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(54) Title: METHODS FOR IMPROVING BONE GROWTH BY ADMINISTERING AN IL-4R ANTAGONIST

(57) Abstract: Methods for improving bone growth in a subject are provided. In one aspect, the methods comprise administering to the subject having a defect in bone growth one or more doses of an interleukin-4 receptor (IL-4R) antagonist, such as an anti-IL-4R antibody or antigen-binding fragment thereof.

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METHODS FOR IMPROVING BONE GROWTH BY ADMINISTERING AN IL-4R ANTAGONIST

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application is being filed on November 22, 2023, as a PCT International Patent Application that claims priority to and the benefit of United States Provisional Patent Application Nos. 63/384,816, filed November 23, 2022, 63/480,717, filed January 20, 2023, and 63/498,946, filed April 28, 2023, the contents of each of which are incorporated by reference herein.

REFERENCE TO A SEQUENCE LISTING XML

[002] This application contains a Sequence Listing which has been submitted electronically in XML format. The Sequence Listing XML is incorporated herein by reference. Said XML file, created on November 17, 2023, is named 40848_0118WOU1_SL.xml and is 267,776 bytes in size.

FIELD OF THE INVENTION

[003] The present disclosure relates to the use of interleukin-4 receptor (IL-4R) antagonists for improving bone growth.

BACKGROUND

[004] Children with atopic dermatitis (AD) are at risk for low bone mineral density (BMD), which is associated with increased prevalence of osteopenia, osteoporosis, and fracture risk (Wu, *et al.*, *Ann Transl Med*, 2021, 9:40. doi: 10.21037/atm-20-4708; Lowe, *et al.*, *J Allergy Clin Immunol*, 2020, 145:563-571). Factors such as restricted nutrition, vitamin D deficiency, poor sleep and corticosteroid use contribute to lower bone alkaline phosphatase (BALP) levels, a marker of bone mineralization, seen in children with moderate-to-severe AD compared with healthy children (Silverberg, *Pediatr Allergy Immunol*, 2015, 26:54-61).

[005] A major determinant for lifetime risk of fractures and osteoporosis is the magnitude of peak bone mass achieved during prepubescent years (Diemar, *et al.*, *Bone*, 2021, 146:115879. doi: 10.1016/j.bone.2021.115879). Low BALP and BMD in children with moderate-to-severe AD could contribute to a higher prevalence of osteopenia and osteoporosis.

SUMMARY

[006] In one aspect, methods for improving bone growth are provided. In some embodiments, the method comprises:

selecting a subject having a defect in bone growth, wherein the subject is a pediatric or adolescent subject less than 18 years old; and

administering to the subject one or more doses of an interleukin-4 receptor (IL-4R) antagonist.

[007] In some embodiments, the IL-4R antagonist is an anti-IL-4R antibody, or an antigen-binding fragment thereof, *e.g.*, comprising one or more CDRs, HCVR, and/or LCVR sequences set forth in Table 1. In some embodiments, the IL-4R antagonist is an anti-IL-4R antibody, or an antigen-binding fragment thereof, that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence LGS, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8.

[008] In some embodiments, the subject has atopic dermatitis (AD). In some embodiments, the subject has moderate-to-severe or severe AD.

[009] In some embodiments, the subject is a pediatric subject having an age of less than 12 years old. In some embodiments, the subject is 6 years old to 11 years old. In some embodiments, the subject is 6 months old to 5 years old.

[010] In some embodiments, the subject is an adolescent aged 12 years old to 17 years old.

[011] In some embodiments, the subject has comorbid asthma.

[012] In some embodiments, the selecting step comprises selecting a subject who exhibits a level of a bone turnover marker that is below a threshold value, wherein the bone turnover marker is bone-specific alkaline phosphatase, carboxy-terminal cross-linked telopeptide of type I collagen (β-CTX), pro-collagen type I N-terminal propeptide (PINP), insulin-like growth factor 1 (IGF-1), or osteocalcin. In some embodiments, the threshold value is the average level of the bone turnover marker for a population of healthy subjects having the same age as the selected pediatric or adolescent subject.

[013] In some embodiments, the bone turnover marker is bone-specific alkaline phosphatase.

[014] In some embodiments, the IL-4R antagonist is administered at a dose of about 50 mg to about 600 mg. In some embodiments, the IL-4R antagonist is administered at a frequency of

once a week (QW), once every two weeks (Q2W), once every three weeks (Q3W), or once every four weeks (Q4W). In some embodiments, the IL-4R antagonist is administered as an initial dose of 100-600 mg followed by one or more subsequent doses of 50-300 mg, wherein each subsequent dose is administered one week to four weeks after the immediately preceding dose.

[015] In some embodiments, the IL-4R antagonist is administered as an initial dose of 200 mg followed by one or more subsequent doses of 200 mg.

[016] In some embodiments, the IL-4R antagonist is administered as an initial dose of 300 mg followed by one or more subsequent doses of 300 mg.

[017] In some embodiments, the IL-4R antagonist is administered as an initial dose of 400 mg followed by one or more subsequent doses of 200 mg.

[018] In some embodiments, the IL-4R antagonist is administered as an initial dose of 600 mg followed by one or more subsequent doses of 300 mg.

[019] In some embodiments, the subject is a pediatric subject aged 6 years old to 11 years old or an adolescent aged 12 years old to 17 years old, and wherein the subject has a baseline weight ≥ 60 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 600 mg followed by one or more subsequent doses of 300 mg Q2W.

[020] In some embodiments, the subject is an adolescent having a baseline weight < 60 kg, and the IL-4R antagonist is subcutaneously administered as an initial dose of 400 mg followed by one or more subsequent doses of 200 mg Q2W.

[021] In some embodiments, the subject is a pediatric subject having an age of 6 to 11 years old and having a baseline weight ≥ 30 kg to <60 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 400 mg followed by one or more subsequent doses of 200 mg Q2W.

[022] In some embodiments, the subject is a pediatric subject having an age of 6 to 11 years old and having a baseline weight ≥ 15 kg to <30 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 600 mg followed by one or more subsequent doses of 300 mg Q4W.

[023] In some embodiments, the subject is a pediatric subject having an age of 6 to 11 years old and having a baseline weight ≥ 15 kg to <60 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 300 mg on Day 1 followed by 300 mg on Day 15, followed by one or more subsequent doses of 300 mg Q4W starting four weeks after the Day 15 dose.

[024] In some embodiments, the subject is a pediatric subject having an age of 6 months to 5 years old and having a baseline weight ≥ 15 kg to < 30 kg, wherein the IL-4R antagonist is subcutaneously administered at a dose of 300 mg Q4W.

[025] In some embodiments, the subject is a pediatric subject having an age of 6 months to 5 years old and having a baseline weight ≥ 5 kg to < 15 kg, wherein the IL-4R antagonist is subcutaneously administered at a dose of 200 mg Q4W.

[026] In some embodiments, the IL-4R antagonist is administered for at least 16 weeks.

[027] In some embodiments, the IL-4R antagonist is administered in combination with a topical AD medication. In some embodiments, the topical AD medication is a TCS.

[028] In some embodiments, treatment with the IL-4R antagonist results in an increase in bone growth in the subject as measured by an increase in a bone turnover marker selected from the group consisting of bone-specific alkaline phosphatase, β-CTX, PINP, IGF-1, and osteocalcin.

[029] In some embodiments, the anti-IL-4R antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:1 and comprises a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:2. In some embodiments, the anti-IL-4R antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:9 and a light chain comprising the amino acid sequence of SEQ ID NO:10. In some embodiments, the IL-4R antagonist is dupilumab.

[030] In some embodiments, the IL-4R antagonist is contained in a container selected from the group consisting of a glass vial, a syringe, a pre-filled syringe, a pen delivery device, and an autoinjector. In some embodiments, the IL-4R antagonist is contained in a pre-filled syringe. In some embodiments, the pre-filled syringe is a single-dose pre-filled syringe. In some embodiments, the IL-4R antagonist is contained in a pen delivery device. In some embodiments, the IL-4R antagonist is contained in an autoinjector.

[031] In another aspect, pharmaceutical compositions for improving bone growth are provided. In some embodiments, the pharmaceutical composition comprises an interleukin-4 receptor (IL-4R) antagonist. In some embodiments, the IL-4R antagonist is an anti-IL-4R antibody, or an antigen-binding fragment thereof, *e.g.*, comprising one or more CDRs, HCVR, and/or LCVR sequences set forth in Table 1. In some embodiments, the IL-4R antagonist is an anti-IL-4R antibody, or an antigen-binding fragment thereof, that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino

acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence LGS, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8. In some embodiments, the pharmaceutical composition is for use in improving bone growth in a pediatric or adolescent subject, *e.g.*, a pediatric or adolescent subject having atopic dermatitis.

[032] In another aspect, provided herein are interleukin-4 receptor (IL-4R) antagonists for the preparation of a medicament for improving bone growth. In some embodiments, the IL-4R antagonist is an anti-IL-4R antibody, or an antigen-binding fragment thereof, *e.g.*, comprising one or more CDRs, HCVR, and/or LCVR sequences set forth in Table 1. In some embodiments, the IL-4R antagonist is an anti-IL-4R antibody, or an antigen-binding fragment thereof, that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence LGS, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8. In some embodiments, the medicament is for use in improving bone growth in a pediatric or adolescent subject, *e.g.*, a pediatric or adolescent subject having atopic dermatitis.

[033] Other embodiments will be apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[034] FIG. 1 shows the geometric mean in bone alkaline phosphatase (BALP) (mcg/L) from baseline by visit for patients treated with placebo + topical corticosteroid (TCS), dupilumab 300 mg Q4W + TCS, or dupilumab 100 mg or 200 mg Q2W + TCS in a 16-week parent study (R668-AD-1652; "LIBERTY AD PEDS") or subsequent open label extension study (R668-AD-1434; "LIBERTY AD PED-OLE"). Visits at Week 8, 12, and 16 were from the parent study, and visits at Week 52 were from the open label extension study. Patients treated with placebo + TCS during the parent study were transitioned to dupilumab 100 mg or 200 mg Q2W or 300 mg Q4W for the open label extension study. ns, not significant; SE, standard error.

[035] FIG. 2 shows osteocalcin levels (ng/mL) for patients treated with placebo + TCS or dupilumab (100/200mg Q2W or 300 mg Q4W) + TCS, at Week 8, Week 12, Week 16, or Week 52 of treatment. Connecting lines represent data coming from the same subject. Boxplots show

median (middle horizontal line) and interquartile range (lower and upper bounds of the box), which correspond to the values at the top of the graph.

[036] FIG. 3 shows pro-collagen type I N-terminal propeptide (PINP) levels(ng/mL) for patients treated with placebo + TCS or dupilumab (100/200mg Q2W or 300 mg Q4W) + TCS, at Week 8, Week 12, Week 16, or Week 52 of treatment. Connecting lines represent data coming from the same subject. Boxplots show median (middle horizontal line) and interquartile range (lower and upper bounds of the box), which correspond to the values at the top of the graph.

[037] FIG. 4 shows insulin-like growth factor 1 (IGF-1) levels (ng/mL) for patients treated with placebo + TCS or dupilumab (100/200mg Q2W or 300 mg Q4W) + TCS, at Week 8, Week 12, Week 16, or Week 52 of treatment. Connecting lines represent data coming from the same subject. Boxplots show median (middle horizontal line) and interquartile range (lower and upper bounds of the box), which correspond to the values at the top of the graph.

[038] FIG. 5 shows carboxy-terminal cross-linked telopeptide of type I collagen (β-CTX) levels (pg/mL) for patients treated with placebo + TCS or dupilumab (100/200mg Q2W or 300 mg Q4W) + TCS, at Week 8, Week 12, Week 16, or Week 52 of treatment. Connecting lines represent data coming from the same subject. Boxplots show median (middle horizontal line) and interquartile range (lower and upper bounds of the box), which correspond to the values at the top of the graph.

[039] FIGS. 6A and 6B show BALP geometric mean over time for female patients (6A) and male patients (6B) in the 6-11 year old treatment group. [a]Dashed lines represent BALP reference intervals for females or males. [b]After Week 16 these patients received active dupilumab treatment when enrolled in the LIBERTY AD PED-OLE trial. Visits at Weeks 8, 12, and 16 are from the LIBERTY AD PEDS trial and visits at Week 52 are from the LIBERTY AD PED-OLE trial. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001, all vs corresponding placebo + TCS. ns, not significant; SE, standard error.

[040] FIG. 7 shows BALP geometric mean from baseline by visit for female (top panels) and male (bottom panels) patients in the 6-11 year old treatment group. Visits at Weeks 8, 12, and 16 are from the LIBERTY AD PEDS trial and visits at Week 52 are from the LIBERTY AD PED-OLE trial. The numbers below the gender and treatment regimen labels represent the group median and the range from lower quartile to upper quartile. [a]After Week 16 these patients received active dupilumab treatment when enrolled in the LIBERTY AD PED-OLE trial. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001, all vs corresponding baseline.

DETAILED DESCRIPTION

Definitions

[041] Before the present invention is described, it is to be understood that the invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[042] 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 invention belongs.

[043] As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[044] As used herein, the terms "treat," "treating," or the like, mean to alleviate symptoms, eliminate the causation of symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition.

[045] As used herein, the term "subject in need thereof" refers to a human or a non-human animal having a defect in bone growth. In some embodiments, a "defect in bone growth" refers to a decreased level of bone mineral density and/or a decreased level of a biomarker of bone formation or bone mineralization, *e.g.*, as compared to a healthy subject or population of subjects. In some embodiments, the term "a subject in need thereof" refers to a pediatric patient who is < 12 years of age, *e.g.*, a patent aged 6 months to 5 years old or a patient aged 6 to 11 years old. In some embodiments, the term "a subject in need thereof" refers to an adolescent patient who is ≥ 12 and < 18 years of age. The terms “subject” and “patient” are used interchangeably herein.

[046] "Atopic dermatitis" or "AD", as used herein, means an inflammatory skin disease characterized by intense pruritus (*e.g.*, severe itch) and by scaly and dry eczematous lesions. The term "atopic dermatitis" includes, but is not limited to, AD caused by or associated with epidermal barrier dysfunction, allergy (*e.g.*, allergy to certain foods, pollen, mold, dust mite, animals, etc.), radiation exposure, and/or asthma. The present disclosure encompasses methods to treat patients with moderate-to-severe or severe AD. As used herein, “moderate-to-severe AD” is characterized by intensely pruritic, widespread skin lesions that are often

complicated by persistent bacterial, viral or fungal infections. Moderate-to-severe AD also includes chronic AD in patients. In many cases, the chronic lesions include thickened plaques of skin, lichenification and fibrous papules. Patients affected by moderate-to-severe AD also, in general, have more than 20% of the body's skin affected, or 10% of skin area in addition to involvement of the eyes, hands and body folds. Moderate-to-severe AD is also considered to be present in patients who require frequent treatment with topical corticosteroids. A patient may also be said to have moderate-to-severe AD when the patient is resistant or refractory to treatment by either a topical corticosteroid or a calcineurin inhibitor. As used herein, "severe AD" is characterized by the presence of widespread skin lesions, unremitting itching, or physically or emotionally disabling disease that significantly compromises a patient's quality of life. In some cases, patients with severe AD also exhibits one or more symptoms such as excoriation, extensive skin thickening, bleeding, oozing, and/or cracking of skin, and alteration of pigmentation. In some embodiments, severe AD is refractory to treatment by a topical therapy (*e.g.*, a topical corticosteroid, calcineurin inhibitor, or crisaborole).

[047] The term "TCS," as used herein, includes group I, group II, group III and group IV topical corticosteroids. According to the Anatomical Therapeutic Classification System of World Health Organization, the corticosteroids are classified as weak (group I), moderately potent (Group II) and potent (Group III) and very potent (Group IV), based on their activity as compared to hydrocortisone. Group IV TCS (very potent) are up to 600 times as potent as hydrocortisone and include clobetasol propionate and halcinonide. Group III TCS (potent) are 50 to 100 times as potent as hydrocortisone and include, but are not limited to, betamethasone valerate, betamethasone dipropionate, diflucortolone valerate, hydrocortisone-17-butyrate, mometasone furoate, and methylprednisolone aceponate. Group II TCS (moderately potent; also referred to interchangeably herein as "medium potency") are 2 to 25 times as potent as hydrocortisone and include, but are not limited to, clobetasone butyrate, and triamcinolone acetonide. Group I TCS (mild; also referred to interchangeably herein as "low potency") includes hydrocortisone.

[048] Although any methods and materials similar or equivalent to those described herein can be used in the practice of the disclosure, the typical methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

Therapeutic Methods

[049] In one aspect, methods for improving bone growth in a subject are provided. In some embodiments, the subject has a defect in bone growth, *e.g.*, a defect in bone formation or bone

metabolism. In some embodiments, the methods comprise administering to the subject one or more doses of an interleukin-4 receptor (IL-4R) antagonist, such as an anti-IL-4Rα antibody or antigen-binding fragment thereof as disclosed herein.

[050] In some embodiments, the subject is a pediatric subject or adolescent subject less than 18 years old. In some embodiments, the subject is ≥6 months to <18 years of age. In some embodiments, the subject is ≥6 years to <18 years of age. In some embodiments, the subject is ≥12 years to <18 years of age. In some embodiments, the subject is ≥6 years to <12 years of age. In some embodiments, the subject is ≥6 months to <12 years of age. In some embodiments, the subject is ≥6 months to <6 years of age.

[051] In some embodiments, the subject is a pediatric or adolescent subject having a body weight < 60 kg at baseline. In some embodiments, the subject is a pediatric or adolescent subject having a body weight < 30 kg at baseline. In some embodiments, the subject has a body weight ≥5 kg and < 30 kg at baseline. In some embodiments, the subject has a body weight ≥5 kg and < 15 kg at baseline. In some embodiments, the subject has a body weight ≥15 kg and < 30 kg at baseline.

[052] In some embodiments, the subject has an atopic disease. In some embodiments, the subject has AD (*e.g.*, moderate-to-severe AD or severe AD). In some embodiments, the subject has chronic atopic dermatitis diagnosed at least 6 months (*e.g.*, at least 9 months or at least 1 year) prior to the start of treatment. In some embodiments, the subject has moderate-to-severe or severe AD that is inadequately responsive to topical therapies (*e.g.*, TCS with or without topical calcineurin inhibitors (TCIs)) or for whom topical therapy is inadvisable (*e.g.*, due to adverse side effects or safety risks). In some embodiments, the subject has moderate-to-severe or severe AD and is a candidate for systemic therapy.

[053] In some embodiments, the subject has AD (*e.g.*, moderate to severe AD or severe AD) and has one or more concomitant allergic conditions (*i.e.*, excluding AD). In some embodiments, the subject has a concurrent atopic or allergic condition selected from the group consisting of allergic rhinitis, asthma, food allergy, non-food allergy, allergic conjunctivitis, hives, chronic rhinosinusitis, nasal polyps, and eosinophilic esophagitis.

[054] In some embodiments, the subject has a defect in bone growth. In some embodiments, the subject has abnormal bone metabolism relative to a healthy control or population of healthy control subjects. In some embodiments, the subject has decreased bone formation relative to a healthy control or population of healthy control subjects. In some embodiments, the subject has decreased bone mineral density relative to a healthy control or population of healthy control subjects. In some embodiments, the subject is at risk for skeletal fractures. In some

embodiments, the subject has a history of skeletal fractures. In some embodiments, the subject has osteopenia. In some embodiments, the subject has osteoporosis (*e.g.*, idiopathic juvenile osteoporosis or secondary osteoporosis). In some embodiments, the subject having a defect in bone growth has a history of treatment with a topical therapy (*e.g.*, a topical corticosteroid, calcineurin inhibitor, or crisaborole).

[055] In some embodiments, a subject having a defect in bone growth is selected based on the level of a bone-specific marker, *e.g.*, a bone formation marker or bone turnover marker. In some embodiments, the marker is bone-specific alkaline phosphatase, carboxy-terminal cross-linked telopeptide of type I collagen (CTX-1), pro-collagen type I N-terminal propeptide (PINP), insulin-like growth factor 1 (IGF-1), or osteocalcin. In some embodiments, the subject is selected on the basis of exhibiting a level of a marker (*e.g.*, bone turnover marker) that is below a threshold value.

[056] In some embodiments, a subject having a defect in bone growth is selected based on the subject's bone mineral density (BMD), *e.g.*, a Z-score calculated for one or more skeletal sites. In some embodiments, the subject is selected on the basis of having a BMD Z-score that is below a threshold value. In some embodiments, the subject is identified as having a defect in bone growth if the subject has a BMD Z-score that is ≤ -2.0, *e.g.*, as measured for the lumbar spine, femur, hip, or another skeletal site.

[057] In some embodiments, the "threshold value" for a parameter or marker as disclosed herein, *e.g.*, a bone turnover marker or a BMD Z-score, is determined by reference to a population of healthy subjects having the same age as the selected pediatric or adolescent subject, or having a range of ages that encompasses the selected pediatric or adolescent subject. For a given parameter or marker, the skilled person in the art can determine a threshold value for a particular age or age range in view of knowledge in the art about the levels of the parameter or marker in a general population. For example, methods for calculating average BMD Z-scores for different age ranges of pediatric and adolescent subjects having AD or healthy control subjects are disclosed in Leung, *et al.*, *Hong Kong Med J*, 2017, 23:470-479; Pedreira, *et al.*, *Pediatr Dermatol*, 2007, 24:613-620; Penterich, *et al.*, *J Pediatr Endocrinol Metab*, 2018, 31:247-260; Silverberg, *et al.*, *J Allergy Clin Immunol*, 2013, 132:1132-1138; Silverberg, *et al.*, *Pediatr Allergy Immunol*, 2015; 26:54-61; and Wu, *et al.*, *Ann Transl Med*, 2021, 9:40. doi: 10.21037/atm-20-4708. Methods for calculating average levels for bone formation/bone turnover markers including bone alkaline phosphatase, osteocalcin, PINP, IGF-1, and β-CTX are disclosed in Diemar, *et al.*, *Bone*, 2021, 146:115879; Penterich, *et al.*, *J Pediatr Endocrinol Metab*, 2018, 31:247-260; Silverberg, *et al.*, *Pediatr Allergy Immunol*, 2015;

26:54-61; and Tobiume, *et al.*, *J Clin Endocrinol Metab*, 1997, 82:2056-2061. In some embodiments, the threshold value is the lower value of a 95% reference interval for a bone turnover marker established for pediatric or adolescent patients, *e.g.*, as shown in Table 3 of Diemar, *et al.*, *Bone*, 2021, 146:115879 or as provided by Mayo Clinic Laboratories Pediatric Catalog (pediatric.testcatalog.org) (incorporated by reference herein).

[058] In some embodiments, the subject is selected on the basis of exhibiting a level of bone alkaline phosphatase that is below a threshold value, *e.g.*, the lower value of a 95% reference interval for bone alkaline phosphatase established for a population of pediatric or adolescent patients. In some embodiments, a subject is selected if the subject has a serum bone alkaline phosphatase level <70 µg/L, <65 µg/L, <60 µg/L, or <55 µg/L.

[059] In some embodiments, a subject is selected if the subject:

is 8-9 years of age and has a serum bone alkaline phosphatase level <53.4 µg/L (for female subjects) or <46.2 µg/L (for male subjects); or

is 10-11 years of age and has a serum bone alkaline phosphatase level < 50.6 µg/L (for female subjects) or <52.7 µg/L (for male subjects); or

is 12-13 years of age and has a serum bone alkaline phosphatase level < 54.6 µg/L (for female subjects) or <49.5 µg/L (for male subjects); or

is 14-15 years of age and has a serum bone alkaline phosphatase level <14.2 µg/L (for female subjects) or < 30.1 µg/L (for male subjects); or

is 16-17 years of age and has a serum bone alkaline phosphatase level < 12.3 µg/L (for female subjects) or < 25.7 µg/L (for male subjects).

[060] In some embodiments, the subject is selected on the basis of exhibiting a level of osteocalcin that is below a threshold value, *e.g.*, the lower value of a 95% reference interval for osteocalcin established for a population of pediatric or adolescent patients. In some embodiments, a subject is selected if the subject:

is 8-9 years of age and has a serum osteocalcin level < 68.5 µg/L (for female subjects) or <54.1 µg/L (for male subjects); or

is 10-11 years of age and has a serum osteocalcin level < 72.2 µg/L (for female subjects) or <55.8 µg/L (for male subjects); or

is 12-13 years of age and has a serum osteocalcin level <82.9 µg/L (for female subjects) or <58.7 µg/L (for male subjects); or

is 14-15 years of age and has a serum osteocalcin level <22.2 µg/L (for female subjects) or <54.1 µg/L (for male subjects); or

is 16-17 years of age and has a serum osteocalcin level <18.8 µg/L (for female subjects) or <61.5 µg/L (for male subjects).

[061] In some embodiments, the subject is selected on the basis of exhibiting a level of PINP that is below a threshold value, *e.g.*, the lower value of a 95% reference interval for PINP established for a population of pediatric or adolescent patients. In some embodiments, a subject is selected if the subject:

is 8-9 years of age and has a serum PINP level <415 µg/L (for female subjects) or <381 µg/L (for male subjects); or

is 10-11 years of age and has a serum PINP level <352 µg/L (for female subjects) or <298 µg/L (for male subjects); or

is 12-13 years of age and has a serum PINP level <387 µg/L (for female subjects) or <168 µg/L (for male subjects); or

is 14-15 years of age and has a serum PINP level <65 µg/L (for female subjects) or <219 µg/L (for male subjects); or

is 16-17 years of age and has a serum PINP level <55 µg/L (for female subjects) or <166 µg/L (for male subjects).

[062] In some embodiments, the subject is selected on the basis of exhibiting a level of β-CTX that is below a threshold value, *e.g.*, the lower value of a 95% reference interval for β-CTX established for a population of pediatric or adolescent patients. In some embodiments, a subject is selected if the subject:

is 8-9 years of age and has a serum β-CTX level <1030 ng/L (for female subjects) or <1080 ng/L (for male subjects); or

is 10-11 years of age and has a serum β-CTX level <1103 ng/L (for female subjects) or <1140 ng/L (for male subjects); or

is 12-13 years of age and has a serum β-CTX level <960 ng/L (for female subjects) or <1100 ng/L (for male subjects); or

is 14-15 years of age and has a serum β-CTX level <330 ng/L (for female subjects) or <1000 ng/L (for male subjects); or

is 16-17 years of age and has a serum β-CTX level <290 ng/L (for female subjects) or <1060 ng/L (for male subjects).

[063] In some embodiments, the subject is selected on the basis of exhibiting a level of IGF-1 that is below a threshold value, *e.g.*, the lower value of a 95% reference interval for IGF-1 established for a population of pediatric or adolescent patients. In some embodiments, a subject is selected if the subject:

is <1 year of age and has a serum IGF-1 level <14 ng/mL (for female subjects) or <18 ng/mL (for male subjects); or

is 1 year of age and has a serum IGF-1 level <23 ng/mL (for female subjects) or <14 ng/mL (for male subjects); or

is 2 years of age and has a serum IGF-1 level <28 ng/mL (for female subjects) or <16 ng/mL (for male subjects); or

is 3 years of age and has a serum IGF-1 level <31 ng/mL (for female subjects) or <22 ng/mL (for male subjects); or

is 4 years of age and has a serum IGF-1 level <33 ng/mL (for female subjects) or <30 ng/mL (for male subjects); or

is 5 years of age and has a serum IGF-1 level <36 ng/mL (for female subjects) or <39 ng/mL (for male subjects); or

is 6 years of age and has a serum IGF-1 level <39 ng/mL (for female subjects) or <47 ng/mL (for male subjects); or

is 7 years of age and has a serum IGF-1 level <44 ng/mL (for female subjects) or <54 ng/mL (for male subjects); or

is 8 years of age and has a serum IGF-1 level <51 ng/mL (for female subjects) or <61 ng/mL (for male subjects); or

is 9 years of age and has a serum IGF-1 level <61 ng/mL (for female subjects) or <67 ng/mL (for male subjects); or

is 10 years of age and has a serum IGF-1 level <73 ng/mL (for female subjects) or <73 ng/mL (for male subjects); or

is 11 years of age and has a serum IGF-1 level <88 ng/mL (for female subjects) or <79 ng/mL (for male subjects); or

is 12 years of age and has a serum IGF-1 level <104 ng/mL (for female subjects) or <84 ng/mL (for male subjects); or

is 13 years of age and has a serum IGF-1 level <120 ng/mL (for female subjects) or <90 ng/mL (for male subjects); or

is 14 years of age and has a serum IGF-1 level <136 ng/mL (for female subjects) or <95 ng/mL (for male subjects); or

is 15 years of age and has a serum IGF-1 level <147 ng/mL (for female subjects) or <99 ng/mL (for male subjects); or

is 16 years of age and has a serum IGF-1 level <153 ng/mL (for female subjects) or <104 ng/mL (for male subjects); or

is 17 years of age and has a serum IGF-1 level <149 ng/mL (for female subjects) or <107 ng/mL (for male subjects); or

is 16-17 years of age and has a serum IGF-1 level <55 µg/L (for female subjects) or <166 µg/L (for male subjects).

[064] In some embodiments, treatment with an IL-4R antagonist improves bone growth, improves or normalizes bone turnover, or reduces the severity of a bone defect (*e.g.*, reducing the occurrence or severity of skeletal fractures, or reducing the severity of osteopenia or osteoporosis).

[065] In some embodiments, treatment with an IL-4R antagonist improves one or more bone-associated parameters in a subject. Examples of "bone-associated parameters" include, but are not limited to, bone formation or bone turnover markers such as bone-specific alkaline phosphatase, β-CTX, PINP, IGF-1, and osteocalcin; and bone mass density, *e.g.*, as measured by dual-energy X-ray absorptiometry (DEXA). An "improvement in a bone-associated parameter" means an improvement (*e.g.*, increase or normalization) from baseline of one or more of the parameters. The term "baseline," as used with respect to a bone-associated parameter, means the numerical value of the bone-associated parameter for a subject prior to or at the onset of administration of a pharmaceutical composition as disclosed herein.

[066] To determine whether a bone-associated parameter has "improved," the parameter is quantified at baseline and at one or more time points after administration of the pharmaceutical composition of the present disclosure. For example, a bone-associated parameter may be measured at day 1, day 2, day 3, day 4, day 5, day 6, day 7, day 8, day 9, day 10, day 11, day 12, day 14, day 15, day 22, day 25, day 29, day 36, day 43, day 50, day 57, day 64, day 71, day 85; or at the end of week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, week 24, or longer, after the initial treatment with a pharmaceutical composition of the present disclosure. The difference between the value of the parameter at a particular time point following initiation of treatment and the value of the parameter at baseline is used to establish whether there has been an "improvement" (*e.g.*, a decrease) in the bone-associated parameter.

[067] In some embodiments, treatment with an IL-4R antagonist according to the methods of the present disclosure results in an increase in bone growth in the subject, as measured by an increase in a bone turnover marker selected from the group consisting of bone-specific alkaline phosphatase, β-CTX, PINP, IGF-1, and osteocalcin. In some embodiments, treatment with an IL-4R antagonist results in an increase from baseline in the level of the marker by week 4, week

8, week 12, week 16, week 24, week 30, week 36, week 48, or week 52 after administration of the first dose of the IL-4R antagonist. In some embodiments, treatment with an IL-4R antagonist results in an increase of at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% in the level of the marker, relative to baseline, by week 4, week 8, week 12, week 16, week 24, week 30, week 36, week 48, or week 52 after administration of the first dose of the IL-4R antagonist.

[068] In some embodiments, treatment with an IL-4R antagonist according to the methods of the present disclosure results in an increase in bone mass in the subject, as measured by bone mineral density (BMD) Z-score. In some embodiments, treatment with an IL-4R antagonist results in an improvement or normalization in the subject's BMD Z-score, relative to baseline, by week 4, week 8, week 12, week 16, week 24, week 30, week 36, week 48, or week 52 after administration of the first dose of the IL-4R antagonist. In some embodiments, treatment with an IL-4R antagonist results in an increase of at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% in the BMD Z-score, relative to baseline, by week 4, week 8, week 12, week 16, week 24, week 30, week 36, week 48, or week 52 after administration of the first dose of the IL-4R antagonist.

Interleukin-4 Receptor Antagonists

[069] In some embodiments, the methods of the present disclosure comprise administering to a subject in need thereof (*e.g.*, a subject having a defect in bone growth) an interleukin-4 receptor (IL-4R) antagonist or a pharmaceutical composition comprising an IL-4R antagonist. As used herein, an "IL-4R antagonist" (also referred to herein as an "IL-4R inhibitor", an "IL-4R blocker," or an "IL-4Rα antagonist") is any agent that binds to or interacts with IL-4Rα or an IL-4R ligand, and inhibits or attenuates the normal biological signaling function of a type 1 and/or a type 2 IL-4 receptor. Human IL-4Rα has the amino acid sequence of SEQ ID NO:11. A type 1 IL-4 receptor is a dimeric receptor comprising an IL-4Rα chain and a γc chain. A type 2 IL-4 receptor is a dimeric receptor comprising an IL-4Rα chain and an IL-13Rα1 chain. Type 1 IL-4 receptors interact with and are stimulated by IL-4, while type 2 IL-4 receptors interact with and are stimulated by both IL-4 and IL-13. Thus, the IL-4R antagonists that can be used in the methods of the present disclosure may function by blocking IL-4-mediated signaling, IL-13-mediated signaling, or both IL-4- and IL-13-mediated signaling. The IL-4R antagonists of the present disclosure may thus prevent the interaction of IL-4 and/or IL-13 with a type 1 or type 2 receptor.

[070] Non-limiting examples of categories of IL-4R antagonists include small molecule IL-4R inhibitors, anti-IL-4R aptamers, peptide-based IL-4R inhibitors (*e.g.*, "peptibody" molecules), "receptor-bodies" (*e.g.*, engineered molecules comprising the ligand-binding domain of an IL-4R component), and antibodies or antigen-binding fragments of antibodies that specifically bind human IL-4Rα. As used herein, IL-4R antagonists also include antigen-binding proteins that specifically bind IL-4 and/or IL-13.

Anti-IL-4Rα Antibodies and Antigen-Binding Fragments Thereof

[071] In certain exemplary embodiments of the present disclosure, the IL-4R antagonist is an anti-IL-4Rα antibody or antigen-binding fragment thereof. The term "antibody," as used herein, includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM). In a typical antibody, each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In some embodiments, the FRs of the anti-IL-4R antibody (or antigen-binding portion thereof) are identical to the human germline sequences. In some embodiments, one or more FRs of the anti-IL-4R antibody (or antigen-binding portion thereof) are naturally or artificially modified.

[072] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and

manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

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

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

[075] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present disclosure include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present disclosure may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain

configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

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

[077] The term "antibody," as used herein, also includes multispecific (*e.g.*, bispecific) antibodies. A multispecific antibody or antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format may be adapted for use in the context of an antibody or antigen-binding fragment of an antibody of the present disclosure using routine techniques available in the art. For example, in some embodiments the methods of the present disclosure comprise the use of bispecific antibodies wherein one arm of an immunoglobulin is specific for IL-4Rα or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety. Exemplary bispecific formats that can be used in the context of the present disclosure include, without limitation, *e.g.*, scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (*e.g.*, common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED) body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab^2 bispecific formats (*see*, *e.g.*, Klein, *et al.*, 2012, *mAbs*, 4:6, 1-11, and references cited therein, for a review of the foregoing formats). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, *e.g.*, wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (*See*, *e.g.*, Kazane, *et al.*, *J. Am. Chem. Soc.* [Epub: Dec. 4, 2012]).

[078] In some embodiments, the antibodies used in the methods of the present disclosure are human antibodies. The term “human antibody,” as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the disclosure may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. 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.

[079] The antibodies used in the methods of the present disclosure may be recombinant human antibodies. The term "recombinant human antibody," as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (*see*, *e.g.*, Taylor, *et al.*, (1992) *Nucl. Acids Res.*, 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

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

[081] According to certain embodiments, the antibodies used in the methods of the present disclosure specifically bind IL-4Rα. The term "specifically binds," as used herein, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. In some embodiments, an antibody that "specifically binds" IL-4Rα binds to IL-4Rα or a portion thereof with an equilibrium dissociation constant (K_D) of less than about 1000 nM, less than about 500 nM, less than about 300 nM, less than about

200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 1 nM, less than about 0.5 nM, less than about 0.25 nM, less than about 0.1 nM or less than about 0.05 nM, as measured in a surface plasmon resonance assay (*e.g.*, BIAcore™, Biacore Life Sciences division of GE Healthcare, Piscataway, NJ). In some embodiments, an antibody that specifically binds to a target antigen (*e.g.*, IL-4Rα) can also specifically bind to another antigen, *e.g.*, an ortholog of the target antigen. For example, in some embodiments, an isolated antibody that specifically binds human IL-4Rα exhibits cross-reactivity to other antigens, such as IL-4Rα molecules from other (non-human) species.

[082] In some embodiments, the IL-4R antagonist is an anti-IL-4Rα antibody, or antigen-binding fragment thereof, comprising a heavy chain variable region (HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising any of the amino acid sequences of the anti-IL-4R antibodies as set forth in US Patent No. 7,608,693, incorporated by reference herein. In some embodiments, the IL-4R antagonist is an anti-IL-4Rα antibody or antigen-binding fragment thereof that comprises the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:1 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:2. In some embodiments, the IL-4R antagonist is an anti-IL-4Rα antibody or antigen-binding fragment thereof that comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence GFTFRDYA (SEQ ID NO:3), the HCDR2 comprises the amino acid sequence ISGSGGNT (SEQ ID NO:4), the HCDR3 comprises the amino acid sequence AKDRLSITIRPRYYGLDV (SEQ ID NO:5), the LCDR1 comprises the amino acid sequence QSLLYSIGYNY (SEQ ID NO:6), the LCDR2 comprises the amino acid sequence LGS, and the LCDR3 comprises the amino acid sequence MQALQTPYT (SEQ ID NO:8).

[083] In some embodiments, the anti-IL-4R antibody or antigen-binding fragment thereof comprises an HCDR1 comprising the amino acid sequence GFTFRDYA (SEQ ID NO:3), an HCDR2 comprising the amino acid sequence ISGSGGNT (SEQ ID NO:4), an HCDR3 comprising the amino acid sequence AKDRLSITIRPRYYGLDV (SEQ ID NO:5), an LCDR1 comprising the amino acid sequence QSLLYSIGYNY (SEQ ID NO:6), an LCDR2 comprising the amino acid sequence LGS, and an LCDR3 comprising the amino acid sequence MQALQTPYT (SEQ ID NO:8), and further comprises an HCVR having at least 85% sequence identity (*e.g.*, at

least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to the amino acid sequence of SEQ ID NO:1 and an LCVR having at least 85% sequence identity (*e.g.*, at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity) to the amino acid sequence of SEQ ID NO:2. In some embodiments, the anti-IL-4R antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO:1 and an LCVR comprising SEQ ID NO:2.

[084] In some embodiments, the anti-IL-4R antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:9. In some embodiments, the anti-IL-4R antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO:10.

[085] An exemplary antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO:9 and a light chain comprising the amino acid sequence of SEQ ID NO:10 is the fully human anti-IL-4R antibody known as dupilumab. According to certain exemplary embodiments, the methods of the present disclosure comprise the use of dupilumab. As used herein, "dupilumab" also includes bioequivalents of dupilumab. The term "bioequivalent," as used herein with reference to dupilumab, refers to anti-IL-4R antibodies or IL-4R-binding proteins or fragments thereof that are pharmaceutical equivalents or pharmaceutical alternatives whose rate and/or extent of absorption do not show a significant difference with that of dupilumab when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose. In some embodiments, the term refers to antigen-binding proteins that bind to IL-4R which do not have clinically meaningful differences with dupilumab in their safety, purity and/or potency.

[086] Other anti-IL-4Rα antibodies that can be used in the context of the methods of the present disclosure include, *e.g.*, the antibody referred to and known in the art as AMG317 (Corren, *et al.*, 2010, *Am J Respir Crit Care Med.,* 181(8):788-796), or MEDI 9314, or any of the anti-IL-4Rα antibodies as set forth in US Patent No. 7,186,809, US Patent No. 7,605,237, US Patent No. 7,638,606, US Patent No. 8,092,804, US Patent No. 8,679,487, US Patent No. 8,877,189, US Patent No. 10,774,141, or International Patent Publication Nos. WO2020/096381, WO 2020/182197, WO2020/239134, WO 2021/213329, WO2022/052974, WO2022/136669, or WO2022/136675, the contents of each of which are incorporated by reference herein.

[087] In some embodiments, an anti-IL-4Rα antibody or antigen-binding fragment thereof for use in the methods of the present disclosure comprises one or more CDR, HCVR, and/or LCVR sequences set forth in Table 1 below.

[088] In some embodiments, an anti-IL-4Rα antibody comprises (i) an HCVR comprising the amino acid sequence of SEQ ID NO:32 (SCB-VH-59), SEQ ID NO:33 (SCB-VH-60), SEQ ID NO:34 (SCB-VH-61), SEQ ID NO:35 (SCB-VH-62), SEQ ID NO:36 (SCB-VH-63), SEQ ID NO:37 (SCB-VH-64), SEQ ID NO:38 (SCB-VH-65), SEQ ID NO:39 (SCB-VH-66), SEQ ID NO:40 (SCB-VH-67), SEQ ID NO:41 (SCB-VH-68), SEQ ID NO:42 (SCB-VH-69), SEQ ID NO:43 (SCB-VH-70), SEQ ID NO:44 (SCB-VH-71), SEQ ID NO:45 (SCB-VH-72), SEQ ID NO:46 (SCB-VH-73), SEQ ID NO:47 (SCB-VH-74), SEQ ID NO:48 (SCB-VH-75), SEQ ID NO:49 (SCB-VH-76), SEQ ID NO:50 (SCB-VH-77), SEQ ID NO:51 (SCB-VH-78), SEQ ID NO:52 (SCB-VH-79), SEQ ID NO:53 (SCB-VH-80), SEQ ID NO:54 (SCB-VH-81), SEQ ID NO:55 (SCB-VH-82), SEQ ID NO:56 (SCB-VH-83), SEQ ID NO:57 (SCB-VH-84), SEQ ID NO:58 (SCB-VH-85), SEQ ID NO:59 (SCB-VH-86), SEQ ID NO:60 (SCB-VH-87), SEQ ID NO:61 (SCB-VH-88), SEQ ID NO:62 (SCB-VH-89), SEQ ID NO:63 (SCB-VH-90), SEQ ID NO:64 (SCB-VH-91), SEQ ID NO:65 (SCB-VH-92), or SEQ ID NO:66 (SCB-VH-93); and (ii) an LCVR comprising the amino acid sequence of SEQ ID NO:12 (SCB-VL-39), SEQ ID NO:13 (SCB-VL-40), SEQ ID NO:14 (SCB-VL-41), SEQ ID NO:15 (SCB-VL-42), SEQ ID NO:16 (SCB-VL-43), SEQ ID NO:17 (SCB-VL-44), SEQ ID NO:18 (SCB-VL-45), SEQ ID NO:19 (SCB-VL-46), SEQ ID NO:20 (SCB-VL-47), SEQ ID NO:21 (SCB-VL-48), SEQ ID NO:22 (SCB-VL-49), SEQ ID NO:23 (SCB-VL-50), SEQ ID NO:24 (SCB-VL-51), SEQ ID NO:25 (SCB-VL-52), SEQ ID NO:26 (SCB-VL-53), SEQ ID NO:27 (SCB-VL-54), SEQ ID NO:28 (SCB-VL-55), SEQ ID NO:29 (SCB-VL-56), SEQ ID NO:30 (SCB-VL-57), or SEQ ID NO:31 (SCB-VL-58). In some embodiments, the anti-IL-4Rα antibody comprises an HCVR comprising the amino acid sequence of SEQ ID NO:64 (SCB-VH-91) and an LCVR comprising the amino acid sequence of SEQ ID NO:17 (SCB-VL-44), SEQ ID NO:27 (SCB-VL-54), or SEQ ID NO:28 (SCB-VL-55).

[089] In some embodiments, an anti-IL-4Rα antibody comprises an amino acid sequence pair selected from the group consisting of: SEQ ID NOs:67/68 (MEDI-1-VH/MEDI-1-VL); SEQ ID NOs:69/70 (MEDI-2-VH/MEDI-2-VL); SEQ ID NOs:71/72 (MEDI-3-VH/MEDI-3-VL); SEQ ID NOs:73/74 (MEDI-4-VH/MEDI-4-VL); SEQ ID NOs:75/76 (MEDI-5-VH/MEDI-5-VL); SEQ ID NOs:77/78 (MEDI-6-VH/MEDI-6/VL); SEQ ID NOs:79/80 (MEDI-7-VH/MEDI-7-VL); SEQ ID NOs:81/82 (MEDI-8-VH/MEDI-8-VL); SEQ ID NOs:83/84 (MEDI-9-VH/MEDI-9-VL); SEQ ID NOs:85/86 (MEDI-10-VH/MEDI-10-VL); SEQ ID NOs:87/88 (MEDI-11-VH/MEDI-11/VL); SEQ ID NOs:89/90 (MEDI-12-VH/MEDI-12-VL); SEQ ID NOs:91/92 (MEDI-13-VH/MEDI-13-VL); SEQ ID NOs:93/94 (MEDI-14-VH/MEDI-14-VL); SEQ ID NOs:95/96 (MEDI-15-VH/MEDI-15-VL); SEQ ID NOs:97/98 (MEDI-16-VH/MEDI-16/VL); SEQ ID NOs:99/100 (MEDI-17-VH/MEDI-17-VL); SEQ ID NOs:101/102 (MEDI-18-VH/MEDI-18-VL); SEQ ID NOs:103/104 (MEDI-19-VH/MEDI-19-VL);

SEQ ID NOs:105/106 (MEDI-20-VH/MEDI-20-VL); SEQ ID NOs:107/108 (MEDI-21-VH/MEDI-21-VL); SEQ ID NOs:109/110 (MEDI-22-VH/MEDI-22-VL); SEQ ID NOs:111/112 (MEDI-23-VH/MEDI-23-VL); SEQ ID NOs:113/114 (MEDI-24-VH/MEDI-24-VL); SEQ ID NOs:115/116 (MEDI-25-VH/MEDI-25-VL); SEQ ID NOs:117/118 (MEDI-26-VH/MEDI-26-VL); SEQ ID NOs:119/120 (MEDI-27-VH/MEDI-27-VL); SEQ ID NOs:121/122 (MEDI-28-VH/MEDI-28-VL); SEQ ID NOs:123/124 (MEDI-29-VH/MEDI-29-VL); SEQ ID NOs:125/126 (MEDI-30-VH/MEDI-30-VL); SEQ ID NOs:127/128 (MEDI-31-VH/MEDI-31-VL); SEQ ID NOs:129/130 (MEDI-32-VH/MEDI-32-VL); SEQ ID NOs:131/132 (MEDI-33-VH/MEDI-33-VL); SEQ ID NOs:133/134 (MEDI-34-VH/MEDI-34-VL); SEQ ID NOs:135/136 (MEDI-35-VH/MEDI-35-VL); SEQ ID NOs:137/138 (MEDI-36-VH/MEDI-36-VL); SEQ ID NOs:139/140 (MEDI-37-VH/MEDI-37-VL); SEQ ID NOs:141/142 (MEDI-38-VH/MEDI-38-VL); SEQ ID NOs:143/144 (MEDI-39-VH/MEDI-39-VL); SEQ ID NOs:145/146 (MEDI-40-VH/MEDI-40-VL); SEQ ID NOs:147/148 (MEDI-41-VH/MEDI-41-VL); SEQ ID NOs:149/150 (MEDI-42-VH/MEDI-42-VL); and SEQ ID NOs:151/152 (MEDI-37GL-VH/MEDI-37GL-VL).

[090] In some embodiments, an anti-IL-4Rα antibody comprises (i) an HCVR comprising the amino acid sequence of SEQ ID NO:153 (AJOU-1-VH), SEQ ID NO:154 (AJOU-2-VH), SEQ ID NO:155 (AJOU-3-VH), SEQ ID NO:156 (AJOU-4-VH), SEQ ID NO:157 (AJOU-5-VH), SEQ ID NO:158 (AJOU-6-VH), SEQ ID NO:159 (AJOU-7-VH), SEQ ID NO:160 (AJOU-8-VH), SEQ ID NO:161 (AJOU-9-VH), SEQ ID NO:162 (AJOU-10-VH), SEQ ID NO:163 (AJOU-69-VH), SEQ ID NO:164 (AJOU-70-VH), SEQ ID NO:165 (AJOU-71-VH), SEQ ID NO:166 (AJOU-72-VH), or SEQ ID NO:167 (AJOU-83-VH); and (ii) an LCVR comprising the amino acid sequence of SEQ ID NO:168 (AJOU-33-VL), SEQ ID NO:169 (AJOU-34-VL), SEQ ID NO:170 (AJOU-35-VL), SEQ ID NO:171 (AJOU-36-VL), SEQ ID NO:172 (AJOU-37-VL), SEQ ID NO:173 (AJOU-38-VL), SEQ ID NO:174 (AJOU-39-VL), SEQ ID NO:175 (AJOU-40-VL), SEQ ID NO:176 (AJOU-41-VL), SEQ ID NO:177 (AJOU-42-VL), SEQ ID NO:178 (AJOU-77-VL), SEQ ID NO:179 (AJOU-78-VL), SEQ ID NO:180 (AJOU-79-VL), SEQ ID NO:181 (AJOU-80-VL), SEQ ID NO:182 (AJOU-86-VL), SEQ ID NO:183 (AJOU-87-VL), SEQ ID NO:184 (AJOU-88-VL), SEQ ID NO:185 (AJOU-89-VL), SEQ ID NO:186 (AJOU-90-VL), or SEQ ID NO:187 (AJOU-91-VL).

[091] In some embodiments, an anti-IL-4Rα antibody comprises (i) an HCVR comprising the amino acid sequence of SEQ ID NO:188 (REGN-VH-3), SEQ ID NO:189 (REGN-VH-19), SEQ ID NO:190 (REGN-VH-35), SEQ ID NO:191 (REGN-VH-51), SEQ ID NO:192 (REGN-VH-67), SEQ ID NO:193 (REGN-VH-83), SEQ ID NO:194 (REGN-VH-99), SEQ ID NO:195 (REGN-VH-115), SEQ ID NO:196 (REGN-VH-147), or SEQ ID NO:197 (REGN-VH-163); and (ii) an LCVR comprising the amino acid sequence of SEQ ID NO:198 (REGN-VL-11), SEQ ID NO:199

(REGN-VL-27), SEQ ID NO:200 (REGN-VL-43), SEQ ID NO:201 (REGN-VL-59), SEQ ID NO:202 (REGN-VL-75), SEQ ID NO:203 (REGN-VL-91), SEQ ID NO:204 (REGN-VL-107), SEQ ID NO:205 (REGN-VL-123), SEQ ID NO:206 (REGN-VL-155), or SEQ ID NO:207 (REGN-VL-171).

[092] In some embodiments, an anti-IL-4Rα antibody comprises (i) an HCVR comprising the amino acid sequence of SEQ ID NO:208 (STSA-C27-VH), SEQ ID NO:209 (STSA-C27-6-33-VH), SEQ ID NO:210 (STSA-C27-7-33-VH), SEQ ID NO:211 (STSA-C27-24-56-VH), SEQ ID NO:212 (STSA-C27-47-56-VH), SEQ ID NO:213 (STSA-C27-33-33-VH), SEQ ID NO:214 (STSA-C27-56-56-VH), SEQ ID NO:215 (STSA-C27-78-78-VH), SEQ ID NO:216 (STSA-C27-82-58-VH), SEQ ID NO:217 (STSA-C27-54-54-VH), SEQ ID NO:218 (STSA-C27-36-36-VH), SEQ ID NO:219 (STSA-C27-53-53-VH), SEQ ID NO:220 (STSA-C27-67-67-VH), SEQ ID NO:221 (STSA-C27-55-55-VH), SEQ ID NO:222 (STSA-C27-59-59-VH), SEQ ID NO:223 (STSA-C27-58-58-VH), SEQ ID NO:224 (STSA-C27-52-52-VH), or SEQ ID NO:225 (STSA-C27-Y2-Y2-VH); and (ii) an LCVR comprising the amino acid sequence of SEQ ID NO:226 (STSA-C27-VL), SEQ ID NO:227 (STSA-C27-6-33-VL), SEQ ID NO:228 (STSA-C27-7-33-VL), SEQ ID NO:229 (STSA-C27-24-56-VL), SEQ ID NO:230 (STSA-C27-47-56-VL), SEQ ID NO:231 (STSA-C27-33-33-VL), SEQ ID NO:232 (STSA-C27-56-56-VL), SEQ ID NO:233 (STSA-C27-78-78-VL), SEQ ID NO:234 (STSA-C27-82-58-VL), SEQ ID NO:235 (STSA-C27-54-54-VL), SEQ ID NO:236 (STSA-C27-36-36-VL), SEQ ID NO:237 (STSA-C27-53-53-VL), SEQ ID NO:238 (STSA-C27-67-67-VL), SEQ ID NO:239 (STSA-C27-55-55-VL), SEQ ID NO:240 (STSA-C27-59-59-VL), SEQ ID NO:241 (STSA-C27-58-58-VL), SEQ ID NO:242 (STSA-C27-52-52-VL), or SEQ ID NO:243 (STSA-C27-Y2-Y2-VL).

[093] In some embodiments, an anti-IL-4Rα antibody comprises (i) an HCVR comprising the amino acid sequence of SEQ ID NO:244 (Y0188-1 VH), SEQ ID NO:245 (Y0188-2 VH), SEQ ID NO:246 (Y0188-3 VH), SEQ ID NO:247 (Y0188-4 VH), SEQ ID NO:248 (Y0188-6 VH), SEQ ID NO:249 (Y0188-8 VH), SEQ ID NO:250 (Y0188-9 VH), SEQ ID NO:251 (Y0188-10 VH), SEQ ID NO:252 (Y0188-14 VH), SEQ ID NO:253 (HV3-15-14 VH), SEQ ID NO:254 (HV3-48-14 VH), SEQ ID NO:255 (HV3-73*2-14 VH), SEQ ID NO:256 (HV3-72-14 VH), SEQ ID NO:257 (Y01-14 VH), SEQ ID NO:258 (162-14 VH), or SEQ ID NO:259 (VH73-14 VH); and (ii) an LCVR comprising the amino acid sequence of SEQ ID NO:260 (Y0188-1 VL), SEQ ID NO:261 (Y0188-2 VL), SEQ ID NO:262 (Y0188-3 VL), SEQ ID NO:263 (Y0188-4 VL), SEQ ID NO:264 (Y0188-6 VL), SEQ ID NO:265 (Y0188-8 VL), SEQ ID NO:266 (Y0188-9 VL), SEQ ID NO:267 (Y0188-10 VL), SEQ ID NO:268 (Y0188-14 VL), SEQ ID NO:269 (Y01-14 VL), SEQ ID NO:270 (164-14

VL), SEQ ID NO:271 (KV4-14 VL), SEQ ID NO:272 (KV1-27-14 VL), SEQ ID NO:273 (KV1-9-14 VL), SEQ ID NO:274 (KV1-NL1-14 VL), or SEQ ID NO:275 (KV1D-43-14 VL).

[094] In some embodiments, an anti-IL-4Rα antibody used in the methods of the present disclosure can have pH-dependent binding characteristics. For example, an anti-IL-4Rα antibody for use as disclosed herein may exhibit reduced binding to IL-4Rα at acidic pH as compared to neutral pH. Alternatively, an anti-IL-4Rα antibody for use as disclosed herein may exhibit enhanced binding to its antigen at acidic pH as compared to neutral pH. The expression "acidic pH" includes pH values less than about 6.2, *e.g.*, about 6.0, 5.95, 5.9, 5.85, 5.8, 5.75, 5.7, 5.65, 5.6, 5.55, 5.5, 5.45, 5.4, 5.35, 5.3, 5.25, 5.2, 5.15, 5.1, 5.05, 5.0, or less. As used herein, the expression "neutral pH" means a pH of about 7.0 to about 7.4. The expression "neutral pH" includes pH values of about 7.0, 7.05, 7.1, 7.15, 7.2, 7.25, 7.3, 7.35, and 7.4.

[095] In certain instances, "reduced binding to IL-4Rα at acidic pH as compared to neutral pH" is expressed in terms of a ratio of the K_D value of the antibody binding to IL-4Rα at acidic pH to the K_D value of the antibody binding to IL-4Rα at neutral pH (or vice versa). For example, an antibody or antigen-binding fragment thereof may be regarded as exhibiting "reduced binding to IL-4Rα at acidic pH as compared to neutral pH" for purposes of the present disclosure if the antibody or antigen-binding fragment thereof exhibits an acidic/neutral K_D ratio of about 3.0 or greater. In certain exemplary embodiments, the acidic/neutral K_D ratio for an antibody or antigen-binding fragment of the present disclosure can be about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 20.0, 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 100.0, or greater.

[096] Antibodies with pH-dependent binding characteristics may be obtained, *e.g.*, by screening a population of antibodies for reduced (or enhanced) binding to a particular antigen at acidic pH as compared to neutral pH. Additionally, modifications of the antigen-binding domain at the amino acid level may yield antibodies with pH-dependent characteristics. For example, by substituting one or more amino acids of an antigen-binding domain (*e.g.*, within a CDR) with a histidine residue, an antibody with reduced antigen-binding at acidic pH relative to neutral pH may be obtained.

Preparation of Human Antibodies

[097] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present disclosure to make human antibodies that specifically bind to human IL-4R.

[098] Using VELOCIMMUNE™ technology (*see*, for example, US 6,596,541, Regeneron Pharmaceuticals) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to IL-4R are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[099] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[0100] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc., using standard procedures known to those skilled in the art. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the disclosure, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0101] In general, the antibodies that can be used in the methods of the present disclosure possess high affinities, as described above, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the disclosure. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0102] In one embodiment, a human antibody or antigen-binding fragment thereof that specifically binds IL-4R and that can be used in the methods disclosed herein comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) having an amino acid sequence of SEQ ID NO:1, and the three light chain CDRs (LCVR1, LCVR2, and LCVR3) contained within a light chain variable region (LCVR) having an amino acid sequence of SEQ ID NO:2. Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. *See*, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani, *et al.*, *J. Mol. Biol.*, 273:927-948 (1997); and Martin, *et al.*, *Proc. Natl. Acad. Sci. USA*, 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

Pharmaceutical Compositions

[0103] In one aspect, the present disclosure provides methods that comprise administering an IL-4R antagonist to a subject, wherein the IL-4R antagonist (*e.g.*, an anti-IL-4R antibody) is contained within a pharmaceutical composition that comprises one or more pharmaceutically acceptable vehicle, carriers, and/or excipients. Various pharmaceutically acceptable carriers and excipients are well-known in the art. *See*, *e.g.*, Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. In some embodiments, the carrier is suitable for intravenous, intramuscular, oral, intraperitoneal, intrathecal, transdermal, topical, or subcutaneous administration.

[0104] Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. In some embodiments, a pharmaceutical composition as disclosed herein is administered intravenously. In some embodiments, a pharmaceutical composition as disclosed herein is administered subcutaneously.

[0105] In some embodiments, the pharmaceutical composition comprises an injectable preparation, such as a dosage form for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (*e.g.*, ethanol), a polyalcohol (*e.g.*, propylene glycol, polyethylene glycol), a nonionic surfactant [*e.g.*, polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, *e.g.*, sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared can be filled in an appropriate ampoule.

[0106] The dose of antibody administered to a subject according to the methods of the present disclosure may vary depending upon the age and the size of the subject, symptoms, conditions, route of administration, and the like. The dose is typically calculated according to body weight or body surface area. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. Effective dosages and schedules for administering pharmaceutical compositions comprising anti-IL-4R antibodies may be determined empirically; for example, subject progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (*e.g.*, Mordenti, *et al.*, 1991, *Pharmaceut. Res.*, *8*:1351). Specific exemplary doses of anti-IL4R antibodies, and administration regimens involving the same, that can be used in the context of the present disclosure are disclosed elsewhere herein.

[0107] In some embodiments, an IL-4R antagonist or a pharmaceutical composition of the present disclosure is contained within a container. Thus, in another aspect, containers comprising an IL-4R antagonist or a pharmaceutical composition as disclosed herein are provided. For example, in some embodiments, a pharmaceutical composition is contained within a container selected from the group consisting of a glass vial, a syringe, a pen delivery device, and an autoinjector.

[0108] In some embodiments, a pharmaceutical composition of the present disclosure is delivered, *e.g.*, subcutaneously or intravenously, with a standard needle and syringe. In some

embodiments, the syringe is a pre-filled syringe. In some embodiments, a pen delivery device or autoinjector is used to deliver a pharmaceutical composition of the present disclosure (*e.g.*, for subcutaneous delivery). A pen delivery device can be reusable or disposable. Typically, a reusable pen delivery device utilizes a replaceable cartridge that contains a pharmaceutical composition. Once the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0109] Examples of suitable pen and autoinjector delivery devices include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany). Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present disclosure include, but are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL).

[0110] In some embodiments, the pharmaceutical composition is delivered using a controlled release system. In one embodiment, a pump may be used (*see* Langer, *supra*; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; *see*, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (*see*, *e.g.*, Goodson, 1984, in Medical Applications of Controlled Release, *supra*, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, *Science*, 249:1527-1533. Other delivery systems are known and can be used to administer the pharmaceutical composition, *e.g.*, encapsulation in liposomes, microparticles, microcapsules,

recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (*see, e.g.*, Wu, *et al.*, 1987, *J. Biol. Chem.*, 262:4429-4432).

[0111] In some embodiments, a pharmaceutical composition comprising an anti-IL-4R antibody is administered using a drug delivery device that is a needle-based injection system as described in Table 1 of section 5.2 of ISO 11608-1:2014(E). As described in ISO 11608-1:2014(E), needle-based injection systems may be broadly distinguished into multi-dose container systems and single-dose (with partial or full evacuation) container systems. The container may be a replaceable container or an integrated non-replaceable container.

[0112] As further described in ISO 11608-1:2014(E), a multi-dose container system may involve a needle-based injection device with a replaceable container. In such a system, each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user). Another multi-dose container system may involve a needle-based injection device with an integrated non-replaceable container. In such a system, each container holds multiple doses, the size of which may be fixed or variable (pre-set by the user).

[0113] As further described in ISO 11608-1:2014(E), a single-dose container system may involve a needle-based injection device with a replaceable container. In one example for such a system, each container holds a single dose, whereby the entire deliverable volume is expelled (full evacuation). In a further example, each container holds a single dose, whereby a portion of the deliverable volume is expelled (partial evacuation). As also described in ISO 11608-1:2014(E), a single-dose container system may involve a needle-based injection device with an integrated non-replaceable container. In one example for such a system, each container holds a single dose, whereby the entire deliverable volume is expelled (full evacuation). In a further example, each container holds a single dose, whereby a portion of the deliverable volume is expelled (partial evacuation).

[0114] An exemplary sleeve-triggered auto-injector with manual needle insertion is described in International Publication WO2015/004052. Exemplary audible end-of-dose feedback mechanisms are described in International Publications WO2016/193346 and WO2016/193348. An exemplary needle-safety mechanism after using an auto-injector is described in International Publication WO2016/193352. An exemplary needle sheath remover mechanism for a syringe auto-injector is described in International Publication WO2016/193353. An exemplary support mechanism for supporting an axial position of a syringe is described in International Publication WO2016/193355.

[0115] In some embodiments, pharmaceutical compositions for use as described herein are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such

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

[0116] Exemplary pharmaceutical compositions comprising an anti-IL-4R antibody that can be used in the context of the present disclosure are disclosed, *e.g.*, in US Patent No. 8,945,559.

Dosage and Administration

[0117] In some embodiments, an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) is administered to a subject (*e.g.*, a subject having a defect in bone growth) according to the methods of the present disclosure in a therapeutically effective amount. As used herein with reference to an IL-4R antagonist, the phrase "therapeutically effective amount" means an amount of IL-4R antagonist that results in one or more of: (a) an improvement in bone formation; (b) an improvement in bone mineralization and/or bone mineral density; (c) a reduction in bone loss; (d) an improvement or normalization (*e.g.*, relative to a healthy control value) in one or more biomarkers of bone formation or bone turnover (such as, but not limited to, bone-specific alkaline phosphatase, carboxy-terminal cross-linked telopeptide of type I collagen, pro-collagen type I N-terminal propeptide, insulin-like growth factor 1, or osteocalcin); and/or (e) a reduction in the occurrence of osteopenia, osteoporosis, or fracture (*e.g.*, relative to a healthy control value).

[0118] In the case of an anti-IL-4R antibody, a therapeutically effective amount can be from about 0.05 mg to about 600 mg, *e.g.*, about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, 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, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg, of the anti-IL-4R antibody. In some embodiments, a therapeutically effective amount is from about 50 mg to about 600 mg, or from about 100 mg to about 600 mg, or from about 200 mg to about 600 mg. In certain embodiments, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, 400 mg, 450 mg, 500 mg, 550 mg, or 600 mg of an anti-IL-4R antibody is administered to a subject.

[0119] The amount of IL-4R antagonist (*e.g.*, anti-IL-4R antibody) contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of subject body weight (*i.e.*, mg/kg). For example, the IL-4R antagonist may be administered to a subject at a dose of about 0.0001 to about 10 mg/kg of subject body weight, *e.g.*, at a dose of about 1 mg/kg to about 10 mg/kg, at a dose of about 2 mg/kg to about 9 mg/kg, or at a dose of about 3 mg/kg to about 8 mg/kg. In some embodiments, the IL-4R antagonist may be administered to a subject at a dose of about 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, or 10 mg/kg.

[0120] In some embodiments, the methods disclosed herein comprise administering an IL-4R antagonist to a subject at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved. In some embodiments, the methods disclosed herein comprise administering an IL-4R antagonist to a subject once every week, once every two weeks, once every three weeks, or once every four weeks. In some embodiments, the methods disclosed herein comprise administering an IL-4R antagonist to a subject once a month or twice a month.

[0121] In some embodiments, multiple doses of an IL-4R antagonist are administered to a subject over a defined time course. In some embodiments, the methods of the present disclosure comprise sequentially administering to a subject multiple doses of an IL-4R antagonist. As used herein, "sequentially administering" means that each dose of IL-4R antagonist is administered to the subject at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). In some embodiments, the methods of the disclosure comprise sequentially administering to the patient a single initial dose of an IL-4R antagonist, followed by one or more secondary doses of the IL-4R antagonist, and optionally followed by one or more tertiary doses of the IL-4R antagonist.

[0122] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the IL-4R antagonist. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "loading dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of IL-4R antagonist, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of IL-4R antagonist contained in the initial, secondary

and/or tertiary doses varies from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment. In certain embodiments, one or more (*e.g.*, 1, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (*e.g.*, "maintenance doses"). In some embodiments, the initial or loading dose and the one or more secondary or maintenance doses each contain the same amount of the IL-4R antagonist. In other embodiments, the initial dose comprises a first amount of the IL-4R antagonist, and the one or more secondary doses each comprise a second amount of the IL-4R antagonist. For example, the first amount of the IL-4R antagonist can be 1.5x, 2x, 2.5x, 3x, 3.5x, 4x or 5x or more than the second amount of the IL-4R antagonist. In some embodiments, one or more maintenance doses of the IL-4R antagonist are administered without a loading dose.

[0123] In some embodiments, a loading dose is a "split dose" that is administered as two or more doses (*e.g.*, 2, 3, 4, or 5 doses) that are administered on separate days. In some embodiments, a loading dose is administered as a split dose wherein the two or more doses are administered at least about one week apart. In some embodiments, a loading dose is administered as a split dose wherein the two or more doses are administered about 1 week, 2 weeks, 3 weeks, or 4 weeks apart. In some embodiments, the loading dose is split evenly over the two or more doses (*e.g.*, half of the loading dose is administered as the first portion and half of the loading dose is administered as the second portion). In some embodiments, the loading dose is split unevenly over the two or more doses (*e.g.*, more than half of the loading dose is administered as the first portion and less than half of the loading dose is administered as the second portion).

[0124] In some embodiments, each secondary and/or tertiary dose is administered 1 to 14 (*e.g.*, 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of IL-4R antagonist which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0125] The methods of the disclosure may comprise administering to a patient any number of secondary and/or tertiary doses of an IL-4R antagonist. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other

embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0126] In some embodiments involving multiple secondary doses, each secondary dose is administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 week, 2 weeks, 3 weeks, or 4 weeks after the immediately preceding dose. Similarly, in some embodiments involving multiple tertiary doses, each tertiary dose is administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 1 week, 2 weeks, 3 weeks, or 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

[0127] In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 300 mg administered every two weeks (Q2W). In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises a loading dose of 600 mg followed by one or more subsequent doses of 300 mg administered every two weeks (Q2W). In some embodiments, no loading dose is administered.

[0128] In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 200 mg administered every two weeks (Q2W). In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises a loading dose of 400 mg followed by one or more subsequent doses of 200 mg administered every two weeks (Q2W). In some embodiments, no loading dose is administered.

[0129] In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 300 mg administered every four weeks (Q4W). In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises a loading dose of 600 mg followed by one or more subsequent doses of 300 mg administered every four weeks (Q4W). In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises a split loading dose of 600 mg (*e.g.*, in which 300 mg is administered on Day 1 and 300 mg is administered on Day 15) followed by one or more subsequent doses of 300 mg administered Q4W starting four weeks after the Day 15 dose. In some embodiments, no loading dose is administered.

[0130] In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 200 mg administered every four weeks (Q4W). In some embodiments, a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises a loading dose of 400 mg followed by one or more subsequent doses of 200 mg administered every four weeks (Q4W). In some embodiments, no loading dose is administered.

[0131] In some embodiments, for a subject who is ≥12 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥12 to <18 years of age), or for a subject who is ≥6 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <18 years of age), or for a subject who is ≥6 to <12 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <12 years of age), a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 300 mg administered every two weeks (Q2W), if the subject is ≥60 kg in weight. In some embodiments, the subject is administered a loading dose of 600 mg followed by one or more subsequent doses of 300 mg administered every two weeks (Q2W), if the subject is ≥60 kg in weight. In some embodiments, no loading dose is administered.

[0132] In some embodiments, for a subject who is ≥12 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥12 to <18 years of age), a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 200 mg administered every two weeks (Q2W), if the subject is <60 kg in weight. In some embodiments, the subject is administered a loading dose of 400 mg followed by one or more subsequent doses of 200 mg administered every two weeks (Q2W), if the subject is <60 kg in weight. In some embodiments, no loading dose is administered.

[0133] In some embodiments, for a subject who is ≥12 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥12 to <18 years of age), or for a subject who is ≥6 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <18 years of age), or for a subject who is ≥6 to <12 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <12 years of age), a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 200 mg administered every two weeks (Q2W), if the subject is ≥30 kg to <60 kg in weight. In some embodiments, the subject is administered a loading dose of 400 mg followed by one or more subsequent doses of 200 mg administered every two weeks (Q2W), if the subject is ≥30 kg to <60 kg in weight. In some embodiments, no loading dose is administered.

[0134] In some embodiments, for a subject who is ≥6 months to <6 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 months to <6 years of age), or for a subject who is ≥6 to <12 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <12 years of age), or for a subject who is ≥6 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <18 years of age), a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 200 mg administered every two weeks (Q2W), if the subject is ≥15 kg to <60 kg in weight. In some embodiments, the subject is administered a loading dose of 400 mg followed by one or more subsequent doses of 200 mg administered every two weeks (Q2W), if the subject is ≥15 kg to <60 kg in weight. In some embodiments, no loading dose is administered.

[0135] In some embodiments, for a subject who is ≥6 months to <6 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 months to <6 years of age), or for a subject who is ≥6 to <12 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <12 years of age), or for a subject who is ≥6 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <18 years of age), a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 300 mg administered every four weeks (Q4W), if the subject is ≥15 kg to <60 kg in weight. In some embodiments, the subject is administered a loading dose of 600 mg followed by one or more subsequent doses of 300 mg administered every four weeks (Q4W), if the subject is ≥15 kg to <60 kg in weight. In some embodiments, the subject is administered a split loading dose of 600 mg (*e.g.*, in which 300 mg is administered on Day 1 and 300 mg is administered on Day 15) followed by one or more subsequent doses of 300 mg administered Q4W starting four weeks after the Day 15 dose. In some embodiments, no loading dose is administered.

[0136] In some embodiments, for a subject who is ≥6 months to <6 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 months to <6 years of age), or for a subject who is ≥6 to <12 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <12 years of age), or for a subject who is ≥6 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <18 years of age), a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 300 mg administered every four weeks (Q4W), if the subject is ≥15 kg to <30 kg in weight. In some embodiments, the subject is administered a loading dose of 600 mg followed by one or more subsequent doses of 300 mg administered every four weeks (Q4W), if the subject is ≥15 kg to <30 kg in weight. In some embodiments, the subject is administered a split loading dose of 600 mg (*e.g.*, in which 300 mg is administered on Day 1 and 300 mg is administered on Day 15)

followed by one or more subsequent doses of 300 mg administered Q4W starting four weeks after the Day 15 dose. In some embodiments, no loading dose is administered.

[0137] In some embodiments, for a subject who is ≥6 months to <6 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 months to <6 years of age), or for a subject who is ≥6 to <12 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <12 years of age), or for a subject who is ≥6 to <18 years of age (*e.g.*, a subject having moderate-to-severe or severe AD who is ≥6 to <18 years of age), a therapeutically effective amount of an IL-4R antagonist (*e.g.*, anti-IL-4R antibody) comprises 200 mg administered every four weeks (Q4W), if the subject is ≥5 kg to <15 kg in weight. In some embodiments, the subject is administered a loading dose of 400 mg followed by one or more subsequent doses of 200 mg administered every four weeks (Q4W), if the subject is ≥5 kg to <15 kg in weight. In some embodiments, the subject is administered a split loading dose of 400 mg (*e.g.*, in which 200 mg is administered on Day 1 and 200 mg is administered on Day 15) followed by one or more subsequent doses of 200 mg administered Q4W starting four weeks after the Day 15 dose. In some embodiments, no loading dose is administered.

Combination Therapies

[0138] In some embodiments, the methods of the present disclosure comprise administering to the subject (*e.g.*, a pediatric or adolescent subject having a defect in bone growth) an IL-4R antagonist according to the disclosure (*e.g.*, an anti-IL-4R antibody) in combination with one or more additional therapeutic agents. In some embodiments, the additional therapeutic agent is a topical therapeutic agent, *e.g.*, a TCS or a topical nonsteroidal medication such as a TCI or crisaborole. In some embodiments, the additional therapeutic agent is a systemic agent, *e.g.*, cyclosporine A, methotrexate, mycophenolate mofetil, azathioprine, systemic or oral corticosteroids, a Janus kinase (JAK) inhibitor, or interferon-gamma. In some embodiments, the additional therapeutic agent is an immunobiologic such as a tumor necrosis factor alpha (TNFα) inhibitor (*e.g.*, an anti-TNFα antibody such as infliximab), a CD11a inhibitor (*e.g.*, an anti-CD11a antibody such as efalizumab), an IgE inhibitor (*e.g.*, omalizumab), or a CD20 inhibitor (*e.g.*, rituximab). As used herein, the expression "in combination with" means that the additional therapeutic agent is administered before, after, or concurrent with the IL-4R inhibitor. The term "in combination with" also includes sequential or concomitant administration of IL-4R inhibitor and the additional therapeutic agent.

[0139] For example, when administered "before" the pharmaceutical composition comprising the IL-4R antagonist, the additional therapeutic agent may be administered about 72 hours,

about 60 hours, about 48 hours, about 36 hours, about 24 hours, about 12 hours, about 10 hours, about 8 hours, about 6 hours, about 4 hours, about 2 hours, about 1 hour, about 30 minutes, about 15 minutes or about 10 minutes prior to the administration of the pharmaceutical composition comprising the IL-4R antagonist. When administered "after" the pharmaceutical composition comprising the IL-4R antagonist, the additional therapeutic agent may be administered about 10 minutes, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours or about 72 hours after the administration of the pharmaceutical composition comprising the IL-4R antagonist. Administration "concurrent" or with the pharmaceutical composition comprising the IL-4R antagonist means that the additional therapeutic agent is administered to the subject in a separate dosage form within less than about 10 minutes (before, after, or at the same time) of administration of the pharmaceutical composition comprising the IL-4R antagonist, or administered to the subject as a single combined dosage formulation comprising both the additional therapeutic agent and the IL-4R antagonist.

[0140] In some embodiments, the additional therapeutic agent is a TCS. In some embodiments, the TCS is a medium-potency TCS. In some embodiments, the TCS is a low-potency TCS. In some embodiments, the additional therapeutic agent is a TCI. In some embodiments, the additional therapeutic agent is crisaborole.

Table 1: Informal Sequence Listing

SEQ ID NO	Sequence	Description
1	EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQAPGKGLEWVSSISGSG GNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLSITIRPRYYGLD VWGQGTTVTVS	Dupilumab HCVR amino acid sequence
2	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLDWYLQKSGQSPQLLIYLGSNR ASGVPDRFSGSGSGTDFTLKISRVEAEDVGFYYCMQALQTPYTFGQGTKLEIK	Dupilumab LCVR amino acid sequence
3	GFTFRDYA	Dupilumab HCDR1 amino acid sequence
4	ISGSGGNT	Dupilumab HCDR2 amino acid sequence
5	AKDRLSITIRPRYYGLDV	Dupilumab HCDR3 amino acid sequence
6	QSLLYSIGYNY	Dupilumab LCDR1 amino acid sequence
	LGS	Dupilumab LCDR2 amino acid sequence
8	MQALQTPYT	Dupilumab LCDR3 amino acid sequence

SEQ ID NO	Sequence	Description
9	EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQAPGKGLEWVSSISGSG GNTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRLSITIRPRYYGLD VWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGA LTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGP PCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYVDG VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKA KGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTP PVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK	Dupilumab heavy chain amino acid sequence
10	DIVMTQSPLSLPVTPGEPASISCRSSQSLLYSIGYNYLDWYLQKSGQSPQLLIYLGSNR ASGVPDRFSGSGSGTDFTLKISRVEAEDVGFYYCMQALQTPYTFGQGTKLEIKRTVAA PSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSK DSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	Dupilumab light chain amino acid sequence
11	MKVLQEPTCVSDYMSISTCEWKMNGPTNCSTELRLLYQLVFLLSEAHTCIPENNGGA GCVCHLLMDDVVSADNYTLDLWAGQQLLWKGSFKPSEHVKPRAPGNLTVHTNVS DTLLLTWSNPYPPDNYLYNHLTYAVNIWSENDPADFRIYNVTYLEPSLRIAASTLKSGI SYRARVRAWAQCYNTTWSEWSPSTKWHNSYREPFEQH	Human IL-4Rα
12	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-39
13	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-40
14	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-41
15	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-42
16	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-43
17	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-44
18	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-45
19	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSAGWTFGQGTKVEIK	SCB-VL-46
20	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-47
21	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-48
22	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-49
23	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSPPWTFGQGTKVEIK	SCB-VL-50
24	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-51
25	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-52
26	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-53
27	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-54
28	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-55

SEQ ID NO	Sequence	Description
29	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-56
30	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIFGASSRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPPWTFGQGTKVEIK	SCB-VL-57
31	EIVLTQSPGTLSLSPGERATLSCRASQSVSNSYLAWYQQKPGQAPRLLIYGASSRAPGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYDHSAGWTFGQGTKVEIK	SCB-VL-58
32	EVQLVESGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-59
33	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-60
34	EVQLVQSGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-61
35	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-62
36	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-63
37	EVQLVESGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-64
38	EVQLVESGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-65
39	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-66
40	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-67
41	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-68
42	EVQLVESGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-69
43	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQG TLVTVSS	SCB-VH-70
44	EVQLVQSGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-71
45	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-72

SEQ ID NO	Sequence	Description
46	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-73
47	EVQLVQSGGGLVHPGRSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-74
48	EVQLVQSGGGLVHPGGSLRLTCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-75
49	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMHWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-76
50	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGEGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-77
51	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDEAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-78
52	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAGDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-79
53	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFDDYAMFWVRQAPGKGLEWVSGIGTG GATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGT LVTVSS	SCB-VH-80
54	EVQLVQSGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-81
55	EVQLVESGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-82
56	EVQLVESGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-83
57	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-84
58	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-85
59	EVQLVQSGGGLVHPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-86
60	EVQLVQSGGGLVQPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTG GATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-87
61	EVQLVESGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-88

SEQ ID NO	Sequence	Description
62	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-89
63	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFPWWGQGTL VTVSS	SCB-VH-90
64	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFDYWGQGTLV TVSS	SCB-VH-91
65	EVQLVQSGGGLVHPGGSLRLSCAGSGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATNYADSVKGRFTISRDNAKNSLYLQMNSLRAEDMAVYYCARGRYYFDYWGQGTL VTVSS	SCB-VH-92
66	EVQLVESGGGLVQPGGSLRLSCAASGFTFSRNAMFWVRQAPGKGLEWVSGIGTGG ATSYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGRYYFPWWGQGTLV TVSS	SCB-VH-93
67	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLDYWGKG TLVTVSS	MEDI-1-VH
68	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSLSANYVFGTGTKLTVL	MEDI-1-VL
69	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-2-VH
70	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSQPPNPLFGTGTKLTVL	MEDI-2-VL
71	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKLLKNPWGKGT LVTVSS	MEDI-3-VH
72	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWFGTPASNYVFGTGTKLTVL	MEDI-3-VL
73	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-4-VH
74	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSSPPQPIFGTGTKLTVL	MEDI-4-VL
75	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYDWGKG TLVTVSS	MEDI-5-VH
76	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSSPPQPIFGTGTKLTVL	MEDI-5-VL
77	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-6-VH
78	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-6-VL
79	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQYWGK GTLVTVSS	MEDI-7-VH
80	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSSPPQPIFGTGTKLTVL	MEDI-7-VL

SEQ ID NO	Sequence	Description
81	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQYWGK GTLVTVSS	MEDI-8-VH
82	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-8-VL
83	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-9-VH
84	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTMYPLFGTGTKLTVL	MEDI-9-VL
85	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYDWGKG TLVTVSS	MEDI-10-VH
86	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVLTPIFGTGTKLTVL	MEDI-10-VL
87	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWFYDWGKG TLVTVSS	MEDI-11-VH
88	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPSMIPLFGTGTKLTVL	MEDI-11-VL
89	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWFYDWGKG TLVTVSS	MEDI-12-VH
90	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTMYPLFGTGTKLTVL	MEDI-12-VL
91	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYDWGKG TLVTVSS	MEDI-13-VH
92	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTLQPLFGTGTKLTVL	MEDI-13-VL
93	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-14-VH
94	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPPTKPLFGTGTKLTVL	MEDI-14-VL
95	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-15-VH
96	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTHRHPLFGTGTKLTVL	MEDI-15-VL
97	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWLYNWGKG TLVTVSS	MEDI-16-VH
98	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-16-VL
99	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQHWGK GTLVTVSS	MEDI-17-VH
100	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVDRPIFGTGTKLTVL	MEDI-17-VL

SEQ ID NO	Sequence	Description
101	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQHWGK GTLVTVSS	MEDI-18-VH
102	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTPMPVFGTGTKLTVL	MEDI-18-VL
103	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKWWWQHWGK GTLVTVSS	MEDI-19-VH
104	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTTYHPIFGTGTKLTVL	MEDI-19-VL
105	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-20-VH
106	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-20-VL
107	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-21-VH
108	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEAVYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-21-VL
109	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-22-VH
110	QPVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-22-VL
111	QVQLVQSGAEVRKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-23-VH
112	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPP GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-23-VL
113	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-24-VH
114	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-24-VL
115	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSASYAQKFQGRVSMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-25-VH
116	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTTATLAITGLQTGDEADYYCGTWVTSTVWEWPFGTGTKLTVL	MEDI-25-VL
117	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-26-VH
118	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-26-VL
119	QVQLVQSGAEVRKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRPEDTAVYYCARGKYWMYDWGK GTQVTVSS	MEDI-27-VH
120	QSVLTQPPLVSAAPGQKVTISCSGGSSNIGNSYVSWYQRLPGTAPKLLIYDNNKRPSG IPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-27-VL

SEQ ID NO	Sequence	Description
121	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGN GTLVTVSS	MEDI-28-VH
122	LPVLTQPPSVSAAPGQKVTISCSGGSSSIGNSYVSWYQQLPGAAPKLLIYDNNKRPSG IPDRFSGFRSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-28-VL
123	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TRVTVSS	MEDI-29-VH
124	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-29-VL
125	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-30-VH
126	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQRLPGAAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-30-VL
127	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-31-VH
128	QSVLTQPPSVSAAPGQKVTISCSGGSSSIGNSYVSWYQQLPGTAPKLLIYDNNKRPSG IPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWATSPVWEWPFGTGTKLTVL	MEDI-31-VL
129	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-32-VH
130	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTAWEWPFGTGTKLTVL	MEDI-32-VL
131	QVQLVQSGAEEKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-33-VH
132	QSALTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-33-VL
133	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVSMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-34-VH
134	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-34-VL
135	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-35-VH
136	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-35-VL
137	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-36-VH
138	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDSSTVWEWPFGTGTKLTVL	MEDI-36-VL
139	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSTSYAQKFQGRVAMTRDTSTSTVYMELSSLRPEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-37-VH
140	QSVLTQPPSVSAAPGQKVTISCSGGGSSIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GVPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-37-VL

SEQ ID NO	Sequence	Description
141	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSASYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGK GTLVTVSS	MEDI-38-VH
142	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYFCGTWDTSTVWEWPFGTGTKLTVL	MEDI-38-VL
143	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPR GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-39-VH
144	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTAWEWPFGTGTKLTVL	MEDI-39-VL
145	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-40-VH
146	QSVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDSSTVWEWPFGTGTKLTVL	MEDI-40-VL
147	QVQLVQSGAEVRKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWMGIINPS GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRPEDTAVYYCARGKYWMYDWGK GTLVTVSG	MEDI-41-VH
148	QSVLTQPPSVSAAPGQKVTISCSGGSTNIGNSYVSWYQRLPGTAPKLLIYDNNKRPP GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTVWEWPFGTGTKLTVL	MEDI-41-VL
149	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWARQAPGQGLEWVGIINPSG GSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSGDTAVYYCARGKYWMYDWGKGT LVTVSS	MEDI-42-VH
150	QAVLTQPPSVSAAPGQKVTISCSGGSSNIGNSYVSWYQRLPGAAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLAITGLQTGDEADYYCGTWDTSTGWEWPFGTGTKLTVL	MEDI-42-VL
151	QVQLVQSGAEVKKPGASVKVSCKASGYAFTSYYMHWVRQAPGQGLEWMGIINPR GGSTSYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYCARGKYWMYDWGKG TLVTVSS	MEDI-37GL-VH
152	QSVLTQPPSVSAAPGQKVTISCSGGGSSIGNSYVSWYQQLPGTAPKLLIYDNNKRPS GIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDTSPVWEWPFGTGTKLTVL	MEDI-37GL-VL
153	EVQLLESGGGLVQPGGSLRLSCAVSGFTFSNYAMSWVRQAPGKGLEWVSAISSGGG NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKLRRYFDYWGQGTLVT VSS	AJOU-1-VH
154	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYAMSWVRQAPGKGLEWVSAISSGGS SIYYADSVKGRFTISRDNSKNTLHLQMNSLRAEDTAVYYCARGPQRSATAVFDYWG QGTLVTVSS	AJOU-2-VH
155	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSWISPNS GNIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARRPLSAAWSHSSYYN AMDVWGQGTLVTVSS	AJOU-3-VH
156	EVQLLESGGGLVQPGGSLRLSCAASGFTFSGYAMSWVRQAPGKGLEWVSLISHSGS NTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPHRAFDYWGQGTLV TVSS	AJOU-4-VH
157	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSGISHGS GSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARPHRAFDYWGQGTLV TVSS	AJOU-5-VH
158	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSGISHGN GSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKTGRHFDYWGQGTLV TVSS	AJOU-6-VH

SEQ ID NO	Sequence	Description
159	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSSISPSGS SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARSYRAFDYWGQGTLVT VSS	AJOU-7-VH
160	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAISPSGG SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARAKRAFDYWGQGTLVT VSS	AJOU-8-VH
161	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAISPGSG STYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKFRRHFDYWGQGTLVT VSS	AJOU-9-VH
162	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAISSGGG NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-10-VH
163	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITSSGR SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLVT VSS	AJOU-69-VH
164	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITSSGA NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-70-VH
165	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITSSGG NIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-71-VH
166	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYAMSWVRQAPGKGLEWVSAITAGG GSIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLV TVSS	AJOU-72-VH
167	EVQLLESGGGLVQPGGSLRLSCAASGFTFSRHAMAWVRQAPGKGLEWVSAITSSGR SIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVHRAFDYWGQGTLVT VSS	AJOU-83-VH
168	QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNYVNWYQQLPGTAPKLLIYDNSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDASLSAYVFGGGTKLTVL	AJOU-33-VL
169	QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNNVSWYQQLPGTAPKLLIYANSKRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDDSLSAYVFGGGTKLTVL	AJOU-34-VL
170	QSVLTQPPSAPGTPGQRVTISCTGSSSNIGSNSVNWYQQLPGTAPKLLIYDDSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCDAWDSSLSAYVFGGGTKLTVL	AJOU-35-VL
171	QSVLTQPPSASGTPGQRVTLSCTGSSSNIGSNYVSWYQQLPGTAPKLLIYADSQRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDDSLSGYVFGGGTKLTVL	AJOU-36-VL
172	QSVLTQPPSASGTPGQRVTISCSSSSSNIGSNYVSWYQQLPGTAPKLLIYSDSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSAYVFGGGTKLTVL	AJOU-37-VL
173	QSVLTQPPSASGTPGQRVTISCTGSSSNIGNNTVSWYQQLPGTAPKLLIYDNSHRPS GVPDRFSGSKSGTSASLAISGLQSEDEADYYCGSWDYSLSAYVFGGGTKLTVL	AJOU-38-VL
174	QSVLTQPPSASGTPGQRVTISCTGSSSNIGNNDVNWYQQLPGTAPKLLIYYDSQRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCATWDASLSAYVFGGGTKLTVL	AJOU-39-VL
175	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNAVNWYQQLPGTAPKLLIYYDNQRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDDSLNGYVFGGGTKLTVL	AJOU-40-VL
176	QSVLTQPPSASGTPGQRVTISCSGSSSNIGNNAVTWYQQLPGTAPKLLIYDDSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGSWDYSLSAYVFGGGTKLTVL	AJOU-41-VL
177	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVL	AJOU-42-VL
178	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVL	AJOU-77-VL

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179	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLRGYVLGGGTKLTVL	AJOU-78-VL
180	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGYWDYSLSGYVLGGGTKLTVL	AJOU-79-VL
181	QSVLTQPPSASGTPGQRVTISCSGSSSNIGSNTFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVL	AJOU-80-VL
182	QSVLTQPPSASGTPGQRVTISCSGSSANSRTDGFNWYQQLPGTAPKLLIYADSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-86-VL
183	QSVLTQPPSASGTPGQRVTISCSGSAQFGSRDNFNWYQQLPGTAPKLLIYADSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-87-VL
184	QSVLTQPPSASGTPGQRVTISCSGSTKQMHNYQFNWYQQLPGTAPKLLIYADSHRP SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-88-VL
185	QSVLTQPPSASGTPGQRVTISCSGSLLRGENLQFNWYQQLPGTAPKLLIYADSHRPS GVPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-89-VL
186	QSVLTQPPSASGTPGQRVTISCSGSPLFPDSGSFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-90-VL
187	QSVLTQPPSASGTPGQRVTISCSGSAALDLSPSFNWYQQLPGTAPKLLIYADSHRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYCGTWDYSLSGYVLGGGTKLTVLG	AJOU-91-VL
188	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGLEWMGWISVY NGKTNYAQKLQGRVTMTTDTSTTTAYMEMRSLRSDDTAVYYCARGSGYDLDYWG QGTLVSVSS	REGN-VH-3
189	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSFWMTWVRQAPGKGLEWVANIKQD GSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDPGRTMVRGGIRY YYGMDVWGQGTTVTVSS	REGN-VH-19
190	EVKLAESGGGLVQPGGSLRLSCAASGFTFSSHWMNWVRQAPGKGLEWVANIKQD GSDKYYVDSVKGRFTISRDNAKNSLYLQLNSLIAEDTAVYYCARDRGVRPPRGAFDIW GQGTMVTVSS	REGN-VH-35
191	QVQLVQSGAEVKKPGASVKVSCKASGYTFNSYGISWVRQAPGQGLEWMGWIRTY NGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARDEARIVVAGTTP YYYGMDVWGQGTTVTVSS	REGN-VH-51
192	QVQLVESGGGLVQPGGSLRLSCAVSGFTISDHYMSWIRQAPGKGLEWISYISSSGSKI YYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARTRQLVGDYWGQGTLVT VSS	REGN-VH-67
193	EVQLVESGGGLVQPGRSLRLSCAASGFTFDNYAMHWVRQAPGKGLEWVSGIRWN SGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKEGGYSGYRPGPFFD YWGQGTLVTVSS	REGN-VH-83
194	QVQLVQSGAEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGLEWMGWISVY NGHTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARGSGYDFDSWGQ GTLVTVSS	REGN-VH-99
195	QVQLVQSGAEVKKPGASVKVSCKASRYTFTSYDINWVRQATGQGLEWMGWMNP NSGNTGYAQKFQGRVTMTRNTSTSTAYMELSSLRSEDTAVYYCARVRRFFDYWGQ GTLVTVSS	REGN-VH-115
196	QVQLVQSGPEVKKPGASVKVSCKASGYTFTNYGISWVRQAPGQGLEWMGWISVY NGNINYAQKLQGRVTMTTDTSTSTAYMDLRSLRSDDTAVYYCARGSGYDFDYWGQ GTLVTVSS	REGN-VH-147
197	QVQLVQSGAEVKKPGASVKVSCKDSAYTFNRYGISWVRQAPGQGLEWMGWISAY TGNTVYAQKLQGRVTMTTDNSTSTAYMELRSLRSDDTAVYYCARDKSIFGVVRGFD YWGQGTLVTVSS	REGN-VH-163
198	AIQMTQSPSSLSASVGDRVTITCRASQGIRNALGWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTFSSLQPEDFATYYCLQDFNYPYTFGQGTKLEIK	REGN-VL-11

SEQ ID NO	Sequence	Description
199	DIQMTQSPSSVSASVGDRVTISCRASQGVSSWLAWYQQKPGNAPKLLISAASSIQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQANSFPLTFGGGTKVEIK	REGN-VL-27
200	DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSFQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYFCQQANSFPLTFGGGTTVEIK	REGN-VL-43
201	DIQMTQSPSSVSASVGDRVTITCRASQDISIWLAWYQQSPGKAPKLLINVASRLQSG VPSRFSGSGSGTDFTLTINSLQPEDFVTYYCQQANSFPITFGQGTRLATK	REGN-VL-59
202	DIQLTQSPSFLSASVGDRVTITCWASQGISSYLAWYQQKPGKAPKLLIFAASTLQSGV PSRFSGSGSGTEFTLTISSLQPEDFATYYCQQLNSYPLTFGGGTKVEIR	REGN-VL-75
203	EIVMTQSPATLSVSPGERATLSCRASQSVNYNLAWYQHKPGQAPRLLIYGASTRATGI PARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPLTFGGGTKVEIK	REGN-VL-91
204	AIQMTQSSSSLSASVGDRVTITCRASQAIRNALGWYQQKPGKAPKVLIYAASSLQSGI PSRFSGSGSGTDFTLTISSLQPEDFATYYCLQDYDYPYTFGQGTKLEIK	REGN-VL-107
205	DIQLTQSPSFLSASVGDRVTITCWASQGIISYLAWYQQKPGKAPKLLIYAASTLHSGVP SRFSGSGSGTEFTLTISSLQPEDFATYYCHQLKSYPITFGQGTRLEIK	REGN-VL-123
206	AIQMTQSPSSLSASVGDRVTITCRASQDIRNALGWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSASGTDFTLTISSLQPEDFAAYYCLQDYNYPYTFGQGTKLEIK	REGN-VL-155
207	EIVMTQSPVTLSLSPGERATLPCRASQSVSSSLAWYQQKAGQSPRLLIYGASTRATGI PARFSGSGSGTEFTLTISNLQSEDFAVYYCQQYNNWPLTFGGGTKVEIK	REGN-VL-171
208	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSNGG STYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVGYRGGMDVWG QGTTVTVSS	STSA-C27-VH
209	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSGSS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRSKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-6-33-VH
210	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSGVS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVKYRGGMDVWGQ GTTVTVSS	STSA-C27-7-33-VH
211	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTSGS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-24-56-VH
212	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTGTS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKGAYRGGMDVWGQ GTTVTVSS	STSA-C27-47-56-VH
213	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSSGSS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVAYRGGMDVWGQ GTTVTVSS	STSA-C27-33-33-VH
214	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSSTS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVLYRGGMDVWGQ GTTVTVSS	STSA-C27-56-56-VH
215	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKSKYRGGMDVWGQ GTTVTVSS	STSA-C27-78-78-VH
216	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISGNSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKLKYRGGMDVWGQG TTVTVSS	STSA-C27-82-58-VH
217	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISHSGTS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVRVLYRGGMDVWGQ GTTVTVSS	STSA-C27-54-54-VH

SEQ ID NO	Sequence	Description
218	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSGVS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVKYRGGMDVWGQ GTTVTVSS	STSA-C27-36-36-VH
219	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSNGG STYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVFVRYRGGMDVWGQ GTTVTVSS	STSA-C27-53-53-VH
220	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKGRYRGGMDVWGQ GTTVTVSS	STSA-C27-67-67-VH
221	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPTGGS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKGRYRGGMDVWGQ GTTVTVSS	STSA-C27-55-55-VH
222	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISHSGN STYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKRRYRGGMDVWGQ GTTVTVSS	STSA-C27-59-59-VH
223	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISPSSNS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-58-58-VH
224	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISSSGSS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKPAYRGGMDVWGQ GTTVTVSS	STSA-C27-52-52-VH
225	EVQLLESGGGLVQPGGSLRLSCAASGFTLSSYAMHWVRQAPGKGLEYVSGISYSSAS TYYANSVKGRFTISRDNPKNTLFLQMSSLRAEDTAVYYCVRVKVRYRGGMDVWGQ GTTVTVSS	STSA-C27-Y2-Y2-VH
226	ETTLTQSPDTLPLSPGDRASLSCRASQSVSSAYLAWYQQKPGQAPRLLIYGTSRRATG VPGRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGSSSVTFGQGTKLEIK	STSA-C27-VL
227	EIVLTQSPGTLSLSPGERATLSCRASQGISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-6-33-VL
228	EIVLTQSPGTLSLSPGERATLSCRASQGISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-7-33-VL
229	EIVLTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGASSVTFGQGTKLEIK	STSA-C27-24-56-VL
230	EIVLTQSPGTLSLSPGERATLSCRASQSVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGASSVTFGQGTKLEIK	STSA-C27-47-56-VL
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236	EIVLTQSPGTLSLSPGERATLSCRASQNISTAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-36-36-VL
237	EIVLTQSPGTLSLSPGERATLSCRASQDASNAYLAWYQQKPGQAPRLLIYGTSRRATG IPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGSSSVTFGQGTKLEIK	STSA-C27-53-53-VL
238	EIVLTQSPGTLSLSPGERATLSCRASQGVSSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGRSSVTFGQGTKLEIK	STSA-C27-67-67-VL

SEQ ID NO	Sequence	Description
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241	EIVLTQSPGTLSLSPGERATLSCRASQDISSAYLAWYQQKPGQAPRLLIYGTSRRATGI PDRFSGSGSGTDFTLTISRLEPEDFAVYYCQLYGATSVTFGQGTKLEIK	STSA-C27-58-58-VL
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245	EVQLIESGGGLVQPKGSLKLSCAASGFTFNMYAMDWVRQAPGKGLEWVARIRSKG SNFETNYADSVKDRFTISRDDSQSMVYLQMINLKTEDTAMYYCVRHRGGAWFAYW GQGTLVSVSA	Y0188-2 VH
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248	EVQLVESGGGLVQPKGSLKLSCAASGFSFNMYAMNWVRQAPGKGLEWVARIRTKS NHYSTYYADSVKDRFTISRDDSASMFYLQMNNLKTEDTAMYFCVRHLRAMDYWG QGTSVTVSS	Y0188-6 VH
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252	EVQLVESGGGLVQPKGSLKLSCAASGFTFNMYGMHWVRQAPGKGLEWVAHIRSKS SNYATYYADSVKDRLTISRDDSQSMLYLQMNNLKTEDTAMYYCVRWFRAMDYWG QGTSVTVSS	Y0188-14 VH
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256	EVQLVESGGGLVQPGGSLRLSCAASGFTFSMYGMHWVRQAPGKGLEWVGHIRSKS SNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARWFRAMDYWGQ GTLVTVSS	HV3-72-14 VH

SEQ ID NO	Sequence	Description
257	EVQLVESGGGLVQPGGSLRLSCAASGFTFSMYGMHWVRQAPGKGLEWVSHIRSKS SNYATYYADSVKDRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARWFRAMDYWGQ GTLVTVSS	Y01-14 VH
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259	EVQLVESGGGLVQPGGSLKLSCAASGFTFSMYGMHWVRQASGKGLEWVGHIRSKS SNYATYYADSVKDRFTISRDDSKNTAYLQMNSLKTEDTAVYYCTRWFRAMDYWGQ GTTVTVSS	VH73-14 VH
260	DIVMTQSHKFMSTSVGDRVSITCKASQDVSTAVAWYQEKPGQSPKLLIYWASTRHT GVPDRFTGSGSGTDYTLTISSVQAEDLALYYCQQHYSTPLTFGAGTKLELK	Y0188-1 VL
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265	DIVVTQSPASLAVSLGQRATISCRASKSVSTSGYSYMHWYQQKPGQPPKLLIYLASNL ESGVPARFSGSGSGTDFTLNIHPVEEEDVAIYYCQHSRELPLTFGAGTKLELK	Y0188-8 VL
266	DIVLTQSPASLAVSLGQRATISCRASKSVSASGYSYMHWYQQKPGQPPKLLIYLASNL QSGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHSRELPPTFGGGTKLEIK	Y0188-9 VL
267	DIVLTQSPASLAVFLGQRATISCRASKSVSTSGYSYMHWYQQKAGQPPKLLIYLASNL ESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCHHSRELPITFGSGTKLEMK	Y0188-10 VL
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275	AIRMTQSPFSLSASVGDRVTITCKASQDVSTAVAWYQQKPAKAPKLFIYWASTRHTG VPSRFSGSGSGTDYTLTISSLQPEDFATYYCQQHYSTPLTFGGGTKVEIK	KV1D-43-14 VL

EXAMPLES

[0141] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the disclosure, and are not intended to limit the scope of what the inventors

regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.*, amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1: Dupilumab Treatment of Children With Moderate-to-Severe Atopic Dermatitis Increases Bone Alkaline Phosphatase, a Marker of Bone Mineralization

[0142] The objective of this analysis is to report the impact of dupilumab treatment on markers of bone formation in children aged ≥ 6 to < 12 years with moderate-to-severe AD.

Methods

[0143] The analysis was performed retrospectively on sera from participants in LIBERTY AD PEDS (NCT03345914) and LIBERTY AD PED-OLE (NCT02612454). In LIBERTY AD PEDS, a double-blind, 16-week, phase 3 trial, children aged 6 to < 12 years were randomized 1:1:1 to 300 mg dupilumab every 4 weeks (300 mg q4w), a weight-based regimen of dupilumab every 2 weeks (100 mg q2w for patients with baseline weight < 30 kg, and 200 mg q2w for those with baseline weight ≥ 30 kg), or placebo; with concomitant medium-potency topical corticosteroids (TCS). After the initial 16-week trial, children aged 6 to < 12 years were enrolled in the open-label extension study LIBERTY AD PED-OLE. Patients received dupilumab 300 mg q4w, which could be titrated up in case of inadequate clinical response at Week 16 (200 mg q2w for patients with baseline weight < 60 kg, and 300 mg q2w for those with baseline weight ≥ 60 kg); with concomitant medium-potency TCS. Bone biomarkers including BALP, procollagen type 1 N-terminal propeptide, C-terminal crosslinking telopeptide of type 1 collagen, osteocalcin, and insulin-like growth factor 1 were analyzed at baseline, 8, 12, 16 and BALP only at 52 weeks.

Results

[0144] Dupilumab treatment led to a rapid and significant increase in geometric mean (standard error) levels of BALP in children with moderate-to-severe AD at 16 weeks compared with patients in the placebo group (77.7(1.02) µg/L vs 65.0(1.04) µg/L; P<0.0001). Additionally, a rapid and significant increase in BALP levels was observed in children from the placebo group once they joined the OLE trial. BALP levels increased over 52 weeks in all treated children, reaching a level of 78–84 µg/L which constitutes a significant improvement compared with baseline, and is comparable to healthy reference intervals. *See* Figure 1.

[0145] Both dupilumab dosing regimens led to significant increases in geometric mean (standard error) levels of BALP at 8, 12, and 16 weeks compared with placebo. For the 100/200

mg q2w group, at Week 8 BALP levels were 72.7(1.03)µg/L for dupilumab vs 62.0(1.05)µg/L for placebo, P<0.0001; at Week 12: 74.7(1.03)µg/L vs 64.3(1.05)µg/L, P=0.0002; at Week 16: 78.0(1.03)µg/L vs 65.0(1.04)µg/L, P<0.0001). For the 300 mg q4w group, at Week 8 BALP levels were 76.7(1.03)µg/L for dupilumab vs 62.0(1.05)µg/L for placebo, P<0.0001; at Week 12: 73.3(1.04)µg/L vs 64.3(1.05)µg/L, P=0.002; at Week 16: 77.3(1.03)µg/L vs 65.0(1.04)µg/L, P<0.0001)]. At 52 weeks, BALP levels were significantly increased vs baseline (placebo vs placebo transitioned to dupilumab: 64.2[1.04]µg/L vs 82.9[1.04]µg/L, P<0.0001; 100/200mg q2w: 62.0[1.05]µg/L vs 83.8[1.03]µg/L, P<0.0001; 300mg q4w: 64.1[1.04]µg/L vs 78.7[1.04]µg/L, P<0.0001), and also increased within reference intervals (Diemar, *et al.*, *Bone*, 2021, 146:115879).

[0146] An increasing trend from baseline to 16 weeks of dupilumab treatment was observed for other biomarkers (osteocalcin, PINP, IGF-1, and β-CTX), although there was a limited number of data points due to insufficient volumes of sera available for analysis. *See* Figures 2-5. Overall, mean biomarker levels measured in dupilumab-treated children improved from below to within reference intervals' levels for osteocalcin, PINP, and β-CTX and from low to approximately mean reference interval levels for BALP and IGF-1, in this age group.

[0147] A subgroup analysis of BALP levels by gender was performed on samples from girls and boys aged 6-12 years with moderate-to-severe AD; the patient group for this analysis were 6-11 years of age at the start of the study. Although reference intervals for BALP vary, girls demonstrate higher values earlier and plateau around the age of 12, while boys' BALP levels continue to increase until around the age of 15. (*See*, Wu, *et al.*, *Ann Transl Med*, 2021, 9:40; Lowe, *et al.*, *J Allergy Clin Immunol*, 2020, 145:563-571; Silverberg, *Pediatr Allergy Immunol.*, 2015, 26:54-61; Diemar, *et al.*, *Bone*, 2021, 146:115879). Treatment with dupilumab increased BALP levels to reference intervals for both female and male patients and reflected this gender difference. At 16 weeks, dupilumab treatment led to a rapid and significant increase in geometric mean (standard error) levels of BALP in girls and boys compared with patients in the placebo group (girls: 80.0 (1.04) µg/L vs 70.1 (1.06) µg/L, P = 0.0018; boys: 75.7 (1.03) µg/L vs 60.4 (1.07) µg/L, P < 0.0001). Dupilumab treatment led to increases in levels of BALP in all treated children, reaching levels up to 90.5 µg/L in girls and 86.6 µg/L in boys. *See*, Figures 6-7.

[0148] A subgroup analysis was also performed to evaluate the impact of dupilumab treatment on BALP levels in children aged 6-12 years with moderate-to-severe AD, with and without comorbid asthma. Regardless of asthma comorbidity, dupilumab treatment led to a rapid and significant increase in geometric mean (standard error) levels of BALP in children with moderate-to-severe AD at 16 weeks compared with patients in the placebo group (with asthma:

76.8 [1.04] µg/L vs 59.1 [1.07] µg/L, P < 0.0001; without asthma: 78.5 [1.03] µg/L vs 70.7 [1.05] µg/L, P = 0.0024). At 52 weeks, geometric mean (standard error) BALP levels were significantly increased vs baseline, and comparable with reference intervals for patients with and without asthma (with asthma: placebo vs placebo transitioned to dupilumab: 62.3 [1.06] µg/L vs 78.3 [1.07] µg/L; dupilumab: 62.1 [1.04] µg/L vs 82.7 [1.04] µg/L; without asthma: placebo vs placebo transitioned to dupilumab: 66.0 [1.06] µg/L vs 87.5 [1.06] µg/L; dupilumab: 64.0 [1.04] µg/L vs 79.9 [1.03] µg/L).

Conclusions

[0149] These placebo-controlled results show, for the first time, a rapid and significant increase in BALP, and a possible trend in other biomarkers, in children with AD during treatment with dupilumab. These results suggest increased bone mineralization during the treatment period.

[0150] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. A method for improving bone growth, the method comprising:

selecting a subject having a defect in bone growth, wherein the subject is a pediatric subject or adolescent subject less than 18 years old; and

administering to the subject one or more doses of an interleukin-4 receptor (IL-4R) antagonist, wherein the IL-4R antagonist is an anti-IL-4R antibody, or an antigen-binding fragment thereof, that comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO:3, the HCDR2 comprises the amino acid sequence of SEQ ID NO:4, the HCDR3 comprises the amino acid sequence of SEQ ID NO:5, the LCDR1 comprises the amino acid sequence of SEQ ID NO:6, the LCDR2 comprises the amino acid sequence LGS, and the LCDR3 comprises the amino acid sequence of SEQ ID NO:8.

2. The method of claim 1, wherein the subject has atopic dermatitis (AD).

3. The method of claim 1 or 2, wherein the subject has moderate-to-severe or severe atopic dermatitis (AD).

4. The method of any one of claims 1 to 3, wherein the subject is a pediatric subject less than 12 years old.

5. The method of claim 4, wherein the subject is 6 years old to 11 years old.

6. The method of claim 4, wherein the subject is 6 months old to 5 years old.

7. The method of any one of claims 1 to 3, wherein the subject is an adolescent subject 12 years old to 17 years old.

8. The method of any one of claims 1 to 7, wherein the subject has comorbid asthma.

9. The method of any one of claims 1 to 8, wherein the selecting step comprises selecting a subject who exhibits a level of a bone turnover marker that is below a threshold value, wherein the bone turnover marker is bone-specific alkaline phosphatase, carboxy-terminal cross-linked telopeptide of type I collagen (β-CTX), pro-collagen type I N-terminal propeptide (PINP), insulin-like growth factor 1 (IGF-1), or osteocalcin.

10. The method of claim 9, wherein the threshold value is the average level of the bone turnover marker for a population of healthy subjects having the same age as the selected pediatric or adolescent subject.

11. The method of claim 9, wherein the bone turnover marker is bone-specific alkaline phosphatase.

12. The method of any one of claims 1 to 11, wherein the IL-4R antagonist is administered at a dose of about 50 mg to about 600 mg at a frequency of once a week (QW), once every two weeks (Q2W), once every three weeks (Q3W), or once every four weeks (Q4W).

13. The method of any one of claims 1 to 11, wherein the IL-4R antagonist is administered as an initial dose of 100-600 mg followed by one or more subsequent doses of 50-300 mg, wherein each subsequent dose is administered one week to four weeks after the immediately preceding dose.

14. The method of any one of claims 1 to 5 and 7 to 13, wherein the subject is a pediatric subject 6 years old to 11 years old or an adolescent subject 12 years old to 17 years old, and wherein the subject has a baseline weight ≥ 60 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 600 mg followed by one or more subsequent doses of 300 mg Q2W.

15. The method of any one of claims 1 to 3 and 7 to 13, wherein the subject is an adolescent subject 12 years old to 17 years old having a baseline weight < 60 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 400 mg followed by one or more subsequent doses of 200 mg Q2W.

16. The method of any one of claims 1 to 5 and 8 to 13, wherein the subject is a pediatric subject 6 to 11 years old having a baseline weight ≥ 30 kg to <60 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 400 mg followed by one or more subsequent doses of 200 mg Q2W.

17. The method of any one of claims 1 to 5 and 8 to 13, wherein the subject is a pediatric subject 6 to 11 years old having a baseline weight ≥ 15 kg to <30 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 600 mg followed by one or more subsequent doses of 300 mg Q4W.

18. The method of any one of claims 1 to 5 and 8 to 13, wherein the subject is a pediatric subject 6 to 11 years old having a baseline weight ≥ 15 kg to <60 kg, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 300 mg on Day 1 followed by 300 mg on Day 15, followed by one or more subsequent doses of 300 mg Q4W starting four weeks after the Day 15 dose.

19. The method of any one of claims 1 to 4, 6, and 8 to 12, wherein the subject is a pediatric subject 6 months to 5 years old having a baseline weight ≥ 15 kg to < 30 kg, wherein the IL-4R antagonist is subcutaneously administered at a dose of 300 mg Q4W.

20. The method of any one of claims 1 to 4, 6, and 8 to 12, wherein the subject is a pediatric subject 6 months to 5 years old having a baseline weight ≥ 5 kg to < 15 kg, wherein the IL-4R antagonist is subcutaneously administered at a dose of 200 mg Q4W.

21. The method of any one of claims 1 to 13 and 18 to 20, wherein the IL-4R antagonist is subcutaneously administered as an initial dose of 200 mg followed by one or more subsequent doses of 200 mg, or as an initial dose of 300 mg followed by one or more subsequent doses of 300 mg.

22. The method of any one of claims 1 to 21, wherein the IL-4R antagonist is administered in combination with a topical AD medication.

23. The method of claim 22, wherein the topical AD medication is a topical corticosteroid.

24. The method of any one of claims 1 to 23, wherein the IL-4R antagonist is administered for at least 16 weeks.

25. The method of any one of claims 1 to 24, wherein administration of the IL-4R antagonist for at least 16 weeks results in an increase in bone growth in the subject as measured by an increase in a bone turnover marker selected from the group consisting of bone-specific alkaline phosphatase, β-CTX, PINP, IGF-1, and osteocalcin.

26. The method of any one of claims 1 to 25, wherein the anti-IL-4R antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO:1 and a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:2.

27. The method of any one of claims 1 to 26, wherein the anti-IL-4R antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO:9 and a light chain comprising the amino acid sequence of SEQ ID NO:10.

28. The method of any one of claims 1 to 27, wherein the IL-4R antagonist is dupilumab.

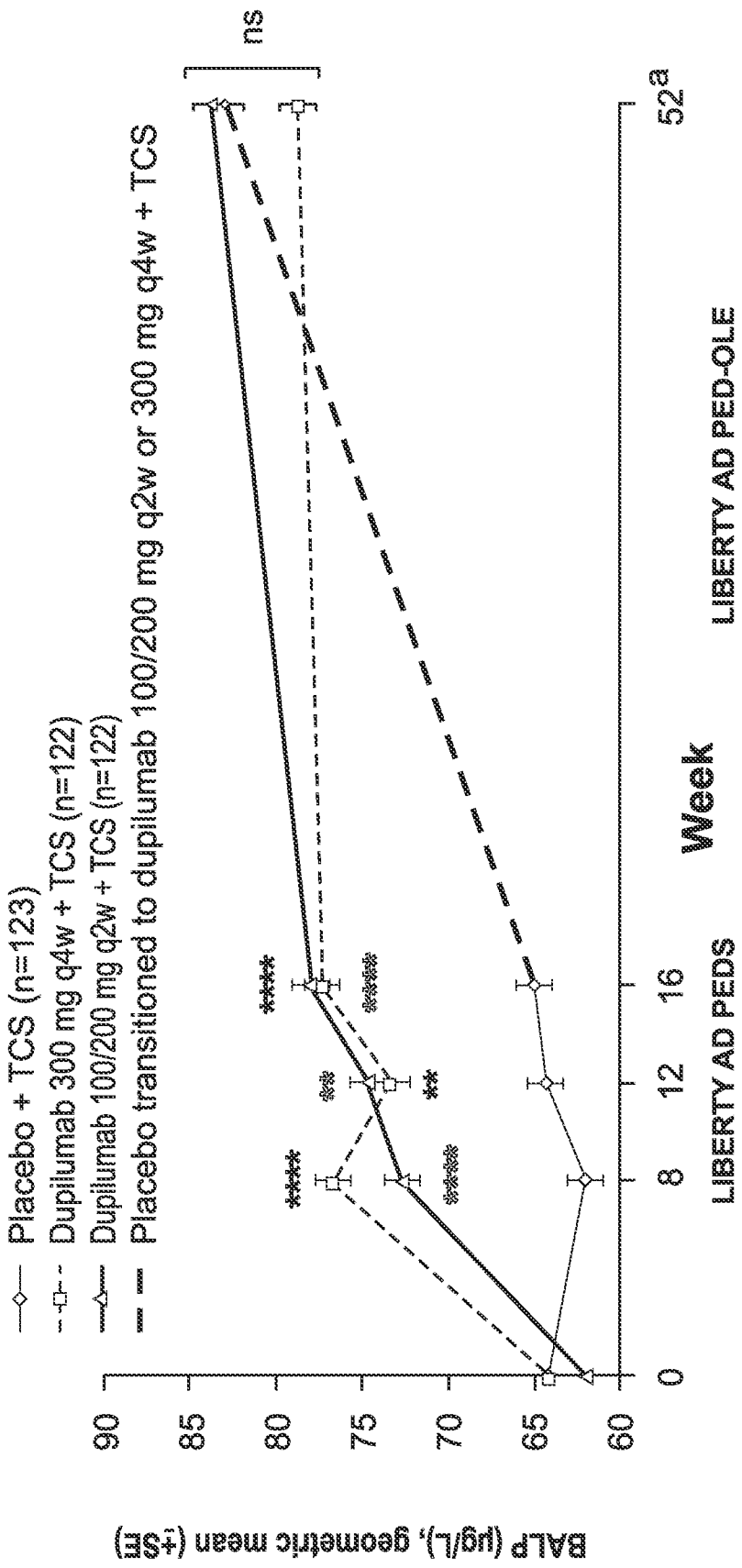
29. The method of any one of claims 1 to 28, wherein the IL-4R antagonist is contained in a container selected from the group consisting of a glass vial, a syringe, a pre-filled syringe, a pen delivery device, and an autoinjector.

30. The method of claim 29, wherein the IL-4R antagonist is contained in a pre-filled syringe.

31. The method of claim 30, wherein the pre-filled syringe is a single-dose pre-filled syringe.

32. The method of claim 29, wherein the IL-4R antagonist is contained in an autoinjector.

33. The method of claim 29, wherein the IL-4R antagonist is contained in a pen delivery device.


Placebo + TCS (n=123)
Dupilumab 300 mg q4w + TCS (n=122)
Dupilumab 100/200 mg q2w + TCS (n=122)
Placebo transitioned to dupilumab 100/200 mg q2w or 300 mg q4w + TCS
BALP (µg/L), geometric mean (±SE)
90
85
80
75
70
65
60
0
8
12
16
52a
Week
LIBERTY AD PEDS
LIBERTY AD PED-OLE
ns
****
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**
****
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FIG. 1

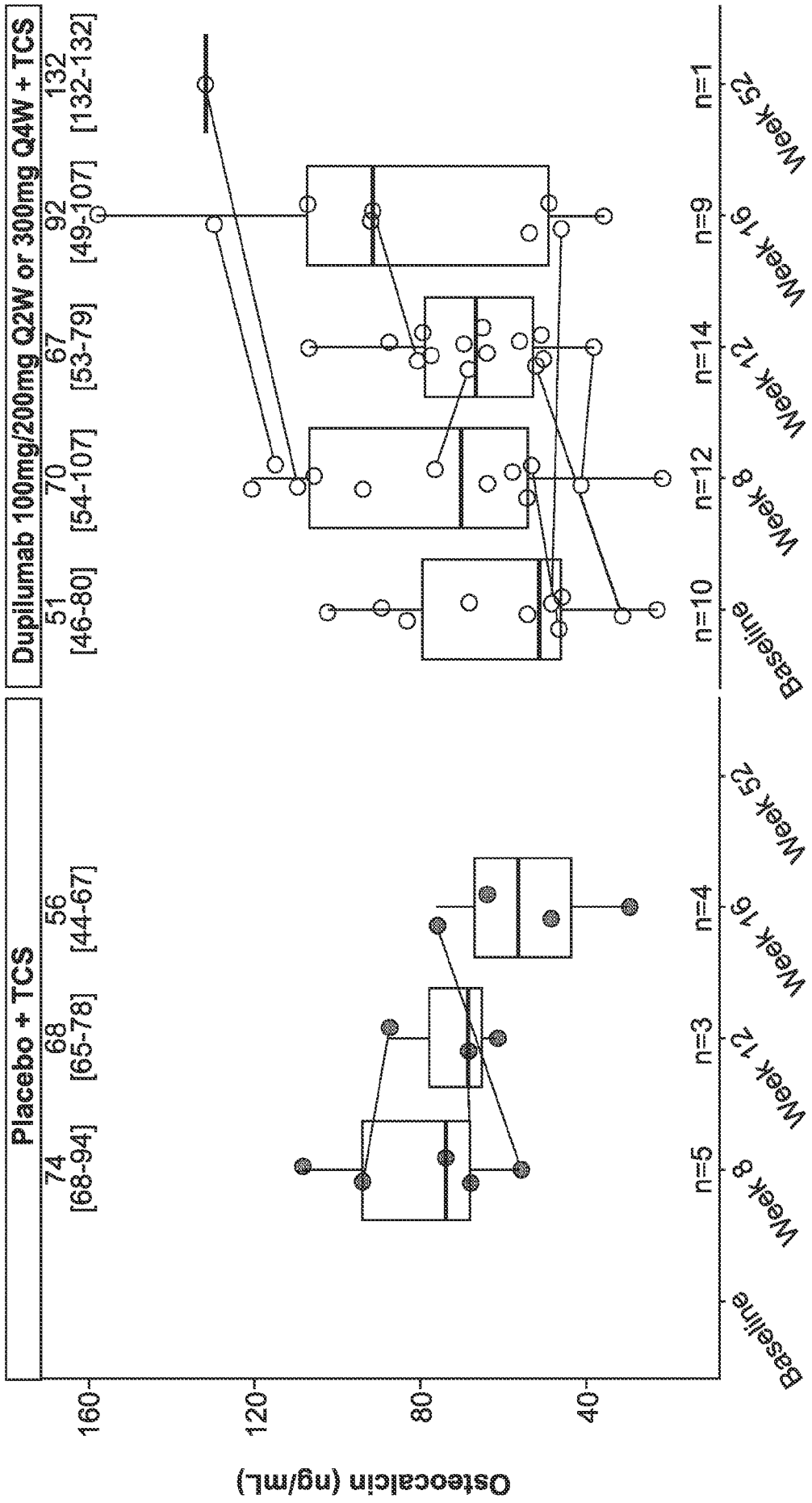

Dupilumab 100mg/200mg Q2W or 300mg Q4W + TCS
51 [46-80]
70 [54-107]
67 [53-79]
92 [49-107]
132 [132-132]
Placebo + TCS
74 [68-94]
68 [65-78]
56 [44-67]
Osteocalcin (ng/mL)
160
120
80
40
n=10
n=12
n=14
n=9
n=1
n=5
n=3
n=4
Baseline
Week 8
Week 12
Week 16
Week 52

FIG. 2

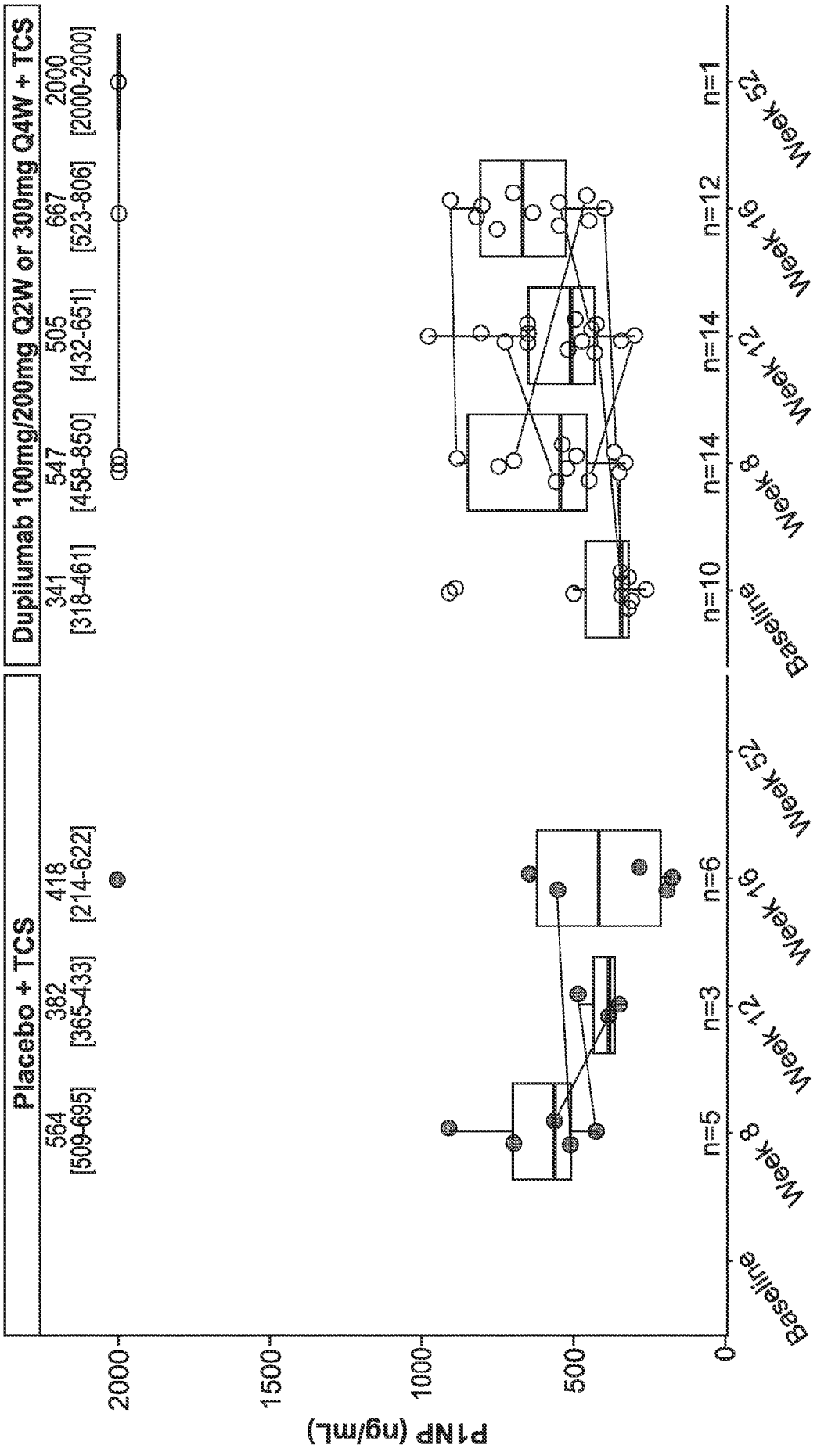

Placebo + TCS
564 [509-695]
382 [365-433]
418 [214-622]
Dupilumab 100mg/200mg Q2W or 300mg Q4W + TCS
341 [318-461]
547 [458-850]
505 [432-651]
667 [523-806]
2000 [2000-2000]
P1NP (ng/mL)
2000
1500
1000
500
0
n=5
n=3
n=6
n=10
n=14
n=14
n=12
n=1
Baseline
Week 8
Week 12
Week 16
Week 52

FIG. 3

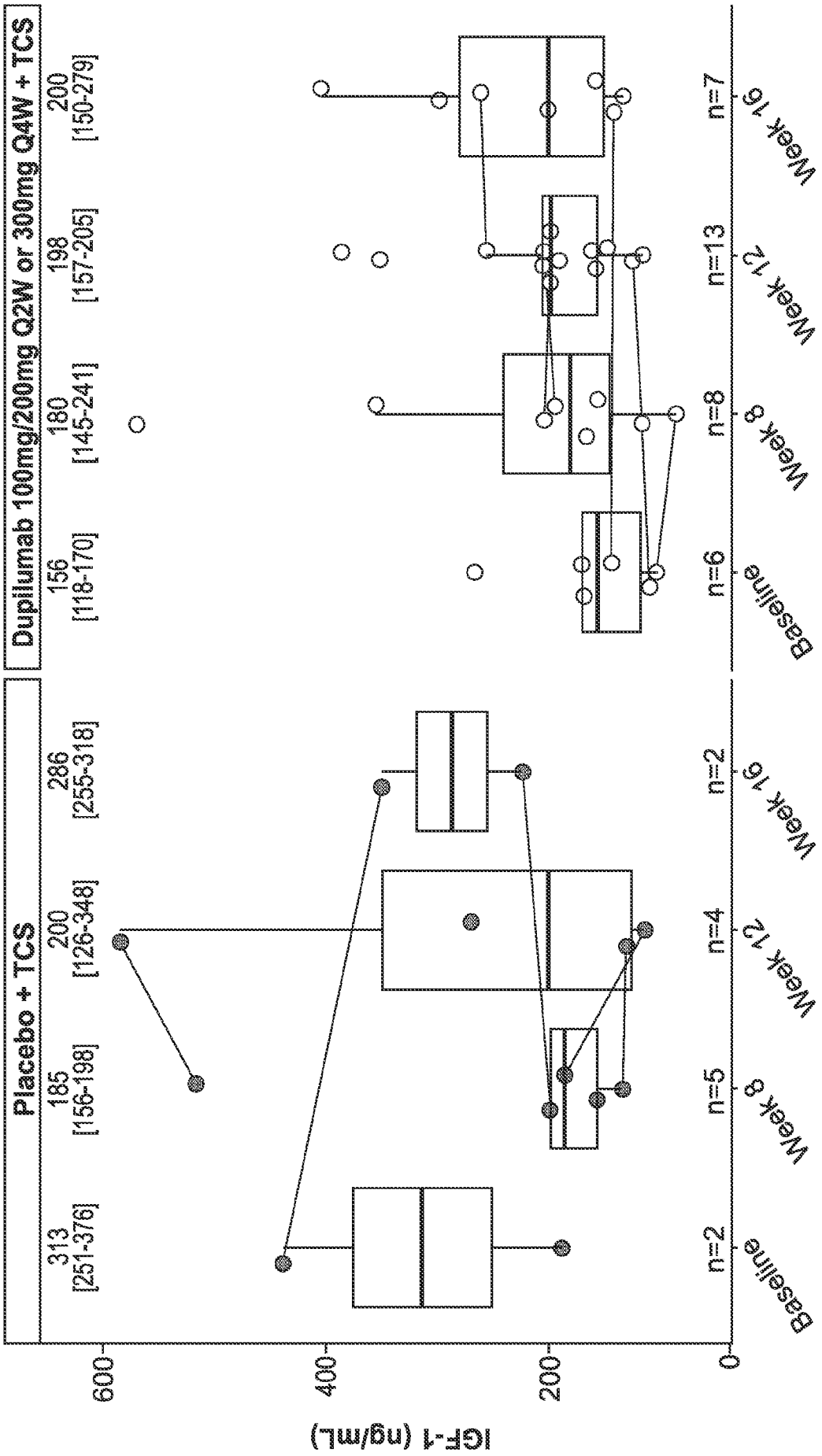

Placebo + TCS
Dupilumab 100mg/200mg Q2W or 300mg Q4W + TCS
313 [251-376]
185 [156-198]
200 [126-348]
286 [255-318]
156 [118-170]
180 [145-241]
198 [157-205]
200 [150-279]
IGF-1 (ng/mL)
0
200
400
600
Baseline
Week 8
Week 12
Week 16
n=2
n=5
n=4
n=2
n=6
n=8
n=13
n=7

FIG. 4

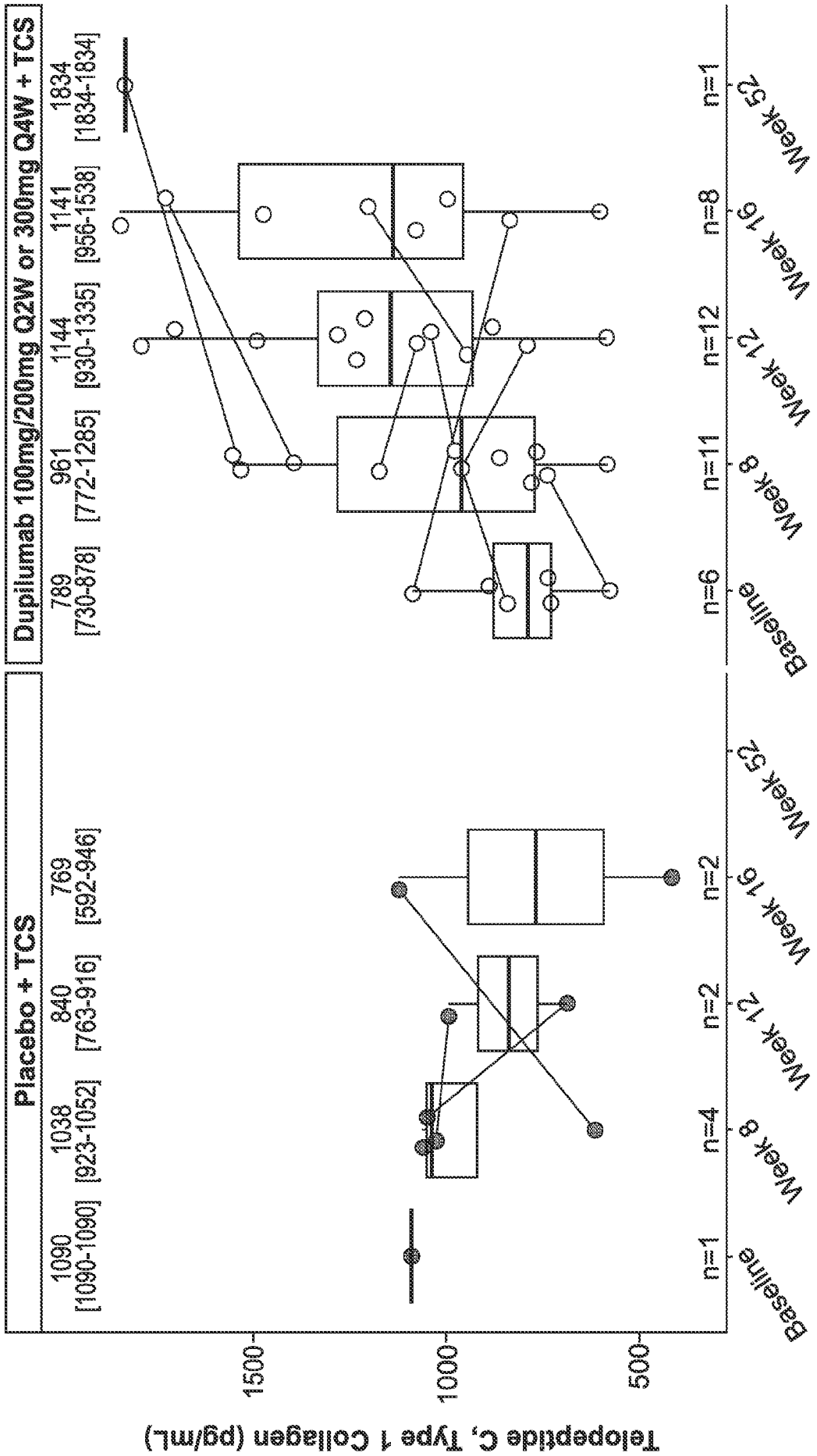

Telopeptide C, Type 1 Collagen (pg/mL)
1500
1000
500
Placebo + TCS
1090 [1090-1090]
1038 [923-1052]
840 [763-916]
769 [592-946]
Dupilumab 100mg/200mg Q2W or 300mg Q4W + TCS
789 [730-878]
961 [772-1285]
1144 [930-1335]
1141 [956-1538]
1834 [1834-1834]
n=1
n=4
n=2
n=2
n=6
n=11
n=12
n=8
n=1
Baseline
Week 8
Week 12
Week 16
Week 52
Baseline
Week 8
Week 12
Week 16
Week 52

FIG. 5

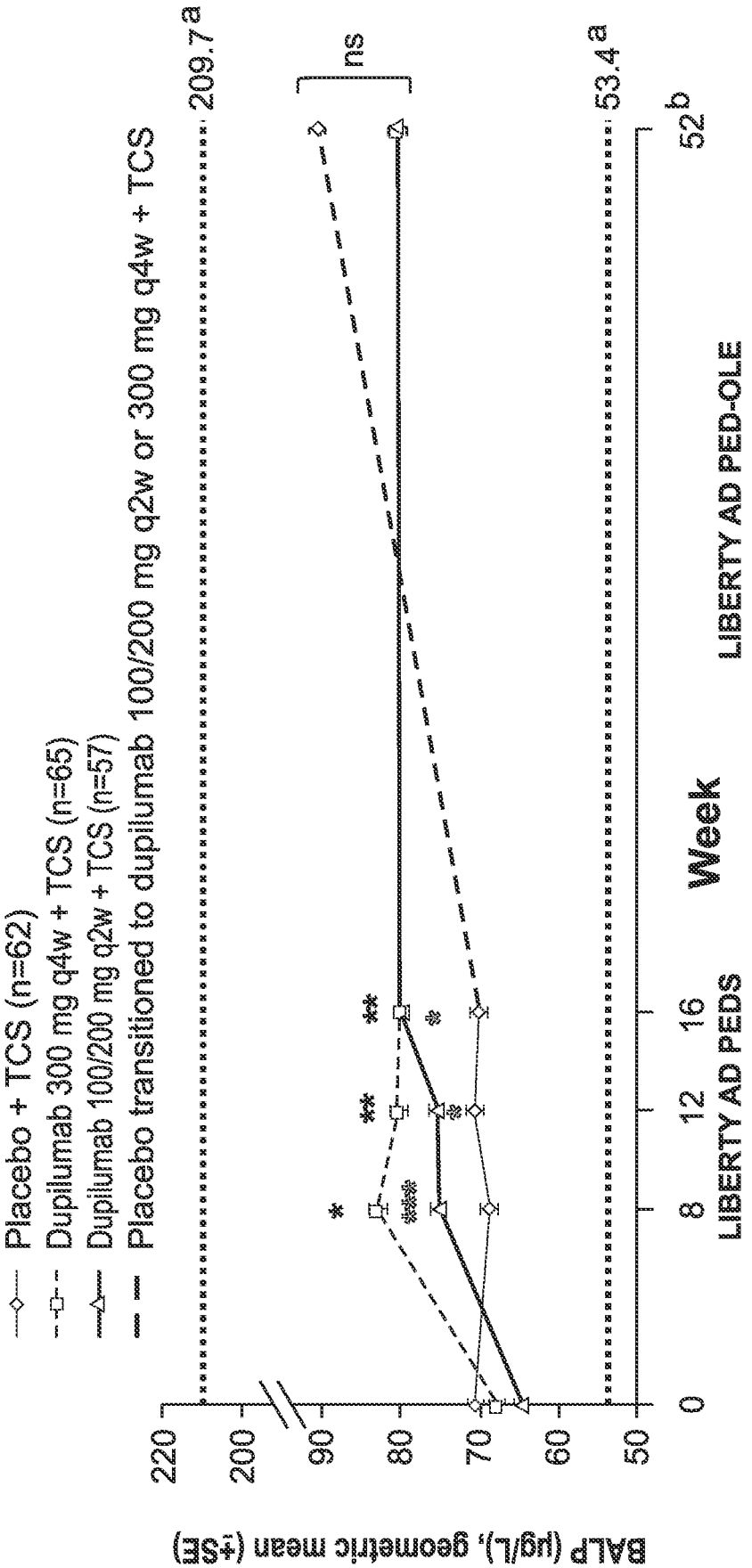

Placebo + TCS (n=62)
Dupilumab 300 mg q4w + TCS (n=65)
Dupilumab 100/200 mg q2w + TCS (n=57)
Placebo transitioned to dupilumab 100/200 mg q2w or 300 mg q4w + TCS
209.7a
ns
53.4a
52b
BALP (µg/L), geometric mean (±SE)
220
200
90
80
70
60
50
0
8
12
16
Week
LIBERTY AD PEDS
LIBERTY AD PED-OLE

FIG. 6A

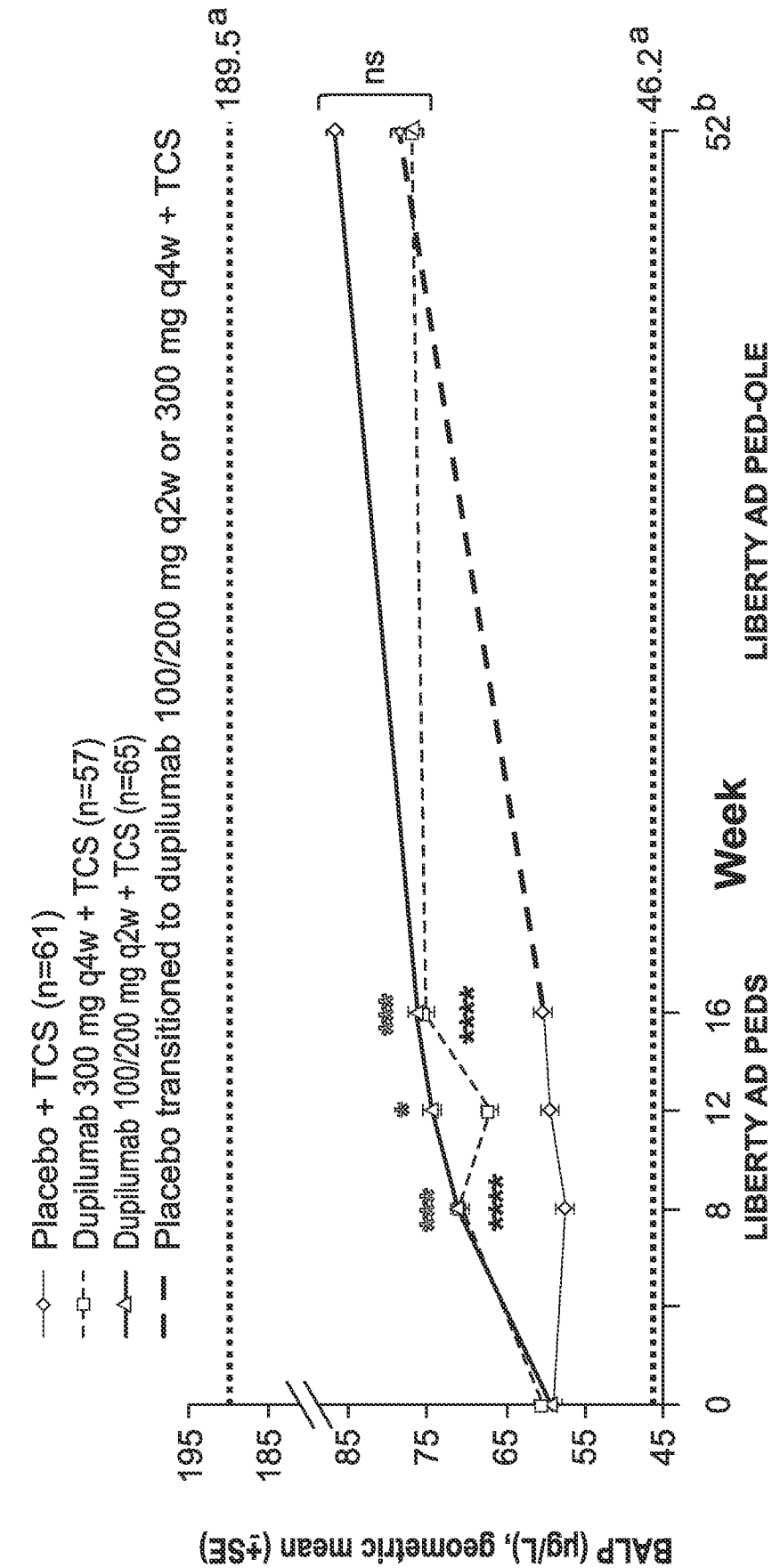
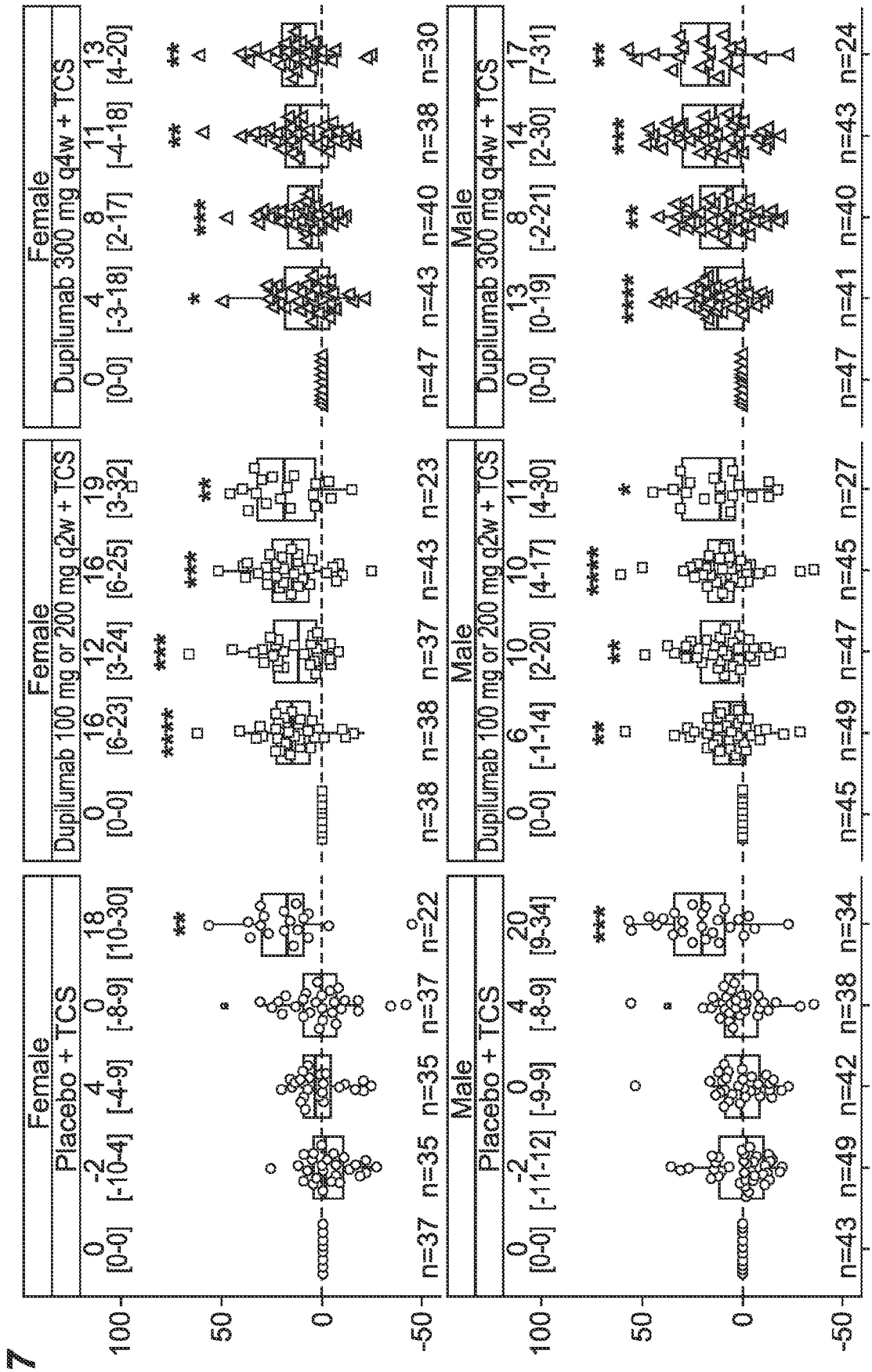

Placebo + TCS (n=61)
Dupilumab 300 mg q4w + TCS (n=57)
Dupilumab 100/200 mg q2w + TCS (n=65)
Placebo transitioned to dupilumab 100/200 mg q2w or 300 mg q4w + TCS
BALP (µg/L), geometric mean (±SE)
195
185
85
75
65
55
45
0
8
12
16
52
Week
LIBERTY AD PEDS
LIBERTY AD PED-OLE
189.5a
46.2a
52b
ns
*
****
****
****
****

FIG. 6B

FIG. 7


Female
Placebo + TCS
Dupilumab 100 mg or 200 mg q2w + TCS
Dupilumab 300 mg q4w + TCS
Male
BALP (µg/L) absolute change from baseline
Baseline
Week 8
Week 12
Week 16
Week 52
n=37 n=35 n=35 n=37 n=22
n=38 n=38 n=37 n=43 n=23
n=47 n=43 n=40 n=38 n=30
n=43 n=49 n=42 n=38 n=34
n=45 n=49 n=47 n=45 n=27
n=47 n=41 n=40 n=43 n=24

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/080989

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61P17/00 A61P19/08 C07K16/28
ADD.

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)
A61K A61P C07K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SIEGFRIED ELAINE C. ET AL: "Effect of Dupilumab on Laboratory Parameters in Adolescents with Atopic Dermatitis: Results from a Randomized, Placebo-Controlled, Phase 3 Clinical Trial", AMERICAN JOURNAL OF CLINICAL DERMATOLOGY, vol. 22, no. 2, 3 March 2021 (2021-03-03), pages 243-255, XP093143648, US ISSN: 1175-0561, DOI: 10.1007/s40257-020-00583-3 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7973645/pdf/40257_2020_Article_583.pdf> Discussion; abstract ----- -/--	1-33

[x] Further documents are listed in the continuation of Box C.
[ ] See patent family annex.

* 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	Date of mailing of the international search report
18 April 2024	02/05/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Saame, Tina

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WU DI ET AL: "Bone mineral density, osteopenia, osteoporosis, and fracture risk in patients with atopic dermatitis: a systematic review and meta- analysis", ANNALS OF TRANSLATIONAL MEDICINE, vol. 9, no. 1, 1 January 2021 (2021-01-01) , pages 40-40, XP093143598, US ISSN: 2305-5839, DOI: 10.21037/atm-20-4708 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7859773/pdf/atm-09-01-40.pdf> cited in the application the whole document	1-33
A	LOWE KATHERINE E ET AL: "Atopic eczema and fracture risk in adults: A population-based cohort study", JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 145, no. 2, 19 November 2019 (2019-11-19), page 563, XP086000366, ISSN: 0091-6749, DOI: 10.1016/J.JACI.2019.09.015 [retrieved on 2019-11-19] cited in the application the whole document	1-33
A	Nct03345914: "Study to Investigate the Efficacy and Safety of Dupilumab Administered With Topical Corticosteroids (TCS) in Participants >=6 to <12 Years With Severe Atopic Dermatitis (AD)", , 13 August 2020 (2020-08-13), XP093143631, Retrieved from the Internet: URL:https://clinicaltrials.gov/study/NCT03345914 cited in the application the whole document	1-33
X,P	Irvine Alan D ET AL: "P93 Dupilumab treatment in children with moderateto-severe atopic dermatitis increases levels of bone mineralization biomarkers", , 1 June 2023 (2023-06-01), XP093143715, Retrieved from the Internet: URL:https://academic.oup.com/bjd/article/188/Supplement_4/ljad113.121/7207210 the whole document	1-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2023/080989

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:

   a. [X] forming part of the international application as filed.

   b. [ ] furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

      [ ] accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. [ ] With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments: