(19) DANMARK

(10) **DK/EP 3687562 T3**

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *A 61 K 38/17 (2006.01)* *A 61 K 38/20 (2006.01)* *A 61 K 39/395 (2006.01)* *A 61 K 47/68 (2017.01)* *A 61 P 9/00 (2006.01)* *A 61 P 29/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2025-04-14**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2025-03-19**

(86) Europæisk ansøgning nr.: **18786587.8**

(86) Europæisk indleveringsdag: **2018-09-26**

(87) Den europæiske ansøgnings publiceringsdag: **2020-08-05**

(86) International ansøgning nr.: **US2018052985**

(87) Internationalt publikationsnr.: **WO2019067639**

(30) Prioritet: **2017-09-26 US 201762563387 P**
2018-01-12 US 201862616819 P
2018-02-01 US 201862625075 P
2018-03-06 US 201862639425 P
2018-04-06 US 201862654291 P
2018-06-28 US 201862691552 P
2018-08-08 US 201862716331 P

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

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(54) Benævnelse: **BEHANDLING AF TILBAGEVENDENDE IDIOPATISK PERICARDITIS VED INDGIVELSE AF INTERLEUKIN-1-RECEPTORANTAGONIST-FUSIONSPROTEIN**

(56) Fremdragne publikationer:
US-A1- 2006 171 948
ANONYMOUS: "Utilisation des anti-IL1 dans la PR", 1 December 2012 (2012-12-01), XP055525909, Retrieved from the Internet <URL:http://www.cri-net.com/ckfinder/userfiles/files/fiches-pratiques/antiIL1/F15A_ANTI-IL1.pdf> [retrieved on 20181122]
EISENBERG R ET AL: "Management of refractory recurrent pericarditis and Familial Mediterranean Fever (FMF) related attacks with IVIG and interleukin 1 inhibition", WORLD ALLERGY ORGANIZATION JOURNAL, vol. 10, no. Suppl. 1, 9 December 2016 (2016-12-09), XP002809311
BRUCATO ANTONIO ET AL: "Pathogenetic mechanisms, new drugs, and old problems in idiopathic recurrent pericarditis: Comment on the article by Picco et al. + Reply", ARTHRITIS & RHEUMATISM, vol. 60, no. 8, 1 August 2009 (2009-08-01), US, pages 2543 - 2544, XP093047605, ISSN: 0004-3591, DOI: 10.1002/art.24755
FERNÁNDEZ-RUIZ IRENE: "The IL-1 trap rilonacept resolves and prevents recurrent pericarditis", NATURE REVIEWS CARDIOLOGY, vol. 18, no. 2, February 2021 (2021-02-01), pages 73, XP037340857, ISSN: 1759-5002, DOI: 10.1038/S41569-020-00491-3

Fortsættes ...

NORMAN T ILOWITE ET AL: "Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis", ARTHRITIS & RHEUMATOLOGY, JOHN WILEY & SONS, INC, US, vol. 66, no. 9, 26 August 2014 (2014-08-26), pages 2570 - 2579, XP072274015, ISSN: 2326-5191, DOI: 10.1002/ART.38699
BENJAMIN W. VAN TASSELL ET AL: "Targeting Interleukin-1 in Heart Disease", CIRCULATION, vol. 128, no. 17, 22 October 2013 (2013-10-22), US, pages 1910 - 1923, XP055526309, ISSN: 0009-7322, DOI: 10.1161/CIRCULATIONAHA.113.003199
APOSTOLOS KONTZIAS: "Anakinra: A Promising Therapy For Refractory Idiopathic Recurrent Pericarditis", 9 December 2015 (2015-12-09), XP055526152, Retrieved from the Internet <URL:https://www.acc.org/latest-in-cardiology/articles/2015/12/09/12/19/anakinra-a-promising-therapy-for-refractory-idiopathic-recurrent-pericarditis> [retrieved on 20181122]
MARIA JAWORSKA-WILCZYNSKA ET AL: "Post-cardiac injury syndrome", POLISH JOURNAL OF CARDIO-THORACIC SURGERY, vol. 1, 1 January 2013 (2013-01-01), pages 20 - 26, XP055526442, ISSN: 1731-5530, DOI: 10.5114/kitp.2013.34299
IRINA JARA CALABUIG ET AL: "Recurrent Pericarditis as the Presenting Form of Adult Still's Disease", REVISTA ESPANOLA DE CARDIOLOGIA, vol. 70, no. 3, 1 March 2017 (2017-03-01), ES, pages 208 - 209, XP055526477, ISSN: 1885-5857, DOI: 10.1016/j.rec.2016.06.016
ANTONIO BRUCATO ET AL: "Effect of Anakinra on Recurrent Pericarditis Among Patients With Colchicine Resistance and Corticosteroid Dependence : The AIRTRIP Randomized Clinical Trial", JAMA THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, vol. 316, no. 18, 8 November 2016 (2016-11-08), US, pages 1906, XP055526374, ISSN: 0098-7484, DOI: 10.1001/jama.2016.15826
GEORGE LAZAROS ET AL: "The Therapeutic Role of Interleukin-1 Inhibition in Idiopathic Recurrent Pericarditis: Current Evidence and Future Challenges", FRONTIERS IN MEDICINE, vol. 4, 12 June 2017 (2017-06-12), XP055525908, DOI: 10.3389/fmed.2017.00078
DEH-MING CHANG ET AL: "Dual biological functions of an interleukin-1 receptor antagonist-interleukin-10 fusion protein and its suppressive effects on joint inflammation", IMMUNOLOGY, vol. 112, no. 4, 1 August 2004 (2004-08-01), pages 643 - 650, XP055014940, ISSN: 0019-2805, DOI: 10.1111/j.1365-2567.2004.01910.x
ANONYMOUS: "Clinical Trial: RHAPSODY Phase 3 Study to Assess the Efficacy and Safety of Rilonacept Treatment in Subjects With Recurrent Pericarditis", 9 November 2018 (2018-11-09), XP055526507, Retrieved from the Internet <URL:https://clinicaltrials.gov/ct2/show/NCT03737110> [retrieved on 20181123]

DESCRIPTION

Description

BACKGROUND

[0001] IL-1α and IL-1β provoke potent, pro-inflammatory events by engaging the IL-1α and IL-1β receptor. Following tissue insult, the release of IL-1α acts as the primary initiating signal to coordinate the mobilization of immune cells to the damaged area, while IL-1β is secreted mostly by macrophages and is a prototypical cytokine of the canonical inflammasome. IL-1α and IL-1β signaling results in a dramatic increase in the production of cytokines that orchestrate the proliferation and recruitment of phagocytes to the site of damage, resulting in inflammation. Moreover, IL-1α and IL-1β signaling also affect other immune-system cells, such as T-cells and B-cells.

[0002] IL-1β's role in the inflammation process has been extensively studied, while in comparison, much is still unknown about the independent function of IL-1α in disease pathology. Despite driving similar immunological outcomes, IL-1α and IL-1β differ substantially in their expression and regulation, and non-redundant roles for IL-1α and IL-1β have been demonstrated in multiple inflammatory diseases. There are disease states in which IL-1β inhibition alone does not appear to be sufficient for disease remission in the absence of IL-1α inhibition. Published studies suggest certain autoinflammatory diseases may, in fact, be pathologically driven primarily by IL-1α.

[0003] Pericarditis is the inflammation of the pericardium, the thin, two-layered, fluid-filled, sac surrounding the heart. Pericarditis often causes chest pain and sometimes other symptoms. The sharp chest pain associated with pericarditis occurs when the irritated layers of the pericardium rub against each other. Signs and symptoms of pericarditis may include some or all of the following: sharp, piercing chest pain over the center or left side of the chest, which is generally more intense when breathing in or reclining; shortness of breath when reclining; heart palpitations; low-grade fever; an overall sense of weakness, fatigue or feeling sick; cough; and abdominal or leg swelling.

[0004] Currently available treatments for pericarditis include medications to reduce the inflammation and swelling associated with pericarditis. These medications include nonsteroidal anti-inflammatory drugs, such as aspirin, ibuprofen or indomethacin; colchicine, which reduces inflammation; and corticosteroids, if a patient doesn't respond to pain relievers or colchicine or if a patient has current symptoms or pericarditis. Colchicine can reduce the duration of pericarditis symptoms and decrease the risk that the condition will recur, but the medication is not safe for patients with pre-existing health conditions like liver or kidney disease or for

patients taking certain medications and may cause side effects, including nausea and diarrhea, that can lead to discontinuation of treatment. Steroids are known to cause significant side effects, particularly with long-term use. Patients with refractory symptoms can be particularly challenging to manage, and as a result, there is a significant and very long-standing need to identify new agents with favorable benefit to risk ratios that can be given systemically to treat pericarditis.

[0005] An information leaflet published in December 2012 by CRI and addressed at adult patients and parents of young children suffering from rheumatoid arthritis describes various uses of IL1 inhibitors. Van Tassell et al. (Circulation. 2013; 128(17):1910-23) describe targeting interleukin-1 (IL-1) in heart disease. Brucato et al. (JAMA 2016; 316(18):1906-1912) report on the effect of anakinra on recurrent pericarditis among patients with colchicine resistance and corticosteroid dependence observed in the Anakinra-Treatment of Recurrent Idiopathic Pericarditis (AIRTRIP) randomized clinical trial. Kontzias described anakinra as a promising therapy for refractory idiopathic recurrent pericarditis in an analysis published on December 09, 2015 on the American College of Cardiology website. US 2006/0171948 Al discloses methods of reducing C-reactive protein (CRP) that comprise administering to a subject a therapeutic amount of an IL-1-binding fusion protein.

[0006] Calabuig et al. (Rev Esp Cardiol. 2017;70(3):208-219) describe a patient with recurrent pericarditis as the presenting form of adult Still's Disease. Eisenberg et al. (World Allergy Organization Journal 207, 10(Suppl 1):A38) describe the management of refractory recurrent pericarditis in a patient suffering from Familial Mediterranean Fever (FMF) with IVIG and interleukin 1 inhibition.

SUMMARY OF THE INVENTION

[0007] The present invention provides an interleukin-1 receptor-Fc fusion protein, namely rilonacept, for use in a method of treating recurrent idiopathic pericarditis in a subject 18 years of age or older, comprising administering to the subject an initial loading dose of rilonacept that is delivered as two injections of 160 mg each and one or more maintenance dose(s) of 160 mg of rilonacept per week to improve, stabilize or reduce one or more symptoms of recurrent idiopathic pericarditis relative to a control, wherein the control is indicative of the one or more symptoms of recurrent idiopathic pericarditis in the subject before the treatment. In particular, the present invention is based on the therapeutic efficacy observed in human recurrent pericarditis patients after administrating this IL-1 receptor-Fc fusion protein. Without wishing to be bound by any theory, it is contemplated that rilonacept acts as a soluble decoy receptor binding IL-1α/IL-1β and prevents their interaction with the IL-1 cell surface receptor. As demonstrated in the Examples below, administration of rilonacept resulted in clinically significant reduction of recurrent idiopathic pericarditis associated inflammation and pain, and clinically significant improvement in cardiac pathology. Moreover, the use of rilonacept according to the present invention resulted in positive safety and tolerability profile. Thus, the present invention addresses the unmet need in recurrent idiopathic pericarditis treatment by

providing a highly safe and efficacious drug for this disease.

[0008] In some embodiments, the idiopathic pericarditis is refractory idiopathic pericarditis. In one embodiment, the step of administering comprises subcutaneous administration. In one embodiment, the subcutaneous administration is through subcutaneous injection.

[0009] In one embodiment, the therapeutically effective dose is delivered as a volume of less than or equal to 2 mL.

[0010] The one or more symptoms of pericarditis can be assessed by a Numerical Rating Scale (NRS) for assessment of pericarditis pain. One or more signs of pericarditis can be assessed by an echocardiogram. The one or more signs of pericarditis assessed by an echocardiogram may comprise pericardial effusion. Altematively, one or more signs of pericarditis can be assessed by an electrocardiogram (ECG). The one or more symptoms of pericarditis assessed by an ECG may comprise widespread ST-elevation and/or PR depression. The one or more signs of pericarditis may comprise fever and/or pericardial rub. One or more signs of pericarditis may be assessed by cardiac magnetic resonance imaging (MRI). The one or more symptoms of pericarditis may be assessed by measuring blood levels of C-reactive protein (CRP). Measuring blood levels of CRP may comprise measuring blood levels of CRP at several time points after an administering an initial loading dose of rilonacept, wherein a linear regression is performed to determine the change of CRP levels from baseline, change of CRP levels from baseline adjusted for placebo effect and/or the slope of blood levels of CRP over time. Change of blood CRP level may not be measured. The one or more symptoms of pericarditis may be assessed by a Quality of Life Questionnaire. The administration of rilonacept may result in a statistically-significant drop on a Numerical Rating Scale (NRS) for assessment of pericarditis pain. The one or more symptoms of pericarditis in the subject before the treatment may comprise a CRP value greater than 1 mg/dL.

[0011] The subject has had at least one recurrent episode of pericarditis. The subject may have an ongoing symptomatic episode of pericarditis.

[0012] The administration of rilonacept may result in no serious adverse events in the subject. The administration of rilonacept may result in serious adverse events that are acceptable in view of the specific treatment benefits. The administration of rilonacept may not result in an adverse effect selected from the group consisting of injection-site reaction, upper respiratory tract infection, headache, nausea, vomiting, diarrhea, sinusitis, arthralgia, flu-like symptoms, abdominal pain, pyrexia, nasopharyngitis, ischemic optic neuropathy and combinations thereof.

[0013] Rilonacept comprises an amino acid sequence of SEQ ID NO: 1. Rilonacept comprises CH1 and CH2 domains derived from a human IgG1.

[0014] Treatment with rilonacept may allow for the withdrawal or weaning of a concurrent therapy selected from the group consisting of NSAIDs, colchicine, corticosteroid and combinations thereof.

[0015] In one embodiment, the subject is diagnosed with refractory recurrent idiopathic pericarditis.

[0016] In one embodiment, the subject is colchicine-resistant, corticosteroid-dependent, corticosteroid-intolerant, corticosteroid-refractory and combinations thereof.

[0017] In one embodiment, the subject is a symptomatic subject with recurrent idiopathic pericarditis with an elevated level of a marker of systemic inflammation, where the CRP level is ≥1mg/dL; or, is a symptomatic subject with recurrent idiopathic pericarditis with non-elevated levels of an inflammatory marker and with pericardial inflammation present using an imaging technique; the subject being NSAID-, corticosteroid- and/or colchicine-resistant or intolerant; or a subject with NSAID-, corticosteroid- and/or colchicine-dependent pericarditis but does not experience symptoms that would meet the diagnostic criteria for a flare of pericarditis.

[0018] Administration of rilonacept may result in a reduced CRP level selected from less than about 2 mg/dL, less than about 1.5 mg/dL, less than about 1 mg/dL, less than about 0.8 mg/dL, less than about 0.6 mg/dL, less than about 0.5 mg/dL, less than about 0.4 mg/dL, less than about 0.3 mg/dL, less than about 0.2 mg/dL, or less than about 0.1 mg/dL in the subject. The reduced CRP level may be less than about 1 mg/dL. The reduced CRP level may range from about 0.3-1 mg/dL. The reduced CRP level may be less than 0.3 mg/dL.

[0019] The CRP level may be reduced to less than 1 mg/dL within 2 weeks, within 1 week, within 6 days, within 5 days, within 4 days, within 3 days, within 2 days, or within 1 day from the first administration of rilonacept. The CRP level may be reduced to less than 1 mg/dL within 1 week from the first administration of rilonacept. The CRP level may be maintained at less than 1 mg/dL for more than about 2 weeks, more than about 4 weeks, more than about 1 month, more than about 2 months, more than about 3 months more than about 4 months, more than about 5 months, more than about 6 months, more than about 7 months, more than about 8 months, more than about 10 months, or more than about 1 year. The CRP level may be maintained at less than 1 mg/dL for more than about 2 weeks, more than about 4 weeks, more than about 1 month, more than about 2 months, more than about 3 months more than about 4 months, more than about 5 months, more than about 6 months, more than about 7 months, more than about 8 months, more than about 10 months, or more than about 1 year, while the patient continues to receive a therapeutic dose of rilonacept at an administration interval and for a treatment period according to the invention. The CRP level may be maintained at less than 1 mg/dL for the above-indicated periods while the subject receives riloncapet in absence of any concurrent therapy.

[0020] The CRP level may be reduced to less than 0.3 mg/dL within 3 weeks from the first administration of rilonacept. The CRP level may be maintained at less than 0.3 mg/dL for more than about 1 week, more than about 2 weeks, more than about 3 weeks, more than about 1 month, more than about 2 months, more than about 3 months more than about 4 months, more than about 5 months, more than about 6 months, more than about 8 months, or more

than about 1 year. The CRP level may be maintained at less than 0.3 mg/dL for the above-indicated periods while the subject continues to receive a therapeutic dose of rilonacept at an administration interval and for a treatment period according to the invention. The CRP level may be maintained at less than 0.3 mg/dL for the above-indicated periods while the subject receives rilonacept in absence of any concurrent therapy.

[0021] Administration of the rilonacept may result in reduction of NRS score to 2 or less.

[0022] The NRS score may be reduced to 2 or less within 3 weeks, within 2 weeks or within 1 week from the first administration of the rilonacept.

[0023] The NRS score may be maintained at 2 or less for more than about 1 week, more than about 2 weeks, more than about 3 weeks, more than about 1 month, more than about 2 months, more than about 3 months more than about 4 months, more than about 5 months, more than about 6 months, more than about 8 months, or more than about 1 year. The NRS level may be maintained at 2 or less for the above-indicated periods while the patient continues to receive a therapeutic dose of rilonacept at an administration interval and for a treatment period according to the invention. The NRS level may be maintained at 2 or less for the above-indicated periods while the subject receives rilonacept in absence of any concurrent therapy.

[0024] The rilonacept may result in a reduced NRS score of 1 or less.

[0025] The NRS score may be reduced to 1 or less within 5 weeks, within 4 weeks, within 3 weeks, within 2 weeks, or within 1 week from the first administration of the rilonacept at an administration interval and treatment period according to the invention.

[0026] The NRS score may be maintained at 1 or less for more than about 1 week, more than about 2 weeks, more than about 3 weeks, more than about 1 month, more than about 2 months, more than about 3 months more than about 4 months, more than about 5 months, more than about 6 months, more than about 8 months, or more than about 1 year. The NRS level may be maintained at 1 or less for the above-indicated periods while the subject receives rilonacept at an administration interval and for a treatment period according to the invention. The NRS level may be maintained at 1 or less for the above-indicated periods while the subject receives rilonacept in absence of any concurrent therapy.

[0027] Administration of rilonacept may result in decreased pericardiac effusion compared to a baseline pericardiac effusion level measured in the subject prior to the treatment. Administration of rilonacept may result in absence of pericardiac effusion.

[0028] The decrease or absence of pericardiac effusion may be maintained for more than about 2 weeks, more than about 4 weeks, more than about 1 month, more than about 2 months, more than about 3 months more than about 4 months, more than about 5 months, more than about 6 months, more than about 8 months, or more than about 1 year. The decrease or absence of pericardiac effusion may be maintained for the above-indicated period,

while the subject continues to receive a therapeutic dose of rilonacept at an administration interval and for a treatment period according to the invention. The decrease or absence of pericardiac effusion may be maintained for the above-indicated period, while the subject receives rilonacept in absence of any concurrent therapy.

[0029] Administration of rilonacept may result in improved cardiac electrical conductivity in the subject as determined by ECG as compared to the control. In some embodiments, the improved cardiac electrical conductivity as determined by ECG comprises reduced ST-elevation and/or reduced SR depression.

[0030] Administration of rilonacept may result in normalized cardiac electrical conductivity in the subject as determined by an ECG evaluation.

[0031] Administration of rilonacept may result in improved cardiac effusion in the subject as determined by echocardiographic evaluation (ECHO) as compared to the control.

[0032] Administration of the rilonacept may result in normalized cardiac function in the subject as determined by ECHO evaluation.

[0033] An improved or normalized cardiac parameter may be maintained for more than about 2 weeks, more than about 4 weeks, more than about 1 month, more than about 2 months, more than about 3 months more than about 4 months, more than about 5 months, more than about 6 months, more than about 8 months, or more than 1 year. For example, the normalized cardiac parameter may be maintained for the above-indicated period while the subject receives rilonacept at an administration interval and for a treatment period according to the invention. The normalized cardiac parameter may be maintained for the above-indicated period while the subject receives rilonacept in absence of any concurrent therapy.

[0034] Administration of the rilonacept may result in improved QoL scores in the subject as compared baseline QoL scores determined in the subject prior to the treatment. The control may be indicative of the QoL when a subject having the disease receives a standard of care therapy, in absence of rilonacept administration.

[0035] In some embodiments, the improved QoL scores comprise one or more assessments selected from: Patient Global Impression of Pericarditis Severity (PGIPS); Physician Global Assessment of Pericarditis Activity (PGA-PA); 36-Item Short Form Health Survey (SF-36); 5-Level EuroQoL-5D (EQ-5D-5L) and Insomnia severity Index (ISI).

[0036] In some embodiments, the improved QoL scores comprise a reduced ISI indicative of clinically insignificant insomnia having a score value of less than 7 in the 5-point Likert scale.

[0037] In some embodiments, the improved QoL scores are maintained for more than 2 weeks, more than 3 weeks, more than 1 month, more than 2 months, more than 3 months, more than 4 months, more than 5 months, more than 6 months, more than 8 months, or more

than 1 year from the date of first administration. In some embodiments, the improved QoL scores are maintained for the above-indicated periods while the subject receives rilonacept. In some embodiments, the improved QoL scores are maintained for the above-indicated periods while the subject receives rilonacept in absence of any concurrent therapy.

[0038] Administration of the rilonacept may result in a period of recurrence-free survival of the subject in absence of other standard of care (SOC) medicines. The recurrence-free period may be at least a month, at least five weeks, at least six weeks, at least seven weeks, at least eight weeks, at least three months, at least four months, at least five months, at least six months, or at least one year.

[0039] The treatment period with rilonacept may last for 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks or 10 weeks. The treatment period may last 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months or 1 year. The treatment period may last for more than 1 year.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] The drawings are for illustration purposes only not for limitation.

Figure 1A-I depicts serum CRP levels and pain in NRS units in nine patients, designated as Subjects A-I respectively after being administered 320 mg loading dose of rilonacept at day 0, followed by 160 mg once a week. X- axis shows days after treatment. Subjects A-I were enrolled under Group 1. The respective concurrent treatments and duration are designated graphically below the X-axis.

Figure 2A-B depicts serum CRP levels and pain in NRS units in a Subject A and Subject B respectively after being administered 320 mg loading dose of rilonacept at day 0, followed by 160 mg once a week. X- axis shows days after treatment. Subject A and Subject B in this figure was enrolled under Group 2. The respective concurrent treatments and duration are designated graphically below the X-axis.

Figure 3A-C depicts serum CRP levels and pain in NRS units in Subjects A-C after being administered 320 mg loading dose of rilonacept at day 0, followed by 160 mg once a week. X-axis shows days after treatment. Subjects A-C in this figure were enrolled under Group 3. The respective concurrent treatments and duration are designated graphically below the X-axis.

Figure 4 depicts a graphic representation of the study protocol for long term efficacy of rilonacept in subjects with recurrent pericarditis. CS=corticosteroid; EOS=end of study, LTE=Long Term Extension; NSAID=nonsteroidal anti-inflammatory drug; RI=run in, RW=randomized withdrawal, SC=subcutaneously, TP=treatment period. a. The first dose given is a loading dose of IL1R-FcFP. In adult subjects ≥18 years old, 320 mg is given as 2 SC doses of 160 mg. In paediatric subjects ≥12 and <18 years old, 4.4 mg/kg is given as 2 SC doses of 2.2 mg/kg. After the loading dose, IL1R-FcFP will be administered as a 160 mg (adults) or 2.2

mg/kg (paediatric subjects) SC dose once weekly. b. Subject's treatment duration will depend on when the subject is enrolled relative to the end of RW. c. The adult dose is 160 mg SC once weekly. The paediatric dose is 2.2 mg/kg SC once weekly. Note: Figure is not drawn to scale.

DEFINITIONS

[0041] In order for the present invention to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the specification.

[0042] *Amino acid:* As used herein, term "amino acid," in its broadest sense, refers to any compound and/or substance that can be incorporated into a polypeptide chain. An amino acid can have the general structure H_2N-C(H)(R)-COOH. An amino acid can be a naturally occurring amino acid. An amino acid can be a synthetic amino acid; an amino acid can be a d-amino acid or an l-amino acid. "Standard amino acid" refers to any of the twenty standard l-amino acids commonly found in naturally occurring peptides. "Nonstandard amino acid" refers to any amino acid, other than the standard amino acids, regardless of whether it is prepared synthetically or obtained from a natural source. As used herein, "synthetic amino acid" encompasses chemically modified amino acids, including but not limited to salts, amino acid derivatives (such as amides), and/or substitutions. Amino acids, including carboxyl- and/or amino-terminal amino acids in peptides, can be modified by methylation, amidation, acetylation, protecting groups, and/or substitution with other chemical groups that can change the peptide's circulating half-life without adversely affecting their activity. Amino acids may participate in a disulfide bond. Amino acids may comprise one or posttranslational modifications, such as association with one or more chemical entities (e.g., methyl groups, acetate groups, acetyl groups, phosphate groups, formyl moieties, isoprenoid groups, sulfate groups, polyethylene glycol moieties, lipid moieties, carbohydrate moieties, biotin moieties, *etc.).* The term "amino acid" is used interchangeably with "amino acid residue," and may refer to a free amino acid and/or to an amino acid residue of a peptide. It will be apparent from the context in which the term is used whether it refers to a free amino acid or a residue of a peptide.

[0043] *Amelioration:* As used herein, the term "amelioration" is meant the prevention, reduction or palliation of a state, or improvement of the state of a subject. Amelioration includes, but does not require complete recovery or complete prevention of a disease condition. Amelioration may include increasing levels of relevant protein or its activity that is deficient in relevant disease tissues. Amelioration may include decreasing levels of relevant protein or its activity that is pathologically elevated in relevant disease tissues.

[0044] *Approximately or about:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value.

The term "approximately" or "about" may refer to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0045] *Delivery:* As used herein, the term "delivery" encompasses both local and systemic delivery.

[0046] *Half-life:* As used herein, the term "half-life" is the time required for a quantity such as nucleic acid or protein concentration or activity to fall to half of its value as measured at the beginning of a time period.

[0047] *Improve, increase, or reduce:* As used herein, the terms "improve," "increase" or "reduce," or grammatical equivalents, indicate values that are relative to a baseline measurement, such as a measurement in the same individual prior to initiation of the treatment described herein.

[0048] *Substantial identity:* The phrase "substantial identity" is used herein to refer to a comparison between amino acid or nucleic acid sequences. As will be appreciated by those of ordinary skill in the art, two sequences are generally considered to be "substantially identical" if they contain identical residues in corresponding positions. As is well known in this art, amino acid or nucleic acid sequences may be compared using any of a variety of algorithms, including those available in commercial computer programs such as BLAS TN for nucleotide sequences and BLASTP, gapped BLAST, and PSI-BLAST for amino acid sequences. Exemplary such programs are described in Altschul, et al., Basic local alignment search tool, J Mol. Biol.,215(3): 403-410, 1990; Altschul, et al., Methods in Enzymology; Altschul et al., Nucleic Acids Res. 25:3389-3402, 1997; Baxevanis et al., Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins, Wiley, 1998; and Misener, et al., (eds.), Bioinformatics Methods and Protocols (Methods in Molecular Biology, Vol. 132), Humana Press, 1999. In addition to identifying identical sequences, the programs mentioned above typically provide an indication of the degree of identity. Two sequences may be considered to be substantially identical if at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more of their corresponding residues are identical over a relevant stretch of residues. The relevant stretch may be a complete sequence. The relevant stretch may be at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500 or more residues.

[0049] *Suitable for subcutaneous delivery:* As used herein, the phrase "suitable for subcutaneous delivery" or "formulation for subcutaneous delivery" as it relates to the pharmaceutical compositions generally refers to the stability, viscosity, tolerability and solubility properties of such compositions, as well as the ability of such compositions to deliver an effective amount of antibody contained therein to the targeted site of delivery.

[0050] *Patient:* As used herein, the term "patient" refers to any organism to which a provided composition may be administered, e.g., for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and/or humans). A patient may be a human. A human includes pre- and post-natal forms.

[0051] *Pharmaceutically acceptable:* The term "pharmaceutically acceptable" as used herein, refers to substances that, within the scope of sound medical judgment, are suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0052] *Recurrence:* As used herein, the term "recurrence" is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis. Recurrence is often used interchangeably with "flare" and "relapse". A pericarditis recurrence is usually indicated by any one or more of the following: an increase in the CRP level of ≥1 mg/dl in peripheral blood; or an increase in pain, determined in an NRS scale of ≥4; or occurrence of pericardial effusion; a pericardial rub; or fever or any other symptomatic indication of the pericardial disease.

[0053] *Subject:* As used herein, the term "subject" can refer to a human or any non-human animal (e.g., mouse, rat, rabbit, dog, cat, cattle, swine, sheep, horse or primate). A human includes pre- and post-natal forms. A subject is typically a human being. A subject can be a patient, which may refer to a human presenting to a medical provider for diagnosis or treatment of a disease. The term "subject" is used herein interchangeably with "individual" or "patient." A subject can be afflicted with or is susceptible to a disease or disorder but may or may not display symptoms of the disease or disorder.

[0054] *Substantially:* As used herein, the term "substantially" refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term "substantially" is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[0055] *Systemic distribution or delivery:* As used herein, the terms "systemic distribution," "systemic delivery," or grammatical equivalent, refer to a delivery or distribution mechanism or approach that affect the entire body or an entire organism. Typically, systemic distribution or delivery is accomplished via body's circulation system, e.g., blood stream. Compared to the definition of "local distribution or delivery."

[0056] *Target tissues:* As used herein, the term "target tissues" refers to any tissue that is affected by a disease or disorder to be treated. Target tissues may include those tissues that

display disease-associated pathology, symptom, or feature.

[0057] *Therapeutically effective amount:* As used herein, the term "therapeutically effective amount" of a therapeutic agent means an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the symptom(s) of the disease, disorder, and/or condition. It will be appreciated by those of ordinary skill in the art that a therapeutically effective amount is typically administered via a dosing regimen comprising at least one unit dose.

[0058] *Treating:* As used herein, the term "treat," "treatment," or "treating" refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of and/or reduce incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease and/or exhibits only early signs of the disease for the purpose of decreasing the risk of developing pathology associated with the disease.

DETAILED DESCRIPTION

[0059] The present invention provides rilonacept for use in a method of treating recurrent idiopathic pericarditis in a subject 18 years of age or older, comprising administering to the subject an initial loading dose of rilonacept that is delivered as two injections of 160 mg each and one or more maintenance dose(s) of 160 mg of rilonacept per week to improve, stabilize or reduce one or more symptoms of recurrent idiopathic pericarditis relative to a control, wherein the control is indicative of the one or more symptoms of recurrent idiopathic pericarditis in the subject before the treatment.

[0060] Various aspects of the invention are described in detail in the following sections. Each section can apply to any aspect of the invention. The use of "or" means "and/or" unless stated otherwise.

Pericarditis

[0061] Pericarditis is swelling and irritation of the pericardium, the thin saclike membrane surrounding the heart. Pericarditis often causes chest pain and sometimes other symptoms. The sharp chest pain associated with pericarditis occurs when the irritated layers of the pericardium rub against each other. Signs and symptoms of pericarditis may include some or all of the following: sharp, piercing chest pain over the center or left side of the chest, which is generally more intense when breathing in or reclining; shortness of breath when reclining; heart palpitations; low-grade fever; an overall sense of weakness, fatigue or feeling sick; cough; and abdominal or leg swelling.

[0062] Pericarditis accounts for 5% of emergency department visits for chest pain in the absence of myocardial infarction (Khandaker et al, Mayo Clin Proc. 2010; 85:572-593). In 80% of cases in developed countries, the cause of pericarditis is either post viral or "idiopathic," in that it cannot be attributed to a specific condition (Imazio et al, Circulation. 2010; 121:916-928; Zayas et al, Am J Cardiol. 1995; 75:378-382). Diagnosis is based on the presence of typical chest pain (improved by sitting up and leaning forward) along with fever, pericardial friction rub, electrocardiographic (ECG) changes, pericardial effusion, or elevated markers of inflammation (white blood cell [WBC] count, C-reactive protein [CRP], or erythrocyte sedimentation rate [ESR]) (Imazio, Revista Espanola de Cardiologia. 2014; 67(5):345-348). The European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Pericardial Diseases define a pericarditis episode as the presence of at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rubs, new widespread ST-elevation or PR depression on ECG, and pericardial effusion (new or worsening). Elevations of markers of inflammation (i.e., CRP, ESR, and WBD) or evidence of pericardial inflammation by an imaging technique (e.g., magnetic resonance imaging [MRI]) are used as supportive findings (Adler et al, Eur Heart J. 2015 Nov 7; 36(42):2921-64). Recurrent pericarditis is a common complication of acute pericarditis and affects 20-30% of patients (Imazio, Revista Espanola de Cardiologia. 2014; 67(5):345-348). It is characterized by the recurrence of signs and symptoms of pericarditis after a symptom-free interval of at least 4-6 weeks (Adler et al, Eur Heart J. 2015 Nov 7; 36(42):2921-64). The underlying pathogenesis of idiopathic recurrent pericarditis (RIP) remains unclear, although immune-mediated mechanisms are believed to play a key role in the pathogenesis (Imazio et al, American Journal of Cardiology, 2005; 96(5):736-739). A growing body of evidence suggests that these immune responses consist of both pathogenic autoimmune and auto-inflammatory processes (Cantarini et al, Autoimmunity Reviews 2015; 14:90-97; Doria et al, Autoimmunity Reviews 2012; 12:22-30). The presence of pro-inflammatory cytokines in the pericardial fluid of RIP patients lends direct support to both an autoimmune and/or auto-inflammatory etiopathogenesis (Pankuwait et al, 2000).

[0063] Currently available treatments for pericarditis include nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and glucocorticoids (Lilly, 2013). Aspirin and other NSAIDs are the first-line approach. Several other NSAID commonly used are, ibuprofen, celecoxib, diclofenac, diflunisal, indomethacin, to name a few. Because high doses are often required, consideration has to be given to gastric protection therapy. Colchicine is another mainstay therapy for RIP and is commonly used with NSAIDs, but a subset of patients has refractory symptoms and significant gastrointestinal side effects, including severe diarrhea, leading to discontinuation for intolerability. Glucocorticoids should be prescribed only to patients with idiopathic pericarditis who are refractory or intolerant to treatment with NSAIDs plus colchicine, because of the side effects associated with long-term corticosteroid therapy and because of a high rate of relapse when the corticosteroid is tapered or stopped (Maisch et al, Eur Heart J. 2004; 25:587-610; Imazio et al, Circulation. 2005; 112:2012-2016; Lotrionte et al, Am Heart J. 2010; 160:662-670), particularly in the absence of colchicine treatment. Patients with refractory symptoms can be particularly challenging to manage, and multiple immunosuppressive medications have been used without consistent benefit (Baskar et al, Cardiol Res Pract. 2016; 2016:7840724).

[0064] The cause of pericarditis is often hard to determine. In most cases, doctors either are unable to determine a cause (idiopathic) or suspect a viral infection. Although the underlying pathogenesis of idiopathic recurrent pericarditis (RIP) (sometimes used interchangeably with recurrent idiopathic pericarditis) remains unclear, immune-mediated mechanisms are believed to play a key role in the pathogenesis (Imazio et al, 2005; 96(5):736-739). A growing body of evidence suggests that these immune responses consist of both pathogenic autoimmune and auto-inflammatory processes (Cantarini et al, Autoimmunity Reviews 2015; 14:90-97; Doria et al, Autoimmunity Reviews 2012; 12:22-30). The presence of pro-inflammatory cytokines in the pericardial fluid of RIP patients lends direct support to both an autoimmune and/or auto-inflammatory etiopathogenesis (Pankuwait et al, 2000).

[0065] Interleukin-1 (IL-1) is a key cytokine that drives the pathophysiology of many inflammatory processes. It is implicated as a causative factor in various inflammatory human diseases. Although the pathogenic mechanism of auto-inflammatory disease is not completely understood, there is a growing body of evidence that IL-1 may be a primary driver of the symptomology and that targeting this cytokine may provide important benefits (Hoffman & Patel, Arthritis and Rheum. 2004 Feb; 50(2): 345-349). In fact, a study of once-daily anakinra (KINERET®), a recombinant form of the human IL-1 receptor antagonist (IL-1RA), showed promising effects in RIP patients when colchicine failed and corticosteroid dependence (or intolerance) developed, with C-reactive protein (CRP) normalization within a mean of 7.1 days in 21 consecutively treated patients (Brucato et al, JAMA. 2016 Nov 8; 316(18):1906-1912; Lazaros et al, J Cardiovasc Med 2016; 17(4):256-62). However, anakinra is a once-daily injection and is known to cause injection site reaction among other adverse events. Thus, rilonacept, with an improved product profile that provides for one or more of patient convenience; less treatment discomfort; effective withdrawal or weaning of NSAIDs, colchicine and/or corticosteroid therapies; and a dosing frequency that facilitates a safe and effective weaning regimen prescribed by a physician, that antagonize binding of both IL-1α and IL-1β and prevents their interaction with IL-1 cell surface receptors, provides a therapeutic opportunity for the treatment of recurrent idiopathic pericarditis.

[0066] There are several different methods for assessing symptoms of pericarditis. One or more symptoms of pericarditis can be assessed by a Numerical Rating Scale (NRS) for assessment of pericarditis pain. NRS score is a self-reported assessment of the level of pain a patient experiences in a scale of 0 to 10. In this 11-point NRS scale, a score of 0 is interpreted as no pain, and a score of 10 is the most severe pain. One or more signs of pericarditis can also be assessed by an echocardiogram. The one or more signs of pericarditis that can be assessed by an echocardiogram comprise pericardial effusion. One or more signs of pericarditis may be assessed by an electrocardiogram (ECG). The one or more signs of pericarditis assessed by an ECG may comprise widespread ST-elevation and/or PR depression. One or more signs of pericarditis may comprise fever and/or pericardial rub. One or more signs and/or symptoms of pericarditis may be assessed by cardiac magnetic resonance imaging (MRI). One or more signs of pericarditis may be assessed by measuring blood levels of C-reactive protein (CRP). Measuring blood levels of CRP may comprise measuring blood levels of CRP at several time points after an administering an initial loading

dose of rilonacept, wherein a linear regression is performed to determine the change of CRP levels from baseline, change of CRP levels from baseline adjusted for placebo effect and/or the slope of blood levels of CRP over time. A CRP level of greater than 1 mg/dL may be considered positive for inflammation. One or more symptoms of pericarditis may be assessed by a Quality of Life (QoL) Questionnaire.

Treatment

[0067] The invention provides rilonacept for use in a method of treating recurrent idiopathic pericarditis in a subject 18 years of age or older, comprising administering to the subject an initial loading dose of rilonacept that is delivered as two injections of 160 mg each and one or more maintenance dose(s) of 160 mg of rilonacept per week to improve, stabilize or reduce one or more symptoms of recurrent idiopathic pericarditis relative to a control, wherein the control is indicative of the one or more symptoms of recurrent idiopathic pericarditis in the subject before the treatment. The terms, "treat" or "treatment," as used herein, refers to amelioration of one or more symptoms associated with the disease, prevention or delay of the onset of one or more symptoms of the disease, and/or lessening of the severity or frequency of one or more symptoms of the disease.

[0068] The subject may have refractory recurrent idiopathic pericarditis. The subject to be treated may be selected from:

1. (i) a symptomatic subject with recurrent idiopathic pericarditis with an elevated level of a marker of systemic inflammation (e.g., CRP ≥1 mg/dL);
2. (ii) a symptomatic subject with recurrent idiopathic pericarditis with non-elevated levels of an inflammatory marker (e.g., CRP <1 mg/dL) and with pericardial inflammation present using an imaging technique (e.g., MRI);
3. (iii) the subject of (i) or (ii), where the subject is NSAID-, corticosteroid- and/or colchicine-resistant or intolerant; and
4. (iv) a subject with NSAID, corticosteroid- and/or colchicine-dependent idiopathic pericarditis not experiencing symptoms that would meet the diagnostic criteria for a recurrence of pericarditis.

[0069] In certain embodiments, the subject administered a therapeutically effective amount of rilonacept may be treated with concomitant medications, such as NSAIDs, colchicine or corticosteroids, and combinations thereof, and optionally weaned from one or more of such concomitant medications following treatment with rilonacept. Typically, exemplary NSAIDs include but are not limited to ibuprufen, aspirin, indomethaxin, celecoxib, diclofenac. Exemplary corticosteroids include prednisone, cortisone, methyl prednisolone, and others.

[0070] In certain embodiments, the subject administered a therapeutically effective amount of

rilonacept in accordance with the invention may also be treated with concomitant medications, such as NSAIDs, colchicine or corticosteroids, and combinations thereof, and optionally weaned from one or more of such concomitant medications following treatment with rilonacept.

[0071] The administration of rilonacept may result in a statistically-significant drop on a Numerical Rating Scale (NRS) for assessment of pericarditis pain. The administration of rilonacept may result in a statistically-significant change on a composite endpoint that includes two or more of the following: NRS, blood levels of CRP, ECHO, pericardial rub, ECG, WBD, ESR and MRI.

[0072] In some embodiments, the step of administering comprises subcutaneous administration. In some embodiments, subcutaneous administration is through subcutaneous injection. In some embodiments, subcutaneous administration is through a subcutaneous pump. In some embodiments, subcutaneous injection of rilonacept can be performed in the upper arm, the anterior surface of the thigh, the lower portion of the abdomen, the upper back or the upper area of the buttock. In some embodiments, the site of injection is rotated.

[0073] One or more symptoms of pericarditis in a subject before treatment may comprise a CRP value equal to or greater than 1 mg/dL. The subject has had at least one recurrent episode of pericarditis. The subject i may have had at least two recurrent episodes of pericarditis. The subject may have had at least three recurrent episodes of pericarditis. A recurrent episode may be defined as at least 1 day with pericarditis pain with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale (NRS) and/or C-reactive protein (CRP) level ≥1 mg/dL. Pericarditis pain ≥4 and CRP ≥1 mg/dL may be present on the same day. Pericarditis pain ≥4 and CRP ≥1 mg/dL may not be present on the same day. The subject being treated may have at least one recurrent episode within 7 days prior to first administration. Alternatively, the subject may have an ongoing symptomatic episode of pericarditis.

Dosage

[0074] The initial loading dose is 320 mg. The initial loading dose is delivered as two injections of 160 mg. A maintenance dose is 160 mg. The maintenance dose is administered weekly.

[0075] In some embodiments, a dose is delivered as a volume of less than or equal to 2.0 mL for each subcutaneous injection. In some embodiments, a dose is delivered as a volume of less than or equal to 1.8 mL. In some embodiments, a dose is delivered as a volume of less than or equal to 1.6 mL. In some embodiments, a dose is delivered as a volume of less than or equal to 1.4 mL. In some embodiments, a dose is delivered as a volume of less than or equal to 1.2 mL. In some embodiments, a dose is delivered as a volume of less than or equal to 1.0 mL. In some embodiments, a dose is delivered as a volume of less than or equal to 0.8 mL. In some embodiments, a dose is delivered as a volume of less than or equal to 0.6 mL.

Treatment Period

[0076] A treatment period of pericarditis with an rilonacept can vary in duration. In some embodiments, the treatment period with rilonacept lasts for more than 1 week. In some embodiments the treatment period with rilonacept lasts for 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks or 10 weeks. In some embodiments, the treatment period lasts 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, 12 months, 13 months, 14 months, 15 months, 16 months, 17 months or 18 months. In some embodiments, the treatment period lasts for more than 18 months. In some embodiments, the treatment period lasts for 2 years.

[0077] In some embodiments, the treatment period is at least one month. In some embodiments, the treatment period is at least two months. In some embodiments, the treatment period is at least three months. In some embodiments, the treatment period is at least six months. In some embodiments, the treatment period is at least nine months. In some embodiments, the treatment period is at least one year. In some embodiments, the treatment period is at least two years. In some embodiments, the treatment period continues throughout the subject's life.

Pharmacokinetics and Pharmacodynamics

[0078] Evaluation of rilonacept concentration-time profiles in serum of subjects with pericarditis may be evaluated directly by measuring systemic serum rilonacept concentration-time profiles. Typically, rilonacept pharmacokinetic and pharmacodynamic profiles are evaluated by sampling the blood of treated subjects periodically. The following standard abbreviations are used to represent the associated pharmacokinetic parameters.

C_{max}
: maximum concentration

t_{max}
: time to maximum concentration

[0079] AUC_{0-t} area under the concentration-time curve (AUC) from time zero to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations

$AUC_{0-\infty}$
: AUC from time zero to infinity calculated using the formula:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$$

where C_t is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant

λ_Z

apparent terminal elimination rate constant, where λ_Z is the magnitude

of the slope of the linear regression of the log concentration versus time profile during the terminal phase

$t_{1/2}$

apparent terminal elimination half-life (whenever possible),

where

$$t_{1/2} = \text{natural log (ln)}(2)/\lambda_Z$$

CL

clearance

Vd

volume of distribution (IV doses only)

Vd/F

apparent volume of distribution (SC doses only)

[0080] Typically, actual blood sample collection times relative to the start of rilonacept administration are used in PK analysis. For example, blood samples are typically collected, for example, within 15 or 30 minutes prior to rilonacept administration (pre-injection baseline or time 0) and at periodic intervals following administration, e.g., hours 1, 4, 8 or 12, or days 1 (24 hours), 2, 3, 4, 5, 6, 7, 10, 14, 17, 21, 24, 28, 31, 38, 45, 52, 60, 70 or 90 days, following administration. The blood samples may be collected prior to an administration timepoint.

[0081] Various methods may be used to measure rilonacept concentration in serum. As a non-limiting example, enzyme-linked immunosorbent assay (ELISA) methods are used.

[0082] Pharmacokinetic parameters may be evaluated at any stage during the treatment, for example, at day 1, day 2, day 3, day 4, day 5, day 6, week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, week 24, or later. In some embodiments, pharmacokinetic parameters may be evaluated at month 1, month 2, month 3, month 4, month 5, month 6, month 7, month 8, month 9, month 10, month 11, month 12, month 13, month 14, month 15, month 16, month 17, month 18, month 19, month 20, month 21, month 22, month 23, month 24, or later during the treatment.

Effectiveness Assessment

[0083] The effectiveness of the treatment using rilonacept may be determined by measuring inflammation, such as measuring the CRP level in peripheral blood. Administration of the rilonacept may result in a reduction of the CRP level compared to a score observed prior to the administration. The CRP level may be reduced to 2 mg/dL or less, 1.5 mg/dL or less, 1 mg/dL or less, 0.8 mg/dL or less, 0.6 mg/dL or less, 0.5 mg/dL or less, 0.4 mg/dL or less, 0.3 mg/dL or less, 0.2 mg/dL or less, 0.1 mg/dL or less in the subject. The reduction of CRP level may be observed within 2 weeks from the first administration. The CRP level may be maintained at 2 mg/dL or less for longer than 2 weeks. The CRP level may be maintained at 2 mg/dL or less for longer than 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months or for longer than 1 year. The CRP level may be maintained at 1 mg/dL or less for longer than 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months or for longer than 1 year. The CRP level may be maintained at 1 mg/dL or less for the indicated period, while the patient continues to receive a therapeutic dose of rilonacept. The CRP level may be maintained at less than 1 mg/dL for the above-indicated periods while the subject receives rilonacept in absence of any concurrent therapy.

[0084] The effectiveness of the treatment using rilonacept may be determined by assessment of pain in the subject, such as by determination of 11-point NRS score. Administration of the rilonacept may result in a reduction of the NRS score compared to a score observed prior to administration. An NRS score of 3 or less may be interpreted as mild to no pain. A reduction in NRS score to a value of 2 or less after administration of the rilonacept from a higher score observed prior to the administration may be considered an improvement of the disease in the patient. The NRS score may be reduced to 2 or less within 2 weeks of the first administration. The NRS score may be reduced to 1 or less. The NRS score may be maintained at 2 or less for longer than 2 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, 10 months, 11 months or for longer than 1 year. The subject may remain pain free for the duration of the extension period of the study. The NRS score may be maintained at 2 or less while the patient continues to receive a therapeutic dose of rilonacept at an administration interval and for a treatment period. The NRS score may be maintained at 2 or less while the patient continues to receive a therapeutic dose of rilonacept in absence of any concurrent therapy.

[0085] Administration of rilonacept may result in improvement of cardiac parameters as indicated by ECG measurements. A reduction in the ST elevation and/or reduction in the depression after administration of rilonacept may be considered an improvement in the cardiac parameter.

[0086] Administration of rilonacept may result in improvement of cardiac effusion as determined by echocardiography (ECHO).

[0087] Administration of rilonacept may result in improvement of cardiac parameters as

determined by CT scanning.

[0088] Administration of rilonacept may result in improvement of cardiac parameters as determined by cardiac magnetic resonance imaging (MRI).

[0089] Administration of rilonacept may result in successful taper of steroids and other concurrent therapies, while the subject continues to receive rilonacept at an administration interval and for a treatment period according to the invention. Administration of rilonacept may result in weaning the subject of steroids and/or other concurrent therapies starting at about 4 weeks, or 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 14 weeks, 16 weeks, 18 weeks, 20 weeks, 22 weeks or 24 weeks after first administration, while the subject continues to receive rilonacept at an administration interval and for a treatment period according to the invention. Administration of rilonacept may result in a successful taper of steroids and/or other concurrent therapies which lasts for at least two weeks. Administration of rilonacept may result in a successful taper of steroids and other concurrent therapies that lasts for at least three weeks. Administration of rilonacept may result in a successful taper of steroids and other concurrent therapies that lasts for at least four weeks. Administration of rilonacept may result in a successful taper of steroids and other concurrent therapies that lasts for at least five weeks. Administration of rilonacept may result in a successful taper of steroids and other concurrent therapies that lasts for at least six weeks, seven weeks, eight weeks, nine weeks, ten weeks, eleven weeks, twelve weeks, thirteen weeks, fourteen weeks, fifteen weeks, sixteen weeks, seventeen weeks, eighteen weeks, nineteen weeks, twenty weeks, twenty one weeks, twenty two weeks, twenty three weeks, or twenty four weeks. Administration of rilonacept may result in a successful taper of steroids and other concurrent therapies that lasts for at least 6 months, 7 months, 8 months, 9 months, 10 months, 11 months, or 1 year. Administration of rilonacept may result in a successful taper of steroids and other concurrent therapies for more than 1 year. Administration of rilonacept may result in the subject being free of steroids and other concurrent therapies for greater than 1 year. The subject may continue to receive rilonacept at a therapeutic dose and administration interval according to the invention. The subject may continue to receive rilonacept without any concurrent therapy.

[0090] Administration of rilonacept may result in improvement of QoL scores. Typically, QoL scores comprise one or more assessments selected from: Patient Global Impression of Pericarditis Severity (PGIPS); Physician Global Assessment of Pericarditis Activity (PGA-PA); 36-Item Short Form Health Survey (SF-36); 5-Level EuroQoL-5D (EQ-5D-5L) and Insomnia severity Index (ISI).

[0091] The effectiveness of treatment using rilonacept may be determined by Patient Global Impression of Pericarditis Severity (PGIPS), and/or Physician Global Assessment of Pericarditis Activity (PGA-PA). The PGIPS is a single-item patient reported outcome (PRO) measure that assesses the subject's impression of overall severity of pericarditis symptoms at the time the questionnaire is administered, using a 7-point rating scale ranging from absent (no recurrent pericarditis symptoms) to very severe (recurrent pericarditis symptoms cannot be ignored). The PGA-PA is a single-item clinician-reported outcome measure that investigators use to rate

their impression of the patient's overall pericarditis disease activity at the time the assessment is completed, using a 7-point rating scale ranging from absent to very severe.

[0092] The effectiveness of the treatment using rilonacept may be determined by a 5-Level EuroQoL-5D (EQ-5D-5L)(additional information in: www.euroqol.org). The EQ-5D-5L is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in assessing a wide range of health conditions and treatments. The EQ-5D-5L includes a descriptive system and the EQ VAS. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The rating scale records the subject's self-rated health on a vertical Visual Analog Scale (VAS). The scores on these 5 dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles (euroqol.org/eq-5d-instruments).

[0093] The EQ-5D-5L may be collected in subjects ≥18 years or older.

[0094] Administration of rilonacept may result in an improved Insomnia Severity Index (ISI). The ISI is a 7-item self-report questionnaire assessing the nature, severity, and impact of insomnia. The usual recall period is the "last 2 weeks" and the dimensions evaluated are severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by the sleep difficulties. A 5-point Likert scale is used to rate each item (e.g., 0=no problem; 4=very severe problem), yielding a total score ranging from 0 to 28. The total score is interpreted as follows: no clinically significant insomnia (0-7); subthreshold insomnia (8-14); clinical (moderate) insomnia (15-21); and clinical (severe) insomnia (22-28) (Morin et al., Sleep. 2011;34(5):601-608). The ISI may be collected in subjects ≥18 years or older. The ISI in a subject after administration of rilonacept may be improved to less than 14, or between 8-14, or less than 7. Administration of rilonacept may result in the ISI of less than or equal to 7 in the subject being treated.

[0095] Administration of rilonacept may result in reduced risk of pericarditis recurrence of less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, less than 5%, less than 2%, or less than 1% or less than 0.5 % or less than 0.25% or less than 0.1% based on statistical analysis of patients population being treated with an rilonacept.

[0096] The effectiveness of treatment with rilonacept may be determined by a recurrence-free period during or subsequent to the treatment. A recurrence-free period of survival typically means that the subject does not experience an episode or occurrence of one or more symptoms of pericarditis or a flare of inflammation during the period. A pericarditis recurrence or flare is usually indicated by any one or more of the following: an increase in the CRP level of ≥1 mg/dl in peripheral blood; or an increase in pain, determined in an NRS scale of ≥4; or occurrence of pericardial effusion (e.g., as determined by ECG or ECHO); a pericardial rub; or fever or any other symptomatic indication of the pericardial disease (e.g., as determined by PGIPS, PGA-PA, SF-36, EQ-5D-5L, or ISI). A subject may continue to receive a therapeutic

dose of rilonacept at an administrative interval and for a treatment period during the recurrence-free period. A subject may be gradually weaned of rilonacept treatment during the recurrence-free period.

[0097] The effectiveness of treatment with rilonacept may be determined by the time period of recurrence-free survival (for examples, Days to flare). The recurrence-free survival period may be at least 30 days, 40 days, 50 days, 60 days, 70 days, 80 days, or 90 days from the first administration of rilonacept. The recurrence-free survival period may be at least 91 days, 92 days, 93 days, 94 days, 95 days, 96 days, 97 days, 98 days, 99 days, 100 days from the first administration of the rilonacept. The recurrence-free survival period may be at least 105 days, or at least 110 days, or at least 115 days, or at least 120 days, or at least 130 days, or at least 140 days, or at least 150 days. The recurrence-free survival period may be at least 200 days or more, while receiving rilonacept at an administration interval (i.e., weekly doses) and for a treatment period according to the invention.

[0098] The recurrence-free survival period may be at least 30 days, 40 days, 50 days, 60 days, 70 days, or at least 80 days from the withdrawal of a pain medicine, or NSAID, while receiving weekly dose of rilonacept. The recurrence-free survival period from the withdrawal of NSAID may be at least 81 days, 82 days, 83 days, 84 days, 85 days, 86 days, 87 days, 88 days, 89 days, 90 days, 91 days, 92 days, 93 days, 94 days, 95 days, 96 days, 97 days, 98 days, 99 days, 100 days, 110 days, 120 days, 130 days, 140 days, 150 days, 160 days, 170 days, 180 days, 190 days or 200 days or more, while receiving rilonacept at an administration interval and for a treatment period according to the invention.

[0099] The recurrence-free survival period may be at least 50 days from the withdrawal of a corticosteroid, while receiving weekly dose of rilonacept. The flare-free survival period from the withdrawal of NSAID may be at least 55 days, 60 days, 65 days, 70 days, 75 days, 80 days, 85 days, 90 days, 95 days, 100 days, 110 days, 120 days, 130 days, 140 days, 150 days, 160 days, 170 days, 180 days, 190 days or 200 days or more, while receiving rilonacept at an administration interval (i.e., weekly doses) and for a treatment period according to the invention.

Adverse Effects

[0100] Adverse effects related to the treatment of pericarditis can include injection-site reaction, upper respiratory tract infection, headache, nausea, vomiting, diarrhea, sinusitis, arthralgia, flu-like symptoms, abdominal pain, pyrexia, herpes, transaminase elevation, ischemic optic neuropathy and nasopharyngitis.

[0101] Administration of rilonacept may result in no serious adverse events in the subject. Administration of rilonacept may not result in one or more of injection-site reaction, worsening of rheumatoid arthritis, upper respiratory tract infection, headache, nausea, vomiting, diarrhea, sinusitis, ischemic optic neuropathy, arthralgia, flu-like symptoms, abdominal pain, pyrexia,

herpes, transaminase elevation and nasopharyngitis.

[0102] The various safety assessments may include pharmacokinetic and pharmacodynamic monitoring, including but not limited to: physical examination, measurement of vital signs, monitoring adverse event (AE), monitoring chest X-ray and screening for signs of tuberculosis.

Interleukin-1 (IL-1) Receptor-Fc Fusion Protein

[0103] The invention relates to an interleukin-1 receptor-Fc fusion protein, namely rilonacept. Rilonacept blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1α and IL-1β (i.e., an IL-1 trap) and prevents their interaction with IL-1 cell surface receptors. The Fc portion of rilonacept comprises CH2 and CH3 domains derived from a human IgG1. Rilonacept comprises the extracellular domains of IL-1R Type 1 and IL-1R accessory protein (IL-1RAcP). Two identical fusion proteins comprising the extracellular domains of IL1R Type 1 and IL-1RAcP and an Fc portion of human IgG1 are covalently linked by disulfide bonds in the Fc region to form a homodimer.

Rilonacept Sequence

SERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYSTAHSAGLTLI
WYWTRQDRDLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTCMLRNTTYCSKV
AFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWYMGCY
KIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLTVKVVGSPKNA
VPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGKKPDDITIDVTI
NESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKVPAPR
YTVEKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQASRIHQ
HKEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKFVENEPNLCYNAQAIFKQKLP
VAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIHFSGVKDRLIVMNVAE
KHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRPVIVSPANETMEVDLGSQIQLI
CNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLITVLNISEIESRF
YKHPFTCFAKNTHGIDAAYIQLIYPVTNSGDKTHTCPPCPAPELLGGPSVFLFPPKPKD
TLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV
LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK **(SEQ ID NO: 1)**

Rilonacept Sequence with N-Terminus Signal Sequence

MVLLWCVVSLYFYGILQSDASERCDDWGLDTMRQIQVFEDEPARIKC
PLFEHFLKFNYSTAHSAGLTLIWYWTRQDRDLEEPINFRLPENRISKEKDVLWFRPTL
LNDTGNYTCMLRNTTYCSKVAFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPN
VDGYFPSSVKPTITWYMGCYKIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENG
RTFHLTRTLTVKVVGSPKNAVPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRN
EVWWTIDGKKPDDITIDVTINESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSA
KGEVAKAAKVKQKVPAPRYTVEKCKEREEKIILVSSANEIDVRPCPLNPNEHKGTIT

WYKDDSKTPVSTEQASRIHQHKEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKF
VENEPNLCYNAQAIFKQKLPVAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLLL
DNIHFSGVKDRLIVMNVAEKHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRPV
IVSPANETMEVDLGSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENP
ANKRRSTLITVLNISEIESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTNSGDKTHTCPPC
PAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN
AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ
PREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK **(SEQ ID NO: 2)**

Extracellular Domain of IL-1RAcP Amino Acid Sequence

SERCDDWGLDTMRQIQVFEDEPARIKCPLFEHFLKFNYSTAHSAGLTLI
WYWTRQDRDLEEPINFRLPENRISKEKDVLWFRPTLLNDTGNYTCMLRNTTYCSKV
AFPLEVVQKDSCFNSPMKLPVHKLYIEYGIQRITCPNVDGYFPSSVKPTITWYMGCY
KIQNFNNVIPEGMNLSFLIALISNNGNYTCVVTYPENGRTFHLTRTLTVKVVGSPKNA
VPPVIHSPNDHVVYEKEPGEELLIPCTVYFSFLMDSRNEVWWTIDGKKPDDITIDVTI
NESISHSRTEDETRTQILSIKKVTSEDLKRSYVCHARSAKGEVAKAAKVKQKVPAPR
YTVE **(SEQ ID NO: 3)**

Extracellular Domain of IL-1R1 Amino Acid Sequence

KCKEREEKIILVSSANEIDVRPCPLNPNEHKGTITWYKDDSKTPVSTEQ
ASRIHQHKEKLWFVPAKVEDSGHYYCVVRNSSYCLRIKISAKFVENEPNLCYNAQAI
FKQKLPVAGDGGLVCPYMEFFKNENNELPKLQWYKDCKPLLLDNIHFSGVKDRLIV
MNVAEKHRGNYTCHASYTYLGKQYPITRVIEFITLEENKPTRPVIVSPANETMEVDL
GSQIQLICNVTGQLSDIAYWKWNGSVIDEDDPVLGEDYYSVENPANKRRSTLITVLNI
SEIESRFYKHPFTCFAKNTHGIDAAYIQLIYPVTN **(SEQ ID NO: 4)**

Fc (IgG1) Amino Acid Sequence

DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV

SNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW
ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYT
QKSLSLSPGK **(SEQ ID NO: 5)**

EXAMPLES

[0104] While certain embodiments of the present invention have been described with specificity in accordance with certain embodiments, the following examples serve only to illustrate the invention and are not intended to limit the same.

Example 1: Treatment of Pericarditis with IL-1 Receptor-Fc Fusion Protein

[0105] The study in this example was a Phase II clinical trial designed to evaluate the safety, tolerability, and PK of rilonacept, an interleukin-1 receptor-Fc fusion protein, in subjects with pericarditis. The study also included exploratory investigations of the effect of the interleukin-1 receptor-Fc fusion protein on clinical effect assessments in symptomatic patients.

[0106] Rilonacept is a recombinant fusion protein including the extracellular domains of human IL-1 cytokine receptor and the Fc portion of human immunoglobulin G1 (IgG1) (SEQ ID NO:1). It acts as a soluble decoy receptor binding IL 1α/IL 1β and prevents their interaction with the IL 1 cell surface receptor.

[0107] Study drug (rilonacept or placebo) is supplied in a single use, 20 ml glass vial containing a sterile, white to off white, lyophilized powder. Each vial is to be reconstituted with 2.3 ml sterile Water for Injection (WFI). A volume up to 2 ml can be withdrawn, which is designated to deliver up to 160 mg of rilonacept or up to 2 ml of placebo for SC injection only. The resulting solution is clear, colorless to pale yellow, and essentially free of particulates.

[0108] Each rilonacept vial contains 220 mg of rilonacept lyophilized powder. After reconstitution with 2.3 ml WFI, the rilonacept vial contains 80 mg/ml rilonacept, 40 mM histidine , 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5. No preservatives are present.

Study Design

[0109] Participating subjects receive a total of 6 weekly doses of the interleukin-1 receptor-Fc fusion protein. Dosing is initiated with a loading dose of 320 mg administered subcutaneously as two 160 mg doses, followed by 160 mg maintenance doses administered subcutaneously once a week. Pericarditis improvement data and safety information are collected. If subjects are deemed to be responsive to treatment, participation in an optional 18 week extension period may be offered. For the duration of the Treatment Period, concomitant NSAIDs and/or colchicine and/or corticosteroids, if present, should be continued at pre-study dose levels until after the 6 dose Treatment Period has concluded; however, should if it is determined that a reduction/tapering of the NSAID, colchicine, and/or corticosteroid dose is medically indicated, the NSAID, colchicine, and/or corticosteroid dose can be down-titrated.

[0110] Opioid analgesics, non-narcotic analgesics (e.g., tramadol), and acetaminophen are allowed as rescue medication for ancillary pain control on an as-needed basis throughout the Treatment Period. Although it is recommended that NSAID dose levels (if present) should remain constant during the active Treatment Period, the concomitant NSAID dose may be temporarily increased (or an NSAID initiated) for ancillary pain control if deemed necessary. At

the discretion of the Investigator, "Treatment Responders" (defined by the investigator as a clinically significant reduction in pericardial pain using the 11-point NRS, normal or near-normal CRP levels, and/or absent or decreasing echocardiographic effusion at the End-of-Trial Visit), will be offered participation in an optional 18-week Extension Period (EP), in which weekly administration of the interleukin-1 receptor-Fc fusion protein can be continued at the same dose as in the Treatment Period for a total duration of treatment of up to 24 weeks. During the EP, the Investigator may choose to wean concomitant NSAIDs, colchicine, and/or corticosteroids according to standard of care paradigms.

Study Treatments

[0111] The interleukin-1 receptor-Fc fusion protein was prepared as a lyophilized formulation. For subcutaneous (SC) administration, the interleukin-1 receptor-Fc fusion protein was manufactured in a dosage form containing 160 mg per vial. The lyophilized powder was reconstituted with 2.3 mL of sterile Water for Injection (WFI) and drug was delivered in 2 mL at a concentration of 80 mg/mL. Dosing initiated with a loading dose of 320 mg administered subcutaneously as two 160 mg doses, followed by 160 mg maintenance doses were administered subcutaneously once a week. After an initial group of subjects were treated, depending on the safety profile observed as well as the magnitude and speed of treatment response (e.g., if an informative number of subjects achieve treatment responded early in the Treatment Period), the protocols allows for the dose administered to a subsequent group of subjects to be decreased to loading dose of 160 mg (2 × 80 mg) administered SC, followed by 80 mg maintenance dose administered SC once a week for 5 additional weeks, in order to determine efficacy at a lower dose.

Subject Inclusion Criteria

[0112] Subjects who have had an index episode of pericarditis which, based on the available data, met the criteria for an acute pericarditis event, using the 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases (Adler et al, European Heart Journal, Volume 36, Issue 42, 7 November 2015, Pages 2921-2964) as a frame of reference - i.e., met at least 2 of the 4 following criteria: pericarditic chest pain, pericardial rubs, new widespread ST-segment elevation or PR-segment depression on ECG, and pericardial effusion (new or worsening). Additional supporting findings included elevations of markers of inflammation (i.e., CRP, erythrocyte sedimentation rate, and white blood cell count) or evidence of pericardial inflammation by an imaging technique (e.g., MRI).

[0113] Subjects also had to have had at least one prior recurrent episode of pericarditis, and subjects had to have an ongoing symptomatic episode of pericarditis at the time of study enrollment, both based upon the available diagnostic information. Also, if a subject used NSAIDs, and/or colchicine and/or corticosteroids (in any combination), they must have received

at stable dose levels for at least 7 days prior to initial dosing (although stable doses for at least 3 days were acceptable if a shorter period of stability was not anticipated to alter the baseline CRP values) with the interleukin-1 receptor-Fc fusion protein and the subject was expected to continue these concomitant medications at these dose levels for the duration of the active Treatment Period.

[0114] The phase 2 open-label pilot study is a 24-week study in up to 40 subjects in total, age 6 to 75 years old, including the following categories of subjects with recurrent pericarditis, referred as the following Groups:

Group 1 enrolling symptomatic subjects with recurrent idiopathic pericarditis (RIP) with an elevated marker of systemic inflammation (C-reactive protein [CRP] ≥ 1 mg/dL);

Group 2 enrolling symptomatic subjects with RIP with CRP <1 mg/dL which, in the opinion of the investigator could be attributed to concomitant medications (e.g., corticosteroids) and with pericardial inflammation present on cardiac magnetic resonance imaging (MRI), confirmed by the imaging core lab;

Group 3 enrolling subjects with corticosteroid-dependent RIP not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis;

Group 4 enrolling symptomatic subjects with recurrent post pericardiotomy syndrome (PPS) with an elevated marker of systemic inflammation (CRP ≥ 1 mg/dL); and

Group 5 enrolling subjects with corticosteroid-dependent recurrent PPS not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis.

Study Assessments

[0115] Blood samples were collected and C-reactive protein (CRP) levels were determined both before study inclusion of a subject and during the study. Some subjects presented with elevated CRP values ≥1 mg/dL at the time of study enrollment. CRP changes and the time course to decrease and resolution of CRP to normal values ≤0.5 mg/dL were assessed.

[0116] The following clinical response assessments were also conducted during the study.

[0117] Echocardiograms (ECHOs) including assessment of pericardial effusion were performed at screening (SCV1); at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit, which, if applicable, occurred during approximately weeks 3-4 of the Treatment Period and Visit 7/End-of-Trial);, at the Interval Evaluation Visit during the EP [if applicable]; and at the Final Study Visit/Visit 8 (SCV8). Pericardial effusion was characterized by accumulation of excess fluid in the pericardial space surrounding the heart and was one of the common features of pericarditis. Echocardiography is a sensitive tool and the most widely

used imaging technique for the detection of pericardial effusion and/or thickening. For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECHO images were assessed by a central reader.

[0118] Twelve-lead electrocardiograms (ECGs) were performed at screening (SCV1 and optional SCV2), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the Extension Period (EP) [if applicable], and at the Final Study Visit/Visit 8. Pericarditis commonly involves changes in the electrophysiologic activity of the heart, resulting in typical ECG findings, namely widespread ST-elevation or PR depression. Changes in ECG findings help determine the pericarditis status of a subject. For the purposes of the analysis of treatment response in all subjects at the end of the study, all ECG tracings were assessed by a central reader.

[0119] Common pericarditis signs include fever and pericardial rub. These pericarditis signs were assessed via documentation of vital signs and physical examinations. Physical examinations and vital signs assessments for pericarditis signs were performed at screening (SCV1 and optional SCV2), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP [if applicable], and the Final Study Visit/Visit 8. If applicable, assessment of pericarditis signs were also performed at unscheduled visits.

[0120] Common pericarditis symptoms include chest discomfort (pericarditis pain). A validated 11-point Numerical Rating Scale (NRS) was used to measure the subject's level of pericarditis (chest) pain intensity (Mannion et al, Nature Clinical Practice Rheumatology 2007; 3 (11): 610-18). The assessment was performed at all study visits on-site during Study Site/Clinic visits and as part of telephone calls/virtual visits during outpatient visits/treatment weeks (weekly during the Treatment Period and monthly during the EP).

[0121] Cardiac MRI was an optional assessment and could be performed at study entry (SCV1) and at the final study visit (Visit 8) to assess any changes in pericardial inflammation. For the purposes of the analysis of treatment response in all subjects at the end of the study, all cardiac MRI images was to be assessed by a central reader.

[0122] A validated Quality of Life Questionnaires was used to assess changes in the subject's overall well-being (Hays et al, Qual Life Res (2009) 18:873-880). The patient's global assessment was performed at screening (SCV1), at Visit 1 (Day 0), at the end of the Treatment Period (Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP, and at the Final Visit (Visit 8).

[0123] An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product. An AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the

medicinal (investigational) product.

[0124] AEs also include: any worsening (i.e., any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the interleukin-1 receptor-Fc fusion protein; abnormal laboratory findings considered by the reporting investigator to be clinically significant; and any untoward medical occurrence.

[0125] In this study, individual elements of pericarditis symptomatology (including pain) are captured as an efficacy parameter. Pericarditis pain is not required to be reported as an AE. However, if the subject experiences new symptoms that had not been previously reported in the constellation of symptoms recorded at baseline, these new symptoms should be reported as an adverse event.

[0126] Primary efficacy endpoints include inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with RIP both at baseline and while on the interleukin-1 receptor-Fc fusion protein treatment. Exploratory endpoints include the following: time course of improvement of measures of pericarditis symptomatology, including pericarditis pain, CRP, and/or resolution of echocardiographic and ECG abnormalities; differential response to different interleukin-1 receptor-Fc fusion protein doses (e.g., 160 mg or 80 mg maintenance doses); time to CRP normalization (≤ 0.5 mg/dL); change over time in CRP levels; number (percentage) of subjects with normalization of CRP; change over time in subjects' assessments of pericarditis pain; explore Patient-Reported Outcome (PRO), biochemical (CRP), and imaging correlates of clinical improvement of pericarditis symptomatology in order to develop a suitable composite primary endpoint for subsequent clinical trials in RIP; number (percentage) of subjects with pericarditis improvement (based on investigator assessment); change over time in subjects' global assessments of overall well-being (using the QoL instrument); change in pericardial inflammation as assessed by cardiac MRI; number of subjects weaned off NSAIDs, colchicine, and/or corticosteroids at end of the EP; time to pericardial flare, the number of patients experiencing recurrence of pericarditis and the number of recurrences of pericarditis.

Example 2: Reduction in CRP levels and pain with interleukin-1 receptor-Fc fusion protein

[0127] This example demonstrates that the Phase II clinical trial described in Example 1 resulted in clinically meaningful efficacy, particularly clinically significant reduction in CRP levels and pain.

[0128] Specifically, fourteen patients (subjects) having pericarditis were treated with a 320 mg loading dose of subcutaneously injected interleukin-1 receptor-Fc fusion protein (rilonacept) at day 0, followed by 160 mg maintenance dose of subcutaneously injected rilonacept once a week. CRP levels and pain scores (using an 11-point Numerical Rating Scale (NRS)) for these patients are shown in **Figures 1A - 3C.** Nine patients were enrolled in Group 1 (symptomatic

idiopathic recurrent pericarditis subjects with elevated CRP), and six patients showed a reduction in CRP and NRS (pain) values even after a single dose of the treatment as shown in Figures 1A-C, E, and H-I. In the case of Subject D, the CRP level was not tested one week after the initial dose of rilonacept; however, at the second week of treatment, the CRP value showed a marked reduction compared to baseline (Figure 1D). Subject F and G showed reduction in CRP levels as shown in Figures 1F and 1G. Each patient was being treated with prior medications for pain and/or inflammation at the indicated doses shown in Figures 1A-I. All Group 1 patients showed a trend towards a persistent reduction in pain and CRP values during subsequent dosing periods compared to baseline as shown in Figures 1A-I. As shown in Figure 1C, after 6 weeks of rilonacept therapy, Subject C in Group 1 stopped taking ibuprofen and after approximately 8 weeks (55 days) of being treated with rilonacept this subject began a six week taper of prednisone. The subject's dose was reduced by 2.5 mg every other week. The subject has remained asymptomatic in the absence of ibuprofen and during the steroid weaning period, while continuing rilonacept therapy during the extension period. As shown in Figure 1C, the subject proceeded through the next 77 days with neither ibuprofen nor prednisone, exhibiting no flare or recurrence, CRP level < 0.5 mg/dl, and no pain.

[0129] Two patients were enrolled in Group 2 (symptomatic RIP subjects with CRP <1 mg/dL and with pericardial inflammation present on cardiac MRI) and showed a reduction in CRP and pain even after a single dose of the treatment, and continued to show a trend towards a reduction in pain and CRP values during the subsequent dosing period compared to baseline as shown in **Figure 2A and 2B.** These patients were being treated with prior medications for pain and inflammation at the indicated doses shown in the figures. Three patients were enrolled in Group 3 (subjects with corticosteroid-dependent RIP not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis), but were judged by the investigator as corticosteroid-dependent, i.e., based upon prior history and experience that the signs and symptoms of pericarditis would return if the corticosteroids were withdrawn. These patients were being treated with prior medications for pain and inflammation at the indicated doses shown in **Figures 3A, 3B and 3C.** After receiving rilonacept (320 mg) at day 0 and prior to withdrawal of concurrent therapies, the patient remained asymptomatic as observed on day 7. During the extension period of the study, the protocol allows the subjects enrolled in Group 3 to be weaned from concomitant pericarditis medications, including steroids, while remaining on rilonacept at the discretion of the medical practitioner. For example, Figure 3B shows that the patient exhibited reduced CRP level and NRS score even at the tapering of prednisone dose to complete weaning at 91 days after the first dose of rilonacept. Subject B continued to show the reduced CRP level and NRS score over the next 28 days of prednisone-free regime, as shown in Figure 3B. Subject A of Group 3 opted out of the extension study at completion of the base treatment period. Additional outcome measures, such as presence of effusion, QoL and ECG changes, acquired from subjects in Groups 1-3 are reported in Table 1. Adverse events reports for these subjects are shown in Table 2.

[0130] Twelve subjects treated with rilonacept have reported some mild adverse events (AEs) (Table 2). None were serious, and none led to discontinuation of study drug. The most commonly reported AEs were injection-site reactions, and all were mild and transient in nature.

These results demonstrate that the interleukin-1 receptor-Fc fusion protein is safe and efficacious for human treatment.

Table 1

Subject	Parameter			Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 10	Week 14	Week 18	Week 22	Week 25
	Visit Day	SCV1	SCV2	Day 0	Day 3 (+/- 1)	Day 7 (+/- 2)	Day 14 (+/- 1)	Day 21 (+/- 2)	Day 28 (+/- 1)	Day 35 (+/- 1)	Day 42 (+/- 6)	Day 63 (+/- 1)	Day 91 (+/- 1)	Day 119 (+/- 2)	Day 147 (+/- 2)	Day 168 (+/- 2)
	Visit Window															
Group 1, Subject A	Pain NRS Score	NR*	NR*	6	NR	1	1	0	0	0	0	0	0	0	0	0
	CRP (mg/dL)	NR*	NR*	8.85		0.66	0.6	0.25	0.11	0.08	0.1	0.05	0.07	0.09	0.07	0.09
	Presence of Effusion	NR*	NR*	Yes							No			No		No
	ECG Changes	NR*	NR*	PR depression							Normal			Normal		Normal
	QoL Total	31		31							42			34		36
Group 1, Subject C	Pain NRS Score	6	6	5	NR	0	2	1	1	0	0	0	0	0	0	0
	CRP (mg/dL)	6.71	4.14	4.68		0.22	0.2	0.5	0.14	1.63	0.06	0.05	NA*	0.1	0.11	0.11
	Presence of Effusion	Yes	NR*	Yes				Yes			No			No		NA
	ECG Changes	Normal	Normal	Normal				Normal			Normal			Normal		NA
	QoL Total	28		25				29			32			27		29
Group 1, Subject B	Pain NRS Score	3	NR*	3	2	2	0	0	0	0	0	0	0	0	0	0
	CRP (mg/dL)	1.03	NR*	1.06		0.8	0.57	0.46	0.57	0.63	0.51	0.55	0.38	0.7	0.82	
	Presence of Effusion	No	NR*	No							No					
	ECG Changes	Normal	NR*	Normal							Normal					
	QoL Total	42		41							43					
Group 1, Subject D	Pain NRS Score	2	NR*	3	6	0	1	1	1	1	1 (same as Week 6)	0	4	0		
	CRP (mg/dL)	2.71	NR*	2.71		NA*	0.15	0.27	0.24	0.28	0.28	0.26	0.17	0.11		
	Presence of Effusion	No	NR*	No							NA					
	ECG Changes	Normal	Normal	Normal							NA					
	QoL Total	27		27							29					

Table 1 continued

Subject	Parameter			Week 1
	Visit Day	SCV1	SCV2	Day 0
	Visit Window			
Group 1, Subject E	Pain NRS Score	NR*	NR*	3
	CRP (mg/dL)	NR*	NR*	0.77
	Presence of Effusion	NR*	NR*	No
	ECG Changes	NR*	NR*	PR depression
	QoL Total	35		35
Group 1, Subject F	Pain NRS Score	6	NR*	5
	CRP (mg/dL)	2.56	NR*	1.56
	Presence of Effusion	Yes	NR*	Yes
	ECG Changes	ST elevation	NR*	ST elevation
	QoL Total	12		12
Group 1, Subject G	Pain NRS Score	2	NR*	6
	CRP (mg/dL)	0.97	NR*	1.22
	Presence of Effusion	No	NR*	No
	ECG Changes	Normal	NR*	Normal
	QoL Total	29		36
Group 1, Subject H	Pain NRS Score	8	8	8
	CRP (mg/dL)	9.12	NR*	19.84
	Presence of Effusion	NA	NR*	NA
	ECG Changes	Normal	NR*	ST elevation
	QoL Total	21		19
Group 1, Subject I	Pain NRS Score	4	NR*	5

Day 3	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 10	Week 14	Week 18	Week 22	Week 25
Day 3 (+/- 1)	Day 7 (+/- 1)	Day 14 (+/- 1)	Day 21 (+/- 1)	Day 28 (+/- 1)	Day 35 (+/- 1)	Day 42 (+6)	Day 63 (+/- 1)	Day 91 (+/- 1)	Day 119 (+/- 1)	Day 147 (+/- 1)	Day 168 (+/- 1)
0	0	0	0	0	0	1	0	0			
	0.12	0.15	0.11	0.13	0.09	0.12	0.09	0.1			
						No					
						FR depression (*abnormal)					
						33					
3	4	6	3	2	5	4	2	2			
	0.19	0.62	0.33	0.21	0.69	0.42	0.28	0.55			
						No					
						Normal					
						19					
8	3	3	0	1	0	0	0				
	0.44	0.18	0.24	0.33	0.26	0.26	0.25				
			Normal	Not recorded yet	Normal	Normal					
			38		42	42					
4	3	2	2								
	0.67	0.08	0.04								
			No								
			Normal								
			21								
0											

Table 1 continued

	Parameter			Week 1	Day 3	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
Subject	Visit Day Visit Window	SCV1	SCV2	Day 0 (+/- 1)	Day 3 (+/- 1)	Day 7 (+/- 1)	Day 14 (+/- 1)	Day 21 (+/- 1)	Day 28 (+/- 1)	Day 35 (+/- 1)	Day 42 (+/- 6)
Group 2, Subject A	CRP (mg/dL)	NA	NR*	NA							
	Presence of Effusion	NA	NR*	NA							
	ECG Changes	NA	NR*	NA		Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet
	QoL Total	NA		NA							
	Pain NRS Score	4	NR*	4	4	1	2	2	1	0	0
	CRP (mg/dL)	0.34	NR*	0.397		0.14	0.26	0.25	0.31	0.58	0.58
	Presence of Effusion	No	NR*	No				No			No
	ECG Changes	Normal	NR*	Normal				Normal			Normal
	QoL Total	26		26			40				40
	Pain NRS Score	NR*	NR*	2	2	1	1	1	0	0	0
	CRP (mg/dL)	NR*	NR*	0.09		0.02	0.04	0.03	0.06	0.63	0.05
	Presence of Effusion	NR*	NR*	No							No
	ECG Changes	NR*	NR*	Normal							Normal
Group 2, Subject B	QoL Total	NR*		33							37
Group 2, Subject C	Pain NRS Score	NR*	NR*	7	7	4	7	7	1	7	7
	CRP (mg/dL)	NR*	NR*	0.17		0.06	0.16	0.07	0.06	0.86	0.06
	Presence of Effusion	NR*	NR*	Yes							No
	ECG Changes	NR*	NR*	Normal							Normal
	QoL Total	21		21							31
Group 2, Subject D	Pain NRS Score	NR*	NR*	1	2	4	4	3	2	0	1
	CRP (mg/dL)	NR*	NR*	0.34		0.10	0.11	0.11	0.15	0.68	0.10

Week 10	Week 14	Week 18	Week 22	Week 25
Day 63 (+/- 1)	Day 91 (+/- 1)	Day 119 (+/- 1)	Day 147 (+/- 1)	Day 168 (+/- 1)
Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet
0	0	Not recorded yet	Not recorded yet 3	Not recorded yet 8
0.58	0.5			
	No			
	NA			
	38			
Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet
[redacted]				
0	0	NA	Not recorded yet	Not recorded yet
0.08	0.12	0.00		

Table 1 continued

	Parameter			Week 1	Day 3	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 10	Week 14	Week 18	Week 22	Week 25
Subject	Visit Day Visit Window	SCV1	SCV2	Day 0	Day 3 (+/- 1)	Day 7 (+/- 1)	Day 14 (+/- 1)	Day 21 (+/- 1)	Day 28 (+/- 1)	Day 35 (+/- 1)	Day 42 (+/- 6)	Day 63 (+/- 1)	Day 91 (+/- 1)	Day 119 (+/- 1)	Day 147 (+/- 1)	Day 168 (+/- 1)
	Presence of Effusion	NR*	NR*	No							No					
	ECG Changes	NR*	NR*	Normal							Abnormal NCS					
	QoL Total	25		19							27					
Group 3, Subject C	Pain NRS Score	NR*	NR*	0	0	0	0	0	0	0	0	NA	Not recorded yet	Not recorded yet	Not recorded yet	Not recorded yet
	CRP (mg/dL)	NR*	NR*	0.16		0.08	0.07	0.1	0.07	0.27	0.12	0.06				
	Presence of Effusion	NR*	NR*	No							No					
	ECG Changes	NR*	NR*	Abnormal NCS							Normal					
	QoL Total	39		39							37					

(grey) = Not Required per protocol
(black) = Not Participating in Extension
NA = Collected, Not Available at time of data cut-off (19 September 2018)
NA‡= Subject lab sample was not processed due to unexpected circumstances
NR = Not Required as per protocol prior to protocol amendment 2.0
NR* = Not Required as screening visits were combined with Day 0 as allowed per protocol
† = The local lab value drawn during the screening visit for subject qualification was 1.5 mg/dL. This value was drawn on the same day as the central lab value referenced in the table.
†† = This is the local lab value. The central lab value drawn during the screening visit was 7.36 mg/dL. This value was drawn on the same day as the local lab value referenced in the table.

Table 2

Subject ID	Reported Term for Adverse Event	Severity	Serious	Relationship to Study Drug	Action Taken on Study Drug	Outcome of Adverse Event
Group 1 Subject B	ISR Redness	Mild	No	Possibly Related	None	Recovered/ Resolved
Group 1 Subject B	ISR Warmness	Mild	No	Possibly Related	None	Recovered/ Resolved
Group 1 Subject E	Headache	Mild	No	Not Related	None	Recovered/ Resolved
Group 1 Subject E	Vertigo	Mild	No	Possibly Related	None	Recovered/ Resolved
Group 1 Subject E	Toothache	Mild	No	Not Related	None	Recovered/ Resolved
Group 1 Subject F	RT Dry Eye	Mild	No	Not Related	None	Not Recovered/ Not Resolved
Group 1 Subject D	Application site redness	Mild	No	Not Related	None	Recovered/ Resolved
Group 1 Subject D	Application site bruise	Mild	No	Not Related	None	Recovered/ Resolved
Group 1 Subject A	Heartburn	Mild	No	Unlikely Related	None	Recovered/ Resolved
Group 1 Subject A	Common cold	Mild	No	Unlikely Related	None	Recovered/ Resolved
Group 1 Subject A	Injection site reaction	Mild	No	Related	None	Recovered/ Resolved
Group 1 Subject A	Worsening of elevated LFTs**	Mild	No	Possibly Related	None	Recovered/ Resolved
Group 1 Subject A	Elevated HDL	Mild	No	Related	None	Not Recovered/ Not Resolved
Group 1						

Subject ID	Reported Term for Adverse Event	Severity	Serious	Relationship to Study Drug	Action Taken on Study Drug	Outcome of Adverse Event
Subject A	Elevated CK	Mild	No	Unlikely Related	None	Recovered/ Resolved
Group 1 Subject A	Intermittent chest discomfort	Mild	No	Possibly Related	None	Not Recovered/Resolved
Group 3 Subject A	Soreness at injection site	Mild	No	Related	None	Recovered/ Resolved
Group 3 Subject A	Pain with inspiration	Mild	No	Not Related	None	Recovered/ Resolved
Group 3 Subject A	Dry cough	Mild	No	Unlikely Related	None	Recovered/ Resolved
Group 3 Subject A	Hand muscle pain	Mild	No	Unlikely Related	None	Recovered/ Resolved
Group 3 Subject A	Worsening shortness of breath when lying flat	Mild	No	Possibly Related	None	Not Recovered/ Not Resolved
Group 3 Subject A	Worsening of elevated liver enzymes*	Mild	No	Not Related	None	Not Recovered/ Not Resolved
Group 3 Subject B	Shortness of breath	Mild	No	Possibly Related	None	Not Recovered/ Not Resolved
Group 3 Subject B	Fatigue	Mild	No	Unlikely Related	None	Not Recovered/ Not Resolved
Group 3 Subject B	Worsening pericarditis symptoms	Mild	No	Possibly Related	None	Recovered/ Resolved
Group 3 Subject B	Injection site reaction	Mild	No	Related	None	Recovered/ Resolved
Group 3 Subject B	Elevated cholesterol	Mild	No	Related	None	Not Recovered/ Not Resolved

Subject ID	Reported Term for Adverse Event	Severity	Serious	Relationship to Study Drug	Action Taken on Study Drug	Outcome of Adverse Event
Group 3 Subject B	Bilateral shoulder pain	Mild	No	Unlikely Related	None	Not Recovered/ Not Resolved
Group 3 Subject C	Injection site reaction	Mild	No	Related	None	Recovered/Resolved
Group 1 Subject C	Pain at injection site	Mild	No	Related	None	Recovered/ Resolved
Group 1 Subject C	Intermittent muscle twitching - bilateral thighs	Mild	No	Possibly Related	None	Recovered/ Resolved
Group 1 Subject C	Hemorrhoids	Mild	No	Not Related	None	Recovered/ Resolved
Group 1 Subject C	Nausea	Mild	No	Not Related	None	Recovered/ Resolved
Group 1 Subject C	Cold	Mild	No	Possibly Related	None	Recovered/ Resolved
Group 2 Subject A	Redness at injection site	Mild	No	Related	None	Recovered/ Resolved
Group 1 Subject G	Atypical Chest Pain	Moderate	Yes	Unlikely Related	None	Recovered/ Resolved
Group 1 Subject G	Bruising at injection site	Mild	No	Related	None	Recovered/ Resolved
Group 1 Subject G	Right lower extremity cellulitis	Mild	No	Unlikely Related	None	Recovered/ Resolved
Group 1 Subject G	Chest pain	Mild	No	Not Related	None	Recovered/ Resolved
Group 1 Subject				Unlikely		Recovered/

Subject ID	Reported Term for Adverse Event	Severity	Serious	Relationship to Study Drug	Action Taken on Study Drug	Outcome of Adverse Event
H	Diarrhea	Mild	No	Related	None	Resolved

Example 3. Long Term Efficacy of the Interleukin-1 Receptor-Fc Fusion Protein in Subjects with Recurrent Pericarditis

[0131] A Phase III, double blind, placebo controlled, randomized withdrawal study with open label extension, is designed to assess the efficacy and safety of rilonacept treatment in subjects with recurrent pericarditis. The primary endpoint is time to pericarditis recurrence, defined as the time from randomization to the date of the first pericarditis recurrence for each subject. Only CEC-confirmed pericarditis recurrence will be considered as an event for the primary analysis. Primary analysis of this study is at the last (22^{nd}) CEC-confirmed pericarditis recurrence and all subjects in the RW period have been treated for 24 weeks. Subjects who have not had an adjudicated pericarditis recurrence will be censored on the day of the last available assessment before data cutoff.

[0132] All suspected pericarditis recurrence events are formally adjudicated by the Clinical Endpoint Committee (CEC), and only events that are confirmed by the CEC as pericarditis recurrences are used in the Primary Endpoint analysis. A multitude of other endpoints are analyzed at various stages of the study as described in the following sections. The overview of the study is depicted in **Figure 4.**

[0133] Subjects eligible for the study are subjects with recurrent pericarditis who do not have pericarditis secondary to prohibited conditions. The study population includes both adult subjects ≥18 years old and pediatric subjects ≥12 and <18 years old with a history of at least 2 prior pericarditis episodes (including the first episode and 1 recurrence). Enrollment of pediatric subjects are limited to up to 20% of the study population. To be eligible for the study, subjects must present at screening with at least a third pericarditis episode, defined as at least 1 day with pericarditis pain measurement ≥4 on the 11-point Numerical Rating Scale (NRS) and C-reactive protein (CRP) level ≥1 mg/dL within 7 days prior to first study drug administration. Pericarditis pain ≥4 and CRP ≥1 mg/dL are not required to be present on the same day.

[0134] Subjects included in the study may be receiving concomitant NSAIDs and/or colchicine and/or oral CS treatment in any combination, provided that the dosages of these medications have been stable (or not increased) for at least 3 days prior to first administration of study drug, and that changes in medications made within this time period (for instance, 1-time use of NSAIDs) are not anticipated by the investigator to significantly alter assessments of baseline disease activity.

[0135] The study has 5 periods:

1. **(1) Screening period,** during which assessment of disease characteristics, baseline therapy, and the pre-treatment workup is completed (up to 4 weeks)
2. **(2) Single-blind Run-In (RI) period** (12 weeks), during which blinded rilonacept (IL-1 receptor-Fc fusion protein, IL1RFcFP) is administered SC once weekly in all subjects. The RI period includes the following:
    - 1-week Stabilization period, during which blinded rilonacept is administered in addition to standard of care (SOC) pericarditis therapy and the ongoing pericarditis episode is treated.
    - 9-week Weaning period, during which subjects are weaned off background SOC pericarditis therapy, as applicable, while treatment with blinded rilonacept continues. The dosages of corticosteroids (CS), NSAIDs, and colchicine are tapered according to the weaning protocol in the Pharmacy Manual (for the purpose of the protocol, aspirin is considered an NSAID). In general, CS doses are tapered off starting at RI Week 1 and are withdrawn by RI Week 10 (over a total of 9 weeks). NSAID and colchicine doses are tapered off starting at RI Week 4 and are withdrawn by RI Week 10 (over a total of 6 weeks).
    - 2-week Monotherapy period during which subjects who have successfully weaned off background SOC pericarditis therapy continue to receive blinded rilonacept.

[0136] In the single-blind RI period (subjects are blinded regarding the time of transition from the single-blind to the double-blind period), adult subjects ≥18 years old will receive rilonacept as an initial loading dose of 320 mg (2 SC injections of 160 mg each) at the RI baseline visit (2 × 2 ml), followed by a 160 mg (2 ml) SC dose once weekly throughout the RI period. Pediatric subjects (≥12 and <18 years old) receive an initial loading dose of rilonacept 4.4 mg/kg (2 SC injections of 2.2 mg/kg each) at the RI baseline visit (maximum 2 × 2 ml), and then 2.2 mg/kg (maximum 2 ml) SC once weekly throughout RI period. Subjects who stopped background pericarditis medications and who achieve Clinical Response at RI Week 12, defined as the weekly average of daily pericarditis pain score ≤2.0 on the 11-point NRS within the 7 days prior to and including the day of randomization on RI Week 12 and a CRP level ≤0.5 mg/dL at RI Week 12/RW baseline visit, proceed into the double-blind placebo-controlled Randomized-Withdrawal (RW) period. Subjects who do not achieve Clinical Response at RI Week 12 on rilonacept monotherapy are discontinued from study drug, transitioned to SOC pericarditis therapy at the investigator's discretion, and followed through the end of the RW period.

[0137] The following secondary endpoints are assessed in this period:

- Proportion of subjects who achieved Clinical Response. Clinical Response is defined as a weekly average of daily pericarditis pain of ≤2.0 on the 11-point NRS during the week preceding randomization AND CRP level ≤0.5 mg/dL at RI Week 12/RW baseline visit.
- Time to CRP normalization (≤0.5 mg/dL)

- Number (percentage) of subjects with normalization of CRP at RI Week 12
- Change from baseline in pericarditis pain at RI Week 12
- Change from baseline in CRP level at RI Week 12
- Resolution of ECHO and ECG abnormalities (yes/no) at RI Week 12
- Percentage of days with no or minimal pain
- Number (percentage) of subjects with absent or minimal pericarditis symptoms based on PGIPS
- Number (percentage) of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L
- Change over time in the subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who were off background pericarditis medication at RI Week 12.

[0138] (3) Double-blind placebo-controlled RW period (pericarditis recurrence event-driven duration, with a minimum of 24 weeks).

[0139] The primary efficacy endpoint, that is the time of pericarditis recurrence for each subject is determined at this stage. Only CEC-confirmed pericarditis recurrence is considered as an event for the primary analysis.

[0140] Major secondary efficacy endpoints for the RW period include:

- Proportion of subjects who maintained Clinical Response at Week 24 of the RW period
- Percentage of days with no or minimal pain (pain ≤1 on the 11-point NRS) in the first 24 weeks of the RW period
- Proportion of subjects with absent or minimal pericarditis symptoms (based on the 7-point rating scale of PGIPS) at Week 24 of the RW period.

[0141] Other secondary endpoints for the RW period include:

- Proportion of subjects without pericarditis recurrence in the first 24 weeks of the RW period
- Time to NRS ≥4
- Time to CRP level ≥1 mg/dL
- Time to pericardial rub
- Time to widespread ST-segment elevation or PR-segment depression on ECG
- Time to new or worsening pericardial effusion on ECHO

- Change over time in CRP levels
- Change over time in subject's assessments of pericarditis pain (weekly average)
- Number (percentage) of subjects with absent or minimal pericarditis activity based on the PGA-PA
- Change over time in SF-36 Physical Component Score
- Change over time in SF-36 Mental Component Score
- Change in EQ-5D-5L
- Change over time in subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects who receive ORT therapy for pericarditis recurrence (analgesics, NSAIDs, and/or colchicine) in the RW period

[0142] During this stage, subjects who were able to stop background pericarditis medication and who achieve Clinical Response at RI Week 12 are randomized in a double-blind manner at a 1:1 ratio to the following:

- Rilonacept 160 mg (2.2 mg/kg in pediatric subjects) SC injections once weekly
- Matching placebo SC injections once weekly

[0143] Subjects report pericarditis associated pain daily based on 11-point pericarditis pain NRS scoring. A sensitivity analysis is done based on the investigator's assessment of the event.

[0144] All statistical tests for the treatment comparison of efficacy endpoints in the RW period are based on the Intent-To-Treat (ITT) analysis set with 1-sided α=0.025.

Pericarditis Recurrence in the RW Period

[0145] Pericarditis recurrence is defined as the recurrence of typical pericarditis pain associated with supportive objective evidence of pericarditis. Upon pericarditis recurrence, subjects who report at least 1 day with pericarditis pain measurement ≥4 on the 11-point NRS and have 1 CRP value ≥1 mg/dL (either on the same day or separated by no more than 7 days) receive bailout rilonacept (2 open-label injections of 160 mg rilonacept [or 4.4 mg/kg for pediatric subjects] followed by once-weekly open-label rilonacept SC injections of 160 mg [or 2.2 mg/kg for pediatric subjects]), irrespective of randomized treatment assignment and as soon as at least 5 days have passed since the last study drug injection. Sequential Oral Rescue Therapy (ORT), i.e., analgesics first, then NSAIDs, and then colchicine, can be added if needed at the discretion of the investigator, as outlined in the protocol and Pharmacy Manual.

[0146] Subjects with pericarditis recurrence who do not meet the protocol criteria for bailout rilonacept continue with the blinded study drug until the protocol criteria for bailout rilonacept are met or through the end of the RW period. For those subjects, sequential ORT can be added to blinded study drug at the discretion of the investigator, as outlined in the protocol and Pharmacy Manual.

[0147] All suspected pericarditis recurrence events in the RW period are formally adjudicated by the Clinical Endpoint Committee (CEC), and only events that are confirmed by the CEC as pericarditis recurrences are used in the Primary Endpoint analysis.

[0148] A subject experiencing a suspected pericarditis recurrence is required to contact the study investigator immediately for evaluation. Required assessments include:

- Evaluation of pericarditis pain on 11-point NRS.
- Evaluation of concomitant medications as well as pericarditis concomitant medications.
- Obtain laboratory samples for CRP (local and central) (the POC device provided by Kiniksa Pharmaceuticals is the preferred method for local laboratory CRP assessment).
- Acquisition of a 12-lead ECG.
- Acquisition of a cardiac ECHO per core laboratory imaging parameters; this ECHO can be read locally for the purpose of pericarditis recurrence assessment and then requires submission to the ECHO core laboratory for central review.
- Performing an abbreviated physical examination, height and body weight.
- Having subjects ≥18 years complete the SF-36, EQ-5D-5L, ISI
- Having subjects complete the PGIPS score.
- The investigator completes the PGA-PA.
- Obtaining central laboratory samples for PK, ADAs, and biomarkers.
- Other procedures deemed necessary per the investigator or delegated site personnel.

[0149] Upon the complete evaluation, if the investigator deems the subject to be having a pericarditis recurrence event, he/she should contact the PPD medical monitor to confirm that all assessments have been performed and collected.

[0150] (4) Long Term Extension Treatment Period (LTE-TP) (24 weeks), during which all subjects completing the RW period (including subjects transitioned to open-label rilonacept upon pericarditis recurrence) have an option to receive up to 24 weeks of open-label rilonacept 160 mg (or 2.2 mg/kg for pediatric subjects) SC injections once weekly based on their clinical status and at the discretion of the investigator, after signing LTE informed consent. Any subject who, in the opinion of investigator, should not continue open-label rilonacept are offered participation in the LTE off study drug and after signing LTE informed consent.

[0151] The endpoints assessed in this phase are listed below. Each endpoint is summarized through Week 24, by subjects who do and do not have an adjudicated pericarditis recurrence in the RW period, respectively, and overall:

- Number (percentage) of subjects with pericarditis recurrences
- Proportion of subjects with Clinical Response
- Change over time in CRP levels
- Change over time in the subject's assessments of pericarditis pain
- Percentage of days with no or minimal pain
- PGIPS
- PGA-PA
- Change over time in the SF-36 Physical Component Score
- Change over time in the SF-36 Mental Component Score
- Change in the EQ-5D-5L
- Change over time in the subject's sleep quality assessed with the ISI
- Change over time in ISI categories
- Number (percentage) of subjects requiring addition of SOC pericarditis therapy.

[0152] (5) Long Term Extension Follow-up Period (LTE-FUP) (24 weeks), during which all subjects in the LTE-TP are followed in the LTE-FUP for safety and potential pericarditis recurrences.

Efficacy and Safety Assessments

[0153] Efficacy assessments include the following: daily pericarditis pain on the 11 point NRS in the subject's electronic diary, CRP level, electrocardiogram (ECG), echocardiography (ECHO), patient Global Impression of Pericarditis Severity (PGIPS), physician Global Assessment of Pericarditis Activity (PGA-PA), 36 Item Short Form Health Survey (SF 36), 5-Level EuroQoL-5D (EQ 5D 5L), insomnia Severity Index (ISI), cardiac magnetic resonance imaging (in a substudy in approximately 10 subjects).

[0154] Pharmacokinetic or pharmacodynamic assessments include: PK analysis, anti-rilonacept antibodies, biomarkers, and/or peripheral blood mononuclear cell isolation (for subjects who sign the separate informed consent for pharmacogenomics assessments)

[0155] Safety assessments during the study will include: physical examination, vital signs measurements, adverse event (AE) monitoring, chest x ray, tuberculosis screening.

[0156] In order to control the overall 1 sided type I error rate at the 0.025 level, a gatekeeping procedure in combination with Hochberg's procedure will be applied to testing the primary and major efficacy secondary endpoints.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US20060171948A1 [0005]

Non-patent literature cited in the description

- **VAN TASSELL et al.**Circulation, 2013, vol. 128, 171910-23 [0005]
- **BRUCATO et al.**JAMA, 2016, vol. 316, 181906-1912 [0005]
- **CALABUIG et al.**Rev Esp Cardiol, 2017, vol. 70, 3208-219 [0006]
- **EISENBERG et al.**World Allergy Organization Journal, vol. 207, 10A38- [0006]
- **ALTSCHUL et al.**Basic local alignment search toolJ Mol. Biol., 1990, vol. 215, 3403-410 [0048]
- **ALTSCHUL et al.**Methods in Enzymology, [0048]
- **ALTSCHUL et al.**Nucleic Acids Res., 1997, vol. 25, 3389-3402 [0048]
- **BAXEVANIS et al.**Bioinformatics: A Practical Guide to the Analysis of Genes and ProteinsWiley19980000 [0048]
- Bioinformatics Methods and ProtocolsMethods in Molecular BiologyHumana Press19990000vol. 132, [0048]
- **KHANDAKER et al.**Mayo Clin Proc., 2010, vol. 85, 572-593 [0062]
- **IMAZIO et al.**Circulation, 2010, vol. 121, 916-928 [0062]
- **ZAYAS et al.**Am J Cardiol., 1995, vol. 75, 378-382 [0062]
- **IMAZIO**Revista Espanola de Cardiologia, 2014, vol. 67, 5345-348 [0062] [0062]
- **ADLER et al.**Eur Heart J, 2015, vol. 36, 422921-64 [0062] [0062]
- **IMAZIO et al.**American Journal of Cardiology, 2005, vol. 96, 5736-739 [0062]
- **CANTARINI et al.**Autoimmunity Reviews, 2015, vol. 14, 90-97 [0062] [0064]
- **DORIA et al.**Autoimmunity Reviews, 2012, vol. 12, 22-30 [0062] [0064]
- **MAISCH et al.**Eur Heart J, 2004, vol. 25, 587-610 [0063]
- **IMAZIO et al.**Circulation, 2005, vol. 112, 2012-2016 [0063]

- **LOTRIONTE et al.**Am Heart J, 2010, vol. 160, 662-670 [0063]
- **BASKAR et al.**Cardiol Res Pract, 2016, vol. 2016, 7840724- [0063]
- **HOFFMANPATEL**Arthritis and Rheum, 2004, vol. 50, 2345-349 [0065]
- **BRUCATO et al.**JAMA, 2016, vol. 316, 181906-1912 [0065]
- **LAZAROS et al.**J Cardiovasc Med, 2016, vol. 17, 4256-62 [0065]
- **MORIN et al.**Sleep, 2011, vol. 34, 5601-608 [0094]
- **ADLER et al.**European Heart Journal, 2015, vol. 36, 422921-2964 [0112]
- **MANNION et al.**Nature Clinical Practice Rheumatology, 2007, vol. 3, 11610-18 [0120]
- **HAYS et al.**Qual Life Res, 2009, vol. 18, 873-880 [0122]

PATENTKRAV

1. Rilonacept til anvendelse i en fremgangsmåde til behandling af tilbagevendende idiopatisk pericarditis hos et individ, der er 18 år eller ældre, omfattende administration til individet af en initialdosis af rilonacept, der indgives som to injektioner på 160 mg hver og én eller flere vedligeholdelsesdoser på 160 mg rilonacept pr. uge for at forbedre, stabilisere eller reducere ét eller flere symptomer på tilbagevendende idiopatisk pericarditis i forhold til en kontrol, hvor kontrollen indikerer det ene eller flere symptomer på tilbagevendende idiopatisk pericarditis hos individet før behandlingen.

2. Rilonacept til anvendelse ifølge krav 1, hvor individet ikke modtager samtidig behandling mod tilbagevendende pericarditis.

3. Rilonacept til anvendelse ifølge krav 1 eller 2, hvor trinnet med administration omfatter subkutan administration.

4. Rilonacept til anvendelse ifølge et hvilket som helst af de foregående krav, hvor det ene eller flere symptomer på pericarditis hos individet før behandlingen omfatter en C-reaktivt protein- (CRP) værdi på mere end 1 mg/dL.

5. Rilonacept til anvendelse ifølge krav 4, hvor CRP-niveauet reduceres til mindre end 1 mg/dL inden for 2 uger, inden for 1 uge, inden for 6 dage, inden for 5 dage, inden for 4 dage, inden for 3 dage, inden for 2 dage eller inden for 1 dag efter den første administration sf rilonacept.

6. Rilonacept til anvendelse ifølge et hvilket som helst af de foregående krav, hvor det ene eller flere symptomer på pericarditis vurderes efter en numerisk vurderingsskala (NRS) til vurdering af pericarditissmerte.

7. Rilonacept til anvendelse ifølge krav 6, hvor NRS-scoren reduceres til 2 eller mindre inden for 3 uger, inden for 2 uger eller inden for 1 uge efter den første administration af rilonacept.

8. Rilonacept til anvendelse ifølge et hvilket som helst af de foregående krav, hvor individet før behandlingen har mindst én tilbagevendende episode med pericarditis med mindst 1 dag med

pericarditissmerte med en måling af pericarditissmerte ≥4 på den 11-punkts numeriske vurderingsskala (NRS) og/eller et C-reaktivt protein- (CRP) niveau ≥1 mg/dL.

DRAWINGS

Drawing

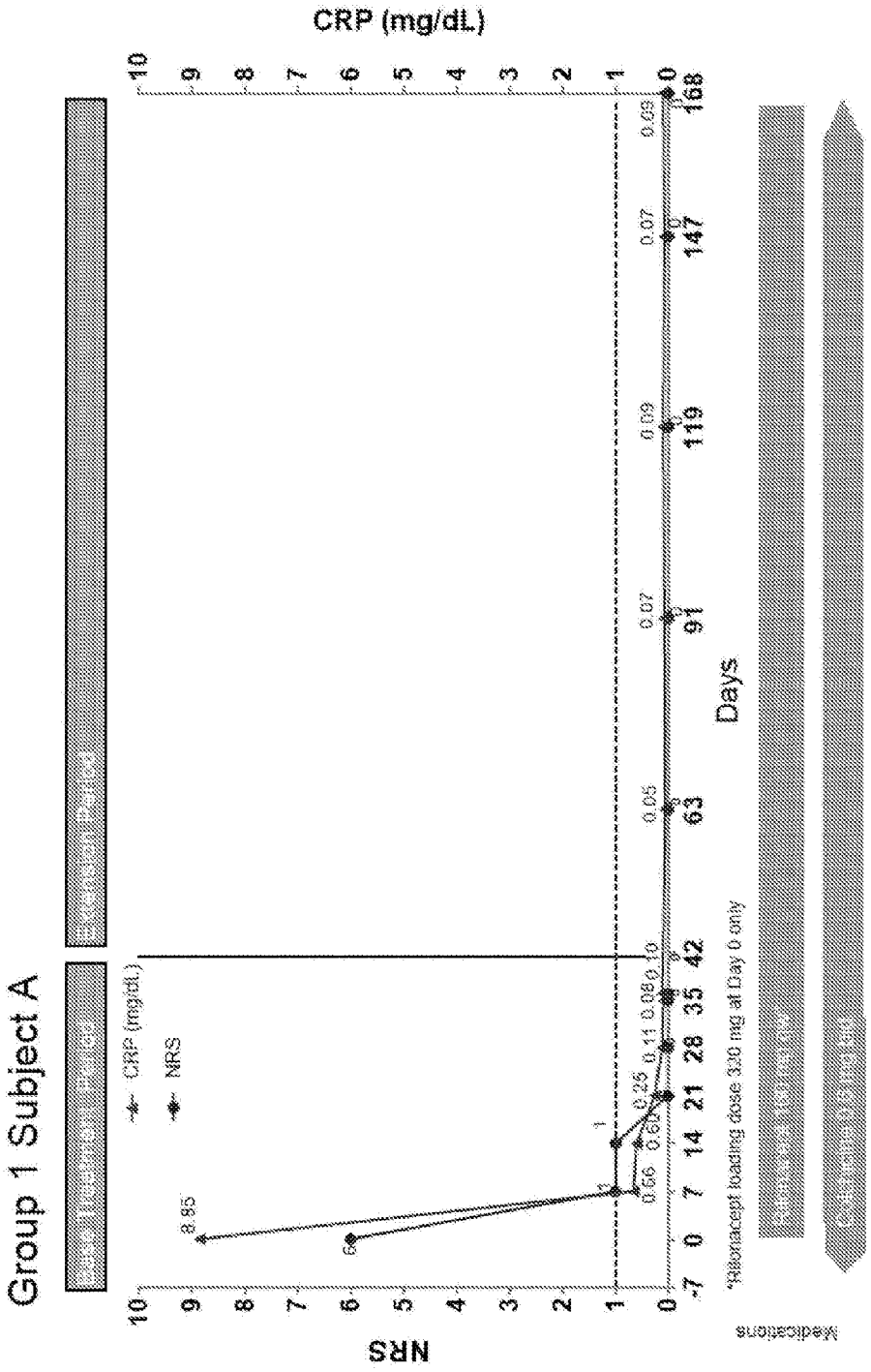

FIGURE 1A

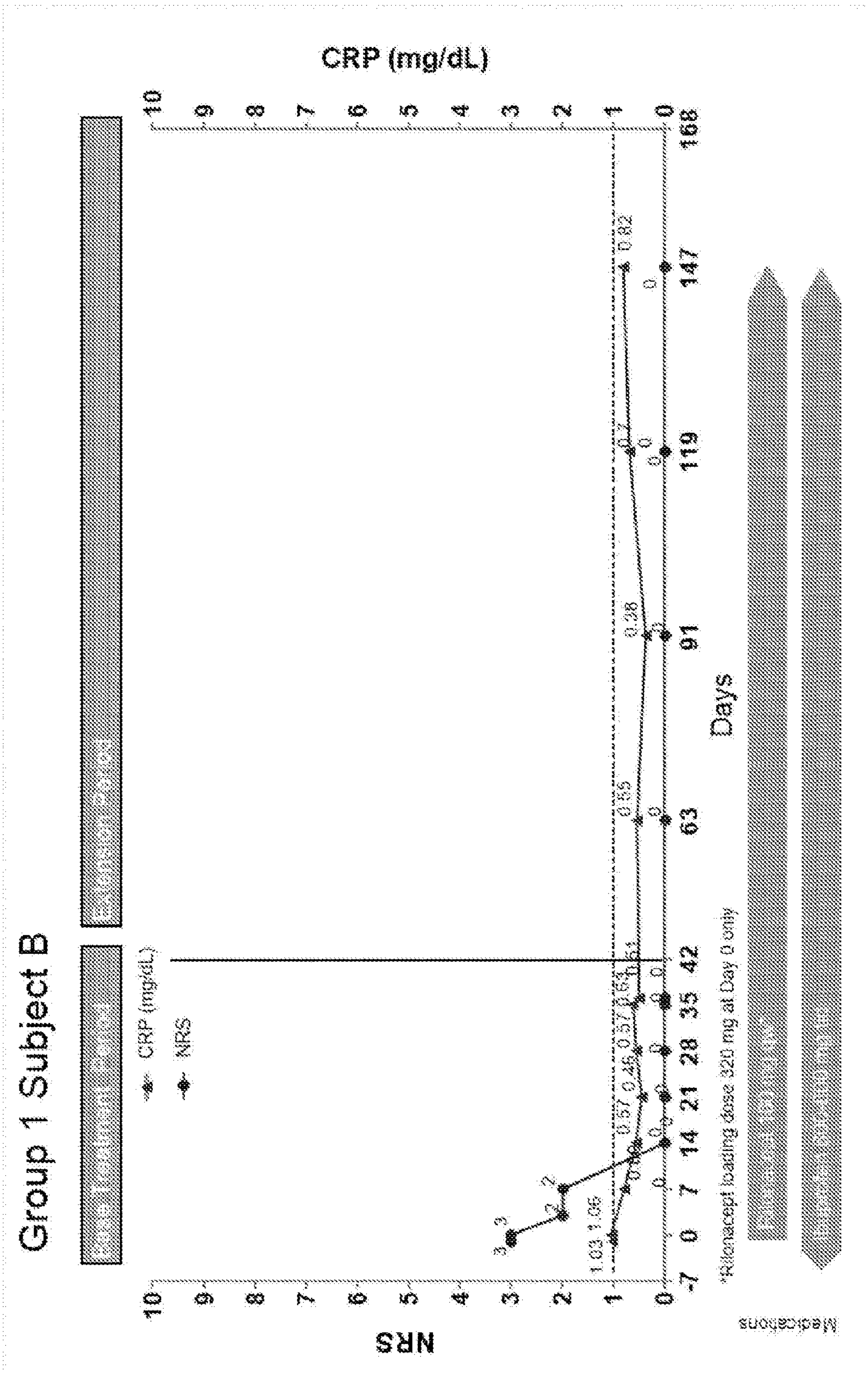
Group 1 Subject B
Base Treatment Period
Extension Period
CRP (mg/dL)
NRS
CRP (mg/dL)
NRS
Days
-7
0
7
14
21
28
35
42
63
91
119
147
168
*Rilonacept loading dose 320 mg at Day 0 only
Medications

FIGURE 1B

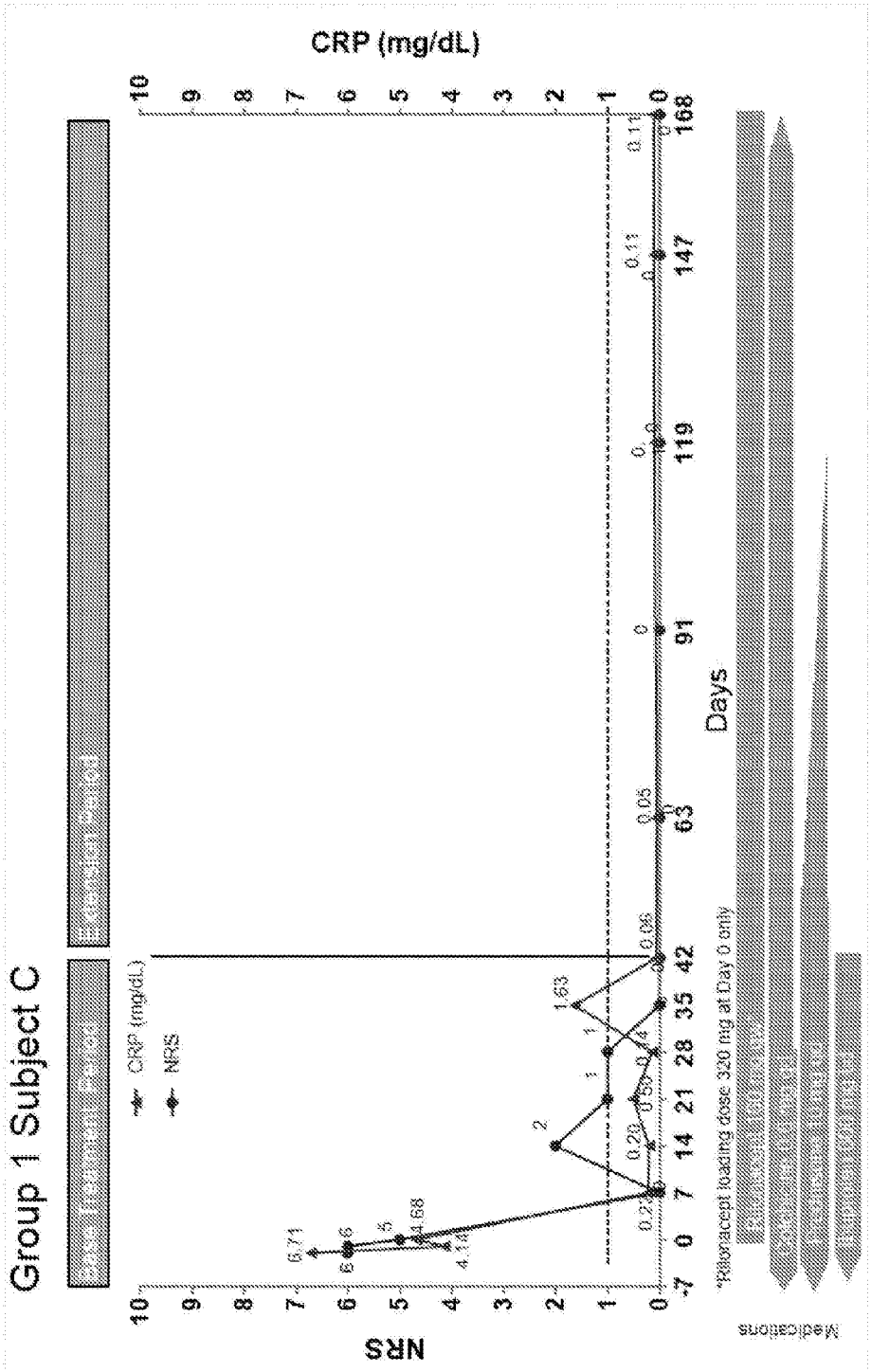
Group 1 Subject C
Pre-Treatment Period
Extension Period
CRP (mg/dL)
NRS
Days
Medications
*Olanzapine loading dose 320 mg at Day 0 only

FIGURE 1C

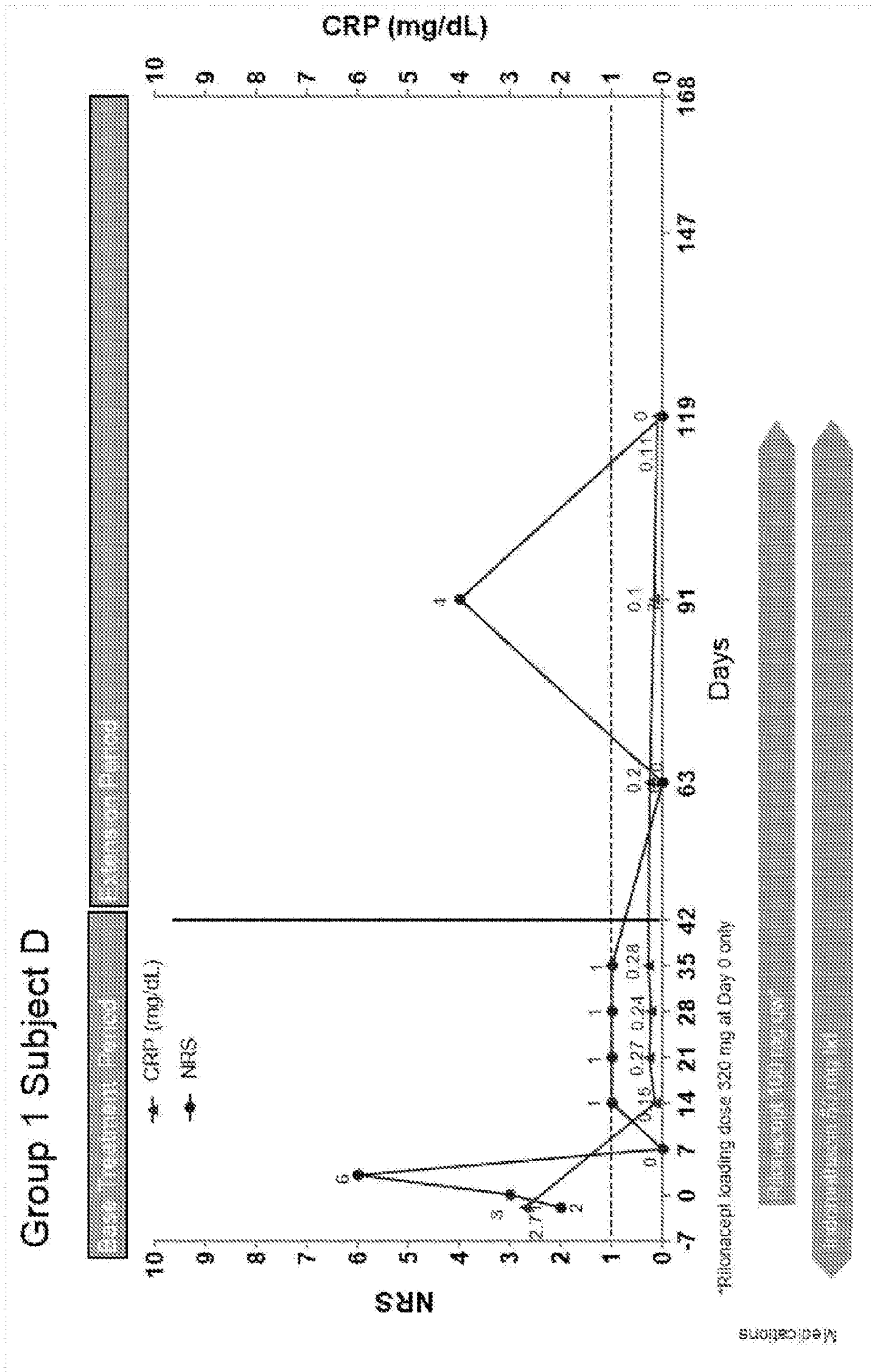
Group 1 Subject D
CRP (mg/dL)
NRS
Days
*Rilonacept loading dose 320 mg at Day 0 only
Medications

FIGURE 1D

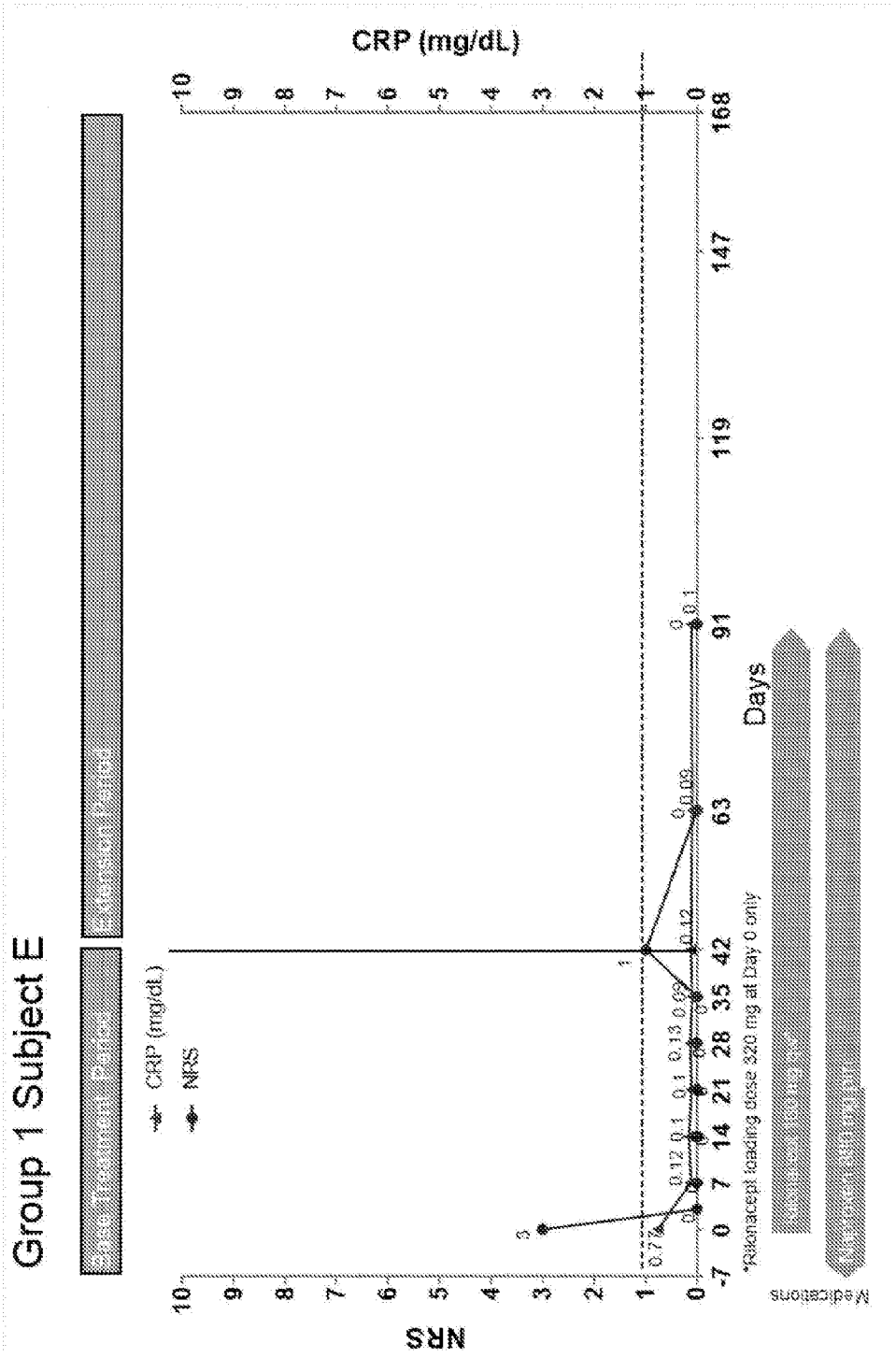
Group 1 Subject E
Study Treatment Period
Extension Period
CRP (mg/dL)
NRS
CRP (mg/dL)
NRS
Days
-7 0 7 14 21 28 35 42 63 91 119 147 168
*Ronacept loading dose 320 mg at Day 0 only
Medications

FIGURE 1E

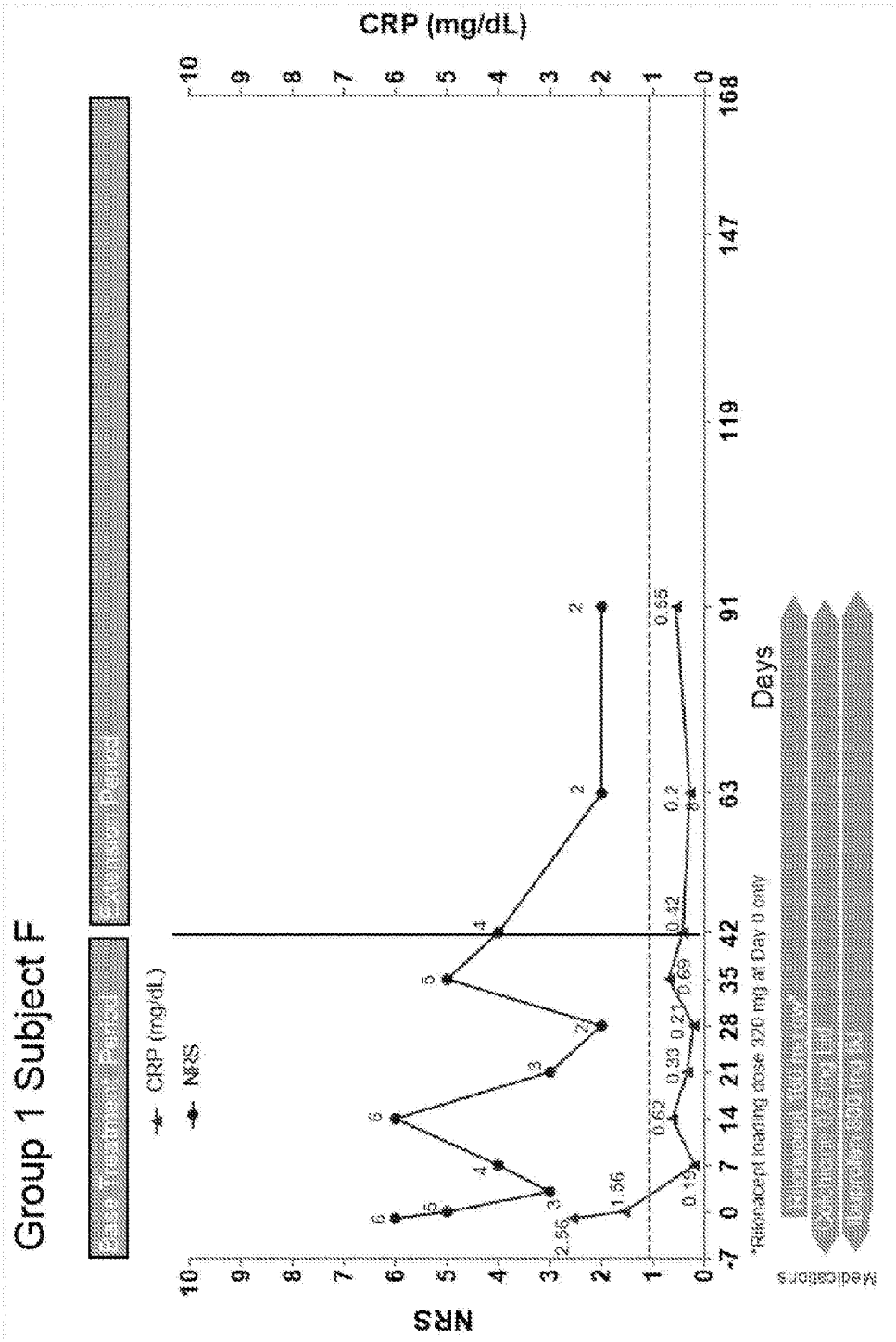
Group 1 Subject F
Baseline Treatment Period
Extension Period
CRP (mg/dL)
NRS
Days
CRP (mg/dL)
NRS
*Rilonacept loading dose 320 mg at Day 0 only
Medications

FIGURE 1F

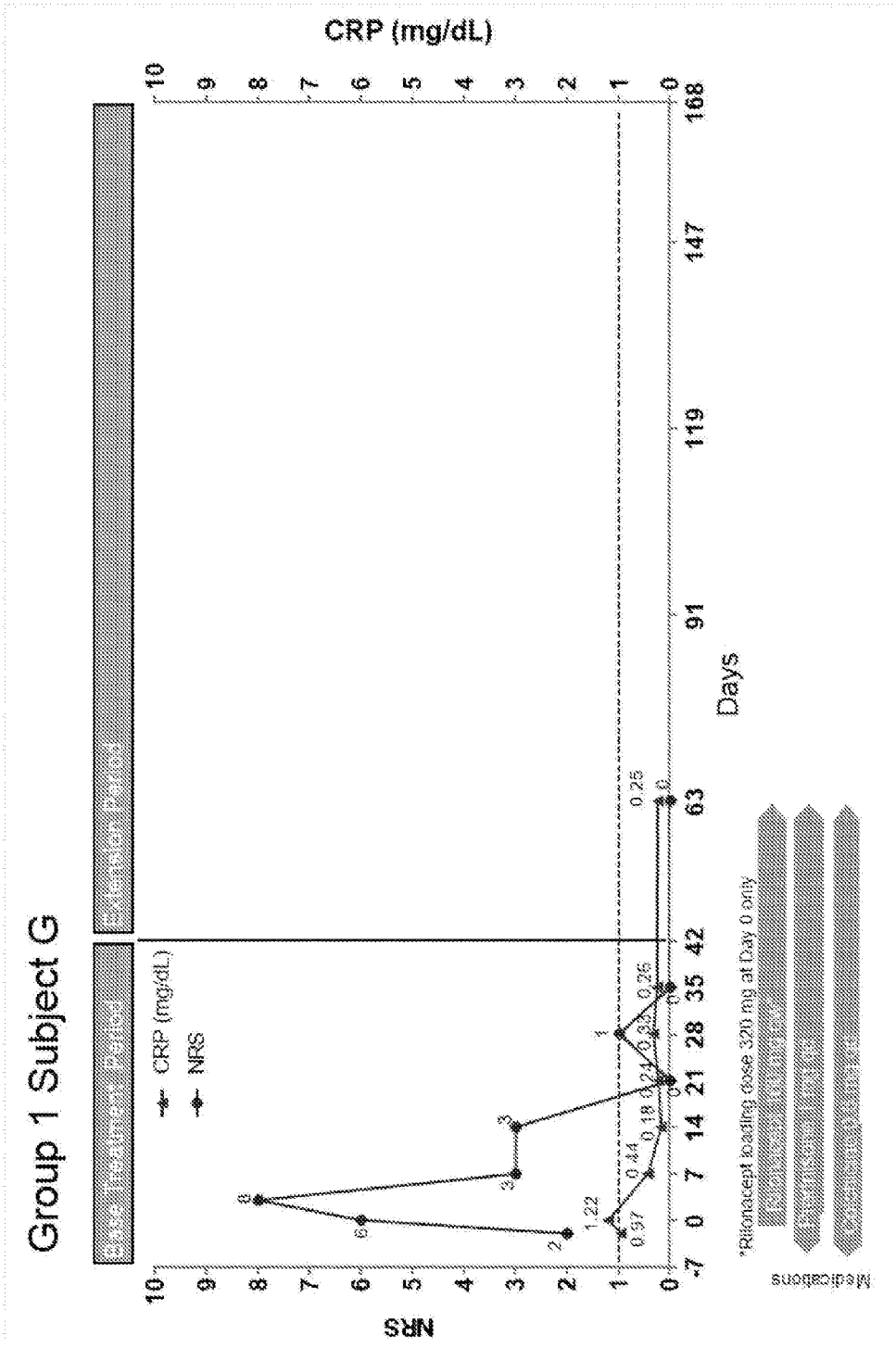
Group 1 Subject G
Base Treatment Period
Extension Period
CRP (mg/dL)
NRS
Days
CRP (mg/dL)
NRS
*Rilonacept loading dose 320 mg at Day 0 only
Medications

FIGURE 1G

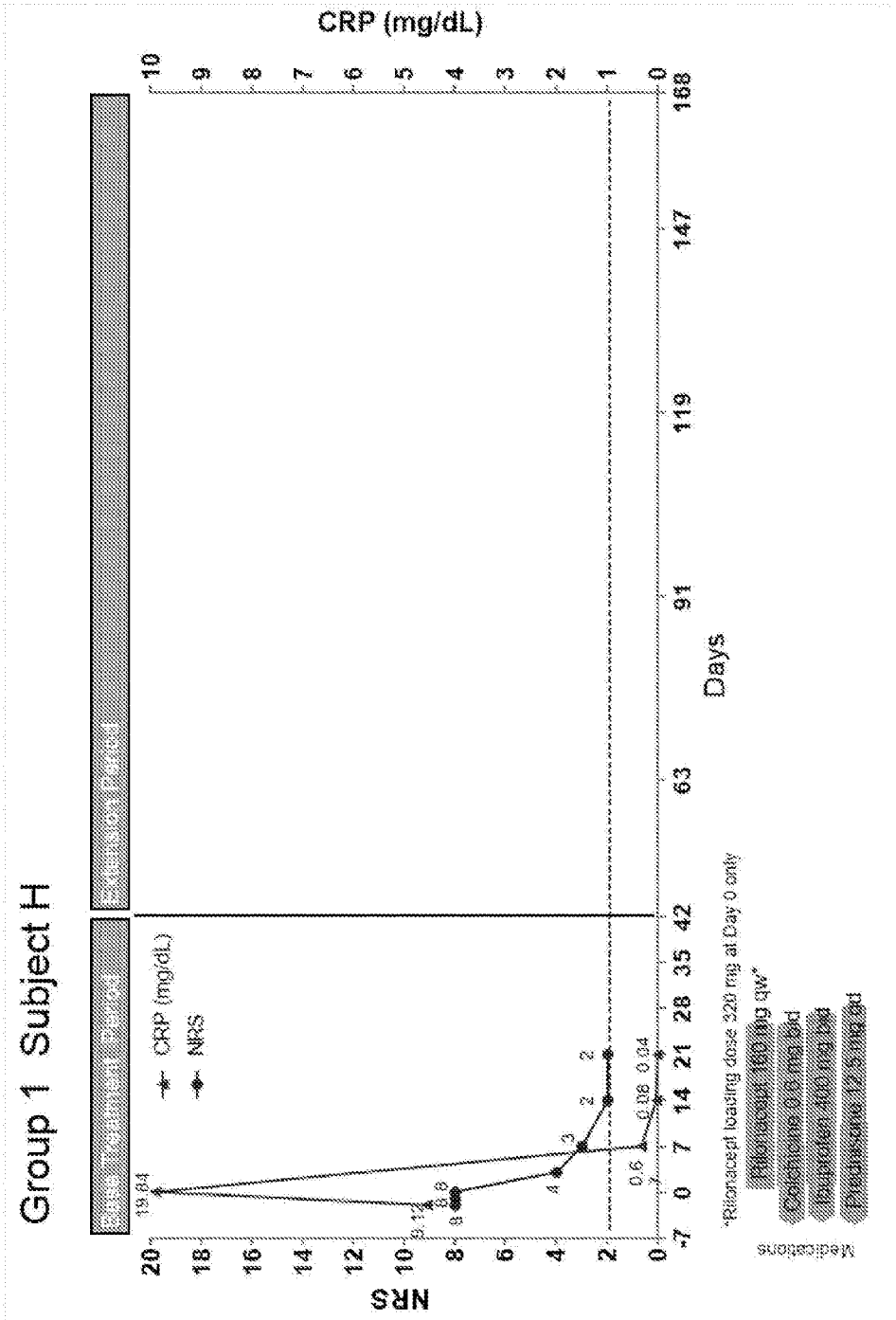
Group 1 Subject H
Baseline Period
Extension Period
CRP (mg/dL)
NRS
Days
Medications
*Rilonacept loading dose 320 mg at Day 0 only
Rilonacept 160 mg qw*
Colchicine 0.6 mg bid
Ibuprofen 600 mg tid
Prednisone 12.5 mg qd

FIGURE 1H

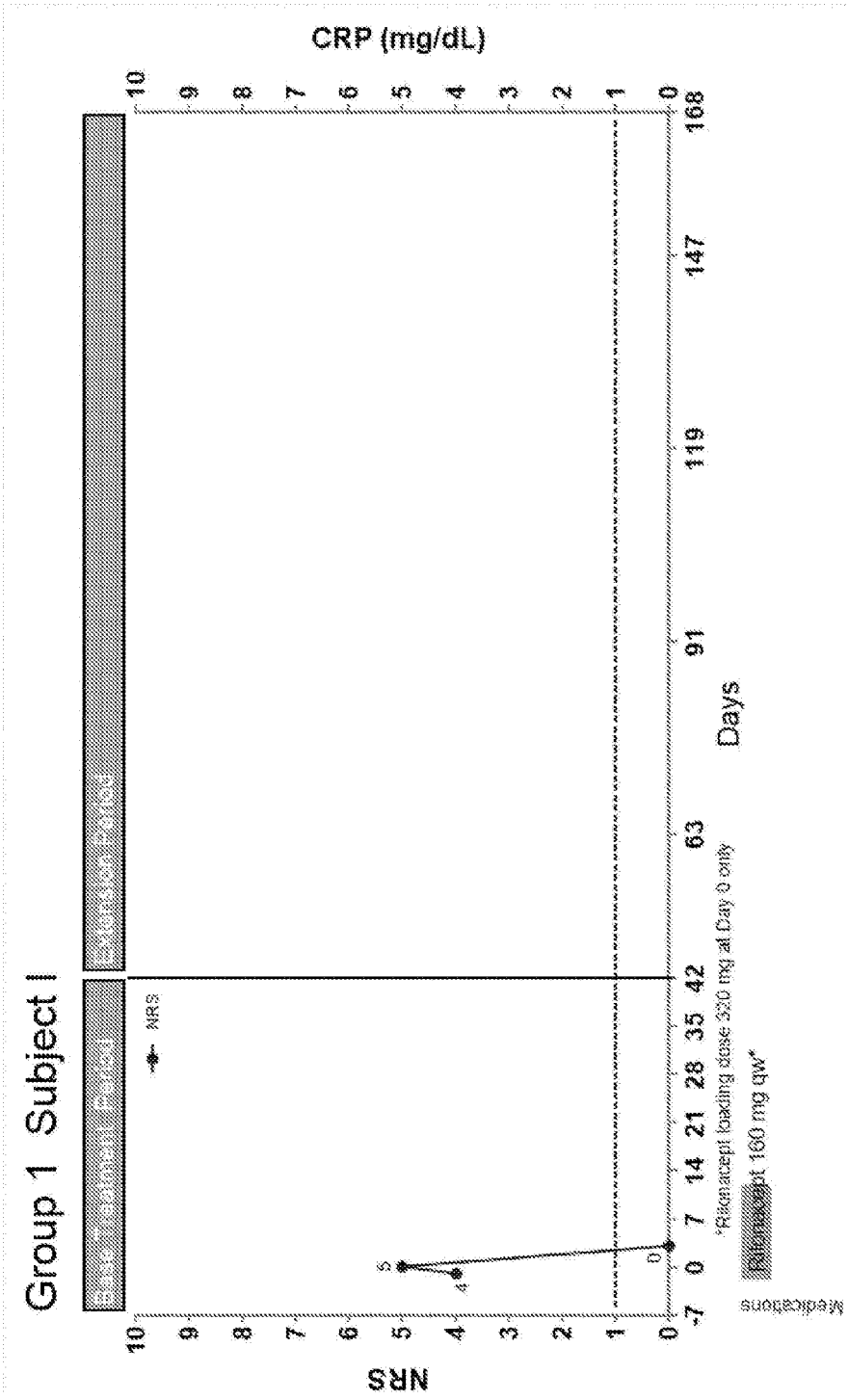
Group 1 Subject I
Baseline Period
Extension Period
NRS
CRP (mg/dL)
MRS
Days
*Rilonacept loading dose 320 mg at Day 0 only
Rilonacept 160 mg qw*
Medications
-7 0 7 14 21 28 35 42 63 91 119 147 168
0 1 2 3 4 5 6 7 8 9 10

FIGURE 11

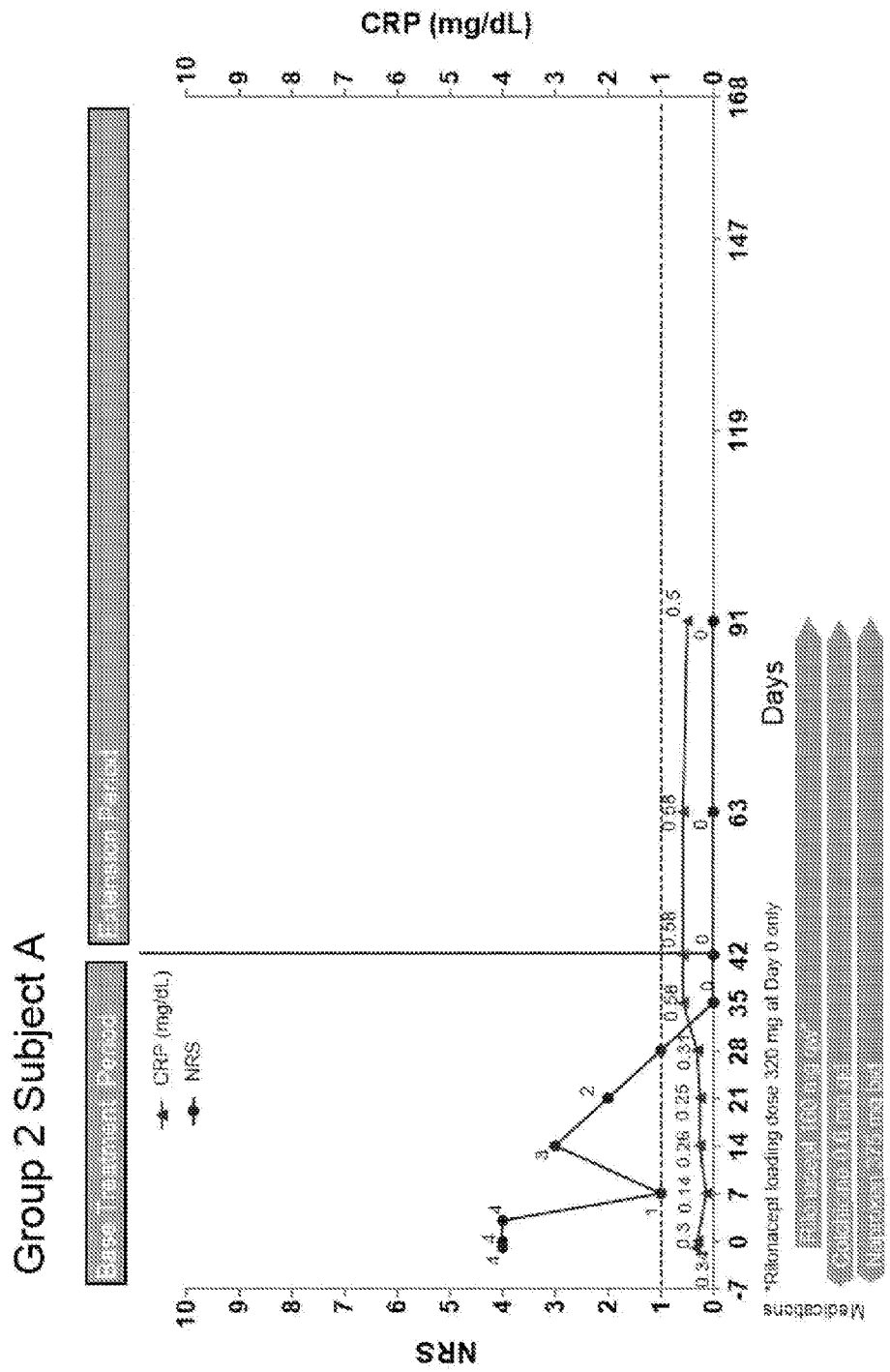
Group 2 Subject A
Base Treatment Period
Extension Period
CRP (mg/dL)
NRS
Days
CRP (mg/dL)
NRS
*Rilonacept loading dose 320 mg at Day 0 only
Medications

FIGURE 2A

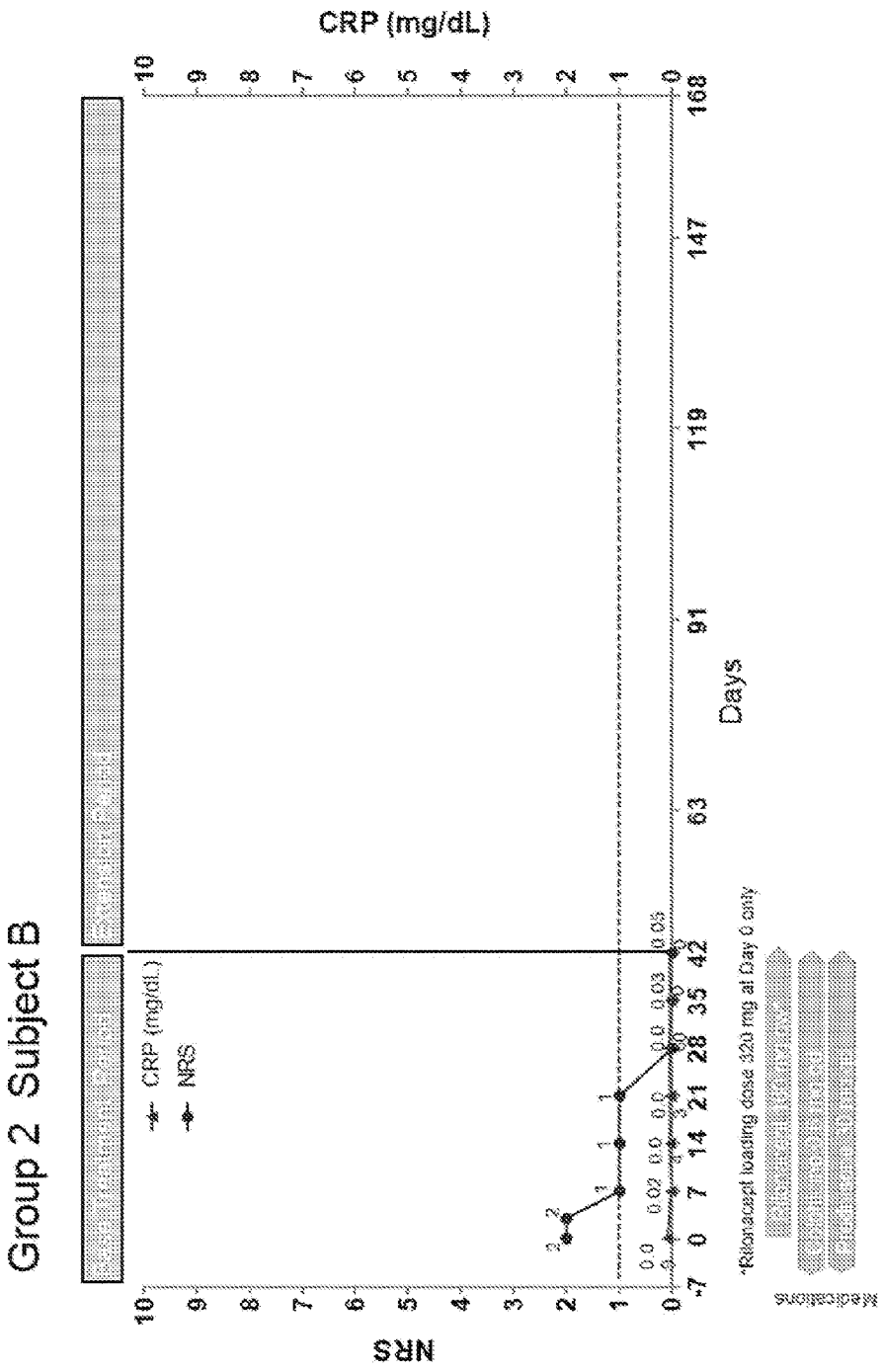
Group 2 Subject B
CRP (mg/dL)
NRS
Days
CRP (mg/dL)
NRS
*Rilonacept loading dose 320 mg at Day 0 only
Medications

FIGURE 2B

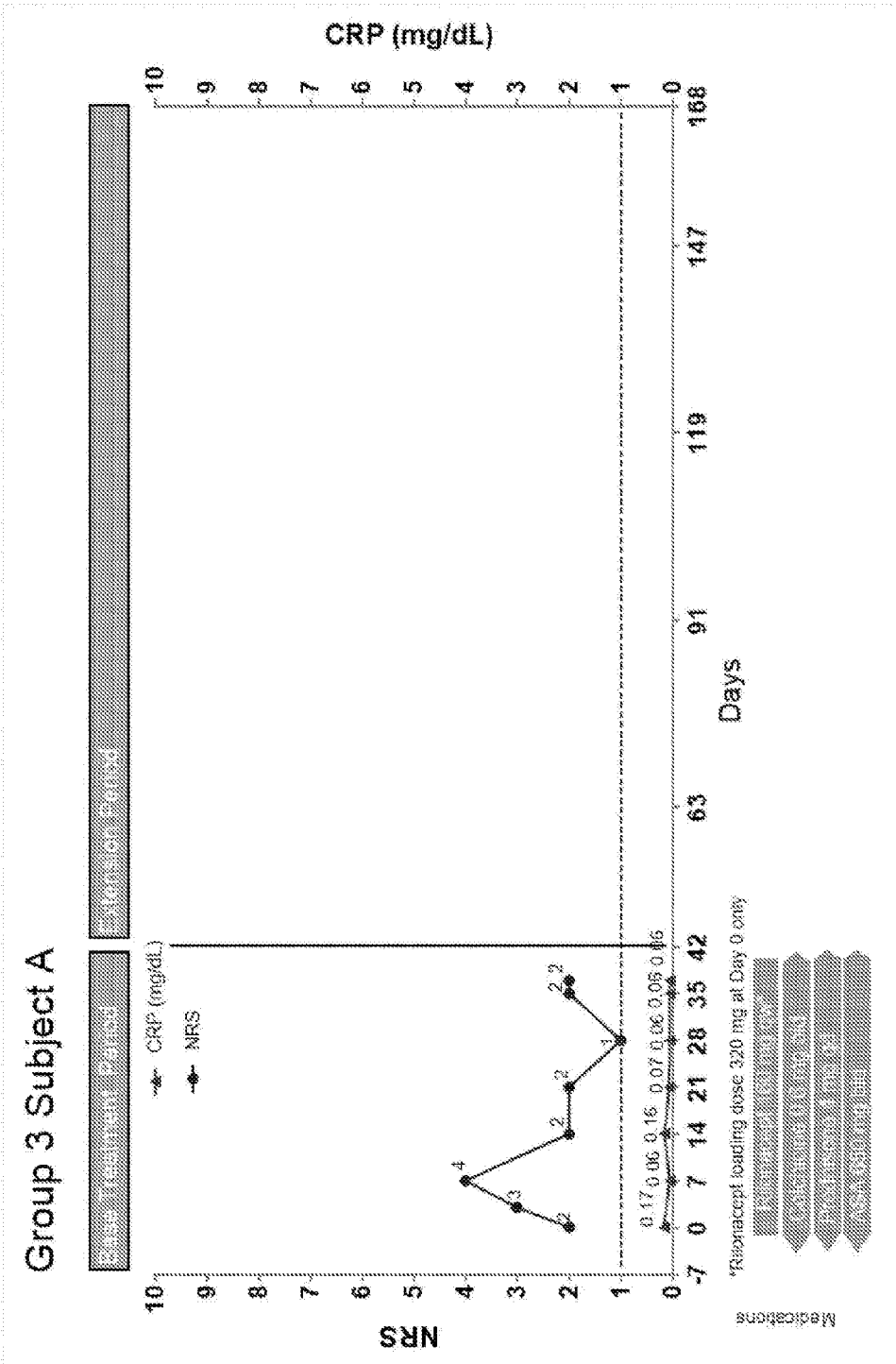
Group 3 Subject A
Study Treatment Period
Follow-up Period
CRP (mg/dL)
NRS
Days
Medications
*Rilonacept loading dose 320 mg at Day 0 only

FIGURE 3A

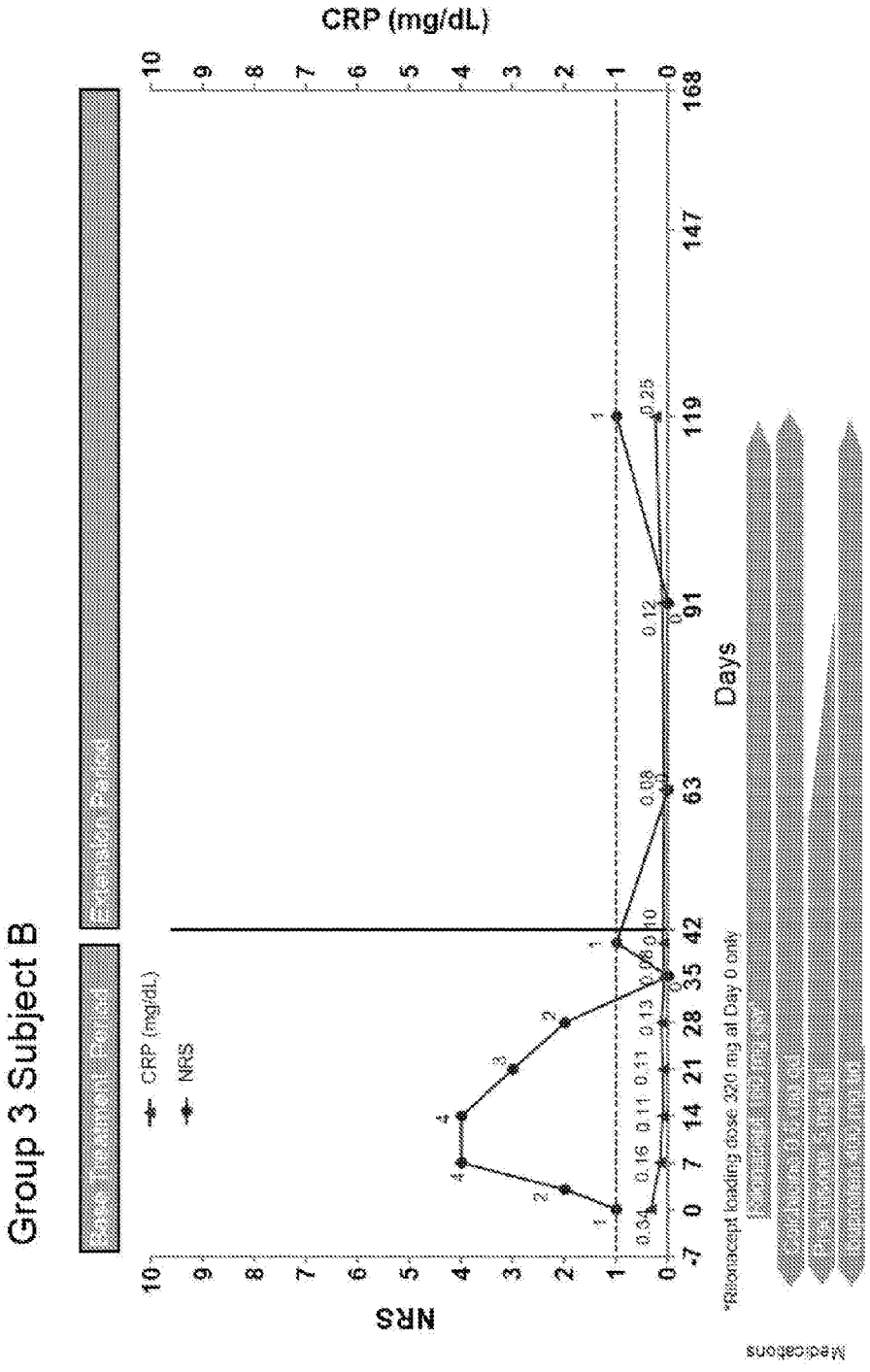
Group 3 Subject B
Baseline/Run-In Period
Extension Period
CRP (mg/dL)
NRS
Days
Medications
*Rilonacept loading dose 320 mg at Day 0 only

FIGURE 3B

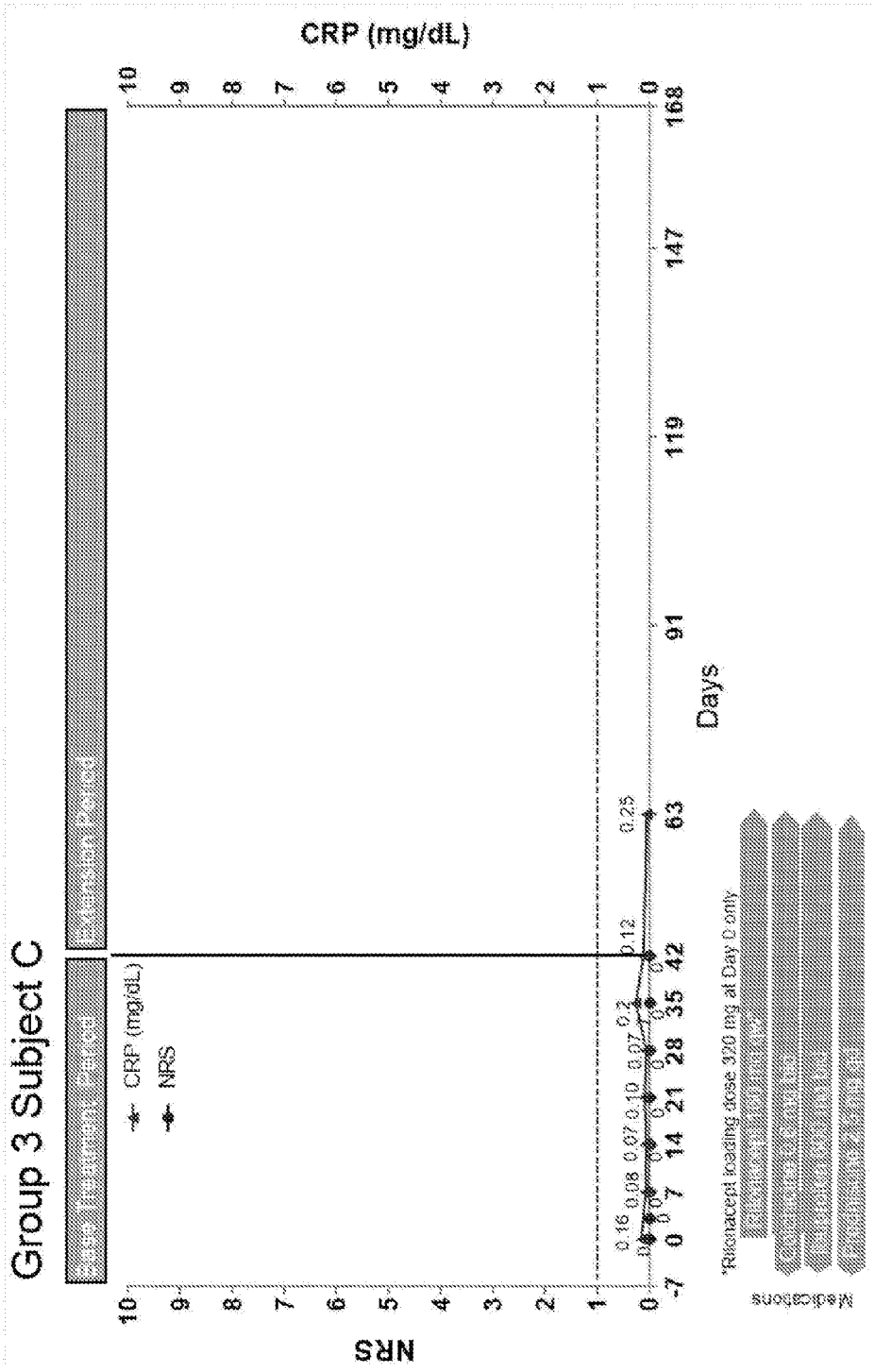
Group 3 Subject C
Active Treatment Period
Extension Period
CRP (mg/dL)
NRS
Days
*Rilonacept loading dose 320 mg at Day 0 only
Medications

FIGURE 3C

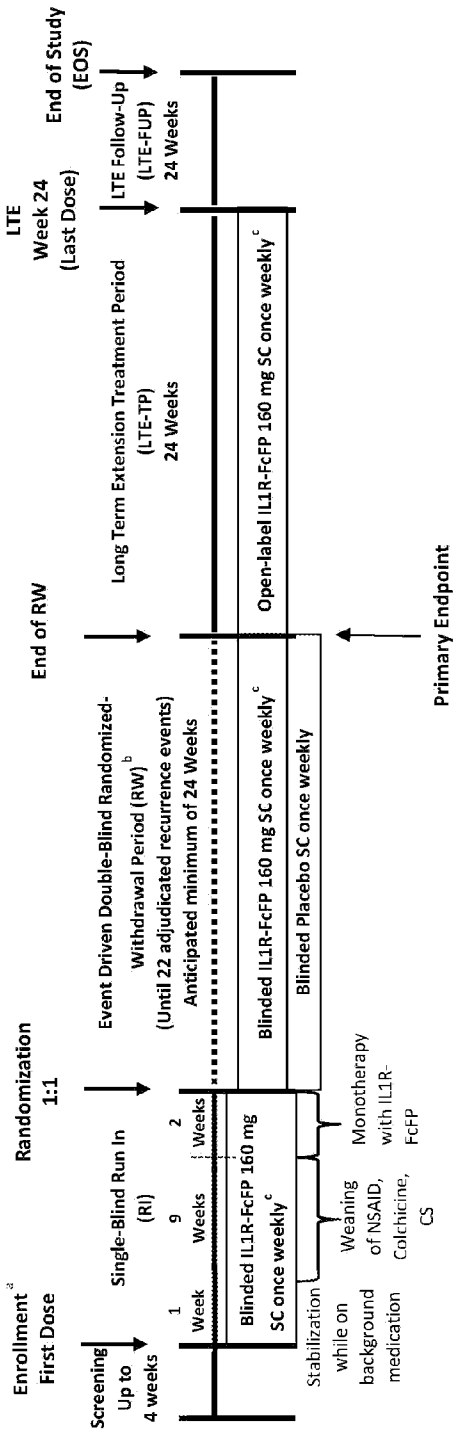
Enrollment [a]
First Dose
Screening
Up to
4 weeks
Randomization
1:1
Single-Blind Run In
(RI)
1
Week
9
Weeks
2
Weeks
Blinded IL1R-FcFP 160 mg
SC once weekly [c]
Stabilization
while on
background
medication
Weaning
of NSAID,
Colchicine,
CS
Monotherapy
with IL1R-
FcFP
Event Driven Double-Blind Randomized-
Withdrawal Period (RW) [b]
(Until 22 adjudicated recurrence events)
Anticipated minimum of 24 Weeks
Blinded IL1R-FcFP 160 mg SC once weekly [c]
Blinded Placebo SC once weekly
End of RW
Primary Endpoint
Long Term Extension Treatment Period
(LTE-TP)
24 Weeks
Open-label IL1R-FcFP 160 mg SC once weekly [c]
LTE
Week 24
(Last Dose)
LTE Follow-Up
(LTE-FUP)
24 Weeks
End of Study
(EOS)

FIGURE 4

SEKVENSLISTE

Sekvenslisten er udeladt af skriftet og kan hentes fra det Europæiske Patent Register.

The Sequence Listing was omitted from the document and can be downloaded from the European Patent Register.