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Current Medical Research & Opinion Vol. 27, No. 1, 2011, 87–98

0300-7995
doi:10.1185/03007995.2010.537317

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Original article

Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response

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Keywords:
Melatonin insomnia – Long-term – Prolonged-release – Sleep latency

Accepted: 1 November 2010; published online: 24 November 2010
Citation: Curr Med Res Opin 2011; 27:87–98

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Abstract

Objectives:
The authors recently reported on efficacy and safety of prolonged-release melatonin formulation (PRM; Circadin 2 mg) in elderly insomnia patients. The age cut-off for response to PRM and the long-term maintenance of efficacy and safety were further evaluated by looking at the total cohort (age 18–80 years) from that study and subsets of patients aged 18–54 and 55–80 years (for whom the drug is currently indicated).

Design:
Randomised, double-blind, placebo controlled trial.

Setting:
Multicentre, outpatients, primary care setting.

Methods:
A total of 930 males and females aged 18–80 years with primary insomnia who reported mean nightly sleep latency (SL) >20 min were enrolled and 791 entered the active phase of the study. The study comprised a 2-week, single-blind placebo run-in period followed by 3 week's double-blind treatment with PRM or placebo, one tablet per day at 2 hours before bedtime. PRM patients continued whereas placebo completers were re-randomised 1:1 to PRM or placebo for 26 weeks followed by 2-weeks run-out on placebo.

Main outcome measures:
SL and other sleep variables derived from sleep diary, Pittsburgh Sleep Quality Index (PSQI), Quality of life (WHO-5), Clinical Global Impression of Improvement (CGI-I) and adverse effects, recorded each visit, withdrawal and rebound effects during run-out.

Results:
In all, 746 patients completed the 3-week and 555 (421 PRM, 134 placebo) completed the 6-month period. The principal reason for drop-out was patient decision. At 3 weeks, significant differences in SL (diary, primary variable) in favour of PRM vs. placebo treatment were found for the 55–80-year group (−15.4 vs. −5.5 min, $p = 0.014$) but not the 18–80-year cut-off which included younger patients. Other variables (SL-PSQI, PSQI, WHO-5, CGI-I scores) improved significantly with PRM in the 18–80-year population, more so than in the 55–80-year age group. Improvements were maintained or enhanced over the 6–month period with no signs of tolerance. No withdrawal symptoms or rebound insomnia were detected. Most adverse events were mild with no significant differences between PRM and placebo groups in any safety outcome.

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Conclusions:
The results demonstrate short- and long-term efficacy of PRM in insomnia patients aged 18–80 years, particularly those aged 55 and over. PRM was well-tolerated over the entire 6-month period with no rebound or withdrawal symptoms following discontinuation.

Study Registry No: ClinicalTrials.gov ID: NCT00397189

Introduction

Melatoninergic drugs are a new class for insomnia pharmacotherapy. Prolonged-release melatonin 2 mg (PRM; Circadin 2 mg) has been approved in Europe in 2007 and since then in additional countries for the short-term treatment of patients aged 55 years and older with primary insomnia. The age limit was based on the well-documented decline in melatonin production with age subsequent to calcification of the pineal gland, a decline in the activity of the master circadian clock residing in the suprachiasmatic nuclei (SCN) of the brain and clinical data supporting efficacy and safety of PRM in this population[1–6]. Some young patients may also have low melatonin levels and the important clinical question is whether the population likely to respond is defined by age or by low melatonin levels. The primary aim of the present study was to investigate whether PRM should be indicated for insomnia in patients of a certain age group, or whether it should be indicated for patients with low endogenous melatonin regardless of their age. The study was therefore designed to include patients aged 18–80 years, and examine cut-offs based on low melatonin excretion (defined as urinary excretion of the main melatonin metabolite, 6-sulphatoxymelatonin [6-SMT] of 8 μg/night or less) or older age (65 years and over) as predictors of response. The primary efficacy variable of the study was shortening of sleep latency after 3 weeks of treatment. Stratification by 6-SMT levels and age group was used to obtain adequate treatment balance within subgroups of elderly/adult patients and patients with low/normal 6-SMT excretions.

Because insomnia, particularly at older age, is often chronic (lasting more than 3 months)[7] the long-term efficacy and safety of insomnia drugs are also of prime interest. A predefined analysis examined the efficacy measures at certain time points during a 6-month double-blind extension period and for different cut-offs (18–80, 45–80, 55–80, and 65–80 years). In order to meet these requirements the study was designed to include a wide age range of patients aged 18–80 years with pre-planned analyses for the relevant subpopulations (elderly, low melatonin excretors) and age-cut-offs, at the pre-specified periods, 3, 13, 21 and 29 weeks of double-blind treatment.

The study design, inclusion and exclusion criteria and results of the primary analyses are described elsewhere[8]. The study reached its goal and provided clear evidence that the primary age cut-off (65 years and over) was a better predictor of response in the 3 weeks' treatment period than endogenous melatonin production regardless of age. There was clear evidence of an increase in response in the elderly beyond the 3 weeks of treatment and up to 3 months. The age cut-off for patients ≥65 years used for the primary analysis in this study, does not preclude response to PRM in younger patients. Rather, there is sufficient evidence in previous studies for an equal or greater response to PRM in patients aged 55 years and older[1–5]. The age cut-off for response to PRM was thus further explored. Here the authors describe the results of the pre-planned analyses of the short-term responses and the long-term maintenance of efficacy and the safety of PRM in the total patient cohort (age 18–80 years) from that study and a subset of the patients aged 55 years and older (for whom the drug is currently indicated).

Patients and methods

Study design

The study protocol and relevant documents were approved by the Huntingdon Multi-centre Research Ethics Committee, Cambridge, UK. All participants provided written informed consent before any study-related procedures were started. The study design, subjects and procedures were described elsewhere[8]. In brief, this was a randomised, double-blind, parallel-group clinical trial comprising a 2-week, single-blind, placebo run-in period, a 3-week double-blind treatment period (treatment weeks 1–3), a 26-week double-blind extension period (treatment weeks 4–29 including four assessments visits at weeks 7, 13, 21 and 29 of the double-blind treatment period) and a 2-week single-blind placebo run-out period.

Study subjects

Patients from Glasgow and surrounding areas who were self-referred or referred from primary to secondary care were pre-screened by telephone using the Sleep History Questionnaire (SHQ) adopted from The Management of Insomnia Guidelines for Clinical Practice[9] and resembled that recommended by Clinical Practice Guideline-Adult Insomnia[7]. Suitable patients were invited to a screening visit during which they were consented and assessed for inclusion.

Men and women aged between 18 and 80 years suffering from primary insomnia according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria with sleep latency longer than 20 min were included in the study.

Major exclusion criteria for the study included the use of benzodiazepine or non-benzodiazepine hypnotics within

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the previous 2 weeks or any psychoactive treatment within the previous 3 months, sleep disorders associated with a psychiatric disorder (e.g., depression, anxiety, dementia), sleep disorders secondary to another medical condition (e.g., sleep apnoea, circadian rhythm sleep disorder), use of prohibited concomitant medication (psychotropic treatments, i.e. neuroleptics, antiepileptics, barbiturates, antidepressants, anxiolytics and lithium, first generation antihistamines, hypnotics or treatments used as a hypnotic, e.g. all benzodiazepines, zopiclone, zolpidem and zaleplon, barbiturates, buspirone and hydroxyzine) or excessive alcohol consumption (intake of more than 30 g of pure alcohol per day and any intake after lunch-time), any chronic medical condition that was likely to be the cause of the sleep problem (e.g., chronic pain, benign prostatic hypertrophy) or might interfere with the conduct of the study or a lifestyle likely to interfere with sleep patterns (e.g., shift work, jet-lag).

A four-step process was used for screening out patients with secondary sleep disorders including depression and other sleep disorders in the study according to DSM-IV criteria. Step 1: The initial prescreening for primary insomnia as defined in DSM-IV was performed on a telephone interview and was based on the sleep history questionnaires (SHQ). The SHQ characterises the primary sleep complaint according to the differential diagnostic criteria (DSM-IV and ICD-10) and also helps in differentiating primary insomnia from insomnia due to medical and psychiatric disorders (including depression and anxiety) and specific insomnia disorders like circadian rhythm disorders, movement disorders, parasomnias and breathing related sleep disorders. Step 2: At the screening visit, a physical examination was performed by a qualified clinician to exclude patients with physical causes of insomnia. Step 3: At the screening visit the patients went through a detailed psychological assessment that included the Raskin Depression scale, Covi anxiety scale and the Mini Mental State (MMS) to exclude psychiatric disorders, including depression anxiety and dementia. In addition, a history of severe psychiatric disorders, especially psychosis, anxiety and depression were major exclusion criteria. Step 4: patients who were using psychotropics (neuroleptics, antiepileptics, barbiturates, antidepressants, anxiolytics or lithium) in the 3 months before the study were excluded. A urine drug screen for benzodiazepines and morphine derivatives was undertaken at baseline. Patients with a positive result were excluded. All hypnotics or treatments used as an hypnotic (e.g., herbal medicines) were not allowed during the study. Hypnotic use was monitored throughout the study. Patients were asked at each visit whether they had taken a hypnotic as well as the study medication and were withdrawn if they had. The common analgesics used in UK for self-limiting intermittent problems such as headache frequently contain codeine. Patients for whom pain was a cause of insomnia were excluded from the study. However, due to the long-term nature of the study intermittent use of common analgesics was allowed.

Men and women aged between 18 and 80 years suffering from primary insomnia according to the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV) criteria with sleep latency longer than 20 min were included in the study. Eligible patients entered the baseline screening run-in period and received 2 weeks of a single-blind treatment with placebo. A urine drug screen for benzodiazepines and morphine derivatives was undertaken by the end of week 2. Patients with a positive result were excluded. There was no exclusion based on response during the placebo run-in phase.

Patients still eligible after the 2 weeks placebo run-in were randomised double-blind in a 1:1 ratio to receive either PRM 2 mg or placebo for 3 weeks. Randomisation was stratified by trial site, 6-SMT levels (low $\leq$ 8 μg/high - 8 μg/night) and age group (<65/$\geq$65 years). After the 3-week treatment period, completing patients were allowed to proceed into the extension period. A second randomisation was performed after the 3 weeks' double-blind treatment in which patients receiving placebo were randomised 1:1 to PRM and placebo, so that altogether 75% of the patients received PRM and 25% placebo during the 26 weeks' extension period to allow more patients to be exposed to the drug for evaluation of safety. At the end of the extension period, all patients received 2 weeks of single-blind placebo in the run-out period to evaluate withdrawal effects.

Patients were instructed to take one tablet daily of study medication orally after food, 1–2 h before going to bed (preferably between 2100 h and 2200 h) and each morning to complete a diary recording sleep latency, sleep maintenance, total sleep time, sleep onset time, sleep offset time, refreshed on waking score, morning alertness score and sleep quality during the previous night.

Endpoints

Efficacy variables were recorded at baseline and each visit. Sleep diary parameters (daytime and night-time) were filled in by the patient each day in the morning in the 7 days preceding each visit; the Pittsburgh Sleep Quality Index (PSQI)[10,11] global score, component scores, and questions 2 and 4 filled in by the investigator with the patient; WHO-5 Well-being Index (1998 version)[12] and – Severity of illness scale (CGI-S)[13] were filled in by the investigator with the patient at the screening visit and end of run-in and the improvement (CGI-I) at each subsequent visit.

The safety variables were assessed at each visit and included spontaneously reported adverse events (AEs); unusual events and AEs recorded by the investigator.

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A complete physical examination was performed at screening, at the end of run-in, at weeks 3 and 29 of the double-blind treatment period and at discontinuation and vital signs (pulse, blood pressure) were recorded at all visits. ECG was performed at the end of baseline, weeks 3, 13 and 29 of the double-blind treatment period and at discontinuation. Clinical laboratory tests (haematology, biochemistry and urinalysis) were assessed at screening visit and then at weeks 3, 7 and 29 of the double-blind treatment period and at discontinuation. Endocrine evaluations were performed at the end of run-in and during week 29 of the double-blind treatment period in 80 patients not using any hormonal contraceptives or hormonal replacement therapies and not suffering from any significant endocrine disease. Cortisol was assessed at the end of run-in and during week 29 of the double-blind treatment period in 56 patients before and after synacthen test. The Tyrer scale assessment[14] was completed by the investigator with the patient at week 29 of the double-blind treatment period and after the 2-week placebo washout period.

Statistical issues

Statistical analyses were performed according to the statistical analysis plan prepared prior to database lock by statisticians at the Robertson Centre for Biostatistics, University of Glasgow using SAS for Windows v. 9.1.3 and Splus v. 7.0. As previously described[8] the predefined primary efficacy analysis was the comparison of sleep latency as measured by the sleep diary after 3 weeks treatment with PRM (2 mg) or placebo in the pre-defined subgroups of patients who were low excretors of melatonin regardless of age and the patients aged 65–80 years, regardless of melatonin levels. The comparison was made using a linear regression model with terms for treatment (PRM vs. placebo), baseline sleep latency and age group (≥65 or <65 years – only for the primary endpoint).

The main study conclusion was based on sleep latency, the predefined primary variable. All other efficacy endpoints were pre-defined as exploratory and aimed at evaluating the primary variable in other age cut-offs, confirming the results of the primary variable using additional instruments (e.g., PSQI) or adding information on other aspects of the sleep and daytime consequences of the treatment.

In compliance with FDA regulatory procedures, no correction for multiple comparisons were performed for the exploratory outcome measures. Accordingly, the overall conclusions from the results are based on the accumulation of evidence for between-treatment differences, which were in many cases correlated or complementary, rather than on isolated *p*-values. To further explore whether the 55–80-year-old patients had more benefit than the younger patients, the interaction between treatment effects (PRM vs. placebo) and the age group (18–54 and 55–80 years) were assessed (ANCOVA).

Short-term period

Sleep latency as recorded in the sleep diary was summarised at baseline, after the 2 weeks run-in period, and after the 3 weeks double-blind treatment (actual and change from baseline) for each treatment group and as a whole using descriptive statistics for continuous variables. At each visit, the mean value of the 7 days prior to the visit was used. Sleep latency as measured by the sleep diary after 3 weeks double-blind treatment was compared using a linear regression model with terms for treatment (PRM vs. placebo), baseline sleep latency and age group (≥65 or <65 years).

The other short-term variables were summarised by the mean values at baseline and after 3 weeks of double-blind treatment (actual and change from baseline) using descriptive statistics of continuous variables for each treatment group. These included: (1) sleep diary variables, calculated as the mean of the values recorded in the 7 days prior to each study visit; (2) PSQI global score, PSQI individual component scores question 2 and question 4 scores; (3) WHO-5 Well-being Index score; (4) CGI-S (baseline); and CGI-I (treatment) scores.

Long-term period

Efficacy variables were summarised by the second randomisation for outcomes at baseline and treatment weeks 4–29, or those visits at which the outcome was recorded. Summaries were given at each visit and for changes between post-baseline visits and baseline. For those outcomes recorded at withdrawal, summaries were given for the change between treatment week 29 and withdrawal weeks. In addition, the changes of PSQI and WHO-5 between treatment week 29 and withdrawal weeks in the run-out period were summarised.

For efficacy outcomes measured at treatment weeks 4–29, a linear mixed-effects model for repeated measures (MMRM) was used to compare outcomes at treatment weeks 4–29, in relation to the treatment currently received. For treatment week 3 measures, treatment was defined by the first randomisation; for subsequent visits, treatment was defined by the second randomisation. Each model included a random individual effect and assumed a general covariance structure for the residuals over time. For each outcome, a model was fitted which included terms for treatment, visit (as a categorical variable), the baseline values of the outcome measure, age group (≥65 or <65 years, except for analyses for the ≥65 years) and baseline 6-SMT (≤8 or >8 μg/night, except for analyses of low excretors). This model was used to estimate the global treatment effect, with a 95% CI and *p*-value.

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Safety outcomes

Adverse event data, laboratory data including hormones (prolactin, ACTH, T3, free T4, TSH, LH, FSH), estradiol (women), free and total testosterone (men), and cortisol (before and after synacthen test), vital signs and withdrawal symptoms were summarised for all subjects randomised to study medication. No formal statistical testing was performed on the safety data.

Sample size

Sample calculations were based on achieving 90% power at the 5% level for the primary and secondary endpoints of assessing the change in sleep latency at 3 weeks in the low excretors sub-group, and in patients aged ≥65 years[8]. Based on these calculations, 690 patients were to be randomised in the study.

Study Registry No: ClinicalTrials.gov ID: NCT00397189

Results

Patient disposition and demographics

A total of 930 patients were enrolled into the study between October 2006 and December 2008 and entered the run-in period; 139 of these patients discontinued during the run-in period. The overall disposition of the patients in this study and the breakdown by age is summarised in Figure 1. A total of 791 patients were randomised to receive PRM or placebo. Two patients (one patient in each group) were not treated with study drug and were excluded from the safety population. Of the 789 patients in the safety population, 43 (5%) withdrew before the end of the 3-week treatment period. The most common reasons for withdrawal were withdrawal of consent (19, 44%), lost to follow-up (nine, 21%) and discontinuation due to an adverse event (five, 12%). The pattern of discontinuation was similar for both treatment groups. A total of 722 patients completed the 3-week double-blind treatment period. Of these patients, 578 were aged 55–80 years.

A total of 711 patients entered the 26-week extension period, received study drug and were included in the safety population. Of these patients, 534 received PRM and 177 received placebo in the extension period giving a 3:1 ratio of PRM to placebo patients. In all, 156 patients (22%) were withdrawn at some time during the 26-week extension period. The most common reasons for withdrawal in the extension period were withdrawal of patient consent (83, 53%) and discontinuation due to adverse event (36, 23%). The patterns of discontinuation were similar by treatment group, baseline 6-SMT level, age and sex.

The study population was predominantly white (713, 99%); four patients were black and four were Asian. Subjects' demographics were similar between groups. Baseline demography of the populations is depicted in Table 1 and comorbidities in Table 2. Comorbidities, particularly cardiovascular and endocrine (diabetes) disorders that prevail in the older age group, were present in a considerable number of study patients (Table 2). The treatment groups were generally well-balanced regarding demographic characteristics, pulse, ECG, blood pressure, compliance, medication use, medical history, physical examination abnormalities and 6-SMT levels. In all, 11.7% of the population were confirmed to be taking common analgesia medications that included codeine and were evenly randomised to PRM and placebo.

Efficacy evaluation

The results of the primary variable analyses (SL diary after 3 weeks) for the extended age cut-offs (18–80, 18–54 and 55–80 years) are presented in Table 3. On average, subjects had mean (SD) sleep latencies for the study populations at baseline of 76.4 (63.2) min in the PRM and 71.2 (60.1) min in the placebo group. A significant mean treatment effect difference in SL diary between PRM- and placebo-treated groups was found in the 55–80-year age cut-off population (−7.8 min, $p = 0.014$), however further extension of the age cut-off to younger age resulted in smaller and insignificant mean treatment differences despite the larger sample size.

The results of the other diary, PSQI, CGI-I and WHO-5 Index variables that showed significant treatment differences in one or more of the populations in the 3-week treatment period are depicted in Table 4. Despite the lack of significant effect on diary-recorded SL in the 18–80-year age cut-off population in the this period, SL measured by the PSQI (question 2) showed significant differences between PRM and placebo in the 18–80 and 55–80 but not 18–54-year age cut-offs, with mean treatment effect differences of –7.8 min ($p = 0.006$) for the age 18–80-year and −9.4 min ($p = 0.003$) for the 55–80-year and population (Table 4). Sleep latency as evaluated in the PSQI component 2 and the PSQI global score which measures sleep quality also improved significantly with PRM compared to placebo in these populations. Again, the mean treatment difference in PSQI global score was larger for the 55–80-year (−0.66; $p = 0.003$) than the 18–80-year (−0.44; $p = 0.027$) populations (Table 4). A consistent and significant advance in time going to bed (diary, relative to midnight) was observed with PRM in the 18–80 and 55–80 but not 18–54-year age cut-offs. Two additional variables, total sleep time (measured by the PSQI question 4) and quality of life (measured by WHO-5 Index), improved significantly after 3 week treatment with PRM compared to placebo in the age 55–80 but not 18–80 or 18–54-year age cut-offs that included

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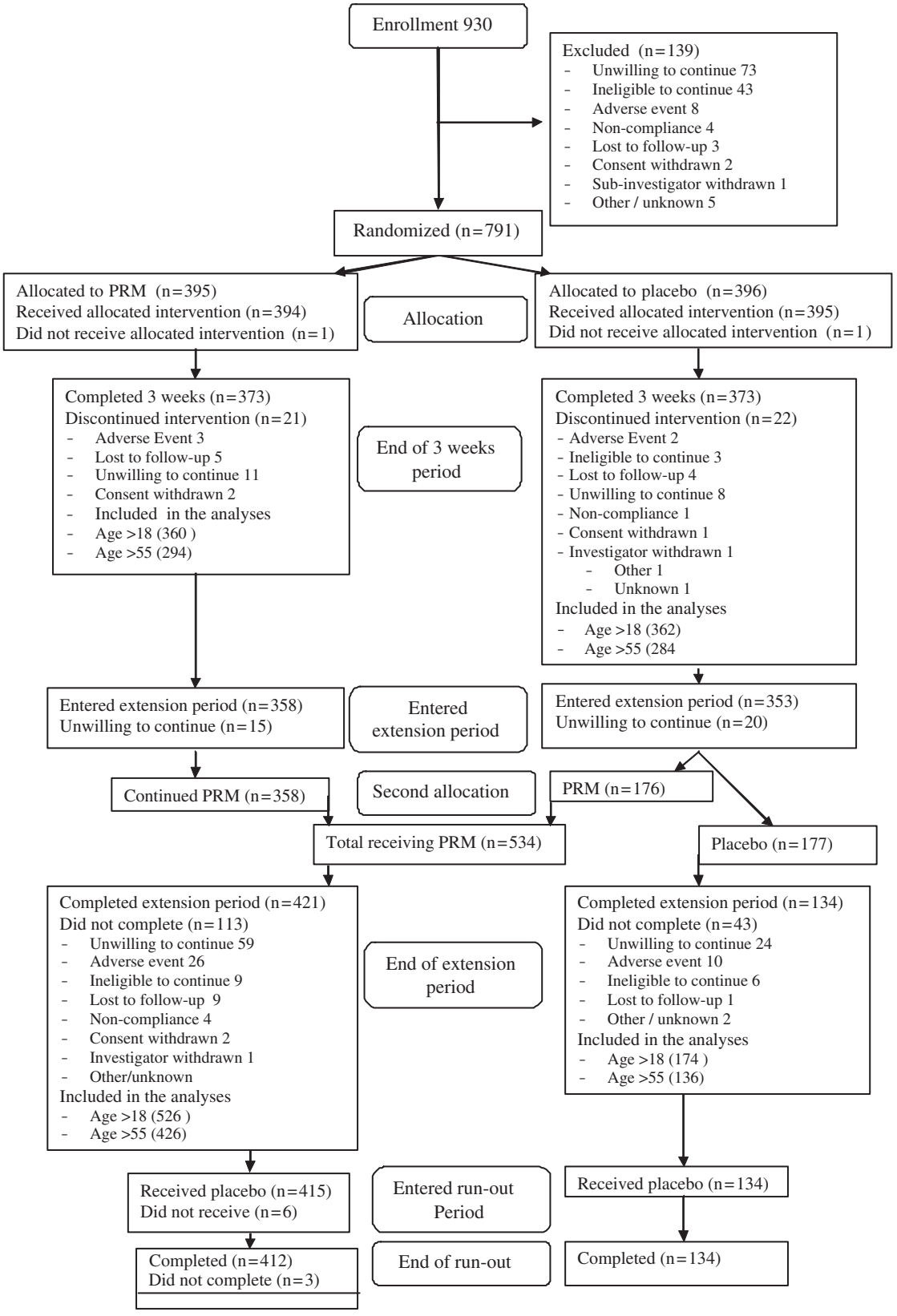

Figure 1. Overall study patient disposition (CONSORT diagram). The study comprised a 2-week, single-blind placebo run-in followed by a 3-week double-blind treatment with PRM or placebo. PRM patients continued whereas placebo completers were re-randomized 1:1 to PRM or placebo for 26 weeks followed by 2 weeks run-out on placebo.

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Table 1. Baseline characteristics of the study population.

Characteristic	Visit	*n*	All	Randomisation	
				PRM	Placebo
			722	360	362
Age (years)	1	Mean (SD)	61.7 (10.2)	61.9 (10)	61.5 (10.5)
Sex		*n* (%) female	497 (68.8%)	253 (70.3%)	244 (67.4%)
Race		*n* (%) white	713 (98.9%)	353 (98.1%)	360 (99.7%)
Height (m)	1	Mean (SD)	1.65 (0.09)	1.65 (0.09)	1.65 (0.09)
Weight (kg)	1	Mean (SD)	73.3 (13.1)	73.1 (13.5)	73.5 (12.7)
BMI (kg/m^2)	1	Mean (SD)	26.9 (3.9)	26.9 (3.8)	27.0 (3.9)
Taking any medications	1	*n* (%)	631 (87.4%)	321 (89.2%)	310 (85.6%)
Confirmed use of codeine analgesic	2	*n* (%)	84 (11.7%)	41 (11.4%)	43 (11.9%)
6-SMT excretion μg/night	1	Mean (SD)		17.9 (13.7)	17.4 (12.5)

Table 2. Medical history of the study safety population ($n = 722$ patients).

System	Ongoing/not ongoing	*n* (%) patients
Ears/eyes/nose/throat	*n* (%) Abnormal, not ongoing	93 (12.9%)
	n (%) Abnormal, ongoing	231 (32.0%)
Cardiovascular	*n* (%) Abnormal, not ongoing	61 (8.5%)
	n (%) Abnormal, ongoing	322 (44.7%)
Respiratory	*n* (%) Abnormal, not ongoing	31 (4.3%)
	n (%) Abnormal, ongoing	132 (18.3%)
Gastrointestinal	*n* (%) Abnormal, not ongoing	78 (10.8%)
	n (%) Abnormal, ongoing	334 (46.3%)
CNS	*n* (%) Abnormal, not ongoing	82 (11.4%)
	n (%) Abnormal, ongoing	124 (17.2%)
Musculoskeletal	*n* (%) Abnormal, not ongoing	72 (10.0%)
	n (%) Abnormal, ongoing	441 (61.1%)
Allergic	*n* (%) Abnormal, not ongoing	4 (0.6%)
	n (%) Abnormal, ongoing	223 (30.9%)
Urogenital	*n* (%) Abnormal, not ongoing	192 (26.7%)
	n (%) Abnormal, ongoing	188 (26.1%)
Dermatological	*n* (%) Abnormal, not ongoing	41 (5.7%)
	n (%) Abnormal, ongoing	212 (29.4%)
Endocrine/metabolic	*n* (%) Abnormal, not ongoing	13 (1.8%)
	n (%) Abnormal, ongoing	150 (20.8%)
Hepatic	*n* (%) Abnormal, not ongoing	15 (2.1%)
	n (%) Abnormal, ongoing	17 (2.4%)
Renal	*n* (%) Abnormal, not ongoing	19 (2.6%)
	n (%) Abnormal, ongoing	13 (1.8%)
Immunological	*n* (%) Abnormal, not ongoing	6 (0.8%)
	n (%) Abnormal, ongoing	5 (0.7%)
Other	*n* (%) Abnormal, not ongoing	67 (9.3%)
	n (%) Abnormal, ongoing	430 (59.6%)

younger patients (Table 4). Analysis of the interaction between treatment effects (PRM vs. placebo) and the age (18–54 and 55–80 years; ANCOVA) indicated that for the short-term period, treatment effects on SL (diary) and PSQI Global score were significantly higher in the 55–80 than the 18–54-year age cut-offs ($p = 0.034$ and $p = 0.043$, respectively). No such differences were noted for the other variables (Table 4)

The results of the long-term analyses comparing PRM and placebo treatment using mixed-effect model for repeated measures (MMRM) are presented in Table 5. As can be seen, all parameters that were significant between PRM and placebo at 3 weeks, continued to differ in the long-term period with no signs of tolerance. Thus significant long-term treatment effects were found for sleep latency as recorded by the diary, PSQI question 2 and PSQI component 2 in the 18–80 as well as the 55–80-year age cut-off. The advance in bedtime (diary) and the improvements in PSQI global score were also sustained over the long-term period in these age cut-offs (Table 5). Effects on SL as well as some additional variables were essentially enhanced over the long-term period in all age cut-offs reaching plateau levels after 3 months of treatment (Table 5; see also Figures 2 and 3 for the effects on SL diary and diary recorded time going to bed, respectively, in the age 55–80-year cut-off). Some variables, in particular quality of life (WHO-5) and clinical status (CGI-I), improved significantly with PRM in the long-term period in all age cut-offs (Table 5).

The number of variables improving significantly with PRM versus placebo and the mean treatment differences were generally larger for the age 55–80 years and lower for the 18–54-year age cut-offs, than the 18–80 that included the 55 years and older as well as younger patients. However, there were no significant differences between treatment effects in the age subgroups in the long-term period (Table 5).

Safety evaluation

The number (%) of patients experiencing an adverse event (AE) during the treatment and extension periods of the study, the most commonly occurring adverse events and other safety evaluations have been already published[8]. In brief, a total of 31 patients reported 42 serious adverse events (SAEs) during the study, including one death in a placebo-treated patient. One patient treated with PRM experienced an SAE of palpitations during the extension period of the study, which was assessed as possibly drug-related. Overall, a total of 59 patients discontinued treatment with study drug due to an AE. AE rates were generally similar in the two treatment groups. The only AEs assessed as definitely related to study drug were in a patient treated with placebo (labrynthitis, burning

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Table 3. Effects of 3 weeks' treatment with PRM and placebo on patient diary-recorded sleep latency in the age 18–80 and 55–80-year cut-offs.

Age cut-off	Sleep latency diary (min)				Treatment effect difference PRM – placebo		
	PRM		Placebo			*p*-value*	
	n		*n*		Estimate (95% CI)	PRM/placebo	≥55/<55
Baseline values		Mean (SD)		Mean (SD)			
18–80 years	360	76.4 (63.2)	362	71.2 (60.1)			
18–54 years	66	81.8 (73.1)	78	75.9 (85.3)			
55–80 years	294	75.1 (60.8)	284	69.9(51.2)			
Change from baseline (3 weeks)		Mean change (SD)		Mean change (SD)			
18–80 years	360	−14.6 (43.9)	362	−7.9 (50.9)	−4.4 (−10.2, 1.3)	$p=0.129$	
18–54 years	66	−11.0 (41.4)	78	−16.6 (71.9)	8.0 (−4.9, 20.9)	$p=0.223$	$p=0.034$
55–80 years	294	−15.4 (44.4)	284	−5.5 (43.2)	−7.8 (−14.1, −1.6)	$p=0.014$	

*ANCOVA treatment effect.

Table 4. Other efficacy measures showing statistically significant differences between treatment groups after 3-weeks in the age 18-80 and 55-80-year cut-offs.

Parameter	Tool	Mean (SD) change from baseline		Treatment effect difference PRM – placebo		
		PRM	Placebo	Estimate (95% CI)	*p*-value*	
					PRM/placebo	≥55/<55
Population age: 18–80 years		$n=360$	$n=362$			
Sleep latency	PSQI Q2 (min)	−20.9 (47.7)	−9.7 (41.0)	−7.8 (−13.4, −2.2)	0.006	
	PSQI C2	−0.38 (0.77)	−0.24 (0.74)	−0.13 (−0.24, −0.02)	0.023	
Total sleep time	PSQI Q4 (h)	0.59 (1.00)	0.46 (0.94)	0.10 (−0.04, 0.23)	0.170	
Time going to bed	Diary (hours from midnight)	−0.21 (0.80)	−0.04 (0.72)	−0.14 (−0.24, −0.03)	0.011	
Sleep quality	PSQI global score	−1.92 (2.89)	−1.32 (2.70)	−0.44 (−0.84, −0.05)	0.027	
Quality of life	WHO-5	1.06 (3.76)	0.31 (3.25)	0.48 (−0.01, 0.96)	0.053	
Population age: 18–54 years		$n=66$	$n=78$			
Sleep latency	PSQI Q2 (min)	−16.1 (49.7)	−9.5 (34.7)	−0.5 (−13.1, 12.1)	0.938	0.21
	PSQI C2	−0.27 (0.69)	−0.33 (0.79)	0.07 (−0.18, 0.31)	0.598	0.09
Total sleep time	PSQI Q4 (h)	0.52 (0.93)	0.58 (0.90)	−0.14 (−0.44, 0.17)	0.387	0.1
Time going to bed	Diary (hours from midnight)	−0.18 (0.74)	−0.02 (0.85)	−0.07 (−0.31, 0.16)	0.532	>0.1
Sleep quality	PSQI global score	−1.65 (3.27)	−1.78 (2.55)	0.37 (−0.51, 1.25)	0.412	0.043
Quality of life	WHO-5	0.47 (4.42)	0.42 (3.26)	−0.34 (−1.42, 0.74)	0.537	>0.1
Population age: 55–80 years		$n=294$	$n=284$			
Sleep latency	PSQI Q2 (min)	−22.0 (47.2)	−9.7 (42.6)	−9.5 (−15.8, −3.3)	0.003	
	PSQI C2	−0.41 (0.78)	−0.22 (0.72)	−0.17 (−0.29, −0.05)	0.005	
Total sleep time	PSQI Q4 (h)	0.61 (1.01)	0.42 (0.95)	0.15 (0.00, 0.31)	0.048	
Time going to bed	Diary (hours from midnight)	−0.22 (0.82)	−0.04 (0.68)	−0.15 (−0.26, −0.03)	0.014	
Sleep quality	PSQI global score	−1.98 (2.80)	−1.20 (2.74)	−0.65 (−1.09, −0.21)	0.003	
Quality of life	WHO-5	1.19 (3.58)	0.29 (3.25)	0.65 (0.12, 1.19)	0.017	

*ANCOVA treatment effect

sensation and pharyngolaryngeal pain). Changes in clinical laboratory results endocrine function (including prolactin, LH and cortisol) were generally small and showed no treatment-related trends. There were no apparent differences between treatment groups in vital signs, ECG, physical examination or any of the safety outcomes recorded in the intent-to-treat 18–80 as well as 55–80-year populations.

There was no evidence of a difference between treatment groups in the proportion of subjects experiencing new symptoms on the Tyrer questionnaire after the withdrawal period (secondary efficacy endpoint), which was about 28% in both groups ($p=0.881$) indicating no withdrawal effects.

Discussion

Melatonin receptor agonists (PRM, ramelteon) constitute a new class of drugs for insomnia. Unlike current hypnotics which are mostly based on GABA-A receptor modulation, melatonin receptor agonists do not impair cognitive functioning and memory, do not increased risk of falls and have a low abuse potential. These drugs may therefore be particularly valuable for elderly insomnia patients.

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Table 5. Efficacy measures showing significant treatment effect differences in the 6-months period in the age 18–80 and 55–80-year cut-offs.

Parameter	Tool	Treatment effect		*p*-value*	
		Mean	95% CI	PRM vs. placebo	≥55 vs. <55
Population age: 18–80 years					
Sleep latency	Diary (min)	−6.0	−10.0, −2.1	0.003	
	PSQI C2	−0.10	−0.20, −0.01	0.032	
	PSQI Q2 (min)	−6.8	−10.9, −2.6	0.001	
Total sleep time	PSQI Q4 (h)	0.09	−0.02, 0.20	0.102	
Time going to bed	Diary (hours from midnight)	−0.13	−0.20, −0.05	0.002	
Sleep quality	PSQI global score	−0.39	−0.71, −0.08	0.014	
Quality of sleep	PSQI C1	−0.08	−0.15, 0.00	0.046	
Daytime functioning	PSQI C7	−0.07	−0.13, 0.00	0.040	
Morning alertness	Diary	−0.07	−0.13, 0.00	0.047	
Quality of life	WHO-5	0.46	0.11, 0.81	0.011	
Clinical status	CGI-I	−0.12	−0.24, −0.01	0.036	
Population age: 18–54 years					
Sleep latency	Diary (min)	−1.5	−9.7, 6.8	0.728	0.205
	PSQI C2	−0.01	−0.21, 0.19	0.934	0.275
	PSQI Q2 (min)	−4.0	−12.8, 4.8	0.371	0.482
Total sleep time	PSQI Q4 (h)	0.02	−0.22, 0.25	0.885	0.458
Time going to bed	Diary (hours from midnight)	−0.15	−0.31, 0.02	0.085	0.805
Sleep quality	PSQI global score	−0.07	−0.73, 0.60	0.840	0.259
Quality of Sleep	PSQI C1	−0.06	−0.22, 0.10	0.441	0.844
Daytime functioning	PSQI C7	−0.04	−0.17, 0.10	0.601	0.645
Morning alertness	Diary	−0.10	−0.23, 0.04	0.171	0.626
Quality of life	WHO-5	0.37	−0.36, 1.11	0.320	0.806
Clinical status	CGI-I	−0.08	−0.32, 0.16	0.516	0.651
Population age: 55–80 years					
Sleep latency	Diary (min)	−8.0	−12.4, −3.7	<0.001	
	PSQI C2	−0.15	−0.25, −0.05	0.004	
	PSQI Q2 (min)	−7.7	−12.3, −3.0	0.001	
Total sleep time	PSQI Q4 (h)	0.13	0.01, 0.26	0.034	
Time going to bed	Diary (hours from midnight)	−0.14	−0.23, −0.05	0.002	
Sleep quality	PSQI global score	−0.53	−0.87, −0.19	0.002	
Quality of sleep	PSQI C1	−0.09	−0.17, −0.01	0.024	
Daytime functioning	PSQI C7	−0.07	−0.14, 0.00	0.036	
Morning alertness	Diary	−0.07	−0.14, 0.00	0.062	
Quality of life	WHO-5	0.52	0.13, 0.90	0.008	
Clinical status	CGI-I	−0.16	−0.29, −0.04	0.01	

MMRM analysis (mixed model repeated measure).

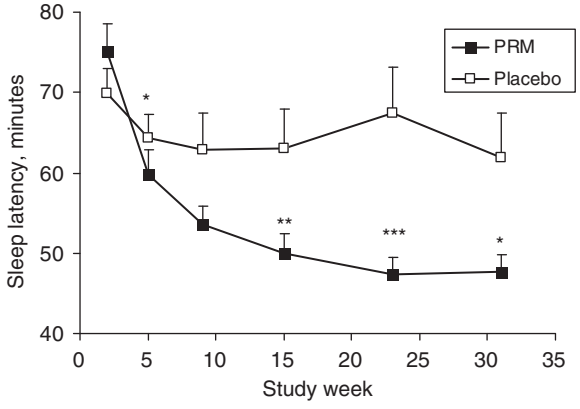

Figure 2. Model-predicted average values (mean ± SEM) for sleep latency from the sleep diary at baseline and weeks 1–29 of the double-blind treatment periods, in the intent-to-treat 55–80-year population. Asterisks denote significant difference between PRM and placebo groups (*$p<0.05$, **$p<0.01$).

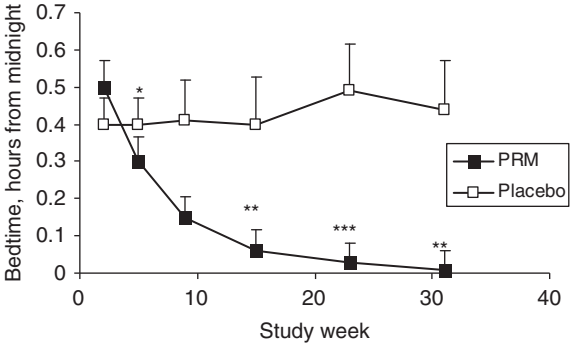

Figure 3. Model-predicted average values (mean ± SEM) for time going to bed (hours relative to midnight) from the sleep diary at baseline and weeks 1–29 of the double-blind treatment periods, in the intent-to-treat 55-80-year population. Asterisks denote significant difference between PRM and placebo groups (*$p<0.05$, **$p<0.01$).

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This study was aimed at addressing a regulatory question on whether PRM should be indicated for insomnia in patients of a certain age group, or whether it should be indicated for patients with low endogenous melatonin regardless of their age. It demonstrated short- and long-term efficacy and safety of PRM in elderly insomnia patients. Inherent to the design, the study also provided extensive data on the efficacy and safety of PRM therapy in a large cohort of insomnia patients aged 18–80 years. This allowed further investigation into the age cut-off for response.

The prevalence of insomnia in the general population and in various age bands[15] and the current demography in the Western world, indicate that patients aged 55 years and older should comprise about 70% of adult insomnia population. In our study the 55-year and older population was somewhat over represented (80%). However, because of the large size of the study cohort, the actual number of recruited patients who were aged <55 years in the study ($n = 186$) was at least as large as the total study population in other insomnia trials, including PRM clinical trials[4]. Furthermore, two-thirds of the patients were females and a quarter of the patients had low 6-SMT levels which conform with the demographic characteristics of insomnia population[3,15]. These characteristics appeared to be representative of the general insomnia patient population. The results obtained in the study are therefore valid for the general primary insomnia patient population.

Based on the short-term effects of PRM on the primary efficacy variable (SL diary), there is evidently significant response in patients aged 55 years and older. Notably, for the age 65–80-year cut-off the reduction in SL diary with PRM compared to placebo was even higher (−19.1 vs. −1.7 min; $p = 0.002$)[8]. Other variables, such as SL-PSQI and the global sleep quality score (PSQI) improved significantly with PRM versus placebo in the total 18–80-year population with somewhat larger effects in the 55-year and older patients comparable to those seen with the age 65–80-year cut-off population[8]. Some improvement in quality of life and total sleep time were noted in the age 55–80-year cut-offs only.

Long-term analyses, estimating global treatment effect in the 18–80 and 55–80-year age cut-off populations showed that the variables that improved significantly during the 3-week period were enhanced or maintained in the long-term period as was the case with the age 65–80-year cut-offs[8]. Beside sleep latency, long-term PRM treatment had significant beneficial effects compared to placebo on sleep quality (PSQI global score), quality of life measured by the WHO-5 and Clinical Global Impression of Improvement (CGI-I). The effects are seen with the 18–80 and 55–80 but not 18–54-year age cut-off and are sustained or enhanced over the longer PRM treatment duration. This efficacy profile of PRM was difficult to demonstrate with other sleep drugs suggesting that the improvements in quality of life and clinical status are not inherently linked to the shortening of SL.

The 55 years and older population appears to have the most benefit from PRM treatment at least during the initial 3-week period. This observation is compatible with the melatonin replacement therapy hypothesis that assumes that patients who are age 55 years or more experience significant age related decline in output of the circadian clock[16–18] and melatonin production capacity[19–21] and are thus more likely to benefit.

An interesting trait is the behavioural change by which patients treated with PRM went significantly earlier to bed than those with placebo in all age-cut-offs. This behavioural change is unlikely due to the participation in the study or the instructions given to the patients to take the drug in the evening (between 9 and 11 pm, 1–2 hours before bedtime) first of all because no such advance in bedtime was seen in the placebo-treated groups. Secondly, induction of fatigue and sleepiness by melatonin should be quite immediate, such as in jet lag or when ingested at times that it is not present endogenously[22–24] whereas the shift in bedtime appears to be progressive in the first 3 months of treatment. A reasonable assumption would be that the advance in bedtime is due to the effect of PRM on the body's internal clock. Studies in totally blind individuals have shown that the time it takes to entrain to the melatonin phase is relatively long (weeks to months) and varies greatly among individuals[25,26]. The authors therefore propose that besides sleep induction, PRM replacement therapy acts to reinstate the internal temporal order that appears to dissipate in older age[16]. This notion is compatible with the change in cortisol peak time and improvement in nocturnal blood pressure rhythm seen with this formulation[27,28]. Another plausible explanation for the gradual evolution of response is recovery of responsiveness to melatonin that is diminished in aging. Studies in rats have demonstrated age-related decline in density of melatonin-binding sites in the brain and the reinstatement of the binding capacity following administration of exogenous melatonin[29]. In humans, brain MT1 melatonin receptors also decline with aging concomitantly with the decline in melatonin production[30]. Whether melatonin replacement therapy is able to reverse this decline remains to be investigated.

The clinical significance of the primary variable (sleep latency) needs to be evaluated in the context of the effects of current hypnotics. With PRM, effects measured by subjective (diary, PSQI) and objective (polysomnography) means are remarkably consistent[5,6]. A similar match between objective and subjective findings has been demonstrated with ramelteon[31] reflecting ability of the patients to correctly evaluate their sleep with these drugs. In contrast, in trials with benzodiazepines and the newer non-benzodiazepine hypnotics (Z drugs), subjectively recorded effects are larger than the actual

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effects[32–34], and the discrepancies are ascribed to the amnesic effects of these drugs, which preclude the patient's ability to correctly assess the circumstances of their sleep[35,36]. It is therefore appropriate to compare subjective and objective values of sleep latency obtained with melatonin receptor agonists to objective rather than subjective values obtained with GABA-A receptor modulators. In a recent meta-analysis, the mean difference from placebo on polysomnographically recorded SL with traditional GABA-A modulators (e.g., triazolam, temazepam, nitrazepam) was 10 min and with newer GABA-A modulators (e.g., zopiclone, zolpidem, eszopiclone, zaleplon) was 12.8 min[37]. The mean difference from placebo on objectively as well as subjectively recorded SL with ramelteon was reportedly 15 min at week 1 and 9 min at 6 months[31]. Mean differences from placebo in sleep latency of approximately 9.4 min at week 3 increasing to 15.4 min at ≥6 months, with PRM as demonstrated in the present and previous studies[5,6,8] are thus comparable to those of current hypnotics. More so, the clinical relevance of the effects of PRM is further demonstrated by the improvements in quality of life and global clinical status, indicating that the apparently modest effects on sleep latency and other sleep parameters are meaningful to the patient.

According to established criteria for clinical meaningfulness of insomnia drugs[31,38], by which a responder is a patient improving in sleep latency to 30 min or less, among the patients who had SL > 30 at baseline (85.6% of the PRM and 87.2% of the placebo group) the responder rate with PRM at 6 months in the age 55–80-year population was significantly higher than placebo (43.0 vs. 29.8%, $p = 0.032$, χ^2 test). Moreover, the rate of patients showing response increased from 29.2% after 3 weeks to 45.1% after 3 months of treatment suggesting that some patients may need more than 3 weeks to attain response. For CGI-I, 37.5% of patients in the intent-to-treat 55–80-year cut-off group improved much or very much by the end of the 6 months' treatment period with PRM compared to 26.9% with placebo ($p = 0.044$). Altogether, these analyses demonstrate that the efficacy profile of PRM is indeed clinically relevant.

PRM was well-tolerated with an adverse-event profile similar to that of placebo, consistent with previous clinical studies. There were no new or unexpected safety findings following short- and long-term treatment with PRM. The safety profile of the two treatment groups was very similar to placebo with respect to AEs, laboratory tests including hormones, vital signs, ECG and physical examination. Additionally, common clinical concerns related to long-term hypnotic use such as tolerance and discontinuation effects were not observed.

A recently published British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders recommended PRM as fist-line treatment for insomnia patients aged 55 years and older[39] but noted that long-term data on safety and efficacy of this drug are lacking. The results of the present long-term study provide evidence that PRM is effective and safe for 6 months in patients aged 18–80 years, particularly those aged 55–80 years for whom the drug is currently indicated.

Conclusions

The results of this study demonstrate short- and long-term efficacy of PRM in insomnia patients, with patients aged 55 years and older having the most benefit. There were no rebound or withdrawal effects upon discontinuation of PRM following long-term use. The safety and efficacy profile of PRM as demonstrated in this study support its continuous use for several months in the treatment of primary insomnia in the target population.

Transparency

Declaration of funding
The study was funded by Neurim Pharmaceuticals, Tel-Aviv, Israel.

Declaration of financial/other relationships
A.G.W. and I.F. have disclosed that they have acted as paid consultants to Neurim. T.N., M.L. and N.Z. have disclosed that they are employees of Neurim.

Acknowledgement
The authors thank Dr G. Crawford and partners, Dr R. Lesley and partners, Dr D. Campbell and partners, Dr M. MacRae and partner, Dr M. Angus and partners and Dr S. Connolly and partners who managed the patients so admirably. The authors are also indebted to the research nurses and management staff of CPS Research without whom the study would not have taken place.

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