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(54) **Title:** METHODS OF TREATING SYSTEMIC LUPUS ERYTHEMATOSUS, SCLERODERMA, AND MYOSITIS WITH AN ANTIBODY AGAINST INTERFERON-ALPHA

(57) **Abstract:** The disclosure relates to methods of treating systemic lupus erythematosus, scleroderma, and myositis comprising the administration of an anti-interferon-alpha antibody. Specifically, the disclosure provides weight-based and fixed dose administration regimes based on pharmacokinetic characteristics. Further disclosed are sequences of complementarity determining regions (CDRs) of heavy chain and light chain variable regions of the antibody. The methods of suppressing an interferon (I FN) pharmacodynamic signature are also provided.



**METHODS OF TREATING SYSTEMIC LUPUS ERYTHEMATOSUS, SCLERODERMA,
AND MYOSITIS WITH AN ANTIBODY AGAINST INTERFERON-ALPHA**

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BACKGROUND OF THE DISCLOSURE**FIELD OF THE DISCLOSURE**

[0001] The present disclosure provides methods for treatment of autoimmune diseases such as systemic lupus erythematosus, scleroderma, and myositis with anti-IFN-alpha antibodies.

BACKGROUND ART

[0002] Type I interferons (IFN) (IFN-alpha, IFN-beta, IFN-omega, IFN-tau) are a family of structurally related cytokines having antiviral, antitumor and immunomodulatory effects (Hardy *et al.* (2001) Blood 97:473; Cutrone and Langer (2001) J. Biol. Chem. 276:17140). The human IFN-alpha locus includes two subfamilies. The first subfamily consists of at least 14 non allelic genes and 4 pseudogenes having at least 75% homology. The second subfamily, alpha-II or omega, contains 5 pseudogenes and 1 functional gene which exhibits 70% homology with the IFN-alpha genes. The subtypes of IFN-alpha have different specific activities but they possess the same biological spectrum (Streuli *et al.* (1981) Proc. Natl. Acad. Sci. USA 78:2848) and have the same cellular receptor (Agnat M. *et al.* (1983) in "Interferon 5" Ed. I. Gresser p. 1-22, Academic Press, London).

[0003] Increased expression of type I interferons has been described in numerous autoimmune diseases (Foulis *et al.* (1987) Lancet 2:1423; Hooks *et al.* (1982) Arthritis Rheum 25:396; Hertzog *et al.* (1988) Clin. Immunol. Immunopathol. 48:192; Hopkins and Meager (1988) Clin. Exp. Immunol. 73:88; Arvin and Miller (1984) Arthritis Rheum. 27:582). The most studied examples of

this are insulin-dependent diabetes mellitus (IDDM) (Foulis (1987) *supra*), systemic lupus erythematosus (SLE) (Hooks (1982) *supra*; Blanco *et al.* (2001) *Science* 294:1540; Ytterberg and Schnitzer (1982) *Arthritis Rheum.* 25:401; Batteux *et al.* (1999) *Eur. Cytokine Netw.*:509), and autoimmune thyroiditis (Prummel and Laurberg (2003) *Thyroid* 13:547; Mazziotti *et al.* (2002) *J. Endocrinol. Invest.* 25:624; You *et al.* (1999) *Chin. Med. J.* 112:61; Koh *et al.* (1997) *Thyroid* 7:891), which are all associated with elevated levels of IFN α , and rheumatoid arthritis (RA) (Hertzog (1988), Hopkins and Meager (1988), Arvin and Miller (1984), *supra*) in which IFN-beta may play a more significant role. For a review on the role of IFN-alpha on organ-targeted autoimmune and inflammatory diseases see Crow (2010) *Arthritis Res. Ther.* 12:S5.

[0004] Systemic Lupus Erythematosus (SLE), often referred to as lupus, is a prototypic systemic autoimmune disease. The disease includes constitutional symptoms and signs, musculoskeletal, cutaneous, renal, gastrointestinal, pulmonary, cardiac, reticuloendothelial, hematological and neuropsychiatric manifestations. The cutaneous manifestations are among the most common in SLE. A substantial body of evidence suggests type I interferons (IFNs), particularly IFN-alpha, play a key role in the pathogenesis of systemic lupus erythematosus (SLE). For a review on the use of anticytokine therapy in the treatment of SLE see Yoo (2010) *Lupus* 19:1460.

[0005] Scleroderma, or systemic sclerosis (SSC), is a progressive, debilitating autoimmune disorder characterized by excess protein deposition into the extracellular matrix by dermal fibroblasts, also referred to as dermal fibrosis. Patients with diffuse cutaneous disease often present unique markers such as upregulation of type I interferon (IFN)-induced genes in skin. Supporting the idea that IFN plays a role in dermal fibrosis are recent reports of scleroderma arising in patients receiving IFN therapy for chronic viral infection. For a review of systemic sclerosis, see Varga & Abraham (2007) *J. Clin. Invest.* 117:557-567. See also Coelho *et al.* (2008) *Immunol. Lett.* 118:110-115.

[0006] Myositis, a general term for inflammation of the muscles, is a group of conditions that are frequently associated with autoimmune conditions. Types of myositis include, *e.g.*, myositis ossificans, fibromyositis, (idiopathic) inflammatory

myopathies, dermatomyositis, juvenile dermatomyositis, polymyositis, inclusion body myositis, and pyomyositis

[0007] Administration of IFN-alpha has been reported to exacerbate underlying disease in patients with psoriasis, autoimmune thyroiditis and multiple sclerosis and to induce an SLE like syndrome in patients without a previous history of autoimmune disease. Interferon α has also been shown to induce glomerulonephritis in normal mice and to accelerate the onset of the spontaneous autoimmune disease of NZB/W mice. Further, IFN-alpha therapy has been shown in some cases to lead to undesired side effects, including fever and neurological disorders. Thus, there are pathological situations in which inhibition of IFN-alpha activity may be beneficial to the patient and a need exists for methods of treatment effective in inhibiting IFN-alpha activity.

BRIEF SUMMARY OF THE DISCLOSURE

[0008] The disclosure provides methods of treating autoimmune diseases such as SLE, SSC, and myositis in a human subject comprising administration of an anti-interferon alpha antibody. These methods can be used for therapeutic, including prophylactic, purposes, for example in situations where the production or expression of interferon alpha is associated with pathological symptoms. In some embodiments sifalimumab (MEDI-545), an investigational fully human IgG1 monoclonal antibody against interferon-alpha, is used.

[0009] In one embodiment, the disclosure provides a method of treating an autoimmune disorder in a human subject comprising administering to the subject an antibody, or antigen-binding fragment thereof, which specifically binds to human interferon alpha, wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL, CL_{ss}, CL/F, or CL_{ss}/F) of between about 99 and about 432 mL/day, an apparent volume of distribution (V_{ss} or V_Z/F) of between about 3 and about 17 L, and a serum half-life of about 14 days to about 48 days is achieved following the administration; and wherein the autoimmune disorder is systemic lupus erythematosus, scleroderma, or myositis.

[0010] In some embodiments, the antibody or antigen binding fragment thereof binds an epitope on human interferon alpha recognized by an antibody

comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22. In other embodiments, the antibody or antigen binding fragment thereof comprises: (a) a heavy chain variable region CDR1 comprising SEQ ID NO: 1; (b) a heavy chain variable region CDR2 comprising SEQ ID NO: 4; (c) a heavy chain variable region CDR3 comprising SEQ ID NO: 7; (d) a light chain variable region CDR1 comprising SEQ ID NO: 10; (e) a light chain variable region CDR2 comprising SEQ ID NO: 13; and (f) a light chain variable region CDR3 comprising SEQ ID NO: 16. In some other embodiments, the antibody or antigen binding fragment thereof comprises: (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19, SEQ ID NO:34, SEQ ID NO: 35, SEQ ID NO:36 or SEQ ID NO:37; and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22.

[0011] The antibody or antigen binding fragment thereof can be a human antibody, a chimeric antibody, a humanized antibody, or an antigen binding fragment thereof. In some embodiments, the antibody or antigen binding fragment thereof is an IgG1 or IgG4 antibody or antigen-binding fragment thereof. In certain embodiments, the antigen binding fragment is a Fab antibody fragment or a single chain antibody (scFv).

[0012] In some embodiments, the antibody or antigen-binding fragment thereof is administered in a dosage dependent on the subject's body weight. In certain embodiments, such weight-based dosage ranges from about 0.01 mg/kg to about 100 mg/kg of the subject's body weight. In some embodiments, such weight-based dosage is chosen from about 0.3 mg/kg body weight, about 1 mg/kg body weight, about 3 mg/kg body weight, and about 10 mg/kg body weight.

[0013] In other embodiments, the antibody or antigen-binding fragment thereof is administered as a fixed dosage. In certain embodiments, such fixed dosage ranges from about 50 mg to about 2000 mg. In other embodiments, the fixed dosage is chosen from about 100 mg, about 200 mg, about 600 mg, and about 1200 mg.

[0014] In some embodiments, the antibody or antigen-binding fragment thereof is administered as a single dose or is administered in two or more doses once per

week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months, once every six months, or at varying intervals. In some embodiments, a loading dose is administered at Day 14.

[0015] In certain embodiments, the administration is by a route chosen from intravenous, intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, inhalation, and a combination of two or more recited routes.

[0016] In some embodiments, the administration is intravenous (IV) administration. In some embodiments, IV administration is by IV infusion over a period of time. In some embodiments, the time to reach maximum plasma concentration ($T_{\max}$ or $T_{\max ss}$) following IV administration is about 0.13 days or less. In some embodiments, a single IV administration of about 0.3 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.12 days or less, a maximum plasma concentration ($C_{\max}$) of about 7 to about 15 $\mu\text{g/mL}$, an area under the plasma concentration-time curve during a dosage interval (τ) (AUC_{τ}) of about 54 to about 104 $\mu\text{g day/mL}$, and a trough plasma concentration (C_{trough}) of about 2 to about 4 $\mu\text{g/mL}$. In other embodiments, a single IV administration of about 0.3 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.07 days, an average $C_{\max}$ of about 11 $\mu\text{g/mL}$, an average AUC_{τ} of about 79 $\mu\text{g day/mL}$, and an average C_{trough} of about 3 $\mu\text{g/mL}$.

[0017] In some embodiments, a single IV administration of about 1 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.12 days or less, a $C_{\max}$ of about 21 to about 43 $\mu\text{g/mL}$, an AUC_{τ} of about 153 to about 290 $\mu\text{g day/mL}$, and a C_{trough} of about 4 to about 12 $\mu\text{g/mL}$. In some embodiments, a single IV administration of about 1 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.08 days, an average $C_{\max}$ of about 32 $\mu\text{g/mL}$, an average AUC_{τ} of about 221 $\mu\text{g day/mL}$, and an average C_{trough} of about 8 $\mu\text{g/mL}$.

[0018] In some embodiments, a single IV administration of about 3 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.13 days or less, a $C_{\max}$ of about 64 to about 143 $\mu\text{g/mL}$, an AUC_{τ} of

about 469 to about 1010 $\mu\text{g day/mL}$, and a C_{trough} of about 12 to about 35 $\mu\text{g/mL}$. In other embodiments, a single IV administration of about 3 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average T_{max} of about 0.09 days, an average C_{max} of about 103 $\mu\text{g/mL}$, an average AUC_T of about 739 $\mu\text{g day/mL}$, and an average C_{trough} of about 23 $\mu\text{g/mL}$.

[0019] In some embodiments, a single IV administration of about 10 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a T_{max} of about 0.13 days or less, a C_{max} of about 141 to about 318 $\mu\text{g/mL}$, an AUC_T of about 979 to about 2241 $\mu\text{g day/mL}$, and a C_{trough} of about 27 to about 76 $\mu\text{g/mL}$. In other embodiments, a single IV administration of about 10 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average T_{max} of about 0.09 days, an average C_{max} of about 230 $\mu\text{g/mL}$, an average AUC_T of about 1610 $\mu\text{g day/mL}$, and an average C_{trough} of about 52 $\mu\text{g/mL}$.

[0020] In some embodiments, the administration of a sufficient number of IV doses of about 0.3 mg/kg at about 14-day intervals achieves a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\text{max ss}}$ of about 0.60 days or less, a $C_{\text{max ss}}$ of about 11 to about 25 $\mu\text{g/mL}$, an $\text{AUC}_T \text{ ss}$ of about 89 to about 197 $\mu\text{g day/mL}$, and a $C_{\text{trough ss}}$ of about 5 to about 11 $\mu\text{g/mL}$ is achieved.

[0021] In some embodiments, a sufficient number of IV doses of about 0.3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from: an average $T_{\text{max ss}}$ of about 0.17 days, an average $C_{\text{max ss}}$ of about 18 $\mu\text{g/mL}$, an average $\text{AUC}_T \text{ ss}$ of about 143 $\mu\text{g day/mL}$, and an average $C_{\text{trough ss}}$ of about 8 $\mu\text{g/mL}$ is achieved.

[0022] In some embodiments, a sufficient number of IV doses of about 0.3 mg/kg are administered at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 99 and about 271 mL/day, an apparent volume of distribution (V_{ss}) of between about 4 and about 9 L, and a serum half-life of about 15 days to about 43 days is achieved.

- [0023]** In certain embodiments, a sufficient number of IV doses of about 0.3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 185 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 29 days is achieved.
- [0024]** In some embodiments, a sufficient number of IV doses of about 1 mg/kg are administered at about 14-day intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max\ ss}$ of about 0.11 days or less, a $C_{max\ ss}$ of about 29 to about 67 $\mu\text{g/mL}$, an $AUC_{T\ ss}$ of about 213 to about 591 $\mu\text{g day/mL}$, and a $C_{trough\ ss}$ of about 9 to about 30 $\mu\text{g/mL}$ is achieved.
- [0025]** In other embodiments, a sufficient number of IV doses of about 1 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from: an average $T_{max\ ss}$ of about 0.07 days, an average $C_{max\ ss}$ of about 48 $\mu\text{g/mL}$, an average $AUC_{T\ ss}$ of about 197 $\mu\text{g day/mL}$, and an average $C_{trough\ ss}$ of about 11 $\mu\text{g/mL}$ is achieved.
- [0026]** In some embodiments, a sufficient number of IV doses of about 1 mg/kg are administered at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 118 and about 348 mL/day, an apparent volume of distribution (V_{ss}) of between about 4 and about 9 L, and a serum half-life of about 15 days to about 32 days is achieved.
- [0027]** In some embodiments, a sufficient number of IV doses of about 1 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 233 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 23 days is achieved.
- [0028]** In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered at about 14-day intervals to achieve a steady state, wherein one

or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ of about 0.33 days or less, a $C_{\max ss}$ of about 75 to about 232 $\mu\text{g/mL}$, an $AUC_{T ss}$ of about 533 to about 1843 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 26 to about 74 $\mu\text{g/mL}$ is achieved.

[0029] In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 0.13 days, an average $C_{\max ss}$ of about 153 $\mu\text{g/mL}$, an average $AUC_{T ss}$ of about 1188 $\mu\text{g day/mL}$, and an average $C_{\text{trough } ss}$ of about 50 $\mu\text{g/mL}$ is achieved.

[0030] In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 136 and about 304 mL/day, an apparent volume of distribution (V_{ss}) of between about 3 and about 7 L, and a serum half-life of about 14 days to about 26 days is achieved.

[0031] In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 220 mL/day, an average apparent volume of distribution (V_{ss}) of about 5 L, and an average serum half-life of about 20 days is achieved.

[0032] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered at about 14-day intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ about 0.82 days or less, a $C_{\max ss}$ of about 288 to about 595 $\mu\text{g/mL}$, an $AUC_{T ss}$ of about 2539 to about 4267 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 93 to about 275 $\mu\text{g/mL}$ is achieved.

[0033] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 0.23 days, an average $C_{\max ss}$ of about 232

µg/mL, an average $AUC_{T_{ss}}$ of about 3403 µg day/mL, and an average $C_{trough_{ss}}$ of about 184 µg/mL is achieved.

[0034] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered at about 14-day intervals to achieve a steady state, wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 157 and about 319 mL/day, an apparent volume of distribution (V_{ss}) of between about 4 and about 7 L, and a serum half-life of about 15 days to about 29 days is achieved.

[0035] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 238 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 22 days is achieved.

[0036] In some embodiments, the number of IV doses at about 14-day intervals required to achieve steady state is about 5 to about 8 doses.

[0037] In some embodiments, the administration is subcutaneous (SC) administration. In certain embodiments, the dosage is 100 mg administered as a single SC dose, or is administered weekly, bi-weekly, or monthly. In some embodiments, a T_{max} or $T_{max_{ss}}$ of between about 2 and about 10 days is achieved after SC administration.

[0038] In some embodiments, a single SC administration of about 100 mg achieves one or more pharmacokinetic characteristics chosen from: a T_{max} of about 2 to about 10 days, a C_{max} of about 4 to about 21 µg/mL, an area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_{last}) of about 175 to about 666 µg day/mL, and an area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) of about 204 to about 751 µg day/mL.

[0039] In some embodiments, a single SC administration of about 100 mg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: a T_{max} of about 6 days, a C_{max} of about 13 µg/mL, an AUC_{last} of about 421 µg day/mL, and an AUC_{∞} of about 477 µg day/mL.

- [0040] In some embodiments, a single SC administration of about 100 mg achieves one or more pharmacokinetic characteristics chosen from a clearance rate (CL/F) of between about 118 and about 432 mL/day, an apparent volume of distribution (V_z/F) of between about 5 and about 12 L, and a serum half-life of about 15 days to about 34 days.
- [0041] In some embodiments, a single SC administration of about 100 mg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from an average clearance rate (CL/F) of about 275 mL/day, an apparent volume of distribution (V_z/F) of about 8 L, and a serum half-life of about 25 days.
- [0042] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ of about 2 to about 7 days, a $C_{\max ss}$ of about 37 to about 93 $\mu\text{g/mL}$, an $AUC_{T ss}$ of about 248 to about 638 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 38 to about 80 $\mu\text{g/mL}$ is achieved.
- [0043] In some embodiments, a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 7-day (weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 4 days, an average $C_{\max ss}$ of about 65 $\mu\text{g/mL}$, an average $AUC_{T ss}$ of about 443 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 59 $\mu\text{g/mL}$ is achieved.
- [0044] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of between about 168 and about 396 mL/day, an apparent volume of distribution (V_z/F) of between about 7 and about 15 L, and a serum half-life of about 22 days to about 35 days is achieved.
- [0045] In some embodiments, a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 7-day (weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 282

mL/day, an average apparent volume of distribution (V_z/F) of about 11 L, and an average serum half-life of about 28 days is achieved.

[0046] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ of about 2 to about 7 days, a $C_{\max ss}$ of about 30 to about 49 $\mu\text{g/mL}$, an $AUC_T ss$ of about 424 to about 567 $\mu\text{g day/mL}$, and a $C_{\text{trough ss}}$ of about 21 to about 40 $\mu\text{g/mL}$ is achieved.

[0047] In some embodiments, a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 14-day (bi-weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 4 days, an average $C_{\max ss}$ of about 39 $\mu\text{g/mL}$, an average $AUC_T ss$ of about 495 $\mu\text{g day/mL}$, and a $C_{\text{trough ss}}$ of about 30 $\mu\text{g/mL}$ is achieved.

[0048] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of between about 172 and about 240 mL/day, an apparent volume of distribution (V_z/F) of between about 6 and about 10 L, and a serum half-life of about 19 days to about 37 days is achieved.

[0049] In some embodiments, a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 14-day (bi-weekly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 406 mL/day, an average apparent volume of distribution (V_z/F) of about 8 L, and an average serum half-life of about 28 days is achieved.

[0050] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ of about 3 to about 8 days, a $C_{\max ss}$ of about 14 to about 34 $\mu\text{g/mL}$, an $AUC_T ss$ of about 326 to about 641 $\mu\text{g day/mL}$, and a $C_{\text{trough ss}}$ of about 6 to about 15 $\mu\text{g/mL}$ is achieved.

[0051] In some embodiments, a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 30-day (monthly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 6 days, an average $C_{\max ss}$ of about 49 $\mu\text{g/mL}$, an average $AUC_{T ss}$ of about 483 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 11 $\mu\text{g/mL}$ is achieved.

[0052] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of between about 152 and about 302 mL/day, an apparent volume of distribution (V_z/F) of between about 5 and about 17 L, and a serum half-life of about 19 days to about 47 days is achieved.

[0053] In some embodiments, a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 30-day (monthly) intervals to achieve a steady state, wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 227 mL/day, an average apparent volume of distribution (V_z/F) of about 11 L, and an average serum half-life of about 33 days is achieved.

[0054] In certain embodiments, the administration of a sufficient number of doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof suppresses an IFN pharmacodynamic signature. In some embodiments, the IFN pharmacodynamic signature is a Type I IFN-alpha inducible expression profile. The Type I IFN-alpha inducible expression profile can comprises the up-regulated expression of a gene marker set comprising IFI44, IFI27, IFI44L, NAPTP, LAMP3, LY6E, RSAD2, HERC5, IFI6, ISG15, OAS3, RTP4, IFIT1, MX1, SIGLEC1, OAS2, USP18, OAS1, EPSTI1, PLSCR1 and IFRG28. In some embodiments, the anti-IFN antibody or antigen-binding fragment thereof neutralizes the pharmacodynamic expression profile of the patient by at least 10%, at least 20%, at least 30% or at least 40%.

In certain embodiments the method the reduces at least one disease symptom .

In certain embodiments, the reduction in symptoms reduces the SLEDAI or BILAG

score. In certain embodiments, the SLEDAI score is reduced by at least 1, at least 2, at least 3, at least 4, or more points.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

- [0055] **FIG. 1** is a graph showing mean sifalimumab concentrations over 14 IV infusion doses. Sifalimumab was administered at 0.3 mg/kg (●), 1.0 mg/kg (■), 3.0 mg/kg (▼) and 10 mg/kg (▲) doses. Error bars show the standard deviation.
- [0056] **FIG. 2A** is a graph showing frequency of anti-sifalimumab antibody titer in a group administered 0.3 mg/kg IV infusion doses.
- [0057] **FIG. 2B** is a graph showing frequency of anti-sifalimumab antibody titer in a group administered 1.0 mg/kg IV infusion doses.
- [0058] **FIG. 2C** is a graph showing frequency of anti-sifalimumab antibody titer in a group administered 3.0 mg/kg IV infusion doses.
- [0059] **FIG. 2D** is a graph showing frequency of anti-sifalimumab antibody titer in a group administered 10 mg/kg IV infusion doses.
- [0060] **FIG. 3** is a graph showing steady state clearance of sifalimumab by titer of anti-sifalimumab antibodies (IM titer). Sifalimumab was administered at 0.3 mg/kg (●), 1.0 mg/kg (■), 3.0 mg/kg (▼) and 10 mg/kg (▲) IV infusion doses.
- [0061] **FIG. 4** is a graph showing steady state clearance of sifalimumab by IM status of patients receiving 0.3, 1.0, 3.0 and 10 mg/kg doses of sifalimumab. IM⁺ and IM⁻ patients are patients testing positive or negative for the presence of anti-sifalimumab antibodies, respectively.
- [0062] **FIG. 5** summarizes the final model goodness-of-fit plots for sifalimumab serum concentrations. The thin solid line (diagonal and horizontal) and thick line represent line of unity and loess fit, respectively. Panel (a) shows population predictions versus observed serum concentrations, panel (b) shows individual predictions versus observed serum concentrations, panel (c) shows population predictions versus weighted residuals, and panel (d) shows time versus weighted residuals.
- [0063] **FIG. 6** provides graphs depicting a visual predictive check for sifalimumab serum concentrations. Panels shows the time versus serum concentration graphs corresponding to 0.3, 1.0, 3.0 and 10 mg/kg doses, respectively. Observed

median (solid line) and corresponding simulation based 95% confidence interval (light area between shaded areas) and the 5% and 95% data percentiles (dashed lines) and corresponding simulations based 95% CI (shaded area) are shown.

[0064] **FIG. 7** is a graph showing the similarity of predicted PK profiles (median, 5th and 95th percentiles) following fixed (200 mg every 14 days) and body weight based (3 mg/kg every 14 days) IV dosing of sifalimumab.

[0065] **FIG. 8** is a graph showing predicted serum concentrations following 200, 600, and 1200 mg monthly IV dosing of sifalimumab (with single loading dose at day 14).

[0066] **FIG. 9** is a graph showing the mean concentration of sifalimumab over 168 days. Sifalimumab was administered in a single subcutaneous dose (●), weekly (■), bi-weekly (▲) or monthly (▼).

[0067] **FIG. 10** is a graph showing sifalimumab clearance by immunogenicity titer in IM⁺ and IM⁻ patients. Sifalimumab was administered in a single subcutaneous dose (■), weekly (▲), bi-weekly (▼) or monthly (◆).

[0068] **FIG. 11** is a graph showing the inhibition of the type 1 IFN pharmacodynamic gene signature by sifalimumab. Sifalimumab was administered in a single 100 mg subcutaneous dose once, once a week, bi-weekly, or monthly.

DETAILED DESCRIPTION

[0069] It must be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise. The terms "a" (or "an"), as well as the terms "one or more," and "at least one" can be used interchangeably herein.

[0070] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

- [0071] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.
- [0072] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.
- [0073] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects or embodiments of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety. Amino acids are referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, are referred to by their commonly accepted single-letter codes.
- [0074] As used herein, the term "autoimmune disease" refers to a disorder, disease state or condition associated with the formation of autoantibodies reactive with the patient's own cells to form antigen-antibody complexes. The term "autoimmune disease" includes conditions such as, *e.g.*, systemic lupus erythematosus, as well as those disorders which are triggered by a specific external agent, *e.g.*, acute rheumatic fever. Examples of autoimmune disorders include, but are not limited to, autoimmune hemolytic anemia, autoimmune hepatitis, Berger's disease, chronic fatigue syndrome, Crohn's disease, dermatomyositis, fibromyalgia, Graves' disease, Hashimoto's thyroiditis, idiopathic thrombocytopenia purpura, lichen planus, multiple sclerosis,

myasthenia gravis, psoriasis, rheumatic fever, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic lupus erythematosus, type 1 diabetes, ulcerative colitis, and vitiligo. In specific embodiments, the autoimmune disease is systemic lupus erythematosus, scleroderma, or myositis.

[0075] As used herein, the term "antibody" is used in its broadest sense and includes monoclonal antibodies, polyclonal antibodies, multivalent antibodies, multispecific antibodies, chimeric antibodies, and humanized antibodies. The term "antibody" as referred to herein includes whole antibodies. An "antibody" refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (C1q) of the classical complement system.

[0076] The terms "fragment thereof," "antigen-binding fragment" and "antigen-binding portion" of an antibody (or simply "antibody portion") are used interchangeably herein, and refer to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., IFN-alpha). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab

fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a F(ab')₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) Nature 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see *e.g.*, Bird *et al.* (1988) Science 242:423-426; and Huston *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0077] An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds IFN-alpha is substantially free of antibodies that specifically bind antigens other than IFN-alpha). An isolated antibody that specifically binds IFN-alpha can, however, have cross-reactivity to other antigens, such as IFN-alpha molecules from other species. Moreover, an isolated antibody can be substantially free of other cellular material and/or chemicals.

[0078] The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0079] The term "human antibody", as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the

antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the disclosure can include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0080] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0081] The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to

human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0082] As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

[0083] The antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; and Morrison *et al*, *Proc. Natl. Acad. Sci. USA* 81:6851-6855 (1984)).

[0084] Basic antibody structures in vertebrate systems are relatively well understood. See, e.g., Harlow *et al.* (1988) *Antibodies: A Laboratory Manual* (2nd ed.; Cold Spring Harbor Laboratory Press).

[0085] In the case where there are two or more definitions of a term that is used and/or accepted within the art, the definition of the term as used herein is intended to include all such meanings unless explicitly stated to the contrary. A specific example is the use of the term "complementarity determining region" ("CDR") to describe the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. This particular region has been described by Kabat *et al.* (1983) U.S. Dept. of Health and Human Services, "Sequences of Proteins of Immunological Interest" and by Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987), which are incorporated herein by reference, where the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The appropriate amino acid residues that encompass the CDRs as defined by each of the above cited references are set forth below in **TABLE 1** as a comparison. The exact residue numbers that encompass a particular CDR will vary depending on the sequence

and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

TABLE 1**CDR Definitions¹**

	Kabat	Chothia
VH CDR1	31-35	26-32
VH CDR2	50-65	52-58
VH CDR3	95-102	95-102
VL CDR1	24-34	26-32
VL CDR2	50-56	50-52
VL CDR3	89-97	91-96

¹Numbering of all CDR definitions in Table 1 is according to the numbering conventions set forth by Kabat *et al.* (see below).

[0086] Kabat *et al.* also defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of "Kabat numbering" to any variable domain sequence, without reliance on any experimental data beyond the sequence itself. As used herein, "Kabat numbering" refers to the numbering system set forth by Kabat *et al.* (1983) U.S. Dept. of Health and Human Services, "Sequence of Proteins of Immunological Interest." Unless otherwise specified, references to the numbering of specific amino acid residue positions in an anti-IL-33 antibody or antigen-binding fragment, variant, or derivative thereof of the present disclosure are according to the Kabat numbering system.

[0087] Antibodies or antigen-binding fragments, variants, or derivatives thereof of the disclosure include, but are not limited to, polyclonal, monoclonal, multispecific, mouse, human, humanized, primatized, or chimeric antibodies, single-chain antibodies, epitope-binding fragments, *e.g.*, Fab, Fab' and F(ab')₂, Fd, Fvs, single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), fragments comprising either a VL or VH domain, fragments produced by a Fab expression library, and anti-idiotypic (anti-Id) antibodies (including, *e.g.*, anti-Id antibodies to anti-IL-33 antibodies disclosed herein). ScFv molecules are known in the art and are described, *e.g.*, in U.S. Pat. No. 5,892,019.

[0088] As used herein, the term "affinity" refers to a measure of the strength of the binding of an individual epitope with the CDR of an immunoglobulin molecule.

See, e.g., Harlow *et al.* (1988) *Antibodies: A Laboratory Manual* (Cold Spring Harbor Laboratory Press, 2nd ed.) pages 27-28.

[0089] As used herein, "specific binding" refers to antibody binding to a predetermined antigen. Typically, the antibody binds with a dissociation constant (K_D) of 10^{-8} M or less, and binds to the predetermined antigen with a K_D that is at least two-fold less than its K_D for binding to a non-specific antigen (e.g., BSA, casein) other than the predetermined antigen or a closely-related antigen. The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen".

[0090] The term " K_{assoc} " or " K_a ", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term " K_{dis} " or " K_d ", as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term " K_D ", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of K_d to K_a and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. One method for determining the K_D of an antibody is by using surface plasmon resonance, e.g., by using a biosensor system such as a Biacore.RTM. system.

[0091] As used herein, the term "high affinity" for an IgG antibody refers to an antibody having a K_D of 10^{-8} M or less, 10^{-9} M or less, or 10^{-10} M or less. However, "high affinity" binding can vary for other antibody isotypes. For example, "high affinity" binding for an IgM isotype refers to an antibody having a K_D of 10^{-7} M or less, or 10^{-8} M or less.

[0092] Anti-IFN-alpha binding molecules, e.g., antibodies or antigen-binding fragments, variants or derivatives thereof of the disclosure can also be described or specified in terms of their binding affinity to a polypeptide of the disclosure, e.g., IFN- alpha, e.g., human, primate, murine, or any combination of human, primate and murine IFN-alpha. Exemplary binding affinities include those with a dissociation constant or K_D less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M,

10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

[0093] As used herein, the terms "treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the progression of an inflammatory condition. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0094] The terms "effective amount" or "amount effective to" or "therapeutically effective amount" includes reference to a dosage of a therapeutic agent sufficient to produce a desired result.

[0095] By "subject" or "individual" or "animal" or "patient" or "mammal," is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. As used herein, the term "subject" includes any human or nonhuman animal. The term "nonhuman animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, bears, chickens, amphibians, reptiles, etc. As used herein, phrases such as "a subject that would benefit from administration of an anti-IFN-alpha antibody" includes subjects, such as mammalian subjects, that would benefit from administration of an anti-IFN-alpha antibody used, *e.g.*, for detection of an anti-IFN-alpha polypeptide (*e.g.*, for a diagnostic procedure) and/or from treatment, *i.e.*, palliation or prevention of a disease, with an anti-IFN-alpha antibody.

Interferon Alpha

[0096] The terms “interferon alpha” and “IFN-alpha” are used interchangeably and intended to refer to IFN-alpha proteins encoded by a functional gene of the interferon alpha gene locus with 75% or greater sequence identity to IFN-alpha 1 (Genbank number NP—076918 or protein encoded by Genbank number NM—024013). Examples of IFN-alpha subtypes include IFN-alpha 1, alpha 2a, alpha 2b, alpha 4, alpha 5, alpha 6, alpha 7, alpha 8, alpha 10, alpha 13, alpha 14, alpha 16, alpha 17 and alpha 21. The term “interferon alpha” is intended to encompass recombinant forms of the various IFN-alpha subtypes, as well as naturally occurring preparations that comprise IFN-alpha proteins, such as leukocyte IFN and lymphoblastoid IFN.

Interferon Alpha Antibodies

[0097] The present disclosure is directed to methods of treating an autoimmune disorder in a subject in need of such treatment comprising administering to the subject an anti-IFN-alpha antibody. Anti-IFN-alpha antibodies can be found in, for example, U.S. Pat. No. 7,741,449, and can further include chimeric, humanized, or human versions of these antibodies (if not already a chimeric, humanized, or human version), and can further include fragments or derivatives thereof.

SLE

[0098] Patients suffering from SLE may exhibit any of a number of symptoms as discussed in, e.g., International Application No. PCT/US2007/024941, or may have a clinical SLEDAI score or BILAG score as discussed in the same. These symptoms may include fatigue, organ damage, malar rash, and alopecia. The patient may be scored using a known clinical scoring system, e.g., SLEDAI which is an index of SLE disease activity as measured and evaluated within the last 10 days (Bombardier C, Gladman D D, Urowitz M B, Caron D, Chang C H and the Committee on Prognosis Studies in SLE: Derivation of the SLEDAI for Lupus Patients. *Arthritis Rheum* 35:630-640, 1992.). Disease activity under the SLEDAI scoring system can range from 0 to 105. The following categories of SLEDAI activity have been defined: no activity (SLEDAI = 0); mild activity (SLEDAI = 1-

5); moderate activity (SLEDAI = 6-10); high activity (SLEDAI = 11-19); very high activity (SLEDAI = 20 or higher). (Griffiths, et al., Assessment of Patients with Systemic Lupus Erythematosus and the use of Lupus Disease Activity Indices).

[0099] Another disease scoring index is the BILAG index which is an activity index of SLE that is based on specific clinical manifestations in eight organ systems: general, mucocutaneous, neurological, musculoskeletal, cardiovascular, respiratory, renal, and hematology results. Scoring is based on a letter system, but weighted numerical scores can also be assigned to each letter, making it possible to calculate a BILAG score in the range of 0-72. (Griffiths, et al., Assessment of Patients with Systemic Lupus Erythematosus and the use of Lupus Disease Activity Indices). Other scoring indices include the PGA score, the composite responder index (CRI), and the ANAM4™ test. The methods described herein, e.g., of treating an autoimmune disorder, may be used for any subject identified as having any activity level of disease activity as measured by any classification methodology known in the art, e.g., mild, moderate, high, or very high. The methods described herein, e.g., of treating an autoimmune disorder, may result in a decrease in a patient's symptoms or may result in an improvement in a score of disease for the patient's type I IFN or an IFN-alpha-inducible disease, disorder, or condition.

Monoclonal Antibodies 13H5, 13H7 and 7H9

[0100] In certain embodiments, antibodies for use in the treatment methods of the disclosure include the human monoclonal antibodies 13H5, 13H7, and 7H9, isolated and structurally characterized as described in the U.S. Patent No. 7,741,449. The VH amino acid sequences of 13H5, 13H7, and 7H9 are shown in SEQ ID NOs: 19, 20, and 21, respectively. The VL amino acid sequences of 13H5, 13H7, and 7H9 are shown in SEQ ID NOs: 22, 23 and 24, respectively. Given that each of these antibodies can bind to IFN-alpha, the VH and VL sequences can be "mixed and matched" to create other anti-IFN-alpha binding molecules of the disclosure. IFN-alpha binding or neutralizing activity of such "mixed and matched" antibodies can be tested using the binding assays described above and in the Examples (e.g., ELISA, Biacore analysis, Daudi cell proliferation assay). In certain embodiments, the VH sequences of 13H5 and 7H9

are mixed and matched, since these antibodies use VH sequences derived from the same germline sequence (VH 1-18) and thus they exhibit structural similarity. Additionally or alternatively, the VL sequences of 13H5, 13H7 and 7H9 can be mixed and matched, since these antibodies use VL sequences derived from the same germline sequence (Vk A27) and thus they exhibit structural similarity.

[0101] Accordingly, in one aspect, an antibody for use in the methods of the disclosure is an isolated monoclonal antibody, or antigen binding portion thereof, comprising:

- (a) a heavy chain variable region comprising an amino acid sequence chosen from SEQ ID NOs: 19, 20, and 21; and
- (b) a light chain variable region comprising an amino acid sequence chosen from SEQ ID NOs: 22, 23, and 24;

wherein the antibody inhibits the biological activity of interferon alpha.

[0102] In certain embodiments, heavy and light chain combinations include:

- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19; and
- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO:22; or
- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 20; and
- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO:23; or
- (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 21; and
- (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO:24.

[0103] In another aspect, the treatment methods of the present disclosure comprise the administration of antibodies that comprise the heavy chain and light chain CDR1s, CDR2s, and CDR3s of 13H5, 13H7, and 7H9, or combinations thereof. The amino acid sequences of the VH CDR1s of 13H5, 13H7, and 7H9 are shown in SEQ ID NOs: 1, 2, and 3. The amino acid sequences of the VH CDR2s of 13H5, 13H7, and 7H9 are shown in SEQ IN NOs: 4, 5, and 6. The amino acid sequences of the VH CDR3s of 13H5, 13H7, and 7H9 are shown in

SEQ IN NOs: 7, 8, and 9. The amino acid sequences of the VL CDR1s of 13H5, 13H7, and 7H9 are shown in SEQ IN NOs: 10, 11, and 12. The amino acid sequences of the VL CDR2s of 13H5, 13H7, and 7H9 are shown in SEQ IN NOs: 13, 14, and 15. The amino acid sequences of the VL CDR3s of 13H5, 13H7, and 7H9 are shown in SEQ IN NOs: 16, 17, and 18. The CDR regions are delineated using the Kabat system (Kabat. E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).

[0104] Given that each of these antibodies was selected based on IFN binding activity and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and VL CDR1, 2 and 3 sequences can be "mixed and matched" (*i.e.*, CDRs from different antibodies can be mixed and match, although each antibody must contain a VH CDR1, 2 and 3 and a VL CDR1, 2 and 3) to create other anti-IFN-alpha molecules of the disclosure. IFN-alpha binding of such "mixed and matched" antibodies can be tested using the binding assays described in the Examples (*e.g.*, ELISA and/or Biacore). In certain embodiments, when VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence is replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VL sequence can be replaced with a structurally similar CDR sequence(s). For example, the VH CDR1s of 13H5 and 7H9 share some structural similarity and therefore are amenable to mixing and matching. It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR region sequences with structurally similar sequences from the CDR sequences disclosed herein for monoclonal antibodies 13H5, 13H7 and 7H9.

[0105] Accordingly, in another aspect, the methods of the present disclosure provide for administration of an isolated monoclonal antibody, or antigen binding portion thereof comprising:

- (a) a heavy chain variable region CDR1 comprising an amino acid sequence chosen from SEQ ID NOs: 1, 2, and 3;

- (b) a heavy chain variable region CDR2 comprising an amino acid sequence chosen from SEQ ID NOs: 4, 5, and 6;
- (c) a heavy chain variable region CDR3 comprising an amino acid sequence chosen from SEQ ID NOs: 7, 8, and 9;
- (d) a light chain variable region CDR1 comprising an amino acid sequence chosen from SEQ ID NOs: 10, 11, and 12;
- (e) a light chain variable region CDR2 comprising an amino acid sequence chosen from SEQ ID NOs: 13, 14, and 15; and
- (f) a light chain variable region CDR3 comprising an amino acid sequence chosen from SEQ ID NOs: 16, 17, and 18;

wherein the antibody the antibody inhibits the biological activity of interferon alpha.

[0106] In one embodiment, the antibody comprises:

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO: 1;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO: 4;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO: 7;
- (d) a light chain variable region CDR1 comprising SEQ ID NO: 10;
- (e) a light chain variable region CDR2 comprising SEQ ID NO: 13; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO: 16.

[0107] In another embodiment, the antibody comprises:

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO: 2;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO: 5;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO: 8;
- (d) a light chain variable region CDR1 comprising SEQ ID NO: 11;
- (e) a light chain variable region CDR2 comprising SEQ ID NO: 14; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO: 17.

[0108] In another embodiment, the antibody comprises:

- (a) a heavy chain variable region CDR1 comprising SEQ ID NO: 3;
- (b) a heavy chain variable region CDR2 comprising SEQ ID NO: 6;
- (c) a heavy chain variable region CDR3 comprising SEQ ID NO: 9;

- (d) a light chain variable region CDR1 comprising SEQ ID NO: 12;
- (e) a light chain variable region CDR2 comprising SEQ ID NO: 15; and
- (f) a light chain variable region CDR3 comprising SEQ ID NO: 18.

Antibodies Having Particular Germline Sequences

- [0109]** In certain embodiments, an antibody to be administered according to the methods of the disclosure comprises a heavy chain variable region from a particular germline heavy chain immunoglobulin gene and/or a light chain variable region from a particular germline light chain immunoglobulin gene.
- [0110]** For example, in one embodiment, the disclosure provides a method of treating an autoimmune disorder in a subject in need thereof, comprising administering to the subject an isolated monoclonal antibody, or an antigen-binding fragment thereof, where the antibody:
- (a) comprises a heavy chain variable region of a human VH 1-18 or 4-61 gene;
 - (b) comprises a light chain variable region of a human V κ A27 gene; and
 - (c) the antibody inhibits the biological activity of interferon alpha.
- [0111]** In one embodiment, the antibody comprises a heavy chain variable region of a human VH 1-18 gene. Examples of antibodies having a VH and V κ gene sequence of VH 1-18 and V κ A27, respectively, include 13H5 and 7H9. In another embodiment, the antibody comprises a heavy chain variable region of a human VH 4-61 gene. An example of an antibody having a VH and V κ gene sequence of VH 4-61 and V κ A27, respectively, is 13H7.
- [0112]** As used herein, a human antibody comprises heavy or light chain variable regions "of" (*i.e.*, the products of) or "derived from" a particular germline sequence if the variable regions of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "of" (*i.e.*, the product of) or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino

acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (*i.e.*, greatest % identity) to the sequence of the human antibody. A human antibody that is "of" (*i.e.*, the product of) or "derived from" a particular human germline immunoglobulin sequence can contain amino acid differences as compared to the germline sequence, due to, for example, naturally-occurring somatic mutations or intentional introduction of site-directed mutation. However, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (*e.g.*, murine germline sequences). In certain cases, a human antibody can be at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a human antibody derived from a particular human germline sequence will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene. In certain cases, the human antibody can display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

[0113] In yet another embodiment, an antibody for use in the treatment methods of the disclosure comprises heavy and light chain variable regions comprising amino acid sequences that share amino acid similarity with or are homologous to the amino acid sequences of the antibodies described herein, where the antibodies retain the desired functional properties of the anti-IFN-alpha antibodies of the disclosure.

[0114] For example, the disclosure provides a method of treating an autoimmune disorder in a subject in need thereof, comprising administering to the subject an isolated monoclonal antibody, or antigen binding fragment thereof, comprising a heavy chain variable region and a light chain variable region, wherein:

- (a) the heavy chain variable region comprises an amino acid sequence that is at least 80% homologous to an amino acid sequence chosen from SEQ ID NOs: 19, 20, and 21;

- (b) the light chain variable region comprises an amino acid sequence that is at least 80% homologous to an amino acid sequence chosen from SEQ ID NOs: 22, 23, and 24;
- (c) the antibody inhibits the biological activity of multiple IFN-alpha subtypes but does not substantially inhibit the biological activity of IFN-alpha 21; and
- (d) the antibody exhibits at least one of the following properties: (i) the antibody does directly inhibit the biological activity of IFN-beta or IFN-omega, but may indirectly inhibit the biological activity of IFN-beta or IFN-omega by interfering with interferon receptor function; (ii) the antibody inhibits IFN-induced surface expression of CD38 or MHC Class I on peripheral blood mononuclear cells; (iii) the antibody inhibits IFN-induced expression of IP-10 by peripheral blood mononuclear cells; (iv) the antibody inhibits dendritic cell development mediated by systemic lupus erythematosus (SLE) plasma.

[0115] In other embodiments, the VH and/or VL amino acid sequences can be 85%, 90%, 95%, 96%, 97%, 98% or 99% homologous to the sequences set forth above. An antibody having VH and VL regions having high (*i.e.*, 80% or greater) homology to the VH and VL regions of SEQ ID NOs: 19, 20, and 21 and 22, 23, and 24, respectively, can be obtained by mutagenesis (*e.g.*, site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding SEQ ID NOs: 19, 20, and 21 and/or 22, 23, and 24, followed by testing of the encoded altered antibody for retained function (*i.e.*, the functions set forth in (c) and (d) above) using the functional assays described herein.

[0116] As used herein, the percent homology or percent similarity between two amino acid sequences is equivalent to the percent identity between the two sequences. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % homology = number of identical positions/total number of positions.times.100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

[0117] The percent identity between two amino acid sequences can be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17 (1988)) which has been incorporated into the ALIGN program

(version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol. Biol. 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a BLOSSUM62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0118] Additionally or alternatively, the protein sequences of the present disclosure can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the XBLAST program (version 2.0) of Altschul, *et al.* (1990) J. Mol. Biol. 215:403-10. BLAST protein searches can be performed with the XBLAST program, score=50, wordlength=3 to obtain amino acid sequences homologous to the antibody molecules of the disclosure. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) Nucleic Acids Res. 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.

Antibodies with Conservative Modifications

[0119] In certain embodiments, an antibody for use in the methods of the present disclosure comprises a heavy chain variable region comprising CDR1, CDR2 and CDR3 sequences and a light chain variable region comprising CDR1, CDR2 and CDR3 sequences, wherein one or more of these CDR sequences comprise specified amino acid sequences based on antibodies described herein (*e.g.*, 13H5, 13H7, or 7H9), or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the anti-IFN-alpha antibodies of the disclosure. For example, certain antibodies of the disclosure include those in which the heavy chain variable region CDR3 sequence comprises the amino acid sequence of SEQ ID NO: 3, or conservative modifications thereof, and the light chain variable region CDR3 sequence comprises the amino acid sequence of SEQ ID NO: 6, or conservative modifications thereof. Accordingly, the

disclosure provides a method for treating an autoimmune disorder in a subject, comprising administering to the subject an isolated monoclonal antibody, or antigen binding fragment thereof, comprising a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein:

- (a) the heavy chain variable region CDR3 sequence comprises the amino acid sequence chosen from SEQ ID NO: 7, 8, and 9, and conservative modifications thereof;
- (b) the light chain variable region CDR3 sequence comprises the amino acid sequence chosen from SEQ ID NO: 16, 17, and 18, and conservative modifications thereof;
- (c) the antibody inhibits the biological activity of multiple IFN-alpha subtypes but does not substantially inhibit the biological activity of IFN-alpha 21;
- (d) the antibody exhibits at least one of the following properties: (i) the antibody does not directly inhibit the biological activity of IFN-beta or IFN-omega, but may indirectly inhibit the biological activity of IFN-beta or IFN-omega by interfering with interferon receptor function; (ii) the antibody inhibits IFN-induced surface expression of CD38 or MHC Class I on peripheral blood mononuclear cells; (iii) the antibody inhibits IFN-induced expression of IP-10 by peripheral blood mononuclear cells; (iv) the antibody inhibits dendritic cell development mediated by systemic lupus erythematosus (SLE) plasma.

[0120] In a further embodiment, the heavy chain variable region CDR2 sequence comprises the amino acid sequence chosen from amino acid sequences of SEQ ID NO: 4, 5, and 6, and conservative modifications thereof; and the light chain variable region CDR2 sequence comprises the amino acid sequence chosen from amino acid sequences SEQ ID NO: 13, 14, and 15, and conservative modifications thereof. In a still further embodiment, the heavy chain variable region CDR1 sequence comprises the amino acid sequence chosen from amino acid sequences of SEQ ID NO: 1, 2, and 3, and conservative modifications thereof; and the light chain variable region CDR1 sequence comprises the amino acid sequence chosen from amino acid sequences of SEQ ID NO: 10, 11, and 12, and conservative modifications thereof.

[0121] As used herein, the term "conservative sequence modifications" is intended to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence. Such conservative modifications include amino acid substitutions,

additions and deletions. Modifications can be introduced into an antibody of the disclosure by standard techniques known in the art, such as site-directed mutagenesis and PCR-mediated mutagenesis. Conservative amino acid substitutions are ones in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine, tryptophan), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, one or more amino acid residues within the CDR regions of an antibody of the disclosure can be replaced with other amino acid residues from the same side chain family and the altered antibody can be tested for retained function (*i.e.*, the functions set forth in (c) and (d) above) using the functional assays described herein.

Antibodies that Bind to the Same Epitope as Anti-IFN-alpha Antibodies of the Disclosure

[0122] In another embodiment, the disclosure provides a method of treating an autoimmune disorder in a subject, comprising administering to the subject an antibody that binds to the same epitope as do the various human IFN-alpha antibodies as described herein, such as other human antibodies that bind to the same epitope as the 13H5, 13H7, and 7H9 antibodies. The term "epitope" as used herein refers to a protein determinant capable of binding to an antibody of the disclosure. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents. Such antibodies can be identified based on their ability to cross-compete (e.g., to competitively inhibit the binding of, in a

statistically significant manner) with antibodies such as 13H5, 13H7 or 7H9, in standard IFN-alpha binding assays. For example, as demonstrated in the Examples of U.S. Patent No. 7,741,449, by Biacore analysis, 13H5 binds with high affinity to IFN-alpha 2a and IFN-alpha 2b. Accordingly, in one embodiment, the disclosure provides antibodies, such as human antibodies, that compete for binding to IFN-alpha 2a or IFN-alpha 2b with another antibody, such as 13H5, 13H7 or 7H9. The ability of a test antibody to inhibit the binding of, e.g., 13H5, 13H7 or 7H9 to IFN-alpha 2a or IFN-alpha 2b demonstrates that the test antibody can compete with that antibody for binding to IFN-alpha 2a or IFN-alpha 2b; such an antibody can, according to non-limiting theory, bind to the same or a related (e.g., a structurally similar or spatially proximal) epitope on IFN-alpha 2a or IFN-alpha 2b as the antibody with which it competes. In one embodiment, the antibody that binds to the same epitope on IFN-alpha 2a or IFN-alpha 2b as, e.g., 13H5, 13H7, or 7H9, is a human monoclonal antibody. Such human monoclonal antibodies can be used in the methods disclosed herein.

[0123] In one embodiment, the IFN-alpha antibody antagonist is sifalimumab. Sifalimumab is a fully human, 147,000 Dalton IgG1k monoclonal antibody (Mab) that selectively binds to multiple interferon-alpha subtypes. Sifalimumab is made from 100% human protein sequences, thereby making it a fully human monoclonal antibody. Fully human monoclonal antibodies have advantages over other forms of monoclonal antibodies, such as chimeric and humanized antibodies, as they have a more favorable safety profile and can be eliminated less rapidly from the human body, thereby reducing the frequency of dosing. Sifalimumab was derived from the IgG4k antibody, 13H5 described above and in U.S. Patent No. 7,741,449, which was selected based on functional assays as having the most desirable properties for a potential therapeutic agent. 13H5 was subsequently converted to an IgG1 antibody isotype, produced in CHO cells. See U.S. Patent No. 7,741,449, U.S. Patent Pub. Nos. 2010-0143372 and 2010-0266610, and PCT Pub. Nos. WO2008/070135, WO2009/061818, WO2008/137838, WO2008/070137, WO2008/137835, WO2009/155559, WO2008/121616, and WO2008/121615, each of which is hereby incorporated herein by reference.

- [0124] The nucleotide and amino acid sequences of the heavy chain variable region of 13H5 are shown in SEQ ID NOs: 25 and 19, respectively.
- [0125] The VH CDR1, CDR2, and CDR3 amino acid sequences of 13H5 are shown in SEQ ID NOs: 1, 4, and 7, respectively.
- [0126] The nucleotide and amino acid sequences of the light chain variable region of 13H5 are shown in SEQ ID NOs: 28 and 22, respectively.
- [0127] The VL CDR1, CDR2, and CDR3 amino acid sequences of 13H5 are shown in SEQ ID NOs: 10, 13, and 16, respectively.

Treatment and Dosing using Anti-IFN-alpha Antibodies

- [0128] The disclosure includes methods of dosing to achieve a desired PK characteristic. In a specific embodiment, the dose is chosen to achieve a desired characteristic chosen from T_{max} (time of maximum observed concentration), $T_{max\ ss}$ (time of maximum observed concentration at steady state), C_{max} (maximum observed concentration), $C_{max\ ss}$ (maximum observed concentration at steady state), AUC_T (area under the curve over the dosing interval), $AUC_{T\ ss}$ (area under the curve over the dosing interval at steady state), C_{trough} (trough observed concentration), $C_{trough\ ss}$ (trough observed concentration at steady state), half-life (terminal elimination half-life, defined as $\ln(2)/\lambda_z$), CL_{ss} (serum steady state clearance, defined as $Dose/AUC_{T\ ss}$), V_{ss} (steady state volume of distribution), AUC_{last} (area under the curve from time 0 to last observed concentration, i.e., C_{last}), AUC_{inf} (area under the curve from 0 to infinity, defined as $(AUC_{last} + C_{last})/\lambda_z$), $AUC_{inf\ extrapolated}$ (percent of the AUC_{inf} curve extrapolated, defined as $((C_{last}/\lambda_{dz})/AUC_{inf}) \times 100$), CL (apparent total body clearance of the drug from plasma), CL/F (apparent serum clearance), V_z/F (apparent terminal volume of distribution), CL_{ss}/F (apparent serum steady state clearance), V_c (central volume), V_p (peripheral volume) or λ_z (slope of the terminal elimination phase).
- [0129] In a specific embodiment, the methods of dosing produce a PK parameter of at least one of the values for the PK characteristics shown in Tables 2, 3, 6, 7, and 8-11. The values of such desired PK characteristics are understood to encompass the CV% as shown in the tables. In a specific embodiment, the methods of the disclosure produce a value chosen from the PK characteristics

shown in Tables 2, 3, 6, 7, and 8-11 and neutralization of a the 21-gene or 4-gene PD marker discussed herein. In a specific embodiment, the methods of the disclosure produce a value chosen from the PK characteristics shown in Tables 2, 3, 6, 7, and 8-11, a neutralization of a the 21-gene or 4-gene PD marker discussed herein, and a reduction in symptoms of SLE, such as a reduction in SLEDAI score.

[0130] The term "dosage form" refers to a pharmaceutical composition comprising one or more active pharmaceutical ingredients (API), *e.g.*, an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab, the composition optionally containing pharmacologically inactive ingredients, *i.e.*, pharmaceutically acceptable carriers, fillers, excipients or combinations thereof such as polymers, suspending agents, surfactants, disintegrants, dissolution modulating components, binders, fillers, lubricants, glidants, stabilizers, antioxidants, osmotic agents, colorants, plasticizers, coatings and the like, that are used to manufacture and deliver active pharmaceutical agents. Examples of pharmaceutical compositions comprising anti-interferon alpha antibodies can be found in U.S. Patent Application Publication No. 2010-0209434 A1 entitled "Antibody Formulation", which is hereby incorporated by reference herein in its entirety.

[0131] An anti-IFN-alpha antibody or antigen-binding fragment thereof, *e.g.*, sifalimumab, can be administered to a human patient in accord with known methods, such as intravenous administration, *e.g.*, as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes, or a combination of two or more recited routes.

[0132] In one embodiment, a formulation comprising an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab for use in the methods of the disclosure is for parenteral administration. In one embodiment, a formulation of the disclosure comprising an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab is an injectable formulation. In one embodiment, a formulation of the disclosure comprising an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab is for

intravenous, subcutaneous, or intramuscular administration. In a specific embodiment, a formulation of the disclosure comprises an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab wherein said formulation is for subcutaneous injection.

[0133] As used herein the term “intravenous administration” refers to the introduction of a composition to a patient into a vein. An anti-IFN-alpha antibody or antigen-binding fragment thereof can be administered intravenously (IV), *e.g.*, as an intravenous infusion or as an intravenous bolus. The term “intravenous infusion” refers to introduction of a drug, *e.g.*, an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab, into the vein of an animal or human patient over a period of time greater than approximately 5 minutes, for example, between approximately 30 to 90 minutes, although, according to the disclosure, intravenous infusion is alternatively administered for 10 hours or less. In one particular embodiment, the duration of the infusion is at least 60 minutes.

[0134] The term “intravenous bolus” or “intravenous push” refers to drug administration, *e.g.*, of an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab, into a vein of an animal or human such that the body receives the drug in approximately 15 minutes or less, for example, 5 minutes or less.

[0135] The term “subcutaneous administration” refers to introduction of a drug, *e.g.*, an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab, under the skin of an animal or human patient, for example, within a pocket between the skin and underlying tissue, by relatively slow, sustained delivery from a drug receptacle. The pocket can be created by pinching or drawing the skin up and away from underlying tissue. In some embodiments, a composition comprising an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab is introduced under the surface of the skin of the patient with a hypodermic needle.

[0136] The term “subcutaneous infusion” refers to introduction of a drug, *e.g.*, an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab, under the skin of an animal or human patient, for example, within a pocket between the skin and underlying tissue, by relatively slow, sustained

delivery from a drug receptacle for a period of time including, but not limited to, 30 minutes or less, or 90 minutes or less. Optionally, the infusion can be made by subcutaneous implantation of a drug delivery pump implanted under the skin of the animal or human patient, wherein the pump delivers a predetermined amount of drug for a predetermined period of time, such as 30 minutes, 90 minutes, or a time period spanning the length of the treatment regimen.

[0137] The term “subcutaneous bolus” refers to drug administration beneath the skin of an animal or human patient of an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab, where bolus drug delivery is less than about 15 minutes, less than about 5 minutes, or less than about 60 seconds. Administration can be within a pocket between the skin and underlying tissue, where the pocket is created, for example, by pinching or drawing the skin up and away from underlying tissue.

[0138] In one embodiment, a formulation for use in the methods of the disclosure is for aerosol administration.

Weight Based Dosage Administration

[0139] In some embodiments, the dosage of anti-IFN-alpha antibody or antigen-binding fragment thereof administered to a patient is calculated, e.g., as a function of the patient body mass (weight), height, or body surface. In certain embodiments, the dosage of anti-IFN-alpha antibody or antigen-binding fragment thereof administered to a patient depends on the patient's body weight. The weight-based dose is generally provided in mg/kg.

[0140] In some embodiments, an anti-IFN-alpha antibody or antigen-binding fragment thereof is administered at a weight-based dosage of about 0.1 mg/kg, or about 0.2 mg/kg, or about 0.3 mg/kg, or about 0.4 mg/kg, or about 0.5 mg/kg, or about 0.6 mg/kg, or about 0.7 mg/kg, or about 0.8 mg/kg, or about 0.9 mg/kg. In other embodiments, an anti-IFN-alpha antibody or antigen-binding fragment hereof is administered at a weight-based dosage of about 1 mg/kg, or about 2 mg/kg, or about 3 mg/kg, or about 4 mg/kg, or about 5 mg/kg, or about 6 mg/kg, or about 7 mg/kg, or about 8 mg/kg, or about 9 mg/kg. In certain embodiments, an anti-IFN-alpha antibody or antigen-binding fragment thereof is administered at a weight-based dosage of about 10 mg/kg, or 15 mg/kg, or 20 mg/kg, or about 25

mg/kg, or about 30 mg/kg, or about 35 mg/kg, or about 40 mg/kg, or about 45 mg/kg, or about 50 mg/kg, or about 55 mg/kg, or about 60 mg/kg, or about 65 mg/kg, or about 70 mg/kg, or about 75 mg/kg, or about 80 mg/kg, or about 85 mg/kg, or about 90 mg/kg, or about 95 mg/kg, or about 100 mg/kg. In specific embodiments, the anti-IFN-alpha antibody or antigen-binding fragment thereof is administered at a weight-base dosage about 0.3 mg/kg, or about 1.0 mg/kg, or about 3.0 mg/kg, or about 10 mg/kg. In certain embodiments, the weight-based dosage is administered intravenously. In other embodiments, the weight-based dosage is administered subcutaneously. In some specific embodiments, the an anti-IFN-alpha antibody is sifalimumab.

[0141] When a series of weight-based doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab, are administered, these doses can, for example, be administered approximately every week, approximately every 2 weeks, approximately every 3, or about every 4 weeks. In some embodiments, weight-based doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof are administered approximately every day, approximately every two days, approximately every three days, approximately every 4 days, approximately every 5 days, approximately every 6 days, or approximately every seven days.

[0142] In a specific embodiment, weight-based doses of an anti-IFN-alpha antibody or antigen-binding fragment are administered every 2 weeks. The weight-based doses of anti-IFN-alpha antibody or an antigen-binding fragment thereof can be administered, for example, for about 1 month, or about 2 months, or about 3 months, or about 4 months, or about 5 months, or about 6 months. The weight-based doses of anti-IFN-alpha antibody or an antigen-binding fragment thereof, can, for example, continue to be administered until disease progression, adverse event, or other parameter occurs as determined by the physician. In a specific embodiment, weight-based doses of anti-IFN-alpha antibody or an antigen-binding fragment thereof, are administered for about 6 months. In a more specific embodiment, weight-based doses anti-IFN-alpha antibody or an antigen-binding fragment thereof, are administered for about 26 weeks.

[0143] In some embodiments, patients can be administered at least one, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14 or at least 15 weight-based doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab. In a specific embodiment, patients are administered at least 14 doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab. In some specific embodiments, patients can be administered at least 14 IV weight-based doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof, such as sifalimumab.

[0144] In some embodiments, weight-based doses of anti-IFN-alpha antibody or an antigen-binding fragment thereof, are administered at equal time intervals. In other embodiment, such weight-based doses are administered at varying intervals. In some embodiments, all administered weight-based doses as essentially identical. In other embodiments, at least one weight-based dose is different with respect to the other doses, e.g., in volume, concentration, route of administration, formulation, etc.

Fixed Dosage Administration

[0145] A "fixed dose" or "fixed dosage" of a therapeutic agent herein refers to a dose that is administered to a human patient without regard for the weight (WT) or body surface area (BSA) of the patient. The fixed dose of anti-IFN-alpha antibody or an antigen-binding fragment thereof, e.g., sifalimumab, is therefore not provided as a mg/kg dose or mg/m² dose, but rather as an absolute amount of the therapeutic agent.

[0146] In some embodiments, an anti-IFN-alpha antibody or antigen-binding fragment thereof is administered at a fixed dosage of about 10 mg, or about 20 mg, or about 30 mg, or about 40 mg, or about 50 mg, or about 60 mg, or about 70 mg, or about 80 mg, or about 90 mg, or about 100 mg. In other embodiments, an anti-IFN-alpha antibody or antigen-binding fragment thereof is administered at a fixed dosage of about 100 mg, or about 150 mg, about 200 mg, or about 300 mg, or about 400 mg, or about 500 mg, or about 600 mg, or about 700 mg, or about 800 mg, or about 900 mg, or about 100 mg, or about 1100 mg, or about

1200 mg, or about 1300 mg, or about 1400 mg, or about 1500 mg, or about 1600 mg, or about 1700 mg, or about 1800 mg, or about 1900 mg, or about 2000 mg.

[0147] In specific embodiments, the anti-IFN-alpha antibody or antigen-binding fragment thereof is administered intravenously at a fixed dosage about 100 mg, or about 150 mg, or about 200 mg, or about 600 mg, or about 1200 mg. In a specific embodiment, the anti-IFN antibody or antigen-binding fragment thereof is administered subcutaneously at a fixed dosage of about 100 mg, or about 200 mg, or about 600 mg, or about 1200 mg. In some embodiments, a loading dose is administered. In some specific embodiments, the anti-IFN-alpha antibody is sifalimumab, or an antigen-binding fragment thereof. In a specific embodiment, the anti-IFN-alpha antibody or antigen-binding fragment thereof is administered intravenously at a fixed dosage about 100 mg, or about 150 mg, or about 200 mg, or about 600 mg, or about 1200 mg once per month, with loading dose at Day 14.

[0148] When a series of fixed doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof are administered, these doses can, for example, be administered approximately every week, approximately every 2 weeks, approximately every 3, or about every 4 weeks. In some embodiments, fixed doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof are administered approximately every day, approximately every two days, approximately every three days, approximately every 4 days, approximately every 5 days, approximately every 6 days, or approximately every seven days. In a specific embodiment, the fixed dose of anti-IFN-alpha antibody or antigen-binding fragment thereof is a 100 mg dose administered daily. In a specific embodiment, the fixed dose of anti-IFN-alpha antibody or antigen-binding fragment thereof is a 150 mg dose administered daily. In specific embodiments, the fixed dose of anti-IFN-alpha antibody is a 100 mg daily dose or a 150 mg daily dose of sifalimumab.

[0149] In a specific embodiment, fixed doses of anti-IFN-alpha antibody or antigen-binding fragment thereof are administered every 2 weeks. These fixed doses can be administered, for example, for about 1 month, or about 2 months, or about 3 months, or about 4 months, or about 5 months, or about 6 months.

Such fixed doses can, for example, continue to be administered until disease progression, adverse event, or other parameter occurs as determined by the physician.. In some embodiments, patients can be administered at least one, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14 or at least 15 fixed doses of anti-IFN-alpha antibody or antigen-binding fragment thereof. In a specific embodiment, patients are administered at least 13 doses of anti-IFN-alpha antibody or antigen-binding fragment thereof. In some specific embodiments, patients can be administered at least 13 subcutaneous fixed doses of sifalimumab.

[0150] In some embodiments, fixed doses of anti-IFN-alpha antibody or antigen-binding fragment thereof are administered at equal time intervals. In other embodiment, fixed doses of anti-IFN-alpha antibody or antigen-binding fragment thereof are administered at varying intervals. In some embodiments, all administered fixed doses are essentially identical. In other embodiments, at least one fixed dose is different with respect to the other doses, *e.g.*, in volume, concentration, route of administration, formulation, etc.

[0151] For the prevention or treatment of autoimmune diseases, *e.g.*, SLE, scleroderma, or myositis, the fixed dose or weight-based of anti-IFN-alpha antibody, *e.g.*, sifalimumab, or antigen-binding fragment thereof will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician.

[0152] In some embodiments, one or more loading dose(s) of the anti-IFN-alpha antibody or antigen-binding fragment thereof, either weigh-based or fixed doses, can be administered, followed by one or more maintenance dose(s), either weigh-based or fixed doses, of the antibody. In another embodiment, a plurality of the same fixed doses of anti-IFN-alpha antibody or antigen-binding fragment thereof are administered to the patient. According to one embodiment of the disclosure, one or more weigh-based or fixed loading doses of anti-IFN-alpha antibody (*e.g.* sifalimumab) or an antigen-binding fragment can be administered,

followed by one or more weigh-based or fixed maintenance doses of the antibody. According to another embodiment of the disclosure, one or more weigh-based or fixed dose(s) of anti-IFN-alpha antibody (e.g. sifalimumab) or an antigen-binding fragment can be administered for up a number of cycles. In another embodiment, a weigh-based or fixed dose of anti-IFN-alpha antibody (e.g., sifalimumab) or an antigen-binding fragment can be administered as a loading dose, followed by one or more maintenance dose(s). About one, two or more maintenance doses of anti-IFN-alpha antibody or antigen-binding fragment thereof can be administered to the patient according to this embodiment.

[0153] Thus, the disclosure provides a method of treating an autoimmune disorder, e.g., SLE, scleroderma, or myositis in a human patient comprising administering at least one fixed dose of sifalimumab to the patient, wherein the fixed dose is about 100 mg, about 200 mg, about 600 mg, or about 1200 mg of sifalimumab.

Dosing to Achieve Desired Pharmacokinetic Characteristics

[0154] The term “pharmacokinetic characteristics” or PK characteristics refers to parameters describing the mechanisms of absorption and distribution of an administered drug, e.g., an anti-IFN-alpha antibody such as sifalimumab or an antigen-binding fragment thereof, the rate at which a drug action begins and the duration of the effect, the physicochemical chemical changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug. The methods disclosed herein, permit dose selection to achieve desired PK characteristics, whether the dosing be based on weight, fixed dosing, and whether the route of administration is, for example, intravenous or subcutaneous.

[0155] Such pharmacokinetic characteristics comprise, e.g., $T_{\max}$ (time of maximum observed concentration), $T_{\max \text{ ss}}$ (time of maximum observed concentration at steady state), $C_{\max}$ (maximum observed concentration), $C_{\max \text{ ss}}$ (maximum observed concentration at steady state), AUC_T (area under the curve over the dosing interval), $AUC_{T \text{ ss}}$ (area under the curve over the dosing interval at steady state), C_{trough} (trough observed concentration), $C_{\text{trough ss}}$ (trough observed concentration at steady state), half-life (terminal elimination half-life, defined as $\ln(2)/\lambda_z$), CL_{ss} (serum steady state clearance, defined as $\text{Dose}/AUC_{T \text{ ss}}$), V_{ss}

(steady state volume of distribution), AUC_{last} (area under the curve from time 0 to last observed concentration, *i.e.*, C_{last}), AUC_{inf} (area under the curve from 0 to infinity, defined as $(AUC_{last} + C_{last}/\lambda_z)$, AUC_{inf} extrapolated (percent of the AUC_{inf} curve extrapolated, defined as $((C_{last}/\lambda_z)/AUC_{inf}) * 100$), CL (apparent total body clearance of the drug from plasma), CL/F (apparent serum clearance), V_z/F (apparent terminal volume of distribution), CL_{ss}/F (apparent serum steady state clearance), V_c (central volume), V_p (peripheral volume) or λ_z (slope of the terminal elimination phase).

[0156] Pharmacokinetic characteristics can be used to determine the appropriate dosage of a drug of interest, *e.g.*, an anti-IFN-alpha antibody or antigen-binding fragment thereof. Characteristics describing the blood plasma curve can be obtained in clinical trials by administration of the active agent to a number of test subjects. The blood plasma values of the individual test persons are then averaged.

[0157] In the context of the present disclosure, pharmacokinetic characteristics, *e.g.*, AUC, C_{max} and T_{max} refer to mean values corresponding to a population of subjects. Further, in the context of the present disclosure, *in vivo* parameters such as values for AUC, C_{max} , T_{max} refer to parameters or values obtained after administration at steady state to human patients.

[0158] To quantify pharmacokinetic characteristics in patients, the patient group comprises between 10 to 200 patients. A reasonable number of patients is, *e.g.*, 10, 20, 30, 40, 50, 75, 100, 125, 150, 175 or 200 patients. Patients are selected according to inclusion and exclusion criteria related to the ability of a physician to adequately discern the symptoms of the condition to be treated and the effect of the tested drug over those symptoms.

[0159] The calculation of pharmacokinetic characteristics can be performed with the WinNonlin program in any of its versions and/or platform implementations. The skilled artisan will understand that such calculations can also be performed using other available software packages or by manual calculation according to formulas and methods known in the art.

[0160] For clarity and convenience herein, the convention is utilized of designating the time of drug administration or initiation of testing as zero hours

($t=0$ hours) or zero days (Day 0) and times following administration in appropriate time units, e.g., $t=30$ minutes or Day 68.

[0161] The term “bioavailability” is defined for purposes of the present disclosure as the extent to which an active agent such as an anti-IFN- α antibody, e.g., sifalimumab, or an antigen-binding fragment thereof is absorbed from the unit dosage forms. AUC provides a measure of bioavailability.

[0162] The term “steady state” means that a plasma level for a given drug, e.g., an anti-IFN- α antibody, e.g., sifalimumab, or an antigen binding fragment thereof, has been achieved and which is maintained with subsequent doses of the drug at a level which is at or above the minimum effective therapeutic level and is below the minimum toxic plasma level. It will be well understood by those skilled in the medical art that after the administration of each dose the concentration passes through a maximum and then again drops to a minimum. Accordingly, the steady state can be described as follows: At the time $t=0$, the time the first dose is administered, the concentration C is also 0. The concentration then passes through a first maximum and then drops to a first minimum. Before the concentration drops to 0, another dose is administered, so that the second increase in concentration doesn't start at 0. Building on this first concentration minimum, the curve passes through a second maximum after the second dose has been administered, which is above the first maximum, and drops to a second minimum, which is above the first minimum. Thus, the blood plasma curve escalates due to the repeated doses and the associated step-by-step accumulation of active agent, until it levels off to a point where dose administered and elimination are in balance. This state, at which dose administered and elimination are in equilibrium and the concentration oscillates constantly between a defined minimum and a defined maximum, is called steady state.

[0163] As used herein, the term “clearance rate” refers to CL (apparent total body clearance of the drug from plasma), CL_{ss} (serum steady state clearance), CL/F (apparent serum clearance) and CL_{ss}/F (apparent serum steady state clearance). As used herein, term “apparent volume of distribution” refers to V_{ss} (steady state volume of distribution) and V_z/F (apparent terminal volume of distribution). As

used herein, the term “half-life” refers to a biological half-life of a particular binding agent (e.g., an anti-INF-alpha antibody, such as sifalimumab, or an antigen binding fragment thereof) *in vivo*. Half-life can be represented by the time required for half the quantity administered to a subject to be cleared from the circulation and/or other tissues in the subject.

[0164] In some embodiments of the present disclosure, an anti-IFN-alpha or antigen-binding fragment thereof is administered in a dosage, such that an effective exposure is provided in a patient, for example as measured by, e.g., clearance rate, apparent volume of distribution, or half-life. The disclosure also includes methods which combine achieving two or more favorable pharmacokinetic characteristics or combinations thereof. Examples of those pharmacokinetic parameters include clearance rate (CL, CL_{ss} , CL/F , or CL_{ss}/F), an apparent volume of distribution (V_{ss} or V_z/F), and a serum half-life. For instance, the formulation administered through the methods of the disclosure can be selected such that when administered to a patient in need thereof, the selected formulation provides the patient with one or more of the desired pharmacokinetic characteristics.

[0165] In some embodiments, one or more desired pharmacokinetic characteristics is achieved after the administration of one or more doses of an anti-INF antibody or an antigen binding fragment thereof to a subject suffering from an autoimmune disorder. In some embodiments, such interferon alpha is human interferon alpha. In other embodiments, the one or more desired pharmacokinetic characteristics are selected, e.g., from the group consisting of from the group consisting of a clearance rate (CL, CL_{ss} , CL/F , or CL_{ss}/F), apparent volume of distribution (V_{ss} or V_z/F), and a serum half-life. In some embodiments, the immune disorder is systemic lupus erythematosus, scleroderma, or myositis.

[0166] In some embodiments, the desired pharmacokinetic characteristics are selected from the group consisting for a clearance rate (CL, CL_{ss} , CL/F , or CL_{ss}/F) of between about 99 and about 432 mL/day, an apparent volume of distribution (V_{ss} or V_z/F) of between about 3 and about 17 L, and a serum half-life

of about 14 days to about 47 days is achieved following the administration of the anti-IFN antibody or antigen-binding fragment thereof.

[0167] In some embodiments, the desired clearance rate (CL, CL_{ss}, CL/F, or CL_{ss}/F) is about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, about 310, about 320, about 330, about 340, about 350, about 360, about 370, about 380, about 390, about 400, about 410, about 420, about 430, or about 440 mL/day .

[0168] In some embodiments the desired apparent volume of distribution (V_{ss} or V_z/F) of about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, or about 17 L. In some embodiments, the desired serum half-life is about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, about 40, about 41, about 42, about 43, about 44, about 45, about 46, or about 47 days.

[0169] In some embodiments, such desired pharmacokinetic characteristics are achieved after the administration of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 doses. In some embodiments, such desired pharmacokinetic characteristics are achieved after the administration of at least 15 doses of an anti-IFN-alpha antibody, e.g., sifalimumab, or an antigen-binding fragment thereof. In some embodiments, such doses are intravenous. In other embodiments, such doses are subcutaneous. In other embodiments, such doses are weight-based, whereas in other cases such doses are fixed doses.

[0170] When fixed doses are administered to achieve the desired pharmacokinetic characteristics, such doses an anti-IFN-alpha antibody or antigen-binding fragment thereof can be of about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg. In other embodiments, an anti-IFN-alpha antibody or antigen-binding fragment thereof is administered at a fixed dosage of about 100

mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 100 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, about 2000 mg. In some embodiments, a loading dose is administered.

[0171] In a specific embodiment, the anti-IFN-alpha antibody or antigen-binding fragment thereof is administered intravenously at a fixed dosage about 100 mg, or about 150 mg, or about 200 mg, or about 250 mg, or about 300 mg, or about 400 mg, or about 500 mg, or about 600 mg, or about 700 mg, or about 800 mg, or about 900 mg, or about 1000 mg, or about 1100 mg, or about 1200 mg, or about 1300 mg, or about 1400 mg, or about 1500 mg, or about 1600 mg, or about 1700 mg, or about 1800 mg, or about 1900 mg, or about 2000 mg once per month, with a loading dose at Day 14.

[0172] In some embodiments, the desired pharmacokinetic characteristics can be achieved by administering doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof approximately every day, approximately every two days, approximately every three days, approximately every 4 days, approximately every 5 days or approximately every 6 days. In some embodiments, the desired pharmacokinetic characteristics can be achieved by administering doses of an anti-IFN-alpha antibody or antigen-binding fragment thereof approximately every week, approximately every 2 weeks, approximately every 3 weeks, or about every 4 weeks. In a specific embodiment, weight-based doses of anti-IFN-alpha antibody or antigen-binding fragment thereof are administered every 2 weeks. In other embodiments, the desired pharmacokinetic characteristics can be achieved by administering doses of an anti-IFN-alpha antibody or antigen binding fragment thereof, for example, for about 1 month, or about 2 months, or about 3 months, or about 4 months, or about 5 months, or about 6 months.

[0173] In some embodiments, the time to reach maximum plasma concentration ($T_{\max}$ or $T_{\max ss}$) following IV administration of an anti-IFN-alpha, such as sifalimumab, or an antigen-binding fragment thereof is about 0.13 days or less.

[0174] In some embodiments, the administration of an anti-IFN-alpha, such as sifalimumab, or an antigen-binding fragment thereof achieves a desired

pharmacokinetic characteristics chosen from clearance rate (CL , CL_{ss} , CL/F , or CL_{ss}/F), apparent volume of distribution (V_{ss} or V_z/F), a serum half-life, T_{max} (time of maximum observed concentration), $T_{max\ ss}$ (time of maximum observed concentration at steady state), C_{max} (maximum observed concentration), $C_{max\ ss}$ (maximum observed concentration at steady state), AUC_T (area under the curve over the dosing interval), $AUC_{T\ ss}$ (area under the curve over the dosing interval at steady state), C_{trough} (trough observed concentration), $C_{trough\ ss}$ (trough observed concentration at steady state), half-life (terminal elimination half-life, defined as $\ln(2)/\lambda_z$), CL_{ss} (serum steady state clearance, defined as $Dose/AUC_{T\ ss}$), V_{ss} (steady state volume of distribution), AUC_{last} (area under the curve from time 0 to last observed concentration, *i.e.*, C_{last}), AUC_{inf} (area under the curve from 0 to infinity, defined as $(AUC_{last}+C_{last})/\lambda_z$), AUC_{inf} extrapolated (percent of the AUC_{inf} curve extrapolated, defined as $((C_{last}/\lambda_z)/AUC_{inf})*100$), CL/F (apparent serum clearance), V_z/F (apparent terminal volume of distribution), CL_{ss}/F (apparent serum steady state clearance), V_c (central volume), V_p (peripheral volume), λ_z (slope of the terminal elimination phase), or combinations thereof.

[0175] In some embodiments a single IV administration of about 0.3 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a T_{max} of about 0.12 days or less, a maximum plasma concentration (C_{max}) of about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14 or about 15 $\mu\text{g/mL}$, an area under the plasma concentration-time curve during a dosage interval (τ) (AUC_T) of about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95, about 100, about 105, or about 110 $\mu\text{g day/mL}$, and a trough plasma concentration (C_{trough}) of about 2.0, about 2.2, about 2.4, about 2.6, about 2.8, about 3.0, about 3.2, about 3.4, about 3.6, about 3.8, or about 4.0 $\mu\text{g/mL}$.

[0176] In some embodiments, a single IV administration of about 0.3 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average T_{max} of about 0.07 days, an average C_{max} of about 11 $\mu\text{g/mL}$, an average AUC_T of about 79 $\mu\text{g day/mL}$, and an average C_{trough} of about 3 $\mu\text{g/mL}$.

- [0177] In some embodiments, a single IV administration of about 1 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.12 days or less, a $C_{\max}$ of about 20, about 25, about 30, about 35, about 40, or about 45 $\mu\text{g/mL}$, an AUC_T of about 150, about 175, about 200, about 225, about 250, about 275, or about 300 $\mu\text{g day/mL}$, and a C_{trough} of about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about, or about 15 $\mu\text{g/mL}$.
- [0178] In some embodiments, a single IV administration of about 1 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.08 days, an average $C_{\max}$ of about 32 $\mu\text{g/mL}$, an average AUC_T of about 221 $\mu\text{g day/mL}$, and an average C_{trough} of about 8 $\mu\text{g/mL}$.
- [0179] In some embodiments, a single IV administration of about 3 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.13 days or less, a $C_{\max}$ of about 60, about 70, about 80, about 90, about 100, about 110, about 120, about 130, about 140, or about 150 $\mu\text{g/mL}$, an AUC_T of about 450, about 500, about 550, about 600, about 650, about 700, about 750, about 800, about 850, about 900, about 950, about 1000, or about 1050 $\mu\text{g day/mL}$, and a C_{trough} of about 12, about 14, about 16, about 18, about 20, about 22, about 24, about 26, about 28, about 30, about 32, about 34, or about 36 $\mu\text{g/mL}$.
- [0180] In some embodiments, a single IV administration of about 3 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.09 days, an average $C_{\max}$ of about 103 $\mu\text{g/mL}$, an average AUC_T of about 739 $\mu\text{g day/mL}$, and an average C_{trough} of about 23 $\mu\text{g/mL}$.
- [0181] In some embodiments, a single IV administration of about 10 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.13 days or less, a $C_{\max}$ of about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, about 310, or about 320 $\mu\text{g/mL}$, an AUC_T of about 900, about 1000, about 1100, about 1200,

about 1300, about 1400, about 1500, about 1600, about 1700, about 1800, about 1900, about 2000, about 2100, about 2200, or about 2300 $\mu\text{g day/mL}$, and a C_{trough} of about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, or about 80 $\mu\text{g/mL}$.

[0182] In some embodiments, a single IV administration of about 10 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average T_{max} of about 0.09 days, an average C_{max} of about 230 $\mu\text{g/mL}$, an average AUC_T of about 1610 $\mu\text{g day/mL}$, and an average C_{trough} of about 52 $\mu\text{g/mL}$.

[0183] In some embodiments, a sufficient number of IV doses of about 0.3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics are chosen from: a $T_{\text{max ss}}$ of about 0.60 days or less, a $C_{\text{max ss}}$ of about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, or about 25 $\mu\text{g/mL}$, an $\text{AUC}_{T \text{ ss}}$ of about 80, about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, or about 200 $\mu\text{g day/mL}$, and a $C_{\text{trough ss}}$ of about 5 or less, about 6, about 7, about 8, about 9, about 10, or about 11 $\mu\text{g/mL}$ is achieved.

[0184] In some embodiments, a sufficient number of IV doses of about 0.3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average T_{max} of about 0.17 days, an average C_{max} of about 18 $\mu\text{g/mL}$, an average AUC_T of about 143 $\mu\text{g day/mL}$, and an average C_{trough} of about 8 $\mu\text{g/mL}$ is achieved.

[0185] In some embodiments, a sufficient number of IV doses of about 0.3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics selected from the group consisting of a clearance rate (CL_{ss}) of about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, or about 270 mL/day , an apparent volume of distribution (V_{ss}) of about 4, about 5, about 6, about 7, about 8, or about 9 L, and a serum half-life of

about 15 days, about 20 days, about 25 days, about 30 days, about 35 days, about 40 days, or about to about 45 days is achieved.

[0186] In some embodiments, a sufficient number of IV doses of about 0.3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics selected from the group consisting of an average clearance rate (CL_{ss}) of about 185 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 29 days is achieved.

[0187] In some embodiments, a sufficient number of IV doses of about 1 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max\ ss}$ of about 0.11 days or less, a $C_{max\ ss}$ of about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, or about 70 $\mu\text{g/mL}$, an $AUC_{T\ ss}$ of about 200, about 250, about 300, about 350, about 400, about 450, about 500, about 550, or about 600 $\mu\text{g day/mL}$, and a $C_{trough\ ss}$ of about 9, about 11, about 13, about 15, about 17, about 19, about 21, about 23, about 25, about 27, about 29, or about 31 $\mu\text{g/mL}$ is achieved.

[0188] In some embodiments, a sufficient number of IV doses of about 1 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average $T_{max\ ss}$ of about 0.07 days, an average $C_{max\ ss}$ of about 48 $\mu\text{g/mL}$, an average $AUC_{T\ ss}$ of about 197 $\mu\text{g day/mL}$, and an average $C_{trough\ ss}$ of about 11 $\mu\text{g/mL}$ is achieved.

[0189] In some embodiments, a sufficient number of IV doses of about 1 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics selected from the group consisting of a clearance rate (CL_{ss}) of about 120, about 140, about 160, about 180, about 200, about 220, about 240, about 260, about 280, about 300, about 320, about 340, or about 360 mL/day, an apparent volume of distribution (V_{ss}) of about 4, about 5, about 6, about 7, about 8, or about 9 L, and a serum half-life of about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22,

about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, or about 32 days is achieved.

[0190] In some embodiments, a sufficient number of IV doses of about 1 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics selected from the group consisting of an average clearance rate (CL_{ss}) of about 223 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 23 days is achieved.

[0191] In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max ss}$ of about 0.35 days or less, a $C_{max ss}$ of about 75, about 100, about 125, about 150, about 175, about 200, about 225, or about 250 $\mu\text{g/mL}$, an $AUC_{\tau ss}$ of about 500, about 600, about 700, about 800, about 900, about 1000, about 1100, about 1200, about 1300, about 1400, about 1500, about 1600, about 1700, about 1800, or about 1900 $\mu\text{g day/mL}$, and a $C_{trough ss}$ of about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, or about 75 $\mu\text{g/mL}$ is achieved.

[0192] In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average $T_{max ss}$ of about 0.13 days, an average $C_{max ss}$ of about 153 $\mu\text{g/mL}$, an average $AUC_{\tau ss}$ of about 1188 $\mu\text{g day/mL}$, and an average $C_{trough ss}$ of about 50 $\mu\text{g/mL}$ is achieved.

[0193] In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics selected from the group consisting of a clearance rate (CL_{ss}) of about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, or about 310 mL/day, an apparent volume of distribution (V_{ss}) of about 3.0, about 4.0, about 4.5, about 5.0, about 5.5, about 6.0, about 6.5, or about 7.0 L,

and a serum half-life of about 14 days, about 15, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, or about 26 days is achieved.

[0194] In some embodiments, a sufficient number of IV doses of about 3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics selected from the group consisting of an average clearance rate (CL_{ss}) of about 220 mL/day, an average apparent volume of distribution (V_{ss}) of about 5 L, and an average serum half-life of about 20 days is achieved.

[0195] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max\ ss}$ of about 0.85 days or less, a $C_{max\ ss}$ of about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 475, about 500, about 525, about 550, about 575, or about 600 $\mu\text{g/mL}$, an $AUC_{T\ ss}$ of about 2500, about 2600, about 2700, about 2800, about 2900, about 3000, about 3100, about 3200, about 3300, about 3400, about 3500, about 3600, about 3700, about 3800, about 3900, about 4000, about 4100, about 4200, or about 4300 $\mu\text{g day/mL}$, and a $C_{trough\ ss}$ of about 90, about 100, about 110, about 120, about 130, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, or about 290 $\mu\text{g/mL}$ is achieved.

[0196] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average $T_{max\ ss}$ of about 0.23 days, an average $C_{max\ ss}$ of about 232 $\mu\text{g/mL}$, an average $AUC_{T\ ss}$ of about 3403 $\mu\text{g day/mL}$, and an average $C_{trough\ ss}$ of about 184 $\mu\text{g/mL}$ is achieved.

[0197] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics selected from the group consisting of a clearance rate (CL_{ss}) of about 150, about 160, about 170, about

180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, about 310, or about 320 mL/day, an apparent volume of distribution (V_{ss}) of about 4.0, about 4.5, about 5.0, about 5.5, about 6.0, about 6.5, or about 7 L, and a serum half-life of about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23 days, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, or about 29 days is achieved.

[0198] In some embodiments, a sufficient number of IV doses of about 10 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 238 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 22 days is achieved.

[0199] In some embodiments, the number of IV doses at about 14-day intervals required to achieve steady state is about 5 to about 8 doses. In some embodiments, the desired pharmacokinetic characteristics are achieved after the antibody or antigen-binding fragment thereof is administered as a single dose or is administered in two or more doses once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months, once every six months, or at varying intervals. In some embodiments, the desired pharmacokinetic parameters are achieved after subcutaneous (SC) administration.

[0200] In some embodiments, the desired pharmacokinetic characteristics are achieved after the administration of 100 mg of anti-IFN-alpha administered as a single dose, or administered weekly, bi-weekly, or monthly. In some embodiments, the desired pharmacokinetic characteristics are achieved after the administration of 150 mg of anti-IFN-alpha administered as a single dose, or administered weekly, bi-weekly, or monthly. In some embodiments, the dose is administered intravenously. In other embodiments the dose is administered subcutaneously.

- [0201]** In some embodiments, at $T_{\max}$ or $T_{\max ss}$ of between about 1.8 and about 9.4 days is achieved. In some embodiments the $T_{\max}$ or $T_{\max ss}$ is about 2 days or lower, about 3 days or lower, about 4 days or lower, about 5 days or lower, about 6 days or lower, about 7 days or lower, about 8 days or lower, about 9 days or lower, or about 10 days or lower.
- [0202]** In some embodiments, a single SC administration of about 100 mg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10 days, a $C_{\max}$ of about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, or about 21 $\mu\text{g/mL}$, an area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_{last}) of about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 475, about 500, about 525, about 550, about 575, about 600, about 625, about 650, or about 675 $\mu\text{g day/mL}$, and an area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) of about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 475, about 500, about 525, about 550, about 575, about 600, about 625, about 650, about 675, about 700, about 725, about 750, or about 775 $\mu\text{g day/mL}$.
- [0203]** In some embodiments, a single SC administration of about 100 mg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 6 days, an average $C_{\max}$ of about 13 $\mu\text{g/mL}$, an average area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_{last}) of about 421 $\mu\text{g day/mL}$, and an average area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) of about 477 $\mu\text{g day/mL}$.
- [0204]** In some embodiments, a single SC administration of about 100 mg achieves one or more pharmacokinetic characteristics chosen from a clearance rate (CL/F) of about 100, about 125, about 150, about 175, about 200, about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, or about 450 mL/day , an apparent volume of distribution (V_z/F) of

about 5.0, about 5.5, about 6.0, about 6.5, about 7.0, about 7.5, about 8.0, about 8.5, about 9.0, about 9.5, about 10, about 10.5, about 11, about 11.5 or about 12 L, and a serum half-life of about 15 days, about 16 days, about 17 days, about 18 days, about 19 days, about 20 days, about 21 days, about 22 days, about 23, about 24 days, about 25 days, about 26 days, about 27 days, about 28 days, about 29 days, about 30 days, about 31 days, about 32 days, about 33 days, or about 34 days .

[0205] In some embodiments, a single SC administration of about 100 mg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from an average clearance rate (CL/F) of about 275 mL/day, an apparent volume of distribution (V_z/F) of about 8 L, and a serum half-life of about 25 days.

[0206] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ of about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, or about 6.5 days, a $C_{\max ss}$ of about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, or about 95 $\mu\text{g/mL}$, an $AUC_{\tau ss}$ of about 225, about 250, about 275, about 300, about 325, about 350, about 375, about 400, about 425, about 450, about 475, about 500, about 525, about 550, about 575, about 600, about 625, or about 650 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, or about 80 $\mu\text{g/mL}$ is achieved.

[0207] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to a population of subjects to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 4 days, an average $C_{\max ss}$ of about 65 $\mu\text{g/mL}$, an average $AUC_{\tau ss}$ of about 443 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 59 $\mu\text{g/mL}$ is achieved.

[0208] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of about 150, about 160, about 170, about 180, about

190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, about 310, about 320, about 330, about 340, about 350, about 360, about 370, about 380, about 390, or about 400 mL/day, an apparent volume of distribution (V_z/F) of about 7, about 7.5, about 8, about 8.5, about 9, about 9.5, about 10, about 10.5, about 11, about 11.5, about 12, about 12.5, about 13, about 13.5, about 14, about 14.5, or about 15 L, and a serum half-life of about 22, about 23, about 24 or less, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, or about 35 days is achieved.

[0209] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to a population of subjects to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 282 mL/day, an average apparent volume of distribution (V_z/F) of about 11 L, and an average serum half-life of about 28 days is achieved.

[0210] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max ss}$ of about 2, about 2.5, about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, or about 7 days, a $C_{max ss}$ of about 30, about 32, about 34, about 36, about 38, about 40, about 42, about 44, about 46, about 48, or about 50 $\mu\text{g/mL}$, an $AUC_{T ss}$ of about 420, about 430, about 440, about 450, about 460, about 470, about 480, about 490, about 500, about 510, about 520, about 530, about 540, about 550, about 560, or about 570 $\mu\text{g day/mL}$, and a $C_{trough ss}$ of about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, about 34, about 35, about 36, about 37, about 38, about 39, or about 40 $\mu\text{g/mL}$ is achieved.

[0211] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to a population of subjects to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{max ss}$ of about 4 days, an average C_{max}

C_{ss} of about 39 $\mu\text{g/mL}$, an average $\text{AUC}_{T_{ss}}$ of about 495 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 30 $\mu\text{g/mL}$ is achieved.

[0212] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of about 170, about 175, about 180, about 185, about 190, about 195, about 200, about 205, about 210, about 215, about 220, about 225, about 230, about 235, or about 240 mL/day, an apparent volume of distribution (V_z/F) of about 6 or less, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, about 9.5, or about 10 L, and a serum half-life of about 18, about 20, about 22, about 24, about 26, about 28, about 30, about 32, about 34, about 36, or about 38 days is achieved.

[0213] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to a population of subjects to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 406 mL/day, an average apparent volume of distribution (V_z/F) of about 8 L, and an average serum half-life of about 28 days is achieved.

[0214] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\text{max } ss}$ of about 3, about 3.5, about 4, about 4.5, about 5, about 5.5, about 6, about 6.5, about 7, about 7.5, or about 8 days, a $C_{\text{max } ss}$ of about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23, about 24, about 25, about 26, about 27, about 28, about 29, about 30, about 31, about 32, about 33, or about 34 $\mu\text{g/mL}$, an $\text{AUC}_{T_{ss}}$ of about 325, about 350, about 375, about 400, about 425, about 450, about 475, about 500, about 525, about 550, about 575, about 600, about 625, or about 650 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 6, about 6.5, about 7, about 7.5, about 8, about 8.5, about 9, about 9.5, about 10, about 10.5, about 11, about 11.5, about 12, about 12.5, about 13, about 13.5, about 14, about 14.5, or about 15 $\mu\text{g/mL}$ is achieved.

[0215] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to a population of subjects to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 6 days, an average $C_{\max ss}$ of about 49 $\mu\text{g/mL}$, an average $AUC_{T ss}$ of about 483 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 11 $\mu\text{g/mL}$ is achieved.

[0216] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, about 300, or about 310 mL/day, an apparent volume of distribution (V_z/F) of about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, or about 17 L, and a serum half-life of about 18, about 20, about 22, about 24, about 26, about 28, about 30, about 32, about 34, about 36, about 38, about 40, about 42, about 44, about 46, or about 48 days is achieved.

[0217] In some embodiments, a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to a population of subjects to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 227 mL/day, an average apparent volume of distribution (V_z/F) of about 11 L, and an average serum half-life of about 33 days is achieved.

Dosing to Achieve Desired Pharmacodynamic Characteristics

[0218] The term "pharmacodynamic characteristics" includes parameters describing the biological effects of an administered drug, *e.g.*, an anti-IFN- α antibody such as sifalimumab or an antigen-binding fragment thereof. One such characteristic is the expression of specific genes, which can serve as PD markers. In particular, certain genes when overexpressed in a patient suffering from an autoimmune disease relative to the genes' expression in a healthy

patient, or relative to the abundance of housekeeping genes, can serve as a type I IFN or IFN-alpha-inducible PD marker expression profile.

[0219] The group of genes included in the type I IFN or IFN-alpha-inducible PD marker expression profile of the patient are (a) IFI27, IFI44, IFI44L, IFI6 and RSAD2; or (b) IFI44, IFI44L, IFI6 and RSAD2; or (c) IFI27, IFI44L, IFI6 and RSAD2; or (d) IFI27, IFI44, IFI6 and RSAD2; or (e) IFI27, IFI44, IFI44L, and RSAD2; or (f) IFI27, IFI44, IFI44L, and IFI6.

[0220] In a specific embodiment, the group of genes included in the type I IFN or IFN-alpha-inducible PD marker expression profile of the patient comprises IFI27, IFI44, IFI44L, IFI6 and RSAD2. In another specific embodiment, the group of genes included in the type I IFN or IFN-alpha-inducible PD marker expression profile of the patient consists of IFI27, IFI44, IFI44L, IFI6 and RSAD2. In a further specific embodiment, the group of genes included in the type I IFN or IFN-alpha-inducible PD marker expression profile of the patient comprises IFI27, IFI44, IFI44L, and RSAD2. In another specific embodiment, the group of genes included in the type I IFN or IFN-alpha-inducible PD marker expression profile of the patient consists of IFI27, IFI44, IFI44L, and RSAD2.

[0221] The IFN-alpha-inducible PD markers in an expression profile may include (a) IFI27, IFI44, IFI44L, IFI6 and RSAD2; or (b) IFI44, IFI44L, IFI6 and RSAD2; or (c) IFI27, IFI44L, IFI6 and RSAD2; or (d) IFI27, IFI44, IFI6 and RSAD2; or (e) IFI27, IFI44, IFI44L, and RSAD2; or (f) IFI27, IFI44, IFI44L, and IFI6.

[0222] The IFN-alpha-inducible PD markers in an expression profile may consist of (a) IFI27, IFI44, IFI44L, IFI6 and RSAD2; or (b) IFI44, IFI44L, IFI6 and RSAD2; or (c) IFI27, IFI44L, IFI6 and RSAD2; or (d) IFI27, IFI44, IFI6 and RSAD2; or (e) IFI27, IFI44, IFI44L, and RSAD2; or (f) IFI27, IFI44, IFI44L, and IFI6.

[0223] An alternative set of genes that may serve as PD markers includes the 21 genes IFI44, IFI27, IFI44L, DNAPTP6, LAMP3, LY6E, RSAD2, HERC5, IFI6, ISG15, OAS3, SIGLEC1, OAS2, USP18, RPT4, IFIT1, MX1, OAS1, EPST1, PLSCR1, and IFRG28, as described in U.S. Patent Application 12/598, 526, file May 5, 2008. See Table 24 following paragraph [0500].

- [0224]** The upregulation or downregulation of the type I IFN or IFN-alpha-inducible PD markers in the patient's expression profile may be by any degree relative to that of a sample from a control (which may be from a sample that is not disease tissue of the patient (e.g., non-lesional skin of a psoriasis patient) or from a healthy person not afflicted with the disease or disorder) or may be relative to that of genes from the patient whose expression is not changed by the disease (so called "house keeping" genes.)
- [0225]** The degree upregulation or downregulation may be at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85, at least 90%, at least 95%, at least 100%, at least 125%, at least 150%, or at least 200%, or at least 300%, or at least 400%, or at least 500% or more that of the control or control sample.
- [0226]** Type I IFN or IFN-alpha-inducible PD marker expression profile may be calculated as the average fold increase in the expression or activity of the set of genes comprised by the PD marker. The Type I IFN or IFN-alpha-inducible PD marker expression profile may also be calculated as the difference between the mean C_t (cycle threshold) for the four target genes and the mean C_t of three control genes.
- [0227]** The average fold increase in the expression or activity of the set of genes may be between at least about 2 and at least about 15, between at least about 2 and at least about 10, or between at least about 2 and at least about 5. The average fold increase in the expression or activity of the set of genes may be at least about 2, at least about 2.5, at least about 3, at least about 3.5, at least about 4, at least about 4.5, at least about 5, at least about 5.5, at least about 6, at least about 6.5, at least about 7, at least about 8, at least about 9 or at least about 10.
- [0228]** The degree of increased expression permits the identification of a fold change cutoff for identifying signature positive and signature negative patients suffering from autoimmune diseases. In one embodiment, the cutoff is at least about 2. In another embodiment, the cutoff is at least about 2.5. In another embodiment, the cutoff is at least about 3. In another embodiment, the cutoff is

at least about 3.5. In another embodiment, the cutoff is at least about 4. In another embodiment, the cutoff is at least about 4.5. In another embodiment, the cutoff is chosen from at least 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, and 4.5. In another embodiment the cutoff is between about 2 and about 8. In one embodiment, the cutoff is the mean of the increased expression levels of at least four of IFI27, IFI44, IFI44L, IFI6 and RSAD2. In another embodiment, the cutoff is the median of the increased expression levels of at least four of IFI27, IFI44, IFI44L, IFI6 and RSAD2.

[0229] The degree of increased expression also permits the identification of a delta C_t cutoff for identifying signature positive and signature negative patients suffering from autoimmune diseases. In one embodiment, the cutoff is at least about 7.6. In another embodiment, the cutoff is 7.56. The fold change cutoff may be used to determine an appropriate delta C_t cutoff (e.g., $1 < \log_2$ of the fold change < 3 corresponds to delta C_t range of 8.65 to 6.56.). Thus, in another embodiment, the delta C_t cutoff is between about 6.56 to about 8.56.

[0230] Furthermore, the patient may overexpress or have a tissue that overexpresses a type I IFN subtype at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, at least 100%, at least 125%, at least 150%, or at least 200%, or at least 300%, or at least 400%, or at least 500% that of the control. The type I IFN subtype may be any one of IFNalpha1, IFNalpha2, IFNalpha4, IFNalpha5, IFNalpha6, IFNalpha7, IFNalpha8, IFNalpha10, IFNalpha14, IFNalpha17, IFNalpha21, IFNbeta, or IFNomega. The type I IFN subtypes may include all of IFNalpha1, IFNalpha2, IFNalpha8, and IFNalpha14.

[0231] The up-regulated expression or activity of any gene detected in a sample, by probes, or by probes in kits in an IFN-alpha-inducible PD marker expression profile may be at least 1.2-fold, at least 1.25-fold, at least 1.3-fold, at least 1.4-fold, at least 1.5-fold, at least 2.0-fold, at least 2.25-fold, at least 2.5-fold, at least 2.75-fold, at least 3.0-fold, at least 3.5-fold, at least 4.0-fold, at least 4.5-fold, at least 5.0-fold, at least 6.0-fold, at least 7.0-fold, at least 8.0-fold, at least 9.0-fold, at least 10.0-fold, at least 15.0-fold, at least 20.0-fold, at least 25.0-fold, or at least 50.0-fold relative to baseline levels of control cells, e.g., cells of healthy

volunteers or cells of control animals or cells not exposed to IFN in culture. All of the genes in the IFN-alpha-inducible PD marker expression profile may have up-regulated expression or activity at the same fold increase. Alternatively, the genes in the PD marker expression profile may have varying levels of up-regulated expression or activity.

Measuring Upregulation

[0232] Up- or down-regulation of gene expression or activity of IFN-alpha-inducible PD markers may be determined by any means known in the art. For example, up- or down-regulation of gene expression may be detected by determining mRNA levels. mRNA expression may be determined by northern blotting, slot blotting, quantitative reverse transcriptase polymerase chain reaction, or gene chip hybridization techniques. See U.S. Pat. Nos. 5,744,305 and 5,143,854 for examples of making nucleic acid arrays for gene chip hybridization techniques. See Establishing and functional characterization of an HEK-293 cell line expressing autofluorescently tagged β -actin (pEYFP-ACTIN) and the neurokinin type 1 receptor (NK1-R) Hrovat, A; Zavec, AB; Pogacnik, A; Frangez, R; Vrecl, M 2010 Cellular & Molecular Biology Letters 1, 55-69, Expression profiles of proliferative and antiapoptotic genes in sporadic and colitis-related mouse colon cancer models Svec, J; Ergang, P; Mandys, V; Kment, M; Pacha, J 2010 International Journal of Experimental Pathology 1, 44-53, and Protein kinase inhibitors emodin and dichloro-ribofuranosylbenzimidazole modulate the cellular accumulation and cytotoxicity of cisplatin in a schedule-dependent manner Kurokawa, T; He, GA; Siddik, ZH 2010 Cancer Chemotherapy and Pharmacology 3, 427-436, for examples of how to use the TAQMAN® method for measuring gene expression.

[0233] Primers that selectively bind to targets in polymerase chain reactions (PCR) can be chosen based on empirically determining primers that hybridize in a PCR reaction and produce sufficient signal to detect the target over background, or can be predicted using the melting temperature of the primer:target duplex as described in Maniatis et al. Molecular Cloning, Second Edition, Section 11.46. 1989. Similarly, probes for detecting PCR products in a

TAQMAN® or related method can be empirically chosen or predicted. Such primers and probes (collectively “oligonucleotides”) may be between 10 and 30 nucleotides or greater in length.

[0234] Up- or down-regulation of gene expression or activity of IFN-alpha-inducible PD markers may be determined by detecting protein levels. Methods for detecting protein expression levels include immuno-based assays such as enzyme-linked immunosorbant assays, western blotting, protein arrays, and silver staining.

[0235] An IFN-alpha-inducible PD marker expression profile may comprise a profile of protein activity. Up- or down-regulation of gene expression or activity of IFN-alpha-inducible PD markers may be determined by detecting activity of proteins including, but not limited to, detectable phosphorylation activity, dephosphorylation activity, or cleavage activity. Furthermore, up- or down-regulation of gene expression or activity of IFN-alpha-inducible PD markers may be determined by detecting any combination of these gene expression levels or activities.

Neutralization of the type I IFN or IFN-alpha-inducible profile in patients

[0236] Treatment with the anti-IFN-alpha antibody or antigen-binding fragment thereof neutralizes the type I IFN or IFN-alpha-inducible profile. Treatment with the anti-IFN-alpha antibody or antigen-binding fragment thereof results in a decrease in one or more symptoms of the type I IFN or an IFN-alpha-mediated disease or disorder. Treatment with the anti-IFN-alpha antibody or antigen-binding fragment thereof results in fewer flare-ups related to the type I IFN or an IFN-alpha-mediated disease or disorder. Treatment with the anti-IFN-alpha antibody or antigen-binding fragment thereof results in improved prognosis for the patient having the type I IFN or an IFN-alpha-mediated disease or disorder. Treatment with the anti-IFN-alpha antibody or antigen-binding fragment thereof results in a higher quality of life for the patient. Treatment with the anti-IFN-alpha antibody or antigen-binding fragment thereof alleviates the need to co-administer second agents (e.g., steroids) or may lessen the dosage of administration of the second agent to the patient. Treatment with the anti-IFN-alpha antibody or

antigen-binding fragment thereof reduces the number of hospitalizations of the patient that are related to the type I IFN or an IFN-alpha-mediated disease or disorder.

[0237] The anti-IFN-alpha antibody or antigen-binding fragment thereof neutralizes a type I IFN or IFN-alpha-inducible profile. Neutralization of the type I IFN or IFN-alpha-inducible profile may be a reduction in at least one, at least two, at least three, at least four genes. Neutralization of the type I IFN or IFN-alpha-inducible profile is a reduction of at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least 8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% of any of the at least one, at least two, at least three, at least four genes up-regulated in the type I IFN or IFN-alpha-inducible profile.

[0238] Alternatively, neutralization of the type I IFN or IFN-alpha-inducible profile refers to a reduction of expression of up-regulated type I IFN or IFN-alpha-inducible genes that is within at most 50%, at most 45%, at most 40%, at most 35%, at most 30%, at most 25%, at most 20%, at most 15%, at most 10%, at most 5%, at most 4%, at most 3%, at most 2%, or at most 1% of expression levels of those type I IFN or IFN-alpha-inducible genes in a control sample. The anti-IFN-alpha antibody or fragment thereof may neutralize the type I IFN or IFN-alpha profile at doses of 0.3 to 30 mg/kg, 0.3 to 10 mg/kg, 0.3 to 3 mg/kg, 0.3 to 1 mg/kg, 1 to 30 mg/kg, 3 to 30 mg/kg, 5 to 30 mg/kg, 10 to 30 mg/kg, 1 to 10 mg/kg, 3 to 10 mg/kg, or 1 to 5 mg/kg. In a specific embodiment, the type I IFN or IFN-alpha profile is neutralized by about 40% when sifalimumab is administered with weekly, subcutaneous dosing of 100 mg.

[0239] All of the references cited above, as well as all references cited herein, are incorporated herein by reference in their entireties.

[0240] The following examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

Intravenous Pharmacokinetics and Immunogenicity of Body Weight-Based Dosing Regimes of Sifalimumab Administered Intravenously to SLE Patients

[0241] The PK and immunogenicity (IM) of intravenous (IV) weight-based doses of sifalimumab administered every 14 days was studied in a Phase Ib study in adult patients with moderate to severe SLE to evaluate the safety profile of sifalimumab.

1. Methods**1.1 Study Design**

[0242] This was a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study with 4 arms for a total of 14 doses in 161 patients with moderate to severe SLE. 161 patients were randomized in a 3:1 ratio to receive sifalimumab or placebo. Sifalimumab was administered every 14 days as a 60-minute IV infusion. Four IV sifalimumab dosages were used: 0.3, 1.0, 3.0, and 10 mg/kg.

[0243] Criteria for inclusion of subjects receiving the antibody or antigen binding fragment thereof intravenously are summarized in clinical trial identifier NCT00482989, accessible via the U.S. National Institutes of Health clinicaltrials.gov database. Thus, inclusion criteria comprise: Male or female adults were between about 18 and about 95 years of age at the time of the first dose of study drug; subjects met at least 4 of the 11 revised American College of Rheumatology classification criteria for SLE (Appendix A, ACR, 1999); subjects had positive anti-nuclear antibody (ANA) test at $\geq 1:80$ serum dilution in the past or at screening; and subjects had at least one system with a score of A or two systems with a score of B on the BILAG index at screening, or had a SELENA-SLEDAI score ≥ 6 .

[0244] Exclusion criteria comprised having received MEDI-545 within 120 days prior to screening or have either detectable levels of MEDI-545 or anti-MEDI-545 antibodies (positive at $> 1:10$ serum dilution) in serum at screening; history of

allergy or reaction to any component of the study drug formulation; have received prednisone > 20 mg/day (or an equivalent dose of another oral corticosteroid) within 14 days before randomization/entry; having received the following dosages of medications within 28 days before randomization/entry: hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day, methotrexate > 25 mg/week, azathioprine > 3 mg/kg/day, or any dose of cyclophosphamide, cyclosporine, or thalidomide; having received leflunomide > 20 mg/day in the 6 months prior to Study Day 0; having received fluctuating doses of antimalarials, mycophenolate mofetil, methotrexate, leflunomide, or azathioprine within 28 days before randomization/entry or fluctuating doses of NSAIDs or oral corticosteroids within 14 days before randomization/entry; treatment with any investigational drug therapy within 28 days before randomization/entry into the study, B cell-depleting therapies within 12 months before randomization/entry, or biologic therapies within 30 days or 5 half-lives of the biologic agent, whichever was longer, before randomization/entry into the study; evidence of clinically significant active infection, including ongoing, chronic infection, within 28 days before randomization/entry; history of severe viral infection as judged by the investigators, including severe infections of either cytomegalovirus or the herpes family such as disseminated herpes, herpes encephalitis, ophthalmic herpes; herpes zoster infection within 3 months before randomization/entry; evidence of infection with hepatitis B or C virus, or HIV-1 or HIV-2, or active infection with hepatitis A, as determined by results of testing at screening; vaccination with live attenuated viruses within 28 days before randomization/entry; pregnancy (women, unless surgically sterile or at least 2 years post-menopausal, had a negative serum pregnancy test within 28 days before receiving the study drug and a negative urine pregnancy test on Study Day 0 before receiving the study drug); breastfeeding or lactating women; history of primary immunodeficiency; history of alcohol or drug abuse < 1 year prior to randomization/entry; history of cancer (except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to randomization/entry); history of active TB infection; history of latent TB infection or newly positive TB skin test (reaction defined as ≥ 10 mm in

diameter if not on systemic immunosuppressive medication or ≥ 5 mm if on systemic immunosuppressive medication) without completion of an appropriate course of treatment or with ongoing prophylactic therapy; elective surgery planned from the time of screening through Study Day 196; at screening blood tests (within 28 days before randomization/entry), any of the following (i) AST $> 2 \times$ upper limit of normal range (ULN), unless caused by SLE, as determined by the investigator, (ii) ALT $> 2 \times$ ULN, unless caused by SLE, as determined by the investigator, (iii) Creatinine > 4.0 mg/dL, (iv) Neutrophils " $1,500/\mu\text{L}$ ($< 1.5 \times 10^9/\text{L}$)," (v) Platelet count " $\text{Platelet count} < 50,000/\mu\text{L}$ ($< 50 \times 10^9/\text{L}$)"; history of any disease, evidence of any current disease (other than SLE), any finding upon physical examination, or any laboratory abnormality that, in the opinion of the investigator or medical monitor, may have compromised the safety of the patient in the study or confound the analysis of the study.

[0245] The inclusion and exclusion criteria listed above are not intended to limit the scope of the present disclosure. A person skilled in the art would understand that other inclusion and/or exclusion parameters may be used to generate a subject population such that the choice of subject does not compromise the safety of the subject or confounds the analysis of the study.

[0246] Trough serum samples were collected for PK concentrations and IM titers at multiple time points. Samples were analyzed for PK using a validated enzyme linked immunosorbent assays (ELISA) and for IM using a validated bridging electrochemiluminescent assay (ECL).

1.2. Measurement of Anti-sifalimumab Antibodies in Human Serum Samples Using a Validated Colorimetric Bridging ELISA Method (pre-study screen samples)

[0247] As part of the pre-study evaluation of subjects for inclusion in the study, serum was evaluated for anti-sifalimumab antibody responses. Serum samples were measured for the presence of anti-sifalimumab antibodies using a colorimetric bridging ELISA. Serum samples were diluted 1:10 and were added to a microtiter plate coated with sifalimumab. Following a wash step, biotinylated-sifalimumab was added to bind the captured anti-sifalimumab antibodies. Plates were washed and streptavidin conjugated with horseradish peroxidase was

added, followed by tetramethylbenzidine substrate for detection of bridged complexes. Plates were measured at a 450 nm wavelength using a Molecular Devices SpectraMax microplate reader and the results were analyzed using SOFTmax[®]PRO software. The color intensity of the reaction was proportional to the amount of anti-sifalimumab antibodies present in the sample.

[0248] The assay employed three positive controls ranging from 15 to 1500 ng/mL and one negative spiked control (0.75 ng/mL) that were prepared by adding goat anti-sifalimumab anti-idiotypic antibody into pooled normal human serum. The negative/positive cutoff value for samples was determined for each assay plate and was calculated by multiplying the mean value of six unique human serum samples measured on the plate by 1.5. Samples with responses below the plate cutoff value were classified as negative and were assigned a titer value of < 10, (less than the reciprocal of the minimum required sample dilution). Samples with responses greater than or equal to the plate cutoff value were classified as positive and were subsequently tested for titer. Titers were performed by serially diluting samples with pooled normal human serum matrix and were reported as the reciprocal of the highest 1:2 dilution (over the 1:10 minimum required sample dilution) that measured positive in the assay, before returning a negative response.

[0249] Method validation met the acceptance criteria for accuracy and precision of classification and titer, intermediate precision, repeatability, robustness, linearity of dilution, specificity of detection, analyte stability in human serum and selectivity in normal human and SLE patient serum samples. The estimated concentration of the cutoff of the assay was determined to be 4.5 ng/mL using the polyclonal goat anti-sifalimumab antibody surrogate control. Concentrations of 500 ng/mL anti-sifalimumab antibody (but not 100 ng/mL) were detectable in serum samples containing 100 ng/mL sifalimumab drug.

1.3. Measurement of sifalimumab in Human Serum Using a Validated Colorimetric ELISA Method

[0250] Sifalimumab was measured in human serum samples using a colorimetric ELISA method that was validated for human serum. In the assay, microtiter plates were coated with 0.5µg/mL goat anti-sifalimumab idio type antibody,

blocked with casein buffer and washed. Calibration standards (0.3 to 160 µg/mL) and control samples were prepared by diluting sifalimumab reference standard into human serum. Standards, controls and unknown samples were diluted 1:1000 in assay buffer that contained 0.5% casein and 5% goat serum and were added to the plate at 50 µL/well.

[0251] Following incubation, plates were washed to remove unbound material and goat anti-human IgG conjugated with horseradish peroxidase was added for binding of captured sifalimumab. Plates were washed and pre-warmed 2,2'-azino-bis-(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) peroxidase substrate was added. The reaction was stopped by addition of 1% sodium dodecyl sulfate (SDS) stop solution.

[0252] Plates were measured at a 405 nm wavelength using a Molecular Devices SpectraMax microplate reader and the results were analyzed using SOFTmax[®]PRO software. The color intensity of the reaction was proportional to the amount of sifalimumab present in the sample. Concentrations of sifalimumab in quality controls and unknown samples were interpolated from standard curves using a 4-parameter logistic fit. The assay lower limit of quantitation (LLOQ) was determined to be 1.25 µg/mL and the upper limit of quantitation (ULOQ) was determined to be 40 µg/mL.

[0253] Method validation demonstrated acceptable accuracy, repeatability, intermediate precision, selectivity (evaluated in serum samples from normal humans and humans with SLE), specificity, dilutional linearity, robustness, and stability of sifalimumab in human serum. Quantitation of sifalimumab at levels of 3.0 and 36.0 µg/mL was not affected in the presence of 2 ng/mL interferon alpha target.

1.4. Measurement of Anti-sifalimumab Antibodies in Human Serum Samples Using a Validated, Sensitive ECL Method

[0254] An ECL, solution-phase, bridging immunoassay that employs Meso Scale Discovery (MSD) technology was developed and validated for the detection, confirmation and titration of anti-sifalimumab antibodies in human serum. In the method, biotinylated sifalimumab and ruthenylated sifalimumab were incubated

overnight with human serum samples. Because of the bivalent nature of antibodies, a portion of anti-sifalimumab antibodies (ADA) present in the sample bound to both conjugated forms of sifalimumab at the same time. Subsequently, samples were incubated on a streptavidin-coated MSD plate for capture of the ADA-bridged complexes.

[0255] The plate was then washed to remove unbound materials, read buffer was added and the plate was placed on the MSD Sector™ Imager for generation and measurement of ECL response. Application of an electrical current to the electrode-containing plate caused the ruthenium chelate conjugated to sifalimumab to emit light in the presence of the tripropylamine-containing read buffer. Samples that contained ADA bound to both biotin and ruthenium conjugated forms of sifalimumab generated ECL signals. The signal intensity, measured by the MSD Sector Imager, was proportional to the amount of anti-sifalimumab antibodies present in the sample.

[0256] The method employed pooled normal human serum as the negative control and pooled normal human serum spiked with a goat anti-sifalimumab idiotype antibody (surrogate control) at two levels above detection (3.0 and 1000 ng/mL) as positive controls. The presence of anti-sifalimumab antibodies was determined relative to a cutoff ECL value that was calculated for each plate as the mean response of 6-8 wells of the negative control multiplied by a 1.18 cut point factor. The 1.18 cut point factor was established during validation from 200 measurements of serum samples obtained from 50 normal individuals and was statistically determined to provide a 5% false positive rate. Samples that measured at or above the cut point ECL value were considered as potential positives for anti-sifalimumab antibodies and were retested in a confirmatory (specificity) assay, both in the absence and presence of excess (300 µg/mL) sifalimumab.

[0257] The confirmatory cut point was established during method validation using the percent inhibition measurements of the above-mentioned samples tested both in the absence and presence of excess (300 µg/mL) sifalimumab. The confirmatory cut point was statistically determined to provide a 0.1% false positive rate and was determined to be 27.0%. The screening cut point factor and

confirmatory cut point for SLE serum samples were evaluated using the measured values of serum samples from fifty individual SLE patients and were calculated to be 1.23% and 37.1%, respectively. Study samples were considered positive for anti-sifalimumab antibodies if the percent inhibition of response in the presence of excess sifalimumab was greater than or equal to 27%, the more conservative confirmatory cut point. Confirmed positive samples were then measured in a titer assay.

[0258] Titers were performed by serially diluting samples with negative control serum and were reported as the reciprocal of the highest 1:2 dilution (over the 1:10 minimum required sample dilution) that measured positive in the assay, before returning a negative response. Titer values for negative samples were reported as <10. Method validation met the acceptance criteria for accuracy and precision of classification and titer, intermediate precision, repeatability, robustness, linearity of dilution, specificity of detection and analyte stability in human serum. Assay sensitivity was estimated using the polyclonal goat anti-sifalimumab antibody surrogate control as well as a monoclonal anti-sifalimumab antibody of known affinity ($K_d=1.30$ nM). The approximate concentration of anti-sifalimumab antibody at the cut point was 0.2 ng/mL for the polyclonal antibody and 4.7 ng/mL for the monoclonal antibody. Monoclonal anti-sifalimumab antibody levels of 250-500 ng/mL and polyclonal anti-sifalimumab antibody levels of 500 ng/mL were detectable in serum containing 100 µg/mL of sifalimumab. (provide temperature at which experiments were conducted).

1.5 Data Analysis

[0259] Pharmacokinetic concentrations were analyzed using non-compartmental methods in WinNonlin (version 5.2.1 Pharsight, Cary, NC).

2. Results

2.1. Pharmacokinetics

[0260] Serum sifalimumab PK results following the first dose and after the last dose on Day 182 are summarized in TABLE 2 and TABLE 3, respectively. After the first dose, sifalimumab peak plasma concentration (C_{max}), area under the

plasma concentration-time curve from time zero to end of dosing interval (AUC_T) and trough concentration (C_{trough}) increased dose-proportionally (TABLE 2). C_{max} values ranged from 10.90 $\mu\text{g/mL}$ for the 0.3 mg/kg dosage to 229.74 $\mu\text{g/mL}$ for the 10 mg/kg dosage. AUC_T values ranged from 79.39 $\mu\text{g}\cdot\text{day/mL}$ for the 0.3 mg/kg dosage to 1,610 $\mu\text{g}\cdot\text{day/mL}$ for the 10 mg/kg dosage. C_{trough} values ranged from 2.75 $\mu\text{g/mL}$ for the 0.3 mg/kg dosage to 51.52 $\mu\text{g/mL}$ for the 10 mg/kg dosage.

TABLE 2

Serum Sifalimumab PK Parameters Following the First Dose				
Parameter	0.3 mg/kg IV	1 mg/kg IV	3 mg/kg IV	10mg/kg IV
T_{max} (day)	0.074 (56.5)	0.079 (53.7)	0.088 (51.6)	0.092 (45.2)
C_{max} ($\mu\text{g/mL}$)	10.90 (37.4)	31.89 (35.2)	103.34 (37.9)	229.74 (38.6)
AUC_T ($\mu\text{g}\cdot\text{day/mL}$)	79.39 (31.5)	220.9 (30.9)	739.4 (36.6)	1610 (39.2)
C_{trough} ($\mu\text{g/mL}$)	2.75 (30.5)	8.01 (52.2)	23.43 (47.5)	51.52 (46.9)
Data presented as mean (%CV). the %Cv is calculated as the Standard deviation/mean*100 for the evaluable subjects.				

[0261] Steady state trough concentrations at each one of the tested doses was achieved in 3 months (FIG. 1, TABLE 3). Represented in the graph in FIG. 1 is the mean and standard deviation value for the nominal time point (scheduled blood draw) of available patients. If the value was below the limit of quantification, the value was treated as missing. Plotted values appear in TABLE 9.

[0262] Steady state peak plasma concentration ($C_{max ss}$) values ranged from 17.74 $\mu\text{g/mL}$ for the 0.3 mg/kg dosage to 441.79 $\mu\text{g/mL}$ for the 10 mg/kg dosage. Steady state area under the plasma concentration-time curve within a dosing interval ($AUC_{T ss}$) values ranged from 143.2 $\mu\text{g}\cdot\text{day/mL}$ for the 0.3 mg/kg dosage to 3,403 $\mu\text{g}\cdot\text{day/mL}$ for the 10 mg/kg dosage. Steady state trough concentration ($C_{trough ss}$) values ranged from 7.89 $\mu\text{g/mL}$ for the 0.3 mg/kg dosage to 183.97 $\mu\text{g/mL}$ for the 10 mg/kg dosage.

[0263] After the last dose on Day 182, the mean steady state clearance (CL_{ss}) ranged from 185 to 238 mL/day, mean terminal half-life ranged from 20 to

29 days across the dosing groups, and steady state volume of distribution (V_{ss}) ranged from 5 to 6 L across the dosing groups (TABLE 3).

TABLE 3

Serum Sifalimumab PK Parameters After Last Dose on Day 182				
Parameter	0.3 mg/kg IV	1 mg/kg IV	3 mg/kg IV	10 mg/kg IV
$T_{max\ ss}$ (day)	0.17 (252.0)	0.07 (59.6)	0.13 (152.2)	0.23 (256.3)
$C_{max\ ss}$ ($\mu\text{g/mL}$)	17.74 (38.7)	48.08 (38.9)	153.07 (51.3)	441.79 (34.7)
$AUC_{T\ ss}$ ($\mu\text{g}\cdot\text{day/mL}$)	143.2 (37.6)	401.8 (47.1)	1188 (55.1)	3403 (25.4)
$C_{trough\ ss}$ ($\mu\text{g/mL}$)	7.89 (36.6)	19.58 (52.2)	50.06 (47.8)	183.97 (49.4)
Half-life (day)	29.1 (47.4)	23.4 (34.9)	19.9 (29.8)	21.9 (30.7)
CL_{ss} (mL/day)	185 (46.3)	233 (49.4)	220 (38.3)	238 (34.1)
V_{ss} (L)	6.30 (40.0)	6.35 (45.2)	5.02 (40.1)	5.58 (29.0)
Data presented as mean (CV%).				

2.2. Immunogenicity

[0264] Twenty-seven out of 121 patients (22.3 %) receiving investigational product and one out of 40 patients (2.5%) receiving placebo tested positive for presence of anti-sifalimumab antibodies. Three out of 26 patients receiving 0.3 mg/kg doses of sifalimumab (11% incidence) (FIG. 2A), seven out of 25 patients receiving 1 mg/kg doses (28% incidence) (FIG. 2B), seven out of 27 patients receiving 3 mg/kg doses (25.9% incidence) (FIG. 2C), and ten out of 43 patients receiving 10 mg/kg doses (23.3% incidence) (FIG. 2D) tested positive for the presence of anti-sifalimumab antibodies. Positive titer values ranged from 10 to 1280, 17 subjects at or below 80, indicating low titers of anti-sifalimumab antibody (FIG. 3).

[0265] The presence of anti-sifalimumab antibodies did not have an impact on sifalimumab clearance (FIG. 4). Accordingly, sifalimumab had an acceptable safety and tolerability profile at the doses tested.

3. Conclusion

[0266] Sifalimumab PK was linear and dose-proportional following intravenous administration over the dose range of 0.3 mg/kg to 10 mg/kg. Serum clearance, volume of distribution and terminal half-life of sifalimumab were

representative of a monoclonal antibody without a significant antigen sink. The overall incidence of anti-sifalimumab antibodies was 22% with positive titers ranging from 10 to 1280. The presence of anti-sifalimumab antibody did not have an impact on the pharmacokinetics of sifalimumab.

Example 2

Population Pharmacokinetics of Sifalimumab in SLE Patients

[0267] The primary objectives of this analysis were to (a) model the population pharmacokinetics (PK) of sifalimumab; (b) to identify and quantitate the impact of patient/disease characteristics on PK variability; and (c) to evaluate fixed versus body weight based dosing regimens.

[0268] Dosing based on fixed-body weight is uncommon, as most biologics are dosed based on body weight. But for an anti-Her2 antibody, the PK data suggested fixed dosing might be possible. See, e.g., U.S. Patent No. 7,449,184. Whether the PK data would support fixed dosing for sifalimumab was uncertain because the body weight of the clinical trial subjects spanned 43 kg to 120 kg. Moreover, unlike the Her2 antibody discussed in U.S. Patent No. 7,449,184, sifalimumab binds multiple targets whose expression may vary among patients, and thus has a potentially more complex PK profile

1. Population Pharmacokinetic Analysis Methodology

[0269] Sifalimumab serum concentration-time data were collected from the study described in Example 1. Sifalimumab serum concentrations were determined with the validated colorimetric ELISA described in Example 1. A non-linear mixed-effect modeling approach was used to analyze sifalimumab pharmacokinetic data. The population pharmacokinetic modeling was performed using NONMEM Version VII software (Globomax LLC, Ellicott City, MD, USA), G-Fortran (<http://gcc.gnu.org/fortran/>) and Perl-speaks-NONMEM (PSN) (<http://psn.sourceforge.net/>). Data management and graphical analyses were performed using S-plus 8.1 (TIBCO Spotfire, Somerville, MA, USA), Xpose 4.0 (University of Uppsala, Uppsala, Sweden) and R 2.7.1 (<http://cran.r-project.org/>)

software. The various steps involved in the modeling processes are described below.

- [0270]** A series of structural models were evaluated for sifalimumab based on Akaike information criteria (AIC) value, objective function values, precision, plausibility of parameter estimates, and goodness-of-fit plots. The between-subject variability in pharmacokinetic parameters was assumed to follow a log-normal distribution and was modeled using exponential functions. The residual variability was evaluated using homoscedastic (additive), heteroscedastic (proportional), or combined proportional and additive models. The precision of the population estimates was evaluated based on percent relative standard errors (RSEs).
- [0271]** After the structural model was identified, covariate model-building was carried out to assess the effect of patient/disease characteristics on the pharmacokinetic parameters. Various patient/disease characteristics including age, gender, ethnicity, region, body weight (WT), baseline steroid use (BSTEROID), baseline systemic lupus erythematosus disease activity Index (BSLEDAI) score, baseline gene signature from 21 genes (BGENE21) and baseline gene signature from 4 genes (BGENE4) were evaluated.
- [0272]** A preliminary assessment of covariate influence was conducted using generalized additive modeling (GAM) approach as implemented in Xpose (Jonsson et al, 1999). Based on GAM results and mechanistic understanding of sifalimumab disposition, the relevant covariates for each parameter were further tested using NONMEM for their significance. The model building was carried out using step-wise forward addition ($p < 0.05$) ($\Delta\text{OFV} > 3.84$), approach followed by backward elimination ($p < 0.01$) ($\Delta\text{OFV} > 6.63$) process. The covariates were included in the final model if $p\text{-value} < 0.01$ ($\Delta\text{OFV} > 6.63$), provided the covariates were reasonable based on the pharmacology of sifalimumab.
- [0273]** Improvement in the model at each step was assessed using following criteria: (a) reduction in objective function value; (b) improvement in agreement between the observed and population/individual predicted serum concentrations; (c) reduction in between and within-subject variability; (d) reduction in the range of weighted residuals; (e) uniformity of the distribution of weighted residuals

versus the predicted concentrations around the line of identity; and (f) improvement in parameter precision. All models were run using the first order conditional estimation (FOCE) with interaction method.

[0274] The relationship between continuous covariates and pharmacokinetic parameters were modeled using non-linear power functions [equation (1)] with the covariate normalized to the population median for the data set. The categorical covariates were modeled using fractional change functions [equation (2)].

$$P = \theta_1 \times \left(\frac{COV}{Median} \right)^{\theta_2} \quad (1)$$

$$P = \theta_1 \times (1 + \theta_2 \times COV) \quad (2)$$

[0275] Where the θ s are the parameters to be estimated and θ_1 represents the typical value of pharmacokinetic parameter (P) in an individual with the median value for the covariate. θ_2 represents the coefficient for particular covariate effect.

[0276] The performance of the final population pharmacokinetic model was evaluated using visual predictive check (VPC), a technique whereby model appropriateness is tested by means of comparing prediction intervals (PIs) of the observed data to simulation data using final model.

[0277] The impact of body-weight based and fixed dosing of sifalimumab was evaluated by comparing predicted steady state serum concentrations (C_{ss}) and variability using population model. A population of 1000 SLE subjects were simulated using covariates (demographic, BGENE21, BSTEROID) distribution from study MI-CP152. The population model was also utilized for predicting pharmacokinetic exposure following various fixed intravenous doses of sifalimumab to support phase II dosing.

2. Results

2.1 Data

[0278] A total of 120 patients provided evaluable PK data with a total of 2,370 serum concentrations (average of 20 samples per patient). One subject from the 10 mg/kg cohort was excluded from the analysis due to very low observed serum

concentrations compared to the average concentrations in the 10 mg/kg cohort. TABLE 4 lists the summary of patient characteristics included in the pharmacokinetic database. A total of 8 subjects (6.67%) did not have baseline gene signature (4 genes) information available; hence a population median value was imputed for these subjects.

2.2 Population Pharmacokinetic Modeling

- [0279] A 2-compartment model was used to fit sifalimumab concentration-time data. The model was parameterized using clearance (CL), central volume of distribution (V_c), peripheral volume of distribution (V_p) and the inter-compartmental clearance (Q). The multiplicative covariate modeling approach was used to study the influence of various covariates including age, gender, ethnicity, region, WT, BSTEROID, BSLEDAI, BGENE21 and BGENE4.
- [0280] The final model functions for typical value of CL, V_c , V_p and Q are presented as follows (equations 3-6).

$$CL = \theta_1 \times \left(\frac{WT}{75}\right)^{\theta_5} \times \left(\frac{BGENE21}{32}\right)^{\theta_6} \times \left(\frac{Dose}{1}\right)^{\theta_7} \times (1 + \theta_8 \times BSTEROID) \quad (3)$$

$$V_c = \theta_2 \times \left(\frac{WT}{75}\right)^{\theta_9} \quad (4)$$

$$V_p = \theta_3 \times \left(\frac{WT}{75}\right)^{\theta_{10}} \quad (5)$$

$$Q = \theta_4 \quad (6)$$

- [0281] Where θ_1 is the typical CL of a standard subject with WT=75 kg, BGENE21=32, Dose=1 mg/kg and BSTEROID=0. θ_2 and θ_3 represent the V_c and V_p of a standard subject with WT=75 kg, respectively. θ_5 to θ_{10} are the exponents of covariate effect on respective pharmacokinetic parameters.
- [0282] The final population pharmacokinetic parameters are presented in TABLE 5. The estimated values of CL, V_c , V_p and Q for a standard subject were about 176 mL/day, 2.9 L, 2.12 L and 171 mL/day, respectively. The estimates of between-subject variability (CV_s) associated with CL, V_c , V_p and Q were 28%, 31%, 58% and 71%, respectively. All of the pharmacokinetic parameters were estimated with good precision, as reflected by RSEs. The performance of the

final model fit is represented by goodness of fit plots as shown in FIG. 5. These figures, FIG.5 panels (a) and (b), show good agreement between observed and model predicted (population/individual predicted) sifalimumab serum concentrations, as all the points are close to the line of identity and the fitted spline curve almost overlap the line of identity. The plots of weighted residual versus the population predicted concentrations, FIG. 5 panel (c), or time, FIG. 5 panel (d), do not show any obvious pattern. VPC results demonstrated good predictability of the final population PK model as shown in FIG. 6.

[0283] Based on the covariate relationships, higher sifalimumab CL was estimated for subjects with higher baseline type I IFN gene signature (21 genes), body weight, sifalimumab dose and steroid use. Both V_c and V_p also increased with increase in baseline body weight. Although the above mentioned covariates were identified as statistically significant covariates, they did not substantially explain inter-individual variability (<7%) in CL, V_c and V_p . This means that a decrease or increase in concentrations in individual patients in a dose group is not governed by body weight since a minimal magnitude of the overall variability in concentrations is explained by body weight. Hence no dosing modifications are necessary to administer sifalimumab.

2.2.1 Comparison of Fixed (mg) Versus Body weight Based (mg/kg) Dosing

[0284] The impact of fixed versus body weight based dosing was evaluated by comparing 200 mg (fixed) with 3 mg/kg (body weight based) every 14-days dosing of sifalimumab in a simulated SLE population of 1000 subjects. The body weight distribution (43 kg -120 kg) from MI-CP152 was used for the simulations. The final population PK model was used to predict 5th, median and 95th percentile concentration-time profiles. Simulation results demonstrate that both fixed and body weight based dosing regimens yield similar median steady state concentrations (C_{ss}) and variability as shown in FIG. 7.

2.2.2 Predicted Serum Concentrations

[0285] The final population PK model was used to predict PK profiles following 200, 600, and 1200 mg monthly (with an additional dose at Day 14) dose of

sifalimumab in a simulated SLE population of 1000 subjects. The predicted PK profiles (median, 5th and 95th percentiles) are shown in FIG 8. The expected steady state PK parameters following 200, 600, and 1200 mg monthly (with an additional dose at Day 14) dose of sifalimumab are presented in TABLE 6. Predicted PK exposure in 40 kg patient and 120 kg patients, at 5th and 95th percentile, appear in TABLE 11.

TABLE 4

Patient demographic characteristics and pharmacodynamic biomarkers
Categorical Variables

	No. of Patients (N)	Categories	Percentage (%)
Treatment Cohort (mg/kg)	26	0.3	21.7
	25	1	20.8
	27	3	22.5
	42	10	35
Sex	6	1 (Male)	5
	114	2 (Female)	95
Region	85	1 (North America)	70.8
	35	2 (South America)	29.2
BSTEROID	32	0 (no)	26.7
	88	1 (yes)	73.3

Continuous Variables

	No. of Patients (N)	Mean	SD	Median	Range
WT (kg)	120	76	19	73	43.1-120
Age (yr)	120	42	11	43	18-71
BSLEDAI	120	11	5	10	2-34
BGENE21	120	32	24	33	0.63-87
BGENE4	120	81	87	56	0.26-337

BSTEROID = Baseline steroid use; WT = Baseline body weight; BSLEDAI = Baseline SLEDAI Scores; BGENE21 = Baseline gene signature for 21 genes; BGENE4 = Baseline gene signature for 4 genes;

TABLE 5

Population pharmacokinetic parameters of sifalimumab from the final model

Parameter (unit)	Typical value (RSE, %)	Between-subject Variability, CV% (RSE, %)
$CL_{std} \{\theta_1\}$ (L/day)	0.176 (7)	28 (13)
$V_{C, std} \{\theta_2\}$ (L)	2.90 (3)	31 (19)
$V_{P, std} \{\theta_3\}$ (L)	2.12 (6)	58 (35)
$Q \{\theta_4\}$ (L/day)	0.171 (12)	71 (33)
Exponent: WT on $CL \{\theta_5\}$	0.481 (6)	
Exponent: BGENE21 on $CL \{\theta_6\}$	0.0558 (33)	
Exponent: Dose on $CL \{\theta_7\}$	0.0542 (17)	
Exponent: BSTEROID on $CL \{\theta_8\}$	0.195 (38)	
Exponent: WT on $V_c \{\theta_9\}$	0.489 (17)	
Exponent: WT on $V_p \{\theta_{10}\}$	0.646 (16)	
Correlation between CL and V_c	0.557 (21)	
Correlation between V_c and V_p	0.131 (8)	
Residual error (CV, %)	27.5 (8)	

CL = Linear clearance; V_c = Central volume of distribution; V_p = Peripheral volume of distribution; Q = Inter-compartmental clearance; BGENE21 = Baseline gene signature for 21 genes; BSTEROID = Baseline steroid use (0=no and 1=yes); WT = Baseline body weight; CV = Coefficient of variance.

CL_{std} = Clearance of a standard subject with WT=75 kg, BGENE21=32, Dose=1 mg/kg and BSTEROID=0; $V_{C, std}$ = Central volume of distribution for a standard subject with WT=75 kg; $V_{p, std}$ = Peripheral volume of distribution for a standard subject with WT=75 kg.

TABLE 6

Sifalimumab Predicted Mean Steady State Parameters

Dosing Regimen	$C_{max,ss}$ ($\mu\text{g/mL}$)	$C_{min,ss}$ ($\mu\text{g/mL}$)	AUC_{ss} ($\mu\text{g}\cdot\text{day/mL}$)
200 mg LD(D14)+ QM]	89	18	1110
600 mg LD(D14)+ QM]	268	53	3329

1200 mg LD(D14)+ QM] 536 106 6659
LD = Loading dose; QM = Every 28 days.

3. Conclusions

[0286] Sifalimumab PK was best described using a 2-compartment linear model with first order elimination. Following IV dosing, the typical clearance (CL) and central volume of distribution (V_c) were estimated to be 176 mL/day and 2.9 L, respectively. The estimates of between-subject variability for CL and V_c were 28% and 31%, respectively. Patient baseline body weight, IFN gene signature (21 genes), steroid use and sifalimumab dose were identified as significant covariates for CL, whereas only baseline body weight was significant covariate for V_c and V_p . Surprisingly, the above mentioned covariates were statistically significant, but they did not explain variability in sifalimumab PK parameters to any relevant extent. Thus leads to the conclusion that no weight-based dosing adjustments are necessary to administer sifalimumab. VPC results demonstrated good predictability of the final population PK model.

[0287] Simulation results demonstrated that both fixed and body weight based dosing regimens yield similar median steady state concentrations (C_{ss}) and variability. Accordingly, fixed sifalimumab doses of 200, 600 and 1200 mg monthly (with a loading dose at day 14) are selected for phase II clinical trial.

[0288] A population PK model of sifalimumab was developed and validated. The population PK analysis also demonstrated the feasibility of evaluating fixed doses of sifalimumab in phase II clinical trials.

Example 3

Pharmacokinetics and Immunogenicity of Single and Multiple Fixed Dosing Regimens of Sifalimumab Administered Subcutaneously to SLE Patients

[0289] The pharmacokinetics (PK) and immunogenicity (IM) of single and multiple subcutaneous (SC) fixed doses of sifalimumab administered to adult patients with moderate to severe SLE was studied in a phase II clinical trial.

1. Methods

1.1 Study design

- [0290] This was a multicenter, randomized, double-blind, placebo-controlled, Phase IIa parallel study with 5 evaluable arms (1:1:2:2:2 ratio).
- [0291] Criteria for inclusion of subjects receiving the antibody or antigen binding fragment thereof subcutaneously are summarized in clinical trial identifier NCT00657189, accessible via the U.S. National Institutes of Health clinicaltrials.gov database. Thus, inclusion criteria comprise: Male or female subjects were over 18 years and below 95 years of age at the time of the first dose of study drug; subjects met at least 4 of the 11 revised ACR classification criteria for SLE; subjects had positive antinuclear antibody test (ANA) at $\geq 1:80$ serum dilution documented in the past or at screening; subjects had at least 1 system with a score of A or 2 systems with a score of B on the BILAG index at screening, or have a SELENA-SLEDAI score ≥ 6 ; and treatment for SLE with antimalarials, oral prednisone or another systemic corticosteroid, mycophenolate mofetil, methotrexate, leflunomide, azathioprine, or dapsone.
- [0292] Exclusion Criteria comprised: having received MEDI-545 within 120 days prior to screening; history of allergy or reaction to any component of the study drug formulation; having received the following medications within 28 days before randomization: systemic cyclophosphamide at any dose, cyclosporine at any dose, thalidomide at any dose, hydroxychloroquine > 600 mg/day, mycophenolate mofetil > 3 g/day, methotrexate > 25 mg/week, azathioprine > 3 mg/kg/day; having received fluctuating doses of the following within 28 days before randomization: antimalarials, mycophenolate mofetil, methotrexate, leflunomide, azathioprine, dapsone; having received leflunomide > 20 mg/day in the 6 months prior to Study Day 0; having received prednisone > 20 mg/day or in fluctuating doses within 14 days before randomization; having received fluctuating doses of non-steroidal anti-inflammatory drugs within 14 days before randomization; treatment with any investigational drug therapy within 28 days before randomization into the study, B cell-depleting therapies within 12 months before randomization, or biologic therapies within 30 days or 5 half-lives of the biologic agent, whichever is longer, before randomization into the study; in the investigator's opinion, evidence of clinically significant active infection, including

ongoing, chronic infection, within 28 days before randomization; a history of severe viral infection as judged by the investigators, including severe infections of either cytomegalovirus or the herpes family such as disseminated herpes, herpes encephalitis, ophthalmic herpes; herpes zoster infection within 3 months before randomization; evidence of infection with hepatitis B or C virus, or human immunodeficiency virus (HIV)-1 or HIV-2, or active infection with hepatitis A, as determined by results of testing at screening; vaccination with live attenuated viruses within 28 days before randomization; pregnancy (women, unless surgically sterile or at least 2 years post-menopausal, had a negative serum pregnancy test within 28 days before receiving the study drug and a negative urine pregnancy test on days of study drug administration before receiving the study drug); breastfeeding or lactating women; history of primary immunodeficiency; history of alcohol or drug abuse < 1 year prior to randomization; history of cancer (except basal cell carcinoma or in situ carcinoma of the cervix treated with apparent success with curative therapy > 1 year prior to randomization); history of active tuberculosis (TB) infection or newly positive TB skin test (defined as a reaction ≥ 10 mm in diameter if not on systemic immunosuppressive medication or ≥ 5 mm if on systemic immunosuppressive medication history of latent TB infection without completion of an appropriate course of treatment; elective surgery planned from the time of screening through Study Day 168; at screening blood tests (within 28 days before randomization), any of the following (i) AST > 2.5 x upper limit of the normal range (ULN), unless caused by SLE, (ii) ALT > 2.5 x ULN, unless caused by SLE, (iii) Creatinine > 4.0 mg/dL, (iv) Neutrophils < 1,500/mm³, (v) Platelet count < 50,000/mm³; history of any disease, evidence of any current disease (other than SLE), any finding upon physical examination, or any laboratory abnormality that, in the opinion of the investigator or medical monitor, may compromise the safety of the subject in the study or confound the analysis of the study.

[0293] The inclusion and exclusion criteria listed above are not intended to limit the scope of the present disclosure. A person skilled in the art would understand that other inclusion and/or exclusion parameters may be used to generate a

subject population such that the choice of subject does not compromise the safety of the subject or confounds the analysis of the study.

[0294] Patients were administered up to 13 doses of either sifalimumab or placebo. Placebo was administered to 22 patients. Eleven patients received a single SC 100 mg fixed dose of sifalimumab. Twenty-one patients received a monthly SC 100 mg fixed dose of sifalimumab, with the last dose being administered on Day 84. Twenty-three patients received biweekly SC 100 mg fixed doses of sifalimumab, with the last dose being administered on Day 84. Ten patients received weekly SC 100 mg fixed doses of sifalimumab, with the last dose being administered on Day 84. Serum samples were collected for PK concentrations and IM titers at multiple time points.

[0295] Samples were analyzed for PK and IM using respectively the validated ELISA and ECL assays described in Example 1.

1.2 Data Analysis

[0296] Pharmacokinetic parameters were obtained using non-compartmental methods using WinNonlin (version 5.2.1 Pharsight, Cary, NC).

2. Results

2.1 Single Dose Administration

[0297] Results corresponding to the administration of a single 100 mg fixed dose of sifalimumab are summarized in TABLE 7 and FIG. 9 (●). Peak concentrations of sifalimumab occurred approximately 1 week after SC administration. Mean apparent extravascular clearance (CL/F) was approximately 275 mL/day. Elimination half-life was approximately 25 days. Plotted values appear in TABLE 10.

2.2 Multiple Dose Administration

[0298] Results corresponding to the administration of multiple 100 mg fixed doses of sifalimumab are summarized in TABLE 8, and FIG. 9 (weekly ■, bi-weekly ▲, or monthly ▼). $C_{\max ss}$ and $C_{\text{trough } ss}$ increased with dosing frequency. Accumulation of AUC and trough concentrations was 11-and 6-fold, respectively,

for weekly administration. Steady state AUC for multiple dose groups was similar to AUC after a single dose. Mean apparent extravascular steady state clearance (CL_{ss}/F) ranged from 206 to 282 mL/day across the dosing groups. Mean half-life ranged from 28 to 33 days. Apparent volume of distribution during terminal phase after non-intravenous administration (V_z/F) ranged from 8 L to 11 L.

2.3 Immunogenicity

[0299] Eight out of 65 patients (12.3%) receiving investigational product tested positive for presence of anti-sifalimumab antibodies (FIG. 10). There was no increase in incidence of immunogenicity across dosing regimens. Two out of 22 patients receiving placebo (9.1%) were M^+ , *i.e.*, they tested positive for the presence of anti-sifalimumab antibodies (titer range 10 to 40). None of the eleven patients receiving a single dose of sifalimumab were M^+ . In contrast, three out of ten patients following a monthly dosing regime (30%) were M^+ (titer range 20 to 160), three out of 23 patients following a bi-weekly dosing regime (13%) were M^+ (titer range 20 to 160) and two out of 21 patients (9.5%) following a weekly dosing regime (9.5%) were M^+ (titer range 20 to 320).

[0300] Presence of anti-sifalimumab antibody did not impact serum concentration-time profiles of sifalimumab. Sifalimumab had a safety/tolerability profile similar to that of placebo at the SC doses tested.

2.4 Effect on IFN Gene Signature

[0301] Pharmacodynamics (PD) markers can be used in methods of treating patients with a therapeutic agent that binds to and modulates IFN- α activity such as sifalimumab. See, *e.g.*, U.S. Patent Appl. No. 2010-0143372, which is hereby incorporated herein by reference in its entirety. Specifically, Example 7 in the 2010-0143372 publication describes 21 genes that can be used as PD markers: IFI44, IFI27, IFI44L, NAPTP, LAMP3, LY6E, RSAD2, HERC5, IFI6, ISG15, OAS3, RTP4, IFIT1, MX1, SIGLEC1, OAS2, USP18, OAS1, EPSTI1, PLSCR1 and IFRG28. Additionally, the 2010-0143372 publication provides methods for how to measure the levels of these 21 gene markers, *e.g.*, Affymetrix arrays and Fluidigm dynamic arrays.

[0302] Only the once-weekly dose of sifalimumab generated a sufficient PK exposure to induce a sustained IFN gene signature decrease over time (FIG. 11). In particular, weekly dosing produced suppression of the gene signature up to 40%.

3. Conclusion

[0303] Comparison of pharmacokinetic exposures of sifalimumab to previous intravenous studies indicated SC bioavailability of approximately 75%. PK of sifalimumab following SC administration was linear and dose-proportional. Pharmacokinetic parameters of sifalimumab following SC dosing were typical of a monoclonal antibody without a significant target sink. The overall incidence of anti-sifalimumab antibodies was 12%, however, the presence of anti-sifalimumab antibody did not impact the pharmacokinetics of sifalimumab.

TABLE 7

Sifalimumab Single Dose PK Parameters	
Parameter	Single 100 mg SC Dose (n = 10)
T_{max} (day)	5.78 (62.2)
C_{max} (µg/mL)	12.68 (68.4)
AUC_{last} (µg·day/mL)	420.6 (58.3)
AUC_{∞} (µg·day/mL)	477.6 (57.2)
AUC_{∞} Extrapolation (%)	12.5 (33.2)
CL/F (mL/day)	275 (57.0)
Half-life (day)	24.6 (37.8)
V_z/F (L)	8.32 (38.4)
Data from PK evaluable patients presented as mean (%CV).	

TABLE 8

Sifalimumab Multiple Dose PK Parameters			
Parameter	100 mg SC Weekly (n = 8)	100 mg SC Bi-weekly (n = 6)	100 mg SC Monthly (n = 6)

$T_{\max \text{ ss}}$ (day)	4.29 (51.6)	4.30 (59.0)	5.64 (35.9)
$C_{\max \text{ ss}}$ ($\mu\text{g/mL}$)	65.05 (42.7)	39.10 (24.2)	23.96 (39.8)
$AUC_{\text{ T ss}}$ ($\mu\text{g}\cdot\text{day/mL}$)	442.7 (44.0)	495.2 (14.4)	483.1 (32.6)
$C_{\text{ trough ss}}$ ($\mu\text{g/mL}$)	58.80 (36.2)	30.10 (31.7)	10.64 (39.6)
$CL_{\text{ ss}} / F$ (mL/day)	282 (40.4)	206 (16.5)	227 (33.1)
Half-life (day)	28.2 (22.8)	28.2 (32.7)	33.3 (41.6)
$V_{\text{ z}} / F$ (L)	11.1 (36.9)	8.19 (26.7)	11.0 (51.9)
Data from PK evaluable patients presented as mean (CV%).			
Parameters calculated after dosing on Day 84			

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TABLE 9

CP-152		Variable = PKConc										
TRTGRP	STUDYID CP152	NomTime										
		0.00	0.04	0.08	9.00	13.00	14.00	28.00	42.00	47.00	56	
MEDI-545 0.3 MG/KG												
N		32	26	26	Missing	Missing	25	26	24	Missing	24	
Mean		0.000	10.092	9.263	Missing	Missing	2.367	4.315	4.750	Missing	5.995	
SD		0.000	4.493	4.263	Missing	Missing	1.208	2.264	2.442	Missing	3.223	
Min		0.00	0.00	0.00	Missing	Missing	0.00	0.00	1.44	Missing	1.69	
Median		0.000	10.185	8.405	Missing	Missing	2.470	3.920	4.345	Missing	5.785	
Max		0.00	22.67	22.01	Missing	Missing	4.91	9.04	11.01	Missing	11.76	
CV%		Missing	44.5	46.0	Missing	Missing	51.0	52.5	51.4	Missing	53.7	
Geometric Mean		Missing	Missing	Missing	Missing	Missing	Missing	Missing	4.210	Missing	5.134	
MEDI-545 1.0 MG/KG												
N		26	25	25	Missing	Missing	24	24	23	Missing	23	
Mean		0.867	29.361	28.199	Missing	Missing	7.957	14.178	15.378	Missing	18.247	
SD		3.991	13.410	8.008	Missing	Missing	4.103	10.808	6.272	Missing	7.277	
Min		0.00	0.00	16.85	Missing	Missing	3.38	6.02	6.13	Missing	7.92	
Median		0.000	28.320	26.070	Missing	Missing	6.765	11.195	13.970	Missing	18.290	
Max		20.32	66.43	51.65	Missing	Missing	19.12	59.58	27.48	Missing	35.22	
CV%		460.6	45.7	28.4	Missing	Missing	51.6	76.2	40.8	Missing	39.9	
Geometric Mean		Missing	Missing	27.206	Missing	Missing	7.137	12.106	14.116	Missing	16.884	
MEDI-545 10.0 MG/KG												
N		44	43	43	1	Missing	40	38	39	Missing	36	
Mean		0.000	210.824	217.006	66.260	Missing	53.094	80.863	90.803	Missing	110.835	
SD		0.000	85.935	84.895	Missing	Missing	25.827	40.513	43.404	Missing	47.480	
Min		0.00	14.47	14.53	66.26	Missing	8.12	17.45	27.43	Missing	3.51	
Median		0.000	211.670	227.300	66.260	Missing	51.595	72.860	83.950	Missing	102.605	
Max		0.00	379.16	382.56	66.26	Missing	114.52	174.90	178.60	Missing	210.80	

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CV%	Missing	40.8	39.1	Missing	Missing	48.6	50.1	47.8	Missing	42.8
Geometric Mean	Missing	185.949	191.651	66.260	Missing	46.223	70.749	80.733	Missing	95.020
MEDI-545 3.0 MG/KG										
N	25	25	25	Missing	Missing	24	25	26	Missing	27
Mean	0.000	99.292	96.112	Missing	Missing	22.367	28.007	40.381	Missing	43.022
SD	0.000	41.106	37.254	Missing	Missing	10.808	15.212	22.740	Missing	23.770
Min	0.00	35.90	28.39	Missing	Missing	6.79	5.66	12.43	Missing	12.31
Median	0.000	94.830	95.100	Missing	Missing	20.050	28.190	32.905	Missing	38.180
Max	0.00	184.95	178.54	Missing	Missing	47.56	70.64	98.31	Missing	116.83
CV%	Missing	41.4	38.8	Missing	Missing	48.3	54.3	56.3	Missing	55.3
Geometric Mean	Missing	90.440	88.707	Missing	Missing	19.868	24.042	34.986	Missing	37.837
TRTGRP										
	70.00	84.00	96.00	98.00	112.00	113.00	126.00	140.00	141.00	154.00
MEDI-545 0.3 MG/KG										
	24	23	Missing	23	23	Missing	1	23	Missing	23
	6.080	6.710	Missing	6.498	6.733	Missing	0.000	6.930	Missing	6.256
	3.522	4.656	Missing	4.477	3.740	Missing	Missing	4.617	Missing	3.201
	0.00	0.00	Missing	0.00	0.00	Missing	0.00	0.00	Missing	0.00
	5.760	5.580	Missing	5.750	6.220	Missing	0.000	6.490	Missing	6.670
	12.34	18.66	Missing	18.52	15.04	Missing	0.00	20.12	Missing	13.66
	57.9	69.4	Missing	68.9	55.6	Missing	Missing	66.6	Missing	51.2
	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing
MEDI-545 1.0 MG/KG										
	21	23	Missing	22	23	Missing	Missing	20	Missing	20
	18.521	18.665	Missing	19.625	20.676	Missing	Missing	22.715	Missing	20.286
	6.361	7.704	Missing	8.486	10.770	Missing	Missing	13.577	Missing	8.708
	9.47	3.12	Missing	7.04	5.06	Missing	Missing	4.97	Missing	4.66
	19.160	17.720	Missing	18.280	19.550	Missing	Missing	19.255	Missing	19.255
	31.94	36.57	Missing	38.25	58.53	Missing	Missing	57.11	Missing	38.43
	34.3	41.3	Missing	43.2	52.1	Missing	Missing	59.8	Missing	42.9
	17.485	16.812	Missing	17.935	18.372	Missing	Missing	19.430	Missing	18.346
MEDI-545 10.0 MG/KG										
	36	38	Missing	36	37	Missing	1	33	Missing	34
	133.145	138.676	Missing	138.143	138.298	Missing	Missing	138.248	Missing	123.058
	66.232	63.355	Missing	82.577	72.621	Missing	Missing	72.618	Missing	86.410
	0.00	26.09	Missing	0.00	21.41	Missing	Missing	8.24	Missing	17.07

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117.345	131.150	Missing	141.825	128.690	196.480	Missing	138.630	118.180	Missing	92.300
285.80	270.67	Missing	359.67	446.72	196.48	Missing	293.67	370.79	Missing	379.66
49.7	45.7	Missing	59.8	52.5	Missing	Missing	52.5	63.7	Missing	70.2
Missing	123.391	Missing	Missing	122.299	196.480	Missing	112.943	96.644	Missing	95.710
MEDI-545 3.0 MG/KG										
27	24	Missing	24	27	Missing	Missing	23	20	1	21
45.782	35.673	Missing	43.089	38.404	Missing	Missing	47.260	47.215	97.700	43.872
42.551	22.427	Missing	26.721	20.672	Missing	Missing	27.640	19.570	Missing	24.521
14.02	0.00	Missing	5.21	9.31	Missing	Missing	10.88	11.29	97.70	5.22
33.990	34.360	Missing	35.770	34.690	Missing	Missing	39.060	46.500	97.700	40.240
240.14	114.21	Missing	130.61	82.73	Missing	Missing	125.58	80.46	97.70	100.60
92.9	62.9	Missing	62.0	53.8	Missing	Missing	58.5	41.4	Missing	55.9
37.292	Missing	Missing	35.931	32.839	Missing	Missing	40.795	42.532	97.700	36.410
TRTGRP										
155.00	160.00	161.00	168.00	174.00	182.00	182.04	182.08	185.00	189.00	195.00
MEDI-545 0.3 MG/KG										
Missing	Missing	Missing	23	1	22	21	21	19	20	Missing
Missing	Missing	Missing	6.376	0.000	6.761	16.730	15.117	11.993	9.961	Missing
Missing	Missing	Missing	2.757	Missing	2.996	7.995	5.830	4.862	3.371	Missing
Missing	Missing	Missing	0.00	0.00	0.00	0.00	0.00	5.62	4.90	Missing
Missing	Missing	Missing	6.070	0.000	7.425	14.360	14.990	11.540	9.180	Missing
Missing	Missing	Missing	11.48	0.00	12.35	34.52	27.60	21.90	18.41	Missing
Missing	Missing	Missing	43.2	Missing	44.3	47.8	38.6	40.5	33.8	Missing
Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	11.163	9.466	Missing
MEDI-545 1.0 MG/KG										
Missing	Missing	Missing	22	Missing	21	21	21	20	22	Missing
Missing	Missing	Missing	19.994	Missing	18.793	46.214	44.425	32.006	23.439	Missing
Missing	Missing	Missing	11.703	Missing	9.483	18.614	17.557	17.999	13.965	Missing
Missing	Missing	Missing	4.28	Missing	4.58	23.82	17.95	0.00	0.00	Missing
Missing	Missing	Missing	18.780	Missing	18.210	36.220	39.590	29.290	20.905	Missing
Missing	Missing	Missing	63.04	Missing	52.00	91.34	83.13	87.45	73.32	Missing
Missing	Missing	Missing	58.5	Missing	50.5	40.3	39.5	56.2	59.6	Missing
Missing	Missing	Missing	17.440	Missing	16.891	43.063	41.342	Missing	Missing	Missing
MEDI-545 10.0 MG/KG										
Missing	Missing	Missing	35	Missing	34	25	26	32	33	Missing
Missing	Missing	Missing	124.736	Missing	127.904	377.440	406.550	230.993	202.535	Missing

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Missing	Missing	Missing	85.858	Missing	87.376	123.078	160.702	113.038	105.993	Missing
Missing	Missing	Missing	17.23	Missing	16.04	212.18	223.72	13.58	5.71	Missing
Missing	Missing	Missing	114.870	Missing	116.635	362.740	379.785	246.100	206.640	Missing
Missing	Missing	Missing	377.85	Missing	318.62	615.91	970.99	465.88	475.09	Missing
Missing	Missing	Missing	68.8	Missing	68.3	32.6	39.5	48.9	52.3	Missing
Missing	Missing	Missing	96.182	Missing	95.198	358.791	381.682	181.495	155.792	Missing

MEDI-545 3.0 MG/KG

Missing	1	1	22	Missing	20	19	19	16	22	1
Missing	2.860	5.580	47.281	Missing	53.743	138.023	140.262	113.571	70.038	20.480
Missing	Missing	Missing	26.448	Missing	29.582	62.191	74.014	81.401	47.081	Missing
Missing	2.86	5.58	6.78	Missing	7.20	51.26	48.40	28.42	19.13	20.48
Missing	2.860	5.580	45.375	Missing	54.155	130.310	114.120	84.925	61.880	20.480
Missing	2.86	5.58	101.36	Missing	122.84	278.99	332.73	317.73	213.48	20.48
Missing	Missing	Missing	55.9	Missing	55.0	45.1	52.8	71.7	67.2	Missing
Missing	2.860	5.580	38.588	Missing	44.482	124.958	125.412	92.032	57.005	20.480

TRTGRP

MEDI-545 0.3 MG/KG	196.00	198.00	201.00	208.00	210.00	238.00	248.00	250.00	266.00	286.00	294.00
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21	Missing	Missing	1	20	21	Missing	Missing	20	Missing	19
7.353	Missing	Missing	3.830	5.156	2.173	Missing	Missing	1.283	Missing	0.208
3.293	Missing	Missing	Missing	2.264	1.822	Missing	Missing	1.411	Missing	0.665
0.00	Missing	Missing	3.83	2.09	0.00	Missing	Missing	0.00	Missing	0.00
7.160	Missing	Missing	3.830	4.960	1.980	Missing	Missing	0.695	Missing	0.000
15.64	Missing	Missing	3.83	11.40	5.73	Missing	Missing	3.61	Missing	2.67
44.8	Missing	Missing	Missing	43.9	83.8	Missing	Missing	110.0	Missing	319.2
Missing	Missing	Missing	3.830	4.708	Missing	Missing	Missing	Missing	Missing	Missing

MEDI-545 1.0 MG/KG

22	Missing	Missing	Missing	22	23	Missing	Missing	22	1	21
17.751	Missing	Missing	Missing	9.783	4.345	Missing	Missing	1.725	0.000	1.021
10.906	Missing	Missing	Missing	5.617	3.610	Missing	Missing	1.998	Missing	1.253
0.00	Missing	Missing	Missing	0.00	0.00	Missing	Missing	0.00	0.00	0.00
17.665	Missing	Missing	Missing	10.470	3.520	Missing	Missing	1.635	0.000	0.000
46.89	Missing	Missing	Missing	21.93	14.35	Missing	Missing	7.48	0.00	3.83
61.4	Missing	Missing	Missing	57.4	83.1	Missing	Missing	115.8	Missing	122.7
Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing	Missing

MEDI-545 10.0 MG/KG

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STUDYID												
	34	Missing	Missing	Missing	34	33	Missing	1	32	Missing	33	
TRTGRP	155.799	Missing	Missing	Missing	76.119	29.602	Missing	0.000	14.674	Missing	6.088	
	102.784	Missing	Missing	Missing	56.379	30.841	Missing	Missing	14.029	Missing	7.600	
	3.06	Missing	Missing	Missing	1.83	0.00	Missing	0.00	0.00	Missing	0.00	
	152.500	Missing	Missing	Missing	66.290	22.090	Missing	0.000	12.210	Missing	4.950	
	388.75	Missing	Missing	Missing	186.81	147.17	Missing	0.00	62.35	Missing	35.80	
	66.0	Missing	Missing	Missing	74.1	104.2	Missing	Missing	95.6	Missing	124.8	
	103.647	Missing	Missing	Missing	47.904	Missing	Missing	Missing	Missing	Missing	Missing	
	196.00	198.00	201.00	208.00	210.00	238.00	248.00	250.00	266.00	286.00	294.00	
MEDI-545 3.0 MG/KG												

	20	Missing	1	Missing	18	21	1	Missing	20	Missing	18
	48.320	Missing	4.400	Missing	27.488	11.900	8.160	Missing	5.619	Missing	2.422
	24.729	Missing	Missing	Missing	13.932	9.746	Missing	Missing	6.392	Missing	2.917
	10.74	Missing	4.40	Missing	5.70	0.00	8.16	Missing	0.00	Missing	0.00
	48.405	Missing	4.400	Missing	28.060	9.800	8.160	Missing	4.300	Missing	2.025
	86.53	Missing	4.40	Missing	59.11	38.62	8.16	Missing	22.83	Missing	12.24
	51.2	Missing	Missing	Missing	50.7	81.9	Missing	Missing	113.8	Missing	120.5
	41.052	Missing	4.400	Missing	23.762	Missing	8.160	Missing	Missing	Missing	Missing

TABLE 10

		STUDYID CPI79											
		NomTime											
TRTGRP		0	3	7	14	21	28	35	36	41	42	49	56
MEDI-545 100MG ONCE													
N		11	10	9	10	10	10	9	Missing	Missing	9	8	8
Mean		0.000	11.552	9.242	9.115	7.336	5.723	5.257	Missing	Missing	4.779	4.063	3.409
SD		0.000	9.161	2.224	4.420	4.496	2.871	2.478	Missing	Missing	2.137	2.063	2.039
Min		0.00	3.31	5.14	4.36	3.15	1.37	3.14	Missing	Missing	2.54	1.51	1.27

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Median	0.000	9.795	9.620	8.690	6.430	4.885	3.670	Missing	4.390	4.055	3.095
Max	0.00	36.69	12.37	19.58	18.16	10.96	9.35	Missing	8.03	7.43	6.52
CV%	Missing	79.3	24.1	48.5	61.3	50.2	47.1	Missing	44.7	50.8	59.8
Geometric Mean	Missing	9.629	8.974	8.295	6.381	5.016	4.797	Missing	4.356	3.588	2.846
MEDI-545 100MG Q1WK											
N	21	19	21	18	19	20	20	1	16	18	18
Mean	0.000	8.543	9.785	16.541	21.436	27.827	31.182	Missing	36.984	37.237	36.583
SD	0.000	5.164	4.193	6.037	7.204	10.194	13.329	Missing	14.132	16.891	17.258
Min	0.00	2.14	4.40	8.66	8.43	13.58	7.25	Missing	18.50	7.69	5.86
Median	0.000	7.480	9.570	17.570	20.890	26.440	29.665	Missing	34.045	34.080	35.655
Max	0.00	21.87	22.28	27.21	34.33	50.09	54.36	Missing	59.08	64.61	74.60
CV%	Missing	60.4	42.9	36.5	33.6	36.6	42.7	Missing	38.2	45.4	47.2
Geometric Mean	Missing	7.152	9.030	15.448	20.268	26.119	28.079	Missing	34.554	32.588	31.355
MEDI-545 100MG Q2WKS											
N	22	21	22	21	18	17	15	1	17	17	16
Mean	0.119	9.856	10.660	8.888	16.981	14.712	18.436	5.470	15.331	20.364	16.719
SD	0.559	5.352	5.160	4.112	7.866	8.329	6.904	Missing	8.322	9.643	8.055
Min	0.00	2.68	3.74	2.94	6.77	5.83	5.42	5.47	2.51	4.05	4.18
Median	0.000	8.680	9.030	7.700	16.145	11.770	20.030	5.470	15.790	20.330	16.450
Max	2.62	21.34	24.42	18.65	35.47	37.58	27.64	5.47	34.89	38.81	32.87
CV%	469.0	54.3	48.4	46.3	46.3	56.6	37.4	Missing	54.3	47.4	48.2
Geometric Mean	Missing	8.518	9.582	8.075	15.375	13.034	16.803	5.470	12.798	17.485	14.540
MEDI-545 100MG Q4WKS											
N	10	9	9	10	9	10	9	Missing	10	10	10
Mean	0.000	8.781	10.136	9.953	8.440	7.251	14.196	Missing	13.297	10.159	8.411
SD	0.000	4.267	3.794	3.283	2.166	1.531	6.100	Missing	5.599	4.694	3.460
Min	0.00	3.88	5.39	6.38	5.09	4.46	4.66	Missing	3.57	1.96	2.65
Median	0.000	8.630	10.260	10.010	8.230	7.325	14.560	Missing	13.600	10.080	8.715
Max	0.00	16.58	17.59	17.07	12.44	10.30	22.86	Missing	23.17	19.07	14.47
CV%	Missing	48.6	37.4	33.0	25.7	21.1	43.0	Missing	42.1	46.2	41.1
Geometric Mean	Missing	7.849	9.503	9.510	8.195	7.099	12.867	Missing	11.962	8.869	7.622
MEDI-545 100MG ONCE											
TRTGRP	63	70	77	84	87	91	98	112	140	168	

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N	6	5	5	5	5	6	5	4	1	0	0	0
Mean	3.377	3.940	3.174	2.316	1.775	1.886	1.518	1.330	Missing	Missing	Missing	Missing
SD	1.801	0.935	0.712	1.003	0.500	0.511	0.201	Missing	Missing	Missing	Missing	Missing
Min	1.36	2.68	2.37	1.52	1.27	1.46	1.35	1.33	Missing	Missing	Missing	Missing
Median	3.495	3.810	3.140	2.060	1.685	1.820	1.460	1.330	Missing	Missing	Missing	Missing
Max	5.30	4.87	4.10	4.02	2.73	2.71	1.80	1.33	Missing	Missing	Missing	Missing
CV%	53.3	23.7	22.4	43.3	28.2	27.1	13.3	Missing	Missing	Missing	Missing	Missing
Geometric Mean	2.929	3.846	3.110	2.174	1.725	1.836	1.508	1.330	Missing	Missing	Missing	Missing
MEDI-545 100MG Q1WK												
N	17	17	17	15	13	14	16	16	16	16	16	14
Mean	41.655	41.936	43.665	49.877	51.812	49.356	38.062	22.339	16.376	12.427	7.001	7.001
SD	16.144	27.702	19.666	27.647	26.100	21.776	19.036	10.016	9.374	7.767	4.619	4.619
Min	18.56	2.15	1.93	20.83	19.34	17.50	14.05	6.15	3.38	1.55	1.45	1.45
Median	35.850	35.930	41.450	39.340	45.230	45.350	33.455	22.275	15.700	11.265	5.975	5.975
Max	71.11	93.34	87.62	115.29	116.84	94.23	80.06	38.08	39.20	27.83	18.26	18.26
CV%	38.8	66.1	45.0	55.4	50.4	44.1	50.0	44.8	57.2	62.5	66.0	66.0
Geometric Mean	38.947	28.364	36.331	44.037	46.256	44.735	33.746	19.825	13.649	9.729	5.669	5.669
MEDI-545 100MG Q2WKS												
N	17	16	15	16	13	17	17	17	16	14	12	10
Mean	19.206	19.028	23.946	19.311	28.338	23.594	24.095	14.793	11.443	7.432	5.179	5.179
SD	7.915	8.785	12.946	10.670	16.436	13.104	15.020	9.576	8.233	6.060	4.151	4.151
Min	6.72	6.20	5.51	5.77	5.32	5.56	3.34	3.01	3.20	1.66	1.96	1.96
Median	20.820	20.650	28.860	16.235	24.410	21.870	19.260	11.280	8.650	4.855	4.115	4.115
Max	29.70	32.25	42.76	38.22	55.21	53.31	60.39	37.78	26.89	20.67	15.93	15.93
CV%	41.2	46.2	54.1	55.3	58.0	55.5	62.3	64.7	71.9	81.5	80.2	80.2
Geometric Mean	17.337	16.613	19.980	16.383	23.321	20.021	19.436	12.038	8.945	5.395	4.195	4.195
MEDI-545 100MG Q4WKS												
N	10	10	10	10	10	10	8	10	8	8	6	6
Mean	16.795	13.237	10.233	12.729	16.217	17.747	15.818	8.434	7.629	4.354	3.522	3.522
SD	10.001	6.304	5.270	11.012	7.734	10.748	9.465	4.445	3.316	2.183	2.065	2.065
Min	3.12	3.48	2.25	1.68	6.39	4.75	3.86	2.56	3.90	1.53	1.65	1.65
Median	16.375	14.475	10.675	11.615	13.340	13.570	13.245	7.790	6.935	4.525	3.015	3.015
Max	35.67	23.28	18.24	39.74	31.35	34.85	31.57	18.86	14.56	7.79	6.58	6.58
CV%	59.5	47.6	51.5	86.5	47.7	60.6	59.8	52.7	43.5	50.1	58.7	58.7

Geometric Mean	13.657	11.516	8.670	9.022	14.655	14.868	13.263	7.444	7.087	3.802	3.031
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TABLE 11

Expected PK Exposure in 40 kg Patient Population				
Dosing Regimen	C _{max,ss}		C _{min,ss}	
	5th Percentile	95th Percentile	5th Percentile	95th Percentile
0.3 mg/kg (Q14D)	6.68	15.25	2.29	8.11
1 mg/kg (Q14D)	21.25	49.29	6.8	24.65
3 mg/kg (Q14D)	61.84	143.96	18.47	68.11
10 mg/kg (Q14D)	200.29	466.6	55.03	210.1
30 mg/kg (Q14D)	584.94	1359.5	148.37	582.22
200 mg [LD(D14)+QM]	80.26	189.51	9.435	48.035
600 mg [LD(D14)+QM]	240.78	568.55	28.305	144
1200 mg [LD(D14)+QM]	481.57	1137.1	56.61	288.21

Expected PK Exposure in 120 kg Patient Population				
Dosing Regimen	C _{max,ss}		C _{min,ss}	
	5th Percentile	95th Percentile	5th Percentile	95th Percentile
0.3 mg/kg (Q14D)	11.64	26.62	3.9	13.95
1 mg/kg (Q14D)	37.02	85.14	11.52	42.55
3 mg/kg (Q14D)	107.61	248.69	31.19	117.59
10 mg/kg (Q14D)	348.51	806.2	92.58	357.74
30 mg/kg (Q14D)	1016.4	2361	249.13	993.96
200 mg [LD(D14)+QM]	46.43	110.61	5.415	28.23
600 mg [LD(D14)+QM]	139.3	331.84	16.245	84.71
1200 mg [LD(D14)+QM]	278.6	663.68	32.49	169.42

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WHAT IS CLAIMED IS:

1. A method of treating an autoimmune disorder in a human subject comprising administering to the subject an antibody, or antigen-binding fragment thereof which specifically binds to human interferon alpha, wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL, CL_{ss}, CL/F, or CL_{ss}/F) of between about 99 and about 432 mL/day, an apparent volume of distribution (V_{ss} or V_z/F) of between about 3 and about 17 L, and a serum half-life of about 14 days to about 48 days is achieved following the administration; and wherein the autoimmune disorder is systemic lupus erythematosus, scleroderma, or myositis.
2. The method of claim 1, wherein the antibody or antigen binding fragment thereof binds an epitope on human interferon alpha recognized by an antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22.
3. The method of claim 1 or claim 2, wherein the antibody or antigen binding fragment thereof comprises: (a) a heavy chain variable region CDR1 comprising SEQ ID NO: 1; (b) a heavy chain variable region CDR2 comprising SEQ ID NO: 4; (c) a heavy chain variable region CDR3 comprising SEQ ID NO: 7; (d) a light chain variable region CDR1 comprising SEQ ID NO: 10; (e) a light chain variable region CDR2 comprising SEQ ID NO: 13; and (f) a light chain variable region CDR3 comprising SEQ ID NO: 16.
4. The method of any one of claims 1 to 3, wherein the antibody or antigen binding fragment thereof comprises: (a) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 19, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID

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NO:36 or SEQ ID NO:37; and (b) a light chain variable region comprising the amino acid sequence of SEQ ID NO: 22.

5. The method of any one of claims 1 to 4, wherein the antibody or antigen binding fragment thereof is a human antibody or antigen binding fragment thereof.

6. The method of any one of claims 1 to 4, wherein the antibody or antigen binding fragment thereof is a chimeric antibody or antigen-binding fragment thereof.

7. The method of any one of claims 1 to 4, wherein the antibody or antigen binding fragment thereof is a humanized antibody or antigen-binding fragment thereof.

8. The method of any one of claims 1 to 7, wherein the antibody or antigen binding fragment thereof is an IgG1 or IgG4 antibody or antigen-binding fragment thereof.

9. The method of any one of claims 1 to 8, wherein the antigen binding fragment is a Fab antibody fragment or a single chain antibody (scFv).

10. The method of any one of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof is administered in a dosage dependent on the subject's body weight.

11. The method of claim 10, wherein the dosage ranges from about 0.01 mg/kg to about 100 mg/kg of the subject's body weight.

12. The method of claim 11, wherein the dosage is chosen from about 0.3 mg/kg body weight, about 1 mg/kg body weight, about 3 mg/kg body weight, and about 10 mg/kg body weight.

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13. The method of any one of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof is administered as a fixed dosage.

14. The method of claim 13, wherein the fixed dosage ranges from about 50 mg to about 2000 mg.

15. The method of claim 14, wherein the fixed dosage is chosen from about 100 mg, about 200 mg, about 600 mg, and about 1200 mg.

16. The method of any one of claims 1 to 15, wherein the antibody or antigen-binding fragment thereof is administered as a single dose or is administered in two or more doses once per week, once every two weeks, once every three weeks, once every four weeks, once a month, once every 3 months, once every six months, or at varying intervals.

17. The method of any one of claims 1 to 16, wherein a loading dose is administered at Day 14.

18. The method of any one of claims 1 to 16, wherein the administration is by a route chosen from intravenous, intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, inhalation, and a combination of two or more recited routes.

19. The method of claim 18, wherein the administration is intravenous (IV) administration.

20. The method of claim 19, wherein IV administration is by IV infusion over a period of time.

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21. The method of claim 19 or claim 20, wherein a time to reach maximum plasma concentration ($T_{\max}$ or $T_{\max \text{ ss}}$) following IV administration of about 0.13 days or less is achieved.

22. The method of any one of claims 19 to 21, wherein a single IV administration of about 0.3 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.12 days or less, a maximum plasma concentration ($C_{\max}$) of about 7 to about 15 $\mu\text{g/mL}$, an area under the plasma concentration-time curve during a dosage interval (τ) (AUC_{τ}) of about 54 to about 104 $\mu\text{g day/mL}$, and a trough plasma concentration (C_{trough}) of about 2 to about 4 $\mu\text{g/mL}$.

23. The method of any one of claims 19 to 21, wherein a single IV administration of about 0.3 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.07 days, an average $C_{\max}$ of about 11 $\mu\text{g/mL}$, an average AUC_{τ} of about 79 $\mu\text{g day/mL}$, and an average C_{trough} of about 3 $\mu\text{g/mL}$.

24. The method of any one of claims 19 to 21, wherein a single IV administration of about 1 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.12 days or less, a $C_{\max}$ of about 21 to about 43 $\mu\text{g/mL}$, an AUC_{τ} of about 153 to about 290 $\mu\text{g day/mL}$, and a C_{trough} of about 4 to about 12 $\mu\text{g/mL}$.

25. The method of any one of claims 19 to 21, wherein a single IV administration of about 1 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.08 days, an

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average $C_{\max}$ of about 32 $\mu\text{g/mL}$, an average AUC_T of about 221 $\mu\text{g day/mL}$, and an average C_{trough} of about 8 $\mu\text{g/mL}$.

26. The method of any one of claims 19 to 21, wherein a single IV administration of about 3 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.13 days or less, a $C_{\max}$ of about 64 to about 143 $\mu\text{g/mL}$, an AUC_T of about 469 to about 1010 $\mu\text{g day/mL}$, and a C_{trough} of about 12 to about 35 $\mu\text{g/mL}$.

27. The method of any one of claims 19 to 21, wherein a single IV administration of about 3 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.09 days, an average $C_{\max}$ of about 103 $\mu\text{g/mL}$, an average AUC_T of about 739 $\mu\text{g day/mL}$, and an average C_{trough} of about 23 $\mu\text{g/mL}$.

28. The method of any one of claims 19 to 21, wherein a single IV administration of about 10 mg/kg achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 0.13 days or less, a $C_{\max}$ of about 141 to about 318 $\mu\text{g/mL}$, an AUC_T of about 979 to about 2241 $\mu\text{g day/mL}$, and a C_{trough} of about 27 to about 76 $\mu\text{g/mL}$.

29. The method of any one of claims 19 to 21, wherein a single IV administration of about 10 mg/kg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: an average $T_{\max}$ of about 0.09 days, an average $C_{\max}$ of about 230 $\mu\text{g/mL}$, an average AUC_T of about 1610 $\mu\text{g day/mL}$, and an average C_{trough} of about 52 $\mu\text{g/mL}$.

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30. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 0.3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics are chosen from: a $T_{\max ss}$ of about 0.60 days or less, a $C_{\max ss}$ of about 11 to about 25 $\mu\text{g/mL}$, an $AUC_{\tau ss}$ of about 89 to about 197 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 5 to about 11 $\mu\text{g/mL}$ is achieved.

31. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 0.3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 0.17 days, an average $C_{\max ss}$ of about 18 $\mu\text{g/mL}$, an average $AUC_{\tau ss}$ of about 143 $\mu\text{g day/mL}$, and an average $C_{\text{trough } ss}$ of about 8 $\mu\text{g/mL}$ is achieved.

32. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 0.3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 99 and about 271 mL/day, an apparent volume of distribution (V_{ss}) of between about 4 and about 9 L, and a serum half-life of about 15 days to about 43 days is achieved.

33. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 0.3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 185 mL/day, an

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average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 29 days is achieved.

34. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 1 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max\ ss}$ of about 0.11 days or less, a $C_{max\ ss}$ of about 29 to about 67 $\mu\text{g/mL}$, an $AUC_{T\ ss}$ of about 213 to about 591 $\mu\text{g day/mL}$, and a $C_{trough\ ss}$ of about 9 to about 30 $\mu\text{g/mL}$ is achieved.

35. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 1 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average $T_{max\ ss}$ of about 0.07 days, an average $C_{max\ ss}$ of about 48 $\mu\text{g/mL}$, an average $AUC_{T\ ss}$ of about 197 $\mu\text{g day/mL}$, and an average $C_{trough\ ss}$ of about 11 $\mu\text{g/mL}$ is achieved.

36. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 1 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 118 and about 348 mL/day, an apparent volume of distribution (V_{ss}) of between about 4 and about 9 L, and a serum half-life of about 15 days to about 32 days is achieved.

37. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 1 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic

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characteristics chosen from an average clearance rate (CL_{ss}) of about 233 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 23 days is achieved.

38. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max\ ss}$ of about 0.33 days or less, a $C_{max\ ss}$ of about 75 to about 232 $\mu\text{g/mL}$, an $AUC_{T\ ss}$ of about 533 to about 1843 $\mu\text{g day/mL}$, and a $C_{trough\ ss}$ of about 26 to about 74 $\mu\text{g/mL}$ is achieved.

39. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 3 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average $T_{max\ ss}$ of about 0.13 days, an average $C_{max\ ss}$ of about 153 $\mu\text{g/mL}$, an average $AUC_{T\ ss}$ of about 1188 $\mu\text{g day/mL}$, and an average $C_{trough\ ss}$ of about 50 $\mu\text{g/mL}$ is achieved.

40. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 3 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 136 and about 304 mL/day, an apparent volume of distribution (V_{ss}) of between about 3 and about 7 L, and a serum half-life of about 14 days to about 26 days is achieved.

41. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 3 mg/kg are administered to a population of subjects at about 14-day

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intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 220 mL/day, an average apparent volume of distribution (V_{ss}) of about 5 L, and an average serum half-life of about 20 days is achieved.

42. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 10 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{max\ ss}$ about 0.82 days or less, a $C_{max\ ss}$ of about 288 to about 595 $\mu\text{g/mL}$, an $AUC_{T\ ss}$ of about 2539 to about 4267 $\mu\text{g day/mL}$, and a $C_{trough\ ss}$ of about 93 to about 275 $\mu\text{g/mL}$ is achieved.

43. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 10 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from: an average $T_{max\ ss}$ of about 0.23 days, an average $C_{max\ ss}$ of about 232 $\mu\text{g/mL}$, an average $AUC_{T\ ss}$ of about 3403 $\mu\text{g day/mL}$, and an average $C_{trough\ ss}$ of about 184 $\mu\text{g/mL}$ is achieved.

44. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 10 mg/kg are administered at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from a clearance rate (CL_{ss}) of between about 157 and about 319 mL/day, an apparent volume of distribution (V_{ss}) of between about 4 and about 7 L, and a serum half-life of about 15 days to about 29 days is achieved.

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45. The method of any one of claims 19 to 21, wherein a sufficient number of IV doses of about 10 mg/kg are administered to a population of subjects at about 14-day intervals to achieve a steady state, and wherein one or more pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 238 mL/day, an average apparent volume of distribution (V_{ss}) of about 6 L, and an average serum half-life of about 22 days is achieved.

46. The method of any one of claims 19 to 21, wherein the number of IV doses at about 14-day intervals required to achieve steady state is about 5 to about 8 doses.

47. The method of claim 18, wherein the administration is subcutaneous (SC) administration.

48. The method of claim 47, wherein the dosage is 100 mg administered as a single dose, or is administered weekly, bi-weekly, or monthly.

49. The method of claim 47 or claim 48, wherein at T_{max} or $T_{max ss}$ of between about 2 and about 10 days is achieved.

50. The method of any one of claims 47 to 49, wherein a single SC administration of about 100 mg achieves one or more pharmacokinetic characteristics chosen from: a T_{max} of about 2 to about 10 days, a C_{max} of about 4 to about 21 $\mu\text{g/mL}$, an area under the plasma concentration-time curve from time zero to time of last measurable concentration (AUC_{last}) of about 175 to about 666 $\mu\text{g day/mL}$, and an area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) of about 204 to about 751 $\mu\text{g day/mL}$.

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51. The method of any one of claims 47 to 49, wherein a single SC administration of about 100 mg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from: a $T_{\max}$ of about 6 days, a $C_{\max}$ of about 13 $\mu\text{g/mL}$, an AUC_{last} of about 421 $\mu\text{g day/mL}$, and an AUC_{∞} of about 477 $\mu\text{g day/mL}$.

52. The method of any one of claims 47 to 49, wherein a single SC administration of about 100 mg achieves one or more pharmacokinetic characteristics chosen from a clearance rate (CL/F) of between about 118 and about 432 mL/day , an apparent volume of distribution (V_z/F) of between about 5 and about 12 L, and a serum half-life of about 15 days to about 34 days.

53. The method of any one of claims 47 to 49, wherein a single SC administration of about 100 mg to a population of subjects achieves one or more pharmacokinetic characteristics chosen from an average clearance rate (CL/F) of about 275 mL/day , an apparent volume of distribution (V_z/F) of about 8 L, and a serum half-life of about 25 days.

54. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max \text{ ss}}$ of about 2 to about 7 days, a $C_{\max \text{ ss}}$ of about 37 to about 93 $\mu\text{g/mL}$, an $\text{AUC}_{\tau \text{ ss}}$ of about 248 to about 638 $\mu\text{g day/mL}$, and a $C_{\text{trough ss}}$ of about 38 to about 80 $\mu\text{g/mL}$ is achieved.

55. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 7-day (weekly) intervals to achieve a steady state, and wherein one or more steady state

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pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 4 days, an average $C_{\max ss}$ of about 65 $\mu\text{g/mL}$, an average $AUC_{T ss}$ of about 443 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 59 $\mu\text{g/mL}$ is achieved.

56. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered at about 7-day (weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of between about 168 and about 396 mL/day, an apparent volume of distribution (V_z/F) of between about 7 and about 15 L, and a serum half-life of about 22 days to about 35 days is achieved.

57. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 7-day (weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 282 mL/day, an average apparent volume of distribution (V_z/F) of about 11 L, and an average serum half-life of about 28 days is achieved.

58. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ of about 2 to about 7 days, a $C_{\max ss}$ of about 30 to about 49 $\mu\text{g/mL}$, an $AUC_{T ss}$ of about 424 to about 567 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 21 to about 40 $\mu\text{g/mL}$ is achieved.

59. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 14-day

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(bi-weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 4 days, an average $C_{\max ss}$ of about 39 $\mu\text{g/mL}$, an average $AUC_{T ss}$ of about 495 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 30 $\mu\text{g/mL}$ is achieved.

60. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered at about 14-day (bi-weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of between about 172 and about 240 mL/day, an apparent volume of distribution (V_z/F) of between about 6 and about 10 L, and a serum half-life of about 19 days to about 37 days is achieved.

61. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 14-day (bi-weekly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 406 mL/day, an average apparent volume of distribution (V_z/F) of about 8 L, and an average serum half-life of about 28 days is achieved.

62. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a $T_{\max ss}$ of about 3 to about 8 days, a $C_{\max ss}$ of about 14 to about 34 $\mu\text{g/mL}$, an $AUC_{T ss}$ of about 326 to about 641 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 6 to about 15 $\mu\text{g/mL}$ is achieved.

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63. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 30-day (monthly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: an average $T_{\max ss}$ of about 6 days, an average $C_{\max ss}$ of about 49 $\mu\text{g/mL}$, an average $AUC_{T ss}$ of about 483 $\mu\text{g day/mL}$, and a $C_{\text{trough } ss}$ of about 11 $\mu\text{g/mL}$ is achieved.

64. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered at about 30-day (monthly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from: a clearance rate (CL_{ss}/F) of between about 152 and about 302 mL/day, an apparent volume of distribution (V_z/F) of between about 5 and about 17 L, and a serum half-life of about 19 days to about 47 days is achieved.

65. The method of any one of claims 47 to 49, wherein a sufficient number of SC doses of about 100 mg are administered to a population of subjects at about 30-day (monthly) intervals to achieve a steady state, and wherein one or more steady state pharmacokinetic characteristics chosen from an average clearance rate (CL_{ss}) of about 227 mL/day, an average apparent volume of distribution (V_z/F) of about 11 L, and an average serum half-life of about 33 days is achieved.

66. The method of any one of the preceding claims, wherein the administration of a sufficient number of doses of an anti-IFN- α antibody or antigen-binding fragment thereof suppresses an IFN pharmacodynamic signature.

67. The method of claim 66, wherein the IFN pharmacodynamic signature is a Type I IFN- α inducible expression profile.

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68. The method of claim 67, wherein the Type I IFN-alpha inducible expression profile comprises up-regulated expression of a gene marker set comprising IFI44, IFI27, IFI44L, NAPTP, LAMP3, LY6E, RSAD2, HERC5, IFI6, ISG15, OAS3, RTP4, IFIT1, MX1, SIGLEC1, OAS2, USP18, OAS1, EPSTI1, PLSCR1 and IFRG28.

69. The method of claim 68, wherein the anti-IFN antibody or antigen-binding fragment thereof neutralizes the pharmacodynamic expression profile of the patient by at least 10%, at least 20%, at least 30% or at least 40%.

70. The method of any of the proceeding claims, wherein at least one disease symptoms is reduced.

71. The method of claim 70, wherein the reduction in at least one disease symptom results in a decrease in the SLEDAI score or BILAG score.

72. The method of claim 71, wherein the SLEDAI score is reduced by at least 1 point.

73. The method of claim 72, wherein the SLEDAI score is reduced by at least 2 points.

74. The method of claim 73, wherein the SLEDAI score is reduced by at least 3 points.

75. The method of claim 74, wherein the SLEDAI score is reduced by at least 4. points.

FIG. 1

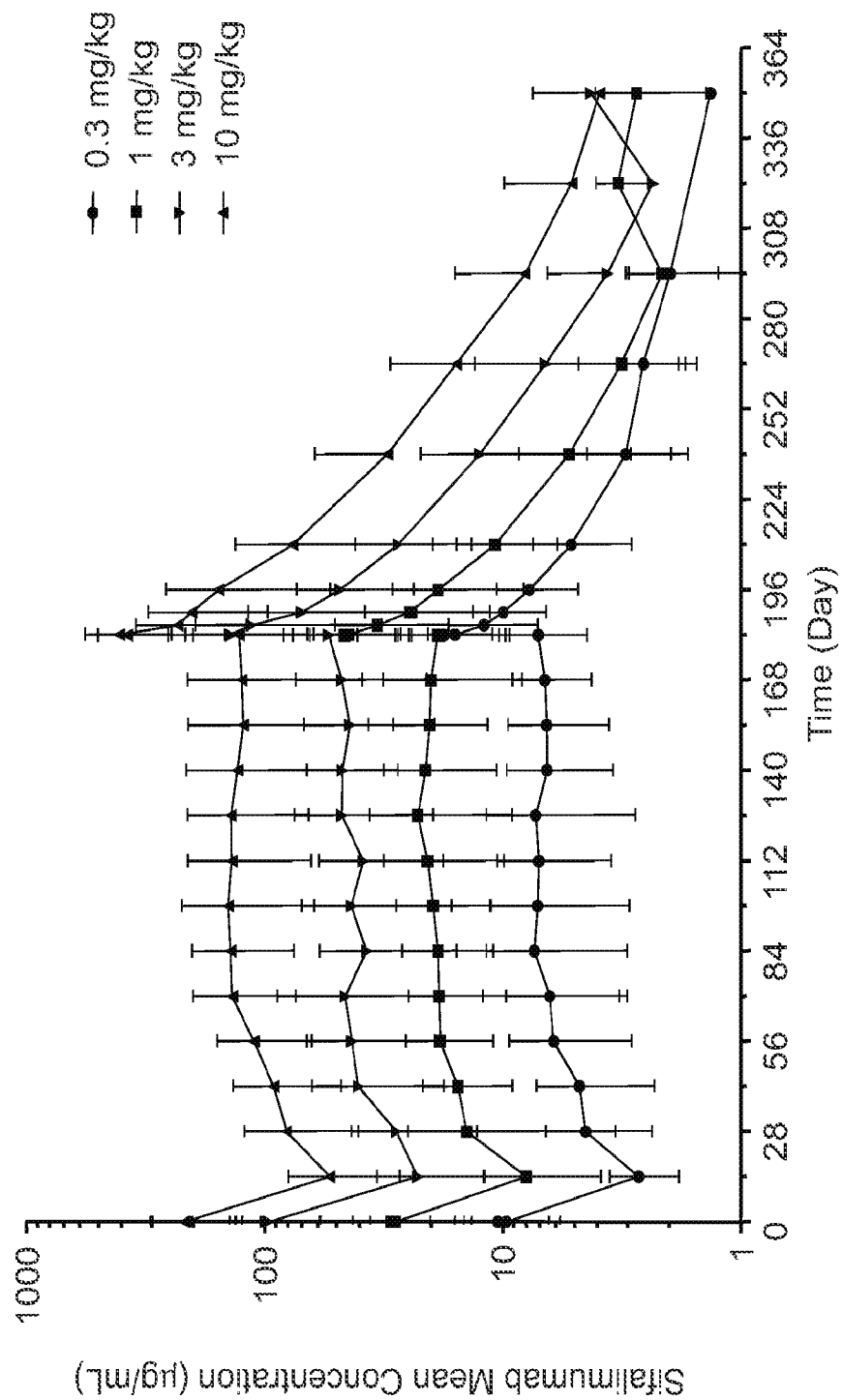


FIG. 2A

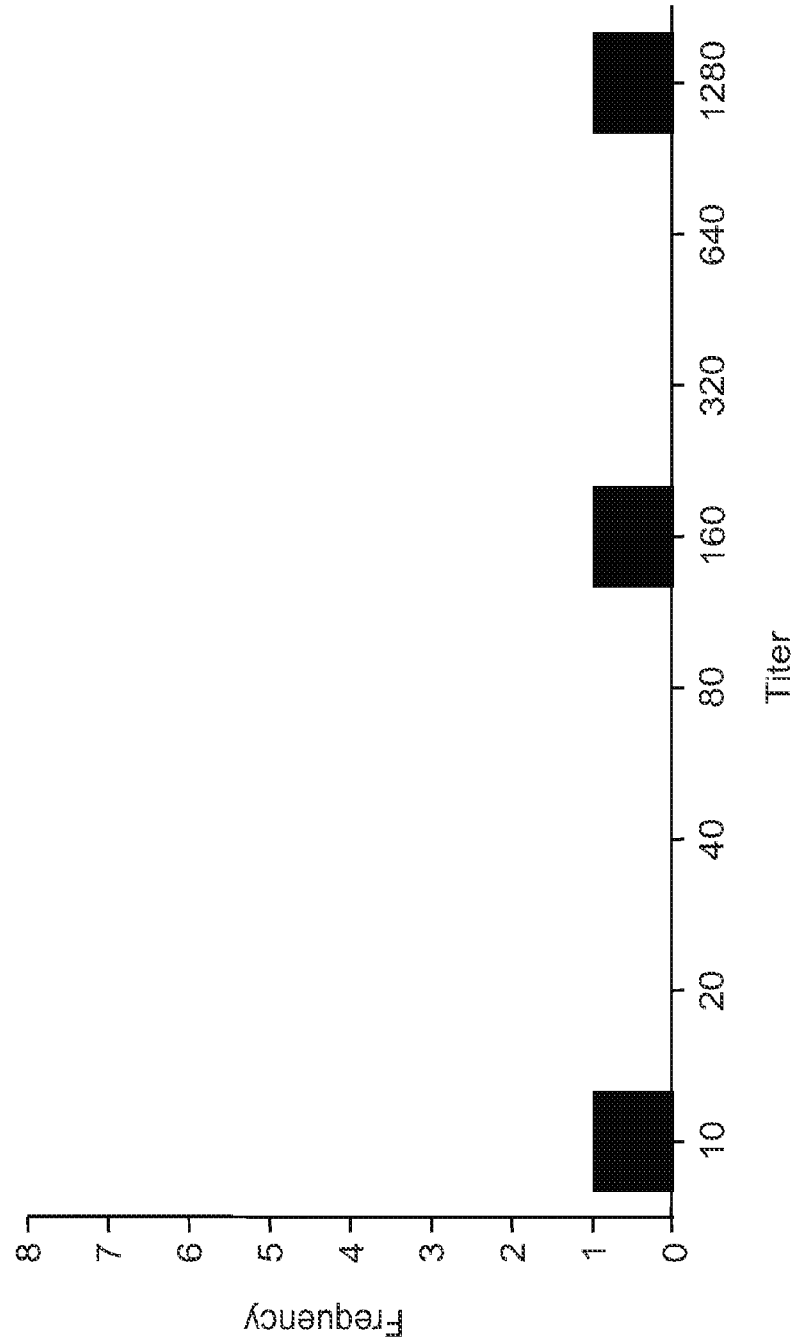


FIG. 2B

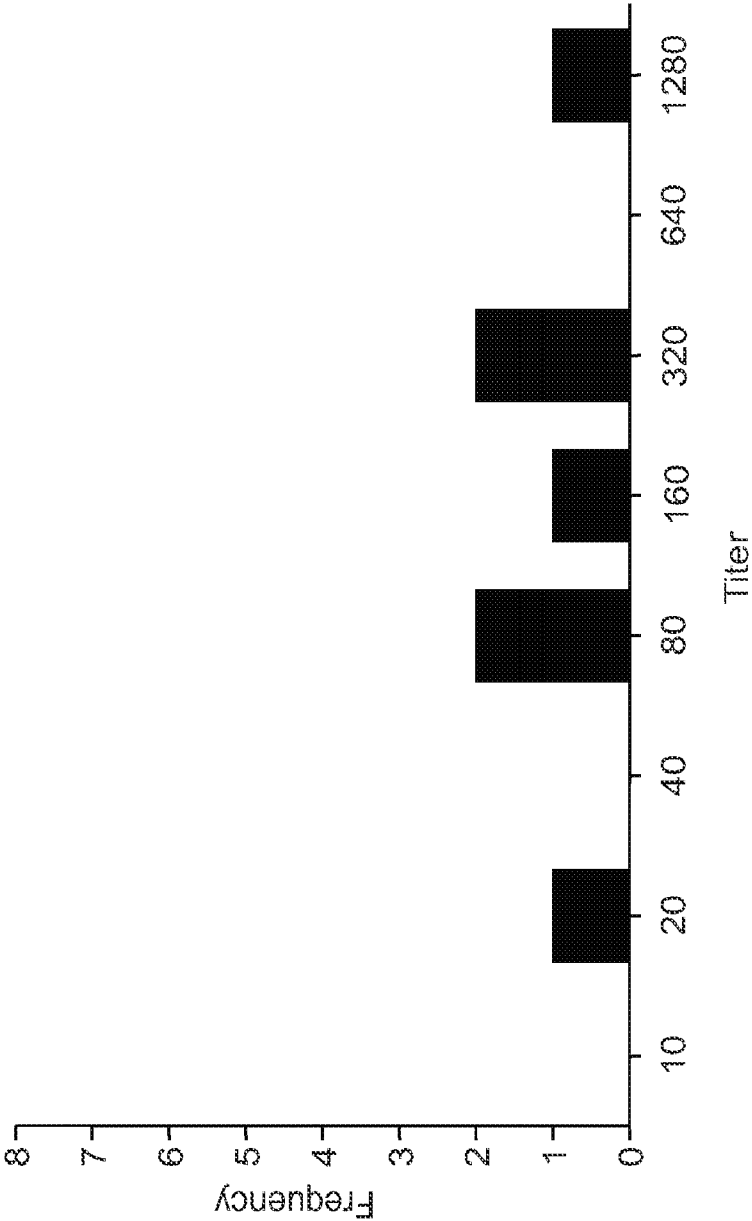


FIG. 2C

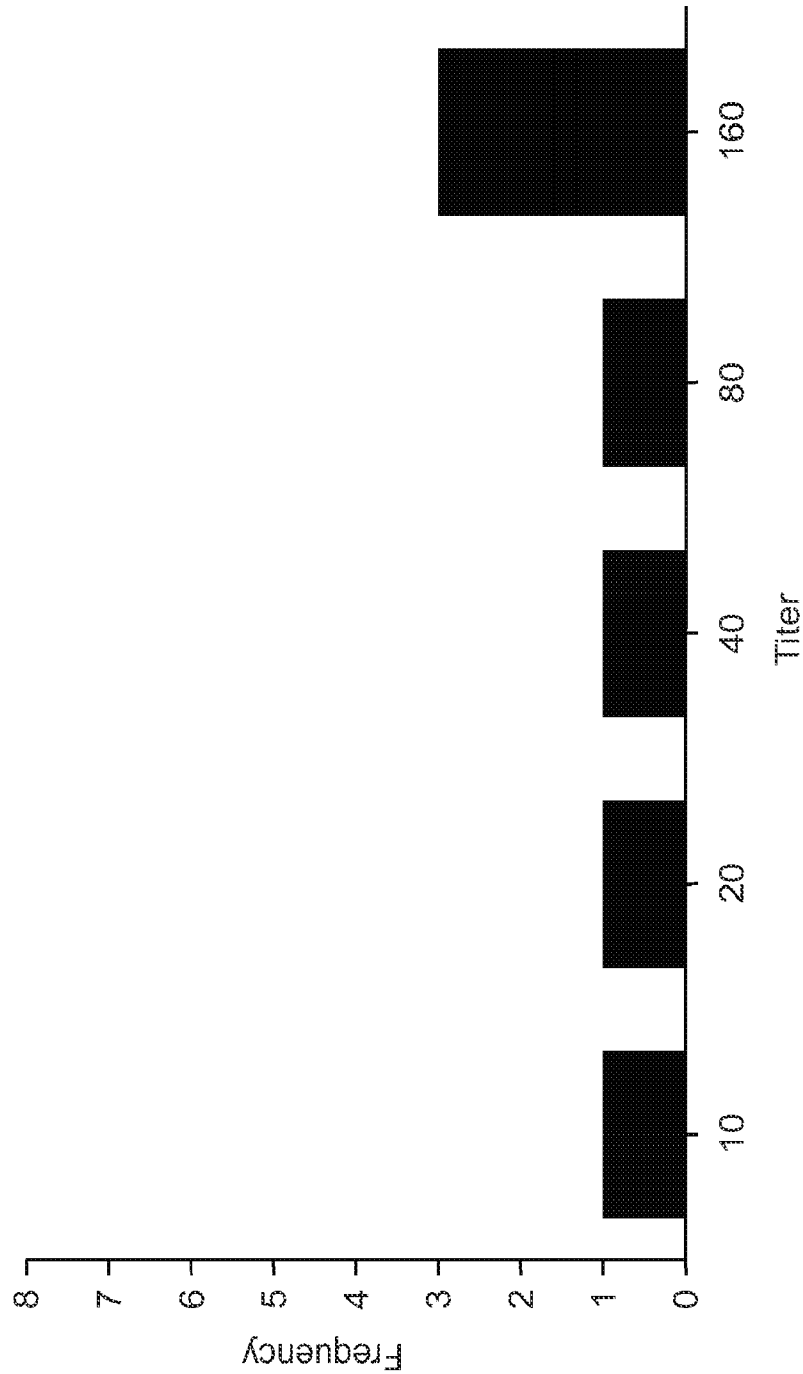
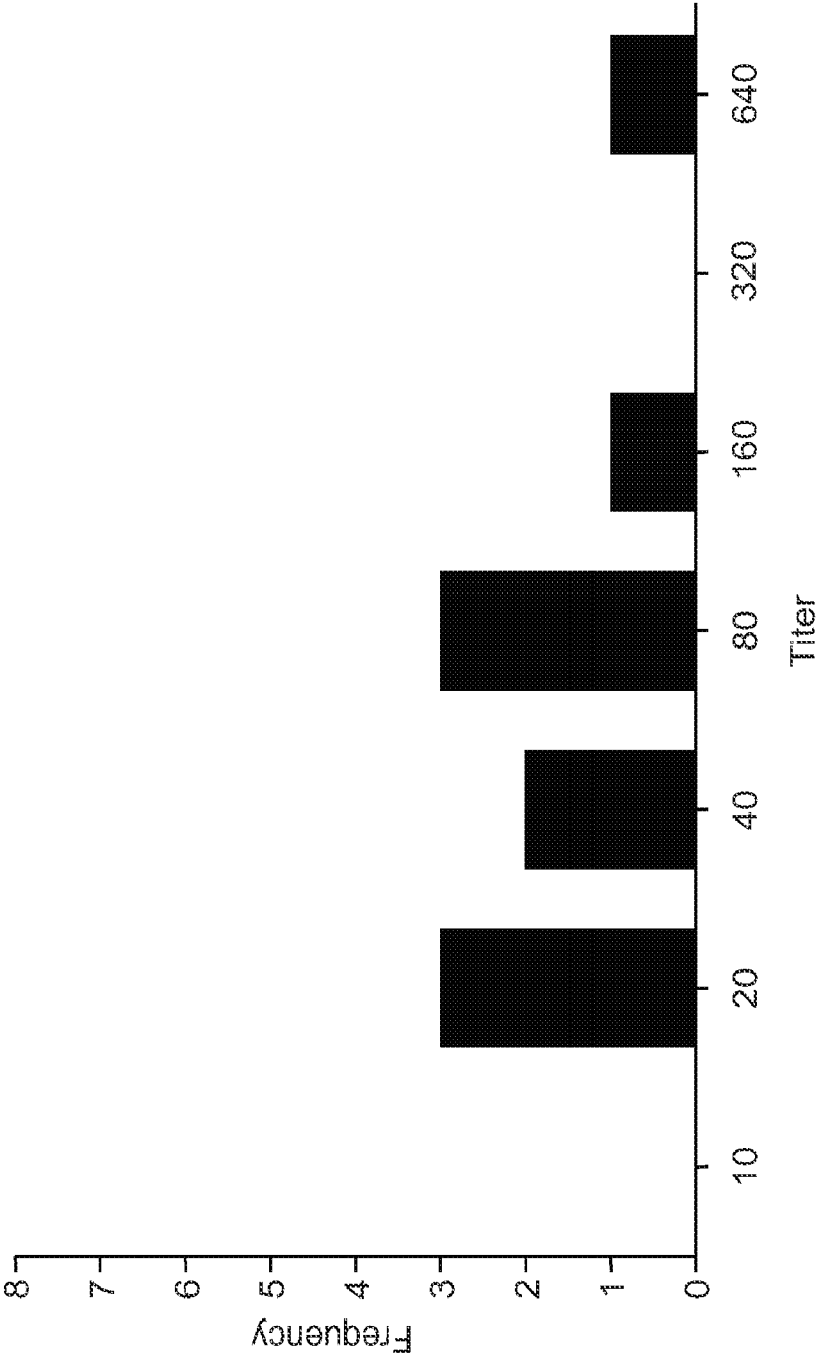
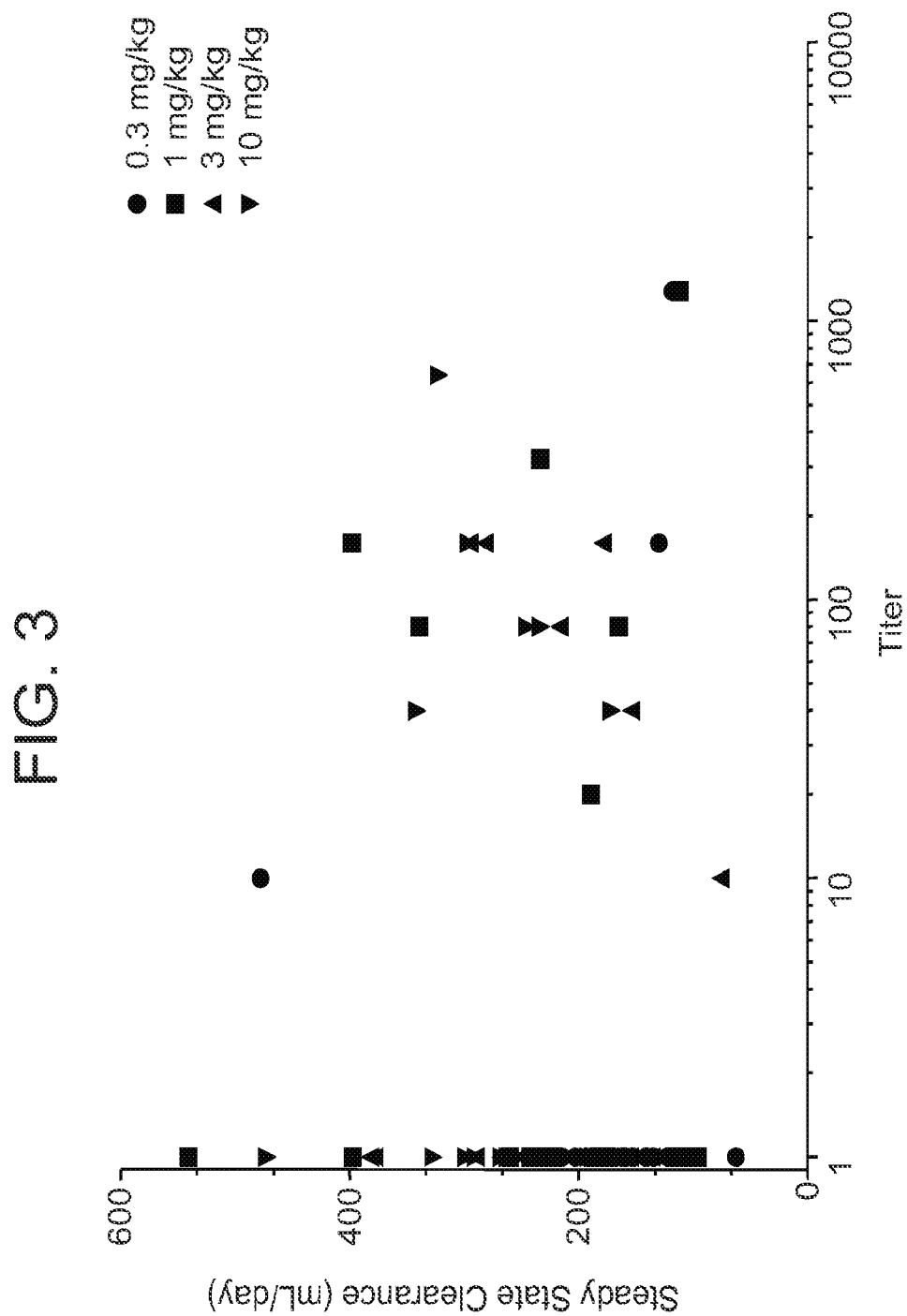


FIG. 2D



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FIG. 4

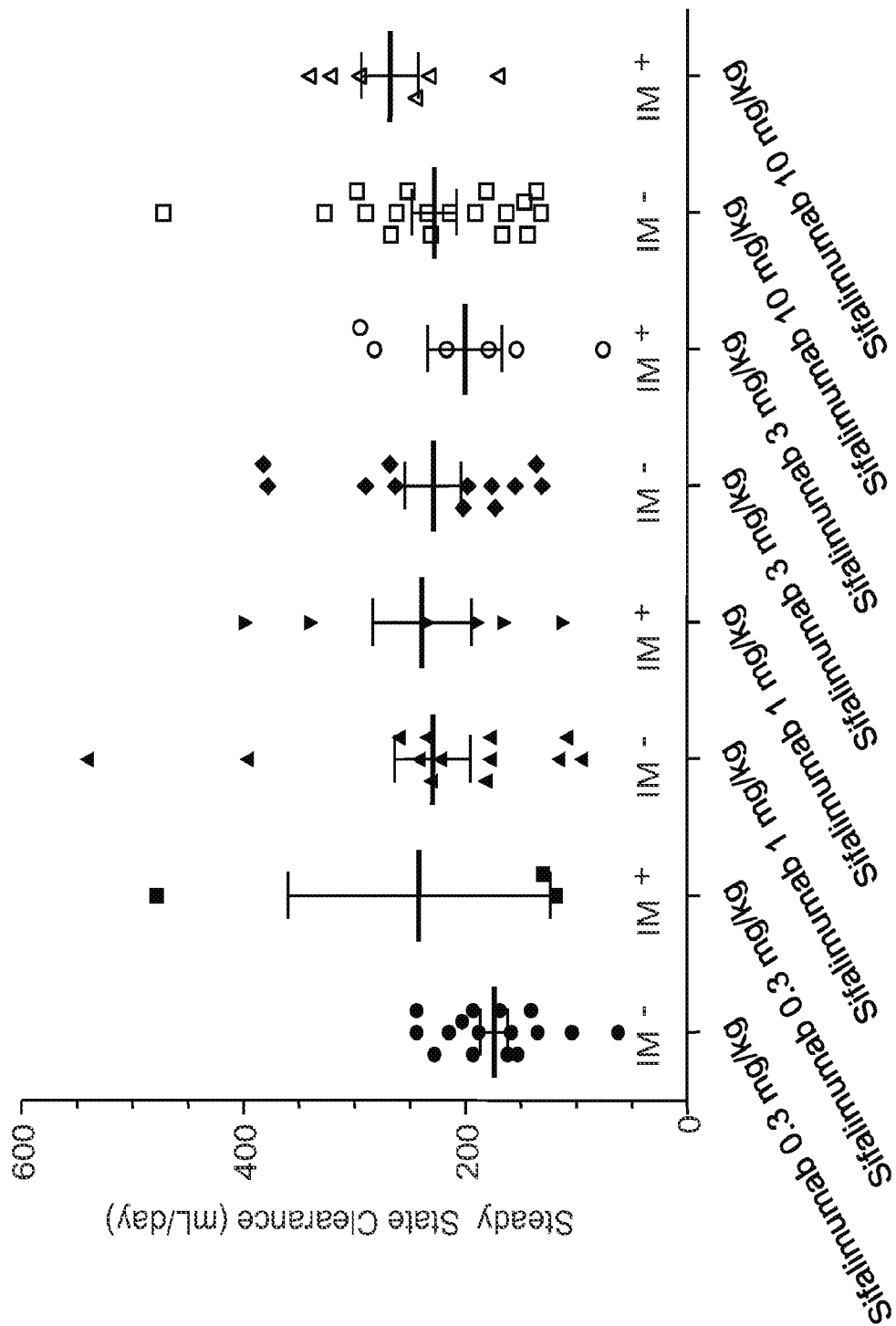


FIG. 5A

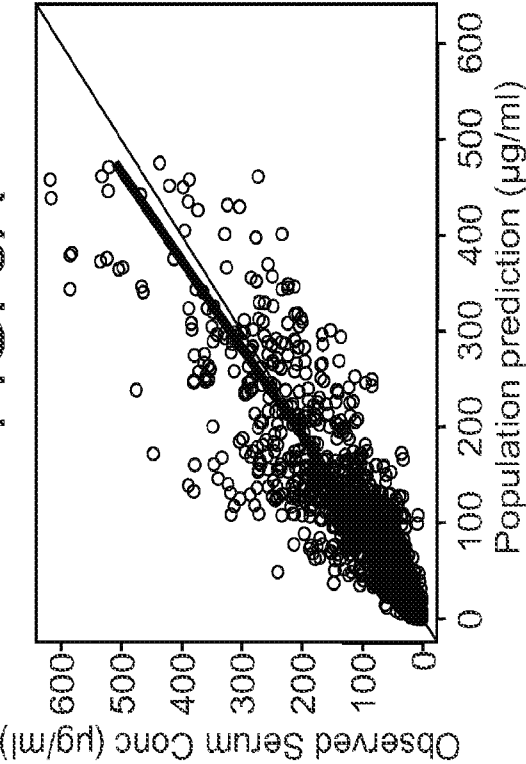


FIG. 5C

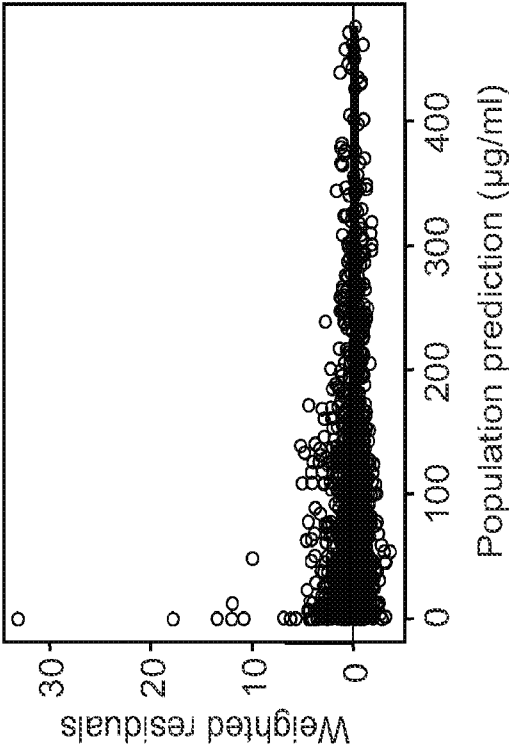


FIG. 5B

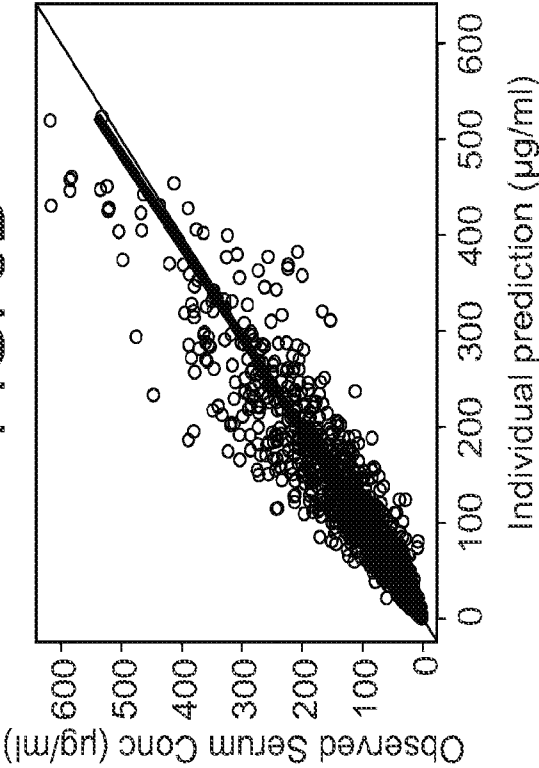
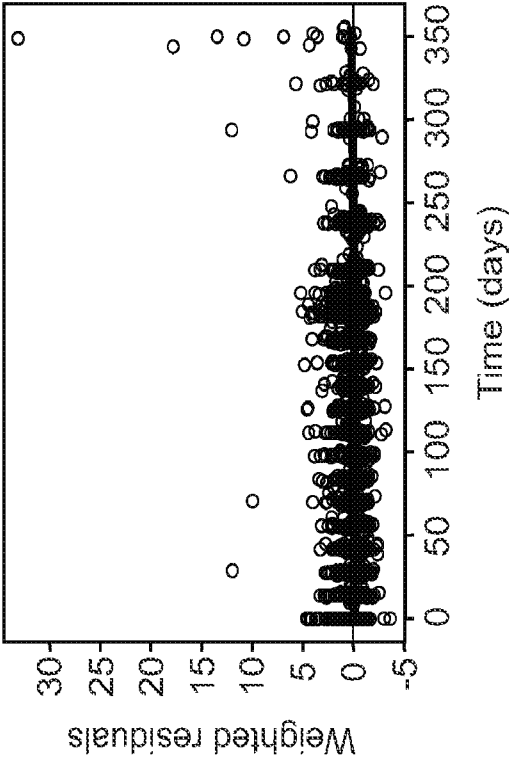


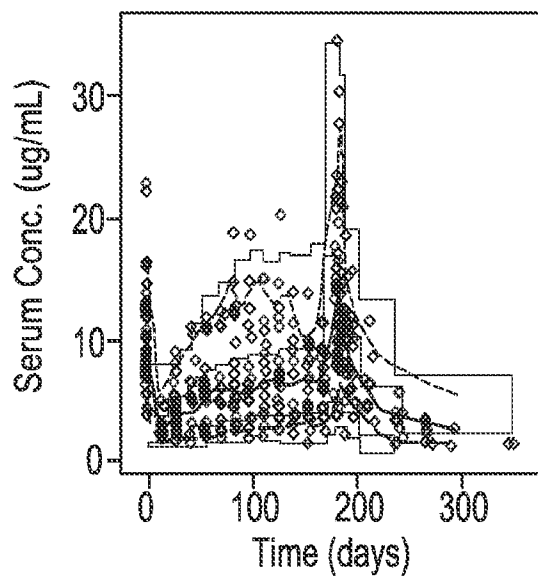
FIG. 5D



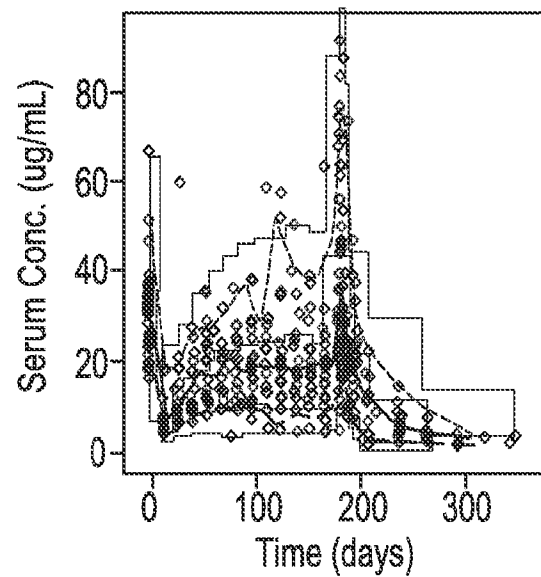
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FIG. 6A

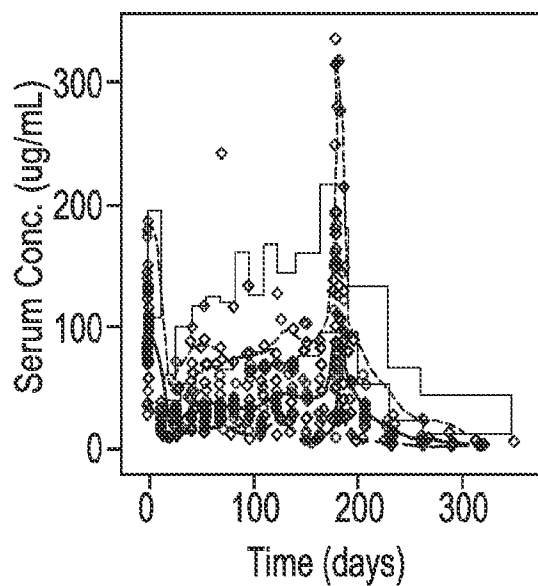
Dose = 0.3 mg/kg

**FIG. 6B**

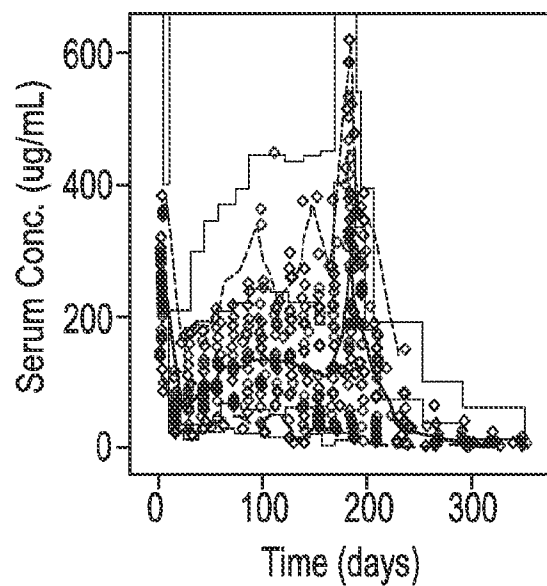
Dose = 1 mg/kg

**FIG. 6C**

Dose = 3 mg/kg

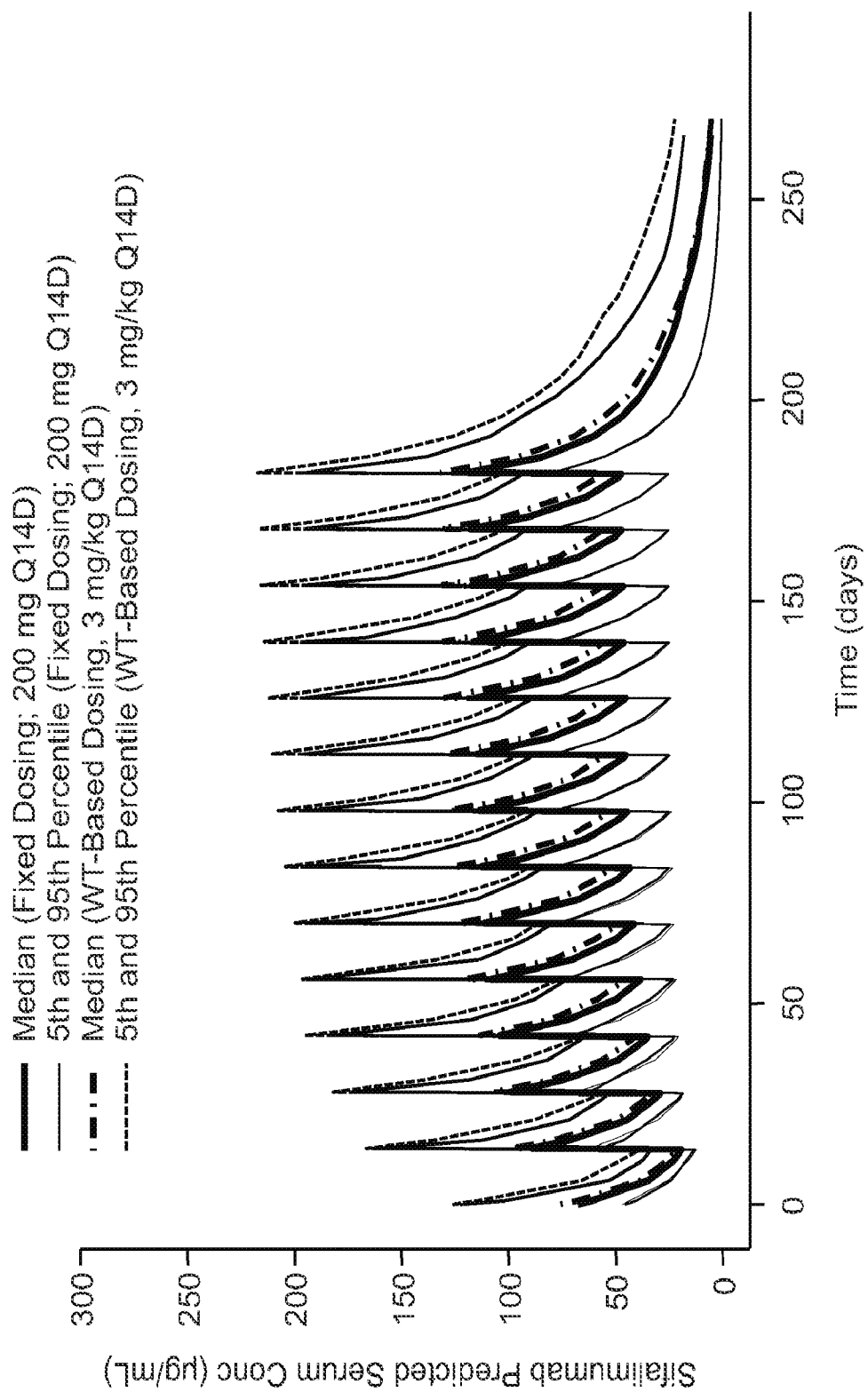
**FIG. 6D**

Dose = 10 mg/kg



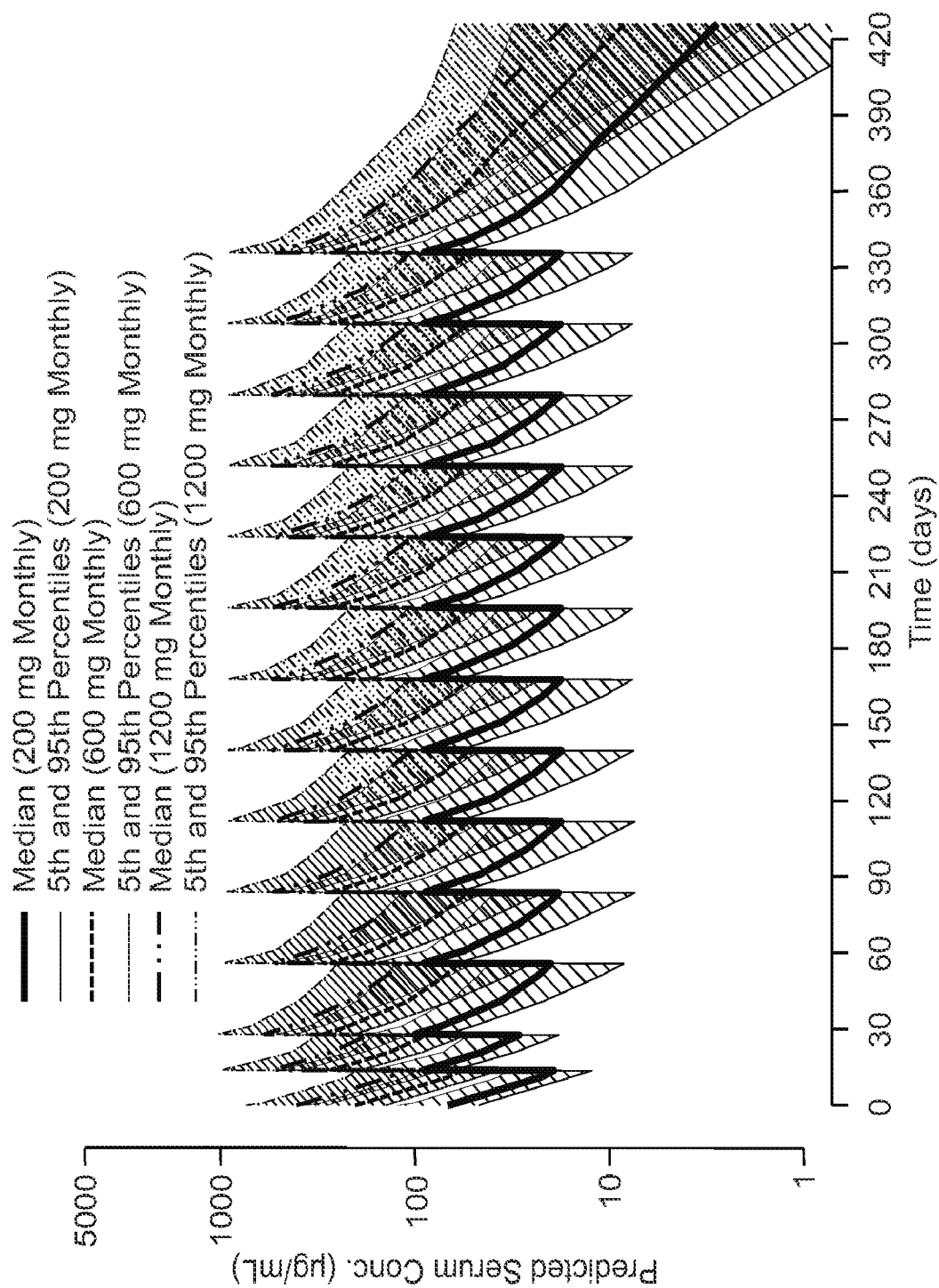
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FIG. 7



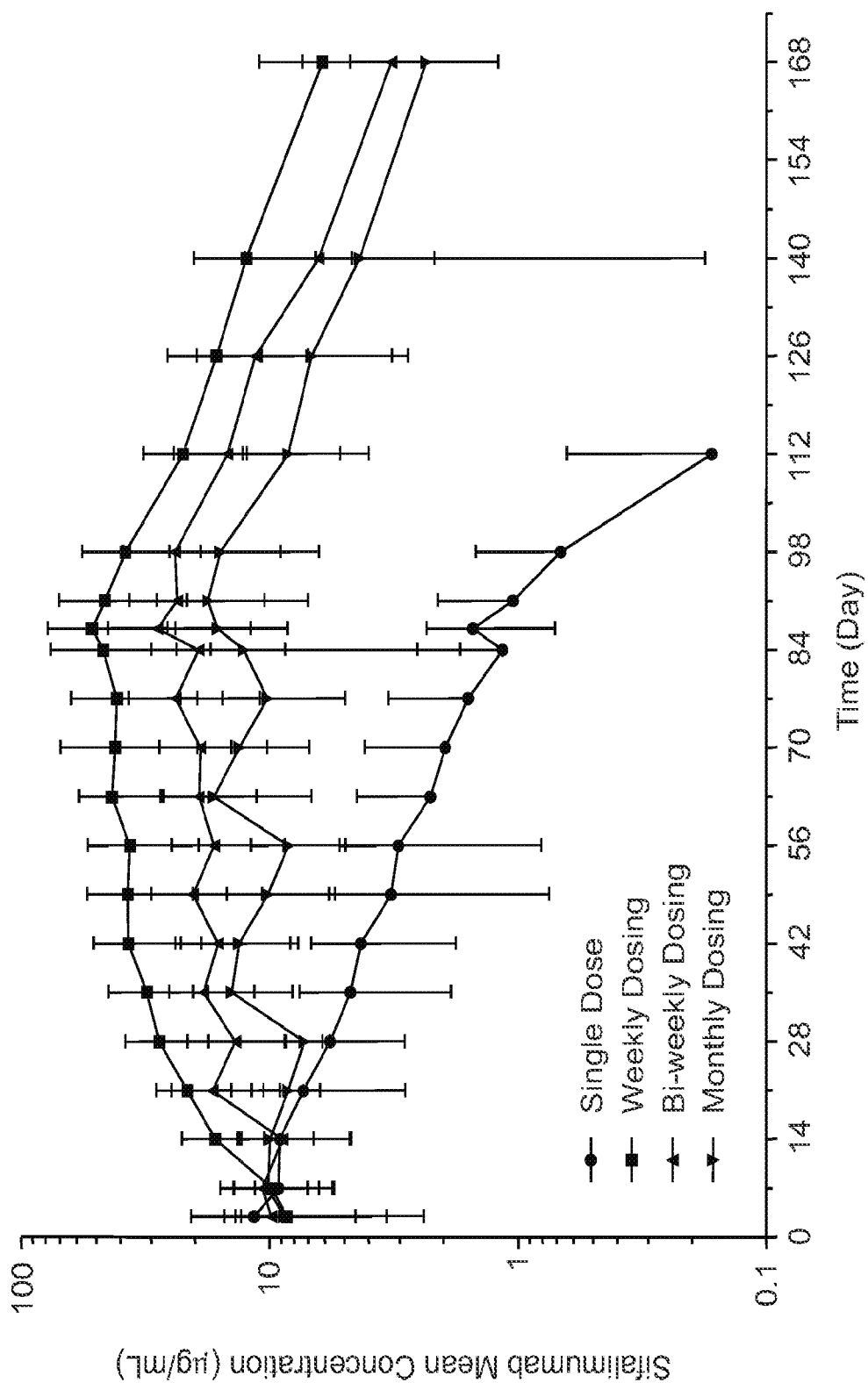
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FIG. 8



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FIG. 9



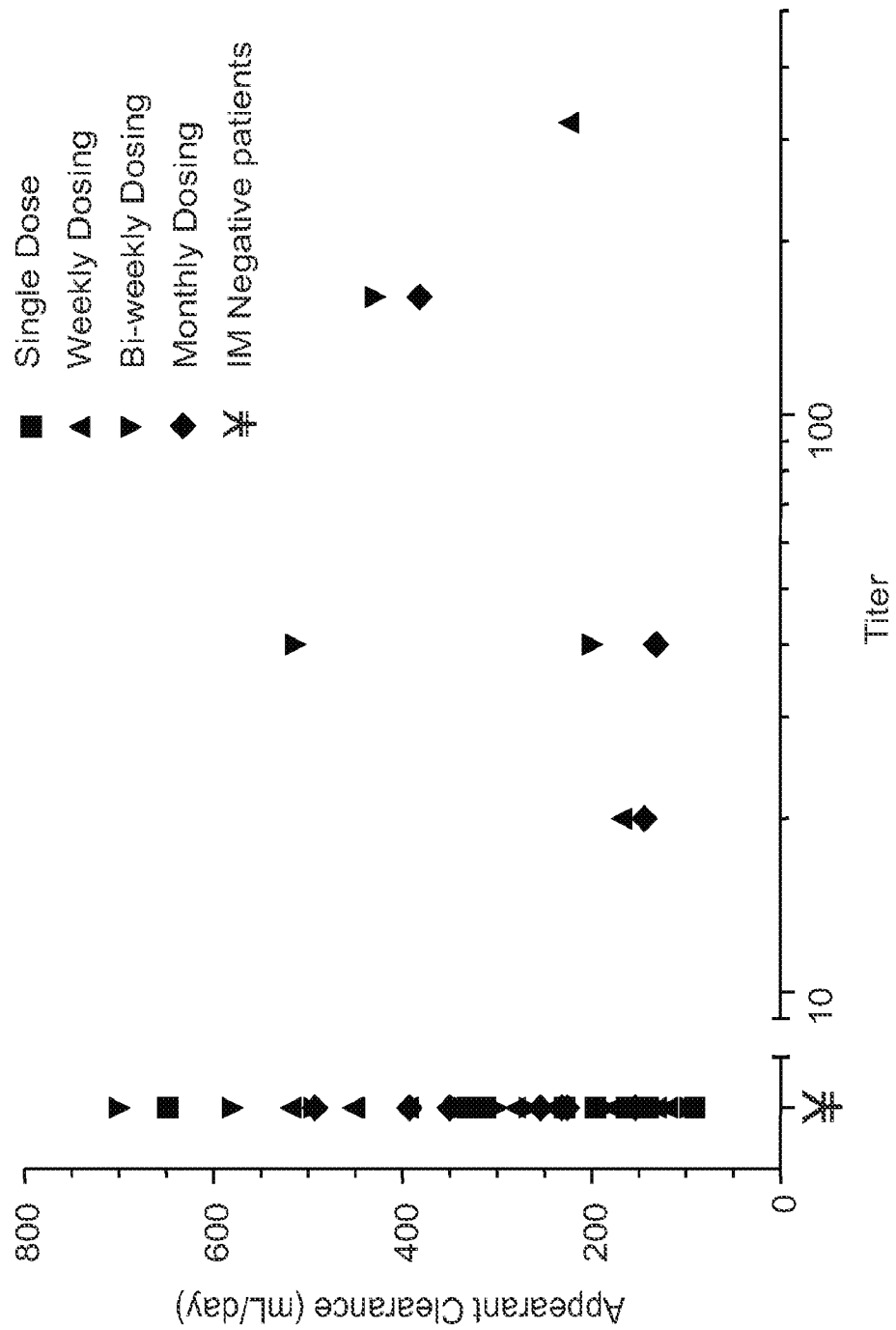
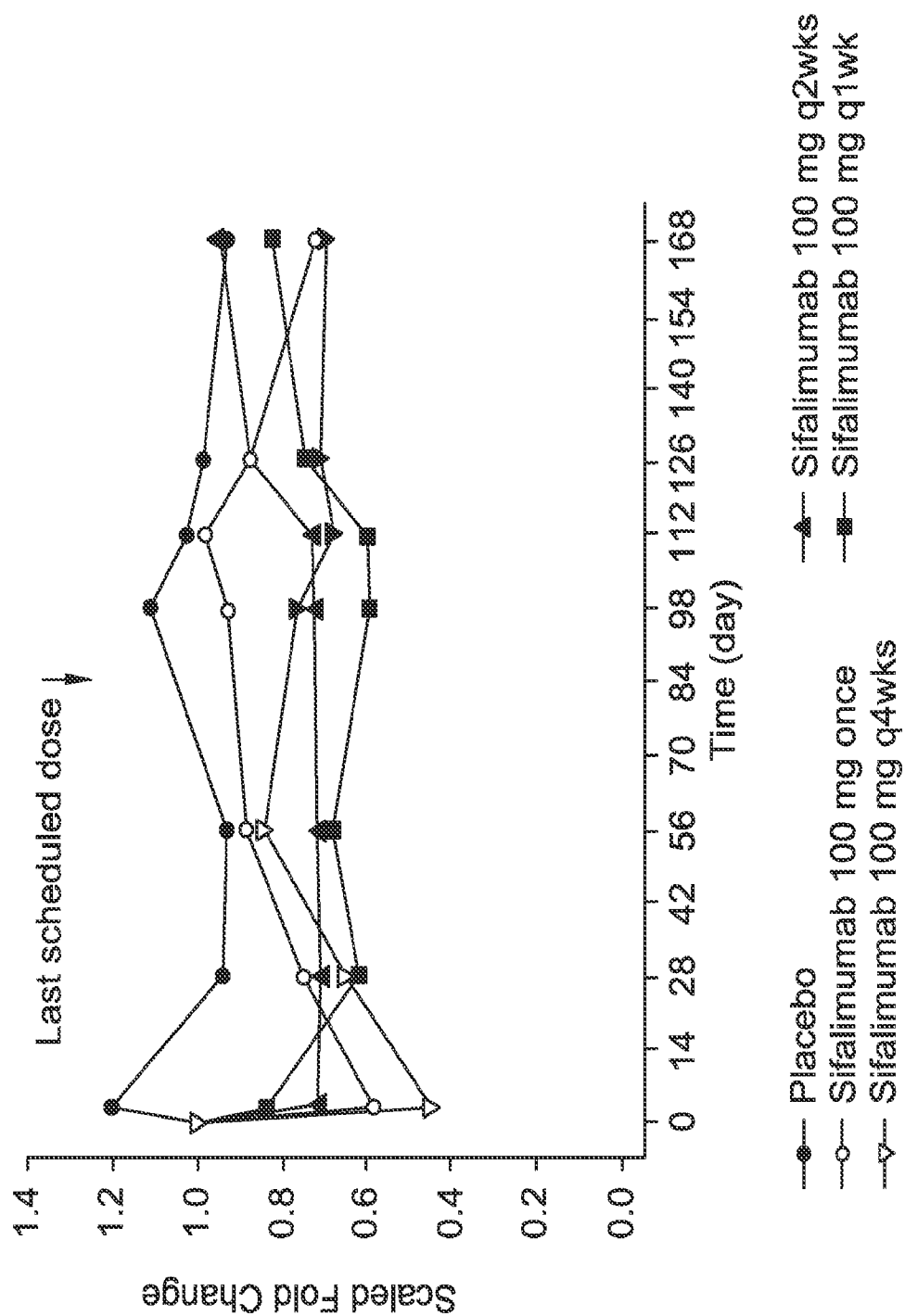


FIG. 11



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/39098

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395; A61K 39/00 (2012.01)

USPC - 424/145.1, 424/141.1; 424/133.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 39/395; A61K 39/00 (2012.01)

USPC - 424/145.1, 424/141.1; 424/133.1; 424/130.1, 424/142.1

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

IPC(8) - A61K 39/395; A61K 39/00 (2012.01) - see keyword below

USPC - 424/145.1, 424/141.1; 424/133.1; 424/130.1, 424/142.1 - see keyword below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST(USPT,PGPB,EPAB,JPAB); Medline, Google: anti-interferon, IFN alpha, antibody, anti-IFN alpha, autoimmune, systemic lupus erythematosus, SLE, scleroderma, myositis, clearance rate, CL, CLss, CL/F, Clss/F, apparent volume of distribution, Vss, Vd, Vz/F, serum, half-life, human, epitope, heavy chain, light chain, variable, CDR, administer, trea

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2009/0324605 A1 (WITTE et al.) 31 December 2009 (31.12.2009), Abstract, para [0008], [0009], [0014], [0056], [0058], [0059], [0094], [0173], [0177], [0290], [0291], [0295], [0301], [0302], SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 7, SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 16, SEQ ID NO: 19, SEQ ID NO: 22, and Fig 1	1-3
Y	McGraw-Hill, CLINICAL PHARMACOKINETIC EQUATIONS AND CALCULATIONS, The McGraw-Hill Companies, Inc. BauerCh2. 2008, pg 28-38. [online]. [Retrieved on 2012.08.02]. Retrieved from the Internet: <URL: http://www.mhprofessional.com/downloads/products/0071476288/BauerCh2.pdf > pg 28, Intraduction; pg 30, para 1 and 3; pg 31, Fig 2-3; para 32, para 1 and middle para, and Fig 2-5; pg 37, para 1; and pg 38, Table 2-1	1-3
A	Kaiser, THE ADAPTIVE IMMUNE SYSTEM, Poster, 2007, [online]. [Retrieved on 2012.08.04]. Retrieved from the Internet: <URL: http://faculty.ccbcmd.edu/courses/bio141/lecguide/unit5/humoral/5classes/5classes.html > PDF file: pg 1-3. Entire documentation, especially pg 1, lower section - 'IgG has a half-life of 7-23 days'	1-3
A	US 2010/0278929 A1 (WEI et al.) 04 November 2010 (04.11.2010), para [0144], para [0285], and para [0286]	1-3
A	TOUTAIN et al. Volumes of distribution. J Vet Pharmacol Ther. 2004, Vol. 27(6), p. 441-53. pg 441, col 1, para 1, and col 2, middle para, and Eqn 1; pg 443, col 2, Eqn 4; pg 445, col 2, Eqn 1	1-3

☒ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

“&” document member of the same patent family

Date of the actual completion of the international search

06 August 2012 (06.08.2012)

Date of mailing of the international search report

16 AUG 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/39098

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Birkett, Pharmacokinetics made easy 11 Designing dose regimens. Poster, 1996 [online]. [Retrieved on 2012.08.02]. Retrieved from the Internet: <URL: http://www.australianprescriber.com/magazine/19/3/76/8/ > PDF file: pg 1-5. Entire documentation, especially pg 1, para 1- 3, and Equations 1 and 2; and Fig 1	1-3
A	US 2007/0059309 A1 (CHUNTHARAPAI et al.) 15 March 2007 (15.03.2007), Abstract	1-3
A	WANG et al. Effect of Dosing Schedule on Pharmacokinetics of Alpha Interferon and Anti-Alpha Interferon Neutralizing Antibody in Mice. Antimicrob Agents Chemother. 2001, Vol. 45(1), p. 176-80. Entire documentation, especially Abstract	1-3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/39098

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

a. (means)

☐

on paper

☒

in electronic form

b. (time)

☐

in the international application as filed

☒

together with the international application in electronic form

☐

subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-75
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.