Introduction

Melatonin, with its soporific action effects and benign safety profile, could be an effective and well-tolerated sleep agent with an appropriate delivery system. Melatonin promotes sleep in a way that resembles the natural onset of sleep, through quiet wakefulness to the sleep state, while maintaining normal sleep architecture. Clinical use of exogenous melatonin as a drug-free hypnotic in initiating and maintaining sleep, is limited since no formulation has been shown to maintain critical blood levels for more than a few hours. A 2 mg prolonged-release melatonin (PR-M) has been approved as a prescription therapy for primary insomnia in Europe, based upon RCT sleep studies demonstrating improvements in sleep quality, wake time after sleep onset, and behavior following waking. While an improved formulation over previous attempts, a lower than anticipated plateau time for PR-M (4.4 hours) resulted from limited absorption in the distal GI tract.

Continuous Release and Absorption Melatonin (CRA-melatonin), with its IPP (Ion-Powered Pump) delivery system, has shown an extended 7-hour pharmacokinetic (PK) plateau time, which may offer a new low-dose, drug-free alternative to prescription hypnotics to treat chronic sleep disturbances.

Methods

The REMfresh Duration Validation (REMVAL) study was designed to validate the results from the first PRO Study, REMDUR, including obtaining clinically relevant information about patients’ past usage of melatonin and non-melatonin sleep aids, sleep patterns prior to taking CRA-melatonin, sleep duration before and after taking CRA-melatonin, frequency of CRA-melatonin usage, improvement in sleep onset, sleep maintenance and sleep quality after taking CRA-melatonin, and overall satisfaction with CRA-melatonin.

Patients with sleep disturbances in the general population who received a sample of CRA-melatonin (REMfresh) from their physicians, were invited to complete a 13-question online survey. The authors noted that there may be inherent bias in these types of open-label studies.

Results

Survey responses were received from 1,116 patients in the general population who had taken CRA-melatonin. 77.5% of patients indicated they take CRA-melatonin after taking CRA-melatonin, more than 91% of patients reported a major/moderate improvement for each of the three sleep parameters measured, as compared to no improvement (p<.0001).

When asked how they would rate their improvement in sleep onset, sleep maintenance and total sleep quality after taking CRA-melatonin?, more than 91% of patients reported a major/moderate improvement for each of the three sleep parameters measured, as compared to no improvement (p<.0001).

Conclusions

After taking CRA-melatonin, the vast majority of patients (78.8%) achieved a sleep duration of ≥ 6 hours (p<.0001).

While more than 91% of patients reported a major/moderate improvement in sleep onset, maintenance and sleep quality (p<.0001 for each parameter).

Of those patients who had never taken melatonin before, 99.4% indicated they were likely or very likely to continue taking CRA-melatonin (p<.0001).

In spite of the inherent bias, the differences reported are very substantial.

REVMAL provides further real-world evidence of a correlation between the 7-hour PK profile and observed hypnotic effects of CRA-melatonin (improvements in sleep duration, onset, maintenance, and quality).

The results of this second PRO study closely validate the findings of the first 500-patient PRO study, REMDUR, peer-reviewed and presented at SLEEP 2018.

References


DISCLOSURES

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Patients with sleep disturbances in the general population who received a sample of CRA-melatonin (REMHealth) from their physicians, were invited to complete a 13-question online survey.

The authors note that there may be inherent bias in these types of open-label studies.

When asked how they would rate their improvement in sleep onset, maintenance and sleep quality after taking CRA-melatonin, more than 93% of patients reported a major/moderate improvement for each of three sleep parameters measured, as compared to no improvement (p<0.0001).

95.8% of patients who previously experienced daily, morbid short sleep duration (27.2% of whom had never previously tried a melatonin brand), reported that they were very likely or likely to continue using CRA-melatonin.

In spite of the inherent bias and other limitations, the differences reported are very substantial. Those results provide real-world evidence that CRA-melatonin, with its extended 7-hour absorption profile, continues to show clear clinical benefits for patients experiencing chronic short sleep duration.

In conclusion, CRA-melatonin provides a clear and sustained clinical benefit for patients with short sleep duration and is the first melatonin formulation specifically designed to target sleep maintenance and quality, thereby improving sleep onset, maintenance and quality.
Introduction

Chronic disorders of sleep and wakefulness affect an estimated 50 to 70 million Americans, and long-term sleep deprivation has been associated with a number of negative health consequences, including an increased risk of diabetes, hypertension, heart attack, stroke, obesity, and depression. Currently available immediate-release melatonin (IR-melatonin) formulations help promote sleep onset, but their non-sustained absorption in the lower gastrointestinal tract makes it more difficult for them to enable adequate sleep maintenance. Sleep maintenance for an optimal duration is becoming even more relevant, since shorter sleep duration is associated with greater mortality as shown in Figure 1.\(^1\)\(^,\)\(^2\)

**Figure 1. Shorter Sleep Duration is Associated with Greater Mortality**

The hazard ratio represents an individual’s relative risk of dying compared with the general population.\(^1\)\(^,\)\(^2\)

The patented Ion Powered Pump (IPP) delivery system utilized in the continuous-release and absorption melatonin (CRA-melatonin) was developed to provide an exogenous melatonin pharmacokinetic (PK) profile that mimics normal endogenous melatonin plasma level patterns through a novel technology. The REM Absorption Kinetics Trial (REMAKT) evaluated the PK profile of CRA-melatonin compared with a leading marketed IR-melatonin formulation. REMAKT had a 1000 pg/mL target of plasma melatonin concentration for sleep maintenance. This target was set at about 10 times the endogenous peak concentration for melatonin found in healthy young subjects,\(^3\) since studies of drug transport across the blood-brain barrier have shown that there is an approximately 10-fold lower concentration of exogenous melatonin in the brain versus plasma.\(^4\)

Methods

- Randomized, crossover, clinical PK evaluation comparing 5 mg CRA-melatonin (REMfresh) with the market-leading 5 mg IR-melatonin in 10 healthy non-smoking adults
- The active ingredient in CRA-melatonin (Ultramel) is an ultra pure (99%) proprietary synthetic melatonin
- Blood was taken pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8 and 12 hours following administration and was assayed for melatonin by a validated LC-MS/MS method
- PK parameters, including the time course, \(C_{\text{max}}\), and \(T_{\text{max}}\) for melatonin were determined
- Time to reach initial target (1000 pg/mL) and duration of time above the target threshold levels for melatonin were determined by interpolation
- Assessment of adverse events was adjudicated by the Medical Monitor, Dr. Lassiter

Results

**Figure 2. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin or 5 mg IR-melatonin**

The median \(C_{\text{max}}\) was 4,690 pg/mL for CRA-melatonin and 23,352 pg/mL for the IR-melatonin. Melatonin levels exceeded the target sleep maintenance threshold level of 1000 pg/mL for a median of 6.7 hours for CRA-melatonin, compared to 3.7 hours for IR-melatonin.

Conclusions

- The market leading IR-melatonin formulation spiked 23X higher than the targeted levels of exogenous melatonin for sleep maintenance
- IR-melatonin also had a rapid decline in serum levels that did not allow melatonin levels to be maintained beyond 4 hours above the targeted maintenance threshold
- CRA-melatonin, a patented novel melatonin formulation, was shown to achieve both quick release of melatonin to induce sleep, and then continuous release and absorption of melatonin to help maintain sleep over 7 hours, by remaining above the targeted maintenance threshold

References


DISCLOSURES

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A Continuous-Release Ion Powered Pump Melatonin Delivery System that Overcomes Challenges of Release and Absorption in the Intestines

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Introduction

Several modified release formulations of melatonin have been developed with the goal of providing exogenous melatonin profiles that mimic normal endogeneous levels, i.e., Mesa Wave-shaped, plasma pharmacokinetic profile for sleep maintenance. There have been difficulties in overcoming the challenges of release and absorption of melatonin in the higher pH environments in the small and large intestines. The initial attempts at employing hydroxypropylmethylcellulose (HPMC) to provide sustained-release and absorption showed that there was a problem in maintaining high plasma melatonin levels after the first 4 hours after administration. Various approaches, including adding a controlled-release coating to melatonin beads, administering immediate-release and controlled-release melatonin tablets simultaneoully, using melatonin soft gels instead of powder, and slow-release pills of melatonin suspended in an 80:20 mixture of peanut oil/beeswax, have been tried. Further improvements in these delivery systems are needed to get closer to the body’s own Mesa Wave-shaped profile (Figure 1A-D). The patented Ion Powered Pump (IPP) delivery system utilized in continuous-release and absorption melatonin (CRA-melatonin) was developed to overcome the challenges of release and absorption in the intestines.

Figure 1. Melatonin Plasma Concentration Time Profiles for Modified-Release Formulations of Melatonin

Methods

- The melatonin was formulated in a polymer matrix that maintains a solubility-enhancing and concentration gradient driven low pH environment (Ion Powered Pump). This facilitates the continuous release and absorption of melatonin in the GI tract, independent of local pH conditions.
- The active ingredient in CRA-melatonin (Ultramel) is an ultra pure (98%) proprietary synthetic melatonin.
- Randomized, crossover clinical PK evaluation comparing 5 mg CRA-melatonin (REMfresh) with the market-leading 5 mg immediate-release melatonin (IR-melatonin) in 10 healthy non-smoking adults.
- Blood was taken pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, and 12 hours following administration and was assayed for melatonin by a validated LC-MS/MS method.
- Pharmacokinetic (PK) parameters, including the time course, Cmax, Tmax, and plateau time for melatonin were determined by inspection.

Results

- The Ion Powered Pump Melatonin Delivery System

CRA-melatonin was designed as a hydrogel matrix tablet. There is rapid release of the melatonin from the surface of the tablet, as the hydrogel release controlling matrix is setting up in the acidic environment (pH of 1 to 3.5) in the stomach. As the tablet moves into the higher pH (5.5 to 6.5) environment of the small intestine, which is above the pKa of melatonin (~4.0), the acidic moity in the tablet maintains the pH within the tablet below 4.0 for 7+ hours. The hydrogel matrix, after proper hydration, allows continuous release of the active melatonin and acidic moity into the lumen of the intestines. This proprietary approach facilitates delivery of the active melatonin to the brush border of the epithelial layers of the small and large intestines for uptake into the bloodstream.

Figure 3. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin

Median concentrations of plasma melatonin 0-12 h after 5 mg of CRA-melatonin. The CRA-melatonin delivery technology allowed burst release and absorption of approximately 50% of the melatonin within the first 3 hours, helping facilitate sleep onset, coupled with sustained release and absorption of approximately 50% of the remaining melatonin within the next 4 hours, to optimize sleep maintenance.

Conclusions

- The patented CRA-melatonin provides a burst release for rapid absorption above threshold levels and maintains successful melatonin release and absorption to address the historical challenges with exogenous melatonin delivery.
- CRA-melatonin provides the desired PK profile, anticipated to result in faster onset of sleep and then helping with sleep maintenance for up to 7 hours.

References


DISCLOSURES

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David C. Brodner, MD, Senior Medical Advisor, Physician’s Seal, LLC
Introduction

Nearly one-third of US adults sleep less than the recommended 7 hours daily. Increasing evidence suggests an association between sleep duration and adverse health outcomes, making sleep maintenance an important factor in achieving optimal health. Extreme short sleep duration has been linked to increased risk of chronic diseases such as heart disease, diabetes, and obesity. Moreover, short sleep is associated with an increased risk of accidents and cognitive decline. Therefore, improving sleep maintenance is crucial for optimal health and well-being.

Methods

1. Prior to taking CRA-melatonin, how often did you suffer from sleep disturbances?  
2. Prior to taking CRA-melatonin, on average, how long did it take you to fall asleep?  
3. Prior to taking CRA-melatonin, on average, how many times a night did you wake up?  
4. Prior to taking CRA-melatonin, how refreshed did you feel when you woke in the morning?  

When asked “How often do you take CRA-melatonin,” 76.6% of survey respondents indicated that they take CRA-melatonin nightly, 17.6% take it every other night, and 4.6% take CRA-melatonin weekly. The proportion of respondents reporting nightly CRA-melatonin use was statistically significantly greater (p<0.0001) compared with the proportion of respondents with less than nightly use (every other night or weekly).

Results

When asked how they would rate their improvement in sleep onset, sleep maintenance, and total sleep quality after taking CRA-melatonin, more than 90% of survey respondents reported a major/moderate improvement for each of the 3 questions. The proportion of respondents with major/moderate improvement was statistically significantly greater (p<0.0001) compared with the proportion of respondents with no improvement for all parameters: sleep onset, sleep maintenance, and total sleep quality.

Conclusions

The REMabsorption Kinetics Trial (REMARTX), peer reviewed and presented at SLEEP 2017, was a randomized, crossover, clinical PK evaluation comparing 5 mg CRA-melatonin with the market-leading 5 mg* immediate release melatonin (IR-melatonin) in 10 healthy, non-smoking adults. The median Cmax was 4,690 pg/mL for CRA-melatonin and 23,352 pg/mL for IR-melatonin. Median levels exceeded the targeted sleep maintenance threshold level of 1,000 pg/mL, for a median of 6.7 hours for CRA-melatonin, compared to 3.7 hours for IR-melatonin.

The post-marketing REMfresh Patient Reported Outcomes Duration (REMURD) study was designed to obtain clinically relevant information about patients’ sleep patterns, duration of sleep before and after CRA-melatonin, daily CRA-melatonin use, onset of action, sleep maintenance, quality of sleep, and overall satisfaction with CRA-melatonin.

Survey responses were received from 500 patients in the general population who had taken CRA-melatonin. The vast majority (77.6%) of respondents reported sleeping 6 hours or more after taking CRA-melatonin, with 23.6% before taking CRA-melatonin. The proportion of respondents with 6 hours or more of sleep after taking CRA-melatonin was statistically significantly greater (p<0.0001) than before taking CRA-melatonin.

References


Figure 2. Hours of Sleep Reported by Respondents Before and After Taking CRA-Melatonin (n=500)

Figure 3. Reported Frequency of Taking CRA-Melatonin (n=500)

Figure 4. Improvement in Sleep Since Taking CRA-Melatonin (n=500)

DISCLOSURES

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** The monthly use vertical bar of 1.2% is not shown in the above chart.
Clinical Evaluation of the Ion Powered Pump Melatonin Delivery System

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Introduction

Melatonin levels decline with age, an important factor in poor quality sleep among older people. In addition to difficulty falling asleep, sleep in older populations is characterized by increased fragmentation of the sleep architecture and sleep maintenance problems. Melatonin supplementation has been shown to promote and maintain sleep in older populations.3 Previously, prolonged-release melatonin (PR-M), which has been marketed internationally, was designed to provide a serum melatonin profile more closely related to the normal physiological release pattern compared with immediate-release melatonin (IR-melatonin).

The median time it took plasma melatonin levels to exceed the initial threshold level of 1000 pg/mL was 0.42 hours for CRA-melatonin. The median Cmax was 4,690 pg/mL for CRA-melatonin, and the median time to reach this concentration (Tmax) was 1.5 hours. Melatonin levels showed a median plateau time of 6.7 hours with CRA-melatonin. There were no treatment-emergent adverse events seen with CRA-melatonin.

Table 1. % Responders to PR-M vs Placebo Showing Concomitant and Clinically Meaningful Improvement in Quality of Sleep and Morning Alertness

<table>
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<th>QOS &amp; BFW Responders</th>
<th>QOS Responders</th>
<th>BFW Responders</th>
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<td>Treatment</td>
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<td>Placebo</td>
<td>PR-M</td>
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<td>% Responders</td>
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A pharmacokinetic study looking at serum melatonin levels in healthy males after ingestion of the 2 mg dose of PR-M shows peak concentration of melatonin in the blood occurring at 2.6 hours and persisting over 3.5 hours after ingestion and decline towards the morning.1 IR-melatonin peaks after 2 hours and rapidly declines over the next 2 hours. In well-conducted sleep studies, PR-M demonstrated statistically significant improvements in sleep quality, morning alertness, sleep latency, and quality of life in patients aged 55 years and older compared with IR-melatonin and placebo.1,2 In addition, as shown in Table 1, the responder rate for concomitant improvement in quality of sleep and morning alertness, and in each of them separately, was significantly higher for PR-M compared with placebo, in studies reported by the PR-M innovator.2

Methods

- Randomized, crossover clinical PK evaluation comparing 5 mg CRA-melatonin (REMfresh) with the market-leading 5 mg IR-melatonin in 10 healthy non-smoking adults
- The active ingredient in CRA-melatonin (Ultramel) is an ultra pure (99%) proprietary synthetic melatonin
- Blood was taken pre-dose and at 0.25, 0.5, 0.75, 1.2, 3, 4.5, 6, 8, and 12 hours following administration and was assayed for melatonin by a validated LC-MS/MS method
- PK parameters, including the time course, Cmax, Tmax, and plateau time for melatonin were determined by interpolation
- Time to reach initial target (1000 pg/mL) and duration of time above the target threshold levels for melatonin were determined by interpolation

References


DISCLOSURES

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