

# ROZEREM<sup>®</sup>(Ramelteon) Product Strategy

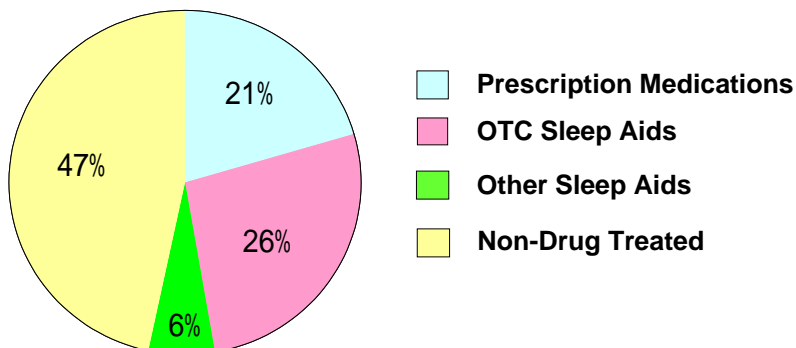
## Strategic Product Planning

General Manager, Kazuaki Ikeya

This presentation contains forward-looking statements such as figures and development progress in the future, all of which are based on the information available to date. It does not aim at any advertisement/promotion or medical advice.

## Market of Therapeutic Drugs for Sleep Disorders in US

Prevalence : 75,960,000 (≥18 years of age)



Source: Sleep in America poll (2005)

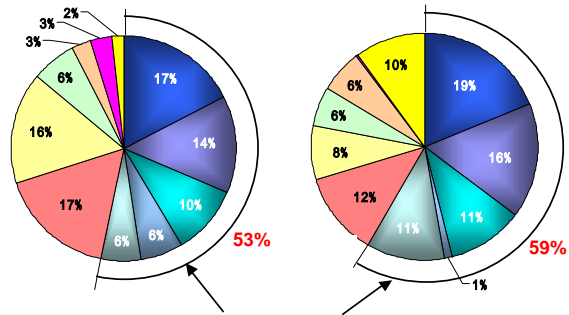
# Consumer Research for Prescription Drugs (Those who don't take prescription drugs)

## Reason for no use of prescription drugs

- Habit formation
- Groggy next day
- Anxiety for long-term effects
- Too strong / knock me out
- Doctor's discourage for use
- Dislike prescription drugs
- Manageable by themselves
- Insomnia doesn't affect the next day ability
- Not so severe
- Not so frequent
- OTC may be adequate
- No major concern about Rx drugs

Those who don't take either RX/OTC  
(# of respondents:436)

Those who take only OTC  
(# of respondents: 323)



Potential Target for Rozerem

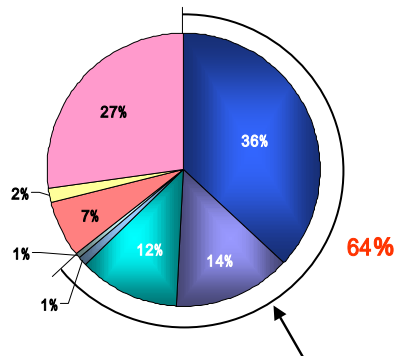
Market Research (March, 2004) <sup>2</sup>

# Consumer Research for Prescription Drugs (Those who take prescription drugs)

## Concerns for use of prescription drugs

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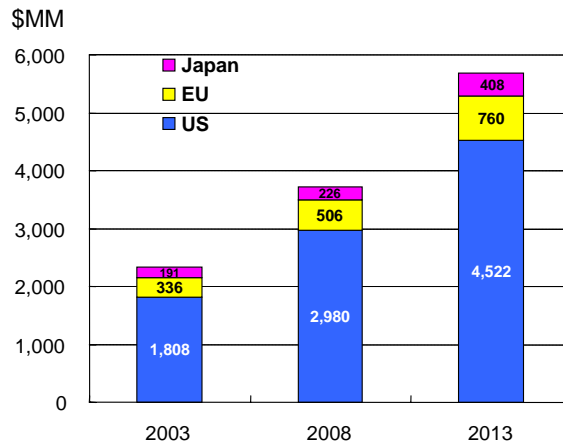
(# of respondents: 241)



Potential Target for Rozerem

Market Research (March, 2004) <sup>3</sup>

## Market Forecast for Insomnia Drugs in US

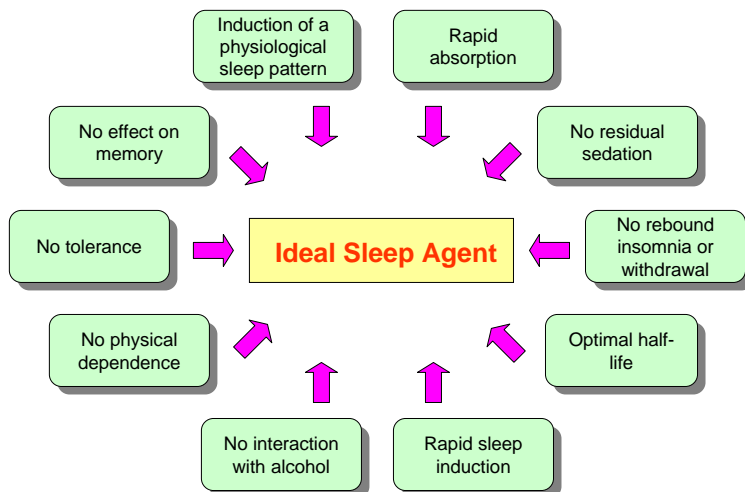


Market will grow, because use of Rx medicines is still limited

Source : Decision Resources (Decision Base 9)

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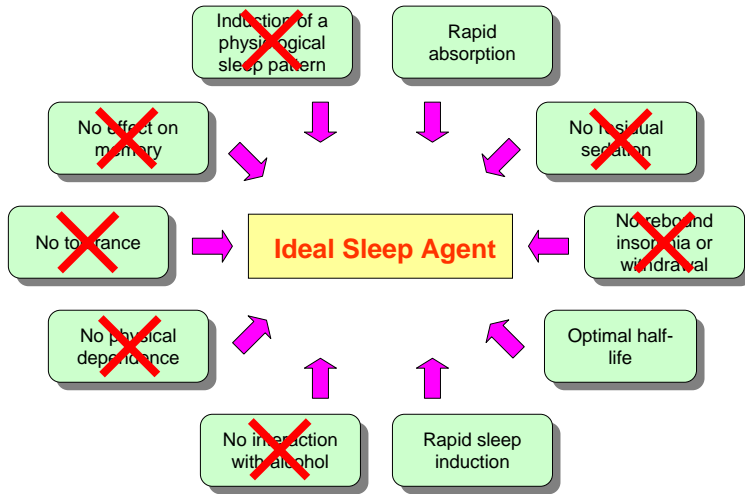
## Characteristics of the Ideal Sleep Agent



Source : DATAMONITOR (2004)

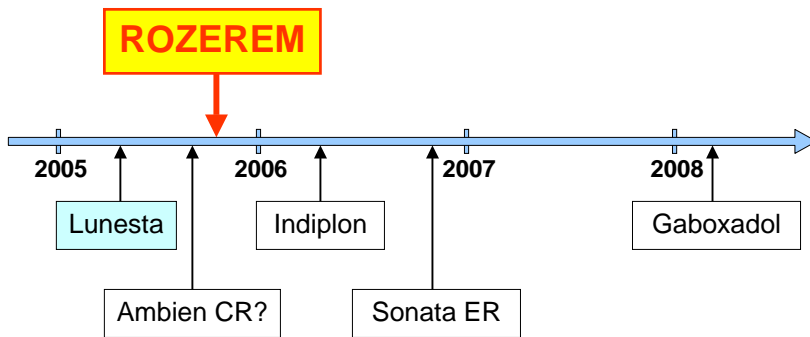
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# GABA<sub>A</sub> Agonists



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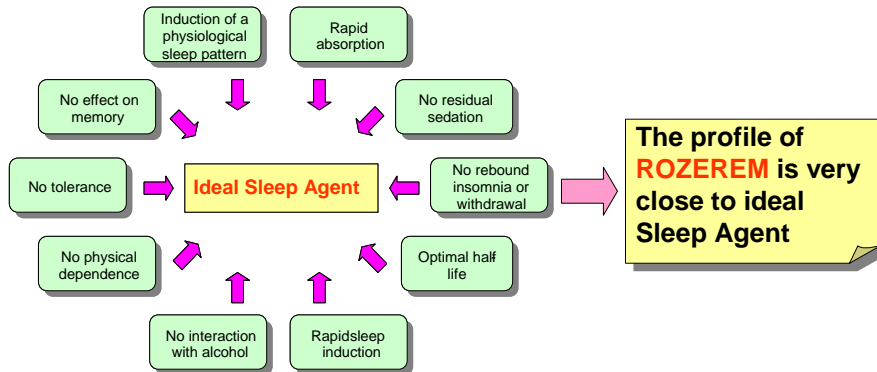
# Competitors



All competitors are GABA<sub>A</sub> receptor agonists and cause sedative sleep.

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# Ideal Sleep Agent



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## Marketing Strategy for ROZEREM

- Sales force: MR500+CSO
- Target physicians : GP/PCP, KOL (sleep specialist), Psychiatrist
- Importance of educational activity to physicians and patients
  - \* What is sleep?
  - \* What are required for the ideal medicine for sleep disorders

- 
- Acquire physicians and patients' understanding of "what is sleep?" and role of sleep
  - Establish that ROZEREM has a novel therapeutic drug causing physiological sleep
  - Establish positioning of first-line therapy for insomnia can be used without safety concern
  - Distinct from all current sedative-hypnotics

Key message :

**Sleep without the Worry**

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# **ROZEREM® (Ramelteon)**

## **Product Profile and Ph III Results**

**Strategic Product Planning Department**

**Project Leader, Masaomi Miyamoto**

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## **Classification of Sleep Disorders**

### **1. Insomnia**

#### **A) Primary Insomnia**

Stress, aging etc.

#### **B) Secondary Insomnia**

a) Psychiatric disorders (GAD, depression, schizophrenia etc.)

b) Neurological diseases (Alzheimer's disease, Parkinson's disease, etc.)

c) Others

### **2. Circadian Rhythm Sleep Disorders (CRSD)**

#### **A) Jet lag**

#### **B) Shift work**

#### **C) Irregular sleep/wake cycle sleep pattern**

#### **D) Delayed sleep phase syndrome (DSPS)**

#### **E) Advanced sleep phase syndrome (ASPS)**

#### **F) Non-24hr sleep/wake cycle syndrome**

# Current Medication of Sleep Disorders

## 1. Insomnia

### GABA<sub>A</sub> receptor agonists

(triazolam, zolpidem, zaleplon, eszopiclone,)

#### 1) Adverse effects

Memory impairment, motor impairment, dependence, drug abuse, hangover, tolerance, rebound, etc.

#### 2) Quality of sleep

Sedative sleep (different from natural sleep)

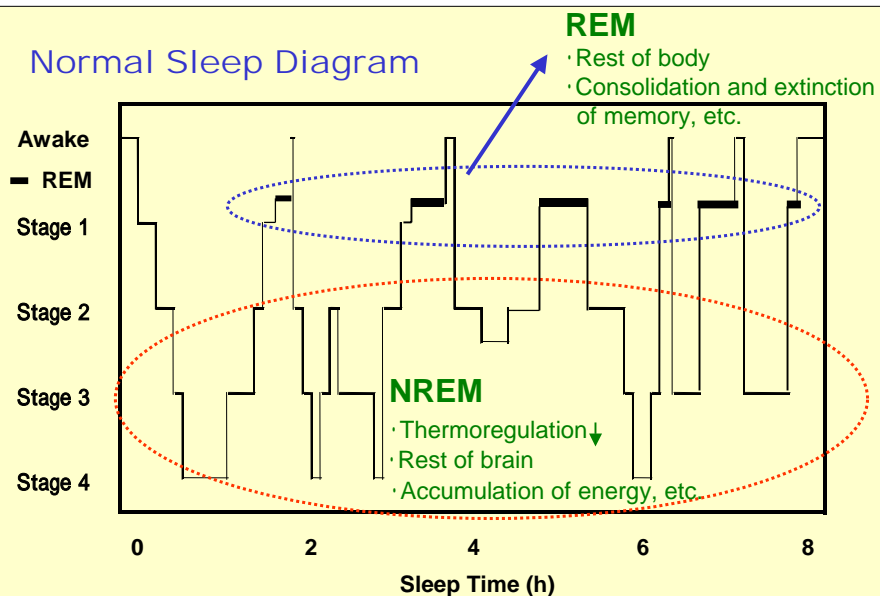
## 2. Circadian Rhythm Sleep Disorder (CRSD)

Currently no drug for CRSD

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# What Is Sleep?

## Normal Sleep Diagram



# Role of NREM and REM Sleep

## NREM Sleep

## REM Sleep

(Thermoregulation at lower level)

1. Rest of brain (cerebral cortex)
2. Secretion of GH
3. Synthesis of protein
4. Activation of immune function

1. Rest of body
2. Memory consolidation and extinction
3. Processing of information, etc.

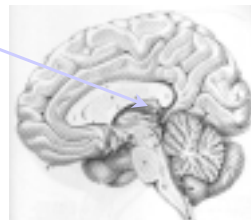
Keep safety during sleep

Reduction of energy consumption

# Melatonin and Natural Sleep

- Melatonin is synthesized from tryptophan in the pineal body, and released during nighttime. Melatonin activates  $MT_1/MT_2$  receptors in the suprachiasmatic nucleus (SCN).
- Physiological action
  - Sleep-promoting action
  - Regulation of circadian rhythm

Pineal body



# Drug Concept (1)

Problems of current hypnotics (GABA<sub>A</sub> agonists; zolpidem, zaleplon, triazolam, eszopiclone, etc)

- 1) Memory impairment, ataxia, dependence, drug abuse, tolerance, residual effects (dizziness), rebound insomnia, etc.
- 2) Sleep is sedative sleep (different from natural one).



Ideal Sleep Agent: Natural sleep without adverse effects



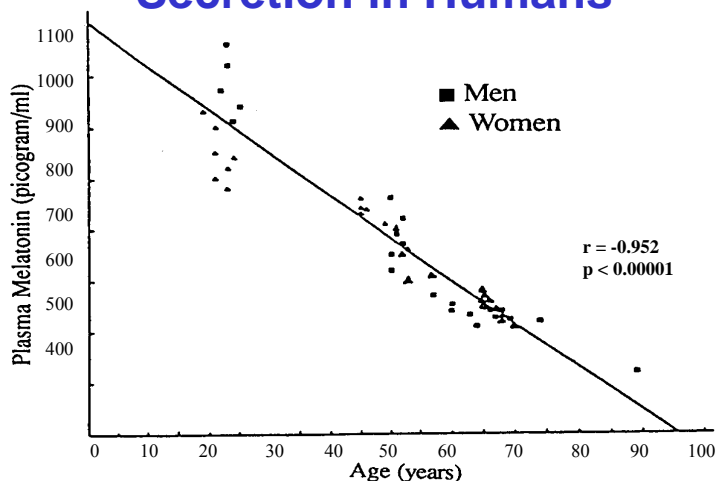
MT<sub>1</sub>/MT<sub>2</sub> Receptor--Sleep promotion, chronobiotic action  
MT<sub>3</sub> binding site - QR2 (quinone reductase)



**MT<sub>1</sub>/MT<sub>2</sub> Receptor Agonist**

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## Age-Related Decrease in Melatonin Secretion in Humans



Nair et al. (1986) 8

## Drug Concept (2)

Age-related decrease in melatonin secretion



Insomnia in middle and elderly people (sleep onset, sleep maintenance and early morning waking up)

Correlation with decreased melatonin secretion ?



MT<sub>1</sub>/MT<sub>2</sub> agonist may provide suitable medication for middle and elderly insomnia patients

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## Drug Concept (3)

*Medication of CRSD  
(Currently no prescription drug)*

- 1) Jet lag
- 2) Shift workers
- 3) ASPS and DSPS, etc.



Adjustment of sleep-wake cycle



Melatonin MT<sub>2</sub>(MT<sub>1</sub>) agonist

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# Ramelteon (ROZEREM®) Chronology

1991.10 BBC reported “Halcion Nightmare”, in which amnesia caused by Halcion (triazolam) had become social problem based on the report by a Dutch psychiatrist, Dr. van der Kroef.

The then COO directed to create a novel drug can be taken without safety concerns.

1992.04 Research start of drug for sleep disorders

1993.12 Research start of melatonin receptor agonist

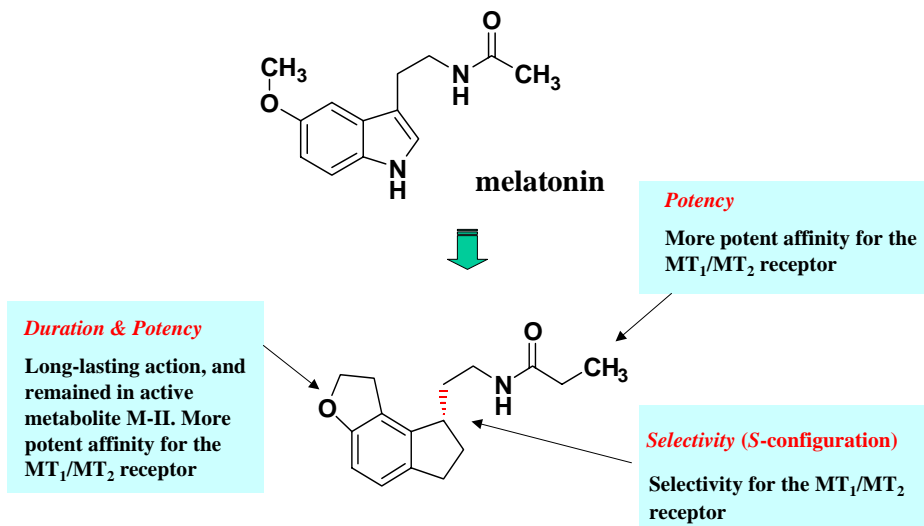
1996.03 Discovery of Ramelteon (TAK-375)

1999.02 Start of clinical trials

2004.09 Submission of Ramelteon NDA to FDA

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## Chemical Structure of Ramelteon



**Rozerem® (Ramelteon, TAK-375)**

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# Summary of Preclinical Pharmacology

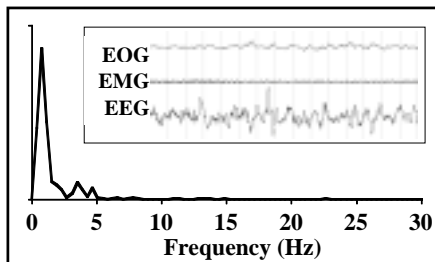
1. Ramelteon is a selective  $MT_1/MT_2$  receptor agonist, and affinity for other receptors and effects on enzymes are negligible. The *in vitro* activity is 3-17 times more potent than melatonin.
2. Ramelteon shows much more potent and long-lasting sleep promoting action compared with melatonin in experimental animals. The activity is about 10 times more potent and the duration is 3-4 times longer than melatonin.
3. Ramelteon enhances reentrainment of circadian rhythm to new LD cycle.
4. Ramelteon has no adverse effects on learning and memory, motor function, drug preference even at high doses, suggesting that its adverse effects are quite low.

**These results suggest that ramelteon is promising as a novel therapeutic drug for sleep disorders.**

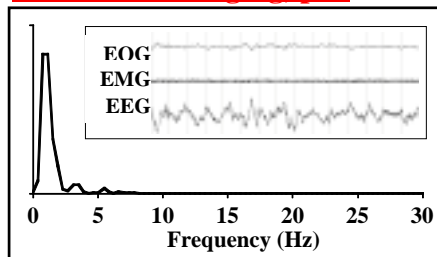
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## Spectral Analysis of Sleep Patterns in Monkeys

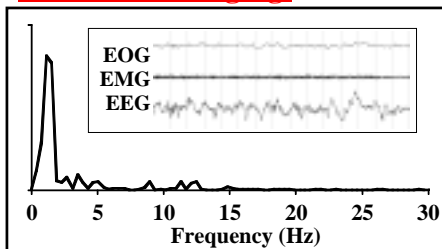
### Control



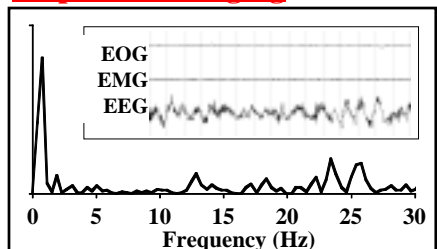
### Rozerem 0.3 mg/kg, p.o.



### Melatonin 1 mg/kg.

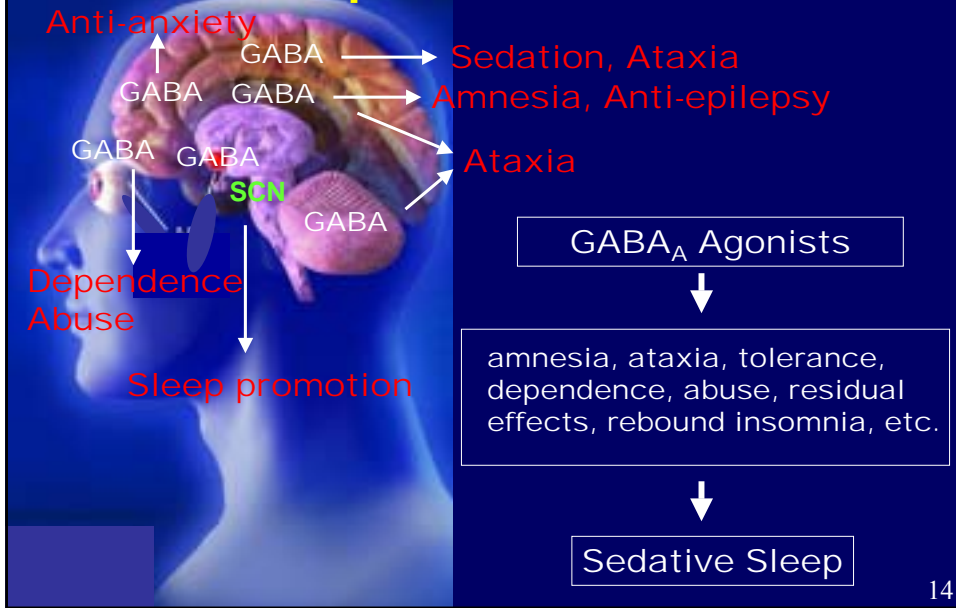


### Zolpidem 30 mg/kg

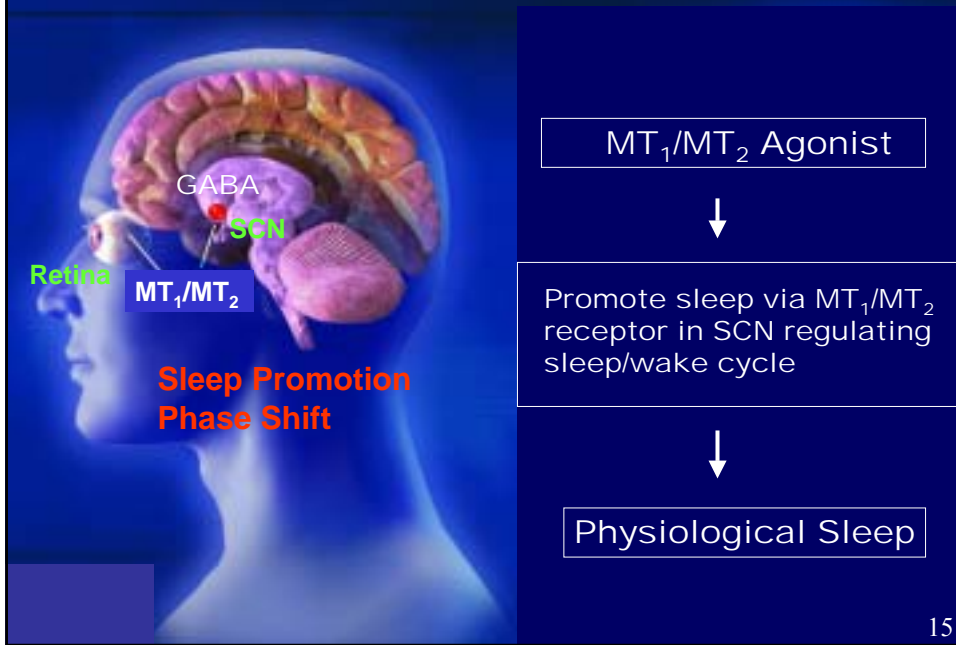


Rozerem shows similar spectrum to control.

# GABA<sub>A</sub> Agonists Stimulate All GABA<sub>A</sub> Receptors in the Brain



# ROZEREM<sup>®</sup> is MT<sub>1</sub>/MT<sub>2</sub>-Selective Agonist



## **Phase Trials**

**(Presentation in the 19th APSS in Denver)**

- 1. Efficacy and safety in adult patients  
by chronic treatment for 5 weeks  
(Mainly objective evaluation by PSG)**
- 2. Efficacy and safety in elderly patients  
by chronic treatment for 5 weeks  
(Subjective evaluation by sleep diary)**

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## **Efficacy of Ramelteon in Adults with Chronic Insomnia**

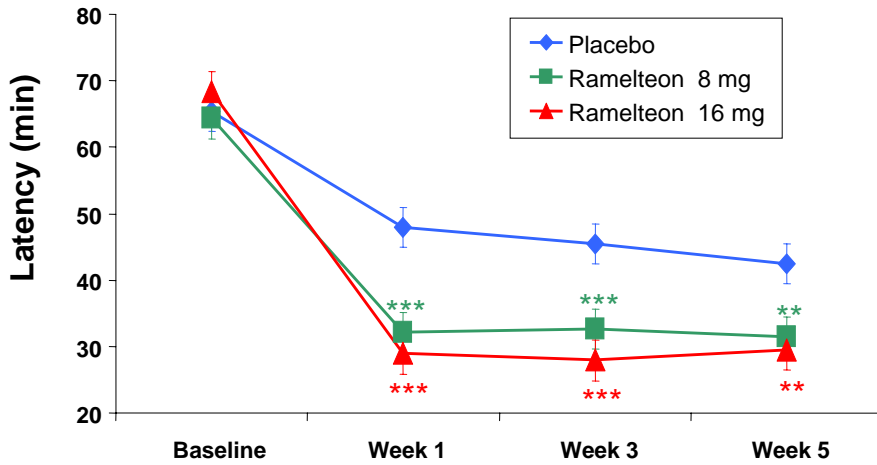
**(APSS #680)**

- Subjects : Adults patients (mean age: 39.3 years)**
- Number of patients : 405 (male 133; female 272)**
- Group : Ramelteon 8mg, 16mg, Placebo**
- Period : 5 weeks treatment, 2-day run-out**
- Efficacy and safety measure:**
  - 1) Mean latency to persistent sleep (LPS) was assessed  
by PSG and patient reports**
  - 2) Next-morning residual effects**
  - 3) Rebound insomnia and withdrawal effects**

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# Objective Sleep Latency (LPS)

(Evaluation by PSG)



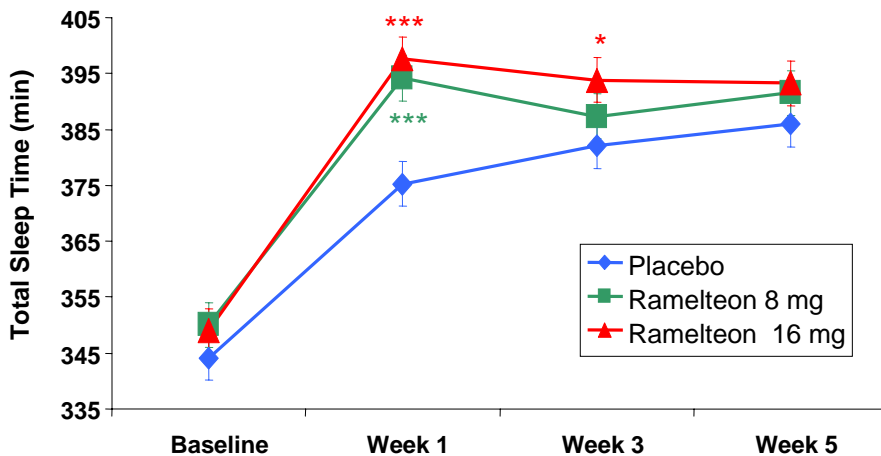
\*\*P<0.01 \*\*\*P<0.001

No tolerance in efficacy

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# Objective Total Sleep Time

(Evaluation by PSG)

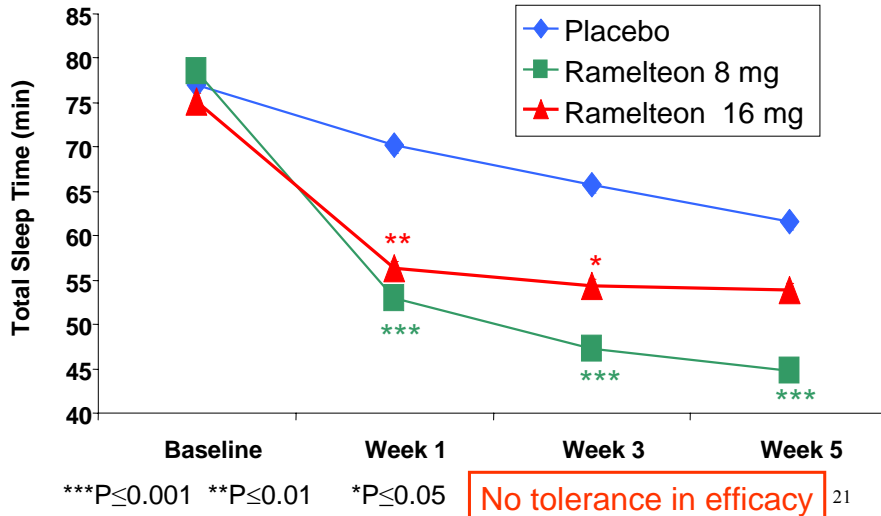


\*\*\*P<0.001 \*P<0.05

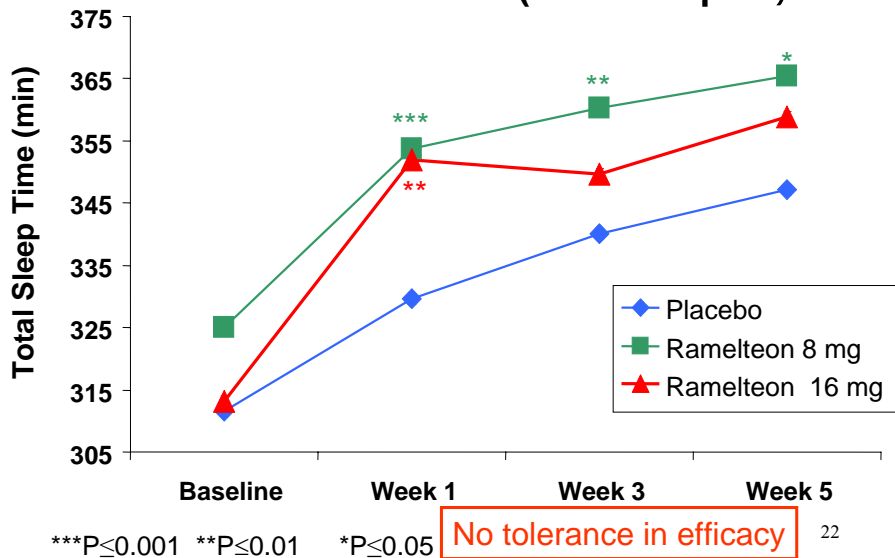
No tolerance in efficacy

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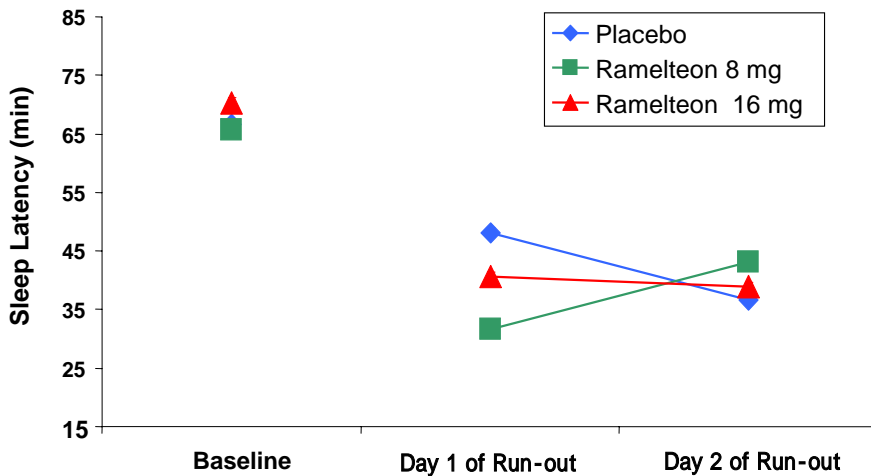
## Subject Sleep Latency (Patient report)



## Subjective Total Sleep Time (Patient report)



## Rebound Insomnia



No rebound was observed

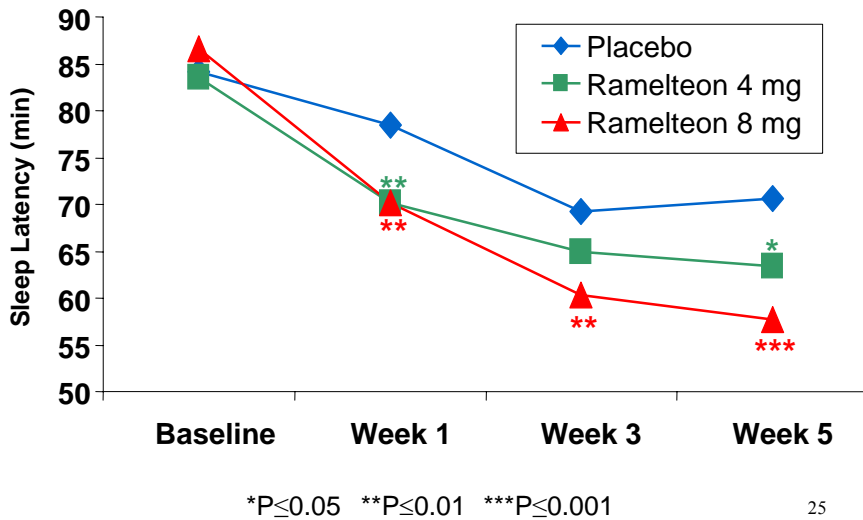
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## Efficacy of Ramelteon in Elderly Patients with Chronic Insomnia (APSS #679)

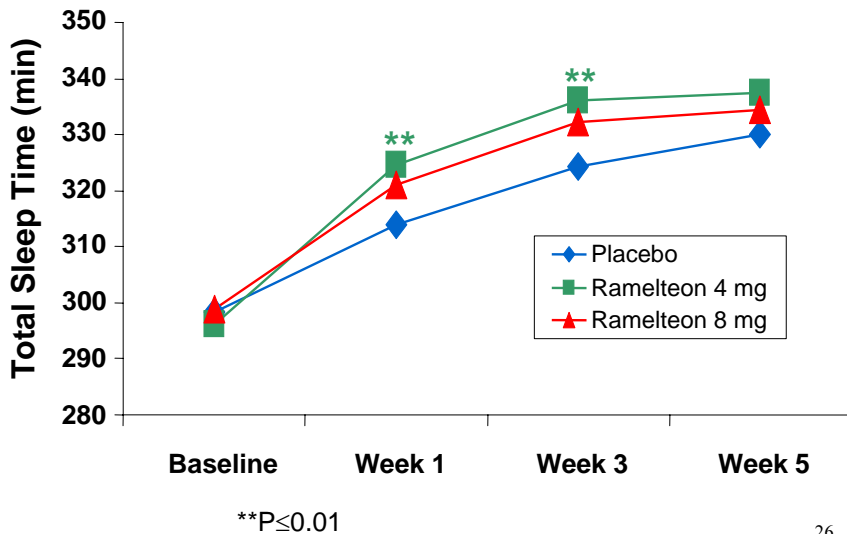
- Subjects: Elderly patients (mean age: 72.4 year)
- Number of patients: 829 (male 341; female 488)
- Group: Ramelteon 4mg, 8mg, Placebo
- Period: 5 weeks treatment and 1 week withdrawal
- Efficacy and safety measure: Sleep latency and total sleep time by sleep diary, rebound insomnia, withdrawal effect, adverse effects

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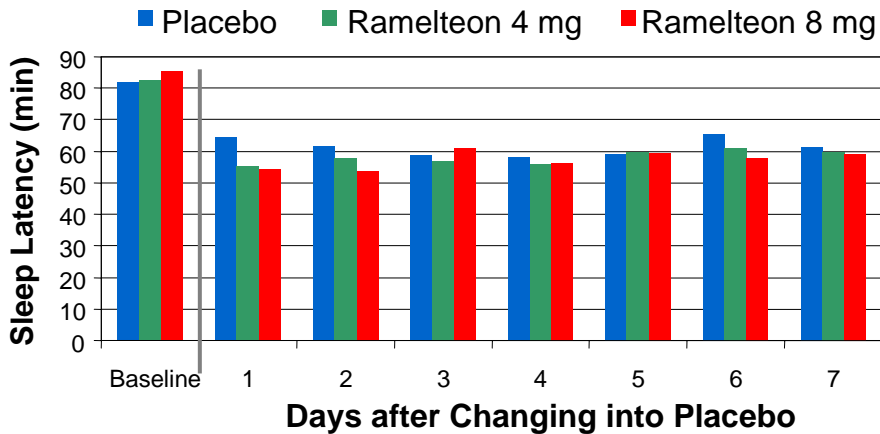
## Subjective Sleep Latency



## Subjective Total Sleep Time



## Rebound Insomnia



No rebound insomnia was observed in elderly patients, too.

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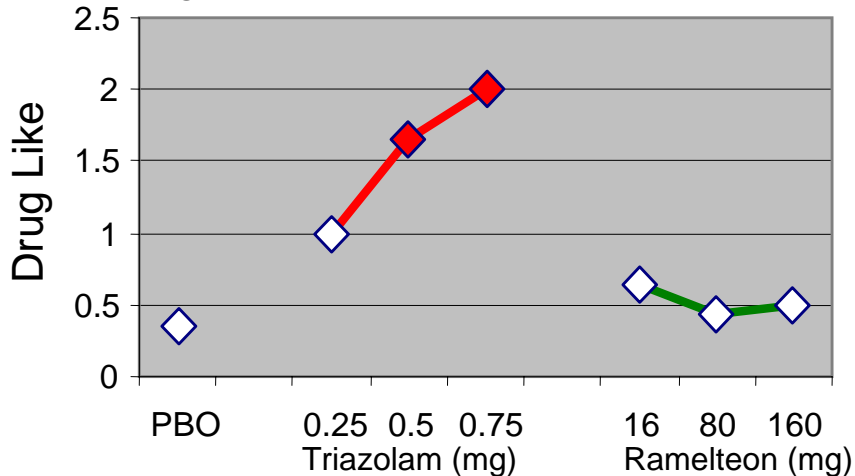
## Drug Abuse Ability in Human (APSS #130)

- Subjects: Subjects with histories of nonmedical sedative-hypnotic use (mean age: 27.6 years)
- Number of subjects: 14 (male 13; female 1)
- Study design: Check abuse ability by alprazolam  
Evaluated by randomized sequence manner  
Ramelteon 16, 80, 160 mg  
Triazolam 0.25, 0.5, 0.75 mg  
Placebo
- Endpoint: Rating by Drug Effect Questionnaires (0-4 points)

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## Drug Liking

(Drug Effect Questionnaires: Scale: 0-4)



**Ramelteon has no drug abuse ability**

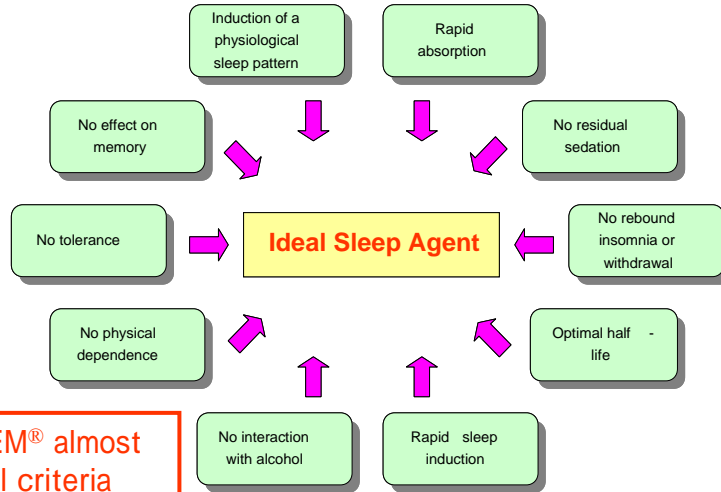
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## Summary of Phase III Results

- Efficacies (sleep latency and total sleep time) have been confirmed by both of objective and subjective evaluations.
- Efficacies did not differ by gender and age, thus ramelteon can be used widely.
- No tolerance was observed by repeated administration.
- No rebound insomnia and withdrawal effects were observed.
- No significant adverse effects were observed.
- No abuse ability was observed.

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# Ideal Sleep Agent



**ROZEREM® almost meets all criteria**

Source : Datamonitor (2004)

# History of Sleep Agents

Generation	Drug	Adverse effects	Type of Sleep
<b>Barbiturates</b> ↓	<b>Barbital</b> <b>Pentobarbital</b> etc.	Respiratory depression, memory impairment, motor impairment, dependence, tolerance, etc.	<b>Sedative</b>
<b>Benzodiazepines</b> ↓ GABA <sub>A</sub> receptor agonists	<b>Triazolam</b> <b>Temazepam</b> etc.	Memory impairment, motor impairment, dependence, abuse, rebound, tolerance, etc.	<b>Sedative</b>
<b>Non-benzodiazepines</b> ↓ GABA <sub>A</sub> receptor agonists	<b>Zolpidem</b> <b>Zaleplon</b> <b>Eszopiclone</b> etc.	Memory impairment, motor impairment, dependence, abuse, reboud, etc.	<b>Sedative</b>
<b>MT<sub>1</sub>/MT<sub>2</sub> receptor agonist</b>	<b>Ramelteon</b> <b>(Rozerem®)</b>	<b>No serious adverse effect</b>	<b>Physiological</b>

## New Generation for Insomnia Treatment

- **Rozerem®** provides physiological sleep via activation of  $MT_1/MT_2$  receptor play a role sleep/wake cycle.
- **Rozerem®** has no serious adverse effects including dependence, abuse ability, memory impairment and motor impairment.

**Now!**

Sedative Sleep



Physiological Sleep

