REM Absorption Kinetics Trial: A Randomized, Crossover, Pharmacokinetics Evaluation of a Novel Continuous-Release and Absorption Melatonin Formulation Versus a Same Strength Immediate-Release Formulation In Healthy Adults

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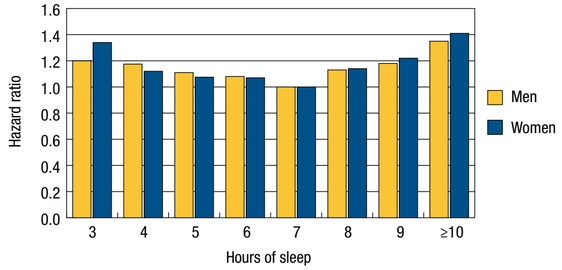
Introduction

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.[1] 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]

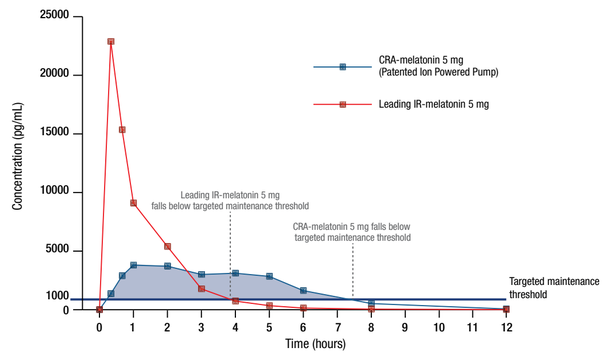
The patented Ion Powered Pump (IPP) delivery system utilized in the continuous-release and absorption melatonin (CRA-melatonin) was developed to provide an exogenous melatonin pharmacokinetic (PK) profile that mimics normal endogenous melatonin plasma level patterns through a novel technology. The REM 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_{max}, and T_{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_{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.

Table 1. Subjects Reporting Treatment-Emergent Adverse Events

Subject/Product/Date Administered	AE Verbatim	Onset	Duration	Related
006/IR-melatonin/Mar 16	Irritability	29-Mar-16	4 h	Possible
009/IR-melatonin/Apr 16	Emesis	13-Apr-16	1 min	Possible
009/IR-melatonin/Apr 16	Stomach Cramps	13-Apr-16	5 days	Possible
009/IR-melatonin/Apr 16	Emesis	16-Apr-16	1 min	Possible
009/IR-melatonin/Apr 16	Nausea	13-Apr-16	3 days	Possible

Five treatment-emergent adverse events (TEAEs) occurred with IR-melatonin. There were no TEAEs associated with CRA-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

1. Institute of Medicine (US) Committee on Sleep Medicine and Research; Colten HR, Altevogt BM, editors. Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. Washington (DC): *National Academies Press (US);* 2006. **2.** Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry.* 2002;59(2):131–136. **3.** Zhdanova IV, Wurtman RJ, Balcioglu A, Kartashov AI, Lynch HJ. Endogenous Melatonin Levels and the Fate of Exogenous Melatonin: Age Effects. *J Gerontology: Biological Sciences*. 1998;53A(4):B293-B298. **4.** Pardridge WM, Mietus LJ. Transport of albumin-bound melatonin through the blood-brain barrier. *J Neurochem.* 1980;34(6):1761-1763.

DISCLOSURES

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