channel activated over a discrete temperature range, cumulatively spanning from noxious cold to noxious heat. TRPM8 belongs to the melastatin subgroup of the TRP channel superfamily. TRPM8 is sensitive to cold temperature and menthol, and thus is also called the cold and menthol receptor-1 (CMR-1). McKemy et al., "Identification of a cold receptor reveals a general role for TRP channels in thermosensation," Nature, Vol. 416, No. 6876, pp. 52-58 (2002). TRPM8 is known to be stimulated by cool to cold temperatures (8 to 28°C) as well as by chemical substances such as menthol and Icilin.

[0012]

TRPM8 is located on primary nociceptive neurons (A-δ and C-fibers) and is also modulated by inflammation-mediated second messenger signals. Abe et al., “Ca2±-dependent PKC activation mediates menthol-induced desensitization of transient receptor potential M8,” Neuroscience Letters, Vol. 397, No. 1-2, p. 140-144 (2006); Premkumar et al., “Downregulation of Transient Receptor Potential Melastatin 8 by Protein Kinase C-Mediated Dephosphorylation,” The Journal of Neuroscience, Vol. 25, No. 49, p. 11322-11329 (2005). TRPM8 is highly expressed in sensory neurons of the trigeminal and dorsal root ganglia. TRPM8 is also known to be expressed in the brain, lung, bladder, gastrointestinal tract, blood vessels, prostate, and immune cells.

[0013]

TRPM8 antagonists and their use in treatments have been disclosed in previous patent filings (see, e.g., U.S. Patent No. 8,987,445; U.S. Patent No. 9,096,527; International Patent Publication No. WO 2014/042238). These disclosures report uses such as for the treatment of chronic pain (e.g., neuropathic pain), urologic disease, gastrointestinal disease, and cephalalgia. None of these disclosures, however, describe treating or preventing vasomotor symptoms with a TRPM8 antagonist.

Solution to Problem

[0014]

The present disclosure is directed to a method for treating or preventing vasomotor symptoms in a subject in need thereof, comprising administering to the subject a lower dose of Compound A or a pharmaceutically acceptable salt thereof.

[0015]

The present disclosure is also directed to a composition comprising a lower dose of Compound A or a pharmaceutically acceptable salt thereof for treating or preventing vasomotor symptoms in a subject and a pharmaceutically acceptable carrier.

[0016]

The accompanying drawings are incorporated in and constitute a part of this specification.

Brief Description of Drawings

[0017]

[Fig. 1]
Figure 1 is a schematic diagram illustrating an integrated model of human thermoregulation (hTR).
[Fig. 2]
Figure 2 shows the study design of a planned Phase I, randomized, double-blind, placebo-controlled study to assess the safety, tolerability and pharmacokinetics of multiple doses of Compound A as described herein in female subjects experiencing vasomotor symptoms.
[Fig. 3]
Figure 3 shows a change in Mean observed value in Vasomotor Symptoms (VMS) frequency over time within 24-hour after the first dose during the 14 days of treatment period. In the Figure 3, each of the triangle or square symbol shows the result for 5 mg of Compound A or Placebo, respectively.
[Fig. 4]
Figure 4 shows a change from baseline in core body temperature over time within 24 hour post-dose on the Visit Day 1 or 7 in placebo (Figure 4A) or 5 mg administered group (Figure 4B). In each of Figures 4A and 4B, each of square or open circle symbol shows the results for 5 mg of Compound A or Placebo on the Visit Day 1 or 7, respectively.
[Fig. 5]
Figure 5 shows a change from baseline in core body temperature over time within 24 hour post-dose on the Visit Day 1 or 7 in 20mg (Figure 5A) or 50 mg (Figure 5B) administered group. In each of Figures 5A and 5B, each of square or open circle symbol shows the results on the Visit Day 1 or 7, respectively.
[Fig. 6]
Figure 6 shows a Study design for a randomized, double-blind, placebo-controlled study to assess the effect of 4-({(4-cyclopropylisoquinolin-3-yl)[4-(trifluoromethoxy)benzyl]amino}sulfonyl)benzoic acid or a pharmaceutically acceptable salt thereof on the frequency and severity of vasomotor symptoms in postmenopausal women.
[Fig. 7]
Figure 7 shows a change in core body temperature over time within 24 hour pre-dose and post dose on Visit 1, 7, 10 and 14 in 5 mg administered group. In this Figure 7, filled circle symbol shows the results for all dosing groups of compound A combined into one single curve on baseline day (Visit day -1), and each of open diamond shape, open square, open circle and cross symbol shows the results for 5mg of compound A on Visit day 1, 7, 10 and 14, respectively.
[Fig. 8]
Figure 8 shows pharmacometrics fructification in virtual clinical trials, and specifically, the simulated pharmacological effects on multiple dose of 5, 10, 20 and 50 mg of Compound A at Day 1 and Day 14. In this Figure 8, upper, middle and lower panels show the changes in Mean simulated value of core body temperature, skin blood flow rate, as a measurable value related with efficiency of heat transfer from core body, and Vasomotor Symptoms (VMS) frequency over time within 24-hour, respectively.

Description of Embodiments

[0018]
DESCRIPTION
It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. It should also be understood that the present disclosure is not

all aspects of thermoregulation.

[0034]

The effect of TRPM8 inhibition or blockade is ultimately manifested through the ability to control various physiological systems in order to better facilitate heat transfer through multiple compartments, with effects on heat within those predicted by the laws of thermodynamics.

[0035]

Doses of scalable and potentially dynamically administered amounts of a TRPM8 inhibitor or blocker, delivered by any of several routes, allows core and peripheral temperature to be maintained or controlled acutely, and over time, in order that the circadian temperature curve can be continuously and dynamically modified. This process of acute, continuous, and dynamically modifiable temperature is dependent of the ability of the thermoregulatory system to variously sense modifications in the intensity, duration, and temporality of TRPM8 signaling. In the average patients with vasomotor symptoms, there is the descriptive flattening of the normal and expected circadian temperature rhythm and cycle. Specifically, the range of normal diurnal temperature change is narrowed.

[0036]

Four thermal compartments are of primary importance. 1. There is an energy and heat generating compartment. 2. There is a core body (head, thorax, and abdomen) compartment. 3. There is a peripheral skin compartment.4. There is an external environmental compartment.

An integrated model of human thermoregulation (hTR) can be understood from elements described in a heat transfer model of human body (modified Gagge's Two-node model, ASHRAE Transactions, 77: 247-62. (1971); Metabolic heat production

model with circadian rhythm, J. Pharmacol. Exp. Ther., 317: 209-19. (2006)) in the context of physiology outlined in a neuronal thermoregulation model (Temperature, 1: 142-9. (2014)).This model can be pictorially represented in Figure 1.

[0037]

In healthy normal function, a heat cycle exists by which heat moves sequentially through these compartments, and by which heat accrues and dissipates in a 24 hour rhythm. Heat is normally dissipated from the central compartment to the peripheral skin, and then to the environment, with a typical evening into night drop in core temperature, followed by accrual and warming before waking. When this normal cycle is disturbed, and heat cannot be efficiently moved to the peripheral skin and dissipated to the external compartment, temperature rises, and non-preferred paths for heat dissipation are recruited. When the face, head, chest, and other areas are recruited acutely, blood is shifted to the surface of these areas, and heat is dissipated to the external compartment in an urgent and in an inefficient manner via surface vasodilatation and resulting sweating. This process is subjectively recognized as a “hot flash”, and is the equivalent of an “emergency relief valve” for accrued body heat. The heat that is dissipated in the burst of a “hot flash” is insufficient to restore the normal physiologic circadian temperature curve, but does allow for return to a functional homeostasis. It is a “short term” fix.

[0038]

Blockade of TRPM8 can be scaled therapeutically to restore homeostasis. Heat production is reduced, which is associated with a greatly lessened need for inefficient heat release via a “hot flash”, hence, a pharmacologic homeostasis. Blockade can also be scaled to restore a more normally physiologic temperature curve that may be predicted to produce additional cardiovascular and sleep benefits.

$$M_c = \begin{cases} M_{day} & \text{for } t \in \{[0, t_{night}], [t_{day}, t_{night} + 24], \dots\} \\ M_{night} & \text{for } t \in \{[t_{night}, t_{day}], [t_{night} + 24, t_{day} + 24], \dots\} \end{cases}$$

$$\frac{dM}{dt} = -k_m \cdot (M - M_c)$$

In summary, this model provides support for an effect of Compound A to provide a beneficial effect on reducing vasomotor symptoms that is based on sensory integration and homeostatic reduction in thermal heat generation, rather than a primary effect to reduce core body temperature. The model supports a predicted optimal human clinical effect at a dose of 10 mg or less per day (see Figure 8).

[0045]
The present disclosure is directed to a method for treating or preventing vasomotor symptoms in a subject in need thereof, comprising administering to the subject a lower dose of Compound A or a pharmaceutically acceptable salt thereof. In some embodiments, the vasomotor symptom is hot flashes. In some embodiments, the subject is a human. The subject may be male or female. It is envisioned that the methods will be used for subjects that are prone to having, are having, or are expected to have vasomotor symptoms, such as hot flashes. The subject in need thereof may suffer from or anticipate suffering from vasomotor symptoms associated with menopause, with the symptoms or effects of a medical condition, with the side effects of a treatment for a medical condition, or with any other trigger or cause of vasomotor symptoms.

[0046]
Subjects include, but are not limited to, menopausal women, subjects who are taking or anticipate taking anti-estrogen drugs (such as tamoxifen or aromatase inhibitors), subjects who are anticipating or have gone through surgery, or subjects having or anticipating having any other condition or undergoing or anticipating undergoing any other treatment that results in changes in hormone levels.

[0047]
Subjects further include, but are not limited to, oncology patients. For example, subjects may include those who are anticipating, are undergoing, or have undergone cancer treatment, such as through surgery or radiation therapy. For example, subjects may include those who are anticipating, are undergoing, or have undergone gonadal ablative therapy or gonadal hormonal suppressive therapy. Where the subject is undergoing or has undergone cancer treatment, the cancer treatment can be a treatment which affects the hormone levels of the subject, for example, hormonal therapy treatment for breast cancer, ovarian cancer and prostate cancer. Examples of hormonal therapies for cancers include: selective estrogen receptor antagonists including tamoxifen (Nolvadex (registered trademark)), raloxifene (Evista (registered trademark)), lasofoxifene (Fablyn) and toremifene (Fareston (registered trademark));

polyvinylpyrrolidone, etc.), an excipient (e.g., lactose, sugar, corn starch, sorbitol, etc.), a lubricant (magnesium stearate, talc, polyethylene glycol, etc.), a disintegrator (e.g., potato starch, etc.) and the like, which are pharmaceutically acceptable. When the composition is used as an injection solution or an infusion solution, it can be formulated by using, e.g., distilled water for injection, physiological saline, an aqueous glucose solution, etc. In certain embodiments, the present disclosure includes a use of a lower dose of Compound A or a pharmaceutically acceptable salt thereof or a composition comprising the same as an active ingredient for treating or preventing vasomotor symptoms in a subject in need thereof. Also in certain embodiments, the present disclosure includes a use of a lower dose of Compound A or a pharmaceutically acceptable salt thereof in a preparation of a medicament for treating or preventing vasomotor symptoms.

[0055]
It is to be understood that the foregoing description as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

Examples

[0056]
Example 1: Phase I, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of Multiple Doses of Compound A in Female Subjects Experiencing Vasomotor Symptoms

[0057]
Study Design: This was a Phase Ib, randomized, double blind, placebo controlled study. The study design is illustrated in Figure 2. Following the initial Screening visit, eligible subjects was given an actigraphy event monitor (watch) to record episodes of flashing as Vasomotor symptoms (VMS) events during a period of 2 weeks during Screening, in order to confirm VMS eligibility criteria ($\geq$7 VMS/day on average during 2 weeks). Subjects may be required to return to the site during the Screening period to read or exchange the actigraphy event monitor. Subjects deemed eligible following review of VMS data were invited to attend the Clinical research unit (CRU) for one residential period of 16 days duration, including 14 days of Investigational Medicinal Product (IMP) administration. Subjects were admitted to the CRU 1 day prior to dosing (Day -1). No medication was administered on Day -1. On Day 1, subjects who meet the study eligibility criteria were randomized to receive one dose level of either Compound A (6 subjects) or a matching placebo (2 subjects) in a double-blind manner. Randomized treatment was administered once nightly, starting on Day 1, for a total duration of 14 days.

[0058]
The anticipated dose levels of Compound A to be administered are 50 mg for Cohort 1, 20 mg for Cohort 2 and 5 mg for Cohort 3. Progression to the next dose level and selection of the dose to be administered in Cohort 2 and Cohort 3 is based on emerging safety and

tolerability data and available core body temperature data from the preceding dose cohort. If the dose escalation stopping criteria are met, then the dose for the subsequent cohort is reduced. The lowest potential dose to be assessed is 5 mg and the maximum dose for the study does not exceed 50 mg. The three cohorts are dosed sequentially with a fourth additional cohort being dosed, if necessary, to investigate other dose levels.

[0059]

Subjects is discharged from the CRU after all 24 hour post-dose procedures are completed in the evening on Day 15 or in the early morning on Day 16 if deemed more convenient by the subjects, and return for a follow up visit on Day 21. The overall duration of participation for each subject is a maximum of 63 days (from the initial Screening visit on Day -42 to follow-up on Day 21).

[0060]

Endpoints:

Primary Assessments

· Safety and tolerability: Vital signs, ECG parameters, Clinical laboratory assessments, Physical examination, Adverse events and Assessment of overall tolerability

Secondary Assessments

· Pharmacokinetics assessments

Core body temperature assessment

· Change from baseline in core body temperature.

Exploratory assessments

· Frequency of VMS and sleep assessments.

· Mood and subjective sleep quality

[0061]

Five (5) mg of Compound A was administered to the female subjects experiencing Vasomotor Symptoms (VMS), and as the above-mentioned assessments, a Frequency of VMS and a Core body temperature assessment were examined.

For the Frequency of VMS, a change in Mean observed value in Vasomotor Symptoms (VMS) frequency was observed over time within 24-hour after the first dose during the 14 days of treatment period. Here a moderate VMS and a severe VMS were counted as a VMS frequency. The mean observed value in VMS frequency on the each Visit Days are summarized in Table 2. Pattern changes of the core body temperature at 1, 7, 10 and 14 days after administration of 5 mg of Compound A were shown in Figure 7.

[Table 2]

VISIT Day	Mean Observed Value	
	Placebo	Compound A
Baseline	14.8	14.5
Day 1	13.5	9.7
Day 2	11.3	7.2
Day 3	9.2	6.3
Day 4	9.3	5.3
Day 5	9.0	8.0
Day 6	8.3	6.3
Day 7	9.8	4.7
Day 8	7.8	3.7
Day 9	7.3	4.5
Day 10	8.3	3.2
Day 11	8.7	3.7
Day 12	6.5	3.2
Day 13	7.0	3.2
Day 14	8.3	4.8

[0062]

Each of the Mean Observed Values in VMS frequency for Placebo and Compound A were plotted as shown in Figure 3. In Figure 3, each of the triangle or square symbol shows the result for 5 mg of Compound A or Placebo, respectively. As shown in Figure 3, Compound A reduced the frequency of VMS significantly and Compound A had an immediate effect because the reduction effect of VMS frequency was shown at during the first night of active drug therapy or later, namely, within a few days of administration, compared to estrogen or selective Serotonin Reuptake Inhibitor such as Paroxetine.

[0063]

For the Core body temperature assessment, a change from baseline in core body temperature of the subjects was observed over time within 24 hours post-dose on the Visit 1 or 7. The test results of placebo (Figure 4A) and 5mg administered group (Figure 4B) are shown in Figure 4. The test results of 20mg (Figure 5A) and 50mg (Figure 5B) administered groups are shown in Figure 5. Each of square or open circle symbol shows the results on the Visit Day 1 or 7, respectively. As shown in Figures 4 and 5, Compound A showed no significant reduced the core body temperature in 5 mg administered group like placebo, in comparison with each administered group given 20 mg and 50 mg, respectively.

[0064]

Example 2: Phase II, A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effect of Compound A on the Frequency and Severity of Vasomotor Symptoms in Postmenopausal Women Subjects Experiencing Vasomotor Symptoms

[0065]

STUDY DESIGN

This was a Phase II randomized, double-blind, placebo-controlled study for dose selection. Subjects meeting eligibility criteria were enrolled in a 2-week single blind Placebo Run-in period. All eligible subjects received single-blind placebo daily before bedtime. Following

the Placebo Run-in period, subjects meeting eligibility criteria entered the 12-week, placebo controlled Double-blind Treatment period. The Double blind Treatment period had 4 arms including: placebo and Compound A 1, 5, and 10 mg. A single daily dose of study medication was administered before bedtime. An End of Study (EOS) Follow-up visit was conducted by phone for safety follow up 30 days after the end of the Double blind Treatment period. Total duration was 20 weeks, inclusive of the Screening and Follow up periods (see Figure 6).

[0066]
A planned interim assessment for safety, and a planned interim analysis for efficacy (futility) and safety was conducted during the study; enrollment proceeded without interruption.

· Interim assessment for safety was conducted when approximately 25% of subjects had completed Week 12 in the Double-blind Treatment period.

· Interim analysis for efficacy (futility) and safety was conducted when approximately 50% of subjects had completed Week 12 in the Double-blind Treatment period.
The primary endpoint was evaluated at Weeks 4 and 12.

[0067]
Endpoints: Co-Primary Efficacy Endpoints

· Change from baseline in the average daily frequency of moderate to severe VMS, defined as the sum of the number of moderate to severe VMS during 1 week divided by number of days with data. The daily score here and below were average scores from a 7-day period. Details were defined in the Statistical Analysis Plan (SAP).

· Change from baseline in the average daily severity score of mild to severe VMS. Baseline VMS severity score was defined as (2xFmo + 3xFse)/(Fmo + Fse), and VMS severity score for a specific week during the double-blind treatment period was defined as (1xFmi + 2xFmo + 3xFse)/(Fmi + Fmo + Fse), where Fmi, Fmo, and Fse are the daily frequencies of mild, moderate, and severe VMS, respectively, during each applicable study week.
Co-primary endpoints were evaluated at Week 4 and Week 12.

[0068]
Secondary Efficacy Endpoints

· Proportion of responders at Weeks 4 and 12 (i.e., subjects with cutoff number * or greater reduction in the average daily frequency of moderate and severe VMS compared to baseline)

· Time to response, defined as time (in weeks) from randomization to the first time the subject meets responder criteria (i.e., cutoff number * or greater reduction from baseline in the average daily frequency of moderate and severe VMS)
*Note: The cutoff was calculated using anchor-based method. The cutoff number