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(54) Title: TREATMENT OF HIDRADENITIS SUPPURATIVA

(57) Abstract: Hidradenitis suppurativa can be treated by administering a pharmaceutical composition that includes a pharmaceutically acceptable carrier and a therapeutically effective amount of an agent that selectively binds interleukin-1α (IL-1α). Disclosed is the use of an antibody targeting and neutralizing interleukin 1 alpha (IL-1α), for the treatment of hidradenitis suppurativa (HS) in a human subject having lesions caused by the disease. More specifically, the use of the monoclonal antibody MABp1 is shown to be effective in reducing the number and/or size of inflammatory lesions in hidradenitis suppurativa.

TREATMENT OF HIDRADENITIS SUPPURATIVA

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the priority of U.S. provisional patent application serial number 62/459,841, entitled "Treatment of Hidradenitis Suppurativa," and filed on February 16, 2017.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH

[0001] Not applicable.

FIELD OF THE INVENTION

[0002] The invention relates generally to the fields of medicine, dermatology, and immunology. More particularly, the invention relates to the use of antibodies (Abs) which specifically bind interleukin-1α (IL-1α) to treat hidradenitis suppurativa.

BACKGROUND

[0003] Hidradenitis suppurativa (HS) is a chronic debilitating skin disease where nodules appearing in areas rich in apocrine glands progressively swell until they rupture and release pus through the skin. Sinus tract formation and scars result. HS is typically treated with antibiotics and surgery, but frequent relapse drastically impairs the patient's quality of life.

SUMMARY

[0004] Disclosed herein is the discovery that an agent that specifically targets IL-1α is useful for treating HS.

[0005] Accordingly, described herein are methods of reducing the severity of HS symptoms in a human subject. These methods can include the step of administering to the subject a pharmaceutical composition including a pharmaceutically acceptable carrier and an amount of an agent that selectively binds IL-1α effective to reduce the number and/or size of inflammatory lesions (e.g., nodule, abscesses, or draining fistulas), prevent their progression, reduce the pain caused by the lesions, or increase the time until new exacerbations. The agent can be an anti-IL-1α antibody (Ab) such as a monoclonal antibody (mAb) (e.g., of the IgG1 isotype), a mAb that includes a complementarity determining region (CDR) of MABp1, or MABp1.

[0006] Another aspect of the invention features a method of reducing the symptoms of HS in a human subject by administering to the subject a pharmaceutical composition including a pharmaceutically acceptable carrier and an amount of an anti-IL-1α Ab (or other agent that specifically and/or selectively binds IL-1α) effective to reduce the number and/or size of inflammatory lesions (e.g., nodule, abscesses, or draining fistulas) in the subject by at least

about 10% (e.g., at least 8, 9, 10, 15, 17, 20, 30, 40, 50, 60, 70, 80, 90, or 100%) as measured by any standard dermatological test.

[0007] The anti-IL-1α Ab can be a mAb such as an IgG1. The anti-IL-1α Ab can be the mAb designated as MABp1 or a mAb that includes one or more (CDRs) of MABp1. The pharmaceutical composition can be administered to the subject by injection, infusion, subcutaneously, intravenously, intramuscularly, or intradermally. In the methods described herein, the dose can be at least 0.25 (e.g., at least 0.2, 0.5, 0.75., 1, 2, 3, 4, or 5) mg/kg, and preferably at between 1-20 mg/kg (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 +/- 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, or 0.9 mg/kg).

[0008] Unless otherwise defined, all technical terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Commonly understood definitions of biological terms can be found in Rieger et al., Glossary of Genetics: Classical and Molecular, 5th edition, Springer-Verlag: New York, 1991; and Lewin, Genes V, Oxford University Press: New York, 1994. Commonly understood definitions of medical terms can be found in Stedman's Medical Dictionary, 27th Edition, Lippincott, Williams & Wilkins, 2000.

[0009] As used herein, an "antibody" or "Ab" is an immunoglobulin (Ig), a solution of identical or heterogeneous Igs, or a mixture of Igs. An "Ab" can also refer to fragments and engineered versions of Igs such as Fab, Fab', and $F(ab')_2$ fragments; and scFv's, heteroconjugate Abs, and similar artificial molecules that employ Ig-derived CDRs to impart antigen specificity. A "monoclonal antibody" or "mAb" is an Ab expressed by one clonal B cell line or a population of Ab molecules that contains only one species of an antigen binding site capable of immunoreacting with a particular epitope of a particular antigen. A "polyclonal Ab" is a mixture of heterogeneous Abs. Typically, a polyclonal Ab will include myriad different Ab molecules which bind a particular antigen with at least some of the different Abs immunoreacting with a different epitope of the antigen. As used herein, a polyclonal Ab can be a mixture of two or more mAbs.

[0010] An "antigen-binding portion" of an Ab is contained within the variable region of the Fab portion of an Ab and is the portion of the Ab that confers antigen specificity to the Ab (i.e., typically the three-dimensional pocket formed by the CDRs of the heavy and light chains of the Ab). A "Fab portion" or "Fab region" is the proteolytic fragment of a papain-digested Ig that contains the antigen-binding portion of that Ig. A "non-Fab portion" is that portion of an Ab not within the Fab portion, *e.g.,* an "Fc portion" or "Fc region." A "constant region" of an Ab is that portion of the Ab outside of the variable region. Generally encompassed within the constant region is the "effector portion" of an Ab, which is the

portion of an Ab that is responsible for binding other immune system components that facilitate the immune response. Thus, for example, the site on an Ab that binds complement components or Fc receptors (not via its antigen-binding portion) is an effector portion of that Ab.

[0011] When referring to a protein molecule such as an Ab, "purified" means separated from components that naturally accompany such molecules. Typically, an Ab or protein is purified when it is at least about 10% (*e.g.*, 9%, 10%, 20%, 30% 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99%, 99.9%, and 100%), by weight, free from the non-Ab proteins or other naturally-occurring organic molecules with which it is naturally associated. Purity can be measured by any appropriate method, *e.g.*, column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis. A chemically-synthesized protein or other recombinant protein produced in a cell type other than the cell type in which it naturally occurs is "purified."

[0012] By "bind", "binds", or "reacts with" is meant that one molecule recognizes and adheres to a particular second molecule in a sample, but does not substantially recognize or adhere to other molecules in the sample. Generally, an Ab that "specifically binds" another molecule has a K_d greater than about 10^5, 10^6, 10^7, 10^8, 10^9, 10^{10}, 10^{11}, or 10^{12} liters/mole for that other molecule. An Ab that "selectively binds" a first molecule specifically binds the first molecule at a first epitope but does not specifically bind other molecules that do not have the first epitope. For example, an Ab which selectively binds IL-1alpha specifically binds an epitope on IL-1alpha but does not specifically bind IL-1beta (which does not have the epitope).

[0013] A "therapeutically effective amount" is an amount which is capable of producing a medically desirable effect in a treated animal or human (*e.g.*, amelioration or prevention of a disease or symptom of a disease).

[0014] Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. All patents, patent applications, and publications mentioned herein are incorporated by reference in their entirety. In the case of conflict, the present specification, including definitions will control. In addition, the particular embodiments discussed below are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF DRAWINGS

[0015] Figure 1 is a graph showing that 60% of patients allocated to treatment with MABp1 achieved positive HiSCR at week 12 compared to 10% of the placebo group; and that the

odds ratio (OR) for positive HiSCR under MABp1 was 13.50 (95% confidence intervals: 1.19-152.51; p= 0.035).

[0016] Figure 2 is a graph showing that the clinical efficacy of MABp1 was maintained until week 24 (i.e., 12 weeks after treatment was stopped), where no patients treated with placebo had a positive HiSCR score (0%) compared to four out of 10 patients (40%) treated with MABp1.

[0017] Figure 3 is a graph showing the percent change of the total AN (sum of inflammatory nodules and abscesses) count in all patients over the first 24 weeks after the start of treatment with MABp1 or placebo.

[0018] Figure 4 is a graph showing the percent change of the total AN count in patients without previous exposure to anti-TNFα over the first 24 weeks after the start of treatment with MABp1 or placebo.

[0019] Figure 5 is a graph showing the percent change of the total AN count in patients with previous anti-TNFα treatment failure over the first 24 weeks after the start of treatment with MABp1 or placebo.

[0020] Figure 6 is a graph showing the percent change in disease activity in patients without previous exposure to anti-TNFα over the first 24 weeks after the start of treatment with MABp1 or placebo.

[0021] Figure 7 is a graph showing the percent change in visual analogue scale (VAS) in all patients over the first 24 weeks after the start of treatment with MABp1 or placebo.

[0022] Figure 8 is a graph showing the median time to new exacerbations in patients without previous exposure to anti-TNFα over the first 24 weeks after the start of treatment with MABp1 or placebo.

[0023] Figure 9 is a graph showing the change in lesion depth in all patients after 12 weeks from the start of treatment with MABp1 or placebo.

[0024] Figure 10 is a graph showing the change in lesion depth in patients with previous anti-TNFα treatment failure after 12 weeks from the start of treatment with MABp1 or placebo.

[0025] Figure 11 is a graph showing the number of patients having at least a 20% reduction in lesion depth in patients treated with MABp1 or placebo.

[0026] Figure 12 is a graph showing the number of patients having at least a 20% reduction in lesion depth in patients treated with MABp1 or placebo, wherein the patient populations were (i) those without previous exposure to anti-TNFα and (ii) those with previous anti-TNFα treatment failure.

DETAILED DESCRIPTION

[0027] The invention encompasses compositions and methods for reducing skin inflammation in HS including ameliorating one or more symptoms of a dermatological pathology in a subject. The below described preferred embodiments illustrate adaptation of these compositions and methods. Nonetheless, from the description of these embodiments, other aspects of the invention can be made and/or practiced based on the description provided below.

General Methodology

[0028] Methods involving conventional immunological and molecular biological techniques are described herein. Immunological methods (for example, assays for detection and localization of antigen-Ab complexes, immunoprecipitation, immunoblotting, and the like) are generally known in the art and described in methodology treatises such as Current Protocols in Immunology, Coligan et al., ed., John Wiley & Sons, New York. Techniques of molecular biology are described in detail in treatises such as Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Sambrook et al., ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2001; and Current Protocols in Molecular Biology, Ausubel et al., ed., Greene Publishing and Wiley-Interscience, New York. Ab methods are described in Handbook of Therapeutic Abs, Dubel, S., ed., Wiley-VCH, 2007. General methods of medical treatment are described in McPhee and Papadakis, Current Medical Diagnosis and Treatment 2010, 49th Edition, McGraw-Hill Medical, 2010; and Fauci et al., Harrison's Principles of Internal Medicine, 17th Edition, McGraw-Hill Professional, 2008. Methods in dermatology are described in James et al., Andrews' Diseases of the Skin: Clinical Dermatology - Expert Consult, 11th Ed., Saunders, 2011; and Burns et al., Rook's Textbook of Dermatology, 8th Ed., Wiley-Blackwell, 2010.

Treatment

[0029] The compositions and methods described herein are useful for HS in a mammalian subject by administering to the subject a pharmaceutical composition including an amount of an anti-IL-1α Ab effective to improve at least one characteristic of the condition in the subject (e.g., reduce the number and/or size of nodules, abscesses, or draining fistulas or prevent their progression). The mammalian subject might be any that suffers from HS including human beings. Human subjects might be male, female, adults, children, seniors (65 and older), and those with other diseases. Particularly preferred subjects are (i) those whose disease has progressed or failed to respond after treatment with other anti-inflammatory (e.g., TNFα inhibitors) or anti-microbial agents; (ii) those with a familial history of HS; (iii) those

in which other anti-inflammatory (e.g., TNFα inhibitors) or anti-microbial agents are not suitable; and (iv) those with higher than 100, 200, 300, 400, 500, or 1000 pg/ml of IL-1α in pus taken from their lesions. Subjects who have developed a human anti-human antibody response due to prior administration of therapeutic antibodies are preferred when the anti-IL-1α Ab is a true human Ab (e.g., one that is naturally expressed in a human subject) such as MABp1.

Antibodies and other Agents that Target IL-1α

[0030] Any suitable type of Ab that specifically binds IL-1α and reduces a characteristic of HS in a subject might be used. For example, the anti-IL-1α Ab used might be mAb, a polyclonal Ab, a mixture of mAbs, or an Ab fragment or engineered Ab-like molecule such as an scFv. The Ka of the Ab is preferably at least 1 $x10^9$ M^{-1} or greater (e.g., greater than 9 $x10^{10}$ M^{-1}, 8 $x10^{10}$ M^{-1}, 7 $x10^{10}$ M^{-1}, 6 $x10^{10}$ M^{-1}, 5 $x10^{10}$ M^{-1}, 4 $x10^{10}$ M^{-1}, 3 $x10^{10}$ M^{-1}, 2 $x10^{10}$ M^{-1}, or 1 $x10^{10}$ M^{-1}). In a preferred embodiment, the invention utilizes a fully human mAb that includes (i) an antigen-binding variable region that exhibits very high binding affinity (e.g., at least nano or picomolar) for human IL-1α and (ii) a constant region. The human Ab is preferably an IgG1, although it might be of a different isotype such as IgM, IgA, or IgE, or subclass such as IgG2, IgG3, or IgG4. One example of a particularly useful mAb is MABp1, an IL-1α-specific IgG1 mAb described in U.S. patent number 8,034,337B2 issued on October 11, 2011. Other useful mAbs are those that include at least one but preferably all the CDRs of MABp1. CDRs may be determined according to known methods such as described in Ofran et al., J. Immunol., 181:6230, 2008; and Antibody Engineering Volume 2, 2d edition, Konterman and Dubel (eds), Springer, 2010. Abs that specifically binds IL-1α and methods of their manufacture are described in more detail in, e.g., U.S. patent no. 9,545,411.

[0031] While the IL-1α specific Abs described above are preferred for use in the methods described herein, in some cases, other agents that specifically target IL-1α might be used so long as their administration leads to improvement of a characteristic of HS. These other agents might include vaccines that cause the production of anti- IL-1α Abs, proteins or peptides that bind IL-1α, and small organic molecules which specifically target IL-1α. Those that do not specifically bind IL-1β are preferred because the use of such agents have been reported to worsen the symptoms of HS (e.g., Tekin et al., Indian J Dermatol Venereol Leprol 2017; 83:615-7), and others have reported that IL-1β promotes healing and repair (e.g., Bersudsky et al., Gut. 2014 Apr; 63(4):598-609).

Pharmaceutical Compositions and Methods

[0032] The anti-IL-1α Ab compositions (and other agents that specifically target IL-1α) may be administered in pharmaceutically acceptable carriers (e.g., sterile saline), that are selected on the basis of mode and route of administration and standard pharmaceutical practice. A list of pharmaceutically acceptable carriers, as well as pharmaceutical formulations, can be found in Remington's Pharmaceutical Sciences, a standard text in this field, and in USP/NF. Other substances may be added to the compositions and other steps taken to stabilize and/or preserve the compositions, and/or to facilitate their administration to a subject.

[0033] For example, the Ab compositions might be lyophilized (see Draber et al., J. Immunol. Methods. 181:37, 1995; and PCT/US90/01383); dissolved in a solution including sodium and chloride ions; dissolved in a solution including one or more stabilizing agents such as albumin, glucose, maltose, sucrose, sorbitol, polyethylene glycol, and glycine; filtered (e.g., using a 0.45 and/or 0.2 micron filter); contacted with beta-propiolactone; and/or dissolved in a solution including a microbicide (e.g., a detergent, an organic solvent, and a mixture of a detergent and organic solvent.

[0034] The Ab compositions may be administered to animals or humans by any suitable technique. Typically, such administration will be parenteral (*e.g.*, intravenous, subcutaneous, intramuscular, or intraperitoneal introduction). The compositions may also be administered directly to the target site (e.g., the skin) by, for example, topical application. Other methods of delivery, e.g., liposomal delivery or diffusion from a device impregnated with the composition, are known in the art. The composition may be administered in a single bolus, multiple injections, or by continuous infusion (e.g., intravenously or by peritoneal dialysis).

[0035] A therapeutically effective amount is an amount which is capable of producing a medically desirable result in a treated animal or human. An effective amount of anti-IL-1α Ab compositions is an amount which shows clinical efficacy in patients as measured by the improvement in one or more symptoms of skin inflammation. As is well known in the medical arts, dosage for any one animal or human depends on many factors, including the subject's size, body surface area, age, the particular composition to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently. Preferred doses range from between 1-20 mg/kg body weight (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 +/- 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, or 0.9 mg/kg body weight). In some cases, a single dose is effective at resolving an episode of skin inflammation. In other cases, doses may be given repeatedly, e.g., semi-weekly, weekly, bi-weekly, tri-weekly, semi-monthly, once every three weeks, monthly, bi-monthly, or as needed (if lesions recur).

Combination Treatment

[0036] HS patients treated with an agent that selectively binds IL-1□ can also be administered other agents. For example, such patients can be treated with corticosteroids, retinoids, resorcinol, hormones, and biologics such as adalimumab or infliximab. Antimicrobials might also be used. In particular, antibiotics or other agents that target *S. aureus* can be used in those patients having or suspected of having *S. aureus* colonization or infection in one or more HS lesions. The use of antibodies that opsonize *S. aureus* are believed to be particularly useful. Preferred anti-*S. aureus* for this use are those having Fab region paratopes that specifically bind to *S. aureus* protein A (SpA) and Fc regions that do not bind SpA such that there are capable of mediating opsinization of *S. aureus* bacteria despite *S. aureus*'s expression of antibody-neutralizing SpA. These are described in U.S. patent no. 9,416,172 (e.g., the antibody designated PA8-G3 therein).

EXAMPLES

[0037] Example 1 – A double-blind, randomized, placebo-controlled clinical trial of the safety and efficacy of MABp1, a True Human™ antibody targeting interleukin-1α, in patients with HS.

[0038] HS patients were screened from those who are currently under follow-up. Inclusion criteria were: written informed consent provided by the patient; age 18 years or older; diagnosis of HS; HS of Hurley II or III stage disease or rapidly progressive HS of Hurley I stage; presence of 3 or more inflamed nodules consistent with HS in the body; at least one of the following: a) previous failure of treatment with any anti-TNFα, regimen; b) previous relapse under treatment with any anti-TNFα, regimen; or c) unwillingness to receive subcutaneous adalimumab treatment.

[0039] Exclusion criteria were: history of systemic lupus erythematosus, of rheumatoid arthritis or of seronegative inflammatory arthritis; treatment with any biologicals or investigational agents within the last 4 weeks (or 5 half-lives, whichever is longer); history of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies; administration of any live (attenuated) vaccine over the last 4 weeks; history of recurrent vein thrombosis or embolism compatible with anti-cardiolipin syndrome; any present serious bacterial infection namely pneumonia, endocarditis, acute pyelonephritis and intraabdominal infection; hepatic dysfunction defined as any value of transaminases, of γ-glutamyl transpeptidase or of bilirubin> 2 x upper normal limit; history of hematological or solid tumor malignancy, arterial hypertension, liver cirrhosis, HIV infection, and hepatitis virus B or C infection; history of episodes mimicking demyelinating

disorders or a definite diagnosis of multiple sclerosis; any creatinine value above 1.5 mg/dl; intake of corticosteroids defined as daily intake of prednisone or equivalent more than 1 mg/kg for the last three weeks; neutropenia defined as <1000 neutrophils/mm3; pregnancy or lactation; history of tuberculosis (latent or active); major surgery within 28 days prior to Day 0.

[0040] Diagnosis of HS was based on the following criteria, set by the 2nd Conference of the HS foundation in San Francisco: disease onset after puberty; involvement of at least two areas of the skin rich in apocrine glands; and history of recurrent painful boils without/with drainage of pus from the affected areas. Once a patient was considered eligible for the study the following procedures were performed: thorough study of record-history and medications; thorough physical examination; skin tuberculin test (any diameter below 5mm is considered negative); chest X-ray; serology for human immunodeficiency virus (HIV), for hepatitis B virus (HBV) and for hepatitis C virus (HCV); serum creatinine; and liver biochemistry. Only patients within normal were enrolled in the study. Patients were randomly 1:1 assigned to receive either placebo or MABp1 (XBiotech USA, Inc.) intravenously. The randomization sequence was built by an independent biostatistician. The investigational drug or matched placebo was administered intravenously with a one-hour infusion every 14 days (+/- 1 day) for 12 weeks, i.e., at week 0 (baseline), week 2, week 4, week 6, week 8, week 10 and week 12 for a maximum of seven infusions. The dose of MABp1 was 7.5 mg/kg.

[0041] XILONIX™, is a sterile injectable liquid formulation of 50 mg/mL MABp1 in a stabilizing isotonic buffer (pH 6.4). Each 10-mL serum vial contains 6 ml of the formulation, and is sealed with a 20-mm grey bromobutyl stopper and flip-off aluminum seal. Product was stored at 2-8°C, with excursions to room temperature permitted. The exact composition of the drug product is shown below:

Composition of the Final Drug Product			
Ingredient	**Grade**	**Manufacturer**	**Concentration**
MABp1 antibody	GMP	XBiotech	50 mg/ml
sodium phosphate dibasic	compendial	JT Baker	12 mg/ml
citric acid monohydrate	compendial	JT Baker	2 mg/ml
Trehalose•2H_2O (high-purity low endotoxin)	compendial	Ferro-Pfanstiehl	60 mg/ml
polysorbate 80	compendial	JT Baker	0.2 mg/ml
Phosphoric acid, to adjust pH	compendial	JT Baker	0.04 mg/ml

water for injection	compendial	Microbix	- -

[0042] The placebo product was manufactured following the same procedures and batch records used to manufacture the MABp1 drug product. The placebo dosage form is a sterile isotonic formulation buffer at pH 6.2-6.5. Each 10-ml Type I borosilicate glass serum vial contains 6mL of the formulation buffer, and is sealed with a 20-mm Daikyo Flurotec butyl rubber stopper and flip-off aluminum seal. The product was stored upright at 2-8°C, with excursions to room temperature permitted. The exact composition of the Placebo Product is shown in the table below:

Composition of Placebo Product			
Ingredient	**Grade**	**Manufacturer**	**Concentration**
trehalose dihydrate	compendial	Ferro-Pfanstiehl (USA)	60 mg/ml
sodium phosphate dibasic	compendial	JT Baker (USA)	12 mg/ml
citric acid monohydrate	compendial	JT Baker (USA)	2 mg/ml
Polysorbate 80	compendial	JT Baker (USA)	0.2 mg/ml
Phosphoric acid, to adjust pH	compendial	JT Baker	0.04 mg/ml
water for injection	compendial	Irvine Scientific (USA)	q.s.

[0043] XILONIX™ was diluted in a 100-mL bag of normal saline prior to infusion. The following calculations were used to determine the volume of drug product to be diluted for each study subject:

50 mg/ml drug product, 7.5 mg/kg dose:

$$\text{Volume of drug product to be diluted} = Vd = \frac{\text{Body Weight X Dosage}}{50\ \text{mg/mL}}$$

(Body Weight was rounded to the nearest whole number)

$$\text{Example for 70 kg Subject at 7.5 mg/kg:} \quad Vd = \frac{70\ \text{kg X 7.5 mg/kg}}{50\ \text{mg/mL}}$$

Vd = 10.5 mL (round to one decimal place)

[0044] The calculated volume (Vd) was withdrawn from the subject's assigned vial(s) using a suitable syringe. The same amount of saline as the calculated drug was removed

from the 100-ml bag. The calculated volume was then injected into the 100-mL IV bag of normal saline (0.9% NaCl), resulting in a final total volume of 100 ml. The drug product was then mixed by gently inverting the bag ten times. After priming the infusion set lines, the delivery pump was programmed to deliver 100 mL of the diluted drug product over a 1-hour period (60 +/- 15 minutes), with the subject being monitored for signs of an infusion reaction. Patients' visits occurred at week 0, at week 2, at week 4, at week 6, at week 8, at week 10, at week 12, at week 16, at week 20 and at week 24. At every visit the following procedures were performed.

Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Weeks	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**16**	**20**	**24**
DQLI	x	-	-		-	-	x	-	-	x
Physical examination	x	x	x	x	x	x	x	x	x	x
HiSCR	x	x	x	x	x	x	x	x	x	x
PGA	x	x	x	x	x	x	x	x	x	x
Disease activity	x	x	x	x	x	x	x	x	x	x
Modified Sartorius	x	x	x	x	x	x	x	x	x	x
VAS for disease	x	x	x	x	x	x	x	x	x	x
VAS for pain	x	x	x	x	x	x	x	x	x	x
Photo	x	-	-	-	-	-	x	-	-	x
Blood sampling	x	-	-	-	--	-	x	-	-	x

DQLI: Dermatology Quality of Life Index
HiSCR: Hidradenitis Suppurativa Clinical Response score
PGA: Physicians' Global Assessment
VAS: Visual Analogue Scale

[0045] Patients were asked to provide an assessment of the severity of their disease using the visual analogue scale (VAS) in mm. They were told that 0 represents no disease activity and 100 the worst disease activity they ever felt. Patients were asked to provide one score for their overall impression about their disease and another score about the physical pain they feel. The investigators asked the patient to provide the frequency of the exacerbation

of his disease and the pain felt at the affected sites. Patients were given the below DLQI score and they were asked to fill it out only at week 0, at week 12 and at week 24.

The Dermatology Quality of Life Index (DQLI). Each question is scored from 0 (absence) to 3 (intense problem)

	Question	Score
1.	How itchy, sore, painful or stinging has your skin condition been?	
2.	How embarrassed or self-conscious have you been because of your skin?	
3.	How much has your skin interfered with you going shopping or looking after your home or garden?	
4.	How much has your skin influenced the clothes you wear?	
5.	How much has your skin affected your social or leisure activities?	
6.	How much has your skin made it difficult for you to do any sport?	
7.	Has your skin prevented you from working or studying?	
8.	How much has your skin created problems with your partner or any of your close friends or relatives?	
9.	How much has your skin caused any sexual difficulties?	
10.	How much of a problem has the treatment for your skin been?	

[0046] The investigators counted the following from each individually affected area and took a photo of that area: the number of fistulas; the number of nodules or abscesses; the number of scars; their impression about the degree of inflammation scored from 0 to 3 as follows: 0, absent, 1, mild; 2, moderate; 3, intense; the two largest dimensions of each lesion in mm. Based on the above the following two scores were assessed at each visit: Hidradenitis Suppurativa Clinical Response (HiSCR) score and Physicians' Global Assessment (PGA) score. For HiSCR, patients were defined as achievers or non-achievers. The probability of achieving a positive HiSCR score was starting from the second visit and it was defined as a $\geq$ 50% reduction in inflammatory lesion count (sum of abscesses and

inflammatory nodules), and no increase in abscesses or draining fistulas in HS when compared with baseline. For PGA, this score was classified as: a) clear when the total number of abscesses is 0, the total number of draining fistulas is 0, the total number of inflammatory nodules is 0 and the total number of non-inflammatory nodules is 0; b) minimal when the total number of abscesses is 0, the total number of draining fistulas is 0, the total number of inflammatory nodules is 0 and there is presence of non-inflammatory nodules; c) mild when the total number of abscesses is 0, the total number of draining fistulas is 0, and the total number of inflammatory nodules is 1-4 or when there is presence of one abscess or draining fistula and absence of any inflammatory nodule; d) moderate when the total number of abscesses is 0, the total number of draining fistulas is 0 and the total number of inflammatory nodules is up to 5 or when there is presence of one abscess or draining fistula and up to one inflammatory nodule; e) severe when the total number of abscesses or draining fistulas is 2-5 and the total number of inflammatory nodules is 5-10; and f) very severe when there are more than 5 abscesses or draining fistulae.

[0047] Disease activity. This is defined as the sum of scores of all affected areas of each patient. Each area was evaluated by the following formula: (multiplication of the two largest diameters in each affected area in mm) x (the degree of inflammation of each lesion).

[0048] The modified Sartorius score. This is the sum of separate scoring for each affected area using the data recorded as follows: a) 3 points per anatomical region involved; b) 6 points for each fistula and 1 point for each nodule or abscess; c) 1 point when the longest distance between two relevant lesions in each affected area is <5 cm; 3 points when it is 5-10 cm; and 9 points when it is >10 cm; and d) 9 points when there is no clear separation of lesions from adjacent normal skin and 0 points when there is.

[0049] The efficacy of MABp1 in patients with moderate to severe HS by HiSCR scoring was assessed by the difference of achievement of positive HiSCR score between the treatment group and the comparator placebo group at week 12. The long-term efficacy of MABp1 in patients with moderate to severe HS by positive HiSCR scoring was assessed by the difference of achievement of HiSCR score between the treatment group and the comparator placebo group at week 24. Analysis was done separately for patients with previous failure or relapse under adalimumab and for patients without previous adalimumab treatment. The short-and long-term efficacy of MABp1 in patients with moderate to severe HS was assessed by the comparisons of all used scoring systems (HiSCR, PGA, DLQI, disease activity, VAS for disease, VAS for pain and modified Sartorius score) on all study visits. Analysis was also done separately for patients with previous failure or relapse under

adalimumab and for patients without previous adalimumab treatment. The effect of MAbp1 on the time to new exacerbation was assessed by comparing the time to new exacerbation from week 0 between the two groups of treatment. Analysis was done separately for patients with previous failure or relapse under adalimumab and for patients without previous adalimumab treatment. Comparisons of HiSCR between the two study groups was done by the Fischer's exact test. Comparisons of severity score for each study visits were done by non-parametric statistics. Comparison of the time to new exacerbation between the two groups was done by the log-rank test.

[0050] Results. Figures 1-12 show the results of the study. Patients treated with MABp1 achieved a significantly greater rate of positive HiSCR scores than comparators. Treatment with MABp1 was associated with significant : increased positive HiSCR scoring at week 24; decreased total AN count (more pronounced in patients without previous anti-TNF exposure); decreased VAS for the disease; prolongation of the time to new exacerbations in patients without previous anti-TNF exposure; and significant decrease of US depth of total body lesions (more pronounced in patients without previous anti-TNF failure).

[0051] Example 2

[0052] The topline results from an investigator sponsored randomized Phase 2 study evaluating MABp1 as a treatment for Hidradenitis Suppurativa (HS) showed that study met its primary endpoint, demonstrating significant improvement of HS patients compared to control after 12 weeks of therapy (response rate of 60% vs 10%, respectively (p=0.035)).

[0053] The 20 patient double-blind, placebo-controlled study was designed to evaluate the safety and efficacy of MABp1, a True Human™ antibody targeting interleukin-1 alpha (IL-1α), in patients with HS not eligible for anti-TNFα therapy. Patients were randomized 1:1 to receive either MABp1 or placebo every 2 weeks for 12 weeks. Patients in the study underwent primary assessment of efficacy using Hidradenitis Suppurativa Clinical Response (HiSCR) scores at 12 weeks, continued by a follow up phase to assess time to relapse after an additional 12 weeks without therapy. Efficacy measures include assessment of HiSCR scores, a validated method for evaluating efficacy in HS patients, as well as quality of life assessment and ultrasonographic evaluation.

[0054] Sixty percent of patients allocated to treatment with MABp1 achieved positive HiSCR at week 12 compared to 10% of the placebo group (Figure 1). The odds ratio (OR) for positive HiSCR under MABp1 was 13.50 (95% confidence intervals: 1.19-152.51; p= 0.035). The total AN count which is the basic component of the HiSCR score was decreased over the first 12 weeks under treatment (Figure 3). The clinical efficacy of MABp1 was maintained until week 24, i.e., 12 weeks after treatment was stopped. At that

time point, as shown in Figure 2, no patients treated with placebo had a positive HiSCR score (0%) compared to four out of 10 patients (40%) treated with MABp1. Treatment with MABp1 was also accompanied by better patient-reported outcomes. Decrease of the visual analogue scale (VAS) was found in 30% (three out of 10) and in 70% (seven out of 10) allocated to placebo and MABp1 respectively. Sub-analysis showed that this was 40% (two out of five) and 33.3% (one out of three) respectively among anti-TNFs naïve patients and 20% (one out of five) and 85.7% (six out of seven) among patients failing previous treatment with anti-TNFs. The median time to the first HS exacerbation was seven weeks in the placebo group and 11 weeks in the MABp1 group. This time did not differ significantly between groups (log-rank: 1.98, p= 0.159). However, when sub-analysis was done among anti-TNFs naïve patients, it was found that the median time until a new HS exacerbation was 4 weeks with placebo treatment and 18.5 weeks with MABp1 treatment (log-rank test: 4.46; p= 0.035; see Fig. 8). A decrease in disease activity was found in all patients treated with MABp1 and who achieved positive HiSCR at weeks 12 and 24. A decrease of at least two of the assessed scores i.e. Physicians' Global Assessment (PGA), disease activity, modified Sartorius score, VAS for pain, and dermatology life quality index (DLQI) at week 12 was found in 40% of patients allocated to placebo and 80% of patients allocated to MABp1 (80%) (OR= 14.50; 95% confidence intervals: 0.96-218.99; p= 0.054). Sub-analysis showed that this was 60% (three out of five) and 100% (three out of three) respectively among anti-TNFs naïve patients and 20% (one out of five) and 71.4% (five out of seven) among patients failing previous treatment with anti-TNFs. Significant changes in variables for skin ultrasound included total lesion vascularity and total lesion depth, which is the sum of the grading of vascularity and the sum of the greatest depth of all involved skin areas, respectively. Both variables were decreased after treatment with MABp1 (Figures 9-12). More than 20% decrease of total lesion depth was selected as a cut-off point, and it was found in 22.2% of patients allocated to placebo compared to 77.8% of patients treated with MABp1 (OR= 12.25; 95% confidence intervals 1.33-113.06; p= 0.027). The effect was pronounced among patients who have failed previous anti-TNFs (Figure 10). Significant improvement in the elasticity of the affected areas was also noted.

[0055] Serum IL-1α was below the lower limit of detection in the sera sampled from all patients both before and at the end of blind treatment. Pus was sampled before treatment from six patients allocated to placebo and seven patients allocated to MABp1. Mean ± SE concentrations of IL-1α were 697.2 ± 440.4 pg/ml and 772.0 ± 221.7 pg/ml respectively (p= 0.412 by the Mann-Whitney U test). Treatment with MABp1 was accompanied by decrease of serum IL-8. More than 30% decrease of IL-8 on week 12 was selected as a cut-

off point. The OR for this cut-off point by MABp1 was 13.50 (95% confidence intervals: 1.19-152.51; p= 0.035). This was consistent with change in levels of IL-8 produced from whole blood stimulated with heat-killed *Staphylococcus aureus*, which was significantly lower among patients treated with MABp1 than patients treated with placebo. The capacities of whole blood to produce both IL-1α and human β-defensin (hBD)-2 were positively associated among placebo-treated patients. Among the same patients, the capacity for hBD-2 production was negatively correlated with the change of the skin depth of the lesions at ultrasound. These correlations ceased to exist among MABp1-treated patients, which suggested an hBD-2-associated mode of action of MABp1 in HS that was mediated through the inhibition of IL-1α.

[0056] Safety – no study drug related adverse events or serious adverse events occurred in the study.

[0057] Analysis of the data using the iHS4 score for all 20 patients who were randomized to receive either placebo or MABp1 therapy in the Phase 2 double-blind study was performed. At least a 30% decrease of the iHS4 score from the baseline at week 12 was associated with 100% sensitivity for positive HiSCR score (the efficacy measure used in the phase 2 study). This change was found in one (10%) and in four (40%) patients allocated to placebo and MABp1, respectively (p= 0.046).

[0058] Patients that had originally been allocated to placebo in the Phase 2 study were allowed to receive treatment with the MABp1 antibody therapy in a so called open label extension (OLE) study. Seven of 10 patients that had originally received placebo were treated with MABp1 for 12 weeks. Main endpoints used in the OLE included safety and HiSCR score at the end of the 12 week treatment. At the conclusion of the double-blinded study, only one patient (1 of 10, or 10%) receiving placebo had achieved HiSCR. During the OLE, five patients (5 of 7, or 71.4%) achieved the HiSCR response (p=0.035). There was a total of 24 HS exacerbations during the blinded portion of the study compared to just 1 exacerbation during the OLE phase.

[0059] "The overall response rate observed in the data is, in my opinion, groundbreaking for the treatment of HS," Dr. Giamarellos-Bourboulis commented, "I am truly encouraged by these results and very much look forward to the future use of MABp1 as a treatment for this devastating condition."

Other Embodiments

[0060] It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not

limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. A method of treating hidradenitis suppurativa in a human subject having lesions associated with hidradenitis suppurativa, the method comprising the step of administering to the subject a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an amount of an anti-IL-1α antibody effective to treat a symptom of hidradenitis suppurativa in the subject.

2. The method of claim 1, wherein the anti-IL-1α antibody is a monoclonal antibody.

3. The method of claim 2, wherein the monoclonal antibody is an IgG1.

4. The method of claim 3, wherein the monoclonal antibody is MABp1.

5. The method of claim 1, wherein the subject's HiSCR score is improved after administration of the pharmaceutical composition

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6. The method of claim 1, wherein the median size of the subject's hidradenitis suppurativa lesions is reduced after administration of the pharmaceutical composition.

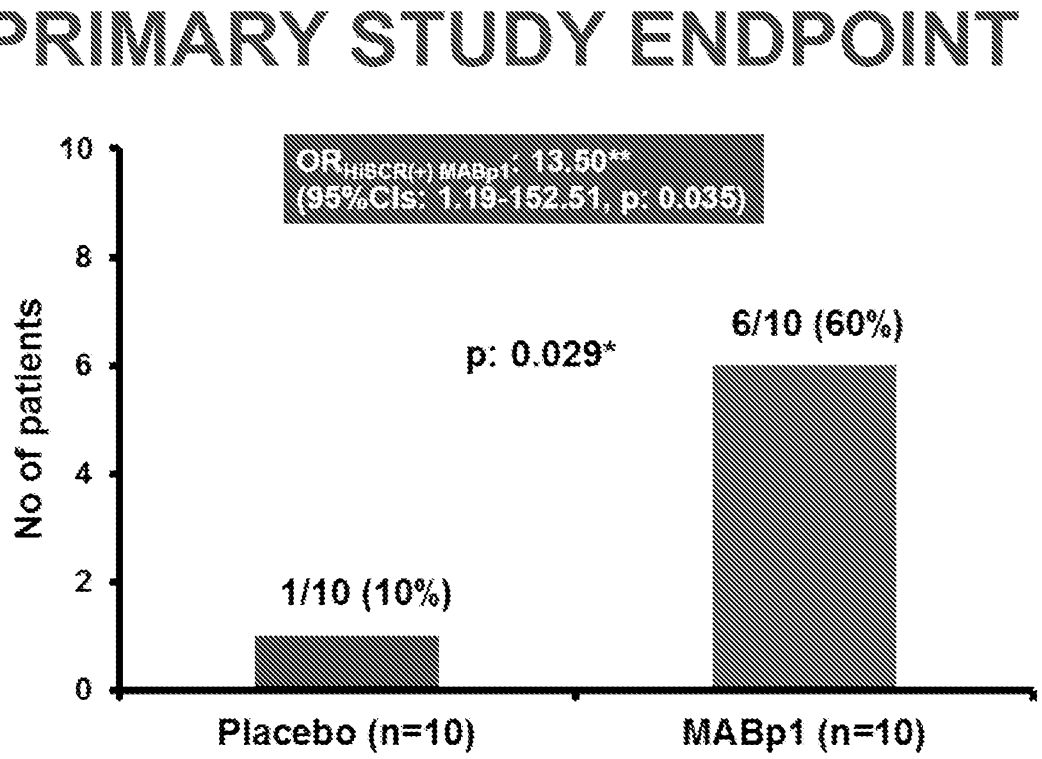
7. The method of claim 1, wherein the subject's pain associated with the subject's hidradenitis suppurativa lesions is reduced after administration of the pharmaceutical composition.

8. The method of claim 1, wherein the subject's time to new hidradenitis suppurativa lesions is increased after administration of the pharmaceutical composition.

9. The method of claim 1, wherein the hidradenitis suppurativa in the human subject has failed to resolve after treatment with tumor necrosis factor alpha inhibitors.

10. The method of claim 1, further comprising the step of administering to the subject a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an anti-*S. aureus* antibody.

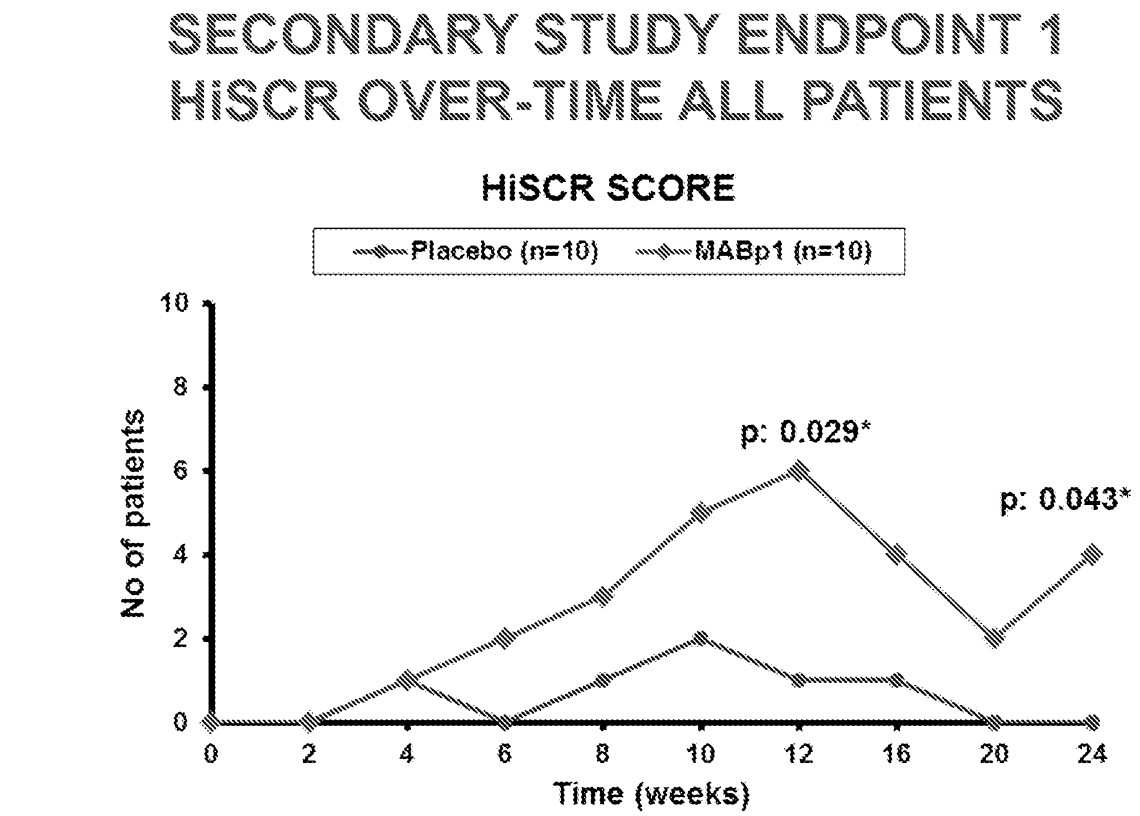
11. The method of claim 10, wherein the anti-*S. aureus* antibody comprises a Fab region paratope that specifically binds to *S. aureus* protein A (SpA) and an Fc region that does not specifically bind SpA.



*Fisher's exact test
**Mantel-Haenszel's statistics

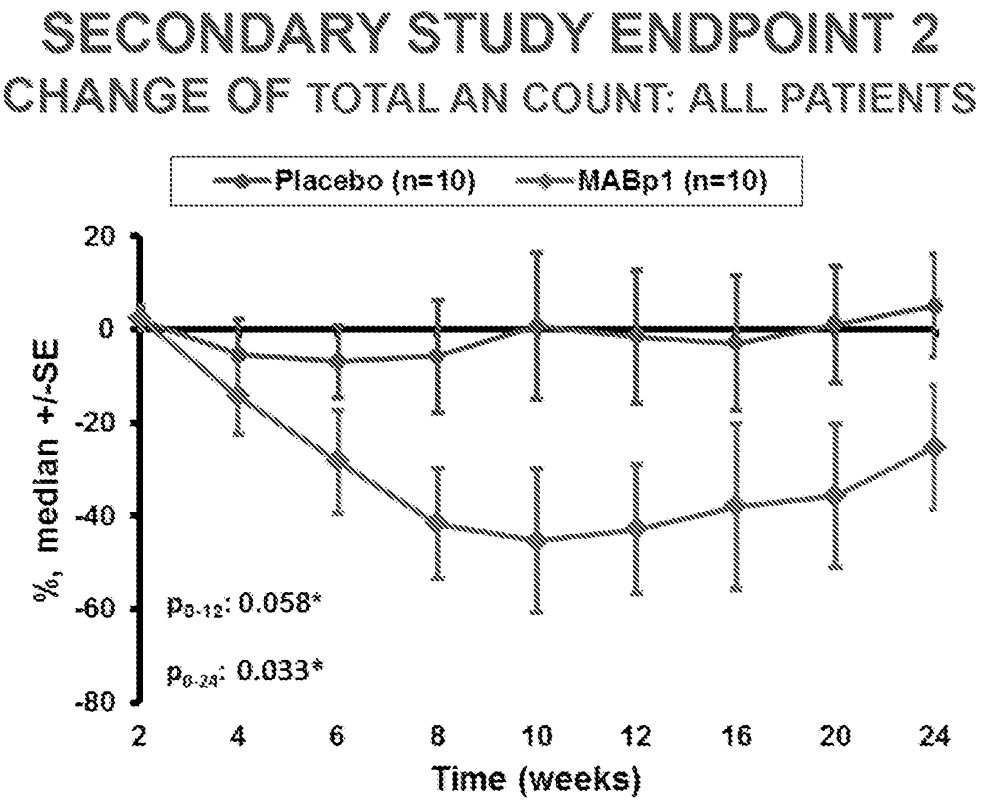
CIs: confidence intervals
OR: odds ratio

FIG. 1



*Fisher's exact test

FIG. 2

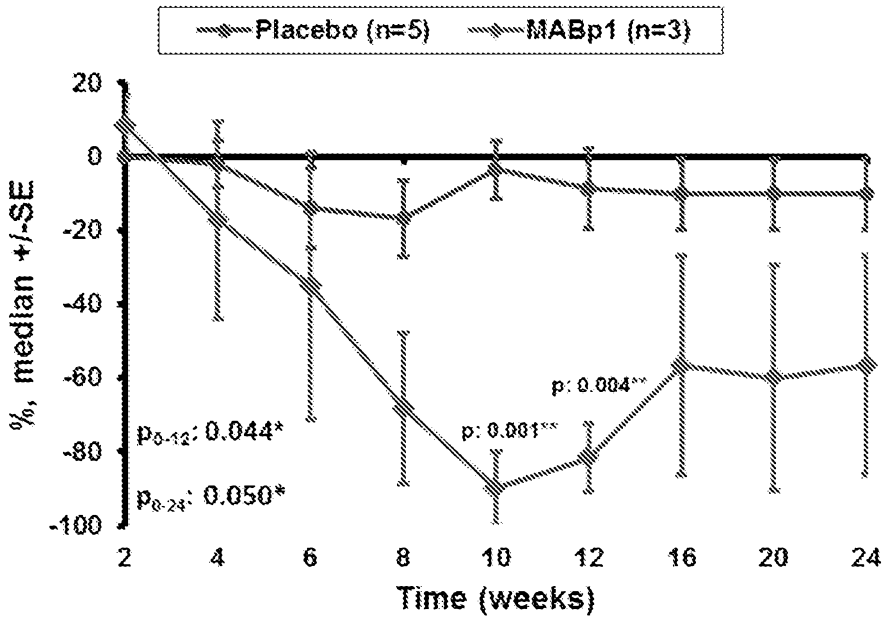


*Comparison of AUCs by the Students "t-test"

FIG. 3

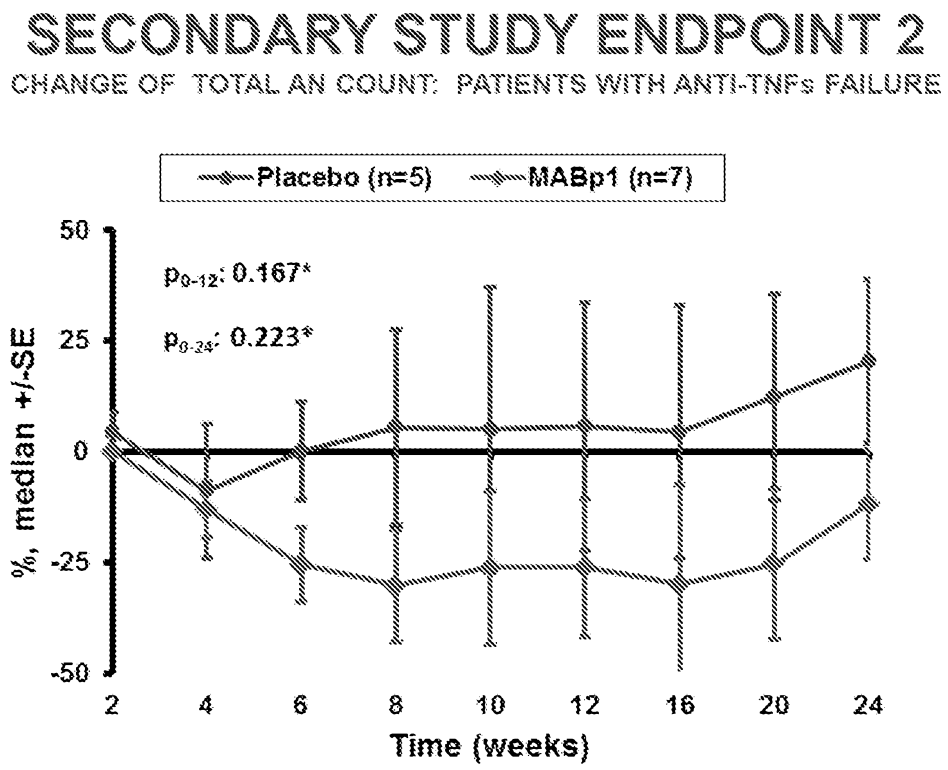
SECONDARY STUDY ENDPOINT 2

CHANGE OF TOTAL AN COUNT: PATIENTS W/O PREVIOUS EXPOSURE TO ANTI-TNFs



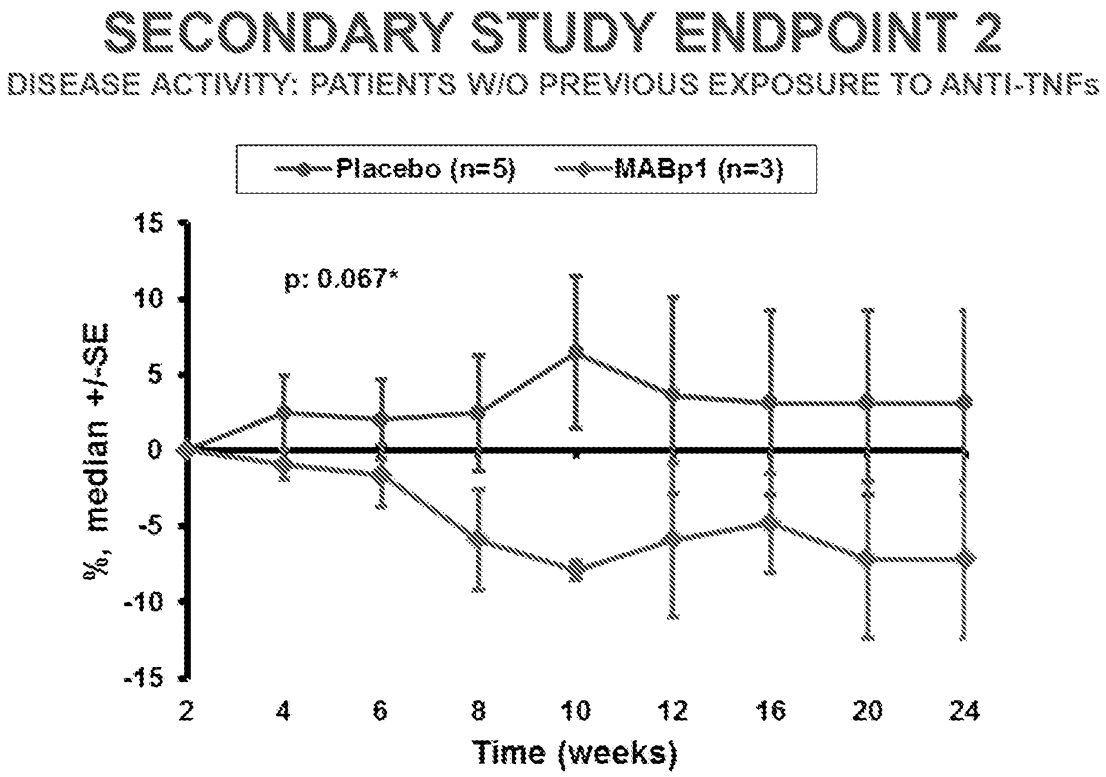
*Comparison of AUCs by the Student's "t-test"
**Comparison of at the indicated time points by the Student's "t-test"

FIG. 4



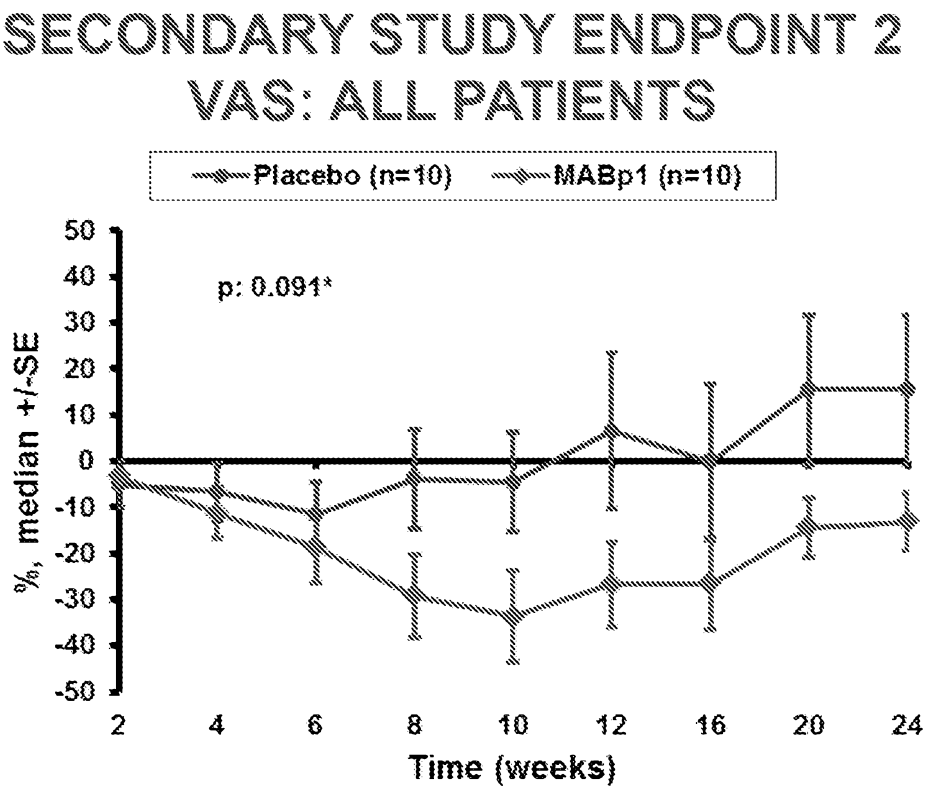
*Comparison of AUCs by the Student's "t-test"

FIG. 5



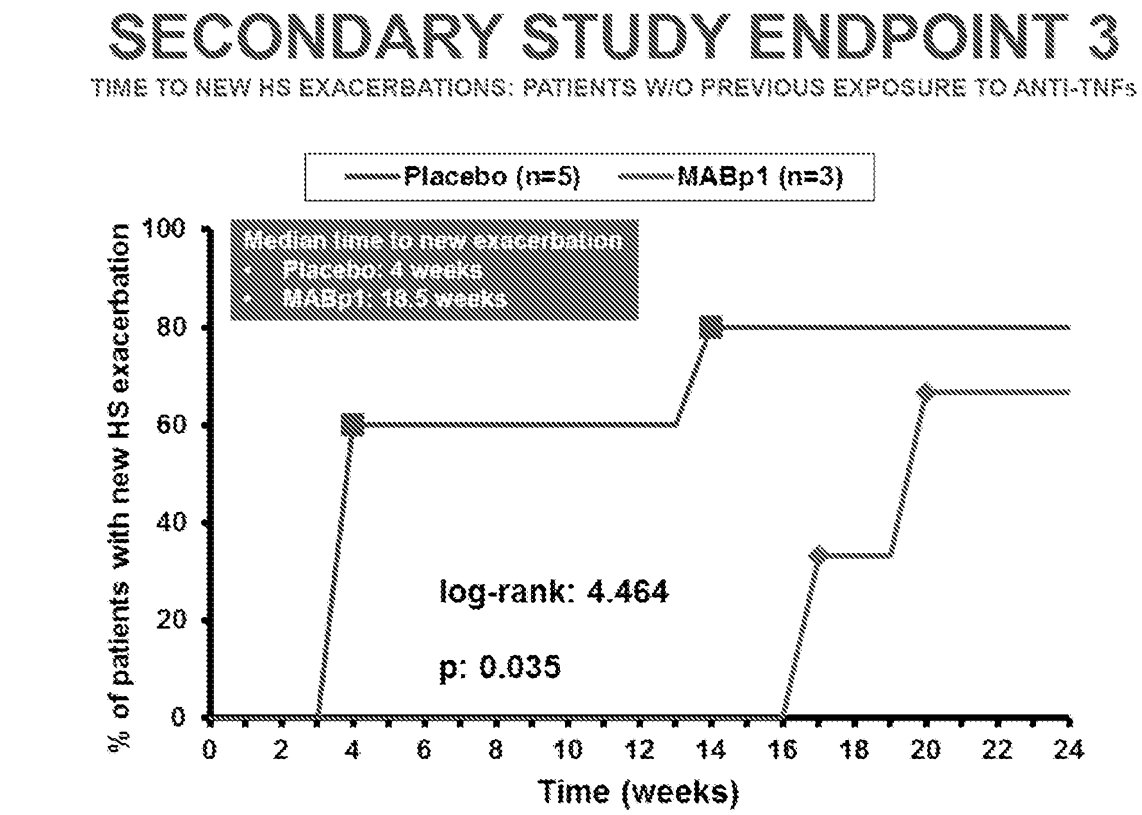
*Comparison of AUCs by the Mann-Whitney U test

FIG. 6



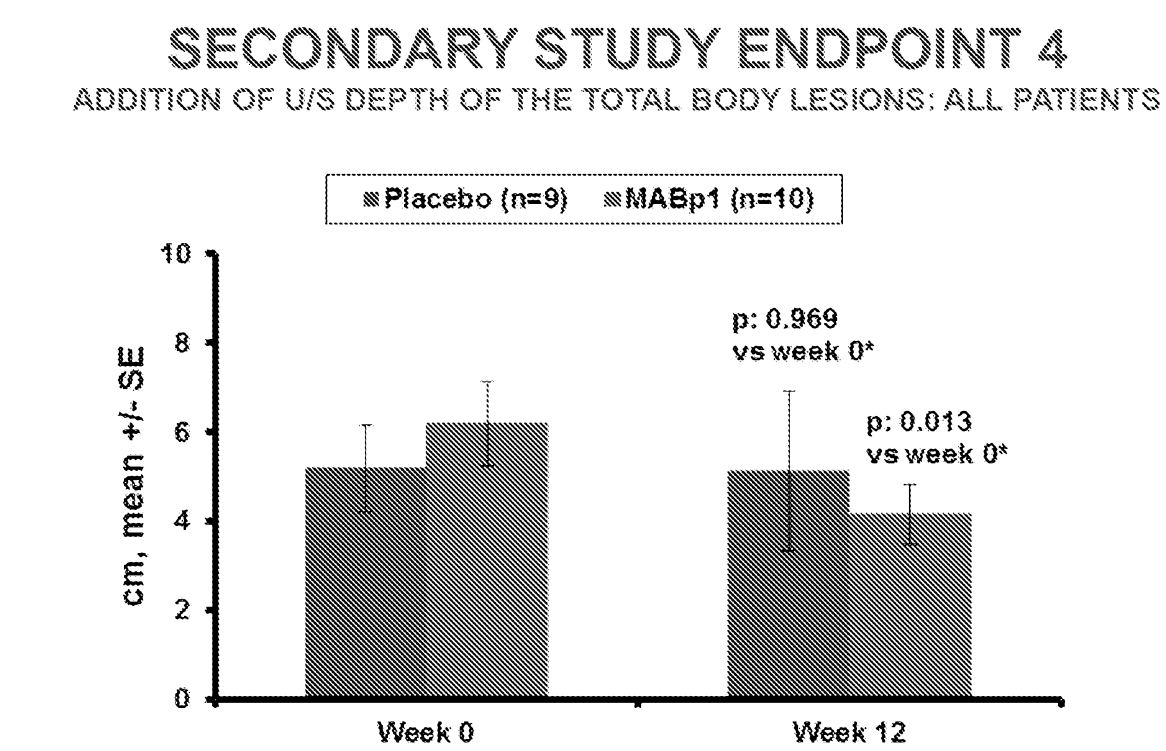
*Comparison of AUCs by the Student's "t- test"

FIG. 7



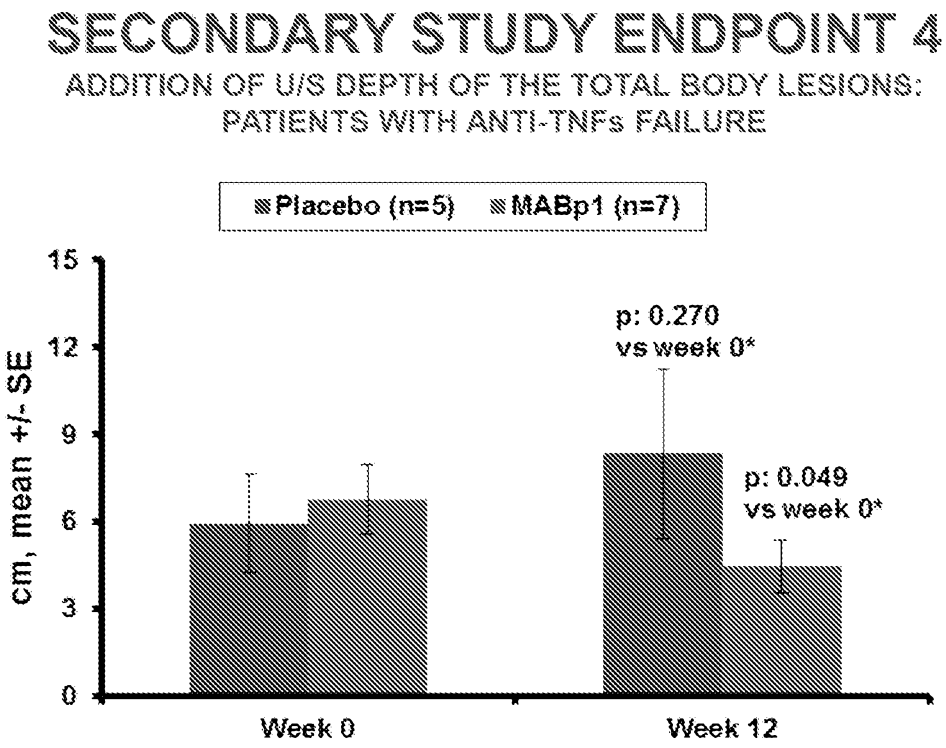
Markers indicate the exacerbations

FIG. 8



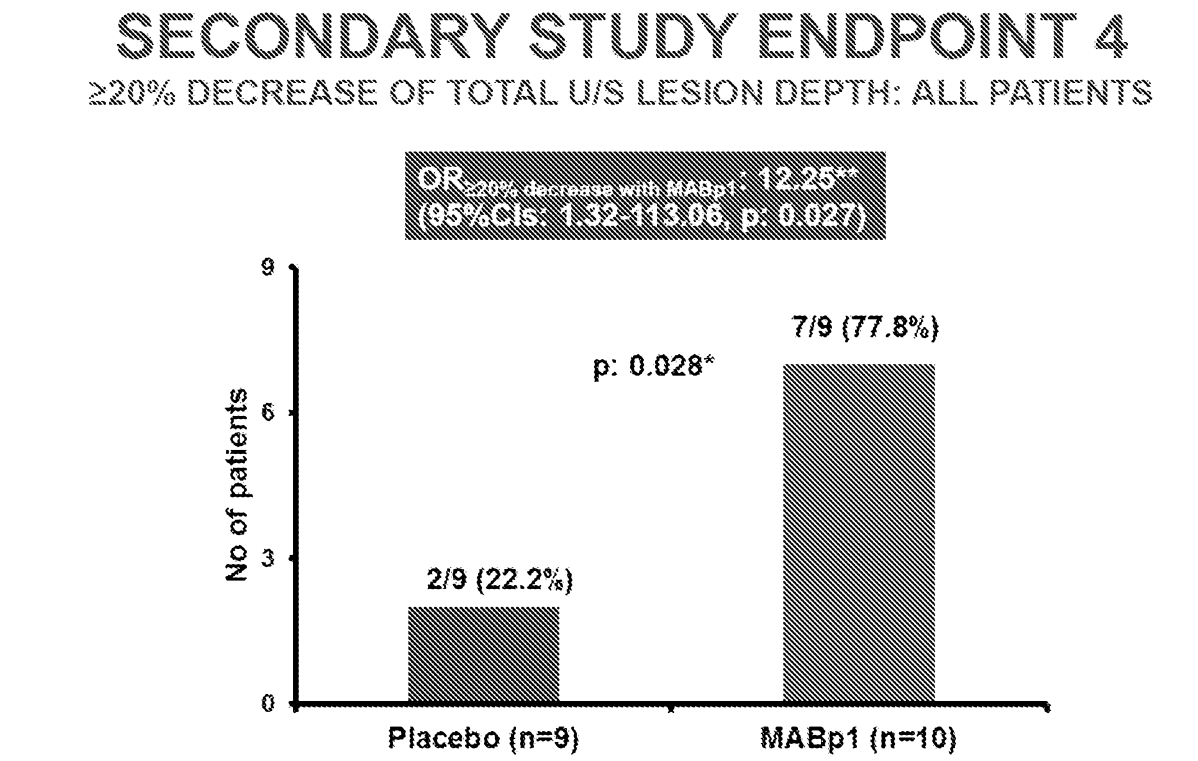
*paired samples "t-test"

FIG. 9



*paired samples "t-test"

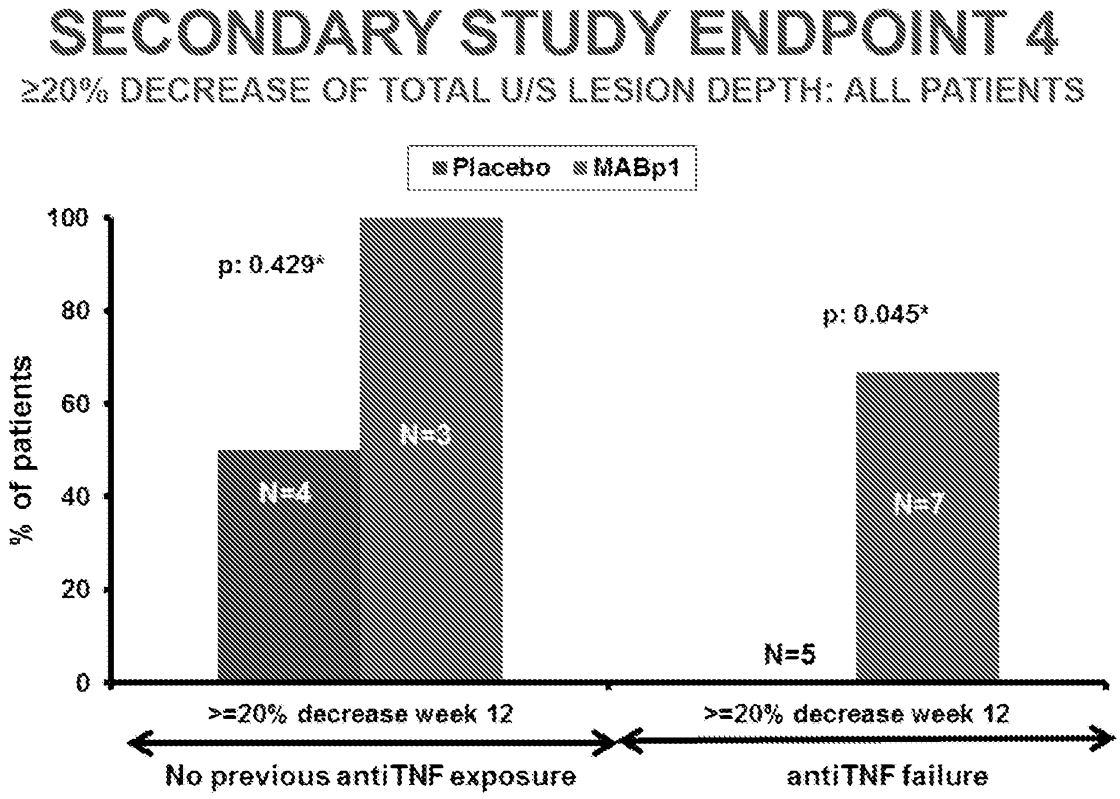
FIG. 10



*Fisher exact test
**Mantel-Haenszel's statistics

CIs: confidence intervals
OR: odds ratio

FIG. 11



*Fisher's exact test

FIG. 12