Experience with Measuring Sleep in Circadian Rhythm Sleep Disorder Targeted Trials

Margaret Moline, PhD
Executive Director, Head Orexin Platform Clinical Development
Neurology Business Group, Eisai Inc

Disclosure

- Margaret Moline is an employee of Eisai, Inc.

Outline

- Assessing sleep variables for insomnia and disorders of hypersomnolence
- Assessing sleep variables in circadian rhythm sleep disorders
  - Delayed Sleep Phase Syndrome
  - Non-24 Sleep-Wake Disorder
  - Irregular Sleep-Wake Rhythm Disorder (ISWRD)
- Phase 2 study in subjects with Alzheimer's dementia and ISWRD
- Summary and conclusions

Assessing Sleep in Patients with Insomnia and/or Disorders of Excessive Daytime Sleepiness

- Insomnia
  - For registration purposes, combination of polysomnography and patient-reported outcomes via sleep diaries required
  - In routine clinical practice, sleep diaries preferably used but often only clinical interviews used for diagnostic purposes
- Sleep-disordered breathing
  - PSG with oximetry
- Narcolepsy and other disorders of hypersomnolence
  - Multiple sleep latency test (MSLT) or multiple wake latency test (MWT) used for registration and clinical diagnosis

Assessing Sleep Variables in Circadian Rhythm Sleep Disorders

- While PSG is gold standard, subjects and patients cannot wear electrodes for many successive days
  - Current ambulatory EEG time limited
- Need acceptable method to track circadian parameters 24/7 for extended periods
  - Actigraphy

Actigraphy in Delayed Sleep Phase Syndrome and Non-24 Sleep-Wake Disorder

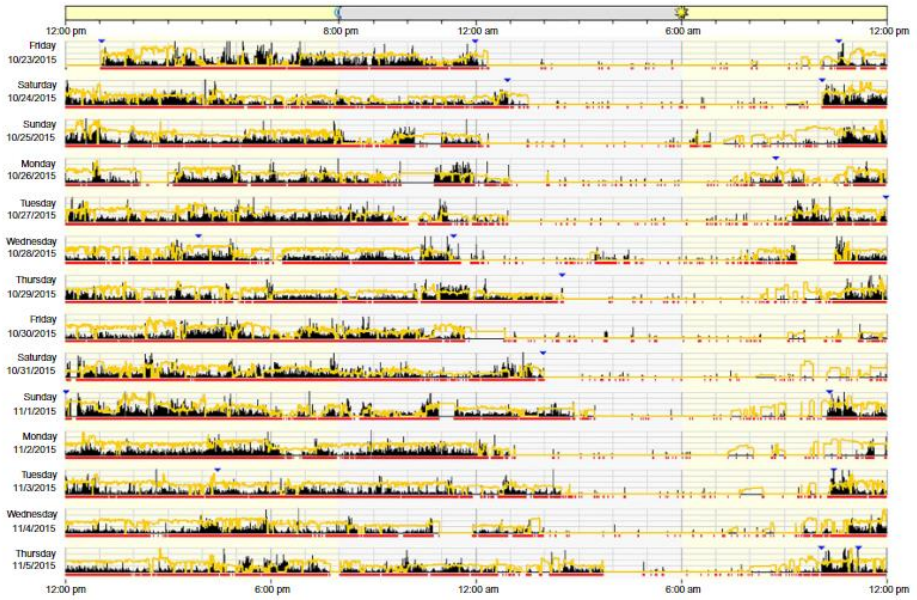


Fig. 24.2. Two-week actigraphy data from a patient with delayed sleep wake phase disorder (DSWPD) showing later than average bedtimes (usually after 12 a.m.) and later wake times (around 11 a.m.).

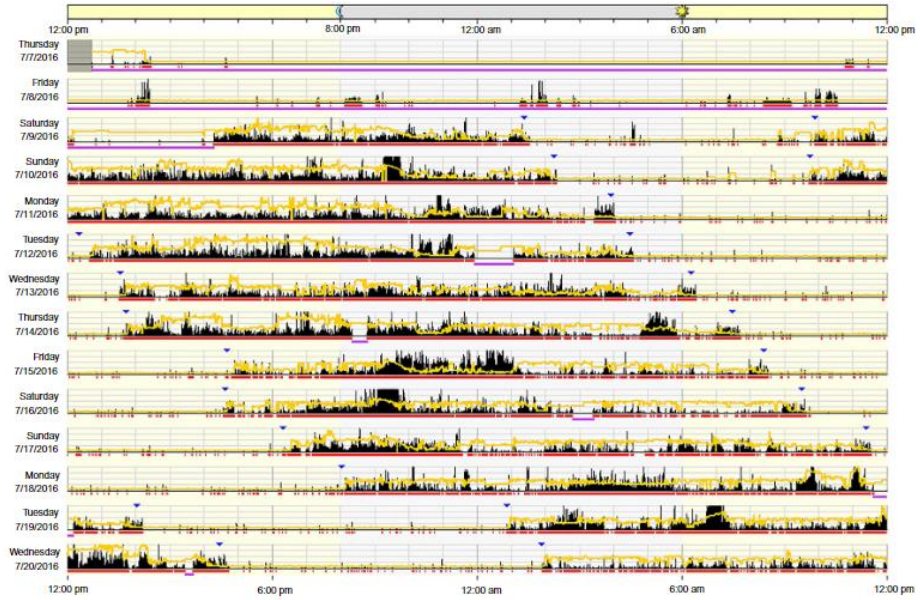


Fig. 24.3. Two-week actigraphy data of a patient with non-24-h sleep-wake disorder (N24SWD) showing a daily shift or delay in the sleep and wake times, consistent with a likely prolonged internal circadian rhythm (>24.2 h).

Saeed Y, Zee PC, Abbott SM. Clinical neurophysiology of circadian rhythm sleep-wake disorders. Handb Clin Neurol. 2019;161:369-380.

ISWRD Is Part of the Behavioral Syndrome of Alzheimer's Disease

- Alzheimer's disease patients commonly exhibit a range of behavioral disorders
  - Personality change, disinhibition
  - Apathy
  - Depression
  - Restlessness, anxiety, irritability, agitation, pacing
  - Perceptual disorders (delusions and hallucinations)
  - Sundowning (circadian pattern)
  - ***Sleep-wake disruption***
- Behavioral issues tend to increase in frequency and severity with increasing dementia severity
  - 25-40% of community-dwelling patients with mild-moderate AD have bothersome sleep-wake disorders

Even Pre-ISWRD, There Is a “Bidirectional” Relationship Between Sleep and Dementia

- Sleep disturbances occur early in the course of AD
  - Preclinical AD (with evidence for brain amyloid) is associated with decreased sleep efficiency
  - Greater amyloid burden is associated with shorter sleep duration
- Sleep and wake disturbances are also risk factors contributing to the development and worsening of AD pathology and symptomatology
  - The glymphatic system clears amyloid from the brain during sleep
  - Sleep disruption results in increased brain amyloid levels (sleep enhancement decreases brain amyloid)
  - Increased sleep fragmentation is associated with an increased risk of developing dementia
- These effects are seen much earlier in the course of AD than the clinical picture of ISWRD

Actigraphy in ISWRD

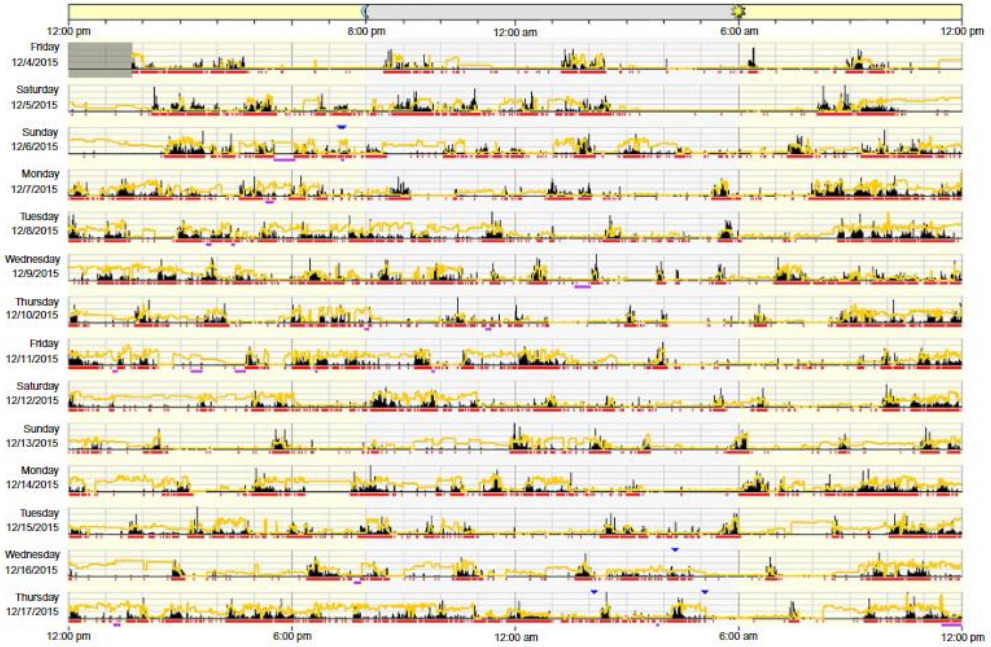


Fig. 24.4. Two-week actigraphy data of a patient with irregular sleep wake rhythm disorder showing greater than three short and irregular sleep periods without a major sleep period within 24 h.

Saeed Y, Zee PC, Abbott SM. Clinical neurophysiology of circadian rhythm sleep-wake disorders. Handb Clin Neurol. 2019;161:369-380.

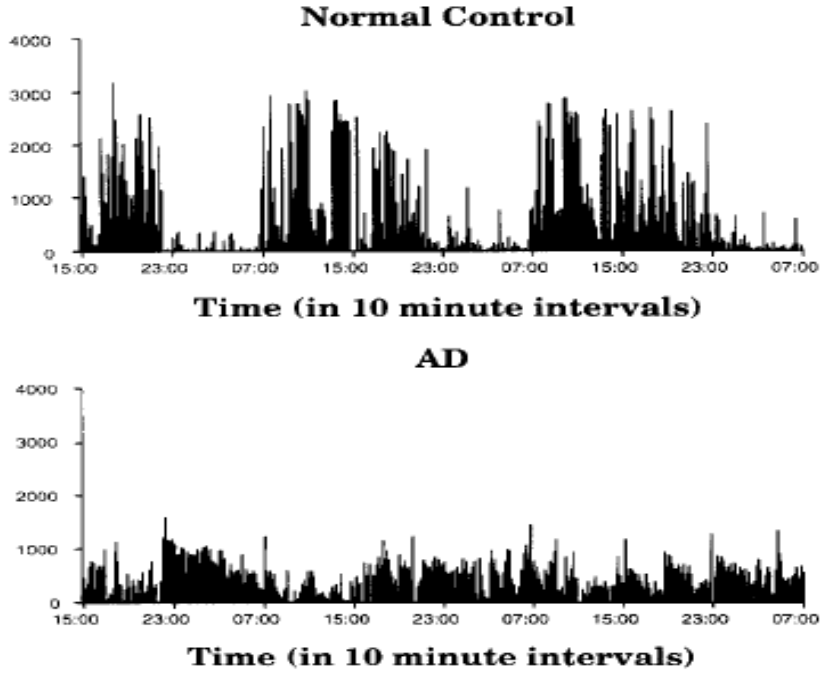


FIG. 1. Representative activity data graphs for an AD subject and a control. Y axis is activity counts, a measure of total activity levels.

AD patient shows both low intradaily stability and high interdaily variability

Satlin A, Volicer L, Stopa EG, Harper D. Circadian locomotor activity and core-body temperature rhythms in Alzheimer's disease. Neurobiol Aging. 1995 Sep-Oct;16(5):765-71.

Distinct Features of Circadian Rhythm Dysfunction in ISWRD

- Irregular sleep-wake rhythm disorder in AD is associated with pathology/dysregulation in the circadian timing system
- In AD, decreases in amplitude of the rest-activity rhythm (actigraphy) correlate with decreased cell numbers in the suprachiasmatic nuclei (CNS circadian pacemaker)
- Other circadian rhythms in AD are altered in addition to sleep-wake rhythms (eg, temperature and melatonin)
  - Manifested as low amplitude, delayed phase
- Irregular sleep-wake rhythm is a risk factor in the development and progression of AD pathology
- Circadian-based therapies (eg, timed bright light) have been shown to increase the amplitude and stability of the rest-activity rhythm in AD

Rationale for Lemborexant Clinical Study: Orexin Disturbances May Underlie Role of Sleep in Development of AD

- Orexin-A increases brain Aβ levels in mouse model
- Interstitial space fluid Aβ decreased with infusion of a DORA
- Chronic administration of a DORA decreased Aβ plaques
- Orexin antagonism led to decreased amyloid deposition in Tg mice, and effect mediated through increased sleep (Roh et al., 2014)

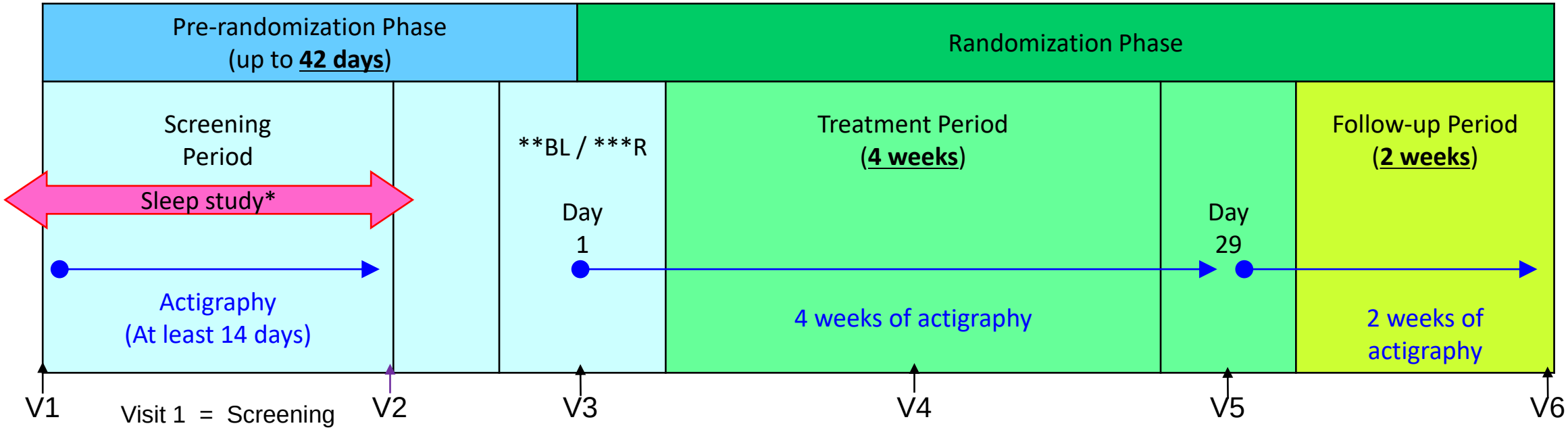
Lemborexant Phase 2 Study

- Background on lemborexant
  - Dual orexin receptor antagonist for the treatment of insomnia in adults
    - Competitive binding with fast on/off kinetics
  - Efficacy endpoints for sleep onset and sleep maintenance as well as safety evaluated in two Phase 3 studies for insomnia (N = 1964)
- Objective of ISWRD Phase 2 study
  - Evaluate circadian, nighttime, and daytime endpoints
  - Choose clinically meaningful endpoints from perspective of patients/caregivers/clinicians
    - Consolidate nighttime sleep
    - Reduce unintentional daytime napping
  - Leverage dose-response strategy from insomnia Phase 2 study
- Employ innovative endpoints using actigraphy
  - Non-invasive technique to measure rest/activity across days to weeks
  - 30 second epochs scored centrally as sleep or wake
  - Well-tolerated; can be worn while bathing

MotionWatch8 Device

Study Design

Study Treatment	**LEM 2.5 / 5 / 10 / 15** mg or **placebo** (1:1:1:1:1)



Visit 1 = Screening
Visit 2 = Caregiver visit; Download actigraphy data
Visit 3 = Confirm eligibility and dispense study drug
Visit 4 = Subject and Caregiver visit; download actigraphy data and perform safety assessments
Visit 5 = End of treatment assessments; download actigraphy data
Visit 6 = End of study assessments; download actigraphy data

V = Visit
**BL = Baseline
***R = Randomization

* Sleep study: Before randomization, the investigator was required to review a report detailing the potential subject's Apnea-Hypopnea Index (AHI) or equivalent

Global Study

- 57 sites: US (47), Japan (9) and UK (1)
- 168 subjects screened, 62 randomized, 62 completed double-blind core study
- Key inclusion criteria
  - Male or female, 60 – 90 years
  - Mini-Mental State Exam (MMSE) 10 – 26
  - Met Diagnostic and Statistical Manual of Psychiatry – 5th Edition criteria for Circadian Rhythm Sleep Disorder, Irregular Sleep-Wake Type
  - Frequency of complaint of sleep and wake fragmentation ≥3 days per week
  - Duration of complaint of sleep and wake fragmentation ≥3 months
  - Mean sleep efficiency measured by actigraphy (aSE) <87.5% in the nocturnal sleep period and mean wake efficiency (aWE) <87.5% during the wake period
  - Confirmation by actigraphy of a combination of at least 4 sleep bouts (>10 minutes each) per 24 hours, ≥ 3 days per week
  - No more than mild sleep apnea
  - Able to tolerate wearing actigraph

Actigraphy Issues During the Study

Reason	During Screening N=214	During Treatment N=62	Post-treatment N=62	Total
Device removed frequently or not worn	11 (5.1%)	3 (4.8%)	2 (3.2%)	16
Battery issues	4 (1.9%)	2 (3.2%)	2 (3.2%)	8
Site error	0	2 (3.2%)	2 (3.2%)	4
Missing/incomplete sleep log	3 (1.4%)	0	0	3
Miscellaneous	2 (0.9%)	0	0	2
Total				33

Efficacy Variables from Actigraphy to Assess Circadian, Nighttime, and Daytime Symptoms

Circadian 24-Hour

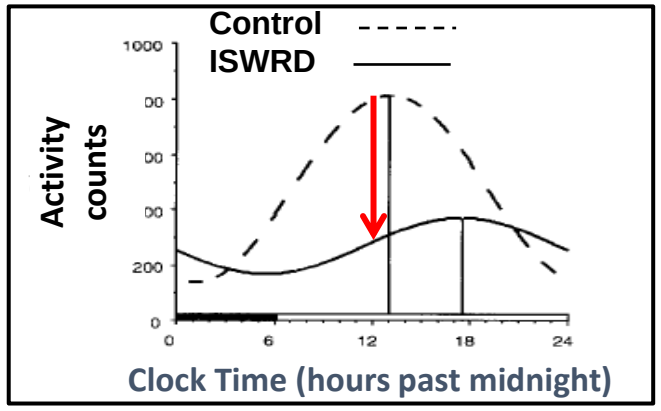
- **Relative Amplitude (RA)**
  - Standardizes for activity level differences across subjects
  - Reflects strength of circadian signal
- **Least Active 5 Hours (L5)**
  - Average activity across the least active 5-hour period of 24-hr sleep-wake rhythm
  - Higher values indicate restlessness
- **Also assessed**
  - Most active 10 hours
  - Interdaily stability
  - Intradaily variability

Nighttime Sleep

- **Sleep fragmentation index (SFI)**
  - Transitions between sleep and wake throughout night
  - Higher value indicates fragmented sleep
- **Total Sleep Time during the Night (TST)**
  - Minutes of sleep during the night
- **Also assessed**
  - Sleep efficiency - TST per nighttime hours
  - Number of wake bouts ≥10 min
  - Average duration of wake bouts

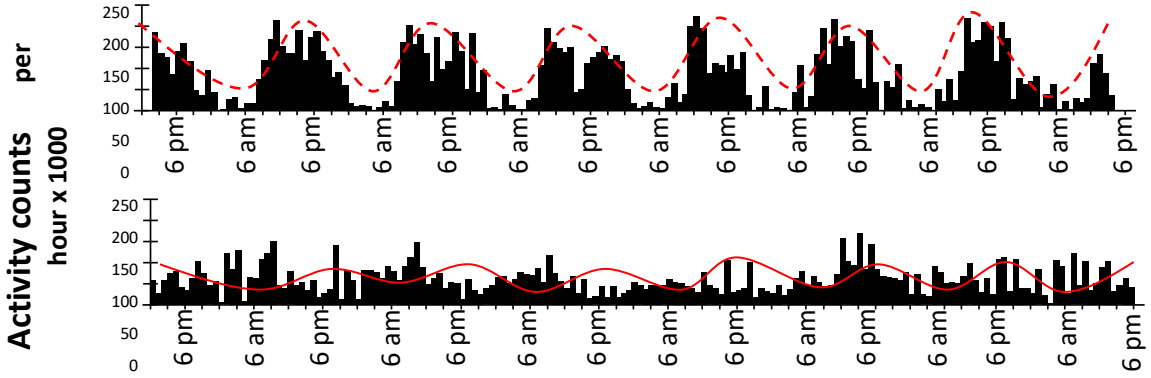
Daytime Wake

- **Average duration of sleep bouts ≥10 mins**
- **Also assessed**
  - Wake efficiency – wake time per daytime hours
  - Wake fragmentation index - transitions between wake and sleep throughout day
  - Number of sleep bouts ≥10 min



Adapted from Satlin A et al. *Neurobiol Aging* 1995;16:765-771.

Circadian rhythm amplitude is reduced, indicating a dysfunction in the circadian timing system



Adapted from van Someren et al (2011) *Handbook of Clinical Neurobiology*, Vol. 98: 55-63.

Studied Typical Mild-Moderate AD Population

Number of Subjects per Dose Group					
PBO	LEM2.5	LEM5	LEM10	LEM15	Total
12	12	13	13	12	**62**

- Age: 74.4 years
- Sex: 25 M / 37 F
- Race: 69.4% White / 11.3 % Black / 17.7% Japanese

Baseline Scores on Cognitive Scales

Scale	Score
MMSE	21
ADAS-Cog	29.2

- Mini-Mental State Exam (MMSE) and Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) scores indicate subjects in lower range of mild AD

Baseline Actigraphy Characteristics	
Time in Bed	8.9 hours
Time Out of Bed	15.1 hours
Total Sleep Time at Night	6.8 hours
Total Sleep Time During the Day	4.5 hours
Least Active 5 Hours	1266 counts
Most Active 10 Hours	10898 counts
Relative Amplitude	77%
Sleep Efficiency	77.2%
Wake Efficiency	70.1%
Number of Nighttime Wake Bouts (≥10 min)	2.4
Sleep Fragmentation Index	54.3
Number of Daytime Sleep Bouts (≥10 min)	5.3
Wake Fragmentation Index	89.5

Summary and Conclusions

- Actigraphy useful in establishing proof of concept
  - Improved 24-hour circadian rhythm variables
    - Lemborexant increased relative amplitude and decreased the least 5 active hours
  - Lemborexant helped consolidate nighttime sleep
    - Longer, more restful, less fragmented
- Identified objective endpoints
  - Characterized the condition
  - Clinically relevant
- Actigraphy well-tolerated in patients with Alzheimer's disease and ISWRD
- Lemborexant well-tolerated
  - No discontinuations from treatment
  - Low rate of TEAEs, consistent with insomnia program