

Treatment of Subpopulation of Patients with Rheumatoid Arthritis

Technical field

The present invention relates to a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative thereof, for use in the treatment of treatment-naïve rheumatoid arthritis, wherein said compound is to be administered with methotrexate (MTX) to a patient subpopulation with active systemic inflammation. In some embodiments said patient subpopulation encompass subjects who are diagnosed with moderate to severe rheumatoid arthritis within 6 months prior to treatment initiation. This patient subpopulation has demonstrated consistent response to the disclosed therapy across several outcome measures.

Background

An arthritic disease is a condition that implies damage or inflammation in one or more joints. The condition often presents with pain, swelling, heat, redness and limitation of movement. There are many different forms of arthritic disorders, the most common types being osteoarthritis and rheumatoid arthritis. Rheumatoid arthritis (RA) is an autoimmune disorder that primarily affects joints and between 0.5-1% of adults in the developed world are affected by RA. While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The goal of current treatments is to reduce pain and inflammation to improve the quality of life of the patients suffering from the condition. Pain medications, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as treatment to reduce symptoms. Disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine and in particular methotrexate (MTX), may be employed in an attempt to slow down the progression of disease.

Melanocortin (MC) receptors (MC1R–MC5R), a family of class A G protein–coupled receptors (GPCRs), are attractive therapeutic targets for a number of conditions due to their wide distribution and diversity of physiological processes they regulate. MC1R regulates UV light–induced skin tanning and other immune responses because of its expression on leukocytes. MC2R regulates cortisol production on the adrenal glands, whereas MC5R plays a role on exocrine glands secretions. MC3R and MC4R exert non-redundant functions on energy homeostasis in addition to specific anti-

inflammatory roles; whereas MC3R activation is particularly protective for joint inflammation such as arthritis, MC4R provides neuroprotection in brain inflammation.

5 Peripheral MC1R and MC3R can be pharmacologically activated to induce anti-inflammation. The endogenous agonist α -melanocyte-stimulating hormone (α MSH), like other protective mediators, is released by immune cells to counterbalance proinflammatory signals, thus preventing excessive tissue damage. In line with the resolution of inflammation concept, therapeutics targeting MC1R and MC3R act by mimicking the body's own protective resources and might be characterized by a lighter
10 burden of side effects.

Shown to be effective in rheumatic diseases since the early 1950s, the use of corticotropin or adrenocorticotropin hormone (ACTH) declined when synthetic glucocorticoids became available. However, the discovery of an alternative anti-
15 inflammatory mechanism for ACTH involving activation of peripheral MC receptors on immune cells has revived the interest in developing novel ACTH-like molecules with no steroidogenic effects for the treatment of joint diseases such as gout or RA. However, the limitation in the translational delivery of novel MC drugs besides the marketed ACTH formulations is imposed by the lack of receptor selectivity achieved so far.

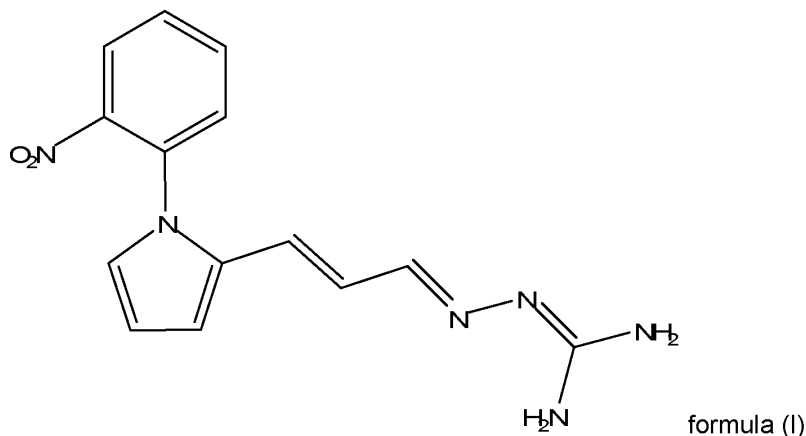
20 The small molecule AP1189 or resomelagon (*(E)*-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidium) is a biased agonist at receptors MC1R and MC3R with anti-inflammatory properties together with a lack of effect on melanogenesis. In vivo, oral AP1189 elicits anti-inflammatory actions in peritonitis and
25 accelerated the resolution phase, and afforded significant reduction of macroscopic and histological parameters of joint disruption in experimental inflammatory arthritis. A synergistic effect of AP1189 and MTX in a mouse model of arthritis has been demonstrated (WO 2020/229297).

30 **Summary**

A multicenter, randomized, double-blind, placebo-controlled, 12-week study was conducted. In the study treatment-naïve RA patients with high disease activity (CDAI > 22) were randomized 1:1 for treatment with either 100 mg AP1189 tablets or placebo
35 tablets for a once daily dose for 12 weeks, concurrently with the initiation of dosing with methotrexate (once weekly).

- The primary efficacy read-out is proportion of patients achieving 20% improvement in ACR (ACR20) at week 12 relative to placebo. In addition, several secondary efficacy endpoints are defined, including ACR50, ACR70, CDAI and DAS-28 change over time,
- 5 Change in Health Assessment Questionnaire – Disability Index (HAQ-DI) and Functional Assessment of Chronic Illness Therapy [FACIT]-Fatigue). Tertiary endpoints are included to further explore the effect of AP1189 on biomarkers and by evaluation of synovial inflammation using magnetic resonance imaging (MRI).
- 10 The data presented herein show that in a subpopulation of RA patients presenting at baseline, i.e. at the initiation of dosing, with elevated blood-levels of C-reactive protein CRP (>3 mg/L), AP1189 improved several outcome measures: Specifically, HAQ-
- 15 disability index (HAQ-DI) was improved, in particular in areas indicating increased hand strength and dexterity. MRI data of wrist and hand joints indicated a reduction in inflammation intensity as compared to placebo, supported by matched reductions in tender and swollen joint counts. Reduced plasma levels of C4M, a biomarker of
- 20 In the patient subpopulation with a baseline CRP >3 mg/L, 70.6 % of patients treated with AP1189 achieved an ACR20 response rate at week 12, compared to 54.3 % of placebo patients. This indicates that patients with systemic inflammation benefits from an improved treatment effect of the tested compound. Furthermore, of the patients with a baseline CRP >3 mg/L, those who were diagnosed with moderate to severe
- 25 further improved ACR20 response rate of 82.1% at week 12.

One aspect of the disclosure provides for a compound of formula (I)



including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable derivative thereof,

for use in the treatment of rheumatoid arthritis in a treatment-naïve subject having a C-Reactive Protein (CRP) level of >3 mg/L,
5 wherein said compound is administered with methotrexate (MTX).

It is also an aspect of the disclosure to provide a combination of methotrexate (MTX) and a compound of formula (I),

10 including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable derivative thereof,

for use in the treatment of rheumatoid arthritis in a treatment-naïve subject with a C-Reactive Protein (CRP) level of >3 mg/L.

15 In one embodiment said rheumatoid arthritis is severe active rheumatoid arthritis, such as rheumatoid arthritis with a CDAI > 22 and/or a DAS28 score of above 5.1.

In one embodiment said subject is diagnosed with rheumatoid arthritis within 6 months prior to treatment initiation.

20 In one embodiment said compound is E-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine (AP1189/resomelagon), or a pharmaceutically acceptable derivative thereof, such as a pharmaceutically acceptable salt thereof.

25 In one embodiment said compound is E-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate.

Definitions

- 5 The term "pharmaceutically acceptable derivative" in the present context includes pharmaceutically acceptable salts, which indicate a salt which is not harmful to the patient. Such salts include pharmaceutically acceptable basic or acid addition salts as well as pharmaceutically acceptable metal salts, ammonium salts and alkylated ammonium salts. A pharmaceutically acceptable derivative further includes esters, solvates and prodrugs, or other precursors of a compound which may be biologically metabolized into the active compound, or crystal forms of a compound.
- 10 The term "acid addition salt" is intended to include "pharmaceutically acceptable acid addition salt" which indicates salts which are not harmful to the patient. Acid addition salts include salts of inorganic acids as well as organic acids. Examples of pharmaceutically acceptable inorganic or organic acid addition salts include the
- 15 pharmaceutically acceptable salts listed in J. Pharm. Sci. 66, 2, (1977) which is incorporated herein by reference.
- Reference to AP1189 and a pharmaceutically acceptable salt of AP1189 ((E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine) including tautomeric and
- 20 isomeric forms thereof, is meant to encompass amorphous forms and well as any polymorphic (crystalline) forms of AP1189 and its salts. Polymorphic forms of pharmaceutically acceptable salts of AP1189 are disclosed in WO 2022/268814. The *E*, *trans* stereoisomer of AP1189 is known by the INN resomelagon.
- 25 Unless otherwise stated, a specified amount or dosage of the compound of the present disclosure is calculated as the free base.
- The term "therapeutically effective amount" of a compound as used herein refers to an amount sufficient to cure, alleviate, prevent, reduce the risk of, or partially arrest the
- 30 clinical manifestations of a given disease or disorder and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a
- 35 matrix of values and testing different points in the matrix, which is all within the ordinary

skills of a trained physician or veterinary. 'Amount' and 'dosage' may be used interchangeably herein.

5 The terms "approximately" and "about" as referred herein are synonymous. In one embodiment, "approximately" and "about" refer to the recited amount, value, or duration $\pm 5\%$, $\pm 4.5\%$, $\pm 4\%$, $\pm 3.5\%$, $\pm 3\%$, $\pm 2.5\%$, $\pm 2\%$, $\pm 1.75\%$, $\pm 1.5\%$, $\pm 1.25\%$, $\pm 1\%$, $\pm 0.9\%$, $\pm 0.8\%$, $\pm 0.7\%$, $\pm 0.6\%$, $\pm 0.5\%$, $\pm 0.4\%$, $\pm 0.3\%$, $\pm 0.2\%$, $\pm 0.1\%$, $\pm 0.09\%$, $\pm 0.08\%$, $\pm 0.07\%$, $\pm 0.06\%$, $\pm 0.05\%$, $\pm 0.04\%$, $\pm 0.03\%$, $\pm 0.02\%$, or $\pm 0.01\%$. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 2.5\%$, $\pm 2\%$, $\pm 1.75\%$, $\pm 1.5\%$, $\pm 1.25\%$, $\pm 1\%$, $\pm 0.9\%$, $\pm 0.8\%$, $\pm 0.7\%$, $\pm 0.6\%$, $\pm 0.5\%$. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 1\%$. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 0.5\%$. In one embodiment, "approximately" and "about" refer to the listed amount, value, or duration $\pm 0.1\%$. In the context of an amount or dosage of the compound of the present disclosure the terms "approximately" and "about" as referred herein refer to the recited amount or dosage $\pm 10\%$, $\pm 9\%$, $\pm 8\%$, $\pm 7\%$, $\pm 6\%$, $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$, $\pm 1.5\%$, $\pm 1\%$, $\pm 0.5\%$.

20 The terms "treatment" and "treating" as used herein refer to the management and care of a patient for the purpose of combating a condition, disease or disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient or subject is suffering. The patient to be treated is preferably a mammal, in particular a human being. Treatment of animals, such as mice, rats, dogs, cats, horses, cows, sheep and pigs, is, however, also within the scope of the present context. The patients to be treated can be of various ages. The term 'subject' and 'patient' may be used interchangeably herein.

30 The terms 'is to be administered' and 'is administered' may be used interchangeably herein.

The term "remission" as used herein refers to reduction or disappearance of the signs and symptoms of the arthritic disease. The remission can be temporary or permanent. Partial remission is a reduction in the signs and symptoms of the arthritic disease, while complete remission is understood herein as a disappearance of the signs and symptoms of the arthritic disease.

By "compound of the disclosure" is meant the compound of formula (I), for example, {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, including a pharmaceutically acceptable salt thereof.

As using herein, "a subject having active systemic inflammation" means that the subject has active systemic inflammation before or at the beginning of the disclosed treatment. The subject need not necessarily continue to have active systemic inflammation throughout treatment, at the end of the treatment, or after the treatment. In some embodiments a subject having active systemic inflammation is characterized by a CRP level of >3 mg/L. In some embodiments a subject having active systemic inflammation is characterized by a CRP level of >3 mg/L in blood, such as in plasma or serum.

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Detailed description

The liver makes C-reactive protein (CRP) in response to inflammation in the body. High blood levels of CRP can indicate inflammation due to an acute or chronic condition. C-reactive protein is measured in milligrams per liter (mg/L). Usually, the blood levels are measured in plasma or serum, not whole blood.

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Minor CRP elevation refers to levels between 0.3 mg/l and 1.0 mg/l. This can occur in people who are sedentary, pregnant, or living with a chronic condition, such as diabetes. Mild infections such as the common cold may also trigger these elevations.

Moderate CRP elevation refers to levels between 1.0 m/dl and 10.0 mg/l, which can signal a more significant issue. A moderate elevation may be due to acute inflammation from an infection or chronic inflammation from a serious disease, such as RA or heart disease. Results equal to or greater than 8 mg/L or 10 mg/L are considered high or as marked elevation.

Severe CRP elevation refers to levels above 50.0 mg/l. This elevation warns of an acute bacterial infection.

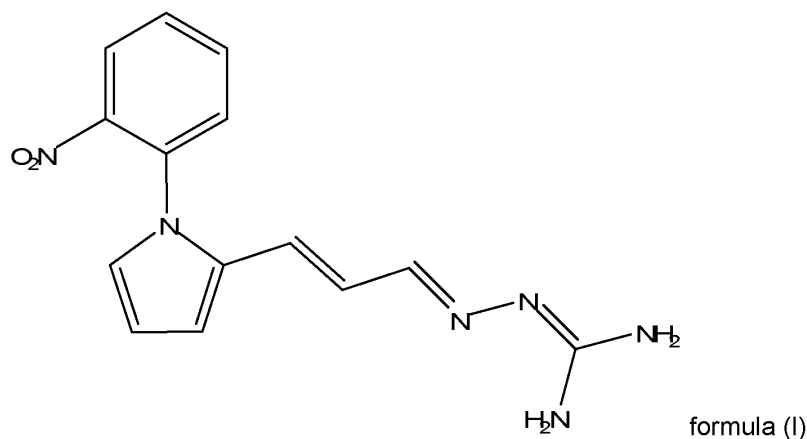
The present inventors have found that AP1189 and MTX administered in combination is effective in treating rheumatoid arthritis in treatment-naïve subjects having active systemic inflammation, such as active systemic inflammation characterized by a CRP

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of >3 mg/L. Furthermore, AP1189 and MTX administered in combination is particularly effective in treating rheumatoid arthritis in treatment-naïve subjects having active systemic inflammation, which are diagnosed with rheumatoid arthritis within 6 months of treatment initiation.

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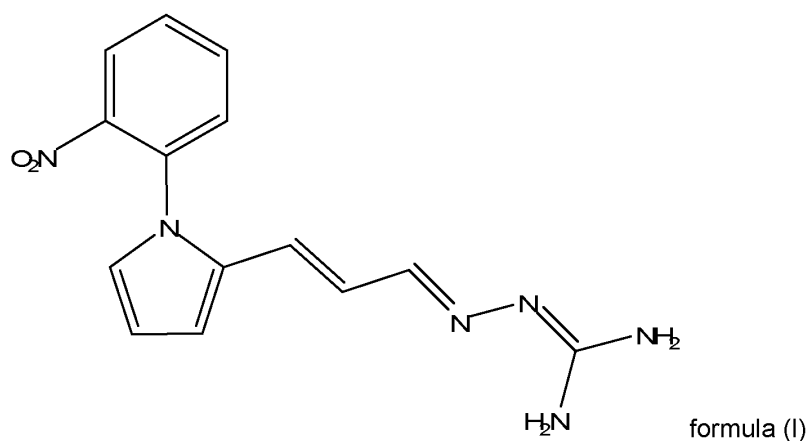
It is an embodiment of the present disclosure to provide a compound of formula (I):



including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable derivative thereof,

10 for use in the treatment of rheumatoid arthritis in a treatment-naïve subject having a C-Reactive Protein (CRP) level of >3 mg/L,
wherein said compound is to be administered with methotrexate (MTX).

15 It is also an embodiment of the present disclosure to provide a combination of methotrexate (MTX) and a compound of formula (I):



including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable derivative thereof,
for use in the treatment of rheumatoid arthritis in a treatment-naïve subject with a C-Reactive Protein (CRP) level of >3 mg/L.

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One embodiment of the present disclosure provides for a use of a combination of methotrexate and the compound of formula (I), including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable derivative thereof,
for the manufacture of a medicament for the treatment of in a treatment-naïve subject
having a C-Reactive Protein (CRP) level of >3 mg/L.

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One embodiment of the present disclosure provides for a method for treating rheumatoid arthritis in a treatment-naïve subject, said method comprising one or more steps of administering to a subject in need thereof a compound of formula (I), including
tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable
derivative thereof,
wherein said subject has a C-Reactive Protein (CRP) level of >3 mg/L,
and further comprising one or more steps of administering methotrexate (MTX).

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Treatment-naïve in the present context means that said subject has not yet been treated for said rheumatoid arthritis, such as has not yet been treated prior to initiation of the claimed therapy such as prior to initiation of treatment with AP1189; in particular said subject has not yet been treated with a Disease-modifying antirheumatic drug. In a particular embodiment said subject has not yet been treated with methotrexate, such
as wherein said subject has not yet been treated with methotrexate prior to initiation of
treatment with AP1189.

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In one embodiment said treatment-naïve subject is DMARD treatment-naïve. DMARDs include conventional synthetic DMARDs, such as methotrexate; biological therapies such as adalimumab; and targeted synthetic DMARDs, such as the JAK inhibitors baricitinib and tofacitinib.

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In one embodiment said treatment-naïve subject is conventional synthetic DMARD treatment-naïve.

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In one embodiment said treatment-naïve subject is methotrexate (MTX) treatment-naïve.

5 In one embodiment said treatment-naïve subject is naïve to methotrexate treatment prior to initiating treatment with the compound of the present disclosure.

In one embodiment the subject with rheumatoid arthritis has not received MTX prior to treatment with the compound of the present disclosure.

10 In one embodiment the subject with rheumatoid arthritis is about to start up-titration with methotrexate.

In one embodiment treatment with said compound occurs concurrently with the initiation of treatment with methotrexate. In one embodiment treatment with said
15 compound occurs concurrently with the initiation of dosing with methotrexate.

In one embodiment the present disclosure the treatment with MTX and the compound of the disclosure is initiated essentially at the same time.

20 In one embodiment the present disclosure the treatment with MTX and the compound of the disclosure is initiated simultaneously.

In one embodiment of the present disclosure, the subject has active systemic inflammation. In one embodiment, the active systemic inflammation is characterized by
25 a CRP level of >3 mg/L. In one embodiment, the active systemic inflammation is characterized by a baseline CRP level of >3 mg/L.

The CRP level is measured in a subject's blood; usually plasma or serum. Usually a CRP test requires only blood drawn from a vein.

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In one embodiment of the present disclosure, the subject has elevated CRP, such as an elevated CRP of >3 mg/L.

In one embodiment said treatment-naïve subject having a CRP level of >3 mg/L, such
35 as having a CRP level of >3 mg/L at baseline, has a CRP level of >3 mg/L in blood. In

some embodiments said subject has a CRP level of >3 mg/L in serum. In some embodiments said subject has a CRP level of >3 mg/L in plasma.

5 In one embodiment is provided a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof,
for use in the treatment of rheumatoid arthritis in a treatment-naïve subject having a C-Reactive Protein (CRP) level of >3 mg/L at baseline,
such as for use in the treatment of rheumatoid arthritis in a treatment-naïve subject
10 having a baseline C-Reactive Protein (CRP) level of >3 mg/L,
wherein said compound is to be administered with methotrexate (MTX).

15 In one embodiment a subject having a baseline CRP level of >3 mg/L is a subject having a baseline CRP > 3 mg/L prior to treatment initiation.

In one embodiment a subject having a baseline CRP level of >3 mg/L is a subject having a baseline a CRP > 3 mg/L at treatment initiation, such as at the start of treatment.

20 'Treatment initiation' and 'at the start of treatment' refers to the treatment of the present disclosure, such as treatment with a compound of the present disclosure alone and in combination with MTX.

25 In one embodiment a subject having a baseline CRP level of >3 mg/L is a subject having a CRP > 3 mg/L at the first day of treatment. In one embodiment a subject having a baseline CRP level of >3 mg/L is a subject having a CRP > 3 mg/L at the first day of treatment with a compound of the present disclosure.

30 In one embodiment the present disclosure provides a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof,
for use in the treatment of moderate to severe rheumatoid arthritis in a treatment-naïve subject having a CRP level of >3 mg/L,
wherein said compound is to be administered with methotrexate (MTX).

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In some embodiments said rheumatoid arthritis is moderate rheumatoid arthritis.

5 In some embodiments said rheumatoid arthritis is rheumatoid arthritis with a CDAI (Clinical disease activity score) score of between 10 and ≤ 22 ; such as moderate rheumatoid arthritis with a CDAI score of between 10 and ≤ 22 .

10 In some embodiments said rheumatoid arthritis is rheumatoid arthritis with a DAS28 score of between 3.2 and ≤ 5 ; such as moderate rheumatoid arthritis with a DAS28 score of between 3.2 and ≤ 5 .

In one embodiment the present disclosure provides a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof, for use in the treatment of severe rheumatoid arthritis in a treatment-naïve subject
15 having a CRP level of >3 mg/L, wherein said compound is to be administered with methotrexate (MTX).

20 In some embodiments said rheumatoid arthritis is rheumatoid arthritis with a CDAI score > 22 ; such as severe rheumatoid arthritis with a CDAI > 22 .

In some embodiments said rheumatoid arthritis is highly active rheumatoid arthritis. In some embodiments said rheumatoid arthritis is high disease activity rheumatoid arthritis.

25 In some embodiments said rheumatoid arthritis is rheumatoid arthritis with a DAS28 score of above 5.1; such as severe rheumatoid arthritis with a DAS28 score of above 5.1.

30 In one embodiment the present disclosure provides a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof, for use in the treatment of rheumatoid arthritis with a CDAI > 22 in a treatment-naïve subject having a CRP level of >3 mg/L, wherein said compound is to be administered with methotrexate (MTX).

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In one embodiment the rheumatoid arthritis is rheumatoid arthritis with active joint disease. In one embodiment the rheumatoid arthritis is rheumatoid arthritis with a CDAI > 22 with active joint disease.

5 In one embodiment the rheumatoid arthritis is early rheumatoid arthritis with active joint disease.

In one embodiment the subject with rheumatoid arthritis tests positive for rheumatoid factor and/or anti-cyclic citrullinated peptide (CCP) IgG antibodies prior to the treatment.

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Diagnosed within 6 months

In one embodiment said subject is diagnosed with rheumatoid arthritis within about 6 months prior to treatment.

15 In one embodiment said subject is diagnosed with rheumatoid arthritis within about 6 months prior to treatment initiation.

'Prior to treatment initiation' and 'prior to treatment' is used interchangeably herein, and refers to diagnosis prior to the treatment (or use) of the present disclosure.

20 It is an embodiment of the present disclosure to provide a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof, for use in the treatment of rheumatoid arthritis in a treatment-naïve subject having a CRP level of >3 mg/L, wherein said subject is diagnosed with rheumatoid arthritis within about 6 months prior to treatment initiation, 25 wherein said compound is to be administered with methotrexate (MTX).

30 It is an embodiment of the present disclosure to provide a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof, for use in the treatment of moderate to severe rheumatoid arthritis in a treatment-naïve subject having a CRP level of >3 mg/L, wherein said subject is diagnosed with rheumatoid arthritis within about 6 months prior to treatment initiation, such as wherein said subject is diagnosed with moderate to 35 severe rheumatoid arthritis within 6 months prior to treatment initiation,

wherein said compound is to be administered with methotrexate (MTX).

It is an embodiment of the present disclosure to provide a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof,
5 for use in the treatment of rheumatoid arthritis with a CDAI > 22 in a treatment-naïve subject having a CRP level of >3 mg/L, wherein said subject is diagnosed with said rheumatoid arthritis within about 6 months prior to treatment initiation,
10 wherein said compound is to be administered with methotrexate (MTX).

In some embodiments said subject is diagnosed with rheumatoid arthritis within about 1 month prior to treatment initiation, within about 2 months prior to treatment initiation, within about 3 months prior to treatment initiation, within about 4 months prior to
15 treatment initiation, within about 5 months prior to treatment initiation, or within about 6 months prior to treatment initiation.

In some embodiments said subject is diagnosed with rheumatoid arthritis 0 to 6 months prior to treatment initiation, such as 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6 months
20 prior to treatment initiation.

In some embodiments said subject was diagnosed with rheumatoid arthritis less than about 6 months prior to treatment initiation; such as less than about 1 month prior to treatment initiation, such as less than about 2 months prior to treatment initiation, such
25 as less than about 3 months prior to treatment initiation, such as less than about 4 months prior to treatment initiation, such as less than about 5 months prior to treatment initiation, such as less than about 6 months prior to treatment initiation.

In a preferred embodiment said subject is diagnosed with rheumatoid arthritis within about 6 months prior to treatment initiation. In a preferred embodiment said subject is
30 diagnosed with rheumatoid arthritis less than about 6 months prior to treatment initiation.

6 months correlates roughly to about 180 to 200 days. In some embodiment said subject is diagnosed with rheumatoid arthritis within about 180 to 200 days prior to treatment initiation.

- 5 6 months correlates roughly to about 26 weeks. In some embodiment said subject is diagnosed with rheumatoid arthritis within about 26 weeks prior to treatment initiation.

RA severity

10 The severity of rheumatoid arthritis (RA), as well as the efficacy of medical treatment, of the subject can be assessed by a number of different clinical score systems, e.g. the DAS28 score, the CDAI score and the ACR-score.

There are a wide range of measures of disease activity in RA including:

- 15 • examination of the subject's joints for swelling and tenderness (Swollen Joint Count, SJC, and Tender Joint Count, TJC),
- 20 • global scores of pain and overall status of the subject,
- 20 • blood markers of inflammation (e.g. Erythrocyte sedimentation rate (ESR or sed rate) that indirectly measures the degree of inflammation present in the body of the subject, and the c-reactive protein test that measures the level of C-reactive protein (CRP) in the blood of the subject)
- 25 • questionnaires (e.g. the Health Assessment Questionnaire Disability Index (HAQ-DI, which assesses subject function) & Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)),
- 25 • Imaging techniques such as X-ray imaging, ultrasound imaging, and magnetic resonance imaging (MRI).

In one embodiment, the use according to the present disclosure results in improved physical function in the subject as determined by the Health Assessment Questionnaire Disability Index (HAQ-DI).

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In one embodiment, the use according to the present disclosure results in improved function in the subject as determined by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue).

In one embodiment, the use according to the present disclosure results in partial or complete remission of one or more arthritis symptoms.

5 In one embodiment, the use according to the present disclosure reduces joint inflammation.

In one embodiment, the use according to the present disclosure reduces the level of C-reactive protein (CRP).

10 In one embodiment, the use according to the present disclosure reduces the number of tender joints and/or reduces the number of swollen joints.

ACR-score

15 The ACR (American College of Rheumatology) Criteria is a standard criterion to measure the effectiveness of various arthritis medications or treatments in clinical trials for RA.

20 The ACR response rates ACR20, ACR50, and ACR70 are defined as $\geq 20\%$, $\geq 50\%$ and $\geq 70\%$ improvement, respectively, in swollen and tender joint counts (SJC/TJC) and 3 of the following 5 assessments: Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, Patient's Assessment of Pain, Health Assessment Questionnaire (HAQ-DI), and C-Reactive Protein (CRP).

25 In one embodiment, the ACR-score is improved by the treatment of the present disclosure. In one embodiment, the present therapy result in a $\geq 20\%$, a $\geq 50\%$ or $\geq 70\%$ improvement in ACR response rates.

30 In one embodiment, the use according to the present disclosure improves ACR20. In one embodiment, the use according to the present disclosure increases the proportion of patients achieving 20% improvement in ACR.

35 In one embodiment, the use according to the present disclosure achieves an ACR20 response rate of at least 60%, such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%. An ACR20 response rate of at least 60% means that 60% of subjects achieved the ACR20 response rate.

In one embodiment, the use according to the present disclosure achieves an ACR20 response rate of 60% to 85%; such as of 60% to 65%, such as of 65% to 70%, such as of 70% to 75%, such as of 75% to 80%, such as of 80% to 85%. In one embodiment,
5 the use according to the present disclosure achieves an ACR20 response rate of 60% to 80%.

In one embodiment, the use according to the present disclosure achieves an ACR20 response rate of about 70.6 %, such as of about 70%.

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In one embodiment, the use according to the present disclosure achieves an ACR20 response rate of about 82.1 %, such as of about 82%, such as of 80 to 85%.

In one embodiment, the use according to the present disclosure achieves the indicated
15 ACR20 response rates by 12 weeks of treatment, such as by week 12.

DAS28 Score

The DAS28 score is a measure of disease activity in rheumatoid arthritis (RA). DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are
20 examined in this assessment.

The DAS28 is a composite score derived from 4 of the above measures. This '28' version is a simplification of the original DAS score, which requires 44 joints to be counted. Other versions of the DAS28 allow the CRP to be used instead of the ESR, or
25 the omission of either. The DAS28-CRP, part of the many DAS scores for RA, is very useful to make an objective, reproducible and comparable assessment of the rheumatoid arthritis activity. DAS28-CRP in particular takes into account the following items:

- TJC28: The number of tender joints (0-28).
- SJC28: The number of swollen joints (0-28).
- CRP: The C-Reactive Protein level (in mg/l).
- GH: The patient global health assessment (from 0=best to 100=worst).

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The 28 tender or swollen joint scores target the same joints (shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints and the knees). The computation of the score can be done through the following equation:

$$DAS28_{CRP} = 0.56 * \sqrt{TJC28} + 0.28 * \sqrt{SJC28} + 0.36 * \ln(CRP + 1) + 0.014 * GH + 0.96$$

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Generally, remission is considered achieved if the score is between 0 and <2.6. Low disease activity corresponds to 2.6 to <3.2. Moderate disease activity is between 3.2 and ≤5.1, while high disease activity is strictly above 5.1.

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In one embodiment the present disclosure provides a compound of formula (I) as defined herein in combination with MTX for use in the treatment of severe rheumatoid arthritis,

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wherein the DAS28 is determined for the subject prior to and after treatment, wherein

the treatment results in a reduced DAS28 score,

such as wherein the treatment results in a DAS28 score below 5.1, such as 5.0 or less, such as 4.8 or less, such as 4.6 or less, such as 4.4 or less, such as 4.2 or less, such as 4.0 or less, such as 3.8 or less, such as 3.6 or less, such as 3.4 or less, such as 3.2 or less, such as 3.0 or less, such as 2.8 or less, such as 2.6 or less, such as 2.4 or less, such as 2.2 or less, such as 2.0 or less, such as 1.8 or less, such as 1.6 or less, such as wherein the treatment results in a DAS28 score below 5.1, below 3.2, more or below 2.6.

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In one embodiment said subject's DAS28 score during and/or after treatment is reduced to between 3.2 and ≤5.1 (moderate disease activity), such as reduced to between 2.6 to <3.2 (low disease activity), such as reduced to between 0 and <2.6 (remission).

25

For DAS28 the mean reduction in the AP1189 treated group was 1.9 points vs 1.2 points in the placebo group, $p < 0.01$.

30

In one embodiment, the use according to the present disclosure results in a reduction in DAS28 score of at least 1.3 points, such as at least 1.4 points, such as at least 1.5 points, such as at least 1.6 points, such as at least 1.7 points, such as at least 1.8 points, such as at least 1.9 points.

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In one embodiment, the use according to the present disclosure results in a reduction in DAS28 score of 1.3 to 2.0 points; such as 1.3 to 1.4 points, such as 1.4 to 1.5 points, such as 1.5 to 1.6 points, such as 1.6 to 1.7 points, such as 1.7 to 1.8 points, such as 1.8 to 1.9 points, such as 1.9 to 2.0 points.

In one embodiment, the use according to the present disclosure achieves the indicated results by 12 weeks of treatment, such as by week 12.

10 *CDAI score*

The CDAI (Clinical Disease Activity Index) is a useful clinical composite score for following patients with rheumatoid arthritis. The CDAI is the sum of 4 outcome parameters: tender and swollen joint counts (28 joints assessed) and patient's and physician's global assessments of disease activity (on a 0–10-cm visual analog scale).

15 The CDAI is the same as the Simplified Disease Activity Index (SDAI), except that the SDAI includes the C-reactive protein level.

Descriptive changes in CDAI where $CDAI = SJC (28) + TJC (28) + PGA + IGA$;

- 20 • SJC (28): Swollen 28-Joint Count (shoulders, elbows, wrists, MCPs, PIPs including thumb IP, knees);
- TJC (28): Tender 28-Joint Count (shoulders, elbows, wrists, MCPs, PIPs including thumb IP, knees);
- PGA: Patient Global Disease Activity (patient's self-assessment of overall RA disease activity on a scale 0-100 where 100 is maximal activity);
- 25 • IGA: Physician's Global Disease Activity (evaluator's assessment of the subject's overall RA disease activity on a scale 0-100 where 100 is maximal activity)

Remission is considered achieved if the score is between 0 and <2.8 ; Low disease activity corresponds to 2.8 to <10 . Moderate disease activity is between 10 and ≤ 22 , while high disease activity is strictly above 22 ($CDAI > 22$).

In one embodiment the present disclosure provides a compound of formula (I) as defined herein in combination with MTX for use in the treatment of rheumatoid arthritis in a subject with a $CDAI > 22$.

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In one embodiment said subject's CDAI score during and/or after treatment is reduced to between 10 and ≤ 22 (moderate activity), such as reduced to between 2.8 to <10 (low activity), such as reduced to between 0 and <2.8 (remission).

5 In one embodiment, the CDAI score is reduced to below 22 by the treatment of the present disclosure (moderate disease activity). In one embodiment, the CDAI score is reduced to below 10 by the treatment of the present disclosure (low disease activity). In one embodiment, the DAS28 score is reduced to below 2.8 by the treatment of the present disclosure (remission).

10

In one embodiment, the subjects CDAI score is reduced by the treatment of the present disclosure by 5 points or more, such as 10 points or more, such as 15 point or more.

15 In one embodiment, the CDAI score is reduced by the treatment of the present disclosure by at least 15 points, such as at least 16 points, such as at least 17 points, such as at least 18 points, such as at least 19 points, such as at least 20 points, such as at least 21 points, such as at least 22 points, such as at least 23 points, such as at least 24 points.

20 In one embodiment, the CDAI score is reduced by the treatment of the present disclosure by at 15 to 25 points, such as 15 to 16 points, such as 16 to 17 points, such as 17 to 18 points, such as 18 to 19 points, such as 19 to 20 points, such as 20 to 21 points, such as 21 to 22 points, such as 22 to 23 points, such as 23 to 24 points, such as 24 to 25 points.

25

In one embodiment, the use according to the present disclosure achieves the indicated results by 12 weeks of treatment, such as by 12 weeks.

HAQ-DI

30 The HAQ-DI (Health Assessment Questionnaire Disability Index) has 8 sections: dressing, arising, eating, walking, hygiene, reach, grip, and activities. There are 2 or 3 questions in each section- Scoring within each section is from 0 (*without any difficulty*) to 3 (*unable to do*). For each section the score given to that section is the worst score within the section, i.e., if one question is scored 1 and another 2, then the score for the section is 2. In addition, if an aide or device is used or if help is required from another

35

individual, then the minimum score for that section is 2. The 8 scores of the 8 sections are summed and divided by 8. The result is the DI.

5 In patients with baseline CRP >3mg/L treated with the compound of the disclosure had an average decrease in their HAQ-DI score of 0.64 which is almost 3 times the minimal clinically important difference (MCID). In the patient population diagnosed within 6 months, the HAQ-DI score was 0.69. The largest mean disability improvements over placebo relate to improvements in hand strength and dexterity. Treated patients reported a 50% improvement in activities relating to eating, 43% in dressing and 10 grooming and 38% in grip as compared to 24%, 25% and 18% respectively for placebo.

15 In one embodiment, the compound of the present disclosure provides for an average decrease in the Health Assessment Questionnaire Disability Index (HAQ-DI) of at least about 0.3, such as at least about 0.4, such as at least about 0.5, such as at least about 0.6, such as at least about 0.65, such as at least about 0.7.

20 In one embodiment, the compound of the present disclosure provides for an average decrease in the HAQ-DI of about 0.3 to 0.7; such as about 0.3 to 0.65; such as about 0.3 to 0.4, such as about 0.4 to 0.5, such as about 0.5 to 0.6, such as about 0.6 to 0.65, such as about 0.6 to 0.7.

25 In one embodiment, the use according to the present disclosure achieves the indicated average decrease in their HAQ-DI score by 12 weeks of treatment, such as by 12 weeks.

Assessment of joint inflammation using MRI

30 The MRI techniques used measure the peak enhancement and rate of enhancement of a contrast agent as indicators of synovial inflammation. Comparing the 12 weeks MRI with the Baseline MRI the AP1189-treated group showed a larger reduction in both mean peak enhancement (3.8 ml vs 1.2 ml) and mean initial rate of enhancement (0.06 ml/sec vs 0.01 ml/sec) compared to the placebo indicating a greater reduction in inflammation intensity.

In one embodiment, the compound of the disclosure reduces mean peak enhancement of a contrast by at least 1.0 ml, such as by at least 1.2 ml, such as by more than 1.2 ml, such as by at least 1.5 ml, such as by at least 2.0 ml, such as by at least 2.5 ml, such as by at least 3.0 ml, such as by at least 3.5 ml, such as by at least 3.8 ml, for example at week 12 compared to baseline.

In one embodiment, the compound of the disclosure reduces the rate of enhancement of a contrast agent by at least 0.02 ml/sec, such as reduced by at least 0.03 ml/sec, such as reduced by at least 0.04 ml/sec, such as reduced by at least 0.05 ml/sec, such as reduced by at least 0.06 ml/sec, for example at week 12 compared to baseline.

In one embodiment the use according to the present disclosure reduces MRI-assessed *tender* joints of about 5.3. In one embodiment the use according to the present disclosure reduces MRI-assessed tender joints of at least 3.0, such as at least 3.5, such as at least 4.0, such as at least 4.5, such as at least 5.0, such as at least 5.3.

In one embodiment the use according to the present disclosure reduces MRI-assessed tender joints of 3.0 to 3.5, such as 3.4 to 4.0, such as 4.0 to 4.5, such as 4.5 to 5.0, such as 5.0 to 5.5.

In one embodiment the use according to the present disclosure reduces MRI-assessed *swollen* joints of about 6.4. In one embodiment the use according to the present disclosure reduces MRI-assessed swollen joints of at least 3.8, such as at least 3.9, such as at least 4.0, such as at least 4.5, such as at least 5.0, such as at least 5.5, such as at least 6.0, such as at least 6.4. In one embodiment the use according to the present disclosure reduces MRI-assessed swollen joints of 3.8 to 4.0, such as 4.0 to 4.5, such as 4.5 to 5.0, such as 5.0 to 5.5, such as 5.5 to 6.0, such as at 6.0 to 6.5.

C4M

C4M is a marker of synovial collagen 4 degradation. Lower levels of C4M mean a lower rate of Collagen 4 degradation which is believed to be a marker for lower synovial inflammation. C4M was significantly reduced in the AP1189-treated group, whereas it was unchanged in the placebo group.

In one embodiment the treatment of the present disclosure reduces C4M. In one embodiment the treatment of the present disclosure reduces the rate of Collagen 4

degradation. In one embodiment the treatment of the present disclosure reduces synovial inflammation.

5 In one embodiment, the use according to the present disclosure achieves the reduced C4M by 12 weeks of treatment, such as by 12 weeks.

Compound

10 In one embodiment of the disclosure, the compound of the disclosure is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable salt thereof.

15 In one embodiment of the present disclosure, said compound is {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable derivative thereof.

20 In one embodiment of the present disclosure, said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable derivative thereof.

In one embodiment of the present disclosure a pharmaceutically acceptable derivative is a pharmaceutically acceptable salt.

25 In one embodiment of the present disclosure, said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable salt thereof.

In one embodiment of the present disclosure a pharmaceutically acceptable derivative thereof is a pharmaceutically acceptable salt of an inorganic acid or an organic acid.

30 In one embodiment a pharmaceutically acceptable salt of an organic acid according to the present disclosure is selected from the group consisting of: formic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, propionic acid, benzoic acid, cinnamic acid, citric acid, fumaric acid, glycolic acid, lactic acid such as L-lactic acid or DL-lactic acid,
35 maleic acid, malic acid, malonic acid, mandelic acid such as DL-mandelic acid, oxalic

acid, picric acid, pyruvic acid, salicylic acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, tartaric acid, ascorbic acid, pantoic acid, bismethylene salicylic acid, ethanedithiolic acid, gluconic acid, citraconic acid, aspartic acid, stearic acid, palmitic acid, EDTA, glycolic acid, p-aminobenzoic acid, glutamic acid, benzenesulfonic acid (besylate), p-toluenesulfonic acid, hippuric acid, oxoglutaric acid such as 2-oxoglutaric acid or 3-oxoglutaric acid, glutaric acid, and adipic acid.

In a particular embodiment said organic acid is acetic acid, succinic acid, tartaric acid or propionic acid.

In a particular embodiment said organic acid is acetic acid. In a particular embodiment said organic acid is succinic acid.

In one embodiment a pharmaceutically acceptable salt of an inorganic acid according to the present disclosure is selected from the group consisting of: hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, sulphuric acid and nitric acid.

In one embodiment of the present disclosure, said compound is selected from the group consisting of:

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium acetate, including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium succinate including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine DL-mandelic acid salt including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine hippuric acid salt including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine L-lactic acid salt including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium besylate including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium oxoglutarate including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine formic acid salt including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1H-pyrrole-2-yl-allylideneamino]-guanidine DL-lactic acid salt including tautomeric and stereoisomeric forms thereof;

(E)-N-[1-(2-nitrophenyl)-1H-pyrrole-2-yl-allylideneamino]-guanidine glutaric acid salt including tautomeric and stereoisomeric forms thereof;

5 (E)-N-[1-(2-nitrophenyl)-1H-pyrrole-2-yl-allylideneamino]-guanidine adipic acid salt including tautomeric and stereoisomeric forms thereof; and

(E)-N-[1-(2-nitrophenyl)-1H-pyrrole-2-yl-allylideneamino]-guanidinium nitrate salt including tautomeric and stereoisomeric forms thereof.

10 In one embodiment the compound is {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, for example (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable salt thereof, such as (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate or (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium
15 succinate.

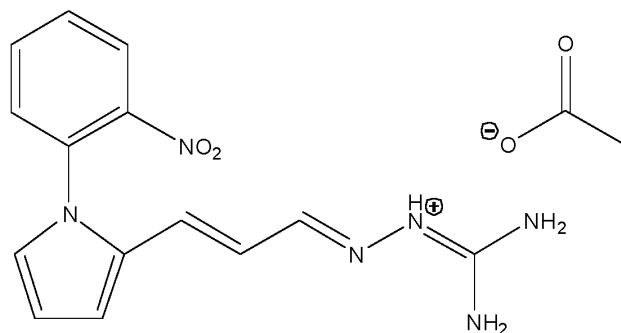
In one embodiment of the present disclosure, said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate and (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-
20 aminoguanidinium acetate.

In one embodiment of the present disclosure, said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium succinate and (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-
25 aminoguanidinium succinate.

In one embodiment of the present disclosure, said compound is selected from the group consisting of (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate and (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-
30 allylidene}-aminoguanidinium succinate.

In preferred embodiments of the present disclosure, said compound is selected from the group consisting of (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate and (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-
35 allylidene}-aminoguanidinium succinate.

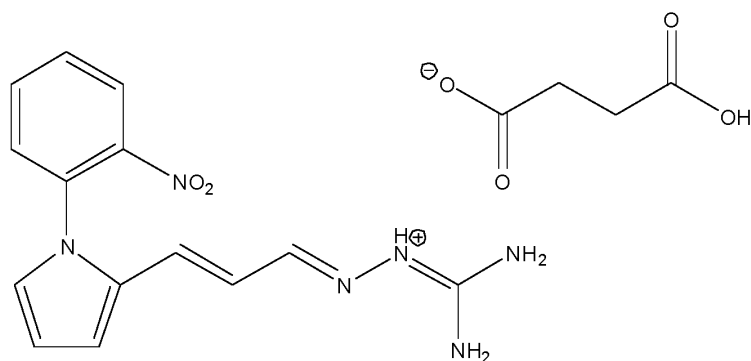
In one embodiment of the present disclosure, said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate ('AP1189'):



formula (II).

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In one embodiment of the present disclosure, said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium succinate:



formula (III).

- 10 In one embodiment, the pharmaceutically acceptable salt of AP1189 according to the present disclosure is a crystalline or polymorphic form of a pharmaceutically acceptable salt of AP1189. Polymorphic forms are prepared and disclosed in WO 2022/268814, the disclosure of which is incorporated by reference herewith.
- 15 In one embodiment, the pharmaceutically acceptable salt of AP1189 according to the present disclosure is a crystalline or polymorphic form of a pharmaceutically acceptable salt of AP1189 selected from the group consisting of: AP1189 acetate, AP1189 succinate, the DL-mandelic acid salt of AP1189, the hippuric acid salt of AP1189, the L-lactic acid salt of AP1189, the besylate salt of AP1189, the oxoglutarate salt of

AP1189, the formic acid salt of AP1189, the DL-lactic acid salt of AP1189, the glutaric acid salt of AP1189, the adipic acid salt of AP1189 and the nitrate salt of AP1189.

5 In one embodiment, the pharmaceutically acceptable salt of AP1189 according to the present disclosure is a crystalline or polymorphic form of AP1189 acetate.

In one embodiment, the compound of the present disclosure is a crystalline form of N-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using
10 Cu K α radiation at 11.5 ± 0.2 , 23.5 ± 0.2 , and 27.0 ± 0.2 .

In one embodiment said crystalline form further exhibits one or more X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K α radiation selected from the group consisting of 11.7 ± 0.2 , 15.6 ± 0.2 , and 24.8 ± 0.2 .

In one embodiment said crystalline form further exhibits one or more X-ray lines (2-
15 theta values) in a powder diffraction pattern when measured using Cu K α radiation selected from the group consisting of 13.0 ± 0.2 , 15.5 ± 0.2 , 16.2 ± 0.2 , 19.6 ± 0.2 , 20.0 ± 0.2 , and 21.1 ± 0.2

MTX

20 In one embodiment of the present disclosure, said MTX is selected from the group consisting of methotrexate (systemic), methotrexate (oral), methotrexate tablet, methotrexate oral solution, methotrexate (injection), methotrexate sodium, Methotrexate LPF Sodium, Trexall (Xatmep), Rheumatrex, Rasuvo, Otrexup, Alltrex, Beltrax, Biotrexate, Caditrex, Carditrex, Cytotrex, Dermotrex, Folitrex, HI-Trex, Imutrex,
25 Merex, Methocip, Methorex, Methotrexate, Metorex, Metrex, Mexate, MTX-Korea, Neotrexate, Nidtrex, Oncotrex, Onotrex, Plastomet, Remtrex, Rextop, Roxate, Tevatrex, Throtex, Trex, Thixilem, Vibzi and Zexate.

Folic acid

30 In one embodiment of the present disclosure there is provided a compound as disclosed herein, for use in the treatment of rheumatoid arthritis, wherein said compound is to be administered with methotrexate (MTX), and further wherein said compound is to be administered with folic acid, or an equivalent thereof.

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In one embodiment of the present disclosure there is provided a combination comprising MTX, folic acid and a compound as disclosed herein, for use in the treatment of rheumatoid arthritis in a subject as defined herein. In one embodiment, the equivalent of folic acid is folate or vitamin B9.

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Dosages

Compound

The dosage used herewith is calculated as AP1189 free base, unless otherwise indicated. For example, about 120 mg (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate corresponds to about 100 mg (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine (free base), as used in the examples. Likewise, a dosage of about 41.5 mg free base corresponds to about 50 mg of the acetate salt, and a dosage of about 83 mg free base corresponds to about 100 mg of the acetate salt of the compound of formula (I) according to the present disclosure.

15

For the sake of clarity, a formulation comprising about 100 mg AP1189 free base will comprise about 120 mg AP1189 acetate (120.482 or 120.5 mg). For the sake of clarity, a formulation comprising about 100 mg AP1189 free base will comprise about 140 mg AP1189 succinate.

20

In one embodiment, the compound of the disclosure is administered daily, preferably once daily. In one embodiment, the compound of the disclosure is administered once daily, once per day or one time per day.

25

In one embodiment of the present disclosure there is provided a compound of formula (I) according to the present disclosure, for use in the treatment of rheumatoid arthritis in a subject with a C-Reactive Protein (CRP) level of >3 mg/L, wherein said compound is to be administered with methotrexate (MTX), and wherein said compound is administered at a dosage of about 10 mg to 500 mg daily; such as about 10 mg to 15 mg, such as about 15 mg to 20 mg, such as about 20 mg to 25 mg, such as about 25 mg to 50 mg, such as about 50 to 75 mg, such as about 75 to 100 mg, such as about 100 mg to 125 mg, such as about 125 mg to 150 mg, such as about 150 mg to 175 mg, such as about 175 to 200 mg, such as about 200 to 225 mg, such as about 225 mg to 250 mg, such as about 250 mg to 275 mg,

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such as about 275 mg to 300 mg, such as about 300 to 350 mg, such as about 350 to 400 mg, such as about 400 mg to 450 mg, such as about 450 mg to 500 mg daily, such as once daily, wherein said dosage is calculated as the free base.

5 In some embodiments said compound is administered at a daily dosage (calculated as the free base) of about 41.5 mg to about 50 mg, such as about 50 mg to about 83 mg, such as about 83 mg to about 100 mg, such as about 100 mg to about 125 mg, such as about 125 mg to about 150 mg, such as about 150 mg to about 175 mg, such as about 175 mg to about 200 mg, such as about 200 mg to about 225 mg, such as about
10 225 mg to about 250 mg, such as about 250 mg to about 300 mg.

In some embodiments said compound is administered at a daily dosage of about 25 mg to about 400 mg, such as about 50 mg to about 300 mg, such as about 50 mg to about 250 mg, such as about 50 mg to about 200 mg, such as about 75 mg to about
15 150 mg (calculated as the free base).

In some embodiments said compound is administered at a daily dosage of about 10 mg to about 100 mg, such as about 10 mg to about 20 mg, such as about 20 mg to about 25 mg, such as about 25 mg to about 50 mg, such as about 50 mg to about 75 mg, such as about 75 mg to about 100 mg (calculated as the free base)
20 mg, such as about 75 mg to about 100 mg (calculated as the free base)

In one embodiment of the present disclosure there is provided a compound of formula (I) according to the present disclosure, for use in the treatment of rheumatoid arthritis in a subject with a C-Reactive Protein (CRP) level of >3 mg/L, wherein said compound is
25 to be administered with methotrexate (MTX),
and wherein said compound is administered at a dosage of about 100 mg daily, such as once daily, wherein said dosage is calculated as the free base.

A dosage of about 100 mg daily, and a daily dosage of about 100 mg, are used
30 interchangeably.

In one embodiment said compound is administered at a dosage of about 100 mg daily (calculated as the free base), which dosage is administered in a once daily dosage.

In one embodiment said compound is administered at a dosage of about 100 mg daily (calculated as the free base), which dosage is divided into a twice daily or three times daily dosage.

- 5 In one embodiment of the present disclosure there is provided a compound of formula (I) according to the present disclosure, for use in the treatment of rheumatoid arthritis in a subject with a C-Reactive Protein (CRP) level of >3 mg/L, wherein said compound is to be administered with methotrexate (MTX),
and wherein said compound is administered at a dosage of about 10 to 100 mg daily,
10 such as once daily, wherein said dosage is calculated as the free base.

In preferred embodiments said compound is (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate.

- 15 In one embodiment said compound is (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate, and is administered at a daily dosage of about 100 mg daily (calculated as the free base), such as a once daily dosage.

- 20 In one embodiment said compound is (E)-N-trans-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate, and is administered at a daily dosage of about 120 mg daily (calculated as acetate salt form), such as a once daily dosage.

MTX

- 25 In one embodiment of the present disclosure, methotrexate (MTX) is administered in an amount or dosage of about 5 mg to about 30 mg once weekly.

In one embodiment of the present disclosure, methotrexate (MTX) is administered in an amount or dosage of about 5 mg to about 30 mg once weekly on the same week day.

- 30 One per week and once weekly are used interchangeably herein. Once per week means once every 7 days, preferably on the same week day.

In one embodiment, MTX is administered at a dosage of about 5 mg to about 10 mg once per week, such as about 5 mg to about 15 mg once per week, such as about 5

mg to about 20 mg once per week, such as about 5 mg to about 25 mg once per week, such as about 5 mg to about 30 mg once per week, such as about 7.5 mg to about 10 mg once per week, such as about 7.5 mg to about 15 mg once per week, such as about 7.5 mg to about 20 mg once per week, such as about 7.5 mg to about 25 mg once per week, such as about 7.5 mg to about 30 mg once per week, such as about 10 mg to about 15 mg once per week, such as about 10 mg to about 20 mg once per week, such as about 10 mg to about 25 mg once per week, such as about 10 mg to about 30 mg once per week, such as about 15 mg to about 20 mg once per week, such as about 15 mg to about 25 mg once per week, such as about 15 mg to about 30 mg once per week, such as about 20 mg to about 25 mg once per week, such as about 20 mg to about 30 mg once per week, such as about 25 mg to about 30 mg once per week.

In one embodiment of the present disclosure said MTX is administered at a dosage of about 5 mg to about 7.5 mg once per week, 7.5 mg to about 10 mg once per week such as about 10 mg to about 15 mg once per week, such as about 15 mg to about 20 mg once per week, such as about 20 mg to about 25 mg once per week, such as about 25 mg to about 30 mg once per week.

In one embodiment of the present disclosure, methotrexate (MTX) is administered at a dosage of about 5 mg to about 30 mg once weekly. In one embodiment of the present disclosure, methotrexate (MTX) is administered at a dosage of about 7.5 mg to about 25 mg once weekly. In one embodiment of the present disclosure, methotrexate (MTX) is administered at a dosage of about 10 mg to about 25 mg once weekly. In one embodiment of the present disclosure, methotrexate (MTX) is administered at a dosage of about 10 mg to about 20 mg once weekly.

In one embodiment of the present disclosure, methotrexate (MTX) is administered at a dosage of no more than 20 mg once weekly.

In one embodiment of the present disclosure, the methotrexate (MTX) is administered at a dosage of about 5 mg once weekly, such as about 7.5 mg once weekly, such as about 10 mg once weekly, such as about 12.5 mg once weekly, such as about 15 mg

once weekly, such as about 17.5 mg once weekly, such as about 20 mg once weekly, such as about 25 mg once weekly, such as about 30 mg once weekly.

- 5 In one embodiment of the present disclosure, the methotrexate (MTX) is administered in a weekly dosage or amount of about 5 mg to about 7.5 mg, such as about 7.5 mg to about 10 mg, such as about 10 mg to about 15 mg, such as about 5 mg to about 20 mg, such as about 10 to about 20 mg, such as about 10 to about 25 mg, such as about 15 to about 20 mg.
- 10 In one embodiment of the present disclosure, the methotrexate (MTX) or prodrug thereof is administered subcutaneously in an amount or dosage of about 5 to about 30 mg once per week/weekly. Once per week means once every 7 days, preferably on the same week day.
- 15 In one embodiment of the present disclosure, the methotrexate (MTX) or prodrug thereof is administered intramuscularly in an amount or dosage of about 5 to about 30 mg once per week/weekly. Once per week means once every 7 days, preferably on the same week day.
- 20 In one embodiment of the present disclosure, the methotrexate (MTX) or prodrug thereof is administered in an oral dosage form in an amount or dosage of about 10 to about 25 mg once per week/weekly. Once per week means once every 7 days, preferably on the same week day.
- 25 In a preferred embodiment MTX or a prodrug thereof is administered once weekly. Commercially available dosage forms of MTX are available, for oral administration or subcutaneous administration. Both dosage forms are to be administered once a week, preferably on the same week day.
- 30 In one embodiment the compound of the disclosure is administered daily, preferable once daily, and MTX is administered once weekly. In one embodiment, the compound of the disclosure is administered at a daily dosage of 50 mg to about 250 mg (calculated as the free base), such as once daily, and said MTX is administered at a dosage of 5 to 30 mg once weekly.

In one embodiment, the compound of the disclosure is administered at a dosage of between about 50 and about 250 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly, such as wherein said compound is administered at a dosage of between about 50 and about 200 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly, such as wherein said compound is administered at a dosage of between about 75 and about 200 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly, such as wherein said compound is administered at a dosage of between about 75 and about 175 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly, such as wherein said compound is administered at a dosage of between about 75 and about 150 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly, such as wherein said compound is administered at a dosage of between about 75 and about 125 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly, such as wherein said compound is administered at a dosage of between about 75 and about 100 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly, such as wherein said compound is administered at a dosage of about 100 mg per day (calculated as the free base) and said MTX is administered at a dosage between about 10 and about 25 mg once weekly; preferably wherein said compound is administered once per day.

In one embodiment, the compound of the disclosure is administered at a dosage of about 10 to about 200 mg per day (calculated as the free base) and said MTX is administered at a dosage of about 7.5 to about 20 mg once weekly, such as wherein said compound is administered at a dosage of about 10 to about 100 mg per day (calculated as the free base) and said MTX is administered at a dosage of about 7.5 to about 20 mg once weekly such as about 7.5 to about 15 mg once weekly.

In one embodiment the subject with rheumatoid arthritis is about to start up-titration with methotrexate. In one embodiment said up-titration with MTX starts with a low dosage and gradually increases the dosage over time.

- 5 In one embodiment the subject with rheumatoid arthritis starts up-titration with methotrexate at 7.5 mg. In one embodiment the subject with rheumatoid arthritis starts up-titration with methotrexate at 10 mg. In one embodiment the subject with rheumatoid arthritis starts up-titration with methotrexate at 12.5 mg. In one embodiment the subject with rheumatoid arthritis starts up-titration with methotrexate at 15 mg.
- 10 In one embodiment the subject with rheumatoid arthritis ends up-titration with methotrexate at 10 mg. In one embodiment the subject with rheumatoid arthritis ends up-titration with methotrexate at 12.5 mg. In one embodiment the subject with rheumatoid arthritis ends up-titration with methotrexate at 15 mg. In one embodiment the subject with rheumatoid arthritis ends up-titration with methotrexate at 17.5 mg. In one embodiment the subject with rheumatoid arthritis ends up-titration with methotrexate at 20 mg. In one embodiment the subject with rheumatoid arthritis ends up-titration with methotrexate at 25 mg.
- 15 In one embodiment the present disclosure provides a compound of formula (I), including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative or salt thereof, for use in the treatment of rheumatoid arthritis in a treatment-naïve subject having a CRP level of >3 mg/L,
- 20 optionally wherein said rheumatoid arthritis is moderate to severe RA, optionally wherein said subject is diagnosed with rheumatoid arthritis within 6 months prior to treatment initiation, wherein said compound is to be administered with methotrexate (MTX), wherein said compound is administered at a daily dosage of about 50 to about 250 mg (calculated as the free base), such as about 50 mg to 200 mg, such as about 75 to 150 mg, such as about 100 mg,
- 25 and said MTX is administered at a dosage of about 10 to about 30 mg once weekly, such as about 10 to about 25 mg once weekly, such as about 10 to about 20 mg once weekly, such as about 10 to about 15 mg once weekly; such as about 10 mg, about 12.5 mg, about 15 mg, about 17.5 mg or about 20 mg once weekly.
- 30
- 35

Folic acid

In one embodiment said folic acid is administered at about 1 to 10 mg folic acid per week, such as about 5 mg folic acid per week, such as at least 5 mg folic acid per
5 week. In one embodiment said folic acid is administered once weekly. In one embodiment said folic acid is administered in daily dosages.

Pharmaceutical composition

The compounds for use according to the present disclosure, including a compound of
10 formula (I) including tautomeric and stereoisomeric forms thereof, or a pharmaceutically acceptable derivative thereof, and methotrexate (MTX), may be provided in any suitable formulation.

MTX

15 In one embodiment of the present disclosure MTX is formulated for oral administration, such as in the form of tablets, capsules or oral solutions or suspensions.

In one embodiment of the present disclosure MTX is formulated as a liquid, such as a liquid suitable for intravenous administration or injection, such as a liquid suitable for subcutaneous or intramuscular injection.

20

AP1189

It is also an aspect of the present disclosure to provide a pharmaceutical composition comprising (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine (compound of formula I), including tautomeric and stereoisomeric forms thereof, and
25 pharmaceutically acceptable salts thereof, for the medical uses disclosed herein.

In one embodiment of the present disclosure the compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, is formulated for oral administration, such as in the form of tablets, capsules, or
30 oral solutions or suspensions.

In one embodiment of the present disclosure the compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, is formulated as a liquid, such as a liquid for intravenous administration or
35 continuous infusion, or a liquid for injection.

In one embodiment of the present disclosure the compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, is formulated for extended release.

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In one embodiment of the present disclosure the compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, is formulated for immediate release.

10 In a particular embodiment the compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, is formulated for oral administration.

15 In one embodiment the compound of the present disclosure is formulated as an solid oral dosage form, such as a tablet.

In one embodiment the compound of the present disclosure is formulated as a powder, such as an oral powder, such as an oral powder suitable for suspension in a liquid.

20 In one embodiment the compound of the present disclosure is formulated as a suspension comprising dissolved oral powder.

In one embodiment the compound of the present disclosure is formulated as an oral suspension, such as a suspension for oral administration.

25 To circumvent degradation at low pH of the gastric compartment, AP1189 has previously been formulated as an enteric coated tablet and later as an alkaline suspension. It has recently been demonstrated that a subset of the pharmaceutically acceptable salts of AP1189, including AP1189 in its acetate salt and succinate salt forms, are highly soluble at low pH and hence do not require protection from gastric pH, allowing the use also of solid oral formulations targeting release in the gastric
30 compartment such as immediate release solid oral formulations. Such formulation are disclosed in WO 2022/268825, which is incorporated by reference herein in its entirety.

In one embodiment there is provided a unit dosage form comprising a compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically
35 acceptable salts thereof, for the uses disclosed herein.

In one embodiment there is provided an oral formulation comprising a compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, for the uses disclosed herein.

5

In one embodiment there is provided an oral formulation comprising a compound selected from the group consisting of:

- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium acetate, including tautomeric and stereoisomeric forms thereof;
- 10 (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium succinate including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine DL-mandelic acid salt including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine hippuric acid salt
- 15 including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine L-lactic acid salt including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium besylate including tautomeric and stereoisomeric forms thereof;
- 20 (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium oxoglutarate including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine formic acid salt including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine DL-lactic acid salt
- 25 including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine glutaric acid salt including tautomeric and stereoisomeric forms thereof;
- (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidine adipic acid salt including tautomeric and stereoisomeric forms thereof; and
- 30 (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium nitrate salt including tautomeric and stereoisomeric forms thereof.

In one embodiment, the pharmaceutically acceptable salt of AP1189 according to the present disclosure is a crystalline or polymorphic form of a pharmaceutically acceptable salt of AP1189 selected from the group consisting of: AP1189 acetate, AP1189

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succinate, the DL-mandelic acid salt of AP1189, the hippuric acid salt of AP1189, the L-lactic acid salt of AP1189, the besylate salt of AP1189, the oxoglutarate salt of AP1189, the formic acid salt of AP1189, the DL-lactic acid salt of AP1189, the glutaric acid salt of AP1189, the adipic acid salt of AP1189 and the nitrate salt of AP1189.

- 5 Polymorphic forms are prepared and disclosed in WO 2022/268814, the disclosure of which is incorporated by reference herewith.

10 In one embodiment there is provided an oral formulation comprising a compound of formula (I) including tautomeric and stereoisomeric forms thereof, and pharmaceutically acceptable salts thereof, and comprising at least one pharmaceutically acceptable excipient, for the uses disclosed herein.

15 In one embodiment said oral formulation delivers or releases said compound to the gastric compartment (or stomach), such as primarily or predominantly delivers or releases said compound to the gastric compartment (or stomach).

20 In one embodiment said oral formulation delivers or releases said compound in the gastric compartment by immediate release, by delayed release, by burst release, or by any means of releasing said compound primarily or predominantly in the gastric compartment.

25 In one embodiment said oral formulation delivers or releases not less than about 65% to about 80% of said compound in the gastric compartment; such as not less than about 65% of said compound, such as not less than about 70%, such as not less than about 75%, such as not less than about 80%, such as not less than about 85%, such as not less than about 90%, such as not less than about 95% of said compound in the gastric compartment.

30 In one embodiment said oral formulation immediately releases said compound in the gastric compartment. In one embodiment said oral formulation releases said compound in the gastric compartment for gastric absorption of said compound. In one embodiment said oral formulation releases said compound in the gastric compartment for absorption of said compound over the gastric mucus layer. In one embodiment said oral formulation is designed for gastric delivery. In one embodiment said oral

formulation is designed for gastric release. In one embodiment said oral formulation is designed for gastric absorption.

5 In one embodiment said oral formulation is a solid oral formulation. In one embodiment said solid oral formulation is a solid oral dosage form. In one embodiment said solid oral dosage form is an immediate release solid oral dosage form.

10 In one embodiment said oral formulation is a tablet. In one embodiment said solid oral formulation is a tablet. In one embodiment said solid oral dosage form is a tablet.

In one embodiment there is provided a solid oral formulation, solid oral dosage form or tablet, comprising a compound of formula (I) as disclosed herein, wherein not less than about 65% to about 80% of said compound is dissolved into solution in the gastric compartment.

15 In one embodiment there is provided a solid oral formulation, solid oral dosage form or tablet, comprising a compound of formula (I) as disclosed herein, wherein not less than about 65%, such as not less than about 70%, such as not less than about 75%, such as not less than about 80%, such as not less than about 85%, such as not less than about 90%, such as not less than about 95% of said compound is dissolved into solution in the gastric compartment.

20 In one embodiment the immediate release solid oral formulation, such as immediate release solid oral dosage form, such as immediate release tablet of the present disclosure comprises

(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium acetate, including tautomeric and stereoisomeric forms thereof, or
(E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium succinate, including tautomeric and stereoisomeric forms thereof,
30 and at least one pharmaceutically acceptable excipient.

In one embodiment there is provided an oral formulation, such as a solid oral formulation, such as an immediate-release solid oral formulation, comprising a compound of formula (I) as disclosed herein, wherein not less than about 65% to about 80% of said compound is dissolved into solution in about 15 minutes.

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In one embodiment there is provided an oral formulation, such as a solid oral formulation, such as an immediate-release solid oral formulation, comprising a compound of formula (I) as disclosed herein, wherein not less than about 65% to about 80% of said compound is dissolved into solution in about 15 minutes at a pH of about 1 to 3, such as a pH of about 0.5 to 3.5; such as a pH of about 0.5 to 1, such as a pH of about 1 to 1.5, such as a pH of about 1.5 to 2, such as a pH of about 2 to 2.5, such as a pH of about 2.5 to 3, such as a pH of about 3 to 3.5.

In one embodiment there is provided an oral formulation, such as a solid oral formulation, such as an immediate-release solid oral formulation, comprising a compound of formula (I) as disclosed herein, wherein not less than about 65% to about 80% of said compound is dissolved into solution in about 15 minutes at a pH of about 1.2.

In one embodiment there is provided an oral formulation, such as a solid oral formulation, such as an immediate-release solid oral formulation, comprising a compound of formula (I) as disclosed herein, wherein not less than about 65% to about 80% of the of the nominal dose of said compound is released in about 15 minutes in a monograph dissolution test.

In one embodiment there is provided an oral formulation, such as a solid oral formulation, such as an immediate-release solid oral formulation, comprising a compound of formula (I) as disclosed herein, wherein not less than about 80% of said compound is dissolved into solution in about 10 to 15 minutes, such as at a pH of about 1.2.

In some embodiments dissolution is measured using a USP 2 paddle equipment at 37 °C at a rotation speed of 50 rpm, as disclosed in WO 2022/268825.

In one embodiment there is provided an oral formulation, such as a solid oral formulation, such as an immediate-release solid oral formulation or dosage form, comprising a compound of formula (I) as disclosed herein, wherein not less than 80% of the compound is dissolved into aqueous solution in 15 minutes at a pH of 1 to 3,

such as at a pH of about 1.2, using a USP 2 paddle equipment at 37 °C at a rotation speed of 50 rpm.

5 In some embodiments not less than 80% of the compound is dissolved into aqueous solution in 15 minutes at pH 1 (0.1 N HCl), using a USP 2 paddle equipment at 37 °C at a rotation speed of 50 rpm.

10 In some embodiments not less than 80% of the compound is dissolved into aqueous solution in 15 minutes at a pH of 1 to 3, such as at a pH of about 1.2, using a USP 2 paddle equipment at 37 °C at a rotation speed of 50 rpm; wherein the dissolution media consist of 500 ml 0.1 N HCl + 50 ml of water.

15 In preferred embodiments the compound is (E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium acetate, including tautomeric and stereoisomeric forms thereof.

In one embodiment there is provided an oral formulation, such as a solid oral formulation, such as an immediate-release solid oral formulation, comprising a compound of formula (I) as disclosed herein, wherein the disintegration time of said
20 oral formulation such as solid oral formulation is from ½ minute to 10 minutes, such as ½ minute to 1 minute, such as 1 to 2 minutes, such as 2 to 3 minutes, such as 3 to 4 minutes, such as 4 to 5 minutes, such as 5 to 6 minutes, such as 6 to 7 minutes, such as 7 to 8 minutes, such as 8 to 9 minutes, such as 9 to 10 minutes.

25 In one embodiment the solid oral dosage form comprises a compound of formula (I) as defined herein at a dosage from about 25 mg to about 650 mg per dosage form, such as about 25 mg, such as about 50 mg, such as about 100 mg, such as about 150 mg, such as about 200 mg, such as about 250 mg, such as about 300 mg, such as about 350 mg, such as about 400 mg, such as about 450 mg, such as about 500 mg, such as
30 about 550 mg, such as about 600 mg, such as about 650 mg compound (calculated as the free base).

Examples

A double-blind, multi-center, randomized, placebo-controlled study of the safety, tolerability, and efficacy of 12 weeks of treatment with AP1189 ((E)-N-[1-(2-nitrophenyl)-1-H-pyrrole-2-yl-allylideneamino]-guanidinium acetate; resomelagon) in Methotrexate (MTX) treatment naïve rheumatoid arthritis (RA) patients with active joint disease (Clinical phase II).

The study population consisted of patients with Rheumatoid Arthritis with high disease activity defined as having a clinical disease activity index (CDAI) > 22 at the start-up of first line treatment with the disease modulation anti rheumatoid drug MTX. At the same day of initiation of MTX patients were allocated to co-treatment with AP1189 or matched placebo. The compound was given once daily as tablet at the 100 mg (free base) dose level.

15

Example 1

This consists of the full patient population where a total of 53 patients completed the 12 weeks dosing with AP1189 and 61 completed dosing with placebo. The mean clinical disease activity index (CDAI) at baseline i.e. at the day of initiation of MTX treatment and cotreatment with AP1189 or placebo was 42.0 in the AP1189-treated patients and 40.3 in the placebo-treated patients.

20

More than 85% of the patients were women and the mean age was 58.0 and 55.2 in the AP1189 and placebo group, respectively.

25

The primary efficacy readout was the ability to reach a 20% reduction in disease activity as evaluated by American College of Rheumatology (ACR) scoring index (ACR20). To reach 20% reduction in disease activity the ACR20 should be reached. In order to reach ACR20 a patient has a reduction of a minimum of 20% in tender and swollen joints based on standardized evaluation of 68 predefined joints evaluated for tenderness and evaluation of 66 joints for swollenness. If a reduction of 20% in tender and swollen joint over the 12-week treatment period was identified, additionally 3 out of 5 measurement scores should also show a minimum 20% reduction. The 5 scores of which 3 should show a 20% reduction to full-fill the requirement to qualify for ACR20 was

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1. the patient's evaluation of global disease activity using a visual analogue score (PGA(VAS));
2. the investigators evaluation of global disease activity using a visual analogue score (PGA(VAS));
- 5 3. the patient's evaluation of pain using a visual analogue score;
4. the evaluation of patients ability to handle normal daily activities using the Health Assessment Questionnaire Disability Index, and;
5. changes in circulating levels of C-reactive protein (CRP).

For all measurements evaluation was conducted at baseline, i.e. at the same day, but
10 prior to initiation of MTX and AP1189/placebo treatment; and the same day of the last dose of AP1189 or placebo was taken (i.e. 12 weeks after the baseline evaluation).

In the AP1189-treated group 54.7% of the patients intended for treatment with the compound reached ACR20. In the placebo group 55.7% of the patients reached
15 ACR20.

Example 2

A subset of the patients on the study had signs of systemic inflammation at baseline, defined as the day MTX and AP1189/placebo treatment were initiated. A total of 34
20 patients treated with AP1189 and 35 patients treated with placebo completed the 12 weeks dosing. Signs of systemic inflammation was identified as circulating levels of C-reactive peptide outside the normal range, i.e. higher than 3 mg/L. Compared to the full patient population where the percentage of patients reaching a 20% reduction in disease activity elevation by ACR20 were comparable between the AP1189- and
25 placebo-treated patients (cf. Example 1), the percentage of-AP1189 treated patients with systemic inflammation was higher than in the placebo-treated patients.

A total of 70.6% of the AP1189-treated patients reached ACR20, as compared to 54.3% in of the placebo-treated patients. This indicates that the AP1189 compound has
30 a specific treatment potential in RA patients where the degree of disease reach a severity that includes systemic inflammation as measured by increased levels of circulating C-reactive peptide (above 3 mg/L).

For HAQ-DI the mean reduction in the AP1189-treated group was 0.64 points.

Example 3

A subset of the patients with C-reactive peptide above 3 mg/L were diagnosed with RA less than 6 months before initiation of treatment, i.e. before the start-up of MTX treatment and co-treatment with AP1189/placebo.

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The AP1189-treated patient group included 28 patients diagnosed within 6 months of treatment initiation, and the placebo-treated group included 27 patients diagnosed within 6 months of treatment initiation. In these patients the percentage of patients reaching ACR20 was as follows:

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- AP1189-treated: 82.1%
- Placebo treated: 51.9%

15

The difference between the two groups reached statistical significance with a p value of 2.3% (Fischer exact test). This finding shows that not only patients with sign of systemic inflammation benefit from AP1189-treatment, but specifically patients where the disease was diagnosed within 6 months from initiation of treatment has specific benefit of AP1189 treatment.

20

This significant treatment effect of AP1189 on disease activity was further substantiated by statistically significantly larger reduction in CDAI, DAS28 and HAQ-DI in the AP1189-treated patients compared to the placebo treated patients.

For CDAI the mean reduction in the AP1189-treated group was 24.6 points vs 14.7 points in the placebo group, $p < 0.01$.

25

For DAS28 the mean reduction in the AP1189-treated group was 1.9 points vs 1.2 points in the placebo group, $p < 0.01$.

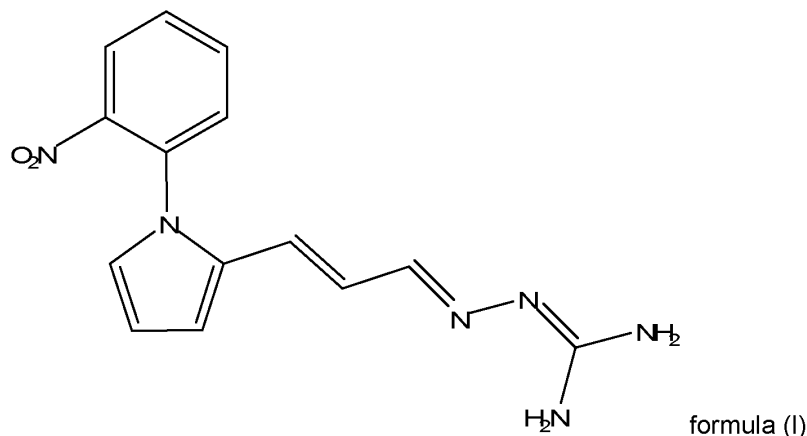
For HAQ-DI the mean reduction in the AP1189-treated group was 0.69 points vs 0.31 points in the placebo group, $p < 0.05$.

30

For all measures the reduction was evaluated by scoring the readouts at the end of the 12 weeks treatment period and compare those to the scoring collected at baseline.

Claims

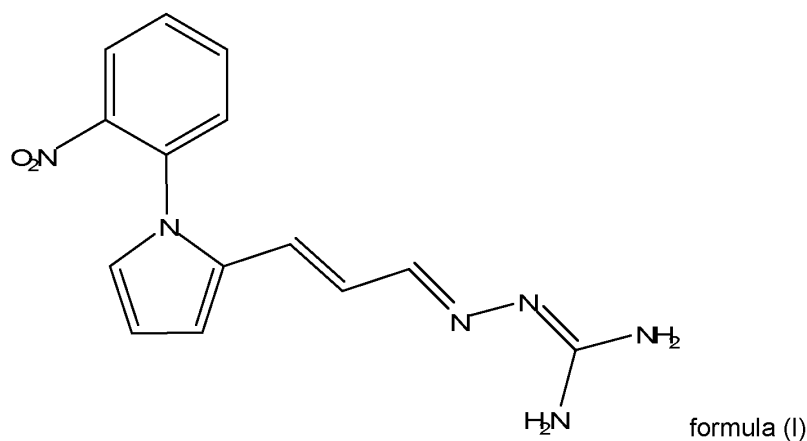
1. A compound of formula (I)



- 5 including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable derivative thereof,
for use in the treatment of rheumatoid arthritis in a treatment-naïve subject having a C-Reactive Protein (CRP) level of >3 mg/L,
wherein said compound is administered with methotrexate (MTX).

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2. A combination of methotrexate (MTX) and a compound of formula (I)



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- including tautomeric and stereoisomeric forms thereof; or a pharmaceutically acceptable derivative thereof,
for use in the treatment of rheumatoid arthritis in a treatment-naïve subject with a C-Reactive Protein (CRP) level of >3 mg/L.

3. The compound for use or the combination for use according to any one of the preceding claims, wherein said treatment-naïve subject is DMARD treatment-naïve.
- 5 4. The compound for use or the combination for use according to any one of the preceding claims, wherein said treatment-naïve subject is conventional synthetic DMARD treatment-naïve.
- 10 5. The compound for use or the combination for use according to any one of the preceding claims, wherein said treatment-naïve subject is methotrexate treatment-naïve.
- 15 6. The compound for use or the combination for use according to any one of the preceding claims, wherein said treatment-naïve subject is naïve to methotrexate treatment prior to initiating treatment with said compound.
- 20 7. The compound for use or the combination for use according to any one of the preceding claims, wherein said treatment-naïve subject has a baseline C-Reactive Protein (CRP) level of >3 mg/L.
- 25 8. The compound for use or the combination for use according to any one of the preceding claims, wherein said treatment-naïve subject has a baseline C-Reactive Protein (CRP) level of >3 mg/L prior to treatment initiation.
- 30 9. The compound for use or the combination for use according to any one of the preceding claims, wherein said rheumatoid arthritis is moderate to severe active rheumatoid arthritis.
- 35 10. The compound for use or the combination for use according to any one of the preceding claims, wherein said rheumatoid arthritis is rheumatoid arthritis with a CDAI score of between 10 and ≤ 22 (moderate).
11. The compound for use or the combination for use according to any one of the preceding claims, wherein said rheumatoid arthritis is rheumatoid arthritis with a DAS28 score of between 3.2 and ≤ 5 (moderate).

12. The compound for use or the combination for use according to any one of the preceding claims, wherein said rheumatoid arthritis is severe rheumatoid arthritis.
- 5
13. The compound for use or the combination for use according to any one of the preceding claims, wherein said rheumatoid arthritis is rheumatoid arthritis with a CDAI > 22 (severe).
- 10
14. The compound for use or the combination for use according to any one of the preceding claims, wherein said rheumatoid arthritis is rheumatoid arthritis with a DAS28 score of above 5.1 (severe).
- 15
15. The compound for use or the combination for use according to any one of the preceding claims, wherein said rheumatoid arthritis is rheumatoid arthritis with active joint disease; such as early rheumatoid arthritis with active joint disease.
- 20
16. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject is diagnosed with rheumatoid arthritis within 6 months prior to treatment initiation.
- 25
17. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject is diagnosed with moderate to severe rheumatoid arthritis within 6 months prior to treatment initiation.
- 30
18. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject is diagnosed with rheumatoid arthritis within 1 month prior to treatment initiation, within 2 months prior to treatment initiation, within 3 months prior to treatment initiation, within 4 months prior to treatment initiation, within 5 months prior to treatment initiation, or within 6 months prior to treatment initiation.
19. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject is diagnosed with rheumatoid arthritis 0

to 6 months prior to treatment initiation, such as 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 5, 5 to 6 months prior to treatment initiation.

- 5 20. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject is diagnosed with rheumatoid arthritis about 0 months prior to treatment initiation, such as less than about 1 month, such as less than about 2 months, such as less than about 3 months, such as less than about 4 months, such as less than about 5 months, such as less than about 6 months prior to treatment initiation.
- 10 21. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject was diagnosed with moderate to severe rheumatoid arthritis within 6 months prior to treatment initiation.
- 15 22. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject is about to start up-titration with methotrexate.
- 20 23. The compound for use or the combination for use according to any one of the preceding claims, wherein treatment with said compound and methotrexate is initiated essentially at the same time.
- 25 24. The compound for use or the combination for use according to any one of the preceding claims, wherein treatment with said compound occurs concurrently with the initiation of dosing with methotrexate.
- 30 25. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine and (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable derivative thereof.
- 35 26. The compound for use or the combination for use according to any one of the preceding claims, wherein said pharmaceutically acceptable derivative is a pharmaceutically acceptable salt of an inorganic acid or an organic acid.

27. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is (*E*)-*N*-*trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidine, or a pharmaceutically acceptable salt thereof, such as a salt of an inorganic acid or an organic acid.
28. The compound for use or the combination for use according to any one of the preceding claims, wherein said organic acid is selected from the group consisting of: formic acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, propionic acid, benzoic acid, cinnamic acid, citric acid, fumaric acid, glycolic acid, lactic acid such as L-lactic acid or DL-lactic acid, maleic acid, malic acid, malonic acid, mandelic acid such as DL-mandelic acid, oxalic acid, picric acid, pyruvic acid, salicylic acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, tartaric acid, ascorbic acid, pamoic acid, bismethylene salicylic acid, ethanedisulfonic acid, gluconic acid, citraconic acid, aspartic acid, stearic acid, palmitic acid, EDTA, glycolic acid, p-aminobenzoic acid, glutamic acid, benzenesulfonic acid, p-toluenesulfonic acid hippuric acid, oxoglutaric acid such as 2-oxoglutaric acid or 3-oxoglutaric acid, glutaric acid, and adipic acid.
29. The compound for use or the combination for use according to any one of the preceding claims, wherein said organic acid is selected from the group consisting of acetic acid, succinic acid, tartaric acid or propionic acid.
30. The compound for use or the combination for use according to any one of the preceding claims, wherein said organic acid is acetic acid.
31. The compound for use or the combination for use according to any one of the preceding claims, wherein said organic acid is succinic acid.
32. The compound for use or the combination for use according to any one of the preceding claims, wherein said inorganic acid is selected from the group consisting of: hydrochloric acid, hydrobromic acid, hydroiodic acid, phosphoric acid, sulphuric acid and nitric acid.

33. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate and (*E*)-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate.
34. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is selected from the group consisting of {3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium succinate and (*E*)-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium succinate.
35. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is selected from the group consisting of (*E*)-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate and (*E*)-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium succinate.
36. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is (*E*)-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium succinate.
37. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is (*E*)-*N-trans*-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate.
38. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound comprises amorphous forms and polymorphic (crystalline) forms.
39. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is a crystalline form of AP1189 acetate.

40. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is a crystalline form of N-{3-[1-(2-nitrophenyl)-1H-pyrrol-2-yl]-allylidene}-aminoguanidinium acetate exhibiting at least X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K α radiation at 11.5 $\pm$ 0.2, 23.5 $\pm$ 0.2, and 27.0 $\pm$ 0.2.
41. The compound for use or the combination for use according to claim 39, wherein said crystalline form further exhibits one or more X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K α radiation selected from the group consisting of 11.7 $\pm$ 0.2, 15.6 $\pm$ 0.2, and 24.8 $\pm$ 0.2.
42. The compound for use or the combination for use according to any one of claims 39 to 40, wherein said crystalline form further exhibits one or more X-ray lines (2-theta values) in a powder diffraction pattern when measured using Cu K α radiation selected from the group consisting of 13.0 $\pm$ 0.2, 15.5 $\pm$ 0.2, 16.2 $\pm$ 0.2, 19.6 $\pm$ 0.2, 20.0 $\pm$ 0.2, and 21.1 $\pm$ 0.2.
43. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of about 10 mg to 500 mg daily; such as about 10 mg to 15 mg, such as about 15 mg to 20 mg, such as about 20 mg to 25 mg, such as about 25 mg to 50 mg, such as about 50 to 75 mg, such as about 75 to 100 mg, such as about 100 mg to 125 mg, such as about 125 mg to 150 mg, such as about 150 mg to 175 mg, such as about 175 to 200 mg, such as about 200 to 225 mg, such as about 225 mg to 250 mg, such as about 250 mg to 275 mg, such as about 275 mg to 300 mg, such as about 300 to 350 mg, such as about 350 to 400 mg, such as about 400 mg to 450 mg, such as about 450 mg to 500 mg; wherein said dosage is calculated as the free base.
44. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of about 25 mg to about 400 mg, such as about 50 mg to about 300 mg, such as about 50 mg to about 200 mg, such as about 75 mg to about 150 mg (calculated as the free base).

45. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of about 41.5 mg (calculated as the free base).
- 5 46. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of about 83 mg (calculated as the free base).
- 10 47. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of about 100 mg (calculated as the free base).
- 15 48. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of 10 to 100 mg (calculated as the free base).
- 20 49. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered as a once daily dosage.
- 25 50. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is selected from the group consisting of methotrexate (systemic), methotrexate (oral), methotrexate tablet, methotrexate oral solution, methotrexate (injection), methotrexate sodium, Methotrexate LPF Sodium, Trexall (Xatmep), Rheumatrex, Rasuvo, Otrexup, Alltrex, Beltrax, Biotrexate, Caditrex, Carditrex, Cytotrex, Dermotrex, Folitrex, HI-Trex, Imutrex, Merex, Methocip, Methorex, Methotrexate, Metorex, Metrex, Mexate, MTX-Korea, Neotrexate, Nidtrex, Oncotrex, Onotrex, Plastomet, Remtrex, Rextop, Roxate, Tevatrex, Throtex, Trex, Thixilem, Vibzi and Zexate.
- 30 51. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 5 mg to about 30 mg once weekly.

52. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 10 mg to about 25 mg once weekly.
- 5 53. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at dosage of about 5 mg to about 10 mg once per week, such as about 5 mg to about 15 mg once per week, such as about 5 mg to about 20 mg once per week, such as about 5 mg to about 25 mg once per week, such as about 5 mg to about 30 mg once per week, such as about 7.5 mg to about 10 mg once per week, such as about 7.5 mg to about 15 mg once per week, such as about 7.5 mg to about 20 mg once per week, such as about 7.5 mg to about 25 mg once per week, such as about 7.5 mg to about 30 mg once per week, such as about 10 mg to about 15 mg once per week, such as about 10 mg to about 20 mg once per week, such as about 10 mg to about 25 mg once per week, such as about 10 mg to about 30 mg once per week, such as about 15 mg to about 20 mg once per week, such as about 15 mg to about 25 mg once per week, such as about 15 mg to about 30 mg once per week, such as about 20 mg to about 25 mg once per week, such as about 20 mg to about 30 mg once per week, such as about 25 mg to about 30 mg once per week.
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54. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 5 mg to about 7.5 mg once per week, such as about 7.5 to 10 mg once per week, such as about 10 mg to about 15 mg once per week, such as about 15 mg to about 20 mg once per week, such as about 20 mg to about 25 mg once per week, such as about 25 mg to about 30 mg once per week.
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55. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 5 mg once per week, such as about 7.5 mg once per week, such as about 10 mg once per week, such as about 12.5 mg once per week, such as about 15 mg once per week, such as about 17.5 mg once per week, such as about 20 mg once per week, such as about 25 mg once per week, such as about 30 mg once per week.
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56. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 7.5 mg to 20 mg once weekly, such as a dosage of about 10 mg to 20 mg once weekly.
57. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 7.5 mg to 15 mg once weekly, such as administered at a dosage of about 10 mg to 15 mg once weekly.
58. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 7.5 mg once weekly.
59. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 10 mg once weekly.
60. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 12.5 mg once weekly.
61. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 15 mg once weekly.
62. The compound for use or the combination for use according to any one of the preceding claims, wherein said MTX is administered at a dosage of about 20 mg once weekly.
63. The compound for use or the combination for use according to any one of the preceding claims, wherein said subject starts up-titration with methotrexate at 7.5 mg, such as at 10 mg, such as at 12.5 mg, such as at 15 mg.

- 5 64. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of about 25 to about 200 mg (calculated as the free base) and said MTX is administered at a dosage of about 10 mg to about 25 mg once weekly.
- 10 65. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is administered at a daily dosage of about 100 mg (calculated as the free base) and said MTX is administered at a dosage about 10 mg to about 15 mg once weekly.
- 15 66. The compound for use or the combination for use according to any one of the preceding claims, wherein the proportion of patients achieving 20% improvement in ACR (ACR20) is increased.
- 20 67. The compound for use or the combination for use according to any one of the preceding claims, wherein at least 60% of subjects achieves 20% improvement in ACR (ACR20), such as at least 65%, such as at least 70%, such as at least 75%, such as at least 80%; such as by 12 weeks treatment.
- 25 68. The compound for use or the combination for use according to any one of the preceding claims, wherein the ACR20 response rate is of 60% to 85%; such as of 60% to 65%, such as of 65% to 70%, such as of 70% to 75%, such as of 75% to 80%, such as of 80% to 85%.
- 30 69. The compound for use or the combination for use according to any one of the preceding claims, wherein the DAS28 score is reduced by at least 1.3 points, such as at least 1.4 points, such as at least 1.5 points, such as at least 1.6 points, such as at least 1.7 points, such as at least 1.8 points, such as at least 1.9 points.
- 35 70. The compound for use or the combination for use according to any one of the preceding claims, wherein the DAS28 score is reduced by 1.3 to 2.0 points; such as 1.3 to 1.4 points, such as 1.4 to 1.5 points, such as 1.5 to 1.6 points, such as 1.6 to 1.7 points, such as 1.7 to 1.8 points, such as 1.8 to 1.9 points, such as 1.9 to 2.0 points.

71. The compound for use or the combination for use according to any one of the preceding claims, wherein the CDAI score is reduced by the treatment of the present disclosure by at least 15 points, such as at least 16 points, such as at least 17 points, such as at least 18 points, such as at least 19 points, such as at least 20 points, such as at least 21 points, such as at least 22 points, such as at least 23 points, such as at least 24 points.
72. The compound for use or the combination for use according to any one of the preceding claims, wherein the CDAI score is reduced by the treatment of the present disclosure by at 15 to 25 points, such as 15 to 16 points, such as 16 to 17 points, such as 17 to 18 points, such as 18 to 19 points, such as 19 to 20 points, such as 20 to 21 points, such as 21 to 22 points, such as 22 to 23 points, such as 23 to 24 points, such as 24 to 25 points.
73. The compound for use or the combination for use according to any one of the preceding claims, wherein the average decrease in the Health Assessment Questionnaire Disability Index (HAQ-DI) is at least about 0.3, such as at least about 0.4, such as at least about 0.5, such as at least about 0.6, such as at least about 0.65, such as at least about 0.7.
74. The compound for use or the combination for use according to any one of the preceding claims, wherein the average decrease in the Health Assessment Questionnaire Disability Index (HAQ-DI) is about 0.3 to 0.7; such as about 0.1 to 0.2, such as about 0.2 to 0.3, such as about 0.3 to 0.4, such as about 0.4 to 0.5, such as about 0.5 to 0.6, such as about 0.6 to 0.65, such as about 0.65 to 0.7.
75. The compound for use or the combination for use according to any one of the preceding claims, wherein the mean peak enhancement of a contrast agent is reduced by at least 1.0 ml, such as by at least 1.2 ml, such as by more than 1.2 ml, such as by at least 1.5 ml, such as by at least 2.0 ml, such as by at least 2.5 ml, such as by at least 3.0 ml, such as by at least 3.5 ml, such as by at least 3.8 ml, for example at week 12 compared to baseline.

76. The compound for use or the combination for use according to any one of the preceding claims, wherein the mean initial rate of enhancement of a contrast agent is reduced by at least 0.02 ml/sec, such as reduced by at least 0.03 ml/sec, such as reduced by at least 0.04 ml/sec, such as reduced by at least 0.05 ml/sec, such as reduced by at least 0.06 ml/sec, for example at week 12 compared to baseline.
77. The compound for use or the combination for use according to any one of the preceding claims, wherein the MRI-assessed tender joints are reduced more than placebo, such as reduced about 5.3 vs 2.9; $p < 0.05$
78. The compound for use or the combination for use according to any one of the preceding claims, wherein the MRI-assessed swollen joints are reduced more than placebo, such as reduced about 6.4 vs 3.7; $p < 0.05$
79. The compound for use or the combination for use according to any one of the preceding claims, wherein the treatment reduces C4M.
80. The compound for use or the combination for use according to any one of the preceding claims, further comprising one or more steps of administering folic acid, or an equivalent thereof.
81. The compound for use or the combination for use according to any one of the preceding claims, further comprising administering about 1 to 10 mg folic acid per week, such as about 5 mg folic acid per week, such as at least 5 mg folic acid per week.
82. The compound for use or the combination for use according to any one of the preceding claims, wherein said folic acid is administered once weekly, or wherein said folic acid is administered in daily dosages.
83. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is formulated in a pharmaceutical composition or pharmaceutical formulation, such as an oral formulation.

84. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is formulated in a solid oral formulation such as a solid oral dosage form.
- 5 85. The compound for use or the combination for use according to any one of the preceding claims, wherein said compound is formulated in a tablet, such as an immediate release tablet.
- 10 86. The compound for use or the combination for use according to any one of the preceding claims, wherein not less than about 65% of said compound, such as not less than about 70%, such as not less than about 75%, such as not less than about 80%, such as not less than about 85%, such as not less than about 90%, such as not less than about 95% of said compound is dissolved into solution in the gastric compartment.
- 15 87. The compound for use or the combination for use according to any one of the preceding claims, wherein not less than about 65% to about 80% of said compound is dissolved into solution in about 15 minutes at gastric pH, such as at a pH of about 1 to 3, such as a pH of about 0.5 to 3.5; such as a pH of about 0.5 to 1, such as a pH of about 1 to 1.5, such as a pH of about 1.5 to 2, such as a pH of about 2 to 2.5, such as a pH of about 2.5 to 3, such as a pH of about 3 to 3.5.
- 20 88. The compound for use or the combination for use according to any one of the preceding claims, wherein not less than 80% of said compound is dissolved into aqueous solution in 15 minutes at a pH of 1 to 3, such as at a pH of about 1.2, using a USP 2 paddle equipment at 37 °C at a rotation speed of 50 rpm
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