

A METHOD OF TREATING LUPUS

CROSS REFERENCE

This application claims the benefit of U.S. Provisional Application Serial No.
5 63/587,308 filed October 2, 2023 which is incorporated herein in its entirety.

DESCRIPTION

The present invention generally relates to a method of treating a disease,
comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-
10 (4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)
piperidin-1-yl) acetamide or a pharmaceutically acceptable salt thereof, wherein said
disease is lupus.

BACKGROUND OF THE INVENTION

15 Toll-like receptors (TLRs) are a family of pattern recognition receptors that
recognize highly conserved components of diverse pathogens and induce innate and
adaptive immune responses (Akira S, Takeda K, T. Kaisho, T., *Nat Immunol.*
2001;2:675–680; Pandey S, Agrawal DK., *Immunol Cell Biol.* 2006;84:333–341; Kawai
T, Akira S. *J Biochem.* 2007;141:137–145). TLR7 and TLR8 have been shown to be
20 expressed in endosomal compartments and to recognize ssRNA molecular patterns.
TLR7 is expressed in B cells and plasmacytoid dendritic cells (pDC); TLR8 is expressed
in monocytes and myeloid dendritic cells (mDC) (Chuang TH, Ulevitch RJ., *Eur*
Cytokine Net. 2000;11:372–378; Iwasaki A, Medzhitov R. *Nat Immunol.* 2004;5:987–
995).
25 Toll-like receptor (TLR)7 and TLR8 are endosomal receptors that recognize short
uracil (U)-rich single-strand ribonucleic acid (RNA). TLR7 is expressed in plasmacytoid
dendritic cells (pDC) and B-cells, as well as in monocytes, macrophages and neutrophils.
TLR7 agonists induce B-cell activation and cytokine production, as well as interferon
alpha (IFN α) production by pDC. TLR8 is expressed in myeloid dendritic cells (mDC),
30 monocytes, macrophages, and neutrophils and induces expression of cytokines such as
interleukin (IL)-6, tumor necrosis factor alpha (TNF α), and IL-10, as well as cell surface
molecules involved in antigen-presenting cell interactions with T cells, including cluster

of differentiation (CD) 40 and CD86. TLR7 and TLR8 are activated by self-RNA as part of the disease pathophysiology of lupus, including systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), and lupus nephritis (LN). This drives multiple responses across cell types forming a cycle of disease with increasing autoantibody
5 production and immune complex formation that acts as a feed-forward loop to accelerate disease progression. Evidence for the role of TLR7 in immune dysregulation in lupus-like disease comes from both mouse models and human translational data. TLR7-deficient mice are highly resistant to disease in mouse lupus models, providing genetic validation for the potential role of TLR7. Data from evaluation of human samples
10 suggest further connections with human disease; the X-linked TLR7 gene has been found to escape X-chromosome inactivation in a large portion of pDC and B-cells in women, leading to increased TLR7 expression and increased responsiveness in B-cells that likely contributes to the higher risk of SLE in women. TLR7 acts on pDC and B-cells in an IFN-independent manner to induce high levels of resistance to glucocorticoids by
15 activating nuclear factor κ B (NF- κ B) pathways, blocking glucocorticoid-induced apoptosis. This induction of glucocorticoid resistance is believed to contribute to the requirement in SLE for much higher glucocorticoid doses than needed in many other autoimmune diseases and provides a rationale for mechanism-based synergy between TLR7 inhibitors and glucocorticoids. There is a difference in the function of TLR8 in the
20 mouse relative to the human, so TLR8-deficient mice cannot be used to elucidate the role of TLR8 in human disease. By contrast, transgenic mice expressing human TLR8 develop autoimmune disease, including inflammation of the salivary glands and joints. The induction of proinflammatory cytokines and increase in expression of molecules involved in antigen presentation observed with TLR8 activation in human cells are
25 expected to contribute to human disease. TLR7/8 inhibitors are, therefore, anticipated to have the potential for steroid-sparing effects in the treatment of patients with lupus and other related autoimmune diseases.

Lupus is a chronic inflammatory autoimmune disease, resulting from a loss of self-tolerance by the immune system and the concomitant production of autoantibodies.
30 The autoantibodies and immune-complexes deposits formed with these autoantibodies can adversely affect healthy tissue in various organs, causing damage to tissue or one or more organs (Maidhof, *Pharmacy and Therapeutics* 37(4) 240-249 (2012)).

Systemic lupus erythematosus (SLE) is the most prevalent form of lupus and is typically a systemic disease affecting more than one organ, including skin, kidneys, lungs, heart, muscles, and nervous system (Fanouriakis et al., *Ann Rheum Dis* 2021;80:14-25).

Cutaneous lupus erythematosus (CLE) is a skin disorder which can occur as
5 isolated skin manifestation or with systemic lupus erythematosus (Okon LG, Werth VP. *Best Pract Res Clin Rheumatol*. 2013;27:391–404; Cohen MR, Crosby D. *J Rheumatol*. 1994;21:1665–1669).

CLE includes three categories of LE-specific skin diseases: acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic
10 cutaneous lupus erythematosus (CCLE). CCLE encompasses discoid lupus erythematosus (DLE), lupus erythematosus tumidus, lupus profundus (also known as lupus panniculitis), chilblain lupus erythematosus, and lichenoid cutaneous lupus erythematosus-lichen planus overlap syndrome. The most common type of CCLE is discoid lupus erythematosus (DLE) accounting for 73% to 85% of CCLE. There are
15 several benefits to studying a cutaneous lupus population for this purpose. During the course of SLE, the key characteristic that unites the LE-specific skin diseases is histopathology. The lesions are apparent on routine physical exam and amenable to pathological evaluation, i.e., biopsy.

The clinical spectrum of CLE is broad, ranging from isolated discoid plaques to
20 widespread skin lesions. Common shared histopathologic features include a vacuolar interface dermatitis (liquefactive degeneration of the basal layer of the epidermis); hyperkeratosis; epidermal atrophy; a superficial, perivascular, and perifollicular mononuclear cell inflammatory infiltrate; thickening of the basement membrane; and pigment incontinence. Histologically, skin lesions present as interface dermatitis
25 (inflammation of the skin in the dermal-epidermal junction mediated by antiepidermal responses) is orchestrated by both innate and adaptive immune pathways that are strongly activated in the formation of skin lesions.

ACLE may present in a localized or generalized form and is frequently (~90%) associated with active SLE. Malar rashes have been reported to be present in up to 52%
30 of SLE patients at the time of diagnosis, with clinical activity of the rash paralleling that of the systemic disease.

SCLE lesions typically occur on visible sun-exposed areas of the body, including

the upper thorax, upper back, and the extensor surfaces of the arms and forearms, and the lesions are highly light sensitive. There are two morphologic variants of SCLE, annular and papulosquamous. The annular type is characterized by scaly annular erythematous plaques, which tend to coalesce and produce a polycyclic array. The papulosquamous variant can resemble eczema or psoriasis, as well as pityriasis in some instances. An estimated 50% of SCLE patients meet criteria for SLE.

DLE is the most common form of CCLE, which can be either localized or generalized. The localized form, characterized by the limited cutaneous involvement of the head and scalp, usually

New methods of treating lupus are desired.

Disclosed herein is a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is lupus.

SUMMARY OF THE INVENTION

The present invention provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is lupus.

These and other features of the invention will be set forth in expanded form as the disclosure continues.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is illustrated by reference to the accompanying drawings described below.

FIG. 1 shows the study design schematic of the double-blind, placebo-controlled clinical trial to assess the effect of afimetoran treatment (30 mg QD) in patients with active cutaneous lupus, either as cutaneous lupus erythematosus or a manifestation of systemic lupus erythematosus, when added to background disease therapy.

FIG. 2 shows the adjusted mean change in the CLASI-A score from baseline for (i) patients dosed with 30 mg QD afimetoran and (ii) for patients dosed with placebo for

16 weeks and for the 4 week follow-up period (weeks 16-20). The symbols were slightly shifted horizontally to prevent possible overlapping of the error bars.

FIG. 3 shows the mean change in the CLASI-A score from baseline for patients having baseline CLASI-A scores of 10-20 (i) dosed with 30 mg QD afimeteran and (ii) dosed with placebo for 16 weeks and for the 4 week follow-up period (weeks 16-20). The symbols were slightly shifted horizontally to prevent possible overlapping of the error bars.

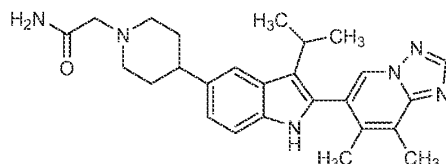
FIG. 4 shows the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) form.

DEFINITIONS

In order that the present description may be more readily understood, certain terms are first defined. Additional definitions are set forth throughout the detailed description.

Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

The compound, 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide, has the structure:



The discovery and synthesis of the compound of Formula (I) is described in WO 2018/005586 A1. The compound, 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide, has the generic name “afimeteran” and is also referred to as “BMS-986256”. As used herein, the terms “afimeteran” and “BMS-986256” and the compound name, 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide, are interchangeable.

As used herein, the dose of 30 mg of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]

pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof refers to 30 mg of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide provided as a non-hydrate, non-solvate, free base. The corresponding dose of a pharmaceutically acceptable salt of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl) acetamide is the amount required to provide the equivalent of 30 mg of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl) acetamide as a non-hydrate, non-solvate, free base. Likewise for a hydrate or solvate of the 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl) piperidin-1-yl)acetamide, or a hydrate or solvate of the pharmaceutically acceptable salt thereof, the corresponding dose is the amount required to provide the equivalent of 30 mg of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl) piperidin-1-yl)acetamide as a non-hydrate, non-solvate, free base.

The terms “treat,” “treating,” and “treatment,” as used herein, refer to any type of intervention or process performed on, or administering an active agent to, the patient with the objective of reversing, alleviating, ameliorating, inhibiting, or slowing down or preventing the progression, development, severity or recurrence of a symptom, complication, condition or biochemical indicia associated with a disease. Treatment includes therapeutic treatment and prophylactic or preventative measures, wherein the object is prevent or lessen the targeted condition or disorder.

The terms “administering” and “administration” refers to the physical introduction of a composition comprising a therapeutic agent to a patient, using any of the various methods and delivery systems known to those skilled in the art. Routes of administration for the TLR7 inhibitor include enteral, topical, and mucosal administration such as oral, topical, sublingual, and intravenous administration, and parenteral administration such as intravenous, intramuscular, and subcutaneous injection.

The term “patient” refers to a human subject who receives therapeutic treatment.

DETAILED DESCRIPTION

The features and advantages of the invention may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to

be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of the invention that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to
5 form sub-combinations thereof. Embodiments identified herein as exemplary or preferred are intended to be illustrative and not limiting.

The first aspect of the invention provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said
10 disease is lupus.

One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is
15 cutaneous lupus erythematosus.

One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is
20 systemic lupus erythematosus.

One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is acute
25 cutaneous lupus.

One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is
30 subacute cutaneous lupus erythematosus.

One embodiment provides a method of treating a disease, comprising

administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is chronic cutaneous lupus erythematosus.

5 One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said disease is discord lupus erythematosus.

10 One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said dose is orally administered.

15 One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said dose is administered once daily.

20 One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, wherein said dose is administered as 15 mg twice daily.

25 The 30 mg dose of the 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide can be administered as a single daily dose (q.d.), divided and administered as a 15 mg dose twice daily (b.i.d.), or divided and administered as a three 10 mg doses three times a day.

30 One embodiment provides a method of treating a disease, comprising administering to a human patient in need thereof, a dose of 30 mg daily of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, in combination with one or

more second agents. Examples of suitable second agents include corticosteroids, antimalarials such as hydroxychloroquine, and immunosuppressants such as azathioprine, mycophenolate mofetil, mycophenolic acid, or methotrexate.

Administration "in combination with" one or more further therapeutic agents includes simultaneous (concurrent) and consecutive (sequential) administration in any order. For example, the 30 mg dosage of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof and the second agent can be administered in either order (consecutive); or together with the 30 mg dosage of 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof.

One embodiment provides 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, for use in the treatment of lupus, wherein said 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof is administered on a dosage regimen of 30 mg daily.

One embodiment provides 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, for use in the treatment of cutaneous lupus erythematosus, wherein said 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof is administered on a dosage regimen of 30 mg daily.

One embodiment provides 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, for use in the treatment of systemic lupus erythematosus, wherein said 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof is administered on a dosage regimen of 30 mg daily.

One embodiment provides 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, for use in the treatment of acute cutaneous lupus, wherein said 2-(4-(2-(7,8-

dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl) acetamide or a pharmaceutically acceptable salt thereof is administered on a dosage regimen of 30 mg daily.

One embodiment provides 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, for use in the treatment of subacute cutaneous lupus erythematosus, wherein said 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof is administered on a dosage regimen of 30 mg daily.

One embodiment provides 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, for use in the treatment of chronic cutaneous lupus erythematosus, wherein said 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof is administered on a dosage regimen of 30 mg daily.

One embodiment provides 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide or a pharmaceutically acceptable salt thereof, for use in the treatment of discord lupus erythematosus, wherein said 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl) acetamide or a pharmaceutically acceptable salt thereof is administered on a dosage regimen of 30 mg daily.

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (mCLASI) allows the clinician to evaluate and score the overall severity of the disease state of the CLE patients. The CLASI-A score represents “CLE activity,” i.e., the overall severity of CLE dermatologic involvement as observed during patient examination at a clinic visit. The CLASI-D score represents “CLE damage,” i.e., the overall extent of scarring, pigmentary change, and alopecia, observed by the clinician.

The modified Cutaneous Lupus Erythematosus Disease Area and Severity Index (mCLASI) was used in this study and is based on the activity portions of CLASI that describe skin erythema, scale/hypertrophy and inflammation of the scalp. Damage, oral ulcers, and alopecia without scalp inflammation were excluded from the mCLASI analysis.

FIG. 4 shows the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) form.

Sources:

Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): An outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol* 2005;125:889 -94. Highlighted area indicates assessment by modified CLASI (mCLASI) criteria.

Bonilla-Martinez ZL, Albrecht J, Troxel, AB, et al. The Cutaneous Lupus Erythematosus Disease Area and Severity Index - A responsive instrument to measure activity and damage in patients with cutaneous lupus erythematosus. *Arch Dermatol* 2008;144(2):173-80.

Use of the modified CLASI assessment:

Merrill JT, Furie R, Werth VP, et al. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. *Lupus Science & Medicine* 2018;5:e000284, doi:10.1136/ lupus-2018-000284

EXAMPLE

A Study to Assess the Safety and Drug Levels of Afimetoran in Participants with Active Cutaneous Lupus Erythematosus (NCT04493541)

A randomized, double-blind, placebo-controlled safety trial to assess the effect of afimetoran treatment in participants with active cutaneous lupus erythematosus, either as cutaneous lupus erythematosus (CLE) or a manifestation of systemic lupus erythematosus (SLE), when added to background disease therapy. The study assessed a population of participants with lupus who have active cutaneous disease either as CLE or SLE with skin involvement to meet this goal.

The modified Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (mCLASI-A) was employed to measure the disease states of the patients at baseline and at 4 weeks intervals for a total period of 20 weeks.

A high mCLASI-A score indicates more severe disease. A low mCLASI-A score indicates less severe disease.

Study Design

FIG.1 shows the study design schematic of the double-blind, placebo-controlled clinical trial to assess the effect of afimetoran treatment in patients with active cutaneous lupus, either as cutaneous lupus erythematosus or a manifestation of systemic lupus erythematosus, when added to background disease therapy.

Male and female patients, ages 18 to 65, inclusive, with a diagnosis of CLE or SLE with cutaneous involvement, modified Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (mCLASI-A) score ≥ 6 , and at least 1 skin lesion amenable to biopsy.

10 Inclusion Criteria:

- a) Must have one of following diagnoses: i) Meet European League Against Rheumatoid (EULAR)/American College of Rheumatology 2019 Classification Criteria for systemic lupus erythematosus (SLE) OR ii) Biopsy-proven acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), or discoid lupus erythematosus (DLE): Participants without a concurrent SLE diagnosis are eligible b) Active cutaneous lupus disease, defined as a modified Cutaneous Lupus Erythematosus Disease Area and Severity Index- Activity (mCLASI-A) score ≥ 6 c) Active cutaneous lupus skin lesion(s) amenable to biopsy.
- 15 Women of childbearing potential (WOCBP) and men must agree to follow instructions for method(s) of contraception, if applicable.
- 20

Exclusion Criteria:

- Active severe or unstable neuropsychiatric SLE
- Active, severe Lupus Nephritis (LN)
- Any British Isles Lupus Assessment Group (BILAG) A or B, unless within the constitutional, musculoskeletal and/or mucocutaneous domains.
- 25 Other protocol-defined inclusion/exclusion criteria apply.

The EULAR/ACR 2019 Classification Criteria for SLE will be administered to all participants at baseline to understand if a skin biopsy is needed for study qualification, i.e., if a participant does not meet criteria for SLE, CLE must be proven by biopsy; and to ensure the correct diagnosis (CLE vs. SLE with active cutaneous disease) at entry, so that the clinical characteristics of the selected population can be described and the study results may be interpreted and generalized appropriately.

30

Approximately 24 participants will be randomized. Sentinel dosing will be used for the first 2 participants. Review of the blinded safety data for the sentinel subset will be conducted after the 2 participants have received at least 21 days of dosing. While dosing continues for the sentinel participants, there will be no further enrollment until the review is completed and the safety is deemed acceptable.

- Overall study participation, including screening for eligibility, will be approximately 24 weeks divided into 3 periods:
- Screening period: up to 4 weeks, following informed consent, during which participants will undergo all screening procedures; if all screening procedures cannot be completed within 4 weeks, the screening period may be extended in consultation with and approval by the Medical Monitor.
 - Treatment period: 16 weeks (from dosing through Week 16), during which participants will receive either oral afimetoran 30 mg or placebo once daily (QD).
 - Follow-up period: 4 weeks (Week 17 through Week 20), during which no study treatment is provided.

The study design schematic is shown in Figure 1.

Objectives and Endpoints:

Objective	Endpoint
Primary	
To assess the safety and tolerability of BMS-986256 in study participants with CLE receiving standard of care treatment	- Adverse events (AEs and SAEs) - Laboratory test abnormalities - Clinically significant changes in physical examination findings, vital signs, and ECG
Secondary	
To determine the PK of BMS-986256 and its metabolite, BMT-271199, in participants with CLE	C_{max}, T_{max}, C_{trough}, and AUC(TAU) of BMS-986256 and metabolite BMT-271199
Tertiary/Exploratory	
- To assess the effects of BMS-986256 on disease and target pathways - To assess the effects of BMS-986256 through ex vivo TE assays in participants with CLE	- Changes in levels of biomarkers (RNA, proteins, etc.) associated with lupus or the TLR7/8 pathway - Change in IL-6 levels using Tru-Culture assays

• To assess the effect of BMS-986256 on active cutaneous lupus	• Change in within-participant CLASI-Activity score from baseline
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AE = adverse event; AUC(TAU) = area under the concentration-time curve over the dosing interval; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLE = Cutaneous Lupus Erythematosus; Cmax = maximum observed plasma concentration; Ctrough = trough observed plasma concentration; ECG =
5 electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event; TE = target engagement; TLR = Toll-like receptor; Tmax = time to maximum concentration

After successfully completing screening, eligible participants will be admitted to the clinical research unit (CRU) one day prior to study treatment administration (Day -1),
10 at which time they will be randomized to receive afimeteran 30 mg or placebo QD. Randomization will be performed in blinded fashion on Day -1 or Day 1, and the ratio of BMS-986256 to placebo will be 2:1. Participants will be discharged on Day 2 after the 24 hour PK sample collection and all scheduled assessments are completed.

Following discharge on Day 2, participants will be ambulatory until they are
15 admitted to the CRU on Day 112 for follow-up evaluation of PK of afimeteran. They will be discharged on Day 114 after all study assessments, including PK sample collection, are complete.

Safety, including all adverse events, changes in physical examination (PE) findings, laboratory test results, and electrocardiograms, will be assessed from dosing
20 through Week 20.

Evaluation of PK, biomarkers, and effects on cutaneous disease will be assessed at various timepoints throughout the study by PE, blood and skin sampling, clinical laboratory testing, and biomarker measurements.

While admitted to the CRU, the daily study drug doses (afimeteran) will be
25 administered in the morning under observation. While the participants are on furlough from the CRU, they will record drug administration and use of any steroid medications (type and total daily dose) in a diary that will be provided to each participant. Participants will bring the diary with them when returning to the CRU, and the Investigator or designee will record the dosing information in the Case Report Form.

30 The study dosage is 30 mg QD administered orally as a 30 mg capsule.

Results

Thirteen patients were enrolled in the trial and randomized to two groups: 8 patients receiving afimetoran 30 mg once daily and 5 patients receiving placebo once daily.

Baseline Demographics Summary:

Demographics	Placebo (n=5)	Afimetoran 30 mg (n=8)	Total (n = 13)
Age, years, mean, (SD)	51.2 (12.4)	46.0 (11.1)	48.0 (11.4)
Age Categorization 18-64	5 (100.0)	8 (100.0)	13 (100.0)
Female, n (%)	4 (80.0)	7 (87.5)	11 (84.6)
Male, n (%)	1 (20.0)	1 (12.5)	2 (15.4)
Body Mass Index (Kg/m ²), (SD)	25.3 (4.0)	26.5 (4.8)	26.1 (4.4)
Weight, kg, mean, (SD)	74.3 (14.5)	76.9 (16.6)	75.9 (15.2)
Race			
White, n (%)	5 (100.0)	8 (100.0)	13 (100.0)
Smoking Status (Tobacco)			
Former	1 (20.0)	1 (12.5)	2 (15.4)
Current	2 (40.0)	6 (75.0)	8 (61.5)

In this trial, there were no demographic differences between the active and placebo arm except for smoking status, whereby a larger number of patients on active therapy were current tobacco users.

	Placebo n=5	Afimetoran n=8	Total n=13
Time from first diagnosis of CLE/SLE to randomization in years, mean, (SD)	8.1 (4.6)	11.8 (8.7)	10.4 (7.4)
Median	9.1	10.6	9.1

	Placebo n=5	Afimetoran n=8	Total n=13
Min, Max	2.2, 14.4	1.7, 26.2	1.7, 26.2
Primary Diagnosis n%			
CLE	2 (40.0)	5 (62.5)	7 (53.8)
SLE Per EULAR/ACR 2019 classification criteria*			
Fever (%)	0	1 (12.5)	1 (7.7)
Leukopenia (%)	1 (20.0)	0	1 (7.7)
Thrombocytopenia (%)	1 (20.0)	0	1 (7.7)
Autoimmune Hemolysis (%)	1 (20.0)	0	1 (7.7)
Seizure (%)	1 (20.0)	0	1 (7.7)
Non-scarring Alopecia (%)	2 (40.0)	3 (37.5)	5 (38.5)
Oral Ulcers (%)	2 (40.0)	0	2 (15.4)
Subacute or Discoid Lupus (%)	5 (100.0)	6 (75.0)	11 (84.6)
Acute Cutaneous Lupus (%)	2 (40.0)	5 (62.5)	7 (53.8)
Pleural or Pericardial Effusion (%)	3 (60.0)	0	3 (23.1)
Joint Involvement (%)	4 (80.0)	2 (25.0)	6 (46.2)
Proteinuria >0.5gm/24 hour (%)	1 (20.0)	0	1 (7.7)
Renal Biopsy class III or IV lupus nephritis (%)	1 (20.0)	0	1 (7.7)
Low C3 or Low C4 (%)	2 (40.0)	1 (12.5)	3 (23.1)
Low C3 and Low C4 (%)	1 (20.0)	0	1 (7.7)
Anti-DSDNA Antibody or Anti-Smith Antibody (%)	4 (80.0)	3 (37.5)	7 (53.8)
Anti-Cardiolipin Antibodies, Anti-2gp1 Antibodies or Lupus Anticoagulant (%)	0	0	0

	Placebo n=5	Afimetoran n=8	Total n=13
mCLASI-A score mean			
Mean (SD)	11.0 (3.0)	14.9 (7.3)	13.4 (6.1)
Median	9.0	13.5	12.0
Min, Max	9, 16	6, 25	6, 25
CLASI-A Score			
Mean (SD)	11.6 (2.7)	15.0 (7.2)	13.7 (6.0)
Median	11.0	13.5	12.0
Min, Max	9, 16	6, 25	6, 25
CLASI-A Score Category 1			
<10 (%)	1 (20.0)	2 (25.0)	3 (23.1)
>=10 (%)	4 (80.0)	6 (75.0)	10 (76.9)
CLASI-A score Category 2			
0-9 Mild (%)	1 (20.0)	2 (25.0)	3 (23.1)
10-20 Moderate (%)	4 (80.0)	4 (50.0)	8 (61.5)
21-70 Severe (%)	0	2 (25.0)	2 (15.4)
CLASI-D Score			
Mean (SD)	5.6 (1.6)	7.6 (9.3)	6.8 (7.0)
Median	6.0	2.0	5.0
Min, Max	4, 8	0, 25	0, 25
Positive Autoantibodies			
ANA (1:>=80) (%)	5 (100.0)	8 (100.0)	13 (100.0)
Anti-Smith (>=7) (%)	1 (20.0)	0	1 (7.7)
Anti-DSDNA (>=25) (%)	3 (60.0)	3 (37.5)	6 (46.2)

	Placebo n=5	Afimetoran n=8	Total n=13
Anti-Ro (SSA) (≥ 7) (%)	1 (20.0)	4 (50.0)	5 (38.5)

Concomitant Medications:

Two patients in the afimetoran arm were on systemic antimalarials on day 1.

None were taking oral corticosteroids in the afimetoran arm.

- 5 In the placebo arm, 4 patients (80%) were on systemic antimalarials and 3 patients (60%) were on oral corticosteroids on day 1.

Patient Disposition

- 10 Twelve patients completed the 16 weeks of treatment. One patient discontinued from the afimetoran arm after 6 weeks of treatment due to symptomatic COVID-19.

FIG. 2 shows the adjusted mean change in the CLASI-A score from baseline for (i) patients dosed with 30 mg QD afimetoran and (ii) for patients dosed with placebo for 16 weeks, with continued evaluation for a 4 week follow-up period.

	Afimetoran 30 mg QD		Placebo		
Week	n	Mean Change in CLASI-A Scores from Baseline (SD)	n	Mean Change in CLASI-A Scores from Baseline (SD)	Difference in adjusted mean change from baseline between afimetoran vs. placebo (SD)
0 (baseline-start)	8	0	5	0	0
4	8	-5.8 (1.1)	5	-2.2 (1.4)	-3.5 (1.8)
8	7	-7.2 (1.4)	5	-2.6 (1.7)	-4.6 (2.3)
12	7	-7.4 (1.3)	5	-2.8 (1.5)	-4.6 (2.0)
16 (end of treatment)	7	-7.6 (1.2)	5	-1.2 (1.4)	-6.4 (1.8)
20 (4 week follow-up)	5	-6.6 (1.5)	5	-1.4 (1.7)	-5.1 (2.3)

follow-up period)					
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n = number of patients

FIG. 3 shows the mean change in the CLASI-A score from baseline for (i) patients having baseline CLASI-A scores of 10-20 dosed with 30 mg QD afimetoran and (ii) patients dosed with placebo for 16 weeks, with continued evaluation for a 4 week follow-up period.

As shown in FIG.2 and FIG.2, patients treated with 30 mg QD of afimetoran, showed larger decreases in their m-CLASI-A scores compared to patients receiving the placebo, indicating treatment with 30 mg QD of afimetoran decreased the severity of CLE in this trial. Additionally, the benefit was maintained for the 4 week period after the last dose was administered (weeks 16-20).

A clinical benefit was observed for patients treated with 30 mg QD afimetoran in this trial.

CLAIMS

What is claimed is:

- 5 1. A compound or a pharmaceutially-acceptable salt thereof, for use in the treatment of lupus in a human subject, comprising administrating a dose of 30 mg of said compound to said human subject, wherein said compound is 2-(4-(2-(7,8-dimethyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-isopropyl-1H-indol-5-yl)piperidin-1-yl)acetamide.
- 10 2. The compound according to claim 1 wherein said lupus is cutaneous lupus erythematosus.
3. The compound according to claim 1 wherein said lupus is systemic lupus erythematosus.
- 15 4. The compound according to claim 3 wherein said lupus is acute cutaneous lupus.
5. The compound according to claim 1 wherein said lupus is chronic cutaneous lupus erythematosus or discord lupus erythematosus.
- 20 6. The compound according to claim 1 wherein said lupus is subacute cutaneous lupus erythematosus.
7. The compound according to claim 1 wherein said dose is orally administered.
- 25 8. The compound according to claim 1 wherein said dose is administered once daily.
9. The compound according to claim 1 wherein said dose is orally administered once daily.
- 30 10. The compound according to claim 1 wherein said human subject is administered a second agent selected from corticosteroids, antimalarials, and immunosuppressants.

11. The compound according to claim 8 wherein said second agent is an antimalarial or a corticosteroid.