start with the first day of initial treatment with the molecule for use according to the present invention applied in the inventive methods, i.e. on the same day. The skilled practitioner will readily be able to determine the desired length of the first predefined period of time, depending on, e.g., the molecule for use according to the present invention, its concentration, formulation, treatment regiment, the type, the physical constitution and findings of the patient (or group of patients), and the predefined period of time.

Adjustment of dose

Methods of the invention may further involve “adjusting” the molecule for use according to the present invention. The term “adjusting” refers to an intentional modification of the molecule for use according to the present invention in order to achieve a number one B-cell/ml serum or less in the treated patient (or group of patients). Thus, the number of B-cells in the blood of a patient is used to adjust the dosage or treatment regimen with the molecule for use according to the present invention such that the number of B-cells in the blood of said patient remains or falls below one B cell/ml serum within a (first) predefined period of time after the initial treatment with said B cell depleting agent. The adjustment (intentional modification) may involve modification of the dosage, treatment regimen, formulation, or the like. For example, if the number of B-cells in the blood of a patient exceeds one B cell/ml serum within a (first) predefined period, a higher dosage of molecule

for use according to the present invention may be administered, or the molecule for use according to the present invention may be administered for a prolonged period of time.

The exact dosage of molecule for use according to the present invention will depend on the purpose of the treatment (e.g. remission maintenance vs. acute flare of disease), type of disease, route of administration, age, body weight, general health, gender, diet, time of administration, drug interaction and the severity of the condition, and will be ascertainable by one skilled in the art using known techniques.

Generally, any modification is conceivable as long as it preferably results in the number of B-cells in the blood of the treated patient (group of patients) being reduced to or maintained at a number of one B-cell/ml serum or less within the predefined period of time. The modification may also include additionally applying further treatments as described herein, and/or administering another T cell engaging polypeptide construct.

Treatment

The term “treatment” in all its grammatical forms includes therapeutic or prophylactic treatment of autoimmune diseases, e.g. of Acromegaly, Acquired aplastic anemia, Acquired hemophilia, Agammaglobulinemia, primary, Alopecia areata, Ankylosing spondylitis (AS), Anti-NMDA receptor encephalitis, Antiphospholipid syndrome (APS) | catastrophic antiphospholipid syndrome (CAPS) / Asherson's syndrome, Arteriosclerosis, Autoimmune Addison’s disease (AAD), Autoimmune autonomic ganglionopathy (AAG) / autoimmune dysautonomia | autoimmune gastrointestinal dysmotility (AGID), Autoimmune encephalitis | acute disseminated encephalomyelitis (ADEM), Autoimmune gastritis, Autoimmune hemolytic anemia (AIHA), Autoimmune hepatitis (AIH), Autoimmune hyperlipidemia, Autoimmune hypophysitis/lymphocytic hypophysitis, Autoimmune inner ear disease (AIED), Autoimmune lymphoproliferative syndrome (ALPS), Autoimmune myelofibrosis, Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis (AIP), Autoimmune polyglandular syndromes, types I, II, & III (APS type 1, APS type 2, APS type 3, APECED), Autoimmune progesterone dermatitis, Autoimmune retinopathy (AIR), Autoimmune sudden sensorineural hearing loss (SNHL), Balo disease, Behçet’s disease, Birdshot chorioretinopathy / birdshot uveitis, Bullous pemphigoid, Castleman disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating

polyneuropathy (CIDP), Chronic autoimmune urticaria, Churg-Strauss syndrome / eosinophilic granulomatosis with polyangiitis (EGPA) , Cogan's syndrome, Cold agglutinin disease, CREST syndrome | limited cutaneous systemic sclerosis, Crohn's disease (CD), Cronkhite-Canada syndrome (CSS), Cryptogenic organizing pneumonia (COP), Dermatitis herpetiformis, Dermatomyositis, Diabetes, type 1, Discoid lupus, Dressler's syndrome / postmyocardial infarction / postpericardiotomy syndrome, Eczema/Atopic Dermatitis, Endometriosis, Eosinophilic esophagitis/eosinophilic gastroenteritis, Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibrosing alveolitis/Idiopathic pulmonary fibrosis (IPF), Giant cell arteritis / temporal arteritis / Horton's disease, Giant Cell Myocarditis, Glomerulonephritis, Goodpasture's syndrome / anti-GBM/anti-TBM disease, Granulomatosis with polyangiitis (GPA) / Wegener's granulomatosis, Graves' disease / thyroid eye disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis / chronic lymphocytic thyroiditis / autoimmune thyroiditis, Henoch-Schönlein purpura / IgA vasculitis, Hidradenitis suppurativa, Hurst's disease / acute hemorrhagic leukoencephalitis (AHLE), Hypogammaglobulinemia, IgA nephropathy / Berger's disease, Immune-mediated necrotizing myopathy (IMNM), Immune thrombocytopenia (ITP) / autoimmune thrombocytopenic purpura / autoimmune thrombocytopenia, Inclusion body myositis, IgG4-related sclerosing disease (ISD), Interstitial cystitis, Juvenile idiopathic arthritis / Adult-onset Still's disease, Juvenile polymyositis | Juvenile dermatomyositis | juvenile myositis, Kawasaki disease, Lambert-Eaton myasthenic syndrome (LEMS), Leukocytoclastic vasculitis, Lichen planus | Lichen planopilaris, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD) | linear IgA bullous dermatosis (LABD), Lupus nephritis, Lyme disease / chronic Lyme disease / post-treatment Lyme disease syndrome (PTLDS), Lymphocytic colitis/microscopic colitis, Lymphocytic hypophystitis/autoimmune hypophystitis, Ménière's disease, Microscopic polyangiitis (MPA)/ANCA-associated vasculitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal motor neuropathy, Multiple sclerosis (MS), Myalgic encephalomyelitis (ME)/ Chronic fatigue syndrome (CFS), Myasthenia gravis (MG), Narcolepsy, Neuromyelitis Optica/Devic's disease, Ocular cicatricial pemphigoid, Opsoclonus-myoclonus syndrome (OMS), Palindromic rheumatism, Paraneoplastic cerebellar degeneration, Paraneoplastic pemphigus, Parry-Romberg syndrome (PRS)/Hemifacial atrophy (HFA)/Progressive facial hemiatrophy, Paroxysmal nocturnal

hemoglobinuria (PNH), Peripheral uveitis/pars planitis, PANS/PANDAS, Parsonage-Turner syndrome, Pemphigus gestationis / herpes gestationis, Pemphigus foliaceus, Pemphigus vulgaris, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Postural orthostatic tachycardia syndrome (POTS), Primary biliary cirrhosis (PBC) / primary biliary cholangitis, Primary sclerosing cholangitis (PSC), Psoriasis, Palmoplantar Pustulosis, Psoriatic arthritis, Pulmonary fibrosis, idiopathic (IPF), Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Rasmussen's encephalitis, Raynaud's syndrome/phenomenon, Reactive arthritis / Reiter's syndrome, Reflex sympathetic dystrophy syndrome (RSD) / Complex regional pain syndrome (CRPS), Relapsing polychondritis, Restless leg syndrome (RLS) / Willis-Ekbom disease, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome / autoimmune polyendocrine syndrome type II / polyglandular autoimmune syndrome, type 2, Scleritis, Scleroderma, Sclerosing Mesenteritis / Mesenteric Panniculitis, Serpiginous choroidopathy, Sjögren's syndrome, Stiff person syndrome (SPS), Small fiber sensory neuropathy, s erythematosus (SLE), Subacute bacterial endocarditis (SBE), Subacute cutaneous lupus, Susac syndrome, Sydenham's chorea, Sympathetic ophthalmia, Takayasu's arteritis (vasculitis), Testicular autoimmunity (vasculitis, orchitis), Tolosa-Hunt syndrome, Transverse myelitis (TM), Tubulointerstitial nephritis uveitis syndrome (TINU), Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis anterior/intermediate/posterior, Vasculitis, VEXAS Syndrome, Vitiligo, Vogt-Koyanagi-Harada syndrome (VKH).

A "therapeutic or prophylactic treatment" comprises prophylactic treatments aimed at the complete prevention of clinical and/or pathological manifestations or therapeutic treatment aimed at amelioration or remission of clinical and/or pathological manifestations. The term "treatment" thus also includes the amelioration or prevention of autoimmune diseases, e.g. SLE, sclerosis, MG, and RA, to mention a few.

The term "treatment" as used herein means in the broadest sense medical procedures or applications that are intended to relieve illness. In the present case, the administration of a T cell engaging polypeptide construct (prepared for administration to a patient) as described herein is for the treatment, amelioration or elimination of autoimmune diseases in patients.

In particular, the present invention relates to the treatment of patients with the above-mentioned autoimmune conditions that do not respond to standard of care treatment or show signs of adverse effects due to standard of care treatment.

In embodiments of the present invention, the administration of a drug reducing or preventing the occurrence of CRS (Cytokine Release Syndrome), e.g., dexamethasone, may occur prior to or concomitantly or following the administration of the molecule that binds CD19 as described in the present disclosure. In additional embodiments of the present invention, the administration of a drug reducing or preventing the occurrence of allergic reactions, e.g., dexamethasone or another corticosteroid may occur prior to or concomitantly or following the administration of the molecule that binds CD19 as described in the present disclosure.

Further methods of treatment are described below:

- A method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3, wherein the first domain comprises the CDR 1, 2, and 3 sequences of a variable light chain depicted in SEQ ID NOs: 20, 21, and 22, and the CDR 1, 2, and 3 sequences of the variable heavy chain depicted in SEQ ID NOs: 17, 18, and 19.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to the preceding embodiment, wherein said molecule is a single chain polypeptide.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the first domain comprises the sequence of the variable light chain depicted in SEQ ID NO: 5 and the sequence of the variable heavy chain depicted in SEQ ID NO: 3.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any

one of the preceding embodiments, wherein the molecule comprises a sequence as depicted in SEQ ID NO: 1.

- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is blinatumomab.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the disease is selected from the group comprising Acromegaly, Acquired aplastic anemia, Acquired hemophilia, Agammaglobulinemia, primary, Alopecia areata, Ankylosing spondylitis (AS), Anti-NMDA receptor encephalitis, Antiphospholipid syndrome (APS) | catastrophic antiphospholipid syndrome (CAPS) / Asherson's syndrome, Arteriosclerosis, Autoimmune Addison's disease (AAD), Autoimmune autonomic ganglionopathy (AAG) / autoimmune dysautonomia | autoimmune gastrointestinal dysmotility (AGID), Autoimmune encephalitis | acute disseminated encephalomyelitis (ADEM), Autoimmune gastritis, Autoimmune hemolytic anemia (AIHA), Autoimmune hepatitis (AIH), Autoimmune hyperlipidemia, Autoimmune hypophysitis/lymphocytic hypophysitis, Autoimmune inner ear disease (AIED), Autoimmune lymphoproliferative syndrome (ALPS), Autoimmune myelofibrosis, Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis (AIP), Autoimmune polyglandular syndromes, types I, II, & III (APS type 1, APS type 2, APS type 3, APECED), Autoimmune progesterone dermatitis, Autoimmune retinopathy (AIR), Autoimmune sudden sensorineural hearing loss (SNHL), Balo disease, Behçet's disease, Birdshot chorioretinopathy / birdshot uveitis, Bullous pemphigoid, Castleman disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic autoimmune urticaria, Churg-Strauss syndrome / eosinophilic granulomatosis with polyangiitis (EGPA) , Cogan's syndrome, Cold agglutinin disease, CREST syndrome | limited cutaneous systemic sclerosis, Crohn's disease (CD), Cronkhite-Canada syndrome (CSS), Cryptogenic organizing pneumonia (COP), Dermatitis herpetiformis, Dermatomyositis, Diabetes, type 1, Discoid lupus, Dressler's syndrome /

postmyocardial infarction / postpericardiotomy syndrome, Eczema/Atopic Dermatitis, Endometriosis, Eosinophilic esophagitis/eosinophilic gastroenteritis, Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibrosing alveolitis/Idiopathic pulmonary fibrosis (IPF), Giant cell arteritis / temporal arteritis / Horton's disease, Giant Cell Myocarditis, Glomerulonephritis, Goodpasture's syndrome / anti-GBM/anti-TBM disease, Granulomatosis with polyangiitis (GPA) / Wegener's granulomatosis, Graves' disease / thyroid eye disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis / chronic lymphocytic thyroiditis / autoimmune thyroiditis, Henoch-Schönlein purpura / IgA vasculitis, Hidradenitis suppurativa, Hurst's disease / acute hemorrhagic leukoencephalitis (AHLE), Hypogammaglobulinemia, IgA nephropathy / Berger's disease, Immune-mediated necrotizing myopathy (IMNM), Immune thrombocytopenia (ITP) / autoimmune thrombocytopenic purpura / autoimmune thrombocytopenia, Inclusion body myositis, IgG4-related sclerosing disease (ISD), Interstitial cystitis, Juvenile idiopathic arthritis / Adult-onset Still's disease, Juvenile polymyositis | Juvenile dermatomyositis | juvenile myositis, Kawasaki disease, Lambert-Eaton myasthenic syndrome (LEMS), Leukocytoclastic vasculitis, Lichen planus | Lichen planopilaris, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD) | linear IgA bullous dermatosis (LABD), Lupus nephritis, Lyme disease / chronic Lyme disease / post-treatment Lyme disease syndrome (PTLDS), Lymphocytic colitis/microscopic colitis, Lymphocytic hypophystitis/autoimmune hypophystitis, Ménière's disease, Microscopic polyangiitis (MPA)/ANCA-associated vasculitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal motor neuropathy, Multiple sclerosis (MS), Myalgic encephalomyelitis (ME)/ Chronic fatigue syndrome (CFS), Myasthenia gravis (MG), Narcolepsy, Neuromyelitis Optica/Devic's disease, Ocular cicatricial pemphigoid, Opsoclonus-myoclonus syndrome (OMS), Palindromic rheumatism, Paraneoplastic cerebellar degeneration, Paraneoplastic pemphigus, Parry-Romberg syndrome (PRS)/Hemifacial atrophy (HFA)/Progressive facial hemiatrophy, Paroxysmal nocturnal hemoglobinuria (PNH), Peripheral uveitis/pars planitis, PANS/PANDAS, Parsonage-Turner syndrome, Pemphigus gestationis / herpes gestationis, Pemphigus foliaceus, Pemphigus vulgaris, Pernicious anemia, POEMS syndrome,

Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Postural orthostatic tachycardia syndrome (POTS), Primary biliary cirrhosis (PBC) / primary biliary cholangitis, Primary sclerosing cholangitis (PSC), Psoriasis, Palmoplantar Pustulosis, Psoriatic arthritis, Pulmonary fibrosis, idiopathic (IPF), Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Rasmussen's encephalitis, Raynaud's syndrome/phenomenon, Reactive arthritis / Reiter's syndrome, Reflex sympathetic dystrophy syndrome (RSD) / Complex regional pain syndrome (CRPS), Relapsing polychondritis, Restless leg syndrome (RLS) / Willis-Ekbom disease, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome / autoimmune polyendocrine syndrome type II / polyglandular autoimmune syndrome, type 2, Scleritis, Scleroderma, Sclerosing Mesenteritis / Mesenteric Panniculitis, Serpiginous choroidopathy, Sjögren's syndrome, Stiff person syndrome (SPS), Small fiber sensory neuropathy, s erythematosus (SLE), Subacute bacterial endocarditis (SBE), Subacute cutaneous lupus, Susac syndrome, Sydenham's chorea, Sympathetic ophthalmia, Takayasu's arteritis (vasculitis), Testicular autoimmunity (vasculitis, orchitis), Tolosa-Hunt syndrome, Transverse myelitis (TM), Tubulointerstitial nephritis uveitis syndrome (TINU), Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis anterior/intermediate/posterior, Vasculitis, VEXAS Syndrome, Vitiligo, Vogt-Koyanagi-Harada syndrome (VKH).

- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the patient is non-responsive to standard of care (SOC) treatment, or not sufficiently responsive to SOC treatment, suffers from side-effects associated with SOC treatment, particularly, wherein the disease is refractory to immunosuppressive treatment, refractory to CAR-T cell treatment, refractory to treatment by plasmapheresis, refractory to treatment selected from the group comprising treatment with glucocorticoids, cyclophosphamide, azathioprine, rituximab baricitinib, hydroxychloroquine, and ruxolitinib, or wherein the patient does not respond to at least one, two, or more standard immunosuppressive drugs.

- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 120 µg.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 112 µg.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 56 µg.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 28 µg.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for

intravenous administration or continuous intravenous administration of a daily dose of about 5µg/m2 to about 15 µg/m2.

- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 7 µg/m2 to about 12 µg/m2.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 8 µg/m2 to about 10 µg/m2.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 9 µg or 9 µg/m2.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is for administration over a period of at least 3 days, preferably at least 4 days, more preferably for at least 5 days.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is for administration over a period of up to 42 days, particularly for 40 days.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising

a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is for administration over a first period and/or a second period of up to 42 days, particularly for 5 days, or for 40 days, at a concentration of 9 µg daily.

- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is for administration over an additional period of up to 42 days, particularly for 5 days, or for 10 days, or for 40 days at a concentration of 28 µg daily.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is for administration over a first period and/or a second period of up to 42 days, particularly for 5 days, or for 40 days, at a concentration of 5 µg/m2.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is for administration over an additional period of up to 42 days, particularly for 5 days, or for 40 days at a concentration of 15 µg/m2.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the molecule is formulated for subcutaneous administration.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is SLE.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising

a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is systemic sclerosis.

- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is Rheumatoid arthritis.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is Myasthenia gravis.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is dermatomyositis.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is Guillain-Barré syndrome (GBS).
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is Hashimoto's thyroiditis.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments, wherein the autoimmune disease is Neuromyelitis Optica/Devic's disease.

- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a pharmaceutical composition comprising a molecule comprising a first domain binding CD19 and a second domain binding CD3 according to any one of the preceding embodiments.
- A method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a nucleic acid molecule, or a mixture of at least two different nucleic acid molecules, encoding (a) a single chain polypeptide comprising a first domain binding CD19 and a second domain binding CD3, or (b) encoding separately at least two or more polypeptides encoding a first domain binding CD19 and/or a second domain binding CD3, for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition, wherein said nucleic acid is selected from the group comprising ribonucleic acid, deoxyribonucleic acid, or mixtures thereof.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a mixture of at least two different nucleic acid molecules, encoding a first domain binding CD19 and a second domain binding CD3 according to the preceding embodiment, wherein said nucleic acid is formulated for administration to said patient.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a pharmaceutical composition comprising the nucleic acid molecules according to the preceding embodiments, wherein the patient is suffering from an autoimmune disease or an autoimmune condition.
- The method of treatment of a patient suffering from an autoimmune disease or an autoimmune condition comprising the step of administering a pharmaceutical composition comprising the nucleic acid molecules according to the preceding embodiments, wherein said pharmaceutical composition comprises ingredients suitable for parenteral or intravenous administration.
- A method of treatment of a patient suffering from an autoimmune disease or autoimmune condition, particularly from systemic sclerosis, SLE, GRA, and RA, particularly from severe systemic sclerosis comprising the step of intravenously administering blinatumomab wherein blinatumomab is administered in a first cycle at a dose of 9 µg/day for 5 days followed by a treatment free period, wherein

blinatumomab is administered in a second cycle at a dose of 9 µg/day for 5 days followed by a treatment free period, wherein blinatumomab is administered in a third cycle at a dose of 28 µg/day for 5 days followed by a treatment free period, and wherein blinatumomab is administered in a fourth cycle at a dose of 28 µg/day for 10 days followed by a treatment free period.

- A method of treatment of a patient suffering from an autoimmune disease or autoimmune condition, particularly from systemic sclerosis, SLE, GRA, and RA, particularly from severe systemic sclerosis, comprising the step of intravenously administering blinatumomab in a first cycle at a dose of 9 µg/day for 5 days followed by a treatment free period, wherein blinatumomab is administered in a second cycle at a dose of 28 µg/day for 10 days followed by a treatment free period.
- A method of treatment of a patient suffering from an autoimmune disease or autoimmune condition, particularly from systemic sclerosis, SLE, GRA, and RA, particularly from severe systemic sclerosis according to the preceding two embodiments, wherein the treatment free period has a duration of 5 to 10 days, particularly, 7 days.
- A method of treatment of a patient suffering from SLE or SLE with Lupus Nephritits according to the preceding embodiments, wherein the subject suffers from active SLE or SLE with Lupus Nephritis.
- A method of treatment of a patient suffering from SLE or SLE with Lupus Nephritis according to the preceding embodiments, comprising administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from SLE or SLE with Lupus Nephritis, wherein the subject suffers from refractory SLE or SLE with Lupus Nephritis.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from SLE, wherein the subject suffers from refractory SLE with nephritis.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering a molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a

patient suffering from SLE or SLE with Lupus Nephritis according to the preceding embodiments, wherein the patient is an adult patient.

- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab, wherein blinatumomab is for subcutaneous administration.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously at a dose of at least 25 micrograms per week.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously at a dose of at least 40 micrograms per week.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously at least 100 micrograms per week.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously at a dose of at least 250 micrograms per week.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously at least 500 micrograms per week.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously at least 1000 micrograms per week.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously for at least 6 weeks.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously for at least 12 weeks.
- A method of treatment of a patient suffering from SLE according to the preceding embodiments, comprising administering blinatumomab subcutaneously wherein the patient is an adult with a diagnosis of an active and refractory SLE and Class III/IV glomerulonephritis who have experienced a failure to respond to previous

standard therapies including immunosuppressive therapies and/or treatment with a biological agent.

- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously at a dose of at least 25 micrograms per week.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously at a dose of at least 40 micrograms per week.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously at a dose of at least 100 micrograms or at least 120 µg per week.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously at a dose of at least 250 micrograms per week.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously at least 500 micrograms per week.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously at least 1000 micrograms per week.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously for at least 6 weeks.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously for at least 12 weeks.
- A method of treatment of a patient suffering from refractory RA comprising administering blinatumomab subcutaneously, wherein the patient has moderate to severe active disease despite having received treatment with a csDMARD and at least two bDMARDs of different mechanisms of action, or one bDMARD and at least one tsDMARD.

Pharmaceutical composition

It is envisaged to administer the molecule for use according to the present invention in the form of a pharmaceutical composition. The term "pharmaceutical composition" particularly refers to a composition suitable for administering to a human or animal, i.e., a composition containing components which are pharmaceutically acceptable. Preferably, a pharmaceutical composition comprises a molecule for use according to the present invention together with one or more pharmaceutical excipients. The composition may also comprise further agents as described elsewhere herein. The term “excipient” includes fillers, binders, disintegrants, coatings, sorbents, anti-adherents, glidants, preservatives, antioxidants, flavoring, coloring, sweeting agents, solvents, co-solvents, buffering agents, chelating agents, viscosity imparting agents, surface active agents, diluents, humectants, carriers, diluents, preservatives, emulsifiers, stabilizers or tonicity modifiers. Pharmaceutical compositions of the invention preferably comprise a therapeutically effective amount of molecule for use according to the present invention and can be formulated in various forms, e.g. in solid, liquid, gaseous or lyophilized form and may be, inter alia, in the form of an ointment, a cream, transdermal patches, a gel, powder, a tablet, solution, an aerosol, granules, pills, suspensions, emulsions, capsules, syrups, liquids, elixirs, extracts, tincture or fluid extracts or in a form which is particularly suitable for the desired method of administration.

Pharmaceutical compositions or formulations for subcutaneous use are disclosed, e.g., in WO2023062188. They can have the following exemplary compositions: In addition to the CD19 and CD3 binding molecule, such as blinatumomab, potassium phosphate (preferably 10 mM), sucrose (preferably 2 % (w/v)), mannitol (preferably 4 % (w/v)), sulfobutylether betacyclodextrin (preferably 1 % (w/v)), polysorbate 80 (preferably 0.01 % (w/v)), pH 7.0. In an alternative embodiment, the subcutaneous formulation comprises, In addition to the CD19 and CD3 binding molecule, such as blinatumomab, L-glutamic acid (preferably 10 mM), sucrose (9% (w/v)), polysorbate 80 (preferably 0.01% (w/v)), pH 4.2.

A better understanding of the present invention and of its advantages will be obtained from the following examples, offered for illustrative purposes only. The example is not intended to limit the scope of the present invention in any way.

Examples

Example 1 - Blinatumomab treatment in a patient suffering from Systemic Sclerosis

A 36 year-old female with an initial diagnosis of limited cutaneous systemic sclerosis in October 2022 was positive for anti-nucleic acid antibodies (ANAs), anti-Scl-70 antibodies, and positive capillary microscopy (after initial symptoms, i.e., Raynaud phenomenon, dry eyes, digital tips ulcer were noticed in summer 2020) was refractory to azathioprine, glucocorticoids and mycolphenolate mofetil. After initial diagnosis, the patient was treated with hydroxychloroquine. About 6 months later the patient suffered from fatigue and skin fibrosis. In view of a planned pregnancy, the treatment was changed to high dose glucocorticoids and azathioprine. About 7 months after treatment with high dose glucocorticoids the symptoms worsened significantly which progressed over the next weeks despite treatment with mycolphenolate mofetil. The patient suffered from painful hands and fingers, loss of mobility of head and neck, morning stiffness, severe skin thickening and hardening, and was then treated with intravenously (by continuous infusion) administered 9 µg/day for 5 days. The haematological analysis over the first week of treatment showed a progressive B cell depletion. Other lymphocyte populations (CD4+, CD8+, all T-lymphocytes, and total number of lymphocytes) also dropped on day 1 of treatment, but rapidly recovered (Fig.2), whereas B cell numbers remained almost completely depleted over 1 week as shown in Fig. 1. There were no serious immune related adverse events, particularly no signs of CRS, ICANS or infection. The HEMATOTOX Score (DAY 0) was zero, i.e. a low risk. C-reactive protein (CRP) dynamics and IL-6 dynamics after Blinatumomab infusion are shown in Fig. 3 (A) and (B). The two latter values increased and then returned to normal (CRP) over a period of 5 days, or dropped significantly over 5 days (FIG. 3 (A) and (B)). One week after the initial treatment, the patient is in excellent clinical condition, and apart from a slight allergic reaction to Blinatumomab on day 3 no adverse events, especially no CRS or ICAN were experienced. The pain above the sternum, which had been so severe that she had not been able to put on a T shirt anymore, has completely disappeared. The preexisting induration above the scapula has disappeared and the skin at the arms was smother than pro treatment with Blinatumomab. The patient was subsequently treated with at the same dose of 9µg/day for 5 days and subsequently at a dose of 28 µg/day for 5 days without significant adverse events and resulting in a surprisingly improved overall health condition. Each treatment cycle was

followed by about 3 week intervals without admistration of Blinatumomab. In a fourth treatment cycle, said patient received the same dose of Blinatumomab for 10 days. Treatment with blinatumomab was well tolerated. Only one short, self-containing episode of self-limiting skin rash on day 3 of the 1st cycle was observed. There

0were no signs of acute or delayed toxicity, in particular no fever, no CRS, no neurotoxicity and no hematotoxicity or infectious complications. Concerning efficacy, the patient reported an amelioration in all symptoms. Clinical examination showed increased mobility of hands and fingers and significantly softer skin on the forearms, resulting in an mRSS of 10 three weeks after the completion of the fourth cycle.

B-cell depletion occurred rapidly upon blinatumomab exposure and lasted in median 14.5 days. The peripheral T cell count significantly dropped on day one of the first cycle but recovered promptly to normal values. Serum IgG and specific antibody titers showed no major changes over the course of treatment.

Example 2 - Blinatumomab treatment in patients suffering from SLE

SLE is a prototypic autoimmune multisystemic disease. Central pathogenic event in SLE is the loss of tolerance of nuclear components, which leads to systemic autoimmunity that can damage tissues and organs.

Among the most severe organ manifestations are renal, cardiac and central nervous manifestations. Dependent on manifestations, SLE is a life-threatening disease. Especially Lupus Nephritis (LN), which develop about 60% of patients with SLE, represents a major cause of morbidity and mortality (Kostopoulou M, et al.).

The clinical activity of the disease can be measured as a global score of disease activity, e.g. SLEDAI score2 or as reporting of disease activity in different organs or systems using the British Isles Lupus Assessment Group (BILAG) index (Hay EM, et al.).

Treatment of SLE usually consists of intense immunosuppressive induction therapy for a three- to six-month period, to induce complete or at least partial remission, which is followed by long-term, less aggressive, maintenance therapy to maintain disease remission and to prevent disease flares. Goals of treatment include long-term preservation of organ

function, prevention of disease flares, management of comorbidities and improvement in disease-related quality of life.

The optimal treatment of severe SLE, including LN remains a challenge. Only 30%–50% of patients achieve a complete remission after induction therapy with standard of care, and >10% of patients with proliferative LN progress to kidney failure despite treatment (Thurman JM).

SLE is an autoimmune disease, which requires the interplay of innate and adaptive immune cells. A suggested genetic contribution of about 44% encompasses immune regulating genes coding for cytokines, T and B cell regulating pathways and apoptotic cell death (Moser KL et al.).

The production of autoantibodies is a prerequisite of SLE and is essential for development and clinical apparent disease.

Almost every SLE patient has at least one specificity of SLE associated autoantibodies, namely anti-nuclear antibodies (ANA) or anti-double strain (ds) deoxyribonucleid acid (DNA) antibodies. Most of these autoantibodies are believed to be directly pathogenic (Tsokos GC.).

Knowledge gains of recent years have not yet led to major advances in the targeted therapy of SLE. Since more than ten years, the only licensed targeted therapy has been the anti-BAFF antibody belimumab. Belimumab blocks B cell stimulation and regulation, but does not completely deplete the circulating B cells, thus leading to control of B cell autoimmunity (Horowitz DL, et al., Pineda L, et al.).

The CD20 directed antibody rituximab (RTX) has not become a pillar of SLE therapy, since several randomized trials in SLE patients (renal and non-renal SLE) have failed (Merrill JT et al.). However, non-randomized studies of RTX have shown efficacy in certain situations among which are refractory lupus nephritis, SLE associated cytopenias and skin disease.

A recent study of the more potent and more profound B cell depleting anti CD20 antibody Obinutuzumab achieved a significant improvement for patients with lupus nephritis (Furie RA, et al.), which is in line with the pathogenic role of B cells in the disease. Since antibody production is among the most relevant pathogenic function of B cells, CD20 is not a perfect antigenic target to achieve depletion of B cell plasmablasts. This subset of B cells, which

is expanded in SLE and has escaped peripheral selection is still expressing CD19, which suggests that blinatumomab could have a significant impact on SLE pathogenesis and reduce the clinical burden in patients considerably (Szelinski F, et al.).

The evidence of B cell depletion was observed already at doses of 5 µg/m2/day and occurred rapidly. On the other hand, the first objective clinical responses in patients with B-cell lymphomas were documented at a dose level of 15 µg/m2/day (Bargou R, et al.).

Blinatumomab monotherapy received EMA approval for the treatment of R/R B-precursor ALL as well as for treatment of ALL in complete hematological remission but positive measurable residual disease (MRD)21. The off-the-shelf availability of BITE molecules and their less intensive side-effects profile make them an attractive solution for treatement of patients with SLE.

In this Phase II trial the safety of single 5-day-treatment course is evaluated and a marked biological effect defined as the reduction of ds-DNA antibody concentrations 12 months after the start of treatment is analyzed.

Endpoints of the study are:

- Immunological response: ds-DNA antibody concentration, B-cell depletion and regeneration and serum IgG concentration
- Clinical response after 12 months according to SLEDAI Index and steroid dosage
- Adverse events and serious adverse events

Study design

This monocentric, single-arm pilot Phase II trial includes patients diagnosed with SLE refractory to ≥ 2 prior immunosuppressive regimens.

Study population

Key inclusion criteria:

1. Age over 18 years (inclusion of pediatric patients at doses described above will take part at a later stage)

2. Diagnosis of SLE according to EULAR/ ACR criteria for more than six months (Aringer M, et al.).
3. Serologically active disease: Positivity for ANA (1:160) and anti dsDNA(>ULN); Hypocomplementemia of C3 or C4
4. Prior treatment failure of at least two immunosuppressive agents
5. Clinical active disease: SLEDAI2k (Touma Z, et al.; Bombardier C, et al.) activity score > 6 and at least two BILAG B and/ or one BILAG A manifestation (Yee CS et al., Isenberg DA et al., Griffiths B et al.).

Key exclusion criteria:

1. Infectious comorbidities (HIV positivity, chronic Hepatitis B/C, latent Tuberculosis)
2. Any other active infection at enrolment
3. Inadequate organ function (heart with LVEF<45%, renal function with GFR <40ml/min hematologic with WBC<1000 cells/µl, platelets<60.000//µl, neutrophils < 1000//µl)
4. Clinically relevant CNS pathology requiring treatment (e.g., unstable epilepsy). Evidence of current CNS (CNS2, CNS 3) involvement by ALL. Subjects with CNS relapse at the time of relapse are eligible if CNS is successfully treated prior to enrollment.
5. Abnormal renal or hepatic function prior to start of treatment (day 1), e.g. (a) serum creatinine levels above upper limit of normal, based on the normal ranges for age and gender of the local laboratories, (b) total bilirubin > 3.0 mg/dL prior to start of treatment (unless related to Gilbert's or Meulengracht disease)

6. Symptoms and/or clinical signs and/or radiological and/or sonographic signs that indicate and acute or uncontrolled chronic infection, and other concurrent disease or medical condition that could be exacerbated by the treatment or would seriously complicate compliance with the protocol.
7. Documented infection with HIV.
8. Known hypersensitivity to immunoglobulins or any of the products or components to be administered during dosing (excluding asparaginase).

Treatment and procedures

All patients underwent:

- Screening: assessment of SELENA SLEDAI activity score prior to application of blinatumomab
- Treatment: prior stop of immunosuppressive regimen except for steroid medication and continuous infusion of 9 µg/d blinatumomab in inpatient unit for five days.
- Follow up for 12 months after inclusion into the study.

Patients will be treated at 9µg/day for 5 days. Retreatment will depend on the clinical course of disease.

All included patients will undergo monitoring of immune regulation during therapy and follow-up. The samples of serum and mononuclear cells will undergo biobanking according to the following schedule:

The laboratory examinations will be performed on: d1, d+7, d+14 and d +28, d+120, d+150, d+270 and d+365 and will include:

- Flow cytometry:

- Lymphocytes (CD3, CD4, CD8, CD16/56, CD19, CD27, HLA-DR, CD38, CD69, gamma/delta T)
- Checkpoint molecules: PD-1, VISTA, TIM, LAG at T/NK/phagocytes
- T-Helper cells 1/2/17
- Regulatory T- cells (incl. CD127 detection)
- Detection of B-cells and quantification of B-cell depletion

- Serology: analysis of MCP-1, IFN-gamma, IL-6, IL-7, IL-8, IL-10, TNF, by luminex techology (MagPix)
- Freezing of additional aliquots (Back-up).

Furthermore, after a short time stimulation of heparinized blood samples cytokine detection in supernatant is performed.

Example 3 – Subcutaneous administration of blinatumomab in subjects with active and refractory Systemic Lupus Erythematosus with nephritis

Patients in this group are treated with blinatumomab, after an initial eligibility screening, for 12 weeks. Patients are subjects older than 18 years with a diagnosis of an active and refractory SLE and Class III/IV glomerulonephritis who have experienced a failure to respond to previous standard therapies including immunosuppressive therapies and treatment with a biological agent.

Patients are treated with blinatumomab subcutaneously once weekly (QW) for 12 weeks as follows:

- Cohort 1: 40 µg (micrograms) weekly for 12 weeks,
- Cohort 2: 120 µg (micrograms) weekly for 12 weeks,

- Cohort 3: 250 µg (micrograms) weekly for 12 weeks.

The following objectives are assessed:

- To assess the safety and tolerability of SC blinatumomab in adult subjects with active and refractory SLE with nephritis
- To assess the efficacy of SC blinatumomab in adult subjects with active and refractory SLE with nephritis
- To evaluate the PK of SC blinatumomab in adult subjects with active and refractory SLE with nephritis
- To evaluate the immunogenicity of SC blinatumomab in adult subjects with active and refractory SLE with nephritis

The treatment is expected to have at least one of the following effects:

Reduction of (change from baseline):

- anti-double stranded DNA (anti-dsDNA) and anti-Smith antibody,

- complement component 3 (C3) and complement component 4 (C4).

Reduction of (change from baseline):

- Total immunoglobulin (Ig), IgG, IgM, IgA, IgE, and vaccine-related antibody levels.

Reduction of (change from baseline):

- CD20+ B-cell counts,
- B-cell subsets such as naïve and memory B-cells, plasma cells and plasmablasts.

Reduction of (change from baseline):

- SLE and immune gene expression signatures such as interferon (IFN), plasma cell, and B-cell receptor (BCR) repertoire,
- - autoimmune disease biomarkers such as additional autoantibodies and biomarkers of kidney inflammation in urine,
- - serum cytokines and additional immunophenotyping for non-B-cell subsets such as natural killer (NK) cells and T-cell subsets.

Example 4 – Use of Blinatumomab in adult patients with refractory RA

Rheumatoid arthritis is a systemic autoimmune inflammatory joint disease with a prevalence of approximately 1% in the adult population (Myasoedova et al, 2010), more frequently affecting women (2 to 3 times more than males) (Crowson et al, 2011). Chronic inflammation leads to progressive joint destruction and functional disability. B-cell implication in RA pathogenesis is supported by several lines of evidence:

The presence of autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are present in most patients and precede the clinical onset of disease. They are associated with more severe symptoms, joint damage, and severe disease evolution (Malmström et al, 2017).

The inflamed synovial compartment contains abundant immune cells including B-cells, plasmablasts, and plasma cells (Jang et al, 2022) that can be organized and considered as tertiary lymphoid tissue or an ectopic lymphoid structure. Tertiary lymphoid tissues are correlated with autoantibody titers, inflammatory cytokine levels, and disease severity in RA patients, indicating that tertiary lymphoid tissues are related to the persistent inflammation in RA (Humby et al, 2009). B-cell depletion using the anti-cluster of differentiation 20 (CD20) targeted antibody rituximab has proven to be effective in the treatment of RA (Edwards et al, 2004).

Over the past 2 decades considerable progress has been made in the treatment of RA with DMARDs and has led to improved patient outcomes. Many drugs with different mechanisms of action have enriched the spectrum of DMARDs. Biologic DMARDs target different pathways including tumor necrosis factor (TNF), interleukin (IL)-6, IL-1, T-cell

co-stimulation, and B-cells. In addition, tsDMARDs (Janus kinase inhibitors) are also approved for RA treatment. Despite the "treat-to-target" strategy and the efficient initiation and titration of DMARDs as recommended by ACR (Fraenkel et al, 2021) and EULAR guidelines (Smolen et al, 2023), an important subgroup of patients is inadequately controlled and refractory to multiple drugs with different modes of action (Tan and Buch, 2022). Depending on threshold and study population (observational studies, registries, or randomized clinical trials) the prevalence of "refractory" RA is estimated to be between 6 to 21% (Bécède et al, 2019). These multidrug-resistant patients represent a considerable clinical challenge and require new therapeutic approaches.

Targeting B-cell depletion with rituximab does not always effectively control the disease and has limited efficacy in resistant RA (Jois et al, 2007). Moreover, rituximab does not sufficiently deplete B-cells in the tissues of patients with RA (Vos et al, 2007). In a study conducted to analyze the effects of rituximab on synovial tissue, although a complete B-cell depletion was observed in peripheral blood in nearly all patients, synovial B-cells were significantly decreased in some patients but were still persistent in a subset of patients. There was also a variability in synovial B-cell depletion kinetic between participants (Thurlings et al, 2008).

In addition to CD20-targeting monoclonal antibodies not thoroughly depleting B-cells in the tissues and lymphatic organs, these therapies do not target plasmablasts and long-lived plasma cells (Kamburova et al, 2013; Thurlings et al, 2008). Cluster of differentiation 19 expression persists on late-stage, antibody-secreting B-cells (plasmablasts and some plasma cells) after CD20 expression has been lost, which may be important in diseases driven by pathogenic autoantibodies such as RA (Tedder, 2009; Otero et al, 2003). Therefore, depleting B-cells with CD19-targeted therapies may offer a more promising therapeutic approach for those patients.

In a small study, 6 multidrug-resistant patients with active and severe RA received intravenous blinatumomab at concentrations known from oncological situations under compassionate use (Bucci et al, 2024). Low doses of blinatumomab led to B-cell depletion with a rapid improvement in RA clinical disease activity in all patients, improved synovitis as measured by ultrasound and Fibroblast Activation Protein Inhibition-based Positron Emission Tomography-Computed Tomography (FAPI-PET-CT) and reduced autoantibody

titers (RF and ACPA). Activated memory B-cells were depleted and replaced by non-class-switched IgD-positive naïve B-cells. The treatment was safe, with a brief increase in body temperature and elevated CRP during the first infusion but no signs of clinically relevant cytokine-release syndrome were observed. These symptoms were absent at the second blinatumomab administration. No neurotoxicity was observed (Bucci et al, 2024). Blinatumomab is a BiTE molecule designed to direct cytotoxic T-cells to CD19 expressing cells. It targets B-cells via the CD19 cell surface antigen while simultaneously engaging T-cells through the CD3 antigen inducing CD19+ B-cell apoptosis (Klinger et al, 2012; Baeuerle and Reinhardt, 2009; Bargou et al, 2008; Hoffmann et al, 2005).

Subcutaneous blinatumomab, via targeting CD19+ B-cells and B-cell precursors, offers a novel targeted therapeutic modality for participants with multidrug-resistant RA.

Rheumatoid arthritis is one of the most prevalent systemic poly-articular chronic autoimmune joint disease with an incidence of 0.5% to 1%. Rheumatoid arthritis is characterized by synovial inflammation and hyperplasia, and production of autoantibodies including RF and ACPA. Rheumatoid arthritis primarily involves the hand and feet joints, leading to progressive cartilage damage, bone deformities, and progressive disability. However, it is also considered as a systemic disease as it can include extra-articular manifestations, such as cardiovascular, pulmonary, psychological, skin, and skeletal disorders, among others (Gravallese and Firestein, 2023; Smolen et al, 2016; Kitas and Gabriel, 2011; McInnes and Schett, 2011). Bone and cartilage damage leads to substantial burden for both the individual and society (Cross et al, 2014). The progressive musculoskeletal deficits are associated with a decline in physical function and quality of life. The resulting functional disability is correlated to an important socioeconomic burden (Sokka et al, 2010). Considerable progress has been made in the past decades in the treatment of the disease with synthetic (conventional or targeted) or bDMARDs and progressive rates of joint damage have decreased over time (Rahman et al, 2011). Remission or low disease activity have been established as treatment targets by ACR (Fraenkel et al, 2021) and EULAR guidelines (Smolen et al, 2023; Singh et al, 2015); this is called “treat to target,” and is achieved by frequent assessment of disease activity in response to treatment. Treatment strategies include different classes of DMARDs:

csDMARDs, bDMARDs, and tsDMARDs. According to both ACR (Fraenkel et al, 2021) and EULAR recommendations (Smolen et al, 2023), treatment should be initiated with a csDMARD, ideally methotrexate which is used as an "anchor" DMARD. If the first treatment cycle fails, a bDMARD or tsDMARD is usually added to methotrexate. If target disease activity is not achieved, bDMARD/tsDMARD therapy may be modified.

Early initiation of DMARDs and the "treat-to-target" approach have led to significantly improved outcomes for the vast majority of patients. Patients with refractory disease are characterized by a lack of clinical response to several consecutive drugs with different modes of action and may exhibit significant progression of joint damage and irreversible disability. There is no formal consensus definition of this category of patients, and they are referred as "difficult to treat" or "refractory" (Tan et al, 2022; Melville et al, 2020; Buch, 2019).

The present invention is considered suitable for a safe, free from treatment-emergent adverse events (e.g., CRS, ICANS, and effective to improve at least one of the above-mentioned symptoms, does not substantially generate autoantibodies to blinatumomab, favorable pharmacokinetic profile of the administered drug.

Participants have the following criteria:

- Age ≥ 18 years (or above legal age within the country if it is older than 18 years) < 75 years of age.
- Diagnosis of RA according to the 2010 ACR/EULAR classification criteria.
- Positive for RF (RF total) and/or ACPA at screening, in accordance with criteria at the central laboratory.

Active disease defined as having all the following criteria:

- DAS28-CRP > 3.2 at screening
- at least 6 tender joints at screening
- at least 6 swollen joints at screening

Refractory disease defined as inadequate response to treatment with:

a csDMARD AND at least two bDMARDs of different mechanisms of action OR one bDMARD AND at least one tsDMARD.

Diagnostic Assessments

Any of the following laboratory abnormalities at screening (1 repeat test may be conducted to confirm results prior to enrollment within the same Screening Period):

- Elevated liver enzymes (AST or ALT > 2.5 × upper limit of normal [ULN])
- Total bilirubin < 1.5 × ULN (unless due to Gilbert's syndrome)
- CD19+ B-cell count < 40 cells/µL
- Absolute neutrophil count < 1200 cells/µL
- Platelet count < 75 000/ µL (or < 75 × 10exp9/L)
- Hemoglobin < 8.0 g/dL
- Total Ig < 600 mg/dL

Dexamethasone will be used for CRS prophylaxis and prophylaxis of first dose effects such as skin rash and pruritus. Dexamethasone 20 mg IV will be administered within 3 hours before the first SC dose on day 1.

The following dose regimens are studied for SC blinatumomab: 40 µg QW (once a week), 120 µg QW, or 250 µg weekly for 12 weeks.

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SEQUENCES

SEQ ID NO:	protein/ nucleic acid	Description	Sequence
1	protein	CD19xCD3 bispecfic single-chain molecule	DIQLTQSPASLAVSLGQRATISCKASQSVDYDGDSYLNWYQQIP GQPPKLLIYDASNLVSGIPPRFSGSGSGTDFTLNIHPVEKVDAA TYHCQQSTEDPWTFGGGTKLEIKGGGGSGGGGSGGGGSQVQLQQ SGAELVRPGSSVKISCKASGYAFSSYWMNWVKQRPGQGLEWIGQ IWPGDGDTNYNGKFKGKATLTADESSSTAYMQLSSLASEDSAVY FCARRETTTVGRYYYAMDYWGQGTTVTVSSGGGGSDIKLQQSGA ELARPGASVKMSCKTSGYTFTRYTMHWVKQRPGQGLEWIGYINP SRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCA RYYDDHYCLDYWGQGTTLTVSSVEGGSGGSGGSGGSGGVDDIQL TQSPAIMSASPGEKVTMTCRASSSVSYMNWYQQKSGTSPKRWIY DTSKVASGVPYRFSGSGSGTSYSLTISSMEAEDAATYYCQQWSS NPLTFGAGTKLELK
2	Nucleic acid	CD19xCD3 bispecfic single-chain molecule	GATATCCAGCTGACCCAGTCTCCAGCTTCTTTGGCTGTGTCTCT AGGGCAGAGGGCCACCATCTCCTGCAAGGCCAGCCAAAGTGTTG ATTATGATGGTGATAGTTATTTGAACTGGTACCAACAGATTCCA GGACAGCCACCCAAACTCCTCATCTATGATGCATCCAATCTAGT TTCTGGGATCCCACCCAGGTTTAGTGGCAGTGGGTCTGGGACAG ACTTCACCCTCAACATCCATCCTGTGGAGAAGGTGGATGCTGCA ACCTATCACTGTCAGCAAAGTACTGAGGATCCGTGGACGTTCGG TGGAGGGACCAAGCTCGAGATCAAAGGTGGTGGTGGTTCTGGCG GCGGCGGCTCCGGTGGTGGTGGTTCTCAGGTGCAGCTGCAGCAG TCTGGGGCTGAGCTGGTGAGGCCTGGGTCCTCAGTGAAGATTTC CTGCAAGGCTTCTGGCTATGCATTCAGTAGCTACTGGATGAACT GGGTGAAGCAGAGGCCTGGACAGGGTCTTGAGTGGATTGGACAG ATTTGGCCTGGAGATGGTGATACTAACTACAATGGAAAGTTCAA GGGTAAAGCCACTCTGACTGCAGACGAATCCTCCAGCACAGCCT ACATGCAACTCAGCAGCCTAGCATCTGAGGACTCTGCGGTCTAT TTCTGTGCAAGACGGGAGACTACGACGGTAGGCCGTTATTACTA TGCTATGGACTACTGGGGCCAAGGGACCACGGTCACCGTCTCCT CCGGAGGTGGTGGATCCGATATCAAACTGCAGCAGTCAGGGGCT GAACTGGCAAGACCTGGGGCCTCAGTGAAGATGTCCTGCAAGAC TTCTGGCTACACCTTTACTAGGTACACGATGCACTGGGTAAAAC AGAGGCCTGGACAGGGTCTGGAATGGATTGGATACATTAATCCT AGCCGTGGTTATACTAATTACAATCAGAAGTTCAAGGACAAGGC CACATTGACTACAGACAAATCCTCCAGCACAGCCTACATGCAAC TGAGCAGCCTGACATCTGAGGACTCTGCAGTCTATTACTGTGCA AGATATTATGATGATCATTACTGCCTTGACTACTGGGGCCAAGG CACCACTCTCACAGTCTCCTCAGTCGAAGGTGGAAGTGGAGGTT CTGGTGGAAGTGGAGGTTCAGGTGGAGTCGACGACATTCAGCTG ACCCAGTCTCCAGCAATCATGTCTGCATCTCCAGGGGAGAAGGT CACCATGACCTGCAGAGCCAGTTCAAGTGTAAGTTACATGAACT GGTACCAGCAGAAGTCAGGCACCTCCCCCAAAAGATGGATTTAT GACACATCCAAAGTGGCTTCTGGAGTCCCTTATCGCTTCAGTGG CAGTGGGTCTGGGACCTCATACTCTCTCACAATCAGCAGCATGG AGGCTGAAGATGCTGCCACTTATTACTGCCAACAGTGGAGTAGT AACCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAGCTGAAA

3	protein	VH anti CD19	QVQLQQSGAELVRPGSSVKISCKASGYAFSSYWMNWVKQRPGQG LEWIGQIWPGDGDTNYNGKFKGKATLTADESSSTAYMQLSSLAS EDSAVYFCARRETTTVGRYYYAMDYWGQGTTVTVSS
4	Nucleic acid	VH anti CD19	CAGGTGCAGCTGCAGCAGTCTGGGGCTGAGCTGGTGAGGCCTGG GTCCTCAGTGAAGATTTCCTGCAAGGCTTCTGGCTATGCATTCA GTAGCTACTGGATGAACTGGGTGAAGCAGAGGCCTGGACAGGGT CTTGAGTGGATTGGACAGATTTGGCCTGGAGATGGTGATACTAA CTACAATGGAAAGTTCAAGGGTAAAGCCACTCTGACTGCAGACG AATCCTCCAGCACAGCCTACATGCAACTCAGCAGCCTAGCATCT GAGGACTCTGCGGTCTATTTCTGTGCAAGACGGGAGACTACGAC GGTAGGCCGTTATTACTATGCTATGGACTACTGGGGCCAAGGGA CCACGGTCACCGTCTCCTCC
5	protein	VL anti CD19	DIQLTQSPASLAVSLGQRATISCKASQSVDYDGDSYLNWYQQIP GQPPKLLIYDASNLVSGIPPRFSGSGSGTDFTLNIHPVEKVDAA TYHCQQSTEDPWTFGGGTKLEIK
6	Nucleic acid	VL anti CD19	GATATCCAGCTGACCCAGTCTCCAGCTTCTTTGGCTGTGTCTCT AGGGCAGAGGGCCACCATCTCCTGCAAGGCCAGCCAAAGTGTTG ATTATGATGGTGATAGTTATTTGAACTGGTACCAACAGATTCCA GGACAGCCACCCAAACTCCTCATCTATGATGCATCCAATCTAGT TTCTGGGATCCCACCCAGGTTTAGTGGCAGTGGGTCTGGGACAG ACTTCACCCTCAACATCCATCCTGTGGAGAAGGTGGATGCTGCA ACCTATCACTGTCAGCAAAGTACTGAGGATCCGTGGACGTTCGG TGGAGGGACCAAGCTCGAGATCAAA
7	protein	VH anti CD3	DIKLQQSGAELARPGASVKMSCKTSGYTFTRYTMHWVKQRPGQG LEWIGYINPSRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTS EDSAVYYCARYYDDHYCLDYWGQGTTLTVSS
8	Nucleic acid	VH anti CD3	GATATCAAACTGCAGCAGTCAGGGGCTGAACTGGCAAGACCTGG GGCCTCAGTGAAGATGTCCTGCAAGACTTCTGGCTACACCTTTA CTAGGTACACGATGCACTGGGTAAAACAGAGGCCTGGACAGGGT CTGGAATGGATTGGATACATTAATCCTAGCCGTGGTTATACTAA TTACAATCAGAAGTTCAAGGACAAGGCCACATTGACTACAGACA AATCCTCCAGCACAGCCTACATGCAACTGAGCAGCCTGACATCT GAGGACTCTGCAGTCTATTACTGTGCAAGATATTATGATGATCA TTACTGCCTTGACTACTGGGGCCAAGGCACCACTCTCACAGTCT CCTCA
9	protein	VL anti CD3	DIQLTQSPAIMSASPGEKVTMTCRASSSVSYMNWYQQKSGTSPK RWIYDTSKVASGVPYRFSGSGSGTSYSLTISSMEAEDAATYYCQ QWSSNPLTFGAGTKLELK
10	Nucleic acid	VL anti CD3	GACATTCAGCTGACCCAGTCTCCAGCAATCATGTCTGCATCTCC AGGGGAGAAGGTCACCATGACCTGCAGAGCCAGTTCAAGTGTAA GTTACATGAACTGGTACCAGCAGAAGTCAGGCACCTCCCCCAAA AGATGGATTTATGACACATCCAAAGTGGCTTCTGGAGTCCCTTA TCGCTTCAGTGGCAGTGGGTCTGGGACCTCATACTCTCTCACAA TCAGCAGCATGGAGGCTGAAGATGCTGCCACTTATTACTGCCAA CAGTGGAGTAGTAACCCGCTCACGTTCGGTGCTGGGACCAAGCT GGAGCTGAAA
11	protein	CD3 CDR-H1	GYTFTRYTMH
12	protein	CD3 CDR-H2	YINPSRGYTNYNQKFKD
13	protein	CD3 CDR-H3	YYDDHYCLDY
14	protein	CD3 CDR-L1	RASSSVSYMN

15	protein	CD3 CDR-L2	DTSKVAS
16	protein	CD3 CDR-L3	QQWSSNPLT
17	protein	CD19 CDR-H1	GYAFSSYWMN
18	protein	CD19 CDR-H2	QIWPGDGDTNYNGKFKG
19	protein	CD19 CDR-H3	RETTTVGRYYYAMDY
20	protein	CD19 CDR-L1	KASQSVDYDGDSYLN
21	protein	CD19 CDR-L2	DASNLVS
22	protein	CD19 CDR-L3	QQSTEDPWT

Claims

1. A molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition wherein the first domain comprises the CDR 1, 2, and 3 sequences of a variable light chain depicted in SEQ ID NOs: 20, 21, and 22, and the CDR 1, 2, and 3 sequences of the variable heavy chain depicted in SEQ ID NOs: 17, 18, and 19.

2. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to claim 1, wherein said molecule is a single chain polypeptide.

3. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 2, wherein the first domain comprises the sequence of the variable light chain depicted in SEQ ID NO: 5 and the sequence of the variable heavy chain depicted in SEQ ID NO: 3.

4. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 3, wherein the molecule comprises a sequence as depicted in SEQ ID NO: 1.

5. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 4, wherein the molecule is blinatumomab.

6. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 5, wherein the disease is selected from

the group comprising Acromegaly, Acquired aplastic anemia, Acquired hemophilia, Agammaglobulinemia, primary, Alopecia areata, Ankylosing spondylitis (AS), Anti-NMDA receptor encephalitis, Antiphospholipid syndrome (APS) | catastrophic antiphospholipid syndrome (CAPS) / Asherson's syndrome, Arteriosclerosis, Autoimmune Addison's disease (AAD), Autoimmune autonomic ganglionopathy (AAG) / autoimmune dysautonomia | autoimmune gastrointestinal dysmotility (AGID), Autoimmune encephalitis | acute disseminated encephalomyelitis (ADEM), Autoimmune gastritis, Autoimmune hemolytic anemia (AIHA), Autoimmune hepatitis (AIH), Autoimmune hyperlipidemia, Autoimmune hypophysitis/lymphocytic hypophysitis, Autoimmune inner ear disease (AIED), Autoimmune lymphoproliferative syndrome (ALPS), Autoimmune myelofibrosis, Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune pancreatitis (AIP), Autoimmune polyglandular syndromes, types I, II, & III (APS type 1, APS type 2, APS type 3, APECED), Autoimmune progesterone dermatitis, Autoimmune retinopathy (AIR), Autoimmune sudden sensorineural hearing loss (SNHL), Balo disease, Behçet's disease, Birdshot chorioretinopathy / birdshot uveitis, Bullous pemphigoid, Castleman disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic autoimmune urticaria, Churg-Strauss syndrome / eosinophilic granulomatosis with polyangiitis (EGPA) , Cogan's syndrome, Cold agglutinin disease, CREST syndrome | limited cutaneous systemic sclerosis, Crohn's disease (CD), Cronkhite-Canada syndrome (CSS), Cryptogenic organizing pneumonia (COP), Dermatitis herpetiformis, Dermatomyositis, Diabetes, type 1, Discoid lupus, Dressler's syndrome / postmyocardial infarction / postpericardiotomy syndrome, Eczema/Atopic Dermatitis, Endometriosis, Eosinophilic esophagitis/eosinophilic gastroenteritis, Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibrosing alveolitis/Idiopathic pulmonary fibrosis (IPF), Giant cell arteritis / temporal arteritis / Horton's disease, Giant Cell Myocarditis, Glomerulonephritis, Goodpasture's syndrome / anti-GBM/anti-TBM disease, Granulomatosis with polyangiitis (GPA) / Wegener's granulomatosis, Graves' disease / thyroid eye disease, Guillain-Barré syndrome (GBS), Hashimoto's thyroiditis / chronic lymphocytic thyroiditis / autoimmune thyroiditis, Henoch-Schönlein purpura / IgA vasculitis, Hidradenitis suppurativa, Hurst's disease / acute hemorrhagic leukoencephalitis (AHLE), Hypogammaglobulinemia, IgA nephropathy / Berger's disease, Immune-mediated necrotizing myopathy (IMNM), Immune thrombocytopenia (ITP) / autoimmune thrombocytopenic purpura / autoimmune thrombocytopenia, Inclusion body myositis, IgG4-related sclerosing disease (ISD), Interstitial cystitis, Juvenile idiopathic arthritis / Adult-onset

Still's disease, Juvenile polymyositis | Juvenile dermatomyositis | juvenile myositis, Kawasaki disease, Lambert-Eaton myasthenic syndrome (LEMS), Leukocytoclastic vasculitis, Lichen planus | Lichen planopilaris, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD) | linear IgA bullous dermatosis (LABD), Lupus nephritis, Lyme disease / chronic Lyme disease / post-treatment Lyme disease syndrome (PTLDS), Lymphocytic colitis/microscopic colitis, Lymphocytic hypophystitis/autoimmune hypophystitis, Ménière's disease, Microscopic polyangiitis (MPA)/ANCA-associated vasculitis, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal motor neuropathy, Multiple sclerosis (MS), Myalgic encephalomyelitis (ME)/ Chronic fatigue syndrome (CFS), Myasthenia gravis (MG), Narcolepsy, Neuromyelitis Optica/Devic's disease, Ocular cicatricial pemphigoid, Opsoclonus-myoclonus syndrome (OMS), Palindromic rheumatism, Paraneoplastic cerebellar degeneration, Paraneoplastic pemphigus, Parry-Romberg syndrome (PRS)/Hemifacial atrophy (HFA)/Progressive facial hemiatrophy, Paroxysmal nocturnal hemoglobinuria (PNH), Peripheral uveitis/pars planitis, PANS/PANDAS, Parsonage-Turner syndrome, Pemphigus gestationis / herpes gestationis, Pemphigus foliaceus, Pemphigus vulgaris, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Postural orthostatic tachycardia syndrome (POTS), Primary biliary cirrhosis (PBC) / primary biliary cholangitis, Primary sclerosing cholangitis (PSC), Psoriasis, Palmoplantar Pustulosis, Psoriatic arthritis, Pulmonary fibrosis, idiopathic (IPF), Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Rasmussen's encephalitis, Raynaud's syndrome/phenomenon, Reactive arthritis / Reiter's syndrome, Reflex sympathetic dystrophy syndrome (RSD) / Complex regional pain syndrome (CRPS), Relapsing polychondritis, Restless leg syndrome (RLS) / Willis-Ekbom disease, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome / autoimmune polyendocrine syndrome type II / polyglandular autoimmune syndrome, type 2, Scleritis, Scleroderma, Sclerosing Mesenteritis / Mesenteric Panniculitis, Serpiginous choroidopathy, Sjögren's syndrome, Stiff person syndrome (SPS), Small fiber sensory neuropathy, s erythematosus (SLE), Subacute bacterial endocarditis (SBE), Subacute cutaneous lupus, Susac syndrome, Sydenham's chorea, Sympathetic ophthalmia, Takayasu's arteritis (vasculitis), Testicular autoimmunity (vasculitis, orchitis), Tolosa-Hunt syndrome, Transverse myelitis (TM), Tubulointerstitial nephritis uveitis syndrome (TINU), Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis anterior/intermediate/posterior, Vasculitis, VEXAS Syndrome, Vitiligo, Vogt-Koyanagi-Harada syndrome (VKH).

7. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 6, wherein the patient is non-responsive to standard of care (SOC) treatment, or not sufficiently responsive to SOC treatment, suffers from side-effects associated with SOC treatment, particularly, wherein the disease is refractory to immunosuppressive treatment, refractory to CAR-T cell treatment, refractory to treatment by plasmapheresis, refractory to treatment selected from the group comprising treatment with glucocorticoids, cyclophosphamide, azathioprine, rituximab baricitinib, hydroxychloroquine, and ruxolitinib, or wherein the patient does not respond to at least one, two, or more standard immunosuppressive drugs.

8. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 7, wherein the molecule is formulated for intravenous administration or continuous intravenous administration.

9. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 8, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 120 µg.

10. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 9, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 112 µg.

11. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 10, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 56 µg.

12. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 11, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg to about 28 µg.

13. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 12, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 5µg/m^2 to about 15 µg/m^2.

14. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 13, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 7 µg/m^2 to about 12 µg/m^2.

15. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 14, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 8 µg/m^2 to about 10 µg/m^2.

16. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 10, wherein the molecule is formulated for intravenous administration or continuous intravenous administration of a daily dose of about 9 µg or 9 µg/m^2.

17. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 16, wherein the molecule is for

administration over a period of at least 3 days, preferably at least 4 days, more preferably for at least 5 days.

18. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 16, wherein the molecule is for administration over a period of up to 42 days, particularly for 40 days.

19. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 16, wherein the molecule is for administration over a first period and/or a second period of up to 42 days, particularly for 5 days, or for 40 days, at a concentration of 9 µg daily.

20. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to claim 19, wherein the molecule is for administration over an additional period of up to 42 days, particularly for 5 days, or for 10 days, or for 40 days at a concentration of 28 µg daily.

21. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a pediatric patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 16, wherein the molecule is for administration over a first period and/or a second period of up to 42 days, particularly for 5 days, or for 40 days, at a concentration of 5 µg/m2.

22. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a pediatric patient suffering from an autoimmune disease or an autoimmune condition according to claim 21, wherein the wherein the molecule is for administration over an additional period of up to 42 days, particularly for 5 days, or for 40 days at a concentration of 15 µg/m2.

23. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an

autoimmune condition according to any of claims 1 to 7, wherein the molecule is formulated for subcutaneous administration.

24. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is SLE or SLE with Lupus Nephritis.

25. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is systemic sclerosis.

26. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is Rheumatoid arthritis.

27. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is Myasthenia gravis.

28. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is dermatomyositis.

29. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is Guillain-Barré syndrome (GBS).

30. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an

autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is Hashimoto's thyroiditis.

31. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to any of claims 1 to 22, wherein the autoimmune disease is Neuromyelitis Optica/Devic's disease.

32. A pharmaceutical composition comprising the molecule as defined in any of the preceding claims for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition.

33. A nucleic acid molecule, or a mixture of at least two different nucleic acid molecules, encoding (a) a single chain polypeptide comprising a first domain binding CD19 and a second domain binding CD3, or (b) encoding separately at least two or more polypeptides encoding a first domain binding CD19 and/or a second domain binding CD3, for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition, wherein said nucleic acid is selected from the group comprising ribonucleic acid, deoxyribonucleic acid, or mixtures thereof.

34. The nucleic acid molecule, or a mixture of at least two different nucleic acid molecules, encoding comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition according to claim 33, wherein said nucleic acid is formulated for administration to said patient.

35. A pharmaceutical composition comprising the nucleic acid molecules according to any of claims 33 and 34 for use in the treatment of a patient suffering from an autoimmune disease or an autoimmune condition.

36. The pharmaceutical composition comprising the nucleic acid molecules according to any of claims 33 to 35 for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, wherein said pharmaceutical composition comprises ingredients suitable for parenteral or intravenous administration.

37. Blinatumomab for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, particularly from systemic sclerosis, SLE, GRA, and RA, particularly from severe systemic sclerosis, wherein blinatumomab is intravenously administered in a first cycle at a dose of 9 µg/day for 5 days followed by a treatment free period, wherein blinatumomab is administered in a second cycle at a dose of 9 µg/day for 5 days followed by a treatment free period, wherein blinatumomab is administered in a third cycle at a dose of 28 µg/day for 5 days followed by a treatment free period, and wherein blinatumomab is administered in a fourth cycle at a dose of 28 µg/day for 10 days followed by a treatment free period.

38. Blinatumomab for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition, particularly from systemic sclerosis, SLE, GRA, and RA, particularly from severe systemic sclerosis, wherein blinatumomab is intravenously administered in a first cycle at a dose of 9 µg/day for 5 days followed by a treatment free period, wherein blinatumomab is administered in a second cycle at a dose of 28 µg/day for 10 days followed by a treatment free period.

39. Blinatumomab for use in the treatment of a patient suffering from an autoimmune disease or autoimmune condition according to claim 36 and 37, wherein the treatment free period has a duration of 5 to 10 days, particularly, 7 days.

40. Blinatumomab for use in the treatment of a patient suffering from SLE, wherein the subject suffers from active SLE.

41. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from SLE according to claim 39, wherein the subject suffers from refractory SLE.

42. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from SLE according to claim 39 and 40, wherein the subject suffers from refractory SLE with nephritis.

43. The molecule comprising a first domain binding CD19 and a second domain binding CD3 for use in the treatment of a patient suffering from SLE according to claim 39 to 41, wherein the patient is an adult patient.

44. Blinatumomab for use in the treatment of a patient suffering from SLE according to any one of claims 40-43, wherein blinatumomab is for subcutaneous administration.

45. Blinatumomab for use in the treatment of a patient suffering from SLE according to claim 44, wherein blinatumomab is for subcutaneous administration, at a dose of at least 25 micrograms per week.

46. Blinatumomab for use in the treatment of a patient suffering from SLE according to claim 44 and 45, wherein blinatumomab is for subcutaneous administration at a dose of at least 40 micrograms per week.

47. Blinatumomab for use in the treatment of a patient suffering from SLE according to claim 44 to 46, wherein blinatumomab is for subcutaneous administration at least 100 micrograms per week.

48. Blinatumomab for use in the treatment of a patient suffering from SLE according to claim 44 to 47, wherein the blinatumomab is for subcutaneous administration at a dose of at least 250 micrograms per week.

49. Blinatumomab for use in the treatment of a patient suffering from SLE according to claim 44 to 48, wherein blinatumomab is for subcutaneous administration at least 500 micrograms per week.

50. Blinatumomab in the treatment of a patient suffering from SLE according to claim 44 to 49, wherein blinatumomab is for subcutaneous administration at least 1000 micrograms per week.

51. Blinatumomab in the treatment of a patient suffering from SLE according to claims 44 to 50, wherein blinatumomab is administered for at least 6 weeks.

52. Blinatumomab in the treatment of a patient suffering from SLE according to claims 44 to 51, wherein blinatumomab is administered for at least 12 weeks.

53. Blinatumomab in the treatment of a patient suffering from SLE according to claims 39 to 52, wherein the patient is an adult with a diagnosis of an active and refractory SLE and Class III/IV glomerulonephritis who have experienced a failure to respond to previous standard therapies including immunosuppressive therapies and/or treatment with a biological agent.

54. Blinatumomab for use in the treatment of a patient suffering from refractory RA, wherein the molecule is for subcutaneous administration.

55. The use of blinatumomab in the treatment of a patient suffering from refractory RA according to claim 54, wherein blinatumomab is for subcutaneous administration, at a dose of at least 25 micrograms per week.

56. The use of blinatumomab in the treatment of a patient suffering from refractory RA according to claim 54 and 55, wherein blinatumomab is for subcutaneous administration at a dose of at least 40 micrograms per week.

57. The use of blinatumomab in the treatment of a patient suffering from refractory RA according to claim 54 to 56, wherein blinatumomab is for subcutaneous administration at least 100 micrograms or at least 120 µg per week.

58. The use of blinatumomab in the treatment of a patient suffering from refractory RA according to claim 54 to 57, wherein blinatumomab is for subcutaneous administration at a dose of at least 250 micrograms per week.

59. The use of blinatumomab in the treatment of a patient suffering from refractory RA according to claim 54 to 58, wherein blinatumomab is for subcutaneous administration at least 500 micrograms per week.

60. The use of blinatumomab in the treatment of a patient suffering from refractory RA according to claim 54 to 59, wherein blinatumomab is for subcutaneous administration at least 1000 micrograms per week.

61. The use of a blinatumomab for use in the treatment of a patient suffering from refractory RA according to claims 54 to 60, wherein blinatumomab is administered for at least 6 weeks.

62. The use of a blinatumomab for use in the treatment of a patient suffering from refractory RA according to claims 54 to 61, wherein blinatumomab is administered for at least 12 weeks.

63. The use of blinatumomab for use in the treatment of a patient suffering from refractory RA according to claims 56 to 62, wherein the patient has moderate to severe active disease despite having received treatment with a csDMARD and at least two bDMARDs of different mechanisms of action, or one bDMARD and at least one tsDMARD.