

COMPOSITIONS AND METHODS FOR TREATING NON-INFLAMMATORY PAIN IN SUBJECTS WITH RHEUMATOID ARTHRITIS

5 RELATED APPLICATIONS

This application claims priority to U.S. Provisional Patent Application Serial Nos. 63/032,035, filed May 29, 2020, and 63/077,378, filed September 11, 2020, and EP Provisional Patent Application Serial No. 21315081.6, filed May 11, 2021. The entire disclosure of each of these applications is hereby incorporated herein by reference in its entirety.

10

FIELD

The present disclosure relates to the field of therapeutic treatment of non-inflammatory pain in subjects who have or who have had rheumatoid arthritis.

15 BACKGROUND

Rheumatoid arthritis (RA) is the most common form of autoimmune inflammatory arthritis, affecting about 1% of the population. It is an autoimmune disease in which the body's immune system attacks the lining of the membranes that surround joints. RA causes chronic inflammation which can result in joint pain, swelling and stiffness. Pain is a core-set domain and a troubling symptom to patients with RA, and may be directly related to inflammation; however, noninflammatory pain (NIP) is also common in patients with RA.

Sarilumab is an interleukin-6 receptor antagonist for treatment of adults with moderately to severely active RA with an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs).

25

SUMMARY

This disclosure provides methods and compositions for treating NIP in a subject who has rheumatoid arthritis. In various embodiments, treating the subject comprises administering a therapeutically effective amount of an antibody that specifically binds IL-6R.

30 In one aspect, the disclosure provides methods for treating non-inflammatory pain (NIP) in a subject in need thereof with rheumatoid arthritis, comprising administering to the subject a therapeutically effective dose of an antibody that specifically binds IL-6 receptor, wherein the antibody comprises a heavy chain variable region comprising complementarity determining regions HCDR1, HCDR2, and HCDR3 and a light chain variable region

comprising complementary determining regions LCDR1, LCDR2, and LCDR3, wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8. In various embodiments, the antibody that specifically binds to the IL-6 receptor comprises a heavy chain variable region sequence SEQ ID NO: 1 and a light chain variable region sequence of SEQ ID NO: 2. In various embodiments, the subject has a tender joint count (TJC) of at least 21. In various embodiments, the tender joint count differs from a swollen joint count by at least 5. In various embodiments, the antibody is administered subcutaneously. In various embodiments, the subject is administered a dose of about 150 mg or about 200 mg of the antibody. In various embodiments, the antibody is administered to the subject at least once every two weeks. In various embodiments, the subject has moderately to severely active rheumatoid arthritis. In various embodiments, the subject is not administered any other DMARD in course of administration with the antibody. In various embodiments, the subject is also administered one or more additional DMARDs with the antibody. In various embodiments, the one or more additional DMARDs comprise methotrexate. In various embodiments, the one or more additional DMARDs comprise a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. In various embodiments, the subject was previously ineffectively treated for rheumatoid arthritis by administering at least one DMARD distinct from the antibody. In various embodiments, the DMARD is methotrexate. In various embodiments, the DMARD is a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. In various embodiments, the subject is intolerant of one or more DMARDs, or wherein the subject is considered an inappropriate candidate for continued treatment with one or more DMARDs. In various embodiments, the subject has had an inadequate response to one or more DMARDs. In various embodiments, the DMARD is methotrexate. In various embodiments, the DMARD is a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol.

In another aspect, the present disclosure provides methods for treating NIP in a subject in need thereof, comprising selecting a subject who has rheumatoid arthritis and NIP; and administering to the subject a therapeutically effective dose of an antibody that specifically

binds IL-6 receptor, wherein the antibody comprises a heavy chain variable region comprising complementarity determining regions HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising complementary determining regions LCDR1, LCDR2, and LCDR3, wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8. In various embodiments, the antibody that specifically binds to the IL-6 receptor comprises a heavy chain variable region sequence SEQ ID NO: 1 and a light chain variable region sequence of SEQ ID NO: 2. In various embodiments, the subject has a TJC of at least 21. In various embodiments, the tender joint count differs from a swollen joint count by at least 5. In various embodiments, the antibody is administered subcutaneously. In various embodiments, the subject is administered a dose of about 150 mg or about 200 mg of the antibody. In various embodiments, the antibody is administered to the subject at least once every two weeks. In various embodiments, the subject has moderately to severely active rheumatoid arthritis. In various embodiments, the subject is not administered any other DMARD in course of administration with the antibody. In various embodiments, the subject is also administered one or more additional DMARDs with the antibody. In various embodiments, the one or more additional DMARDs comprise methotrexate. In various embodiments, the one or more additional DMARDs comprise a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. In various embodiments, the subject was previously ineffectively treated for rheumatoid arthritis by administering at least one DMARD distinct from the antibody. In various embodiments, the DMARD is methotrexate. In various embodiments, the DMARD is a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. In various embodiments, the subject is intolerant of one or more DMARDs, or wherein the subject is considered an inappropriate candidate for continued treatment with one or more DMARDs. In various embodiments, the subject has had an inadequate response to one or more DMARDs. In various embodiments, the DMARD is methotrexate. In various embodiments, the DMARD is a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol.

In another aspect, the present disclosure provides antibodies for use in treating NIP in a patient in need thereof with rheumatoid arthritis, wherein the antibodies specifically bind IL-6 receptor, and wherein the antibodies comprise a heavy chain variable region comprising complementarity determining regions HCDR1, HCDR2, and HCDR3 and a light chain variable region comprising complementary determining regions LCDR1, LCDR2, and LCDR3, wherein: HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and LCDR3 comprises the amino acid sequence of SEQ ID NO: 8. In various embodiments, the antibody specifically binds to the IL-6 receptor comprises a heavy chain variable region sequence SEQ ID NO: 1 and a light chain variable region sequence of SEQ ID NO: 2. In various embodiments, the subject has a TJC of at least 21. In various embodiments, the tender joint count differs from a swollen joint count by at least 5. In various embodiments, the antibody is administered subcutaneously. In various embodiments, the subject is administered a dose of about 150 mg or about 200 mg of the antibody. In various embodiments, the antibody is administered to the subject at least once every two weeks. In various embodiments, the subject has moderately to severely active rheumatoid arthritis. In various embodiments, the subject is not administered with any other DMARD in course of administration with the antibody. In various embodiments, the subject is also administered one or more additional DMARDs with the antibody. In various embodiments, the one or more additional DMARDs comprise methotrexate. In various embodiments, the one or more additional DMARDs comprise a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. In various embodiments, the subject was previously ineffectively treated for rheumatoid arthritis by administering at least one DMARD different from the antibody. In various embodiments, the DMARD is methotrexate. In various embodiments, the DMARD is a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol. In various embodiments, the subject is intolerant of one or more DMARDs, or wherein the subject is considered an inappropriate candidate for continued treatment with one or more DMARDs. In various embodiments, the subject has had an inadequate response to one or more DMARDs. In various embodiments, the DMARD is methotrexate. In various embodiments, the DMARD is

a TNF antagonist. In various embodiments, the TNF antagonist is selected from the group consisting of etanercept, infliximab, adalimumab, golimumab and certolizumab pegol.

BRIEF DESCRIPTION OF THE FIGURES

5 The foregoing and other features and advantages of the present invention will be more fully understood from the following detailed description of illustrative embodiments taken in conjunction with the accompanying drawings.

FIG. 1 shows percentage of patients who had NIP by week 12 and 24, by treatment.

FIG. 2 shows NIP status of sarilumab or adalimumab responders at week 24.

10

DETAILED DESCRIPTION

 Inflammation is a key driver of pain in rheumatoid arthritis (RA). However, some patients experience more pain than would be expected based on the amount of synovitis observed, which may indicate the presence of noninflammatory pain (NIP). This disclosure
15 provides pharmaceutical compositions and methods of using these compositions for the treatment of NIP in subjects with RA. These compositions and methods include at least one antibody that specifically binds interleukin-6 receptor (hIL-6R).

 As used within the claims, the Summary, and the Detailed Description herein, the term “about” in quantitative terms refers to plus or minus 10% of the value it modifies (rounded up
20 to the nearest whole number if the value is not sub-dividable, such as a number of molecules or nucleotides). For example, the phrase “about 100 mg” would encompass 90 mg to 110 mg, inclusive; the phrase “about 2500 mg” would encompass 2250 mg to 2750 mg. When applied to a percentage, the term “about” refers to plus or minus 10% relative to that percentage. For example, the phrase “about 20%” would encompass 18-22% and “about 80%” would
25 encompass 72-88%, inclusive. Moreover, where “about” is used herein in conjunction with a quantitative term it is understood that in addition to the value plus or minus 10%, the exact value of the quantitative term is also contemplated and described. For example, the term “about 23%” expressly contemplates, describes, and includes exactly 23%.

 It is to be noted that the term “a” or “an” entity refers to one or more of that entity; for
30 example, “a symptom,” is understood to represent one or more symptoms. As such, the terms “a” (or “an”), “one or more,” and “at least one” can be used interchangeably herein.

 Furthermore, “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,”

“A” (alone), and “B” (alone). Likewise, the term “and/or” as used in a phrase such as “A, B and/or C” is intended to encompass each of the following aspects: A, B and C; A, B or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

It is understood that wherever aspects are described herein with the language
5 "comprising," otherwise analogous aspects described in terms of “consisting of” and/or “consisting essentially of” are also provided.

The term “pain” refers to discomfort caused by intense or damaging stimuli, including illness, injury, or mental anguish. In some embodiments, pain has both physical and emotional components and it is experienced as an unpleasant sensation that can range from mild, localized
10 discomfort to agony.

As used herein, “acute pain” refers to pain that lasts less than 3 months. In some embodiments, acute pain is associated with soft tissue damage and gradually resolves as the damage heals. Acute pain is detected by specialized nerve receptors (nociceptors) that detect and respond to strong signals that relay information about danger to the organism, presumably
15 so that the organism can mobilize defenses. In RA, persistent signaling from within inflamed joints can lead to lowering of the threshold for stimulation of nociceptors with resultant hypersensitivity to nociceptive stimulation (peripheral sensitization). It is likely that local factors, such as cytokines, may exert direct, noninflammatory effects on sensory neurons.

The term “chronic pain” refers to pain that lasts at least 3 months. In some
20 embodiments, chronic pain is described as pain that extends beyond the expected period of healing. In some embodiments, chronic pain includes unanticipated prolonged pain in patients with RA who appear to be in remission. Chronic pain is often associated with central sensitization and may be a manifestation of aberrant neuronal activity from peripheral sensitization of primary sensory neurons and subsequent or additional sensitization of neurons
25 in the CNS. There may be little or no relationship to prior or current inflammation in this state.

The term “non-inflammatory pain” or “NIP” refers to pain not associated with inflammation, as described above. In some cases, the NIP may be due to arthralgia or polyarthralgia. NIP typically presents with an absence of systemic symptoms such as fever or weight loss. NIP can also present without swelling or warmth. NIP can also be characterized
30 by minimal morning stiffness which is intermittent, lasts less than 60 minutes and/or stiffness which is made worse, not improved, by activity. In some embodiments, NIP includes acute or chronic pain. In some embodiments, NIP includes allodynia, enhanced pain and neuropathic pain. In some embodiments, a subject with NIP also is experiencing central sensitization. In some embodiments, subjects with NIP are earlier in the course of RA. In some embodiments,

these subjects have not been diagnosed with RA and do not show symptoms of inflammation. In some embodiments, subjects with NIP have extra-articular or diffuse pain.

As used herein, “central sensitization” refers to anomalies in spinal and brain pain processing which result in increased pain sensitivity at diffuse sites and result in a heightened overall response state throughout the central nervous system (CNS) in response to sensory impulses, which are interpreted in the brain through a complex filter as enhanced pain. This category may include psychosocial interplay with pain perception to a chronic pain state. In central sensitization, new nociceptive pathways are created, for example, by recruiting mechanoreceptors to conduct pain. This occurs mainly by producing increased sensitization in the spine and, in time, this state can become self-perpetuating even in the absence of injury, and unrelated to any protective purpose.

Thus, in some embodiments, in a patient with underlying inflammatory pain from RA which might intrinsically cause mild pain only. As used herein, “hyperalgesia” or “enhanced pain” refers to relatively mild pain that is exaggerated and experienced as a much more intense pain. Sensations of pain in this state may also be produced from usually nonpainful stimuli such as movement (for example, making a fist) which are normally interpreted as informational inputs. As used herein, “allodynia” refers to pain that results from typically nonpainful stimuli. Clinical observation suggests a disconnect between pain and inflammation in some cases of early RA, for example, bilateral symmetrical small arthralgias can occur prior to any objective evidence of joint inflammation. Conversely, some patients with RA may present with joint inflammation (and joint damage) only, without pain (the “robust rheumatoid” type). In some embodiments, there is a spectrum of RA presentation with phenotypes ranging from patients with mainly identifiable synovitis with accompanying pain to those who present with pain only. Attempts have been made to identify these latter patients with RA who have noninflammatory pain earlier in the course of disease, for example through the use of the swollen to tender joint count ratio.

Discordance between patient self-reported pain and objective evaluation of inflammation has been reported, and patient-reported pain appears to correlate poorly with physicians’ assessments and measures of inflammation across studies. The view that pain is not solely derived from inflammation is also supported by observations that anti-cytokine treatments produce pain relief well before reduction in inflammation, and that residual pain persists in some 12–50% of patients in remission, and in 82% of patients with “somewhat to completely controlled” disease following treatment of the inflammatory component of RA. Rheumatologists often attribute this residual pain to fibromyalgia or to underlying joint damage

from RA, but the latter explanation seems unlikely given radiographic damage has been shown to account for only 2.1% of patient-reported pain. The proportion of patients with RA fulfilling fibromyalgia classification criteria increases also throughout the course of disease progression, which again suggests central pain augmentation.

5 RA is a disease involving joints, but, in some embodiments, pain is often reported as being extra-articular and it may be diffuse, with widespread achiness in remote, non-articular sites as well as in joints, and can vary in location and time. This pain does not appear to be related to synovitis and is likely due to alteration of central pain processing. To the perceptive clinician there are sometimes clues hinting that aspects of pain in patients with RA may derive
10 from nervous system involvement, for example, when sensations of pain are reported as tingling, burning, or as sharp. CNS involvement is getting clearer; a substantial proportion of patients with RA have some form of identifiable neuropathic involvement. Autonomic neuropathy too is increasingly identified as associated with RA. As such, in some embodiments the CNS is a significant associated organ system in RA.

15 The many clinically apparent dissociations between pain and inflammation suggests some RA pain may be an independent problem overlapping with, but not solely due to inflammation with multiple mechanisms involved. In some embodiments, patient pain in RA originates with some form of inflammation or injury, but, in addition, RA patients feel pain that is also concurrently and independently triggered (with no or minor sensory stimulation),
20 passed on by the peripheral nervous system, amplified in the spinal cord and experienced in the CNS. In the brain, the sensations from more distally are interwoven with external psychosocial factors. Indeed, pain has been described as “an opinion.” In various embodiments, this pain is a distinct entity from the pain of inflammation, and this form of pain is at least partly due to aberrancies related to cytokine dysregulation.

25 In some embodiments, cytokines cause joint inflammation (which in turn causes pain), but there can be other effects of cytokines on peripheral and also other parts of the nervous system that lead to pain more directly, and do not necessarily correlate with inflammation. In some embodiments, the cytokine IL-6 plays an important role in this.

In some embodiments, NIP is defined as a difference between the 28-joint tender joint count (TJC) and swollen joint count (SJC), using the established formula: $TJC - SJC \geq 7$.
30

In some embodiments, pain experienced in the previous week is measured. In some embodiments, pain experienced in the previous 2, 3, 4, 5, 6, 7, 8 or more weeks is measured. In some embodiments, pain experienced in the previous month is measured. In some embodiments, pain experienced in the previous, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or more months

is measured. In some embodiments, pain experienced in the previous year is measured. In some embodiments, pain experienced for the previous 2, 3, 4, 5, 6, 7, 8, 9, 10 or more years is measured.

IL-6 interacts directly with the IL-6R α subunit and the IL-6/IL-6R α pair forms a high affinity complex with the glycoprotein 130 (gp130) subunit and initiates intracellular signaling via the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) (JAK/STAT) and Ras Raf-mitogen-activated protein kinase (MAPK) pathways. IL-6R α also exists in a soluble form, which is involved in trans-signaling and allows IL-6 to affect cells that do not express IL-6R α including synovial cells in the joint.

Sarilumab (SAR153191), also designated as REGN88, is a recombinant IgG1 kappa monoclonal antibody of fully human sequence directed against the alpha subunit of the IL-6 receptor complex (IL-6R α). Sarilumab blocks the binding of IL-6 and interrupts the cytokine-mediated signaling cascade.

15

Antibodies

The present disclosure includes methods that comprise administering to a subject an antibody, or an antigen-binding fragment thereof, that binds specifically to hIL-6R. As used herein, the term “hIL-6R” means a human cytokine receptor that specifically binds human interleukin-6 (IL-6). In certain embodiments, the antibody that is administered to the patient binds specifically to the extracellular domain of hIL-6R.

The term “antibody,” as used herein, refers to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (e.g., IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region comprises one domain (CL1). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In some embodiments, the FRs of the antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be

naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

The term “antibody,” as used herein, also includes antigen-binding fragments of full antibody molecules. The terms “antigen-binding portion” of an antibody, “antigen-binding
5 fragment” of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the
10 manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to
15 introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')₂ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity
20 determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g., monovalent nanobodies, and bivalent nanobodies), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also
25 encompassed within the expression “antigen-binding fragment,” as used herein.

An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a VH domain associated with a
30 VL domain, the VH and VL domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain VH-VH, VH-VL or VL-VL dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric VH or VL domain.

In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody include: (i) VH-CH1; (ii) VH-CH2; (iii) VH-CH3; (iv) VH-CH1-CH2; (v) VH-CH1-CH2-CH3; (vi) VH-CH2-CH3; (vii) VH-CL; (viii) VL-CH1; (ix) VL-CH2; (x) VL-CH3; (xi) VL-CH1-CH2; (xii) VL-CH1-CH2-CH3; (xiii) VL-CH2-CH3; and (xiv) VL-CL. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may in various embodiments consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody may in various embodiments comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric VH or VL domain (e.g., by disulfide bond(s)).

In certain embodiments, the antibody or antibody fragment for use in a method disclosed herein may be a monospecific antibody. In certain embodiments, the antibody or antibody fragment for use in a method disclosed herein may be a multispecific antibody, which may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context certain embodiments involves the use of a first immunoglobulin (Ig) CH3 domain and a second Ig CH3 domain, wherein the first and second Ig CH3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig CH3 domain binds Protein A and the second Ig CH3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second CH3 may further comprise an Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second CH3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q,

and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of certain embodiments. Any multispecific antibody format, including the exemplary bispecific antibody formats disclosed herein, may in various embodiments be adapted for use in the context of an antigen-binding fragment of an anti-IL-6R antibody using routine techniques available in the art.

The fully-human anti-IL-6R antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present disclosure includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are back-mutated to the corresponding germline residue(s) or to a conservative amino acid substitution (natural or non-natural) of the corresponding germline residue(s) (such sequence changes are referred to herein as "germline back-mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline back-mutations or combinations thereof. In certain embodiments, all of the framework residues and/or CDR residues within the VH and/or VL domains are mutated back to the germline sequence. In other embodiments, only certain residues are mutated back to the germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. Furthermore, included herein are antibodies that may contain any combination of two or more germline back-mutations within the framework and/or CDR regions, i.e., wherein certain individual residues are mutated back to the germline sequence while certain other residues that differ from the germline sequence are maintained. Once obtained, antibodies and antigen-binding fragments that contain one or more germline back-mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present disclosure.

The constant region of an antibody is important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

The term "human antibody," as used herein, is intended to include antibodies having
5 variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies featured in the disclosure may in various embodiments nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in some embodiments CDR3. However, the term
10 "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "recombinant human antibody," as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such
15 as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene
20 sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant
25 antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo.

Human antibodies can exist in two forms that are associated with hinge heterogeneity. In an embodiment, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain
30 disulfide bond. In another embodiment, the dimers are not linked via inter-chain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). In certain embodiments, these forms have been extremely difficult to separate, even after affinity purification.

The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form to levels typically observed using a human IgG1 hinge. The instant disclosure encompasses in various embodiments antibodies having one or more mutations in the hinge, CH2 or CH3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

An "isolated antibody," as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody." In various embodiments, the isolated antibody also includes an antibody in situ within a recombinant cell. In other embodiments, isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. In various embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an antibody that "specifically binds" IL-6R, as used herein, includes antibodies that bind IL-6R (e.g., human IL-6R) or portion thereof with a KD of less than about 1000 nM, less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or about 0.5 nM, as measured in a surface plasmon resonance assay. In some embodiments, the antibody binds IL-6R (e.g., human IL-6R α) with a KD of from about 0.1 nM to about 1000 nM or from about 1 nM to about 100 nM. In some embodiments, the antibody binds IL-6R (e.g., human IL-6R α) with a KD of from about 1 pM to about 100 pM or from about 40 pM to about 60 pM. Specific binding can also be characterized by a dissociation constant of at least about 1×10^{-6} M or smaller. In other embodiments, the dissociation constant is at least about 1×10^{-7} M, 1×10^{-8} M,

or 1×10^{-9} M. An isolated antibody that specifically binds human IL-6R may, however, have cross-reactivity to other antigens, such as IL-6R molecules from other (non-human) species.

The term “surface plasmon resonance,” as used herein, refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE® system (Biacore Life Sciences division of GE Healthcare, Piscataway, NJ).

The term “KD,” as used herein, is intended to refer to the equilibrium dissociation constant of an antibody-antigen interaction.

The term “epitope” refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstance, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

The anti-IL-6R antibodies useful for the methods described herein may in various embodiments include one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences from which the antibodies were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present disclosure includes in various embodiments methods involving the use of antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as “germline mutations”). Numerous antibodies and antigen-binding fragments may be constructed which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the VH and/or VL domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence,

e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a certain germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. The use of antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present disclosure.

The present disclosure also includes methods involving the use of anti-IL-6R antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present disclosure includes the use of anti-IL-6R antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

According to the present disclosure, the anti-IL-6R antibody, or antigen-binding fragment thereof, in various embodiments comprises a heavy chain variable region (HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising any of the amino acid sequences of the anti-IL-6R antibodies described in U.S. Patent No. 7,582,298, incorporated herein by reference in its entirety. In certain embodiments, the anti-IL-6R antibody or antigen-binding fragment thereof comprises the heavy chain complementarity determining regions (HCDRs) of a HCVR comprising the amino acid sequence of SEQ ID NO: 1 and the light chain complementarity determining regions (LCDRs) of a LCVR comprising the amino acid sequence of SEQ ID NO: 2. According to certain embodiments, the anti-IL-6R antibody or antigen-binding fragment thereof comprises three HCDRs (i.e., HCDR1, HCDR2 and HCDR3) and three LCDRs (i.e., LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 3; the

HCDR2 comprises the amino acid sequence of SEQ ID NO: 4; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 5; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 6; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 8. In yet other embodiments, the anti-IL-6R antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 1 and an LCVR comprising the amino acid sequence of SEQ ID NO: 2.

In another embodiment, the anti-IL-6R antibody or antigen-binding fragment thereof comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 and a light chain comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the extracellular domain of hIL-6R comprises the amino acid sequence of SEQ ID NO: 11. According to certain exemplary embodiments, the methods of the present disclosure comprise the use of the anti-IL-6R antibody referred to and known in the art as sarilumab, or a bioequivalent thereof.

The amino acid sequence of SEQ ID NO: 1 is

EVQLVESGGGLVQPGRSLRLSCAASRFTFDDYAMHWVRQAPGKGLEWVSGI
SWNSGRIGYADSVKGRFTISRDN AENSLFLQMNGLR AEDTALYYCAKGRDSFDIWG
QGTMTVTVSS.

The amino acid sequence of SEQ ID NO: 2 is

DIQMTQSPSSVSASVGDRVITITCRASQGISSWLAWYQQKPGKAPKLLIYGASS
LESGVPSRFSGSGSGTDFTLTISLQPEDFASYCQQANSFPYTFGQGTKLEIK.

The amino acid sequence of SEQ ID NO: 3 is RFTFDDYA.

The amino acid sequence of SEQ ID NO: 4 is ISWNSGRI.

The amino acid sequence of SEQ ID NO: 5 is AKGRDSFDI.

The amino acid sequence of SEQ ID NO: 6 is QGISSW.

The amino acid sequence of SEQ ID NO: 7 is GAS.

The amino acid sequence of SEQ ID NO: 8 is QQANSFPYT.

The amino acid sequence of SEQ ID NO: 9 is

EVQLVESGGGLVQPGRSLRLSCAASRFTFDDYAMHWVRQAPGKGLEWVSGISWNS
GRIGYADSVKGRFTISRDN AENSLFLQMNGLR AEDTALYYCAKGRDSFDIWGQGT
MTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTF
PAVLQSSGLYSLSSVTVTPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP
CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVH
NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG

QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFCSSVMHEALHNHYTQKSLSLSPGK.

The amino acid sequence of SEQ ID NO: 10 is

DIQMTQSPSSVSASVGDRVITICRASQGISSWLAWYQQKPGKAPKLLIYGASSLESGV
5 PSRFGSGSGTDFTLTISSLQPEDFASYCQQANSFPYTFGQGTKLEIKRTVAAPSVFIF
PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYS
LSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNRGEC.

The sequence of SEQ ID NO: 11 is

MVAVGCALLAALLAAPGAALAPRRCPAQEVARGVLTSLPGDSVTLTCTPGVEPEDNA
10 TVHWVLRKPAAGSHPSRWAGMGRRLLRSVQLHDSGNYSCYRAGRPAGTVHLLVD
VPPEEPQLSCFRKSPLSNVCEWGPRSTPSLTTKAVLLVRKFQNSPAEDFQEPQCYSQ
ESQKFSCQLAVPEGDSSFYIVSMCVASSVGSKFSKTQTFQGCILQPDPPANITVTAV
ARNPRWLSVTWQDPHSWNSSFYRLRFELRYAERSKTFTTWMVKDLQHHCVIHDA
WSGLRHVVQLRAQEEFGQGEWSEWSPEAMGTPWTESRPPAENEVSTPMQALTTN
15 KDDDNILFRDSANATSLPVQD.

The term “bioequivalent” as used herein, refers to a molecule having similar bioavailability (rate and extent of availability) after administration at the same molar dose and under similar conditions (e.g., same route of administration), such that the effect, with respect to both efficacy and safety, can be expected to be essentially same as the comparator molecule.

20 Two pharmaceutical compositions comprising an anti-IL-6R antibody are bioequivalent if they are pharmaceutically equivalent, meaning they contain the same amount of active ingredient (e.g., IL-6R antibody), in the same dosage form, for the same route of administration and meeting the same or comparable standards. Bioequivalence can be determined, for example, by an in vivo study comparing a pharmacokinetic parameter for the two compositions.
25 Parameters commonly used in bioequivalence studies include peak plasma concentration (C_{max}) and area under the plasma drug concentration time curve (AUC).

The disclosure in certain embodiments relates to methods comprising administering to the subject an antibody which comprises the heavy chain variable region comprising sequence SEQ ID NO: 1 and the light chain variable region comprising sequence SEQ ID NO: 2.

30 The disclosure provides pharmaceutical compositions comprising such antibody, and methods of using these compositions.

The antibody in various embodiments comprises the heavy chain variable region comprising sequence SEQ ID NO: 1 and the light chain variable region comprising sequence SEQ ID NO: 2 is an antibody that specifically binds human interleukin-6 receptor (hIL-6R).

See international publication number WO2007/143168, incorporated herein by reference in its entirety. In one embodiment, the antibody comprises the heavy chain variable region comprising sequence SEQ ID NO: 9 and the light chain variable region comprising sequence SEQ ID NO: 10. In various embodiments, the antibody is sarilumab.

5

DMARDs

Disease-modifying antirheumatic drugs (DMARDs) are drugs defined by their use in rheumatoid arthritis to slow down disease progression. DMARDs have been classified as synthetic (sDMARD) and biological (bDMARD). Synthetic DMARDs include non-exhaustively methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. Biological DMARDs include non-exhaustively adalimumab, golimumab, etanercept, abatacept, infliximab, rituximab, and tocilizumab. In some embodiments, the DMARD is a TNF antagonist. TNF antagonists include, but are not limited to, etanercept, infliximab, adalimumab, golimumab and certolizumab pegol.

15

Methods of Administration and Formulations

The methods described herein comprise administering a therapeutically effective amount of an anti-IL-6R antibody to a subject. As used herein, an “effective amount” or “therapeutically effective amount” is a dose of the therapeutic that results in treatment of NIP. In certain embodiments, effective amount is a dose of the therapeutic that results in treatment of NIP that persists despite inflammation control (IC). As used herein, “treating” refers to causing a detectable improvement in one or more symptoms associated with NIP or causing a biological effect (e.g., a decrease in the level of a particular biomarker) that is correlated with the underlying pathologic mechanism(s) giving rise to the condition or symptom(s). For example, a dose of anti-IL-6R antibody which causes a reduction in NIP is deemed a “therapeutically effective amount.”

An “improvement” in an NIP-associated symptom in various embodiments refers reduction in the incidence of the pain symptom which may correlate with an improvement in one or more pain-associated tests, scores or metrics (as described herein). For example, the improvement may correlate a decrease from baseline of one or more of pain criteria. In various embodiments, improvement may comprise a decrease in VAS from baseline. As used herein, the term “baseline,” with regard to a pain-associated parameter, means the numerical value of the pain-associated parameter for a patient prior to or at the time of administration of the antibody of the present technology. A detectable “improvement” can also be detected using at

least one test, score or metric described herein. In various embodiments, the improvement is detected using VAS. In various embodiments, the improvement is characterized by its relation to a subject's PASS status.

5 In various embodiments, previous treatment with a DMARD other than an anti-IL-6R antibody (such as sarilumab) has been inadequate (e.g., as assessed by the subject and/or a physician), has been ineffective and/or has not resulted in a detectable improvement in one or more parameters or symptoms associated with NIP and/or has not caused a biological effect that is correlated with the underlying pathologic mechanism(s) giving rise to the condition or symptom(s) of NIP.

10 In various embodiments, a IL-6R antibody is administered subcutaneously. In various embodiments, the IL-6R antibody is sarilumab.

In various embodiments, a therapeutically effective amount of anti-IL-6R antibody that is administered to the subject will vary depending upon the age and the size (e.g., body weight or body surface area) of the subject as well as the route of administration and other factors well known to those of ordinary skill in the art.

15 In various embodiments, the dose is a fixed dose regardless of the body weight or surface area of the subject. In various embodiments, the subject is at least 18 years old. In various embodiments, the subject is from 30 to 100 years old. In various embodiments, the subject is from 35 to 100 years old. In various embodiments, the subject is from 35 to 8 years old. In various embodiments, the subject is from 40 to 70 years old.

20 The disclosure provides methods of using therapeutic compositions comprising anti-IL-6R antibodies or antigen-binding fragments thereof and, optionally, one or more additional therapeutic agents. The therapeutic compositions of the present disclosure will be administered with suitable carriers, excipients, and/or other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN®), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax.

30 Various delivery systems are known and can be used to administer pharmaceutical compositions provided herein, e.g., encapsulation in liposomes, microparticles, microcapsules, receptor mediated endocytosis. Methods of introduction include, but are not limited to,

intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other
5 biologically active agents. Administration can be systemic or local. The IL-6R antibody can be administered subcutaneously.

The pharmaceutical composition can also be delivered in a vesicle, such as a liposome. In certain embodiments, the pharmaceutical composition can be delivered in a controlled release system, for example, with the use of a pump or polymeric materials. In certain
10 embodiments, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose.

The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, local injection, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the
15 injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as
20 an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc.). As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate
25 ampoule.

The antibody is typically formulated as described herein and in international publication number WO2011/085158, incorporated herein by reference in its entirety.

In various embodiments, the antibody is administered as an aqueous buffered solution at about pH 6.0 containing

- 30
- about 21 mM histidine,
 - about 45 mM arginine,
 - about 0.2% (w/v) polysorbate 20,
 - about 5% (w/v) sucrose, and
 - between about 100 mg/mL and about 200 mg/mL of the antibody.

In another embodiment, the antibody is administered as an aqueous buffered solution at about pH 6.0 containing

- about 21 mM histidine,
- about 45 mM arginine,
- 5 - about 0.2% (w/v) polysorbate 20,
- about 5% (w/v) sucrose, and
- at least about 130 mg/mL of the antibody.

In another embodiment, the antibody is administered as an aqueous buffered solution at about pH 6.0 containing

- 10 - about 21 mM histidine,
- about 45 mM arginine,
- about 0.2% (w/v) polysorbate 20,
- about 5% (w/v) sucrose, and
- about 131.6 mg/mL of the antibody.

15 In another embodiment, the antibody is administered as an aqueous buffered solution at about pH 6.0 containing

- about 21 mM histidine,
- about 45 mM arginine,
- about 0.2% (w/v) polysorbate 20,
- 20 - about 5% (w/v) sucrose; and
- about 175 mg/mL of the antibody.

In other embodiments, the antibody is administered as an aqueous buffered solution at pH 6.0 containing

- 21 mM histidine,
- 25 - 45 mM arginine,
- 0.2% (w/v) polysorbate 20,
- 5% (w/v) sucrose, and
- between 100 mg/mL and 200 mg/mL of the antibody.

In another embodiment, the antibody is administered as an aqueous buffered solution at pH 6.0 containing

- 30 - 21 mM histidine,
- 45 mM arginine,
- 0.2% (w/v) polysorbate 20,

- 5% (w/v) sucrose, and
- at least 130 mg/mL of the antibody.

In another embodiment, the antibody is administered as an aqueous buffered solution at pH 6.0 containing

- 5
- 21 mM histidine,
 - 45 mM arginine,
 - 0.2% (w/v) polysorbate 20,
 - 5% (w/v) sucrose, and
 - 131.6 mg/mL of the antibody.

10 In another embodiment, the antibody is administered as an aqueous buffered solution at pH 6.0 containing

- 21 mM histidine,
- 45 mM arginine,
- 0.2% (w/v) polysorbate 20,
- 15 - 5% (w/v) sucrose; and
- 175 mg/mL of the antibody.

In various embodiments, the antibody is administered in a stable pharmaceutical formulation comprising: (i) histidine at a concentration of from 25 mM to 100 mM; (ii) arginine at a concentration of from 25 mM to 50 mM; (iii) sucrose in an amount of from 3% to 10% w/v; and (iv) polysorbate 20 in an amount of from 0.1% to 0.2%, wherein the formulation has a pH of about 5.8, about 6.0, or about 6.2, and at least 90% of the native form of the antibody is recovered after 1 month of storage at 45°C, as determined by size exclusion chromatography. In various embodiments, about 150 mg of the antibody (e.g., sarilumab) is administered to the subject.

25 In various embodiments, the antibody is administered in a stable pharmaceutical formulation comprising: (i) histidine at a concentration of from about 10 mM to about 25 mM; (ii) arginine at a concentration of from about 25 mM to about 50 mM; (iii) sucrose in an amount of from about 5% to about 10% w/v; and (iv) polysorbate in an amount of from about 0.1% to about 0.2% w/v, wherein the formulation has a pH of about 5.8, about 6.0, or about 6.2, and at least 90% of the native form of the antibody is recovered after 1 month of storage at 45°C, as determined by size exclusion chromatography. In various embodiments, about 150 mg of the antibody (e.g., sarilumab) is administered to the subject.

Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients.

Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc.

In various embodiments, the anti-IL-6R antibody (or pharmaceutical formulation comprising the antibody) can be administered to the patient using any acceptable device or mechanism. For example, the administration can be accomplished using a syringe and needle or with a reusable pen and/or autoinjector delivery device. The methods of the present disclosure include the use of numerous reusable pen and/or autoinjector delivery devices to administer an anti-IL-6R antibody (or pharmaceutical formulation comprising the antibody). Examples of such devices include, but are not limited to AUTOPEN® (Owen Mumford, Inc., Woodstock, UK), DISETRONIC® pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX® 75/25 pen, HUMALOG® pen, HUMALIN® 70/30 pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN® I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR® (Novo Nordisk, Copenhagen, Denmark), BD® pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN®, OPTIPEN PRO®, OPTIPEN STARLET®, and OPTICLIK® (Sanofi-Aventis, Frankfurt, Germany). Examples of disposable pen and/or autoinjector delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present disclosure include, but are not limited to the SOLOSTAR® pen (Sanofi-Aventis), the FLEXPEN® (Novo Nordisk), and the KWIKPEN® (Eli Lilly), the SURECLICK® Autoinjector (Amgen, Thousand Oaks, CA), the PENLET® (Haselmeier, Stuttgart, Germany), the EPIPEN® (Dey, L.P.), and the HUMIRA® Pen (AbbVie Inc., North Chicago, IL), to name only a few.

In various embodiments, the antibody is administered with a prefilled syringe. In various embodiments, the antibody is administered with a prefilled syringe containing a safety system. For example, the safety system prevents an accidental needle-stick injury. In various embodiments, the antibody is administered with a prefilled syringe containing an ERIS safety system (West Pharmaceutical Services Inc.).

In various embodiments, the antibody is administered with an auto-injector. In various embodiments, the antibody is administered with an auto-injector featuring the PUSHCLICK® technology (SHL Group). In various embodiments, the auto-injector is a device comprising a syringe that allows for administration of a dose of the composition and/or antibody to a subject.

The use of a microinfusor to deliver an anti-IL-6R antibody (or pharmaceutical formulation comprising the antibody) to a patient is also contemplated herein. As used herein, the term “microinfusor” means a subcutaneous delivery device designed to slowly administer large volumes (e.g., up to about 2.5 mL or more) of a therapeutic formulation over a prolonged

period of time (e.g., about 10, 15, 20, 25, 30 or more minutes). Microinfusors are particularly useful for the delivery of large doses of therapeutic proteins contained within high concentration (e.g., about 100, 125, 150, 175, 200 mg/mL or more) and/or viscous solutions.

In various embodiments, an inadequate response to prior treatment refers to subjects
5 whose pain is not well controlled after receiving the prior treatment at the maximum tolerated typical dose. In an embodiment, an inadequate response to prior treatment refers to subjects who have moderate or high disease activity and features of poor prognosis despite prior treatment. In various embodiments, an inadequate response to prior treatment refers to subjects with a pain symptom (e.g., any symptom listed herein) that has not improved or that has
10 worsened despite prior treatment.

Patient Population

As used herein, “subject” means a human subject or human patient.

An antibody as described herein is in various embodiments administered to subjects
15 who have rheumatoid arthritis and are suffering from NIP. In various embodiments, the subject has NIP and rheumatoid arthritis. In various embodiments, the subject was previously ineffectively treated for rheumatoid arthritis by administering one or more DMARDs different from the IL-6R antibody.

A subject who is considered “ineffectively treated” by his or her physician is a subject
20 who in various embodiments either has shown to be intolerant to the one or more DMARDs tested by the physician, and/or a subject who has shown an inadequate response to the one or more DMARDs tested by the physician, typically a subject who is still considered by the physician to present with, or to have, NIP despite the previous one or more DMARDs administered.

25 In various embodiments, a subject with rheumatoid arthritis has:

- at least 6 of 66 swollen joints and 8 of 68 tender joints, as counted by the physician in a typical quantitative swollen and tender joint count examination,
- High sensitivity C-reactive protein (hs-CRP) ≥ 8 mg/L or ESR ≥ 28 mm/H
- DAS28ESR > 5.1 .

30 In various embodiments, the subject, who was previously ineffectively treated for rheumatoid arthritis by administering at least one DMARD different from the antibody, is a subject who was previously ineffectively treated for NIP by administering a DMARD. In various embodiments, the DMARD is selected from the group consisting of methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. In various embodiments, the DMARD is

methotrexate. In various embodiments, the DMARD is a TNF- α antagonist. In various embodiments, the DMARD is adalimumab.

In various embodiments, the subject, who was previously ineffectively treated for NIP by administering one or more DMARDs different from the antibody, is a subject who had an
5 inadequate response or intolerance to methotrexate.

In various embodiments, the subject, who was previously ineffectively treated for NIP by administering one or more DMARDs different from the antibody, is a subject who had an inadequate response or intolerance to adalimumab.

In various embodiments, for those subjects previously ineffectively treated for NIP by
10 administering one or more DMARDs different from the IL-6R antibody, the one or more DMARDs is/are not administered anymore to the subject, and the IL-6R antibody is in various embodiments administered alone, in monotherapy to the subject.

In various embodiments, the subject is intolerant to the DMARD due to one or more physical reactions, conditions or symptoms from the treatment with the DMARD. Physical
15 reactions, conditions or symptoms can include allergies, pain, nausea, diarrhea, azotemia, bleeding of the stomach, intestinal bleeding, canker sores, decreased blood platelets, perforation of the intestine, bacterial infection, inflammation of gums or mouth, inflammation of the stomach lining or intestinal lining, bacterial sepsis, stomach ulcer, intestinal ulcer, sun sensitive skin, dizziness, loss of appetite, low energy, and vomiting. In certain embodiments,
20 intolerance can be determined by the subject or by a medical professional upon examination of the subject. In various embodiments, the DMARD is selected from the group consisting of methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. In certain embodiments, the DMARD is methotrexate. In certain embodiments, the DMARD is adalimumab.

In certain embodiments the disclosure provides administering to the subject one or more
25 additional therapeutic agents in combination with the IL-6R antibody. As used herein, the expression “in combination with” means that the additional therapeutic agents are administered before, after, or concurrent with the pharmaceutical composition comprising the IL-6R antibody. In certain embodiments, the subject is administered the antibody with a DMARD and/or TNF- α antagonist.

30

EXAMPLE

Example 1: Sarilumab, NIP Status and Disease Activity

In the present study, the prevalence of non-inflammatory pain (NIP), the effect of sarilumab on NIP, and the association between sarilumab treatment, disease activity,

and NIP status at baseline was investigated and then again after 3 and 6 months of sarilumab treatment.

Data Sources

5 Patient data were pooled from two placebo-controlled RCTs of sarilumab 150 mg and 200 mg q2w (MOBILITY, NCT01061736; TARGET, NCT01709578), and one adalimumab-controlled RCT of sarilumab 200 mg q2w (MONARCH, NCT02332590).

10 *Study Endpoints*

 NIP was defined as a difference between the 28-joint tender joint count (TJC) and swollen joint count (SJC), using the established formula: $TJC - SJC \geq 7^{10,11}$. Patients were assessed for NIP at study baseline and for change in NIP status at weeks 12 and 24. Finally, proportions of patients achieving American College of Rheumatology 20/50/70
15 (ACR20/50/70) criteria, Clinical Disease Activity Index (CDAI) ≤ 10 , and 28-joint Disease Activity Score with C-reactive protein (DAS28-CRP) < 3.2 at week 24 were assessed in patients with and without baseline NIP.

Results

20 *Demographic and Baseline Disease Characteristics by NIP Status*

 Patients with baseline NIP had higher composite measures of disease activity versus patients without NIP, although measures of inflammation were similar (Table 1). Of the 2112 patients who were included in the analysis, 490 (23%) had NIP at baseline (MOBILITY, 25% [294/1197]; TARGET, 19% [106/546]; MONARCH, 24% [90/369]). Patients with and
25 without baseline NIP had similar demographic characteristics at baseline (Table 2).

Table 1: Baseline Disease Characteristics by NIP status

**Table 1: Baseline Disease Characteristics by NIP Status:
Pooled MOBILITY, TARGET[®] and MONARCH[®] Data**

	With NIP (n=490)	Without NIP (n=1622)
Duration of RA, years	9.1 ± 8.6	9.7 ± 6.4
TJC (range 0–28)	21.7 ± 4.7	14.3 ± 6.2
SJC (range 0–28)	10.7 ± 4.3	13.1 ± 6.0
CRP, mg/L	22.7 ± 27.0	22.9 ± 24.0
HAQ-DI (range 0–3)	1.8 ± 0.6	1.7 ± 0.6
DAS28-CRP	6.4 ± 0.7	5.9 ± 0.9
CDAI	46.0 ± 9.4	40.4 ± 13.0
Pain VAS (range 0–100)	72 ± 18	67 ± 21

All values mean ± SD; HAQ-DI=Health Assessment Questionnaire-Disability Index; VAS=visual analog scale

5

Table 2: Baseline Demographics by NIP status

Parameter	With NIP (n=490)	Without NIP (n=1622)
Age, mean ±SD, years	53 ±11	51 ±12
Women, n (%)	415 (85)	1316 (81)
Race, n (%)		
White	416 (85)	1338 (82)
Black	12 (2)	40 (2)
Asian	24 (5)	90 (6)
Other	38 (8)	154 (9)
Hispanic ethnicity, n (%)	160 (33)	612 (38)
Weight, mean ±SD, kg	75 ±19	75 ±19
BMI group, n (%)		
< 25 kg/m ²	151 (31)	546 (35)
≥25 kg/m ² and <30 kg/m ²	172 (35)	550 (34)
≥30 kg/m ²	166 (34)	520 (32)
Opioid use, n (%)	57(12)	214 (13)

Sarilumab, NIP Status, and Disease Activity

Among patients with baseline NIP, those who received sarilumab were more likely to have no NIP at weeks 12 and 24 versus patients who received placebo or adalimumab (FIG. 1). In all three studies (MOBILITY, TARGET and MONARCH), the relative difference between sarilumab and control treatments appeared to increase with treatment duration. In MONARCH, a higher proportion of sarilumab- than adalimumab-treated patients achieved therapeutic response at week 24, regardless of the presence of baseline NIP (FIG. 2). The relative differences between treatment groups were larger among patients with baseline NIP for all assessments except ACR50. After 3 and 6 months of treatment, there was a greater prevalence of noninflammatory pain in patients treated with placebo and adalimumab, compared with patients treated with sarilumab. Further, regardless of noninflammatory pain at baseline, a higher proportion of patients achieved low disease activity with sarilumab than adalimumab after 6 months of treatment.

Conclusion

At weeks 12 and 24, NIP was less prevalent in patients treated with sarilumab than in patients treated with placebo or adalimumab. This data shows that NIP contributes to pain in RA patients, and that NIP in RA patients can be treated with composition in the present disclosure.

References

1. Boyden SD, et al. *Curr Rheumatol Rep* 2016; 18:30.
2. Choy EHS, Calabrese LH. *Rheumatology (Oxford)* 2018; 57:1885-95.
3. Brenn D, et al. *Arthritis Rheum* 2007; 56:351-9.
4. Zhou YQ, et al. *J Neuroinflammation* 2016; 13:141.
5. KEVZARA (sarilumab) [Summary of Product Characteristics]. Bridgewater, NJ: Sanofi.
6. KEVZARA (sarilumab) [Prescribing Information] 2017. Bridgewater, NJ: Sanofi.
7. Strand V, et al. *Arthritis Res Ther* 2016; 18:198.
8. Strand V, et al. *RMD Open* 2017; 3:e000416.
9. Burmester GR, et al. *Ann Rheum Dis* 2017; 76:840-7.
10. Duran J, et al. *Rheumatology (Oxford)* 2015; 54:2166-70.
11. Pollard LC, et al. *Rheumatology (Oxford)* 2010; 49:924-8.

12. Schaible H. Nociceptive neurons detect cytokines in arthritis. *Arthritis Res Ther.* 2014; 16(5):470.
13. Turk D, Okifuji A. Pain terms and taxonomies. *Bonica's Management of Pain.* 3rd ed: Lippincott Williams & Wilkins; 2001.
- 5 14. Yang S, Chang M. Chronic pain: Structural and functional changes in brain structures and associated negative affective states. *Int J Mol Sci.* 2019;20(13):3130.
15. Schaible H. Nociceptive neurons detect cytokines in arthritis. *Arthritis Res Ther.* 2014;16(5):470.
16. Cazzola M, et al. Physiopathology of pain in rheumatology. *Reumatismo.* 2014;66(1):4–
- 10 13.
17. Deane KD, et al. Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation. *Rheum Dis Clin North Am.* 2010;36(2):213–41.
18. de Haas WH, et al. Rheumatoid arthritis, typus robustus. *Ann Rheum Dis.* 1973;32(1):91–2.
- 15 19. Kristensen LE, et al. Is swollen to tender joint count ratio a new and useful clinical marker for biologic drug response in rheumatoid arthritis? results from a Swedish cohort. *Arthritis Care Res (Hoboken).* 2014;66(2):173–9
20. Challa DN, et al. Patient-provider discordance between global assessments of disease activity in rheumatoid arthritis: A comprehensive clinical evaluation. *Arthritis Res Ther.* 20 2017; 19(1):212.
21. Khan NA, et al. Determinants of discordance in patients' and physicians' rating of rheumatoid arthritis disease activity. *Arthritis Care Res (Hoboken).* 2012; 64(2):206–14.
22. Studenic P, et al. Discrepancies between patients and physicians in their perceptions of rheumatoid arthritis disease activity. *Arthritis Rheum.* 2012; 64(9):2814–23.
- 25 23. Hammer H, et al. Major reduction of ultrasound detected synovitis during subcutaneous tocilizumab treatment; results from a multicenter 24 weeks study of patients with rheumatoid arthritis [abstract]. *Arthritis Rheumatol.* 2018; 70(suppl 10).
24. Maini RSC, E. W., et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant

- methotrexate: A randomised phase III trial. ATTRACT study group. *Lancet*. 1999; 354(9194):1932–9.
25. Lee YC, et al. Pain persists in DAS28 rheumatoid arthritis remission but not in ACR/EULAR remission: A longitudinal observational study. *Arthritis Res Ther*. 2011; 13(3):R83.
26. Taylor P, et al. Patient perceptions concerning pain management in the treatment of rheumatoid arthritis. *J Int Med Res*. 2010; 38(4):1213–24.
27. Sarzi-Puttini P, et al. Correlation of the score for subjective pain with physical disability, clinical and radiographic scores in recent onset rheumatoid arthritis. *BMC Musculoskelet Disord*. 2002; 3:18.
28. McWilliams DF, Walsh DA. Pain mechanisms in rheumatoid arthritis. *Clin Exp Rheumatol*. 2017; 35(5):94–101.
29. Flodin P, et al. Intrinsic brain connectivity in chronic pain: A resting-state fMRI study in patients with rheumatoid arthritis. *Front Hum Neurosci*. 2016; 10:107.
30. Biswas M, et al. Prevalence, types, clinical associations, and determinants of peripheral neuropathy in rheumatoid patients. *Ann Indian Acad Neurol*. 2011; 14(3):194–7.
31. Adlan A, et al. Autonomic function and rheumatoid arthritis: A systematic review. *Semin Arthritis Rheum* 2014; 44(3):283–304.
32. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. *Nat Rev Rheumatol*. 2014; 10(10):581–92.
33. Ramachandran VS, Blakeslee S. *Phantoms in the brain: human nature and the architecture of the mind*: HarperCollins; 1998.
34. Taylor et al., *Nucl. Acids Res*. 1992; 20:6287-6295.
35. Angal et al., *Molecular Immunology*; 1993 30:105.
36. Powell *et al.* "Compendium of excipients for parenteral formulations" *PDA J Pharm Sci Technol* 1998; 52:238-311.
37. Wu *et al.* *J. Biol. Chem.* 1987; 262:4429-4432.
38. *Langer Science* 1990; 249:1527-1533.
39. U.S. Patent No. 5,215,534.

40. U.S. Patent No. 9,248,242.
41. U.S. Patent No. 9,427,531.
42. U.S. Patent No. 9,566,395.
43. U.S. Patent No. 6,629,949.
- 5 44. U.S. Patent No. 6,659,982.
45. Meehan et al., J. Controlled Release 1996; 46:107-116.
46. Rose-John et al., J Leukoc Biol. 2006; 80(2), 227-36.
47. Committee for Medicinal Products for Human Use, Assessment Report, April 27, 2017
EMA/292840/2017, available at
- 10 www_dot_ema_dot_europa_dot_eu/documents/assessment_report/kevsara_epar_public_assessment_report_en_dot_pdf.