NOCDURNAR®
Desmopressin Orally
Disintegrating Tablet (Melt)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)
January 12, 2015
NOCDURNA® Introduction
Desmopressin Orally
Disintegrating Tablet (Melt)

Brenda Marczi, PharmD
Vice President, US Regulatory Affairs,
Ferring Pharmaceuticals
Proposed Indication for NOCDURNA

NOCDURNA is indicated for treatment of nocturia due to nocturnal polyuria, in adults who awaken two or more times each night to void.

Prior to treatment with NOCDURNA, lifestyle changes and other treatable medical causes of nocturia should be addressed.
Study Population Appropriate for Proposed Indication

- Indication accurately reflects
  - Population studied
  - Unmet medical need
  - Mechanism of action of active ingredient
Nocturia is Awakening at Night to Void

- Nocturia definition: awakening ≥ 1 time to void at night\(^1\)
- Threshold for clinical relevance: awakening ≥ 2 times to void\(^2,3\)
  - Can significantly impact sleep, daily functioning and overall health and well-being\(^4,5\)

1. Van Kerrebroeck, et al., 2002
2. Tikkinen et al, 2010
3. Yu JH et al., 2006
4. Asplund and Aberg, 1996
5. Van Kerrebroeck, et al., 2014
Desmopressin Acts as a Vasopressin Agonist to Decrease Urine Output

Nielsen et al., 1993
Nocturia Clinical Development Program

- 3 NOCTUPUS pivotal, global trials and 2 extension trials with tablets
- U.S. NOCDURNA Program with melt
  - Initial pivotal study CS29
  - 1 extension trial to evaluate long-term safety (CS31)
  - Confirmatory pivotal studies CS40 (Women) and CS41 (Men) under Special Protocol Assessment (SPA)
Desmopressin has been approved in various indications for decades:

- **1972**: CDI Intranasal, Denmark
- **1978**: PNE-children Intranasal, Oral Tablet, US
- **1990-95**: Nocturia Associated with NP Oral Tablet, EU
- **2001**: CDI, PNE, Nocturia Associated with NP Melt, EU
- **2005**: Nocturia Associated with NP Melt, Oral Tablet 80 countries, NOCDURNA approved in Canada (Women: 25μg, Men: 50μg)

CDI: Central Diabetes Insipidus
PNE: Primary Nocturnal Enuresis
NP: Nocturnal Polyuria
Desmopressin History Leading to Gender-Specific Low Doses for Nocturia

- **Low dose**
  - 50 μg: Central Diabetes Insipidus
  - 200 μg: PNE in Children
  - 100 μg: Nocturia ≤ 65 years
  - 60 μg: Nocturia ≤ 65 years
  - 25 μg: Nocturia

- **High dose**
  - 1200 μg

- **Oral Tablet**
  - Melt formulation allows for lower doses
  - US: Proposing gender specific doses for adults of ALL ages
  - Improved safety

PNE: Primary Nocturnal Enuresis
NOCDURNA Formulated for Optimal PD Profile for Nocturia due to NP

- Anti-diuretic effect occurs 15-30 minutes after administration
- Reaches maximum effect in 1-2 hours
- Duration of action
  - Dose-dependent
  - ~5 hours
  - Rapid anti-diuretic effect at nighttime, significantly reduced by morning
# Agenda

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturia due to Nocturnal Polyuria</td>
<td>Eric Rovner, MD&lt;br&gt;Professor of Urology&lt;br&gt;Medical University of South Carolina</td>
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<tr>
<td>Efficacy Results</td>
<td>Jens Peter Norgaard, MD, DMSc&lt;br&gt;Professor of Urology, Global Scientific Affairs, Urology, Ferring Pharmaceuticals</td>
</tr>
<tr>
<td>Additional Clinical Relevance/Sleep</td>
<td>Donald Bliwise, PhD&lt;br&gt;Professor of Neurology, Emory University School of Medicine, Atlanta, GA</td>
</tr>
<tr>
<td>Patient Reported Outcomes/QoL</td>
<td>Raymond Rosen, PhD&lt;br&gt;Chief Scientist&lt;br&gt;New England Research Institutes, Inc.</td>
</tr>
<tr>
<td>Safety</td>
<td>Vladimir Yankov, MD&lt;br&gt;Vice President, Reproductive Health &amp; Urology&lt;br&gt;Ferring Pharmaceuticals</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Joseph Verbalis, MD&lt;br&gt;Professor and Chief Division of Endocrinology and Metabolism, Georgetown University</td>
</tr>
<tr>
<td>Benefit Risk/Conclusion</td>
<td>Eric Rovner, MD</td>
</tr>
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</table>
# Additional Experts

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Cantor, MD, PhD (Moderator)</td>
<td>Senior Vice President Clinical and Nonclinical R&amp;D Ferring Pharmaceuticals</td>
</tr>
<tr>
<td>Fredrik Andersson, PhD</td>
<td>Senior Director, Global Health Economics and Outcomes Research, Ferring Pharmaceuticals Associate Professor at the University of Linköping, Sweden</td>
</tr>
<tr>
<td>Leslie Krause, MD</td>
<td>Specialist Director, Global Pharmacovigilance Ferring Pharmaceuticals</td>
</tr>
<tr>
<td>Egbert van der Meulen, PhD</td>
<td>Senior Director, Global Biometrics Ferring Pharmaceuticals</td>
</tr>
</tbody>
</table>
Nocturia due to Nocturnal Polyuria

Eric Rovner, MD
Professor of Urology
Director Voiding Dysfunction and Female Urology and Urodynamics
Medical University South Carolina
Presentation Overview

- Nocturia symptoms
  - Threshold for clinical relevance
  - Patient burden
  - Causes
- Nocturia due to nocturnal polyuria (NP)
  - Target treatment population
  - Diagnosis algorithm
- Limitations of current treatment options
  - Current use of desmopressin in U.S.
Nocturia is the Complaint of Waking at Night to Urinate

- Can result from nocturnal polyuria with or without other lower urinary tract conditions (e.g. BPH, OAB, etc.)
- Occurs in men and women of all ages\(^1\)
- Becomes more frequent with age\(^1\)
- Threshold of 2 or more voids at night is associated with significant bother and disease burden\(^2,3\)

1. CDC, NHANES, 2009
2. Kupelian et al., 2011
3. Tikkininen et al., 2010
Significant Bother and Disease Burden with Nocturia ≥ 2 voids/night

Voids

Nocturia (e.g. Nocturnal Polyuria)

Clinically Relevant: ≥ 2 voids/night with bother\(^1,^2\)

Sleep

Sleep Disruption

Low Sleep Quality

Daily Life

Feeling Tired

Decrease in QoL

Decrease in Productivity

1. Kupelian et al., 2011
2. Tikkininen et al., 2010
Pathophysiology of Nocturia Can be Urological or Non-Urological/Medical

**Urological**
- Diminished bladder capacity
  - Overactive bladder (OAB)
  - Bladder outlet obstruction (BOO)
    - Benign prostate hyperplasia (BPH)
  - Gynecologic abnormality
  - Neurogenic bladder

**Non-Urological or Medical**
- 24-hour polyuria
  - Uncontrolled diabetes mellitus, insipidus
  - Primary polydipsia
- Nocturnal polyuria
  - Heart disease, sleep apnea, venous disease etc.
  - NP due to AVP dysregulation
Pathophysiology of Nocturia: 3 Broad Categories*

- Bladder Storage Problems OAB/BPH
- Diminished bladder capacity during nighttime sleep
- 24-hour Polyuria >2,800 mL/24 hr
- Nocturnal Polyuria Night volume: >33% of daily total volume

*Not intended to represent true prevalence or overlap
Rembratt et al., 2002
Target Treatment Population: Nocturia due to Nocturnal Polyuria (NP)

- Nighttime urine production in excess of 33%*
  - Not due to polydipsia/24 hour polyuria or comorbid medical conditions that require treatment
- Patients with NP have other conditions of the lower urinary tract (OAB, BPH, etc.)

*International Continence Society
Nocturia due to Nocturnal Polyuria is a Diagnosis of Exclusion

- If Not Bothered
  - Assess for medical conditions and if none, no further workup
- If Bothered
  - History, PE, U/A

Screen:
- Lifestyle behavioral factors (polydipsia, medication, etc.)
  - Lifestyle modification
- Medical conditions (sleep apnea, edema, etc.)
  - Referral to medical specialist

Further Evaluation

Van Kerrebroeck et al., 2014
PE: Physical Examination, U/A: Urine Analysis, PVR: Post Void Residual
Further Evaluation to Differentiate Nocturnal Polyuria from OAB or BPH

Clinical Evaluation

Predominantly Daytime Symptoms

- OAB
- OAB & BPH
- BPH

Both Day and Night

Mixed Causality (Voiding Diary)

Predominantly Nocturia

Nocturnal Polyuria
Urological Treatment Approaches Do Not Address Nocturia due to Nocturnal Polyuria

<table>
<thead>
<tr>
<th>Drug Classes</th>
<th>FDA Approved Indications*</th>
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<tbody>
<tr>
<td></td>
<td>OAB</td>
<td>BPH</td>
<td>Nocturia</td>
<td></td>
</tr>
<tr>
<td>Antimuscarinics</td>
<td>✓</td>
<td></td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Alpha blockers</td>
<td></td>
<td>✓</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>5-ARI</td>
<td></td>
<td>✓</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Beta 3 agonists</td>
<td>✓</td>
<td></td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Antimuscarinic + alpha blocker</td>
<td>✓</td>
<td>✓</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>5-ARI + alpha blocker</td>
<td></td>
<td>✓</td>
<td>NO</td>
<td></td>
</tr>
</tbody>
</table>

*Package inserts for corresponding drug classes
Desmopressin Recommended in Multiple Guidelines

- American Urological Association BPH guideline\(^1\)
  - "Nocturia should be managed... by reducing fluid intake, and that other treatments, such as desmopressin, can also be considered."
- International Consultation on Incontinence (ICI)\(^2\)
  - Oxford level 1 evidence, Grade A recommendation
- Recommended/included in guidelines from
  - European Association of Urology (EAU)\(^3\)
  - International Consultation on Urological Diseases (ICUD)\(^4\)
  - UK National Institute for Health and Clinical Excellence (NICE)\(^5\)
- FDA-approved in U.S. only for other indications at higher doses

1. McVary et al., 2010
2. Abrams et al., 2013
3. Oelke et al., 2013
4. Wein, 2014
5. Smith et al., 2013
Nocturia due to Nocturnal Polyuria
An Unmet Medical Need

- NP is a main cause of nocturia symptoms
- Can coexist with other conditions (OAB, BPH)
- Can result in high bother and patient burden if ≥ 2 awakenings/night to void
- Patient should be treated with antidiuretic
- Defined diagnostic/management algorithms
- Need effective, safe and appropriately labelled treatment
Efficacy Results

Jens Peter Norgaard, MD, DMSc
Professor of Urology
University of Aarhus, Denmark
Global Scientific Affairs, Urology
Ferring Pharmaceuticals
Overall Clinical Development Program Led to Efficacious, Safe Treatment in Target Population

- Nine phase 3 studies from 1997-present
- Early NOCTUPUS trials
  - “Enriched” for NP as recommended by FDA
  - Higher treatment effect
- Recent NOCDURNA trials
  - Population reflects clinical practice
  - 90% NP population through medical history
- Overall goal: maximize safety, maintain efficacy
First Study of Melt Formulation: 4 Doses Against Placebo (CS29)

**CS29/31**
- Randomized, Placebo-Controlled, Multiple Dose Study (Randomized N=799)
- **Doses:** 10, 25, 50, 100 µg

**Co-Primary Endpoints**
- Change from Baseline to Day 28 in Mean Number of Nocturnal Void
  - ≥ 33% Responders

**CS31:**
- Extension

**CS40 (Women)**
- Randomized, Placebo-Controlled, Single Dose Study (Randomized N=268)
- **Doses:** 25 µg

**Co-Primary Endpoints**
- Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Void
  - ≥ 33% Responders

**CS41 (Men)**
- Randomized, Placebo-Controlled Multiple Dose Study (Randomized N=395)
- **Doses:** 50, 75 µg

**Co-Primary Endpoints**
- Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Void
  - ≥ 33% Responders
Clear Dose Response in Decrease in Mean Volume of Nocturnal Urine (CS29)

- Placebo: N=140, Change = -109 mL
- 10 µg: N=137, Change = -164 mL
- 25 µg: N=144, Change = -224 mL
- 50 µg: N=138, Change = -272 mL
- 100 µg: N=135, Change = -313 mL

*Statistically significant difference versus placebo
CS29 studied both women and men

Weiss et al., 2012
Pharmacodynamic Effect at Lower Doses in Women Than in Men (CS29)

Weiss et al., 2012
*p<0.05; **p<0.01 NOCDURNA vs placebo
CS29 studied both women and men
CS40/CS41: Key Confirmatory Trials

**CS29/31**
- Randomized, Placebo-Controlled, Multiple Dose Study (Randomized N=799)
- **Doses:** 10, 25, 50, 100 μg
- **Co-Primary Endpoints**
  - Change from Baseline to Day 28 in Mean Number of Nocturnal Void
  - ≥ 33% Responders
- **CS31:** Extension

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- **Doses:** 50, 75 μg
- **Co-Primary Endpoints**
  - Change from Baseline during 3 Months of Treatment in Mean Number of Nocturnal Void
  - ≥ 33% Responders
Trial Design of CS40 in Women

- Screening
- Treatment Period
  - Week 1
  - Month 1
  - Month 2
  - Month 3

Day 21

1  4  8  29  57  85

Randomization
N=268

NOCDURNA 25 μg

Placebo
Trial Design of CS41 in Men

Screening

Week 1

Treatment Period

Month 1

Month 2

Month 3

Day 21

1 4 8 15 22 29 57 85

Randomization

N=395

NOCDURNA 50 µg

NOCDURNA 75 µg

Placebo
Key Inclusion Criteria

- Same in CS40 and CS41
- $\geq 2$ voids per night$^{1,2}$
  - Determined by 3-day frequency-volume chart during screening period

1. Kupelian et al., 2011
2. Tikkinen et al., 2010
Key Exclusion Criteria

- Evidence of severe daytime voiding dysfunction causing bladder related nocturia (avoiding significant diminished bladder capacity)
  - Urge urinary incontinence, urgency or frequency (OAB)
  - Suspicion of bladder outlet obstruction (BPH)
- Underlying medical conditions associated with nocturia due to nocturnal polyuria, such as
  - Syndrome of Inappropriate Antidiuretic Hormone (SIADH)
  - Uncontrolled Diabetes Mellitus
  - Renal insufficiency
  - Suspicion or evidence of cardiac failure
  - Sleep apnea
Three Categories of Efficacy Endpoints Demonstrate Clinical Relevance

- Co-primary endpoints
- Secondary endpoints
- Supportive endpoints – QoL and sleep
CS40/CS41: Co-Primary Endpoints Analyzed Longitudinally

- All data used during 3 months in a repeated measures model to avoid spurious results at selected time point
- Studies powered to show statistically significant effect on both co-primary endpoints
CS40/CS41: Similar Void Parameters at Baseline Between Groups

- Average of 2.9 voids per night
- Mean time to first nocturnal void was approximately 2.5 hours (145 min)
- ~90% of patients had clinically significant nocturnal polyuria
- Mean baseline NPI ≥ 45%
NOCDURNA Met Co-Primary in CS40 (Women): Mean Decrease in Nocturnal Voids

25 µg vs placebo: Δ=0.22, p=0.028

Longitudinal Analysis (95% CI)
NOCDURNA Met Co-Primary in CS41 (Men): Mean Decrease in Nocturnal Voids

50 μg vs placebo: Δ=0.37, p=0.0003
75 μg vs placebo: Δ=0.41, p<0.0001

Longitudinal Analysis (95% CI)
Co-Primary CS40 and CS41: Doubled Odds of Achieving ≥ 33% Reduction in Voids

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Odds</th>
<th>Odds Ratio</th>
<th>Favors NOCDURNA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS40 (Women)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 μg</td>
<td>130</td>
<td>3.23</td>
<td>1.85</td>
<td></td>
<td>0.0061</td>
</tr>
<tr>
<td>Placebo</td>
<td>125</td>
<td>1.75</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS41 (Men)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50 μg</td>
<td>116</td>
<td>2.01</td>
<td>1.98</td>
<td></td>
<td>0.0009</td>
</tr>
<tr>
<td>Placebo</td>
<td>142</td>
<td>1.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 μg</td>
<td>122</td>
<td>2.08</td>
<td>2.04</td>
<td></td>
<td>0.0004</td>
</tr>
<tr>
<td>Placebo</td>
<td>142</td>
<td>1.02</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Longitudinal Analysis (95% CI)
Change from Baseline with NOCDURNA Similar to Earlier Trials

Mean Reduction in Nocturnal Voids per Night

- Desmopressin
- Placebo

Earlier Clinical Trials with Tablet (NOCTUPUS)

<table>
<thead>
<tr>
<th>Trial</th>
<th>100 µg-400 µg</th>
<th>10-100 µg</th>
<th>25 µg</th>
<th>50-75 µg</th>
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<tbody>
<tr>
<td>2A</td>
<td>1.2</td>
<td>CS29</td>
<td>CS40</td>
<td>CS41</td>
</tr>
<tr>
<td>3A</td>
<td>1.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4A</td>
<td>1.6</td>
<td></td>
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NOCDURNA
Several Factors May Contribute to High Placebo Effect

- Commonly seen in lower urinary tract dysfunction studies
- No placebo or active run-in before randomization
- Regression to the mean
- Inclusion of lifestyle modifications and behavioral reinforcement during trials
- Multiple questionnaires and diaries
Three Categories of Efficacy Endpoints Demonstrate Clinical Relevance

- Co-primary endpoints
- Secondary endpoints
- Supportive endpoints – QoL and sleep
CS40/CS41: Secondary Endpoints Analyzed at End of Treatment*

- Change in mean number of nocturnal voids
- Proportion of 33% responders
- Mean time to first nocturnal void
- Mean nocturnal urine volume
- Mean 24-hour urine volume

*Cross-sectional data analyzed at month 3
CS40 (Women): Sustained Increase in Time to First Nocturnal Void

- **NOCDURNA 25 µg (N=132)**
- **Placebo (N=128)**

Change in Time to First Void (hours)

- 0
- Wk 1
- Month 1
- Month 2
- Month 3

Time

**Cross-sectional Analyses (95% CI)**

Sand PK et al., 2013

- \( p = 0.09 \)
- \( p = 0.02 \)
- \( p = 0.02 \)
- \( p = 0.003 \)

\( \Delta = 49 \text{ min} \)
Three Categories of Efficacy Endpoints Demonstrate Clinical Relevance

- Co-primary endpoints
- Secondary endpoints
- Supportive endpoints – QoL and sleep
CS40 (Women): Self-Rated Quality of Sleep Improved Consistently Over 3 Months

Treatment Contrast: 6.7% (95% CI: 2.5-10.9%)
CS41 (Men): Self-rated Quality of Sleep Improved Consistently Over 3 Months

![Graph showing the change in quality of sleep over months for NOCDURNA 50μg and Placebo groups. The graph includes error bars and a treatment contrast of 3.9% (95% CI: 0.22-7.64%)]

Treatment Contrast: 3.9% (95% CI: 0.22-7.64%)
NOCDURNA Demonstrated Consistent and Statistically Significant Efficacy Across Key Endpoints in Women (CS40) and Men (CS41)

Women (CS40):
Total Efficacy
p=0.0009 (O’Brien)

Men (CS41):
Total Efficacy
p=0.0006 (O’Brien)

- Placebo
- 25 mcg

- Placebo
- 50 mcg

Noct Volume
NQoL Total
Sleep Quality
FUSP

Number Voids
33% Response
NOCDURNA Consistently Demonstrated Efficacy Across Pivotal Trials

- Three Phase 3 trials: 1443 subjects
- Study population reflects adults (all ages) seeking treatment in clinical practice
- Met co-primary endpoints agreed upon with FDA in SPA with statistical significance
Additional Clinical Relevance/Sleep

Donald Bliwise, PhD
Professor of Neurology
Emory University School of Medicine
Atlanta, GA
Nocturnal Voiding: Leading Self-Attributed Cause of Sleep Disturbance

Q: How often do the following disturb your sleep?

% of Self-Reporting by Causes of Sleep Disturbance

N=1424
55-84 yrs of age

## Factors Known to be Associated With Poor Sleep

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>2.49 (1.61, 3.87)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.28 (1.06, 4.89)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.85 (1.35, 2.55)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>1.75 (1.31, 2.35)</td>
</tr>
<tr>
<td>Female</td>
<td>1.64 (1.20, 2.23)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.52 (1.01, 2.30)</td>
</tr>
</tbody>
</table>

Multivariable modeling controlling for other self-reported conditions
Bliwise et al., Sleep Med 2009; 10: 540-8
## Time to First Void Increased With NOCDURNA

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Group</th>
<th>Reduction in # of Nocturnal Voids Relative to Placebo</th>
<th>Increase in Mean Time to 1st Void Relative to Placebo (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS29¹</td>
<td>Females</td>
<td>0.34</td>
<td>76</td>
</tr>
<tr>
<td>CS29¹</td>
<td>Males</td>
<td>0.29</td>
<td>32</td>
</tr>
<tr>
<td>CS40²</td>
<td>Females</td>
<td>0.22</td>
<td>49</td>
</tr>
<tr>
<td>CS41³</td>
<td>Males</td>
<td>0.37</td>
<td>39</td>
</tr>
</tbody>
</table>

1. Weiss et al., 2012
2. Weiss et al., 2013
3. Sand et al., 2013

CS40/41 data based on longitudinal effect estimates during 3 months; CS29 data are based on the effect estimate at D28.
Potential Impact of Nocturia on Sleep Stages

Stages 3 and 4 May be Interrupted by First Voiding Episode

van Kerrebroeck et al., 2007
## Stages 3/4 Reduced for Entire Night with Early First Voiding Episode

<table>
<thead>
<tr>
<th>Sleep Measure</th>
<th>First Void <em>During</em> First 2 Sleep Cycles</th>
<th>First Void <em>After</em> First 2 Sleep Cycles</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep</td>
<td>306 (54)</td>
<td>330 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>Stages 1 and 2 sleep</td>
<td>170 (41)</td>
<td>171 (33)</td>
<td>NS</td>
</tr>
<tr>
<td>Stages 3 and 4 sleep</td>
<td><strong>37 (24)</strong></td>
<td><strong>56 (22)</strong></td>
<td>0.023</td>
</tr>
<tr>
<td>REM sleep</td>
<td>95 (35)</td>
<td>103 (25)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Torimoto et al., 2012
Torimoto et al., 2013
Time to First Void Associated with Conventional Measure of Sleep Quality (PSQI*) (CS29)

1 hour increase in time to 1st void associated with significant improvement in 7 out of 8 components

<table>
<thead>
<tr>
<th>PSQI Scale Component</th>
<th>Regression Coefficient</th>
<th>SE</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Global</td>
<td>-0.488</td>
<td>0.054</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>-0.106</td>
<td>0.012</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Latency</td>
<td>-0.079</td>
<td>0.015</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>-0.068</td>
<td>0.013</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Efficiency</td>
<td>-0.102</td>
<td>0.018</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
<td>-0.044</td>
<td>0.012</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sleep Medication</td>
<td>-0.016</td>
<td>0.016</td>
<td>0.30</td>
</tr>
<tr>
<td>Daytime Dysfunction</td>
<td>-0.075</td>
<td>0.014</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Bliwise D et al, *Sleep Medicine* 2014, in press

*PSQI: Pittsburgh Sleep Quality Index; data combined across all doses
Increases in Time to First Void are Associated With Greater Odds of Achieving >6 Hours of Sleep (CS29)

Based on GEE re-analyses of first uninterrupted sleep period data in Weiss et al. *Neurol Urodyn.*, 2012
NOCDURNA May Increase Sleep More than Traditional Sleep Medications

- NOCDURNA increase of uninterrupted sleep relative to placebo: 32-76 minutes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Treatment Difference (Active vs. Placebo) First 4-6 Hrs of Sleep Period (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eszopiclone (Lunesta)® 3mg&lt;sup&gt;1&lt;/sup&gt;</td>
<td>25.0</td>
</tr>
<tr>
<td>Doxepin (Silenor)® 6mg&lt;sup&gt;2&lt;/sup&gt;</td>
<td>22.2</td>
</tr>
<tr>
<td>Zolpidem-MR (Ambien-MR)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>16.0</td>
</tr>
</tbody>
</table>

1. Zammit et al., 2004
2. Roth et al., 2010
3. Roth et al., 2006
Patient Reported Outcomes/QoL

Raymond Rosen, PhD
Chief Scientist
New England Research Institutes, Inc.
Nocturia Quality of Life (N-QOL) Scale: FDA Questions and Concerns

- Content validity
- Recall period
- Consistency of results
N-QoL: Background and Assessment on Content Validity

- Gold standard for QoL assessment in nocturia trials since 2004\(^1\)
- Translated and validated in 29 languages, included in 11 major studies, and included in 40+ peer-reviewed publications
- Content validity confirmed by qualitative interviews with \(~100\) patients in 2 independent studies\(^2,3\)

1. Abraham et al., 2004
2. Mock et al., 2008
3. Booth et al., 2010
Suitability of a 2-week Recall Period to Assess Patient Benefit

- Optimal recall period depends on disease and type of therapy\(^1\)
- 2 or 4-week recall period is consistently used in research and clinical practice
  - IPSS\(^2\) (BPH) – 1 month
  - DCP\(^3\) (Diabetes) – 1 month
  - AQLQ\(^4\) (Asthma) – 2 weeks
  - PAC-QOL\(^5\) (Constipation) – 2 weeks

1. Norquist et al, 2012
2. Barry et al., 1992; IPSS: International Prostate Symptom Score
3. Fitzgerald et al., 1996; DCP: Disease Control Priorities
4. Juniper et al., 1992; AQLQ: Asthma Quality of Life Questionnaire
5. Marquis et al., 2005; PAC-QoL: The Patient Assessment Constipation-Quality of Life
Consistency of N-QOL Results within and Across Trials: Improvements in Women (CS40) at 1 and 3 Months

- **Month 1**
  - 25 μg: Mean Improvement = 20.8, N=126
  - Placebo: Mean Improvement = 19.8, N=122

- **Month 3**
  - 25 μg: Mean Improvement = 27.2, N=113
  - Placebo: Mean Improvement = 21.9, N=108

**P-values:**
- Month 1: p=0.66
- Month 3: p=0.02
## Consistency of Patient Benefit Evident Across Multiple QoL Measures

<table>
<thead>
<tr>
<th>QoL Questionnaire</th>
<th>CS40 (Women 25 µg)</th>
<th>CS41 (Men 50 µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>NOCDURNA</td>
</tr>
<tr>
<td>N-QoL: Total Score (Avg of domains)</td>
<td>n=221</td>
<td></td>
</tr>
<tr>
<td>N-QoL: Bother/Concern Domain</td>
<td>n=221</td>
<td></td>
</tr>
<tr>
<td>N-QoL: Sleep/Energy Domain</td>
<td>n=221</td>
<td></td>
</tr>
<tr>
<td>N-QoL: Global Score (Overall QoL)</td>
<td>n=221</td>
<td></td>
</tr>
<tr>
<td>Diary: How do you feel?</td>
<td>n=220</td>
<td></td>
</tr>
<tr>
<td>Diary: Refreshed?</td>
<td>n=220</td>
<td></td>
</tr>
<tr>
<td>Diary: Sleep quality?</td>
<td>n=220</td>
<td></td>
</tr>
<tr>
<td>WPAI Activity Impairment</td>
<td>n=220</td>
<td></td>
</tr>
<tr>
<td>WPAI Work Productivity</td>
<td>n=57</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment Effect range: -15 to 15
- N-QoL: QoL Questionnaire - Nephrology-Quality of Life
Safety

Vladimir Yankov, MD
Vice President
Reproductive Health & Urology
Ferring Pharmaceuticals
Desmopressin: Over 40 Years of Worldwide Use

- Long history of safety use at much higher doses than proposed for NOCDURNA
- Desmopressin cumulative patient exposure for oral formulations:
  - Oral overall: 4.2 million patient-years
  - Melt: 1.1 million patient-years
  - Oral overall in nocturia: 246,000 patient-years
    - Hyponatremia reporting rate: 2.8 cases/10,000 patient-years (nocturia indication, desmopressin melt and tablet, 60-240 μg doses)
- Melt: reported AEs consistent with known safety profile of tablet

As of 31 Dec 2013
NOCDURNA Integrated Safety Set

3 Randomized Phase 3 Studies
N=1443 unique subjects

CS29 Part I
Men/Women
1 Month
N=798
- 10 µg
- 25 µg
- 50 µg
- 100 µg
- Placebo

CS29 Part II
28 Days to
CS31 96 Weeks
N=542
- 10 µg
- 25 µg
- 50 µg
- 100 µg

CS40
Women
3 Months
N=261
- 25 µg
- Placebo

CS41
Men
3 Months
N=384
- 50 µg
- 75 µg
- Placebo

CS41
Extension Study
1 Month
N=327
- 100 µg
Adverse Events with Incidence $\geq 5\%$ in any Treatment Group – Women (CS40) and Men (CS41)

<table>
<thead>
<tr>
<th>MedDRA Preferred Terms</th>
<th>CS40 (Women)</th>
<th>CS41 (Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 $\mu$g</td>
<td>50 $\mu$g</td>
</tr>
<tr>
<td></td>
<td>N=135</td>
<td>N=119</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>60 (44%)</td>
<td>46 (39%)</td>
</tr>
<tr>
<td></td>
<td>57 (45%)</td>
<td>49 (40%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>6 (4%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td></td>
<td>4 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>7 (5%)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (4%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td></td>
<td>10 (8%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>4 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>6 (5%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td></td>
<td>3 (2%)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7 (5%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td></td>
<td>4 (3%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td></td>
<td>5 (3%)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (1%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td></td>
<td>1 (&lt;1%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blood sodium decreased</td>
<td>0</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>2 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>
Serious Adverse Events with Incidence ≥ 1% in Any Treatment Group (Integrated Safety Set*)

- No deaths in 3-month treatment period

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>10 µg N=194</th>
<th>25 µg N=331</th>
<th>50 µg N=311</th>
<th>75 µg N=122</th>
<th>100 µg N=194</th>
<th>Placebo N=429</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>3 (2%)</td>
<td>2 (&lt;1%)</td>
<td>5 (2%)</td>
<td>5 (4%)</td>
<td>3 (2%)</td>
<td>4 (&lt;1%)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>0</td>
<td>2 (&lt;1%)</td>
<td>4 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Serum sodium levels ≤ 125 mmol/L required reporting as SAE (CS40 and CS41)
- All but 1 subject experienced asymptomatic hyponatremia
- All other SAEs: <1%

*CS29, CS40, CS41 combined; males and females combined
Clinical Trial Monitoring Program Utilized in CS40 and CS41

Treatment Period

Women CS40
Baseline D4 D8 Mo 1 Mo 2 Mo 3

Men CS41
Baseline D4 D8 Wk 2 Wk 3 Mo 1 Mo 2 Mo 3
Per Protocol Guidance for Monitoring Serum Sodium

- 126 to 134 mmol/L: subject allowed to remain on treatment; investigator scheduled a follow-up visit
  - If determined as clinically significant by investigator, reported as AE
- ≤ 125 mmol/L: subject discontinued from drug
  - Reported as SAE (except CS29)
- Subjects followed at least until serum sodium values were >130 mmol/L
Hyponatremia: Early Onset, Mild, Reversible in Clinical Trials

- Baseline serum sodium <135 - predictor
- Study results
  - Dose-dependent
  - Gender-dependent
  - Age-dependent
  - Usually occurs early in treatment
- Low rate*: 0-3% ≤ 125 mmol/L, 0-4% 126-129 mmol/L
- Most asymptomatic
- Transient: sodium returns to normal in 1 to 3 weeks while on treatment in most subjects

*CS40/41, including 75 μg (Men)
CS40: No Females Experienced Serum Sodium Below 125 mmol/L
CS41: No Men Experienced Serum Sodium Below 125 mmol/L at 50 µg Dose
Measures to Further Reduce Risk of Hyponatremia in Clinical Practice

- Proposed sodium monitoring plan
- Contraindications and precautions in label
- Communication plan, and post-marketing surveillance
Proposed Label: Contraindications

- Habitual or psychogenic polydipsia
- Hyponatremia, history of hyponatremia
- Moderate to severe renal impairment (eGFR <60 mL/min)
- History of known or suspected cardiac insufficiency or other edema forming diseases
- Known or suspected SIADH
Proposed Label: Warnings and Precautions

- In addition to baseline sodium monitoring, additional monitoring of patients ≥ 65 and adults of all ages at risk.
- Use caution for concomitant use with drugs associated with causing hyponatremia (monitor sodium for specified drugs).
- Advise patients to restrict fluid (1 hr before to 8 hrs after NOCDURNA administration).
- Halt NOCDURNA use during acute intercurrent illnesses requiring increased fluid intake.
### Labeling, Communication, and Post-Marketing Surveillance to Minimize Risk

| Label/Package | Sodium monitoring plan as a label recommendation  
|               | • All patients at baseline – normal sodium  
|               | • Patients ≥ 65 yrs  
|               | • Patients at increased risk of hypernatremia  
| NOCDURNA initiation packaging availability |
| Communication | Medication guide and website |
|               | Healthcare professional education program |
| Post-Marketing Assessment | Post-marketing enhanced safety surveillance of hypernatremia |
|               | Prescription claim database study to monitor risk of severe hypernatremia |
NOCDURNA Safety Conclusions

- NOCDURNA: favorable safety profile and well-tolerated at proposed doses
  - 1% subjects experienced severe hyponatremia (≤125 mmol/L)
- Hyponatremia
  - Tends to be asymptomatic
  - Dose-, age-, and gender-dependent
  - Tends to occur early
  - Substantially decreased with lower gender-specific doses
- Extensive global post-marketing experience confirms safety is consistent with AEs observed in clinical trials
Hyponatremia

Joseph G. Verbalis, MD
Professor and Chief of Endocrinology and Metabolism
Director, Georgetown-Howard Universities Center for Clinical and Translational Science
Georgetown University
What is Hyponatremia?

- Decreased serum sodium concentration
- Major cause is dilution from vasopressin-mediated water retention\(^1\)

**Serum Sodium Lab Values**

- Mild: 134-130 mmol/L
- Moderate: 129-125 mmol/L
- Severe: <125 mmol/L

**Potential Symptoms\(^1\)**

- Headache
- Irritability
- Nausea
- Mental slowing
- Gait instability
- Falls
- Confusion
- Disorientation
- Delirium
- Seizures
- Stupor
- Coma
- Respiratory arrest

---

Prevalence of Hyponatremia in the General Population

- Overall prevalence in the general population low: <2\%\textsuperscript{1,2}
- Increased prevalences seen with:
  - Increased age (≥ 65): 5-7\%\textsuperscript{3,4}
  - Hospitalization: 15-30\%\textsuperscript{2}
  - Disease states (CHF, cirrhosis, COPD)
  - Medications

Which Drugs are Associated with Increased Risk of Hyponatremia?

- Many drugs (>50) have been associated with the production of hyponatremia\(^1\)
- The most common are:
  - SSRIs: 0.5-32% hyponatremia incidence\(^2\)
  - Thiazide diuretics: 11-30% hyponatremia incidence\(^3\)
  - Anti-epileptic drugs, carbamazepine: 4.8-40%\(^4\)

1. Verbalis, Diseases of the Kidney, Brenner & Rector, 2014
Risk of Hyponatremia with NOCDURNA

- Incidence of clinically significant hyponatremia in NOCDURNA trials in same range or lower than other commonly used drugs
- No guidelines on acceptable levels of hyponatremia or hyponatremia symptoms
- No currently approved drugs require or recommend hyponatremia monitoring plans
- NOCDURNA: proposed monitoring plan would be the first
Proposed Monitoring Plan for Label to Further Reduce Hyponatremia

- **Baseline** – ALL patients should have normal sodium before starting NOCDURNA
- **Week 1 (4-8 days after initiated treatment)** – following initiation pack for patients at increased risk of hyponatremia (≥ 65 years, on concomitant medications associated with hyponatremia: e.g., SSRI, thiazide, antiepileptics)
- **Month 1** – following additional prescription for patients at increased risk
- **Sodium <135 mmol/L at ANY time** → discontinue treatment
Proposed Monitoring Plan Reduces Risk of Clinically Significant Hyponatremia: CS40 (Women)

Red circles = Sodium value < 130

Without monitoring

With monitoring
Proposed Monitoring Plan Reduces Risk of Clinically Significant Hyponatremia: CS41 (Men)

Red circles = Sodium value < 130

Without monitoring

With monitoring
Long-Term Serum Sodium Levels with Monitoring Plan Applied in Women (CS29/31)

Red circles = Sodium value < 130

With monitoring

Sodium (mmol/L)

Days
Long-Term Serum Sodium Levels with Monitoring Plan Applied in Men (CS29/31)

Red circles = Sodium value < 130

With monitoring

Sodium (mmol/L)

Days
Suitability of NOCDURNA Use in Patients ≥ 65 Years of Age

- **NODURNA does not** need to be restricted to patients <65 yrs
- Low rate of moderate/severe hyponatremia in elderly
- All severe and virtually all moderate hyponatremia would be eliminated by monitoring plan
  - Subjects eliminated from treatment
Appropriateness of Proposed Serum Sodium Monitoring Plan

- Proposed monitoring plan is optimal
- Longer-term monitoring will not detect clinically significant hyponatremia
  - Should be used with at risk patients
- Trial monitoring time points: Day 7 and Day 30
  - Most hyponatremia occurs in first month of treatment
- Only 4 subjects developed symptoms possibly related to hyponatremia before Day 4
  - Consistent with mode of action of desmopressin

FDA briefing book, section 4.3
Management of Subjects with Markedly Decreased Serum Sodium (<130 mmol/L)

- Serum sodium ≤130 mmol/L: 12 subjects (8%) instructed to return for repeated serum sodium measurement
  - 11 returned within 16 days (median)
    - 10 of the 11 increased serum sodium to ≥130 mmol/L by next repeat level
    - 1 of the 11, serum sodium increased to ≥130 mmol/L by second repeat (14 days)
Management of Subjects with Markedly Decreased Serum Sodium (<130 mmol/L)

- 3 men had multiple markedly abnormal decreased serum sodium values <130 mmol/L
  - 2 had 2 occurrences
  - 1 had 5 occurrences
- 2 of the 3 would have been captured by monitoring plan
- Subjects with serum sodium values ≤125 mmol/L stopped treatment immediately
- 7 chronic hyponatremia cases (<135 mmol/L for ≥ 3 months)
- With proposed monitoring plan
  - 3 cases of MILD chronic hyponatremia remained
  - No cases persisted

FDA briefing book, section 4.3
Hyponatremia Summary

- Recognized and well-understood risk
- Unique steps taken to reduce incidence:
  - Dosages reduced to minimum effective doses
  - Gender-specific dosing
  - Sodium monitoring plan
- Sodium monitoring plan results:
  - Only mild, non-clinically significant hyponatremia
  - Within ranges of other drugs associated with hyponatremia
Benefit Risk/Conclusion

Eric Rovner, MD
Professor of Urology
Department of Urology
Medical University of South Carolina
Treatment of Nocturia due to Nocturnal Polyuria is Important

- NP is a major underlying cause of nocturia
- Nocturia due to NP affects sleep, daytime functioning, physical and mental well-being
- Undertreated, mistreated or treated off-label
- No FDA-approved therapies for nocturia due to NP
FDA Briefing Book: New Trial for More Homogeneous and Severe NP Population

- Unlikely to provide additional value
  - Previously studied in NOCTUPUS
  - NOCDURNA trials inclusion/exclusion criteria achieved ~90% NP population
  - Many patients with OAB/BPH have nocturia likely due to NP and would benefit from antidiuretic treatment
  - Pivotal study population consistent with current medical practice
Benefit-Risk of NOCDURNA

**Desmopressin**
- 40 years of global experience
- Lower dose melt formulation
- Gender-specific dosing
- Directed at the specific underlying cause: NP

**Benefits**
- Decreases # of nighttime voids
- Improves sleep, sleep quality and patient well-being
- Addresses unmet medical need for patients of all ages
- Provides optimal medical treatment option

**Managing Risks**
- Minimizes clinically significant hyponatremia
- Proposed thorough post-marketing risk minimization plan
NOCDURNA: Summary and Conclusion

- Clear unmet medical need
- Pivotal trial designs/population agreed in SPA
- Met primary and key secondary endpoints across trials
- Totality and consistency of data demonstrate clinical relevance and improvements in sleep and QoL
- Safety has been appropriately addressed
- Favorable benefit-risk profile
NOCDURNA®
Desmopressin Orally Disintegrating Tablet (Melt)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

January 12, 2015
Back-up Slides
Communications plan

Objectives

- To inform physicians on disease condition; appropriate patient selection; risk of hyponatremia; and importance of monitoring serum sodium levels

Execution of Communication Plan

- Email sent within 60 days of product approval, and at 12 and 24 months post approval to HCPs likely to prescribe NOCDURNA: GPs, family practitioners, internists, urologists
- Similar e-mail sent at above time points to key professional organizations for distribution to members

Website and Factsheet for Prescribers

- Prescriber educational website
- Factsheet distributed to prescribers at initial detailing visits with HCPs after product approval

Website and Medication Guide for Patients

- Patient educational website
- Medication guide targeted to patients provided in NOCDURNA packaging
## Demographics and Baseline Voiding Parameters by Gender Across Studies

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Full Analysis Set</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td></td>
<td></td>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CS29</td>
<td>CS40</td>
<td>CS29</td>
<td>CS41</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N=341</td>
<td>N=261</td>
<td>N=416</td>
<td>N=385</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.1 (13.7)</td>
<td>59.8 (14.2)</td>
<td>65.1 (11.5)</td>
<td>60.6 (13.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>30.5 (7.9)</td>
<td>30.3 (6.9)</td>
<td>28.8 (5.4)</td>
<td>29.2 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal voids</td>
<td>3.22 (1.12)</td>
<td>2.86 (0.84)</td>
<td>3.34 (1.16)</td>
<td>2.93 (0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime voids</td>
<td>7.68 (2.40)</td>
<td>5.64 (1.27)</td>
<td>7.27 (2.19)</td>
<td>5.68 (1.20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FUSP (min)</td>
<td>112 (67.5)</td>
<td>145 (57.2)</td>
<td>117 (61.0)</td>
<td>146 (55.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI (%)</td>
<td>46.8 (12.1)</td>
<td>46.2 (12.7)</td>
<td>48.4 (12.2)</td>
<td>45.4 (12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturnal Volume (mL)</td>
<td>805 (367)</td>
<td>617 (333)</td>
<td>824 (396)</td>
<td>625 (327)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FUSP = First Undisturbed Sleep Period
NPI = Nocturnal polyuria index
NOCDURNA - Exposure Data from Canada

- NOCDURNA approved/launched in Canada
  - 25 µg in females launched August 2014
  - 50 µg in males launched November 2014
- 344 patients-years* of exposure for 25 µg in women
- 323 patients-years* of exposure for 50 µg in men

*30 November 2014
Post-marketing NOCDURNA – Three Cases of Hyponatremia

- Woman treated with 25 µg NOCDURNA was hospitalized for hyponatremia; No other information is available
- Man treated with 25 µg NOCDURNA; serum sodium decreased from 131 mmol/L to 125 one week later; non-serious
- An unknown age/sex patient with 25 µg NOCDURNA; serum sodium decreased from 135 mmol/L to 127; non-serious
## Nocturnal Diuresis at Baseline in Both Women (CS40) and Men (CS41)

<table>
<thead>
<tr>
<th>Urine Volume</th>
<th>CS40 (Women)</th>
<th>CS41 (Men)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 µg</td>
<td>Placebo</td>
</tr>
<tr>
<td>&lt;90 mL/hr</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td>100 (75)</td>
<td>96 (75)</td>
</tr>
<tr>
<td>≥ 90 mL/hr</td>
<td>22 (25)</td>
<td>32 (25)</td>
</tr>
</tbody>
</table>

**Total NP Population = 25%**
### Co-Primary 2 Endpoint of 33% Responder Rate in NP Populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Urine Volume</th>
<th>Placebo</th>
<th>NOCDURNA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Odds</td>
<td>N</td>
</tr>
<tr>
<td>Women (CS40)</td>
<td>≥ 33% NPI</td>
<td>111</td>
<td>1.59</td>
</tr>
<tr>
<td></td>
<td>≥ 90 mL/hr</td>
<td>31</td>
<td>1.42</td>
</tr>
<tr>
<td>Men (CS41)</td>
<td>≥ 33% NPI</td>
<td>127</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>≥ 90 mL/hr</td>
<td>36</td>
<td>0.85</td>
</tr>
</tbody>
</table>

![Odds Ratio Graph](image-url)
Change in Serum Sodium Over Time in Female Patients on 25 mcg

Box Plot of Serum Sodium Change from Baseline by Visit
Treatment: 25 µg
Change in Serum Sodium Over Time in Male Patients on 50 mcg

Box Plot of Serum Sodium Change from Baseline by Visit - Part I
Treatment: 50 μg

- Day 4
- Week 1
- Week 2
- Week 3
- 1 Month
- 2 Months
- 3 Months

Change from Baseline (mmol/L)
# No Efficacy Difference in Patients with Hyponatremia

<table>
<thead>
<tr>
<th>Serum Sodium Level (Lowest level at any given time point)</th>
<th>N</th>
<th>Δ Mean Change Noct. Voids Co-Primary 1</th>
<th>Δ Baseline Noct. Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>≥135:&lt;135</td>
<td></td>
</tr>
<tr>
<td>CS40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 135 mmol/L</td>
<td>120</td>
<td>-1.45</td>
<td>-1.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.515</td>
<td></td>
</tr>
<tr>
<td>&lt;135 mmol/L</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 135 mmol/L</td>
<td>108</td>
<td>-1.19</td>
<td>-1.64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p=0.098</td>
<td></td>
</tr>
<tr>
<td>&lt;135 mmol/L</td>
<td>11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Causes of Placebo Effect

- Placebo effect common in lower urinary tract symptom trials with up to 64%\(^1\) reduction from baseline

- Several factors may contribute
  - Clinical trial setting
    - Lifestyle modifications
    - Physician-patient interaction
  - Regression to the Mean due to inclusion criteria
  - Effect of taking a tablet

Ref: 1. van Leeuwen JH, 2006 (urge incontinence episodes)
Regression to the Mean (RTM) Effect: 32% in Women (CS40) and 45% in Men (CS41) of Placebo Effect

<table>
<thead>
<tr>
<th>Population Mean Nocturnal Voids (Screened Population)</th>
<th>RTM Effect * (Mean # Voids Reduction)</th>
<th>RTM Effect as % of Total Placebo Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Women (CS40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Men (CS41)</td>
</tr>
<tr>
<td>2.0</td>
<td>0.33</td>
<td>27%</td>
</tr>
<tr>
<td>2.5</td>
<td>0.40</td>
<td>32%</td>
</tr>
<tr>
<td>2.9</td>
<td>0.51</td>
<td>41%</td>
</tr>
</tbody>
</table>

- Total placebo effect over 3 months:
  - 1.24 mean # voids reduction – Women (CS40)
  - 0.88 mean # voids reduction – Men (CS41)

* Estimation using Barnett et al (2004) utilizing data from women (CS40) and men (CS41) placebo arm (Month 2 and 3).
### Falls and Fractures Reported in Women (CS40) and Men (CS41)

| MedDRA Preferred Term | CS40 (Women) | | | CS41 (Men) | | |
|-----------------------|--------------|---|---|----------------|---|
|                       | 25µg N=135   | Placebo N=126 | 50µg N=119 | 75µg N=122 | Placebo N=143 |
| Falls                 | 0            | 1 (<1)       | 0           | 1 (<1)       | 1 (<1)       |

| MedDRA Preferred Term | CS40 (Women) | | | CS41 (Men) | | |
|-----------------------|--------------|---|---|----------------|---|
|                       | 25µg N=135   | Placebo N=126 | 50µg N=119 | 75µg N=122 | Placebo N=143 |
| Ankle Fracture        | 1 (<1)       | 0           | 0           | 0            | 0            |
| Wrist Fracture        | 0            | 1 (<1)      | 0           | 0            | 0            |

All Serum Sodium Normal
Nocturnal Voids Increased in Treatment Free Phase Despite Lifestyle Modifications

![Bar chart showing mean number of nocturnal voids over time for men and women.](chart.png)