

METHOD OF IMPROVING SLEEP

CROSS-REFERENCE TO RELATED APPLICATIONS

5 This application claims the benefit of co-pending US Provisional Patent Application Serial No. 62/805,057, filed 13 February 2019, which is hereby incorporated herein as though fully set forth.

BACKGROUND

Circadian Rhythm and Sleep

10 The timing of human sleep is governed by two regulatory processes. The first—the sleep homeostat—preserves the balance between waking hours, during which fatigue accumulates, and sleeping hours, which are restorative and prepare an individual for the next episode of wakefulness. The second—an endogenous rhythm regulated by the circadian pacemaker in the suprachiasmatic nucleus (SCN)—counteracts the
15 effects of fatigue with signals emanating from the circadian pacemaker. In the evening, when the homeostatic drive for sleep is high, wakefulness-promoting signals peak. Then, as an individual approaches bedtime, output from the SCN subsides and sleep ensues.

20 Sleep-wake disturbances may result from a misalignment of the individual's circadian pacemaker and his/her scheduled sleep time. Such a disturbance is classified as a circadian rhythm sleep disorder (CRSD) and includes various sub-types, including shift work sleep disorder (SWSD), delayed sleep-wake phase disorder (DSWPD), jet lag, and non-24-hour sleep-wake disorder (Non-24).

25 Several circadian clock genes have been identified. These include the cryptochrome circadian clock 1 (CRY1), cryptochrome circadian clock 2 (CRY2), period 1 (PER1), period 2 (PER2), and period 3 (PER3) genes. Variations in these genes may lead to differences in circadian and sleep/wake cycle phenotypes.

30 Mutation of the CRY1 gene, for example, has been associated with delayed sleep wake phase disorder (DSWPD), a form of insomnia in which sleep onset and offset are shifted to later times. DSWPD is the most commonly diagnosed type of CRSD, estimated to occur in 0.2%–10% of the general population. Currently, the pathophysiology of DSWPD remains obscure with suspected causes including a differential susceptibility of an individual's circadian clock to environmental
35 entrainment cues such as the light/dark cycle and altered properties of the oscillator affecting its period length. A particular CRY1 allele, rs184039278, has been

associated with familial DSPD. This gain-of-function CRY1 variant causes reduced expression of key transcriptional targets and lengthens the period of circadian molecular rhythms, providing a mechanistic link to DSWPD symptoms. In animal studies, expression of this protein resulted in an increase of approximately half an hour in the circadian period.

Melatonin

Melatonin has a distinct circadian pattern. In a healthy nocturnal-sleeping individual, circulating melatonin concentration is low during the waking day, shows a distinct rise about one to three hours before bedtime, remains high throughout sleep, and decreases close to wake-up time. The onset, offset, and midpoint are often used to mark the phase of the endogenous melatonin rhythm. Measurement of circadian phase such as the dim light melatonin onset (DLMO) improves diagnosis and treatment of sleep wake disorders. DLMO may be measured to collect a reliable, non-invasive, circadian phase marker. In DSWPD patients, consistent with a phase delay, entrained DLMO occurs significantly later, well after the time expected in a subject of normal chronotype

Tasimelteon

Tasimelteon is a circadian regulator that acts as a melatonin receptor agonist with selective activity at Melatonin, Type 1 (MT₁) and Type 2 (MT₂), receptors. Tasimelteon (HETLIOZ[®]) has received market authorization for the treatment of the Circadian Rhythm Sleep-Wake Disorder, Non-24, in people over 18 years of age by the Food and Drug Administration and specifically in the totally blind from the European Medicines Agency.

Clinical studies have demonstrated the efficacy of tasimelteon to phase advance the circadian timing system (CTS) and to improve nighttime sleep and decrease daytime sleep, as well as to speed the synchronization of the body clock in totally blind patients with Non-24.

SUMMARY

In a first aspect, the invention provides, in a method of treating patients with a circadian rhythm sleep disorder (CRSD) consisting essentially of administering to said patients an amount of tasimelteon effective to treat said disorder, the improvement comprising: selecting a patient for said treatment by identifying that

said patient has a cryptochrome circadian clock 1 (CRY 1) genotype associated with said disorder.

In another aspect, the invention provides a method for treating a patient exhibiting one or more symptoms of a circadian rhythm sleep disorder, which comprises:

5 identifying that said patient has a cryptochrome circadian clock 1 (CRY 1) genotype associated with said disorder, and administering an amount of tasimelteon to said patient effective to treat said disorder.

In still another aspect, the invention provides a method for improving one or more sleep parameters in an individual, the method comprising: identifying that said

10 individual possesses a variant of the cryptochrome circadian clock 1 (CRY 1) genotype associated with a circadian rhythm sleep disorder (CRSD); and administering to said individual daily, at a time proximately before the individual's established bedtime, an amount of tasimelteon effective to improve one or more sleep parameters in said individual.

15 In yet another aspect, the invention provides, in a method of treating patients with a circadian rhythm sleep disorder (CRSD) consisting essentially of administering to said patients an amount of tasimelteon effective to treat said disorder, the improvement comprising: selecting a patient for said treatment by identifying that said patient has a period 1 (PER1) genotype associated with said disorder.

20 In another aspect, the invention provides a method for treating a patient exhibiting one or more symptoms of a circadian rhythm sleep disorder, which comprises: identifying that said patient has a period 1 (PER1) genotype associated with said disorder, and administering an amount of tasimelteon to said patient effective to treat said disorder.

25 In still another aspect, the invention provides a method for improving one or more sleep parameters in an individual, the method comprising: identifying that said individual possesses a variant of the period 1 (PER1) genotype associated with a circadian rhythm sleep disorder (CRSD); and administering to said individual daily, at a time proximately before the individual's established bedtime, an amount of

30 tasimelteon effective to improve one or more sleep parameters in said individual.

BREIF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows total sleep time (TST) data for two groups of individuals treated with tasimelteon according to the invention—wild type (WT) individuals who do not

35 possess the rs184039278 cryptochrome circadian clock 1 (CRY 1) allele and mutant

type (MT) individuals who do possess at least one copy of the rs184039278 CRY1 allele.

FIG. 2 shows TST during the final third of the night for WT individuals (0/0) who do not possess the rs112474322 PER1 allele and MT individuals who do possess a copy of the rs112474322 allele.

DETAILED DESCRIPTION

In a study of genetic variations associated with sleep-wake patterns, Applicant found a significant association between the rs184039278 CRY1 allele and efficacy of treatment with tasimelteon. Specifically, following the administration of tasimelteon before bedtime, individuals having at least one copy of the rs184039278 CRY1 allele exhibited improvements in one or more sleep parameters selected from a group consisting of: latency to persistent sleep (LPS); sleep efficiency (%) during the first, second, and/or final thirds of the night; rapid eye movement (REM) sleep duration; total sleep time (TST), including during the first two-thirds of the night; and wake after persistent sleep (WASO).

Table 1 below shows TST and sleep efficiency data for two individuals diagnosed with DSWPD and having at least one copy of the rs184039278 CRY1 allele who were administered 20 mg of tasimelteon prior to bedtime. As can be seen, these individuals exhibited high TST and sleep efficiency.

Table 1

Group	ID and genotype	Total Sleep Time In First Two-Thirds Of Night (min)	percentage of total sleep time
20 mg tasimelteon	VP-VEC-162-3107-1 G/T	308	96
20 mg tasimelteon	VP-VEC-162-3107-2 G/T	293.5	91

FIG. 1 shows TST data for individuals having at least one copy of the rs184039278 CRY1 allele (MT) compared to individuals not having at least one copy of the rs184039278 CRY1 allele (WT). Both groups were treated with 20 mg of tasimelteon before bed. As can be seen, TST for WT individuals was both lower and more variable than for MT individuals.

As noted above, the rs184039278 CRY1 allele has been associated with familial DSWPD. What was not known, and not predictable from the literature, was the association between the rs184039278 CRY1 allele and the efficacy of tasimelteon in treating sleep disorders generally or DSWPD specifically.

Other variants of the CRY1 and PER1 genes were also found to be associated with DSWPD. These include the rare rs780614131 allele, which leads to a deletion of exon 6.

For example, Table 2 below shows the observed sleep times of three individuals determined to be heterozygous for the rs780614131 allele. As can be seen, the sleep period of each is delayed as compared to what would be considered a normal or typical sleep period.

Table 2

	Age	Sleep Period
Individual 1, male	33	2:30+30'–11:00
Individual 2, male	57	3:00+20'–11:00
Individual 3, female	28	3:30+10'–13:00

Similarly, individuals heterozygous for the rs112474322 allele exhibited late-shifted sleep during the final third of the night as compared to individuals without the rs112474322 allele. These results are shown in FIG. 2.

Aspects of the invention are applicable to the treatment of any individual having a loss-of-function (LOF) genotype. A LOF genotype is one in which the function of a gene associated with a CRSD (e.g., CRY1 and/or PER1) is reduced or lost, as compared to a wild-type or non-LOF genotype. As one skilled in the art would recognize, a genotype resulting in the complete loss of gene function is a LOF genotype. As one so skilled would also recognize, a genotype resulting in reduced gene function as compared to a wild-type genotype would also constitute a LOF genotype where the reduction in gene function is clinically or phenotypically

measurable.

While this invention has been described in conjunction with the specific
embodiments outlined above, it is evident that many alternatives, modifications and
variations will be apparent to those skilled in the art or are otherwise intended to be
embraced. Accordingly, the embodiments of the invention as set forth above are
intended to be illustrative, not limiting. Various changes may be made without
departing from the spirit and scope of the invention as defined in the following
claims. All patents, patent application, scientific articles and other published
documents cited herein are hereby incorporated in their entirety for the substance of
their disclosures.

CLAIMS

What is claimed is:

- 5 1. In a method of treating patients with a circadian rhythm sleep disorder (CRSD) consisting essentially of administering to said patients an amount of tasimelteon effective to treat said disorder, the improvement comprising:
 selecting a patient for said treatment by identifying that said patient has a
10 cryptochrome circadian clock 1 (CRY1) genotype associated with said disorder.
2. The improvement of claim 1, wherein the CRY1 genotype associated with said disorder includes at least one copy of the rs184039278 allele.
3. The improvement of claim 1, wherein the CRY1 genotype associated with
15 said disorder includes at least one copy of the rs780614131 allele.
4. The improvement of claim 1, wherein the CRY1 genotype associated with said disorder is a loss-of-function (LOF) genotype.
- 20 5. The improvement of claim 1, wherein said disorder is delayed sleep wake phase disorder (DSWPD).
6. The improvement of claim 1, wherein treating the patient includes administering tasimelteon to the patient once daily before bedtime.
- 25 7. The improvement of claim 6, wherein administering tasimelteon to the patient includes administering 20 mg of tasimelteon.
8. The improvement of claim 1, wherein treating the patient with tasimelteon
30 improves at least one sleep parameter selected from a group consisting of: latency to persistent sleep (LPS); sleep efficiency (%) during the first, second, and/or final thirds of the night; rapid eye movement (REM) sleep duration; total sleep time (TST), including during the first two-thirds of the night; and wake after persistent sleep (WASO).
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9. A method for treating a patient exhibiting one or more symptoms of a circadian rhythm sleep disorder, which comprises:
- identifying that said patient has a cryptochrome circadian clock 1 (CRY1) genotype associated with said disorder, and
- 5 administering an amount of tasimelteon to said patient effective to treat said disorder.
10. The method of claim 9, wherein the CRY1 genotype associated with said disorder includes at least one copy of the rs184039278 allele.
- 10 11. The method of claim 9, wherein the CRY1 genotype associated with said disorder includes at least one copy of the rs780614131 allele.
12. The method of claim 9, wherein the cRY1 genotype is a loss-of-function (LOF) genotype.
- 15 13. The method of claim 9, wherein said disorder is delayed sleep wake phase disorder (DSWPD).
14. The method of claim 9, wherein the amount of tasimelteon is 20 mg.
- 20 15. The method of claim 9, wherein treating said disorder includes improving at least one sleep parameter selected from a group consisting of: latency to persistent sleep (LPS); sleep efficiency (%) during the first, second, and/or final thirds of the night; rapid eye movement (REM) sleep duration; total sleep time (TST), including
- 25 during the first two-thirds of the night; and wake after persistent sleep (WASO).

16. A method for improving one or more sleep parameters in an individual, the method comprising:

identifying that said individual possesses a variant of the cryptochrome circadian clock 1 (CRY1) genotype associated with a circadian rhythm sleep disorder (CRSD); and

administering to said individual daily, at a time proximately before the individual's established bedtime, an amount of tasimelteon effective to improve one or more sleep parameters in said individual.

17. The method of claim 16, wherein the variant of the CRY1 genotype associated with a CRSD is the rs184039278 allele.

18. The method of claim 16, wherein the variant of the CRY1 genotype associated with the CRSD includes the rs780614131 allele.

19. The method of claim 16, wherein the variant of the CRY1 genotype associated with the CRSD is a loss-of-function (LOF) genotype.

20. The method of claim 16, wherein the CRSD is delayed sleep wake phase disorder (DSWPD).

21. The method of claim 16, wherein the amount of tasimelteon is 20 mg.

22. The method of claim 16, wherein improving sleep includes improving at least one sleep parameter selected from a group consisting of: latency to persistent sleep (LPS); sleep efficiency (%) during the first, second, and/or final thirds of the night; rapid eye movement (REM) sleep duration; total sleep time (TST), including during the first two-thirds of the night; and wake after persistent sleep (WASO).

23. In a method of treating patients with a circadian rhythm sleep disorder (CRSD) consisting essentially of administering to said patients an amount of tasimelteon effective to treat said disorder, the improvement comprising:
selecting a patient for said treatment by identifying that said patient has a
period 1 (PER1) genotype associated with said disorder.
24. The improvement of claim 23, wherein the PER1 genotype associated with said disorder includes at least one copy of the rs112474322 allele.
25. The improvement of claim 23, wherein the PER1 genotype is a loss-of-function (LOF) genotype.
26. The improvement of claim 23, wherein said disorder is delayed sleep wake phase disorder (DSWPD).
27. The improvement of claim 23, wherein treating the patient includes administering tasimelteon to the patient once daily before bedtime.
28. The improvement of claim 27, wherein administering tasimelteon to the patient includes administering 20 mg of tasimelteon.
29. The improvement of claim 23, wherein treating the patient with tasimelteon improves at least one sleep parameter selected from a group consisting of: latency to persistent sleep (LPS); sleep efficiency (%) during the first, second, and/or final thirds of the night; rapid eye movement (REM) sleep duration; total sleep time (TST), including during the first two-thirds of the night; and wake after persistent sleep (WASO).

30. A method for treating a patient exhibiting one or more symptoms of a circadian rhythm sleep disorder, which comprises:

identifying that said patient has a period 1 (PER1) genotype associated with said disorder, and

5 administering an amount of tasimelteon to said patient effective to treat said disorder.

31. The method of claim 30, wherein the PER1 genotype associated with said disorder includes at least one copy of the rs112474322 allele.

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32. The method of claim 30, wherein the PER1 genotype associated with said disorder is a loss-of-function (LOF) genotype.

33. The method of claim 30, wherein said disorder is delayed sleep wake phase disorder (DSWPD).

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34. The method of claim 30, wherein the amount of tasimelteon is 20 mg.

35. The method of claim 30, wherein treating said disorder includes improving at least one sleep parameter selected from a group consisting of: latency to persistent sleep (LPS); sleep efficiency (%) during the first, second, and/or final thirds of the night; rapid eye movement (REM) sleep duration; total sleep time (TST), including during the first two-thirds of the night; and wake after persistent sleep (WASO).

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36. A method for improving one or more sleep parameters in an individual, the method comprising:
- identifying that said individual possesses a variant of the period 1 (PER1) genotype associated with a circadian rhythm sleep disorder (CRSD); and
- 5 administering to said individual daily, at a time proximately before the individual's established bedtime, an amount of tasimelteon effective to improve one or more sleep parameters in said individual.
37. The method of claim 36, wherein the variant of the PER1 genotype associated with the CRSD includes the rs112474322 allele.
- 10 38. The method of claim 36, wherein the variant of the PER1 genotype associated with the CRSD is a loss-of-function (LOF) genotype.
- 15 39. The method of claim 36, wherein the CRSD is delayed sleep wake phase disorder (DSWPD).
40. The method of claim 36, wherein the amount of tasimelteon is 20 mg.
- 20 41. The method of claim 36, wherein improving sleep includes improving at least one sleep parameter selected from a group consisting of: latency to persistent sleep (LPS); sleep efficiency (%) during the first, second, and/or final thirds of the night; rapid eye movement (REM) sleep duration; total sleep time (TST), including during the first two-thirds of the night; and wake after persistent sleep (WASO).