SER120 Nasal Spray
Serenity Pharmaceuticals

Bone, Reproductive and Urologic Drugs Advisory Committee

October 19, 2016

Introductory Remarks

Seymour Fein, MD

Chief Medical Officer
Serenity Pharmaceuticals, LLC

Nocturia

- **Multifactorial medical condition with documented associated morbidity and mortality[1,2,3,4]**
- **Majority of patients have nocturnal polyuria but some also have OAB or BPH[2]**
- **Unmet medical need which impacts activities of daily living[5,6]**

[1]Lightner, *BJU Int*. 2012, 119(6):848
[2]Weiss, *Rev Urol*. 2012; 14(3-4) 48-55
[3]Abrams et al. *Neurourol Urodyn*, 2004, 23; 466
[4]Chang et al. *Urology*, 2006; 67: 541 – 4
[5]Tikkinen et al. *Eur Urol* 2010;57:488–496. 15D instrument: Sintonen. *Ann Med* 2001;33: 328–336
[6]Kobelt, *BJU* Int. 2003, 91, 190-195

Nocturia Treatment Today

- **No FDA approved product specifically for treatment of nocturia**
- **OAB and BPH drugs relatively ineffective for nocturia[1]**
- **Anti-diuretic drug therapy has shown the most potential for treating nocturia and filling this gap**

[1]Weiss, *Rev Urol.* 2012; 14(3-4) 48-55

Desmopressin

- Synthetic peptide analogue of vasopressin
- Anti-diuretic pharmacology can reduce nocturnal urine production
- Highly selective V2 agonist with minimal hemodynamic effects

Desmopressin

- **In-vitro studies suggest no significant liver metabolism**
- **Elimination depends on proteolytic degradation and significant amounts of desmopressin (30-45%) are excreted unchanged in the urine[1]**
- **Approved by FDA since 1979 in various dose forms for central diabetes insipidus (CDI) and primary nocturnal enuresis (PNE)**

[1]Agerso, H. *Br. J. Clin. Pharmacol*. 2004.

Desmopressin for Nocturia

- **Current problem is unwanted prolongation of anti-diuretic effect beyond the hours of sleep creating risk of water retention and hyponatremia**
- **The solution is low dose desmopressin with a predictable and consistent PK profile which controls PD duration of the anti-diuretic effect**
- **SER120 provides the solution**

SER120 Nasal Spray

- **Novel, very low dose desmopressin formulation specifically engineered for the treatment of nocturia**
- **Preservative-free, metered-dose nasal spray manufactured aseptically**
- **Contains cyclopentadecanolide (CPD), a cyclic fatty acid as permeation enhancer to facilitate systemic absorption through nasal mucosa**

SER120 Proposed Indication

SER120 is indicated for the treatment of nocturia in adults who wake up 2 or more times per night to void

Agenda of Core Presentation

Nocturia – An Unmet Medical Need	**Alan J. Wein MD, PhD (Hon)** *Founders Professor and Chair of Urology* *Perelman School of Medicine, University of Pennsylvania*
Clinical Pharmacology and Efficacy	**Seymour Fein, MD** *Chief Medical Officer* *Serenity Pharmaceuticals, LLC*
Patient Treatment Benefit Patient-Reported Outcomes	**Kristin M. Khalaf, PharmD, PhD** *Assistant Director, Global Health Economics and Outcomes Research* *Xcenda, LLC*
Integrated Summary of Safety	**Seymour Fein, MD**
Benefit-Risk Assessment and REMS	**Annette Stemhagen, DrPH, FISPE** *Senior Vice President* *UBC, Safety, Epidemiology, Registries and Risk Management*
Concluding Remarks	**Steven Kaplan, MD** *Professor of Urology* *Icahn School of Medicine at Mount Sinai*

Nocturia – An Unmet Medical Need

Alan J. Wein MD, PhD (Hon)

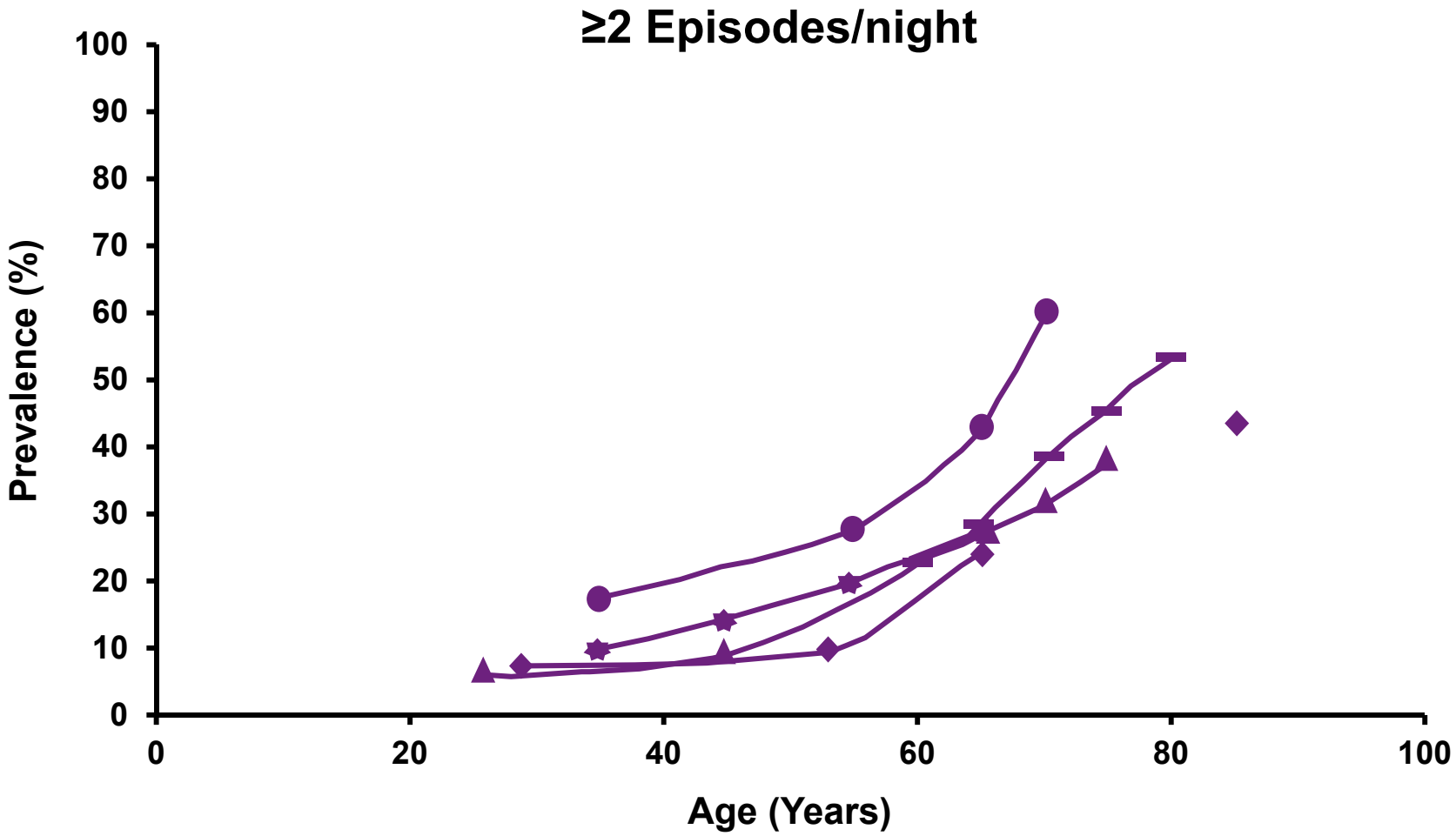
Founders Professor and Chair of Urology
Perelman School of Medicine
University of Pennsylvania
Chief of Urology
University of Pennsylvania Health System

Nocturia: Issues

- **Under recognized**
- **Not simply due to OAB in women, BPH in men**
- **Has significant adverse consequences and negatively impacts quality of life**

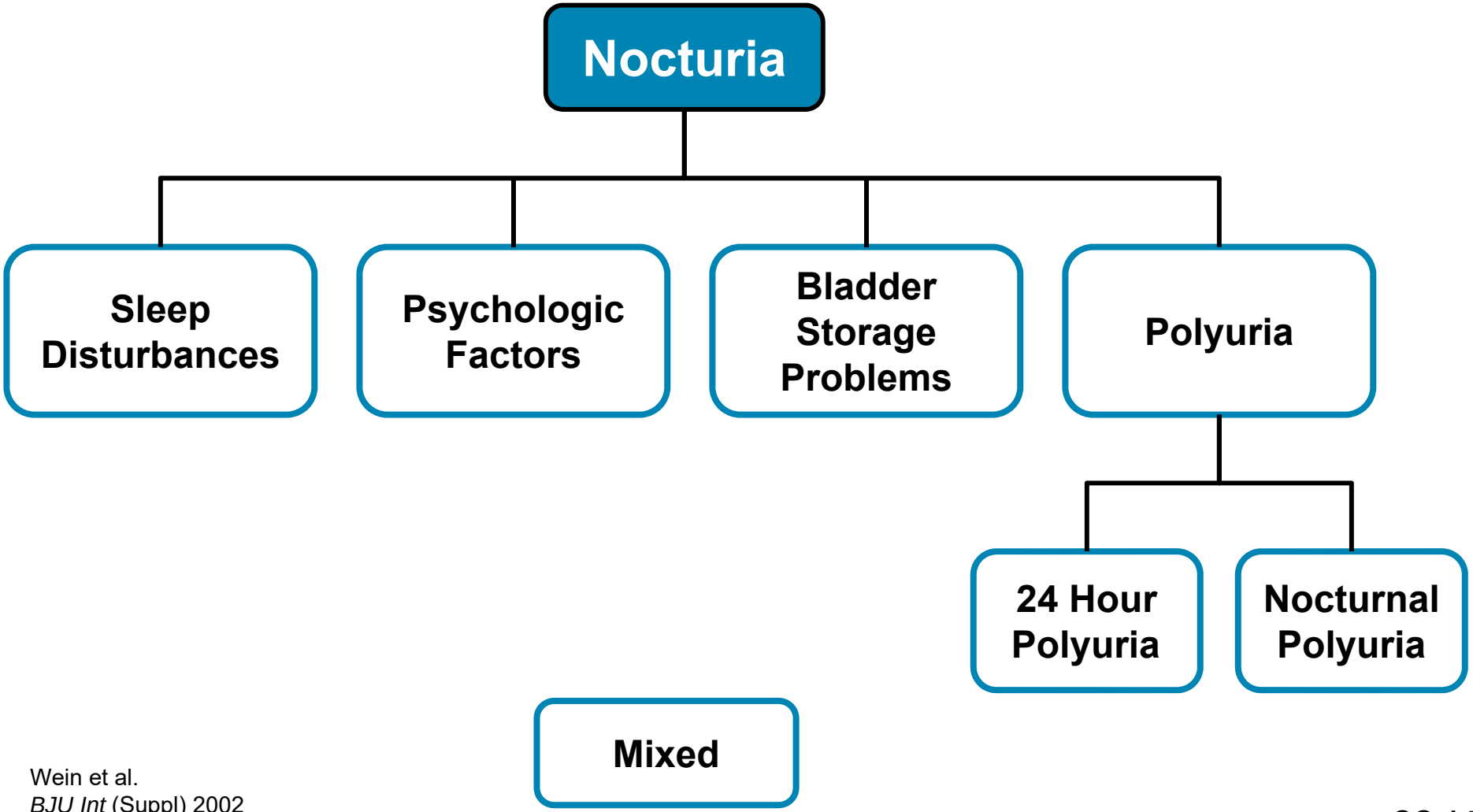
Weiss J et al. *BJU* Int, 2011
Drake, M *Campbell-Walsh Urology*, 2011
Weiss J *Campbell-Walsh Urology*, 2016

Prevalence of Nocturia in Men and Women Based on Multiple Studies



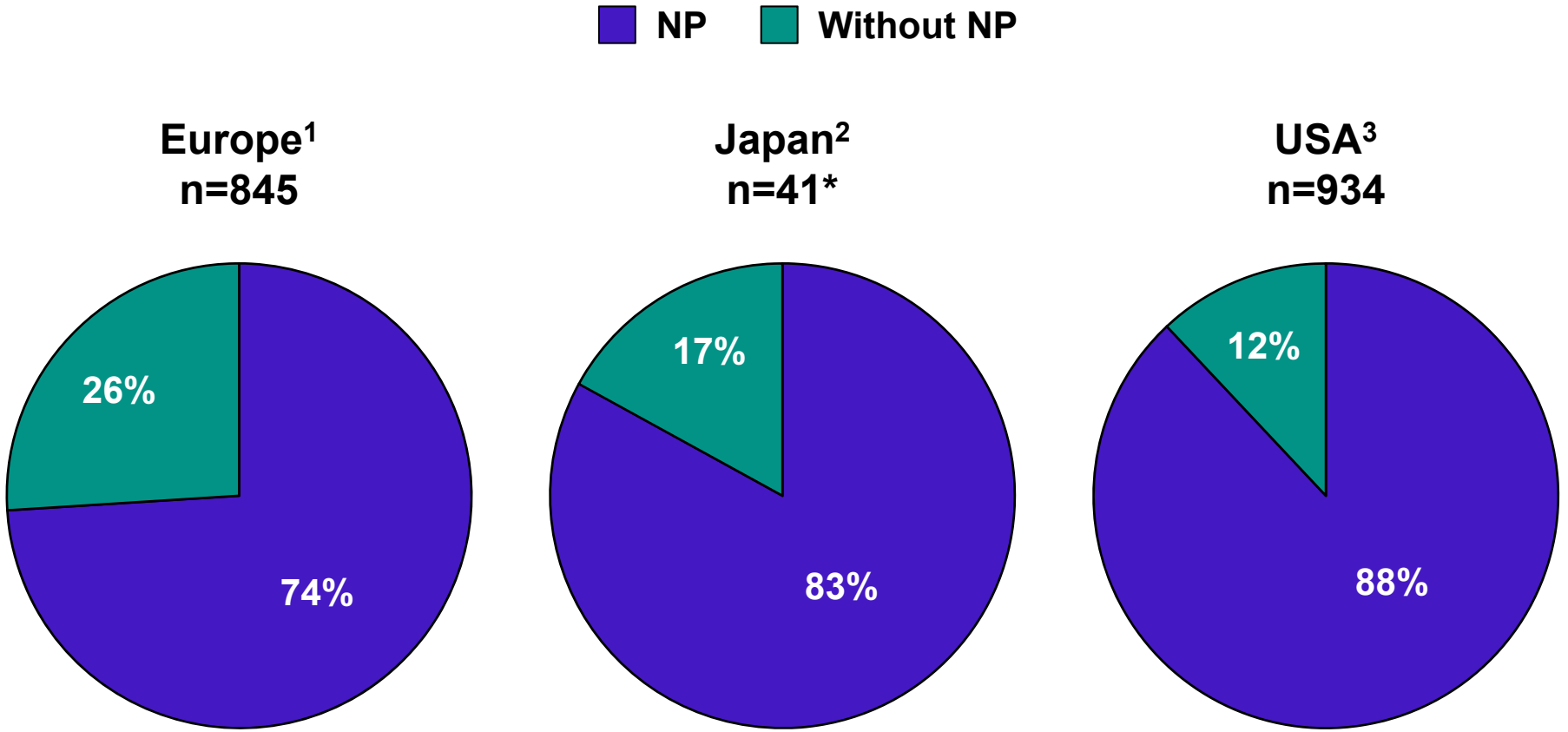
Bosch JLHR and Weiss JP: The prevalence and causes of nocturia. *J Urol* 184: Aug 2010

Nocturia: Etiology



Wein et al.
BJU Int (Suppl) 2002

Nocturnal Polyuria (NP) is Present in the Majority of All Nocturia Patients



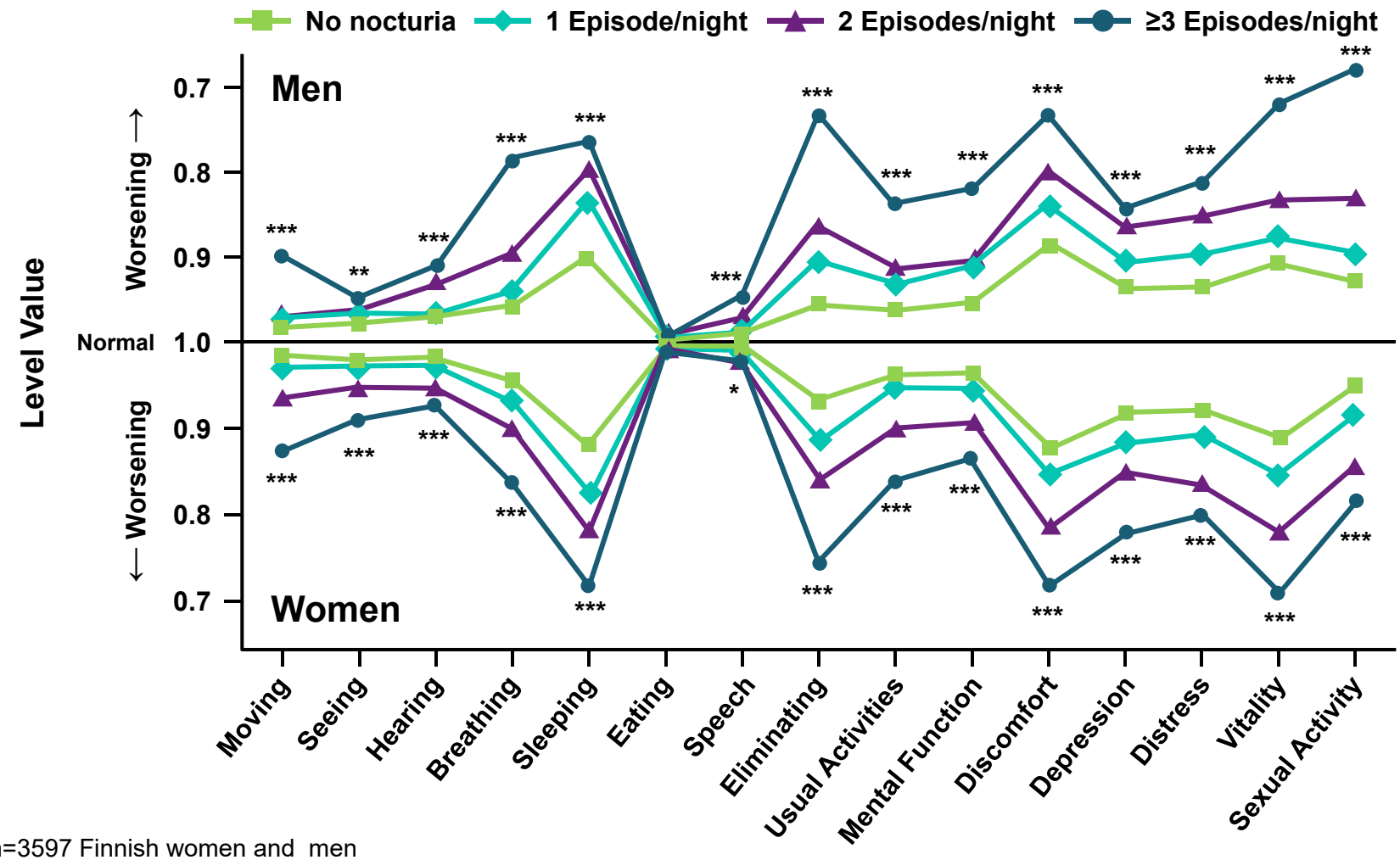
*Males only

[1]Abrams et al. *Neurourol Urodyn* 2004;23:466. Abstract 48

[2]Chang et al. *Urology* 2006;67:541-544.

[3]Weiss et al. *J Urol* 2009:181:538

15D (HRQL) Dimensions and Nocturia



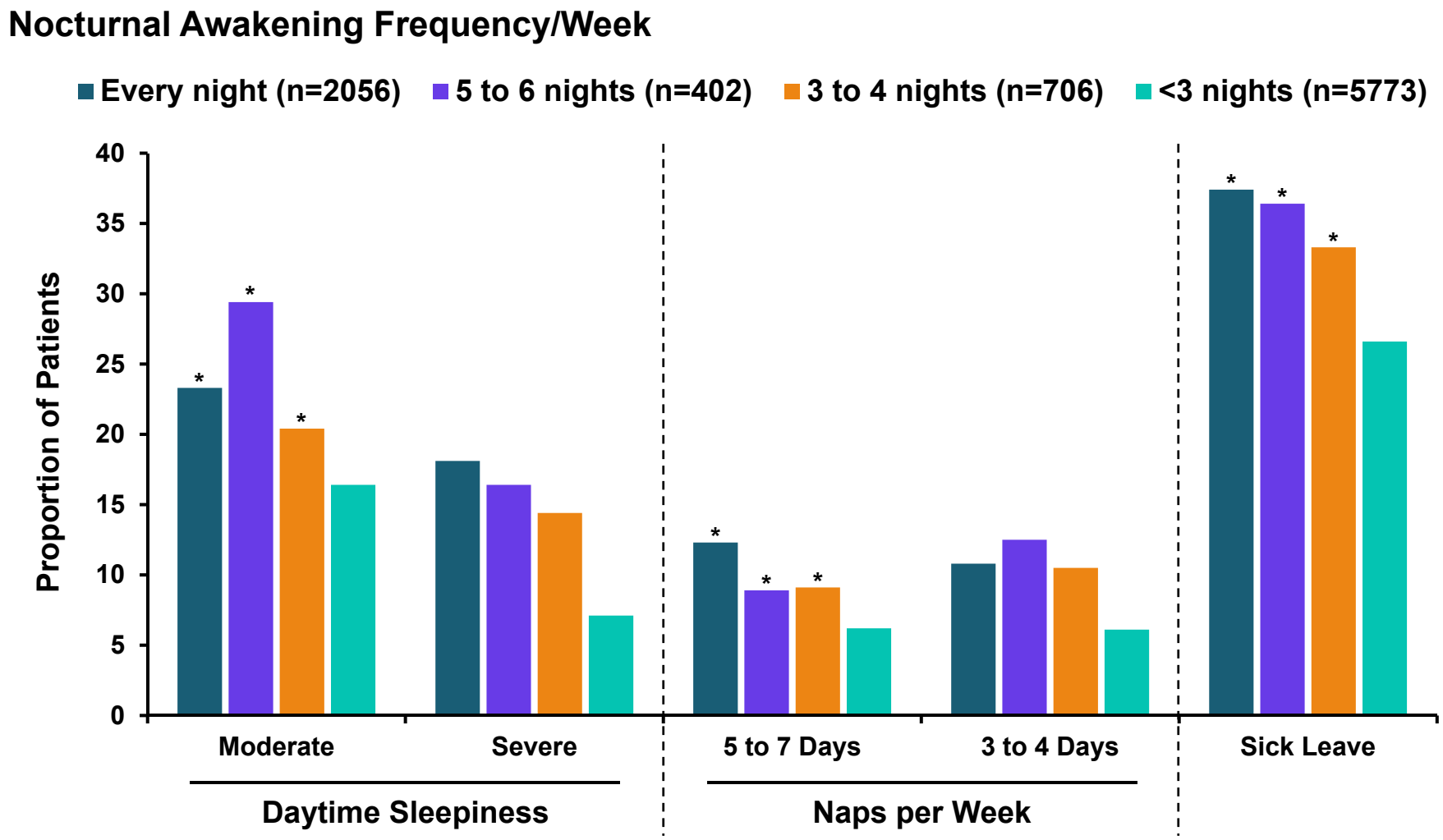
n=3597 Finnish women and men
*p <0.05; **p <0.01, *** p<0.001 (test for trend)
Tikkinen et al. *Eur Urol* 2010;57:488–496. 15D instrument: Sintonen. *Ann Med* 2001;33: 328–336

Nocturia Severity and Bothersomeness (N=3474)

	Bother			
Nocturia episodes	None %	Small %	Moderate %	Major %
One	52.2	41.1	5.9	0.7
Two	29.3	53.8	13.9	3.1
Three	17.4	26.7	41.9	14.0
Four or more	11.3	7.0	46	35.7

Tikkinen et al. *Eur Urol* 2010;57:488–496.

Nocturic Nights vs. Sleepiness, Naps and Sick Leave



*p<0.001 vs. awaking <3 nights/week

Ohayon, *J Psychiatr Res* 2009: 43: 48-54

Falls in Elderly Patients With Nocturia

- **5872 community-dwelling US men aged ≥65 years**
- **Primary outcome: 1-year cumulative incidence of falls with moderate/severe vs mild LUTS at baseline**
- **Nocturia was among the LUTS most strongly associated with falls**

	2-3 Episodes/Night % RR (95% CI)	4-5 Episodes/Night % RR (95% CI)
Relative risk of at least 1 fall	5 1.05 (0.96, 1.16)	23 1.23 (1.08, 1.41)
Relative risk of at least 2 falls	11 1.11 (1.08-1.41)	42 1.42 (1.16, 1.74)

LUTS=Lower urinary tract symptom
Parsons et al. *BJU Int* 2009;104:63-68

Current Nocturia Therapy

- **Behavioral modification has not shown durable efficacy in clinical practice**
- **Drugs for OAB and BPH have marginal efficacy**
- **Desmopressin has shown consistent and sustained efficacy**

Conclusions

- **Nocturia is a significant medical condition associated with significant morbidity**
- **Nocturia disrupts normal sleep, causing daytime fatigue, loss of productivity and impairs ability to perform daily activities**
- **Nocturia increases the risk of falls**
- **No FDA approved treatment specifically for nocturia**

Clinical Pharmacology and Efficacy

Seymour Fein, MD

Chief Medical Officer
Serenity Pharmaceuticals, LLC

SER120 Clinical Program (N >2300)

Phase I/IIA

NS 200801 N=12 (Phase I)	Single Dose Cross over	**CRI 201002** (impaired renal function) N=16 (Phase I)	single dose	**NS 200802** N=43 (Phase IIA)	12 days

Initial Phase III Studies

DB1 N=301	50 days	**DB2** N=326	50 days

Phase III Pivotal Studies

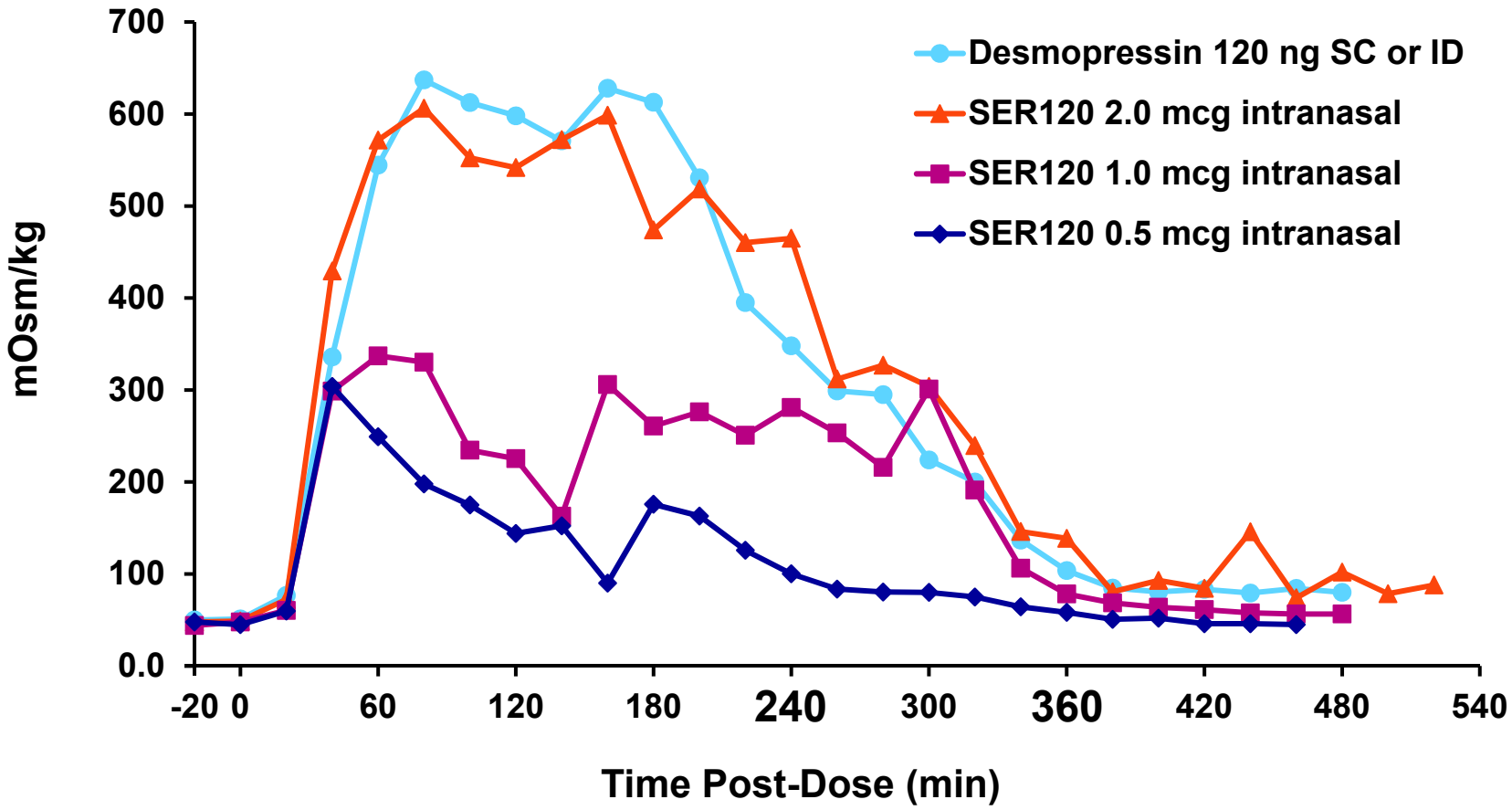
DB3 N=745	99 days	**DB4** N=797	99 days

Open-Label Studies

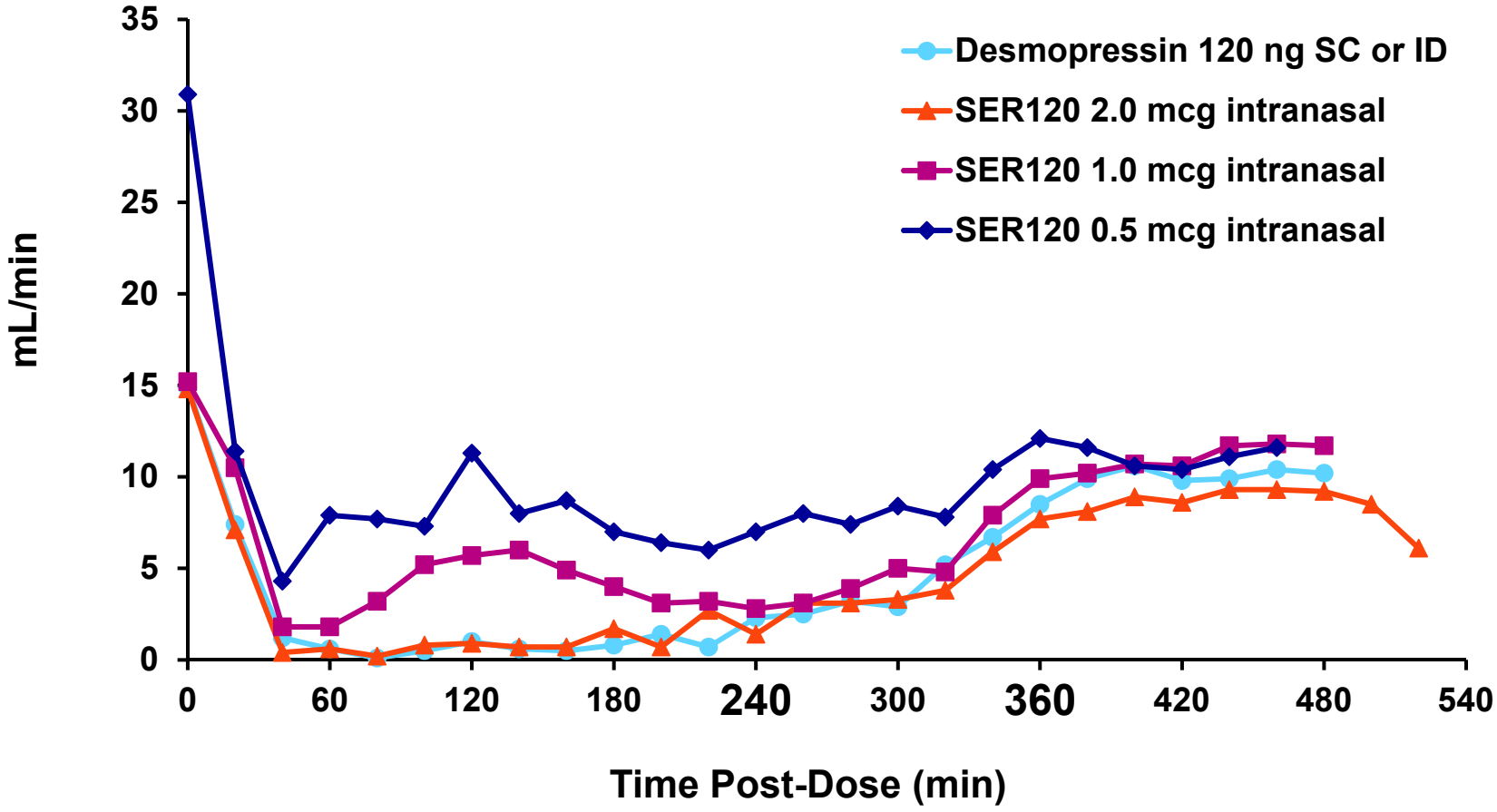
ELD (elderly patients) N=32 (Age range: 75 to 85)	56 days	**OL1** (Long-term) N=376	43 weeks	**DB3-A2** (Long-term) N=393	Up to 126 weeks

Urine Osmolality

Phase I Single Dose Crossover Study



Urine Output
Phase I Single Dose Crossover Study



Comparison of SER120 2 mcg IN and 120 ng Desmopressin SC (RIA)
Phase I PK/PD

PK Parameter	SER120 2.0 mcg Intranasal Mean ± SD (CV%)	Desmopressin 120 ng Subcutaneous Mean ± SD (CV%)
C_{max} (pg/mL)	N=12	N=6
	6.24 ± 2.25 (36.0)	**2.77 ± 0.98 (35.4)**
T_{max} (h)	N=12	N=6
	0.354 ± 0.188 (53.2)	**0.883 ± 0.349 (39.5)**
AUC_{α} (pg.h/mL)	N=8	N=3
	11.5 ± 7.9 (68.6)	**10.2 ± 4.9 (47.5)**
$T_{1/2}$ (h)	N=8	N=3
	1.33 ± 0.56 (42.3)	**2.09 ± 0.32 (15.4)**

RIA=Radio Immune Assay

Pooled PK Analyses
Phase 2/ELD/CRI/DB1/DB3

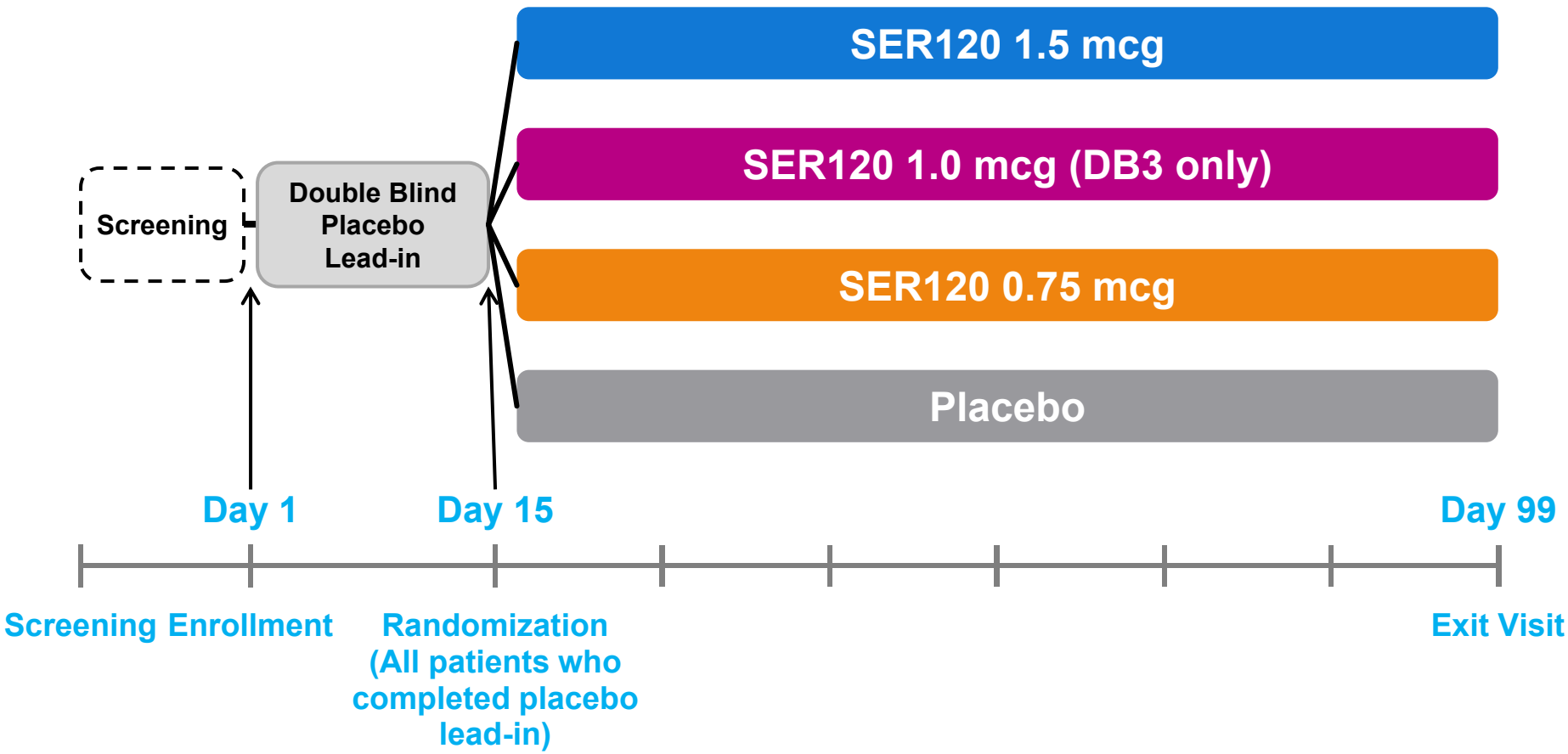
- **Pooled PK analyses of 5 SER120 studies showed**
  - C_{max} unaffected by age, gender, BMI or renal function (eGFR)
  - AUC_t unaffected by age, gender, BMI or renal function (eGFR)
  - $T_{1/2}$ unaffected by age, gender or BMI
    - However, renal function showed statistically significant prolongation of $T_{1/2}$ in patients with eGFR less than 50 mL/min/1.73m^2

Phase 3 Pivotal Studies

DB3 Study – SER120 1.5, 1.0 and 0.75 mcg and placebo

DB4 Study – SER120 1.5 and 0.75 mcg and placebo

Study Design
DB3 and DB4 Study



Patient Demographics
ISE DB3/DB4 Studies, ITT Population

Demographic Characteristics	Statistics	Placebo N=446 n (%)	SER120 1.5 mcg N=439 n (%)	SER120 0.75 mcg N=448 n (%)
Age (years)	Mean, years (SD)	65.9 (9.4)	66.1 (9.3)	66.4 (8.9)
	<65	202 (45.3)	201 (45.8)	203 (45.3)
	≥65	244 (54.7)	238 (54.2)	245 (54.7)
BMI (kg/m^2)	Mean	29.5 (6.2)	30.0 (6.4)	29.2 (5.7)
Gender	Male	258 (57.8)	251 (57.2)	252 (56.3)
	Female	188 (42.2)	188 (42.8)	196 (43.8)
Race	Caucasian	352 (78.9)	332 (75.6)	361 (80.6)
	African American	60 (13.5)	60 (13.7)	41 (9.2)
	Asian	7 (1.6)	11 (2.5)	8 (1.8)
	Hispanic	23 (5.2)	32 (7.3)	33 (7.4)
	Other	4 (0.9)	4 (0.9)	5 (1.1)

Nocturia Etiology by History

ISE DB3/DB4 Studies, ITT Population

Presumed Etiology for Nocturia	Placebo N=446 n (%)	SER120 1.5 mcg N=439 n (%)	SER120 0.75 mcg N=448 n (%)
Nocturnal polyuria	359 (80.5)	345 (78.6)	363 (81.0)
BPH	187 (41.9)	162 (36.9)	169 (37.7)
OAB	113 (25.3)	131 (29.8)	122 (27.2)
Polyuria	18 (4.0)	13 (3.0)	17 (3.8)
Unknown	106 (23.8)	92 (21.0)	111 (24.8)

Primary Efficacy Variables

- **Reduction in mean nocturic episodes**
- **Percent of responders (≥50% reduction in mean nocturic episodes)**

Co-primary Efficacy Variable 1 – Reduction in Mean Number of Nocturic Episodes
DB3 and DB4 Studies, ITT Population

	DB3 Study				DB4 Study		
Period	**Placebo N=186**	**SER120 1.5 mcg N=179**	**SER120 1.0 mcg N=183**	**SER120 0.75 mcg N=186**	**Placebo N=260**	**SER120 1.5 mcg N=260**	**SER120 0.75 mcg N=262**
Screening[1]							
LS Mean	3.4	3.2	3.3	3.4	3.2	3.3	3.3
Treatment Period[2]							
LS Mean	2.1	1.7	1.9	1.9	2.1	1.8	1.9
Change from Screening							
LS Mean	-1.2	-1.6	-1.4	-1.4	-1.2	-1.5	-1.4
Std. Err.	0.07	0.07	0.07	0.07	0.06	0.06	0.06
Comparison to Placebo, p-value		<0.0001[3]	0.0377[3]	0.0093[3]		0.0005[3]	0.0055[3]
95% CI		-0.6, -0.2[4]	-0.4, 0.0[4]	-0.4, -0.1[4]		-0.4, -0.1[5]	-0.4, -0.1[5]

[1]Average of last 6 nights during screening.
[2]Average of recorded diaries as specified by the protocol during the Treatment Period.
[3]P-Value for change from screening based on ANCOVA. Model is: change = Screening Episodes/Day + Treatment Group + Study Center + Age Group + Gender.
[4]95% CI for treatment group difference: 3 active doses of SER120 to placebo based on LS means for both observed and change from screening data.
[5]95% CI for treatment group difference: 2 active doses of SER120 to placebo based on LS means for both observed and change from screening data.

Co-primary Efficacy Variable 2 – Percent of Responders (≥50% Reduction in Mean Nocturic Episodes)
DB3 and DB4 Studies, ITT Population

	DB3 Study				DB4 Study		
Responder	**Placebo N=186 n (%)**	**SER120 1.5 mcg N=179 n (%)**	**SER120 1.0 mcg N=183 n (%)**	**SER120 0.75 mcg N=186 n (%)**	**Placebo N=260 n (%)**	**SER120 1.5 mcg N=260 n (%)**	**SER120 0.75 mcg N=262 n (%)**
Yes	61 (32.8)	93 (52.0)	73 (39.9)	77 (41.4)	74 (28.5)	121 (46.5)	93 (35.5)
Comparison to Placebo, p-value		0.0002[1]	0.1608[1]	0.0899[1]		<0.0001[1]	0.0854[1]

[1]P-Value based on Cochran-Mantel-Haenszel test stratifying by Age Group and Gender.

Integrated Summary of Efficacy

DB3 and DB4 Studies

Co-primary Efficacy Variable 1 – Reduction in Mean Number of Nocturic Episodes
ISE DB3/DB4 Studies, ITT Population

Period	Placebo N=446	SER120 1.5 mcg N=439	SER120 0.75 mcg N=448	Treatment Group Comparison to Placebo: SER120 1.5 mcg p-value	Treatment Group Comparison to Placebo: SER120 0.75 mcg p-value
Screening[3]					
LS Mean (SE)	3.3	3.3	3.4	0.8829[1]	0.1359[1]
Treatment Period[4]					
LS Mean	2.1	1.8	1.9		
Change from Screening					
LS Mean	-1.2	-1.5	-1.4		
Std. Err.	0.05	0.05	0.05		
95% CI – change from screening[5]		(-0.4, -0.2)	(-0.3, -0.1)		
Treatment Comparison to Placebo				<0.0001[2]	<0.0001[2]

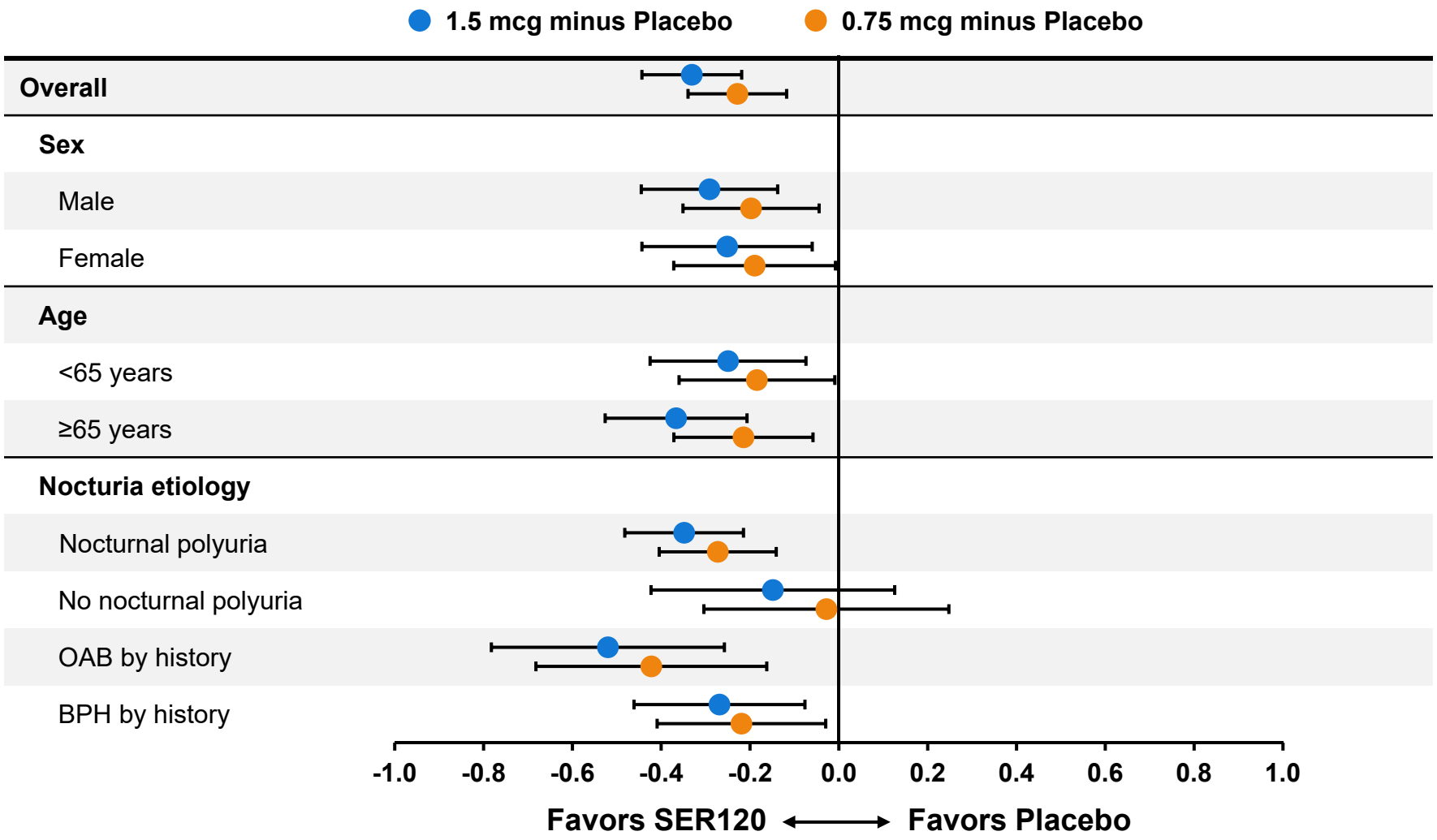
[1]P-Value for Screening based on ANOVA. Model is: response = Treatment Group + Study + Study Center (Study) + Age Group + Gender.
[2]P-Value for change from screening based on ANCOVA. Model is: change = Screening Nocturic Episodes/Night + Treatment Group + Study + Study Center (Study) + Age Group + Gender.
[3]Average of last 6 nights during screening.
[4]Average of recorded diaries as specified by the protocol during the Treatment Period.
[5]95% CI for treatment group difference based on L.S. Means: 2 active doses of SER120 to placebo.

Co-primary Efficacy Variable 2 – Percent of Responders Patients (≥50% Reduction in Mean Nocturic Episodes)
ISE DB3/DB4 Studies, ITT Population

				Treatment Group Comparison to Placebo	
Responder	**Placebo N=446 n (%)**	**SER120 1.5 mcg N=439 n (%)**	**SER120 0.75 mcg N=448 n (%)**	**SER120 1.5 mcg p-value**	**SER120 0.75 mcg p-value**
Yes	135 (30.3)	214 (48.7)	170 (37.9)	<0.0001[1]	0.0159[1]
No	311 (69.7)	225 (51.3)	278 (62.1)		

[1]P-Value based on Cochran-Mantel-Haenszel test stratifying by Study, Age Group and Gender.

Co-primary Efficacy Variable 1 – Reduction in Mean Nocturic Episodes by Gender, Age and Nocturia Etiology
ISE DB3/DB4 Studies, ITT Population



Co-primary Efficacy Variable 2 – Percent of Responders (≥50% Reduction in Nocturic Episodes) by Gender and Age ISE DB3/DB4 Studies, ITT Population

Responder Sub-Population		Statistics	Placebo N=446 n (%)	SER120 1.5 mcg N=439 n (%)	SER120 0.75 mcg N=448 n (%)	Treatment Group Comparison to Placebo: SER120 1.5 mcg p-value	Treatment Group Comparison to Placebo: SER120 0.75 mcg p-value
Gender	Male	**N**	**258**	**251**	**252**		
		Yes	63 (24.4)	110 (43.8)	84 (33.3)	<0.0001[1]	0.0227[1]
	Female	**N**	**188**	**188**	**196**		
		Yes	72 (38.3)	104 (55.3)	86 (43.9)	0.0009[1]	0.2661[1]
Age	<65 Years	**N**	**202**	**201**	**203**		
		Yes	79 (39.1)	112 (55.7)	90 (44.3)	0.0007[2]	0.2875[2]
	≥65 Years	**N**	**244**	**238**	**245**		
		Yes	56 (23.0)	102 (42.9)	80 (32.7)	<0.0001[2]	0.0184[2]

[1]P-Value based on Cochran-Mantel-Haenszel test stratifying by Study and Age Group.
[2]P-Value based on Cochran-Mantel-Haenszel test stratifying by Study and Gender.

Co-primary Efficacy Variable 2 – Percent of Responders (≥50% Reduction in Nocturic Episodes) by Nocturia Etiology ISE DB3/DB4 Studies, ITT Population

Responder Sub-Population		Statistics	Placebo N=446 n (%)	SER120 1.5 mcg N=439 n (%)	SER120 0.75 mcg N=448 n (%)	Treatment Group Comparison to Placebo: SER120 1.5 mcg p-value	Treatment Group Comparison to Placebo: SER120 0.75 mcg p-value
Nocturia etiology	Nocturnal Polyuria	N	349	342	354		
		Yes	96 (27.5)	164 (48.0)	132 (37.3)	<0.0001[1]	0.0055[1]
	OAB	N	113	131	122		
		Yes	32 (28.3)	64 (48.9)	49 (40.2)	0.0005[1]	0.0452[1]
	BPH	N	187	162	169		
		Yes	42 (22.5)	62 (38.3)	53 (31.4)	0.0012[1]	0.0541[1]
	No Nocturnal Polyuria	N	97	96	93		
		Yes	39 (40.2)	50 (52.1)	37 (39.8)	0.0875[1]	0.7567[1]

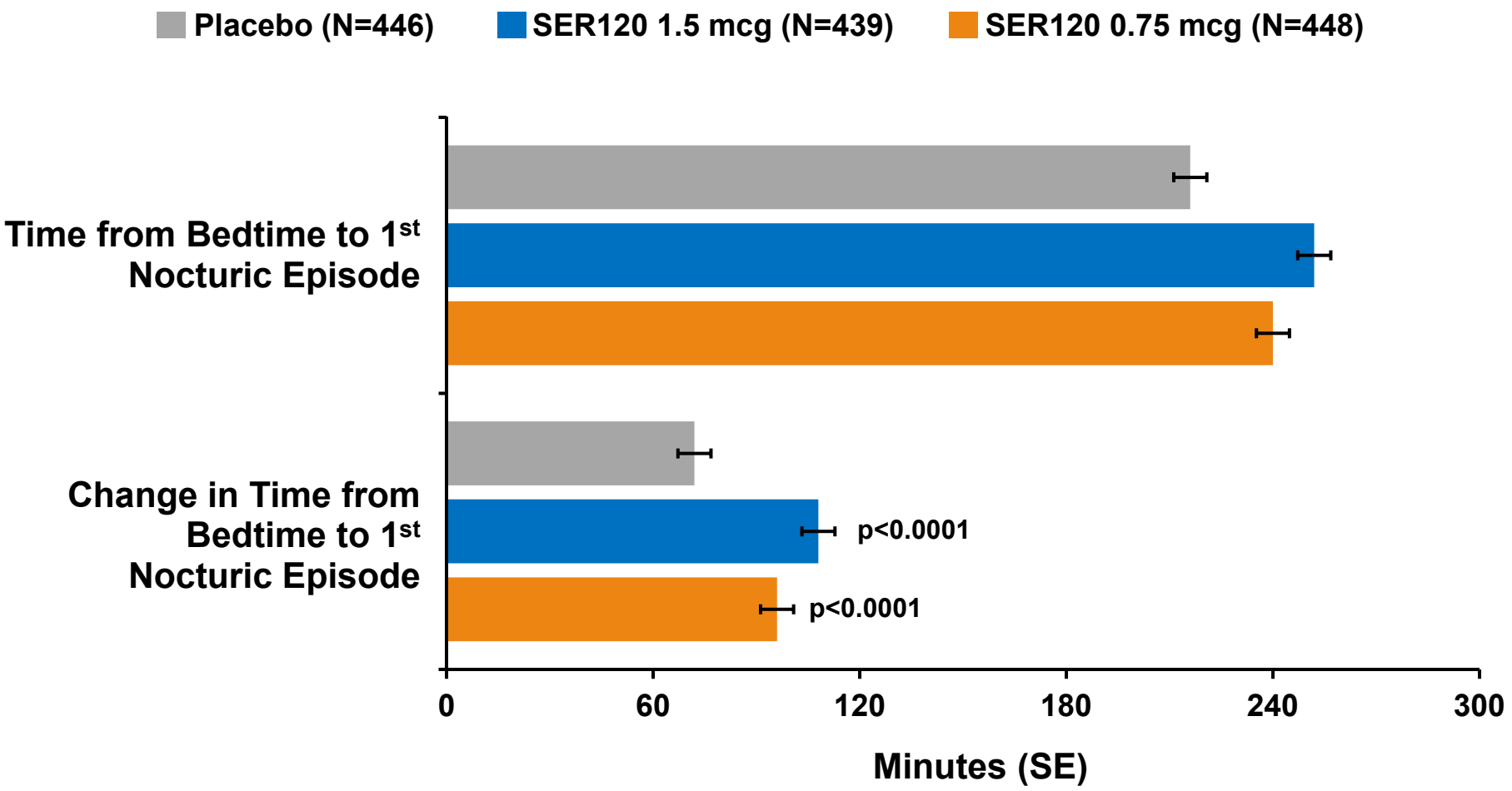
[1]P-Value based on Cochran-Mantel-Haenszel test stratifying by Study, Age Group and Gender.

Secondary Efficacy Variables

- **5 secondary endpoints**
- **Selected for clinical relevance**
- **PRO was first endpoint (DB4)**

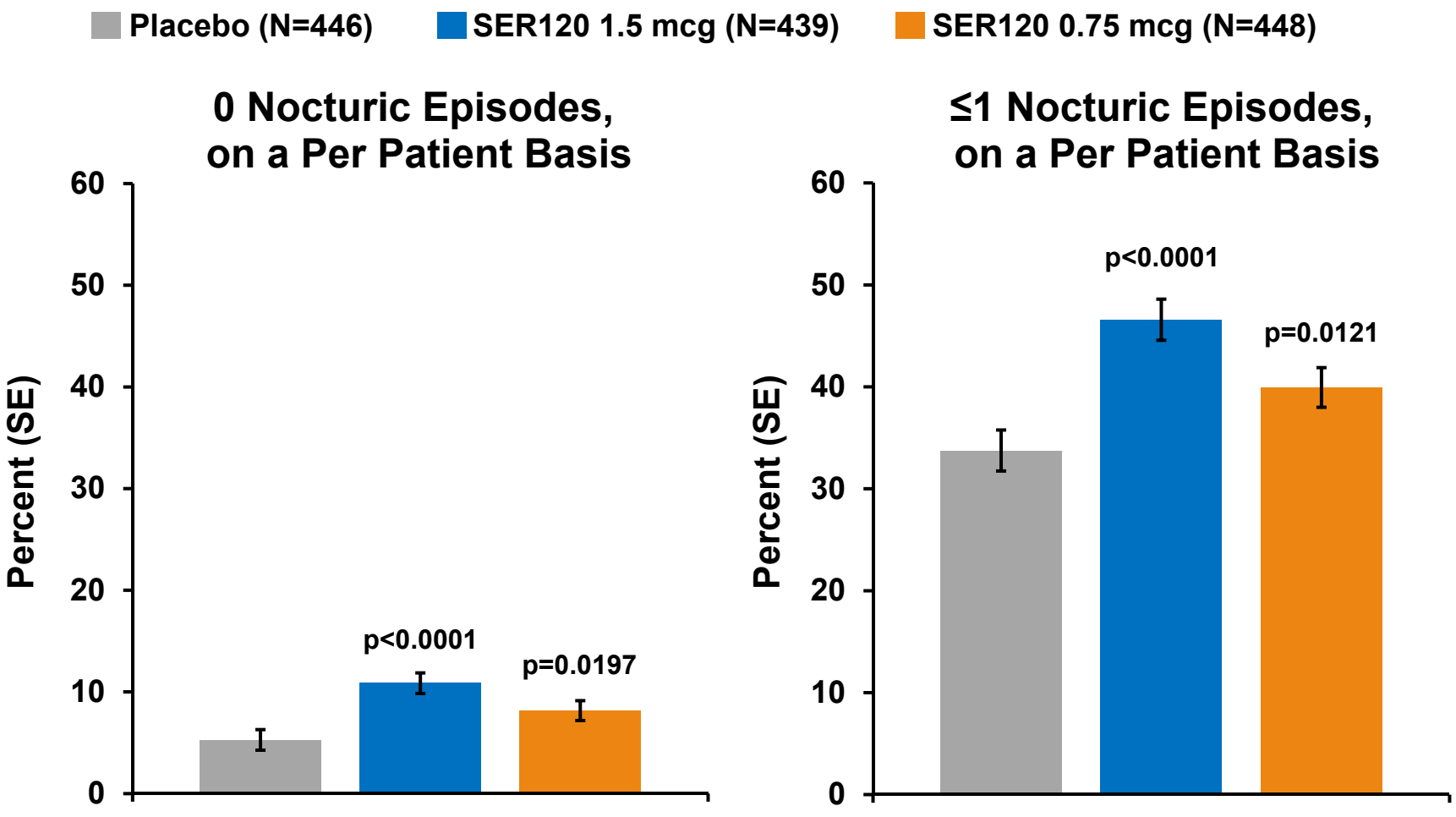
Secondary Efficacy Variable 1 – Change in Time from Bedtime to First Nocturic Episode

ISE DB3/DB4 Studies, ITT Population



Data reported as LSM (least squares mean) ± SE (standard error) unless otherwise indicated

Secondary Efficacy Variables 2 and 3 – Percent Change in Nights with 0 or ≤1 Nocturic Episodes
ISE DB3/DB4 Studies, ITT Population



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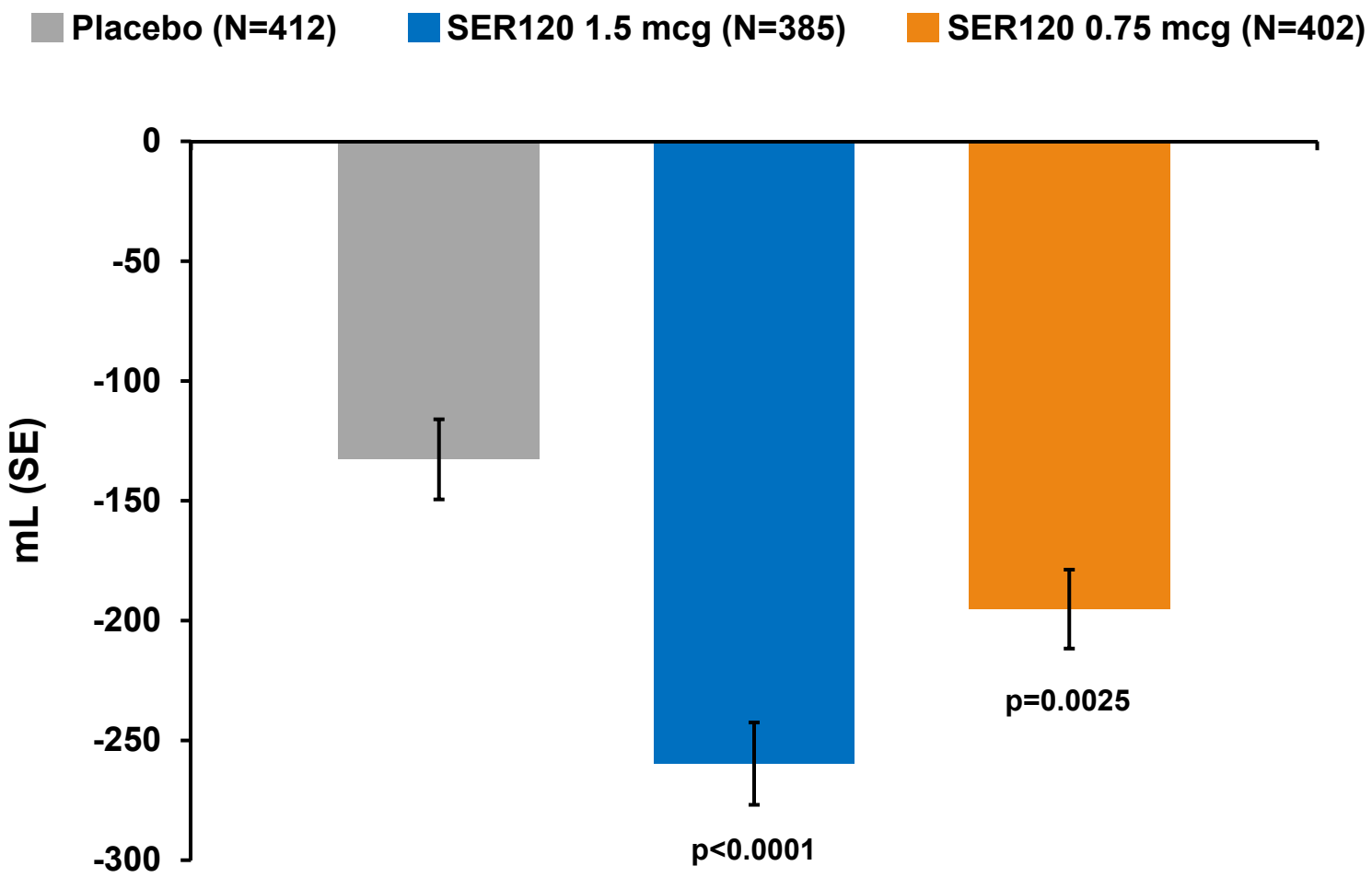
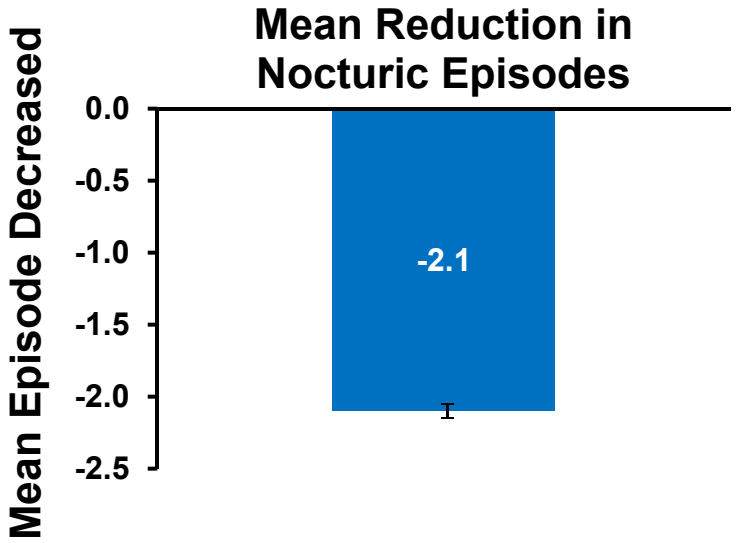
Secondary Efficacy Variable 4 – Reduction in Nocturnal Urine Volume

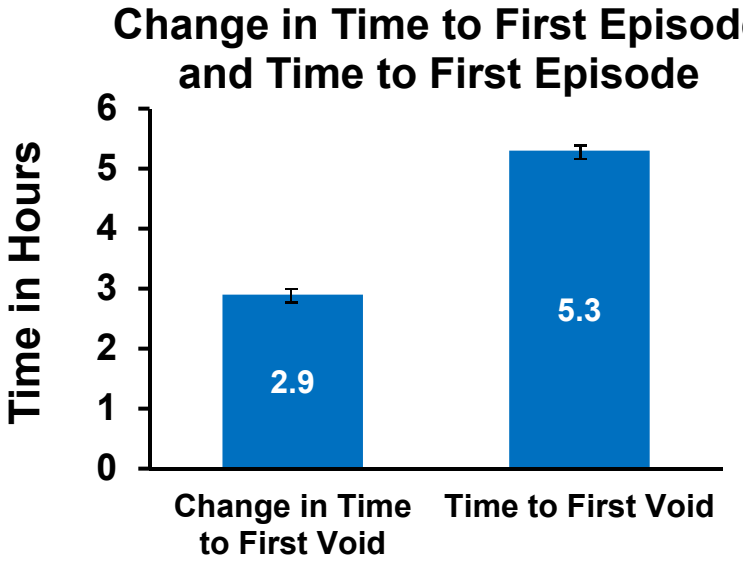
ISE DB3/DB4 Studies, ITT Population

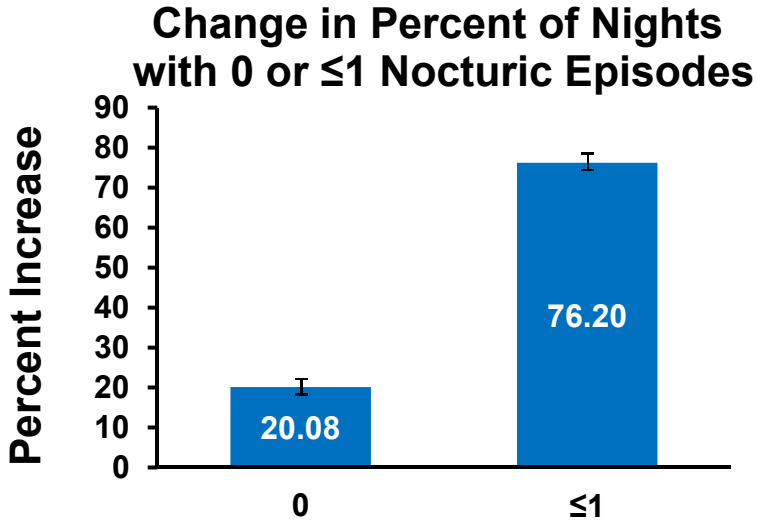


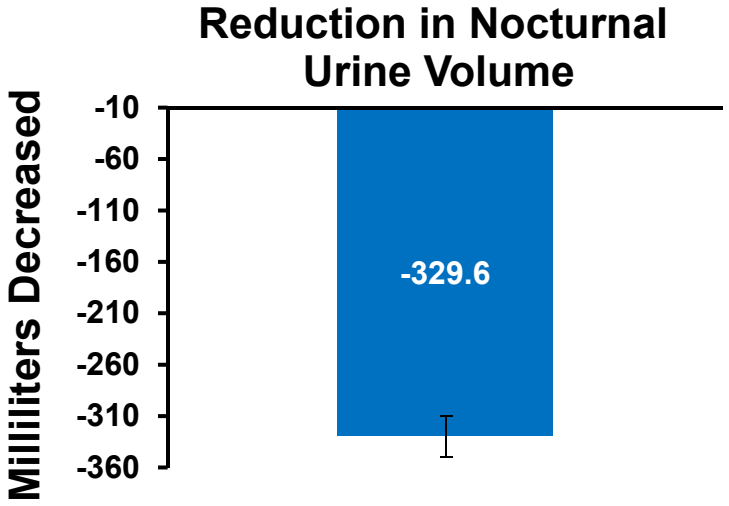
Data reported as LSM (least squares mean) ± SE (standard error) unless otherwise indicated

Magnitude of Change in Responders for Various Efficacy Variables in 1.5 mcg Treatment Group (N=214)



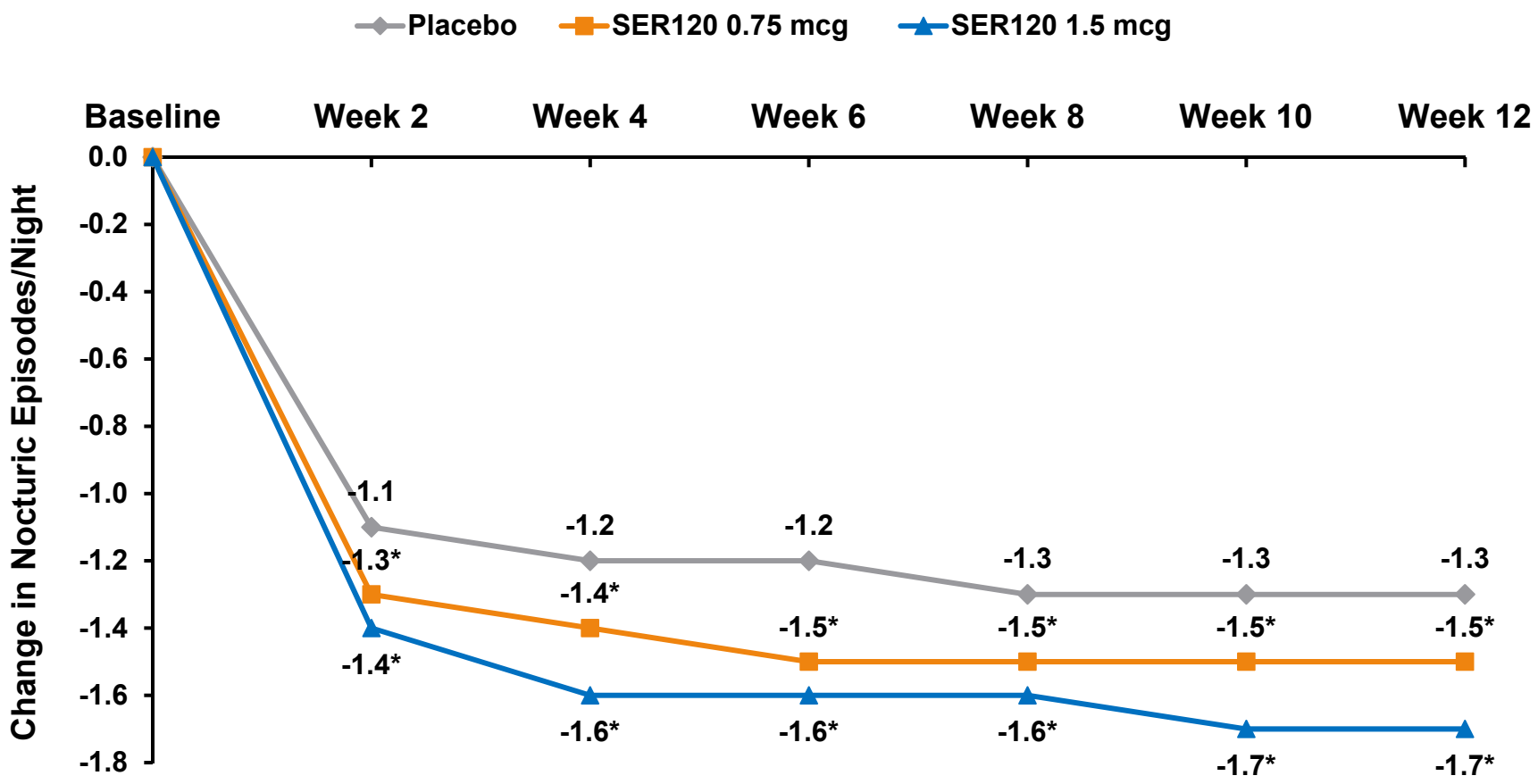






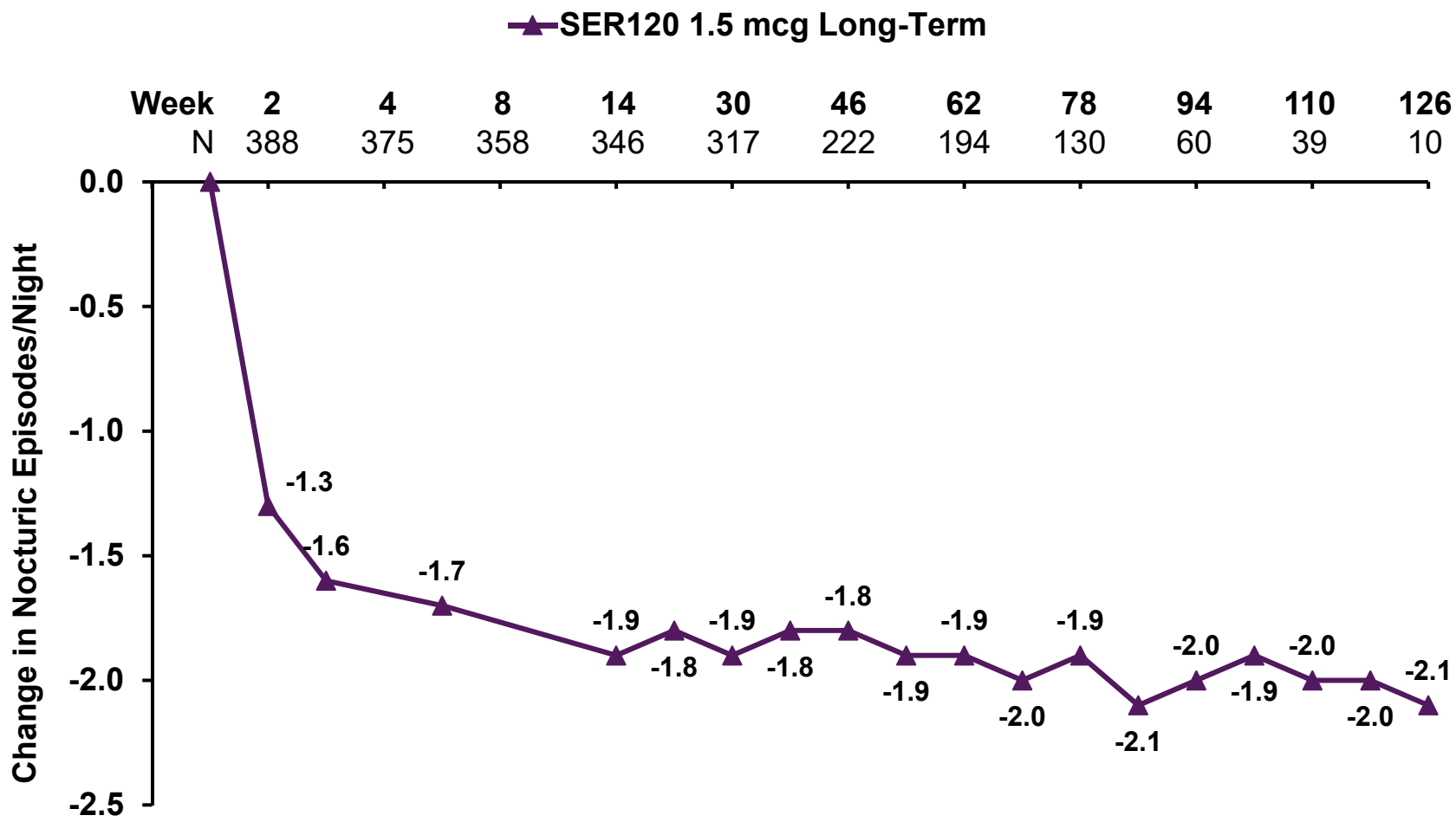
Reduction in Mean Nocturic Episodes Post Randomization by Week

ISE DB3/DB4 Studies, ITT Population



*Denotes statistical significance
Statistically significant at all time points for both 0.75 mcg and 1.5 mcg based on MMR measures analyses.
Model is: change = Screening Episodes/Night + Treatment Group + Study Center + Age Group + Gender + visit + Treatment Group * Visit interaction.

Reduction in Mean Nocturic Episodes by Visit
DB3-A2 Study, ITT Population



Patient Treatment Benefit Patient-Reported Outcomes

Kristin M. Khalaf, PharmD, PhD

Assistant Director, Global Health Economics and Outcomes Research
Xcenda, LLC

Objectives

- **Provide overview of the Impact of Nighttime Urination Questionnaire (INTU)**
- **Discuss INTU results from DB4 study**

Rationale for Development of the INTU

- **Patient reported outcomes (PRO) are an important component of assessing treatment benefit**
- **In consultation with the FDA, the INTU was developed and validated to assess impact of nocturia for use in the DB4 study**
  - Consistent with FDA PRO guidance*
  - Developed and validated specifically for nocturia
  - Developed for both men and women
  - 24-hour recall period

*Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

INTU Development and Validation

Literature Review

- 4 nocturia-specific PROs identified
- Available tools (e.g., N-QOL) had limitations in development and validation

Qualitative Development

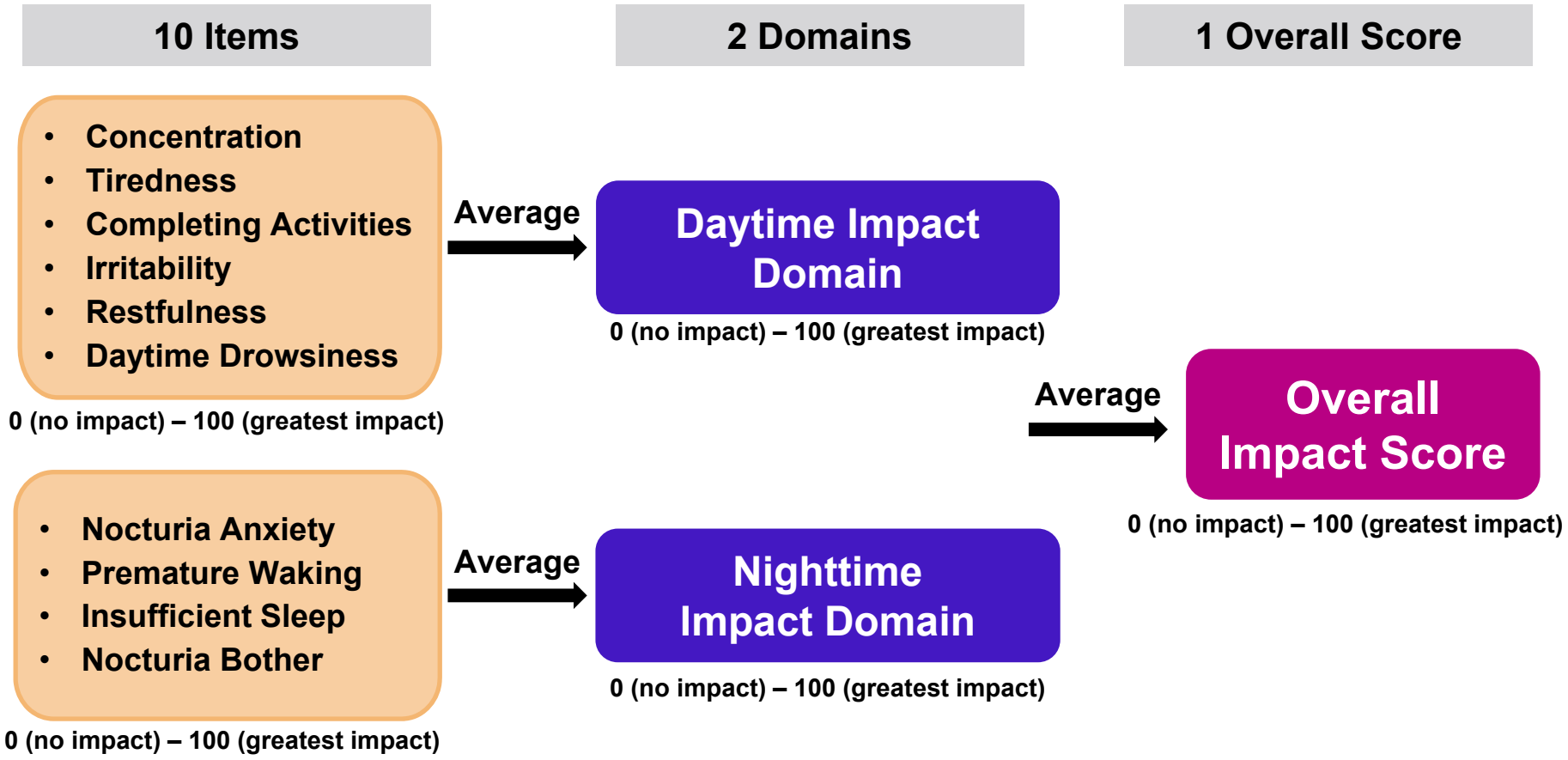
- Concept elicitation: Assess nocturia patient impact
- Cognitive debriefing: Ease of item response/interpretability
- Development of conceptual framework

Quantitative Validation

- Independent behavioral modification study
- Psychometric analyses conducted to evaluate reliability and validity of INTU

INTU consists of 10-items and is a reliable and valid patient-reported outcome that measures impact of nocturia

INTU Overview



Scoring the INTU: Step 1 – Record patient responses; Step 2 – Transform item scores; Step 3 – Calculate summary scores

Analysis of INTU in DB4

First (of 5) pre-specified secondary endpoints	• Mean change in INTU **Overall** Impact Score
Pre-specified exploratory endpoints	• Mean change in INTU **Nighttime** Impact Score • Mean change in INTU **Daytime** Impact Score
Key supportive analyses	• Change in INTU item-level scores • Responders on Treatment Benefit Scale (TBS) • Cumulative distribution function (CDF) plots

Note: Mean change in INTU scores were evaluated between screening (Week -2 and -1) and treatment (Week 8 and 14)

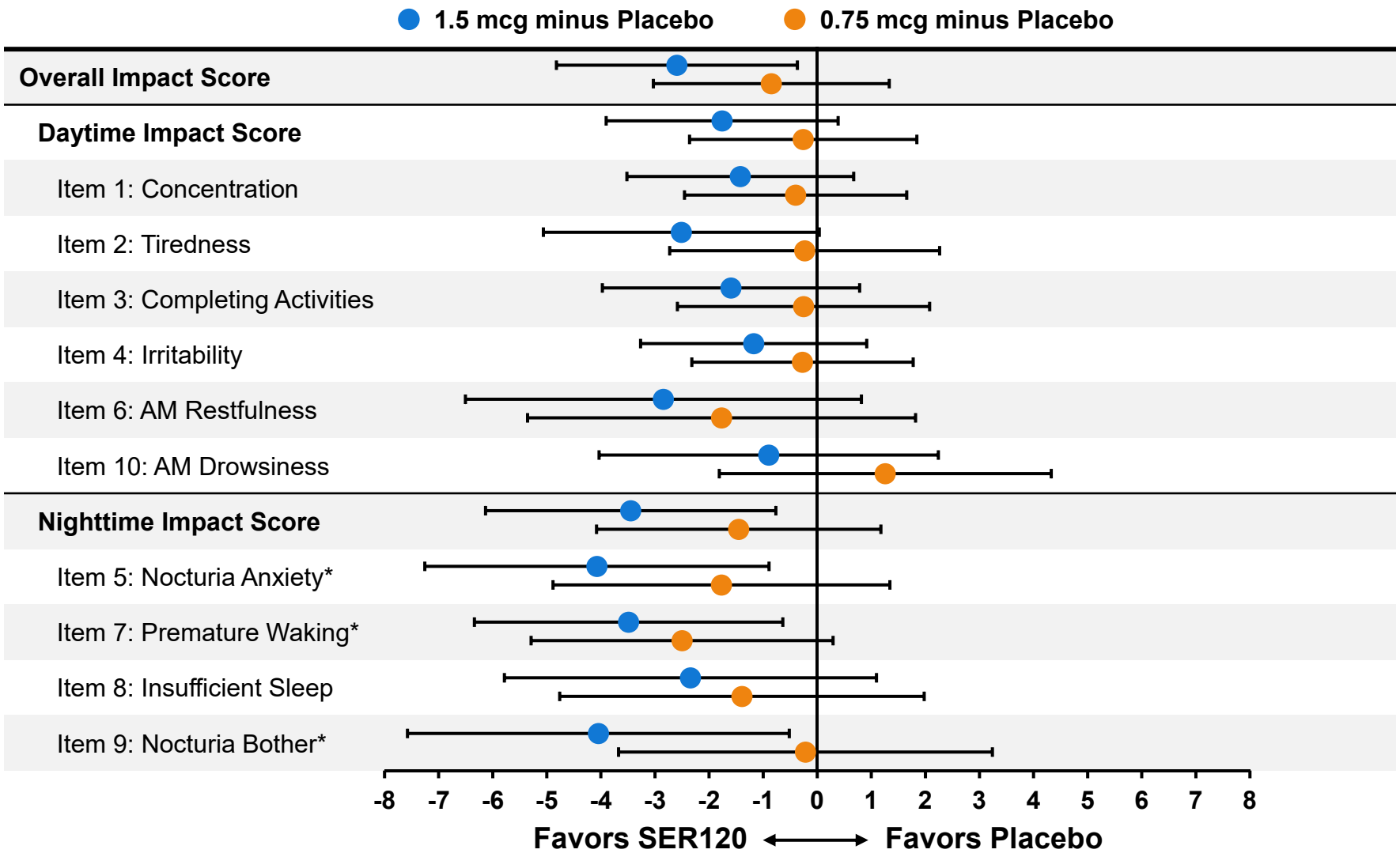
INTU Mean Change Between Screening and Treatment Period for SER120
ITT Population

Mean Change from Screening Period to Treatment Period (Week 8 and 14)

				Treatment Group Comparison to Placebo	
	Placebo N=243 (%)	SER120 1.5 mcg N=247 (%)	SER120 0.75 mcg N=249 n (%)	SER120 1.5 mcg p-value	SER120 0.75 mcg p-value
Overall Impact					
Mean (screening period)	31.3	33.0	31.8	0.3009[1]	0.7417
Change	-11.5	-14.1	-12.4	0.0225[2]	0.4452
Nighttime Impact					
Mean (screening period)	34.4	35.9	34.5	0.4513[1]	0.9854
Change	-14.5	-18.0	-16.0	0.0118[2]	0.2785
Daytime Impact					
Mean (screening period)	28.1	30.0	29.1	0.2158[1]	0.5015
Change	-8.6	-10.3	-8.8	0.1079[2]	0.8084

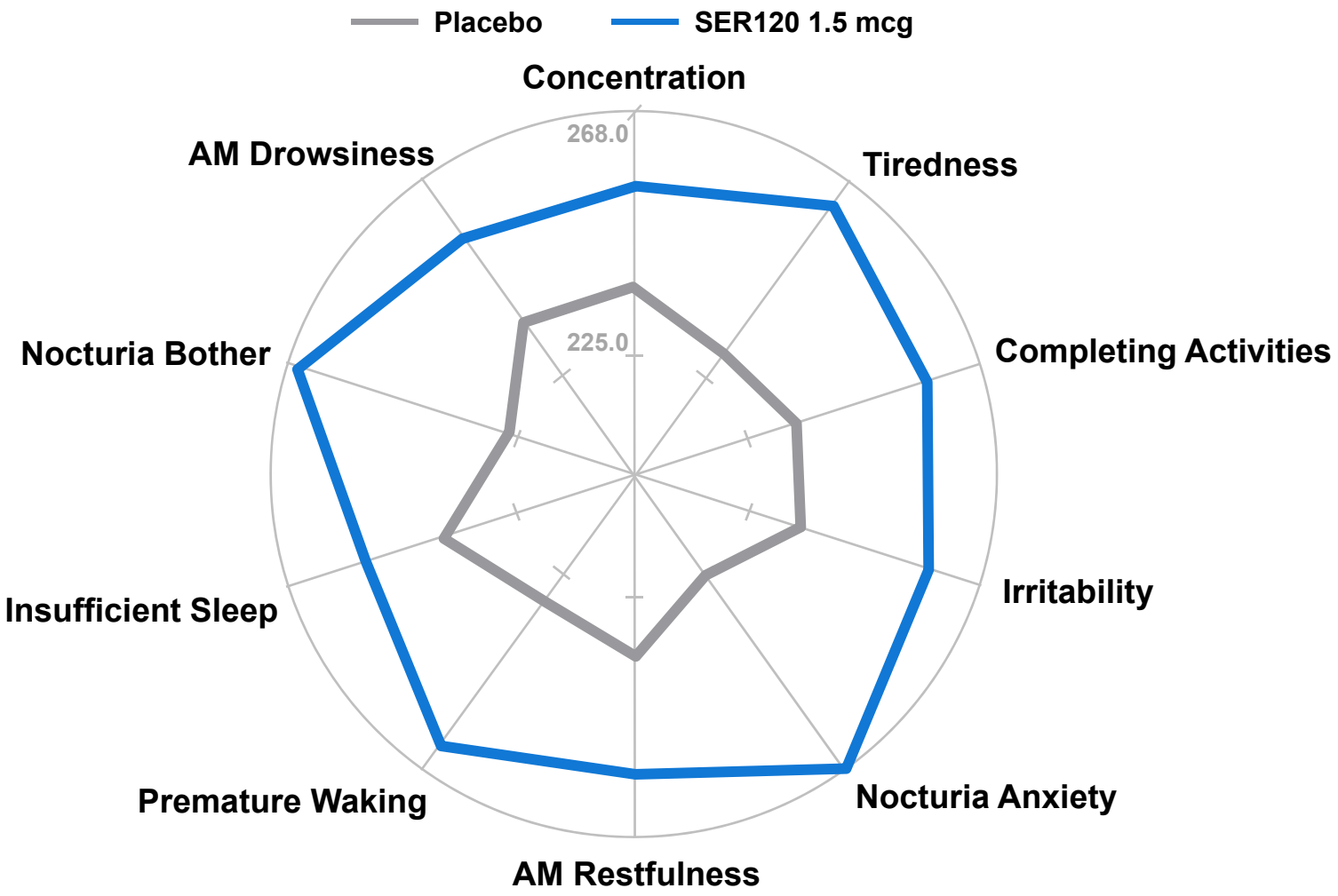
[1]P-Value for Screening based on ANOVA. Model is: response = Treatment Group + Study + Study Center (Study) + Age Group + Gender.
[2]P-Value for change from screening based on ANCOVA. Model is: change = Screening INTU score + Treatment Group + Study + Study Center (Study) + Age Group + Gender.

INTU Items: Placebo-Subtracted Mean Change Scores
ITT Population



*SER120 1.5 mcg dose shows significant improvement vs. placebo

O'Brien Multivariate Rank Analysis for INTU Items – Change from Screening to Treatment
ITT Population (N=482)



Axis Length is Mean Rank. The highest rank represents the greatest reduction among all change values of an outcome variable in the pooled set of two samples

Treatment Benefit Scale (TBS)

Please complete the following question by considering your current nighttime urination compared to before you received any study treatment in this trial.

My condition (waking up at night to urinate) is now:

- Much better
- Somewhat better
- Not changed
- Somewhat worse
- Much worse

- **Administered at Study Exit; evaluates patient perception of treatment benefit**
- **Provides additional context for interpreting INTU scores**

Coleman et al , Urology 2008, 74(2): 803-7

Summary of Treatment Benefit Scale Results
ITT Population

	Placebo N=260 n (%)	SER120 1.5 mcg N=260 n (%)	SER120 0.75 mcg N=262 n (%)
Much better	91 (35.4)	111 (43.2)	96 (37.4)
Somewhat better	97 (37.7)	96 (37.4)	95 (37.0)
Not changed	69 (26.6)	50 (19.5)	66 (25.7)
Somewhat worse	0	0	0
Much worse	0	0	0

Classification of responders vs. non-responders

Much better/somewhat better (responders)	188 (73.2)	207 (80.5)*	191 (74.3)
Not changed/somewhat worse/much worse (non-responders)	69 (26.8)	50 (19.5)	66 (25.7)

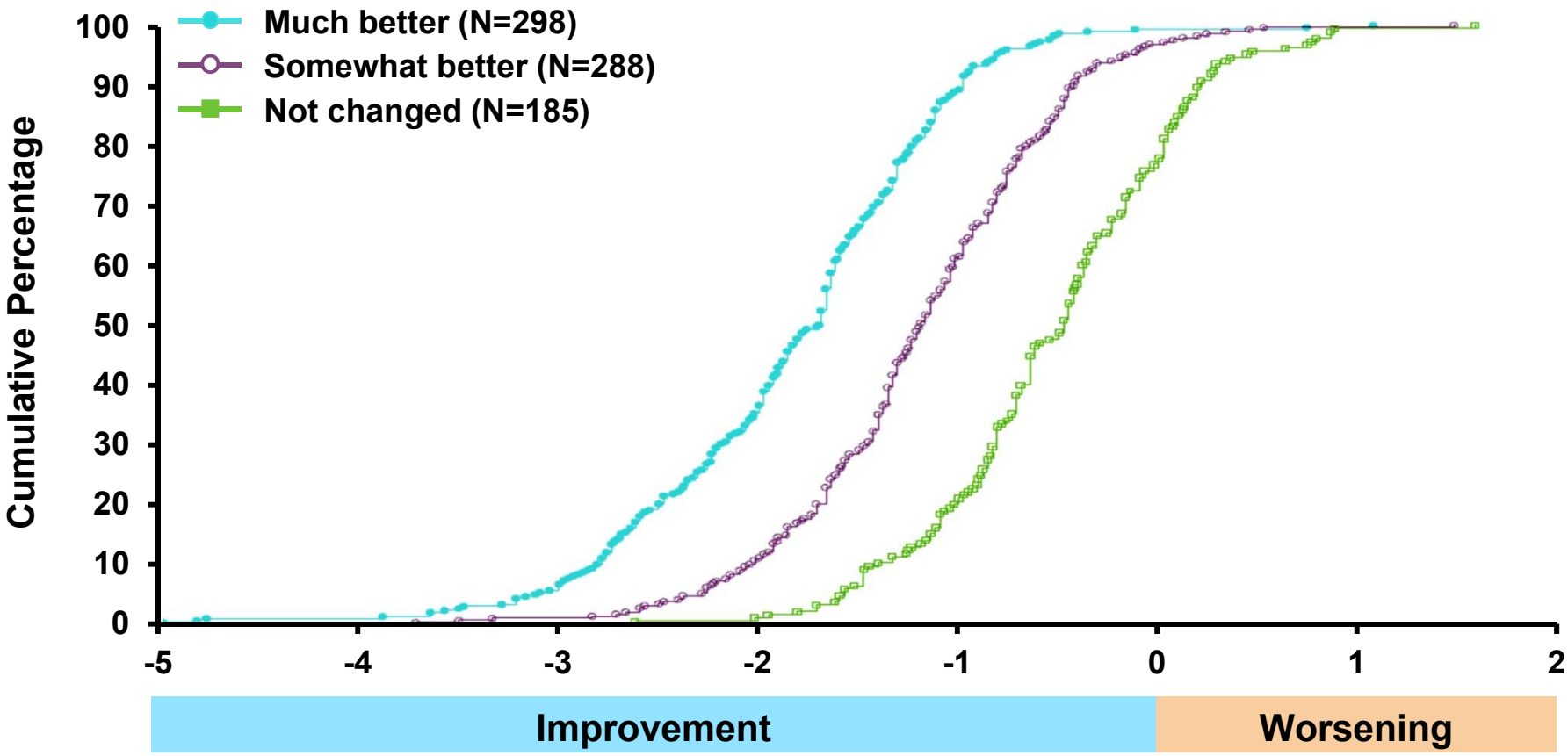
Significantly greater proportion of TBS responders for patients who received SER120 1.5 mcg compared to placebo

*p=0.0452

[1] p-value based on Cochran-Mantel-Haenszel test stratifying by Age Group and Gender

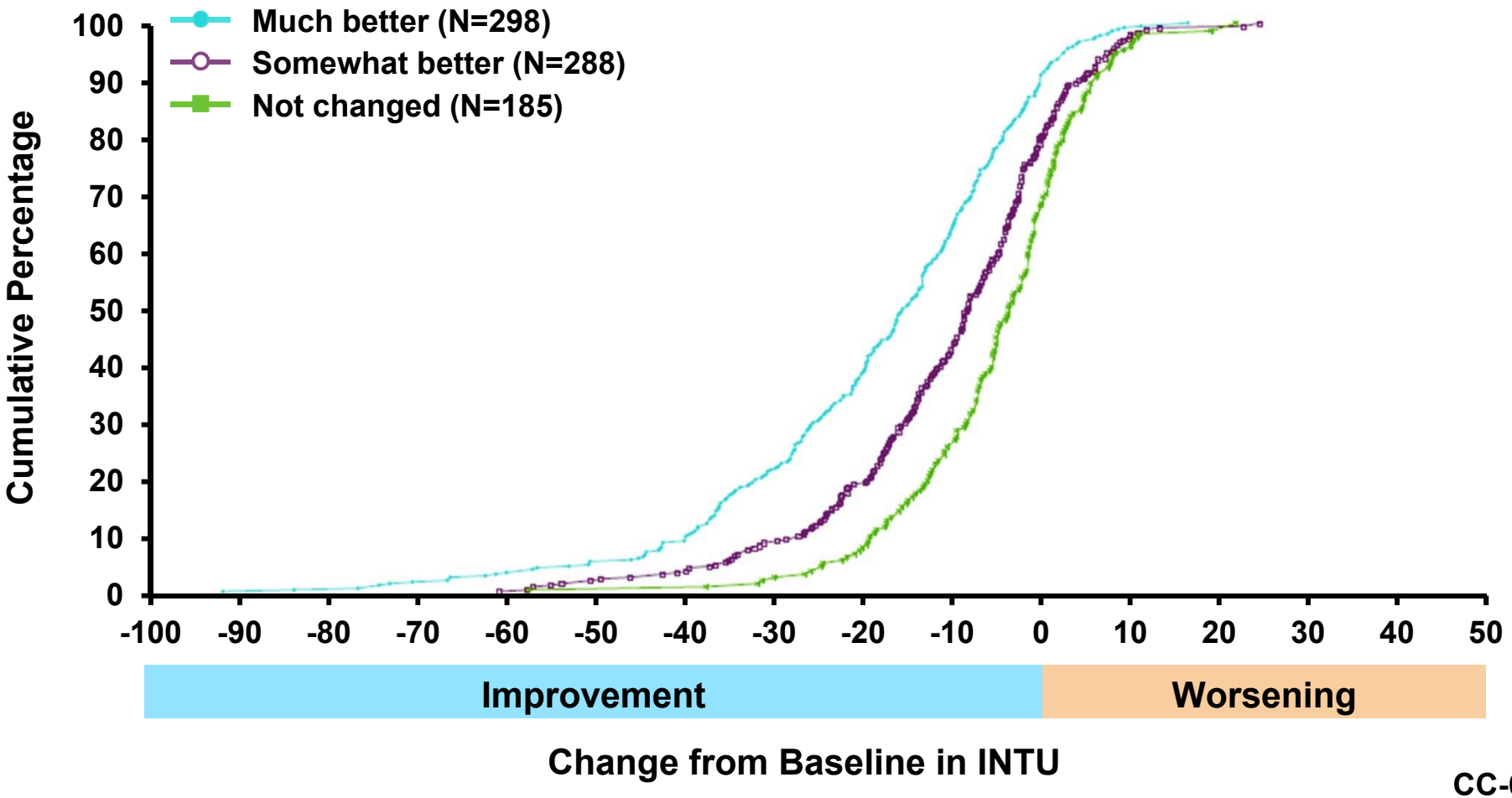
Change from Screening to Treatment Period in Mean Nocturic Episodes by TBS Response
ITT Population

Relationship of TBS with Study Outcomes – Cumulative Distribution Function (CDF) Plot



Change from Screening to Treatment Period in INTU Scores by TBS Response
ITT Population

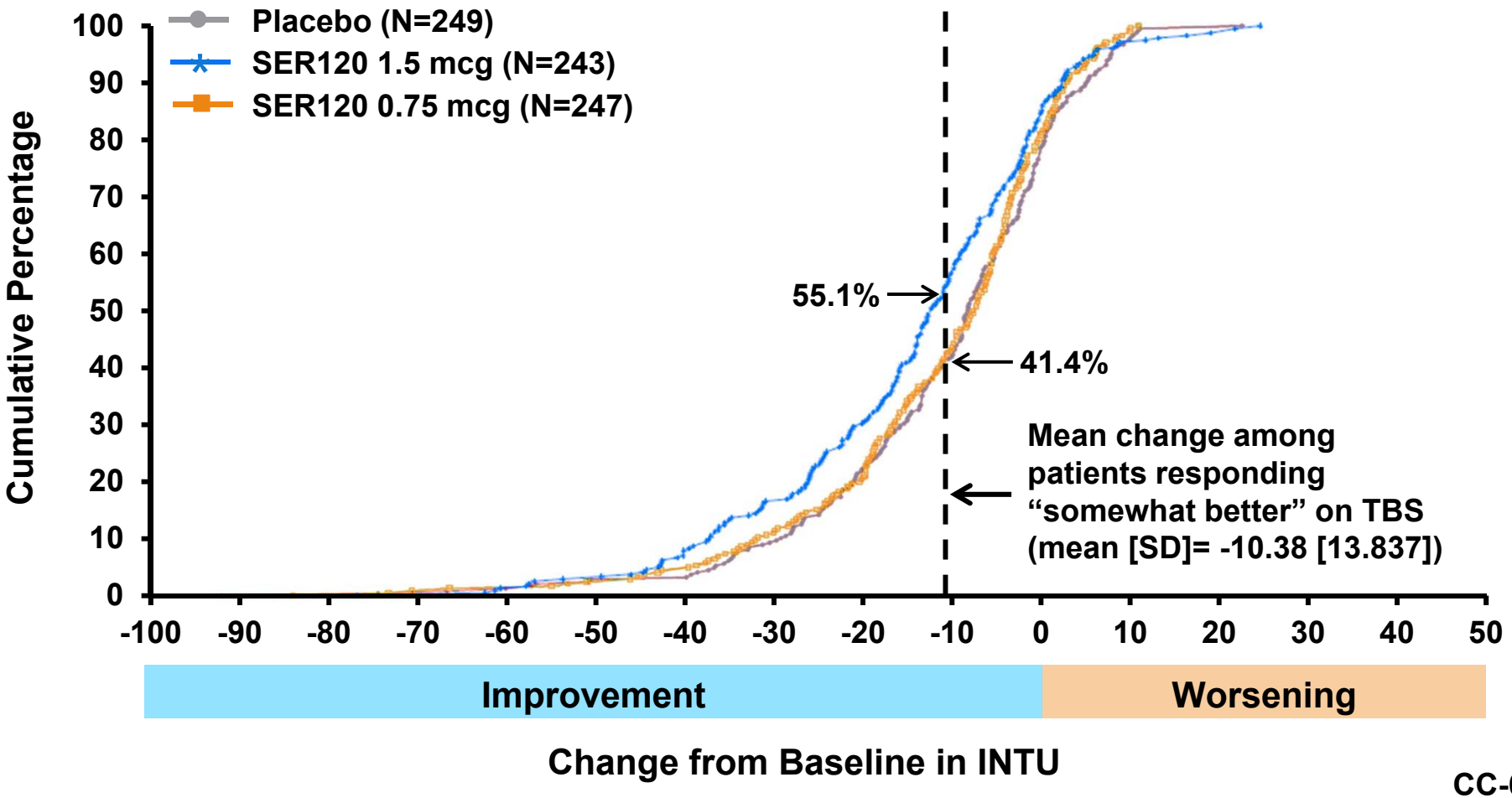
Relationship of TBS with Study Outcomes – Cumulative Distribution Function (CDF) Plot



Change From Screening to Treatment Period in INTU Overall Impact Score

ITT Population

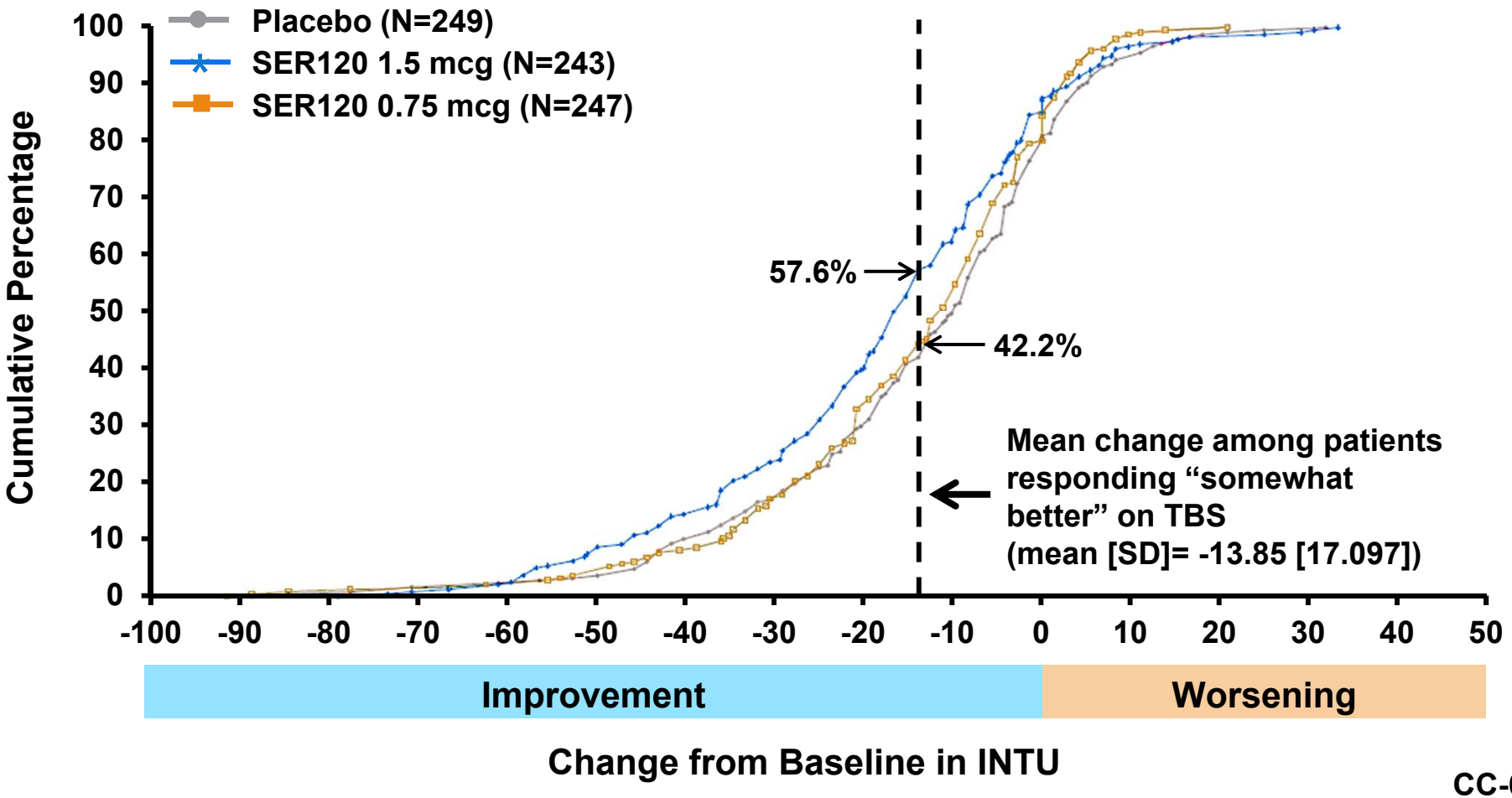
Cumulative Distribution Function (CDF) Plot by Treatment Group



Change From Screening to Treatment Period in INTU Nighttime Impact Score

ITT Population

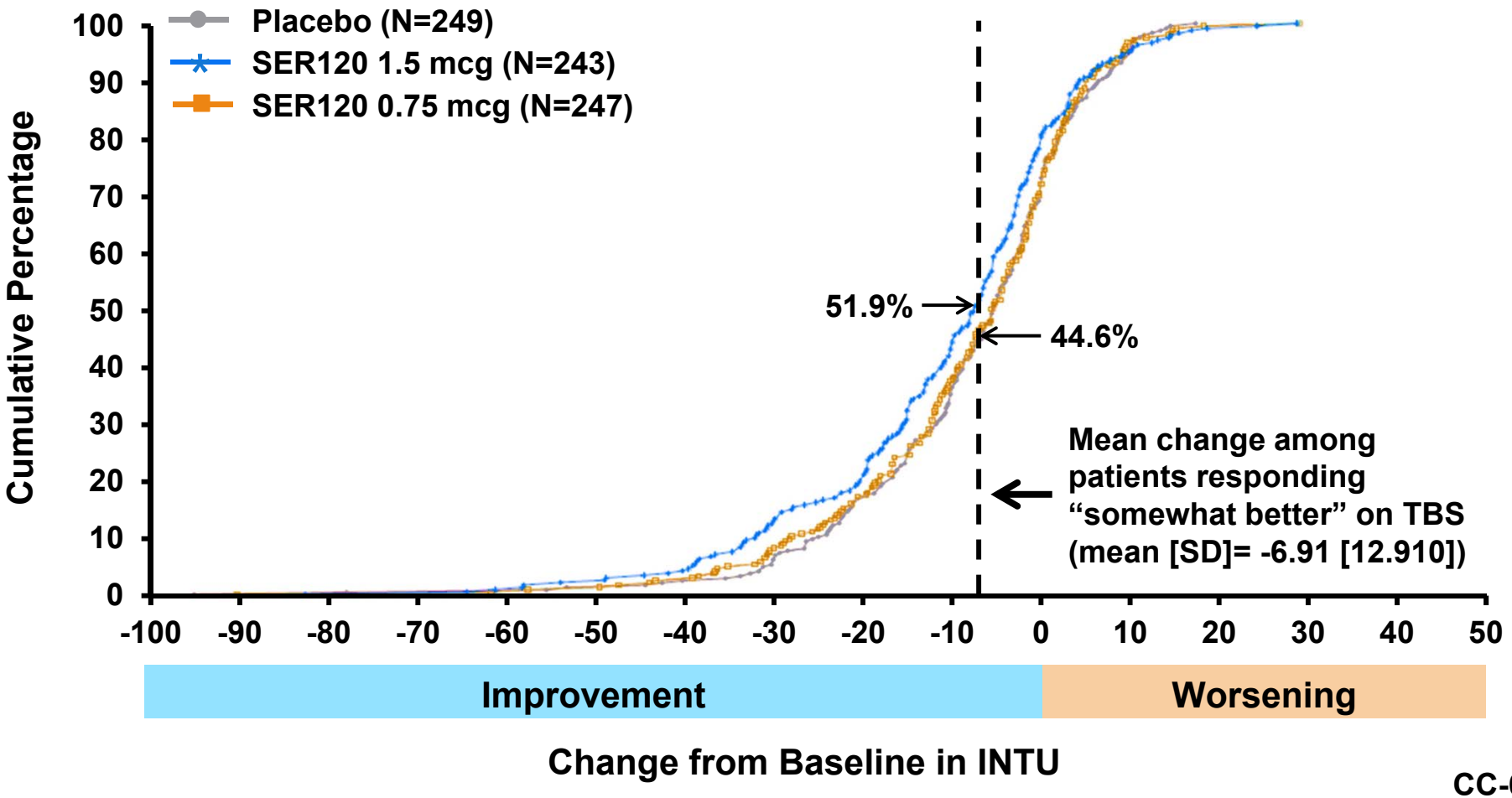
Cumulative Distribution Function (CDF) Plot by Treatment Group



Change From Screening to Treatment Period in INTU Daytime Impact Score

ITT Population

Cumulative Distribution Function (CDF) Plot by Treatment Group



Summary and Conclusions

- **Statistically significant improvements demonstrated in INTU Overall and Nighttime Impact in 1.5 mcg vs. placebo**
- **Significant greater proportion of TBS responders for patients who received SER120 1.5 mcg vs. placebo**
- **More patients in 1.5 mcg vs. placebo improved on INTU scores among patients perceiving improvement on the TBS**

SER120 demonstrated a clinically meaningful improvement in patient-reported impacts of nocturia on daily living

Integrated Summary of Safety

DB1/DB2/DB3/DB4 Double Blind Studies and OL1/DB3-A2/ELD Open Label Long Term Studies

Seymour Fein, MD

Chief Medical Officer
Serenity Pharmaceuticals, LLC

Incidence of Patients with Nadir Serum Sodium Post Baseline

ISS DB1/DB2/DB3/DB4 Studies, Safety Population

Serum Sodium Range (mmol/L)	Placebo N=766 n (%)	SER120 1.5 mcg N=448 n (%)	SER120 1.0 mcg* N=186 n (%)	SER120 0.75 mcg N=657 n (%)
130-134	30 (3.9)	50 (11.2)	17 (9.1)	44 (6.7)
126-129	1 (0.1)	9 (2.0)	6 (3.2)	9 (1.4)
≤125	1 (0.1)	5 (1.1)	3 (1.6)	0

*DB3 only

Hyponatremia is defined as serum sodium between 126 to 129 mmol/L with clinical symptoms or ≤125 mmol/L with or without clinical symptoms.

Incidence of Patients with Nadir Serum Sodium Post Baseline – by Gender

ISS DB1/DB2/DB3/DB4 Studies, Safety Population

Sub-Population	Serum Sodium Range (mmol/L)	Placebo n (%)	SER120 1.5 mcg n (%)	SER120 1.0 mcg n (%)	SER120 0.75 mcg n (%)
Male		N=450	N=256	N=111	N=390
	130-134	19 (4.2)	28 (10.9)	10 (9.0)	22 (5.6)
	126-129	1 (0.2)	7 (2.7)	2 (1.8)	4 (1.0)
	≤125	1 (0.2)	4 (1.6)	1 (0.9)	0
Female		N=316	N=192	N=75	N=267
	130-134	11 (3.5)	22 (11.5)	7 (9.3)	22 (8.2)
	126-129	0	2 (1.0)	4 (5.3)	5 (1.9)
	≤125	0	1 (0.5)	2 (2.7)	0

Incidence of Patients with Nadir Serum Sodium Post Baseline – by Age Group

ISS DB1/DB2/DB3/DB4 Studies, Safety Population

Sub-Population	Serum Sodium Range (mmol/L)	Placebo n (%)	SER120 1.5 mcg n (%)	SER120 1.0 mcg n (%)	SER120 0.75 mcg n (%)
<65 Years		N=337	N=202	N=85	N=308
	130-134	13 (3.4)	18 (8.9)	8 (9.4)	12 (3.9)
	126-129	1 (0.3)	0	1 (1.2)	2 (0.6)
	≤125	0	0	1 (1.2)	0
≥65 Years		N=389	N=246	N=101	N=349
	130-134	17 (4.4)	32 (13.0)	9 (8.9)	32 (9.2)
	126-129	0	9 (3.7)	5 (5.0)	7 (2.0)
	≤125	1 (0.3)	5 (2.0)	2 (2.0)	0
≥75 Years		N=143	N=100	N=33	N=134
	130-134	9 (6.3)	15 (15.0)	2 (6.1)	18 (13.4)
	126-129	0	3 (3.0)	3 (9.1)	3 (2.2)
	≤125	0	2 (2.0)	1 (3.0)	0

Incidence of Patients with First Occurrence of Serum Sodium ≤129 mmol/L in Study Specified Time Points
ISS DB1/DB2/DB3/DB4 Studies, Safety Population

Visit	Placebo N=766 n	SER120 1.5 mcg N=448 n	SER120 1.0 mcg N=186 n	SER120 0.75 mcg N=657 n
Number of patients with at least 1 sodium level ≤129 mmol/L	N=2	N=14	N=9	N=9
Incidence of first occurrence in study specified time points				
Week 2	0	7	4	4
Week 4	1	1	1	2
Week 6	0	0	1	2
Week 8	1	2	1	0
Week 10	0	1	0	0
Week 12	0	3	2	1

Note: Each cell shows the number of subjects at each time point based on the total number of patient with one or more serum sodium levels ≤129 mmol/L

Incidence of Patients with Nadir Serum Sodium Post Baseline – by Serum Sodium Range

ISS ELD/OL1/DB3-A2 Studies, Safety Population

Serum Sodium Range (mmol/L)	SER120 1.5 mcg N=358 n (%)	SER120 1.0/1.5 mcg N=390 n (%)	SER120 0.75 mcg N=238 n (%)
130-134	43 (12.0)	51 (13.1)	13 (5.5)
126-129	1 (0.3)	8 (2.1)	0
≤125	0	3 (0.8)	0

Note: The N (%) from 0.75 mcg group is based on the number of patients from the ELD and OL1 studies.
Treatment period for the ELD study was 8 weeks while the treatment period for the OL1 study was 43 weeks.

TEAEs with ≥2% Incidence in Any Group
ISS DB1/DB2/DB3/DB4 Studies, Safety Population

Adverse Event	Placebo N=766 n (%)	SER120 1.5 mcg N=448 n (%)	SER120 1.0 mcg N=186 n (%)	SER120 0.75 mcg N=657 n (%)
Number of patients with at least 1 TEAE	414 (54.0)	209 (46.7)	92 (49.5)	358 (54.5)
Nasal discomfort	131 (17.1)	25 (5.6)	9 (4.8)	78 (11.9)
Nasopharyngitis	20 (2.6)	17 (3.8)	2 (1.1)	23 (3.5)
Blood pressure increased/hypertension	8 (1.8)	14 (3.1)	1 (0.5)	10 (1.5)
Headache	37 (4.8)	13 (2.9)	5 (2.7)	29 (4.4)
Nasal congestion	20 (2.6)	12 (2.7)	1 (0.5)	18 (2.7)
Rhinorrhea	52 (6.8)	11 (2.5)	4 (2.2)	30 (4.6)
Back pain	8 (1.0)	10 (2.2)	4 (2.2)	10 (1.5)
Sneezing	55 (7.2)	10 (2.2)	2 (1.1)	39 (5.9)
Upper respiratory infection	16 (2.1)	10 (2.2)	0	13 (2.0)
Dizziness	16 (2.1)	9 (2.0)	0	11 (1.7)
Urinary tract infection	9 (1.2)	7 (1.6)	3 (1.6)	17 (2.6)
Sinusitis	5 (0.7)	6 (1.3)	5 (2.7)	7 (1.1)
Nasal mucosal disorder	13 (1.7)	6 (1.3)	4 (2.2)	6 (0.9)
Cough	13 (1.7)	5 (1.1)	4 (2.2)	11 (1.7)
Fatigue	5 (0.7)	4 (0.9)	4 (2.2)	3 (0.5)
Throat irritation	12 (1.6)	0 (0.0)	4 (2.2)	6 (0.9)

Serious TEAEs

ISS DB1/DB2/DB3/DB4 Studies, Safety Population

Serious Adverse Event	Placebo N=766 n (%)	SER120 1.5 mcg N=448 n (%)	SER120 1.0 mcg N=186 n (%)	SER120 0.75 mcg N=657 n (%)
Number of patients with at least 1 serious TEAE	13 (1.7)	8 (1.8)	3 (1.6)	11 (1.7)
Number of deaths	0	0	1 (0.5)	2 (0.3)
Arteriosclerosis coronary artery (DB1:15S021)	0	0	0	1 (0.2)
Cardiac arrest secondary to aneurysm (DB3: 77S003)	0	0	1 (0.5)	0
Sudden death (DB4: 65S004)	0	0	0	1 (0.2)
Number of patients with at least 1 SAE judged by PI to be possibly or probably related	1 (0.1)	2 (0.4)	0	0
Hyponatremia (DB4: 11S014 and 42S033)	1 (0.1)	1 (0.2)	0	0
Hypertension (DB3 25S002)	0	1 (0.2)	0	0

Serious TEAEs
ISS ELD/OL1/DB3-A2 Studies, Safety Population

Serious Adverse Event	SER120 1.5 mcg N=358 n (%)	SER120 1.0/1.5 mcg N=392 n (%)	SER120 0.75 mcg N=238 n (%)
Number of patients with at least 1 serious TEAE	37 (10.3)	40 (10.2)	21 (8.8)
Number of deaths	1 (0.3)	0	1 (0.4)
Myocardial infarction* (OL1: 82S007)	0	0	1 (0.4)
Peritonitis secondary to cecal perforation (DB3-A2: 59S024)	1 (0.3)	0	0
Number of patients with at least 1 SAE judged by PI to be possibly or probably related	0	1 (0.3)	0
Thrombocytopenia (DB3-A2: 38S903)	0	1 (0.3)	0

*Patient had history of MI and TIA, sodium level prior to event was 139 mmol/L

Benefit-Risk Assessment and REMS

Annette Stemhagen, DrPH, FISPE
Senior Vice President
UBC
Safety, Epidemiology, Registries and Risk Management

Benefit-Risk Assessment: Benefit

- **Doses of 1.5 mcg and 0.75 mcg were effective**
  - Decreased the number of nocturic episodes
  - Increased hours of first uninterrupted sleep to ≥4 hours
  - Increased the number of nights with ≤1 nocturic episodes per night
  - Improved daily living in patients with nocturia
- **Rapid absorption with no depot and with a plasma level of less than 10 pg/mL limits the anti-diuretic effect to 4 to 6 hours while patients are asleep**

Benefit-Risk Assessment: Risk

- **Low incidence of hyponatremia (1.1% at 1.5 mcg and 0% at 0.75 mcg)**
  - 1600 patients in both randomized and long-term studies
- **Rapid onset of efficacy and effect on sodium enables early benefit-risk assessment and implementation of effective risk mitigation**

Key Risk Mitigation Messages
Patient Selection and Management

- **Important messages aligned with SER120 label**
  - Appropriate patient selection prior to initiating SER120
    - Serum sodium concentration should be within normal limits
    - Calculated eGFR based on serum creatinine should be ≥50 mL/min/1.73m^2
    - No systemic corticosteroid use
  - Dosing
    - Start at the lower dose of SER120 (0.75 mcg) for 2-4 weeks
    - Escalate to higher dose of 1.5 mcg based on individual patient efficacy and tolerability

Key Risk Mitigation Messages
Patient Monitoring and Counseling

- **Monitoring patients during SER120 treatment**
  - Monitor serum sodium concentration within 14 days after initiating therapy or increasing the dose, and check periodically if clinically appropriate
  - Discontinue SER120 during systemic corticosteroid use
  - Temporarily discontinue SER120 if intercurrent illness affecting electrolyte balance
- **Patient Counseling**
  - Educate patients to recognize symptoms of hyponatremia and seek medical advice as appropriate
  - Caution patients with medical conditions that may cause electrolyte imbalance such as vomiting or diarrhea, fever or serious infection

REMS Goals

- **The goal of the REMS is to minimize the risk of hyponatremia associated with SER120 by**
  - Informing healthcare professionals (HCPs) about
    - Risk of hyponatremia
    - Importance of proper patient selection
    - Appropriate dosing
    - Patient monitoring
    - Patient counseling
  - Informing patients about the risk of hyponatremia and its signs and symptoms

Comprehensive Risk Management

- **Education and outreach with clear, implementable messages**
- **Risk Evaluation and Mitigation Strategy (REMS)**
  - Medication Guide for patients
  - Communication Plan for HCPs
  - Continual assessment and feedback

REMS Components
Medication Guide

- Describes risk of hyponatremia and its signs and symptoms
- Instructs patients to call their HCP if symptoms occur
- Emphasizes importance of calling physician if they have an illness leading to potential electrolytes loss (e.g., excessive vomiting, diarrhea, fever, serious infections)
- Reminds patients to discontinue SER120 while taking corticosteroids and consult HCP to restart

REMS Components
Communication Plan

- **REMS letter for health care providers**
  - Wide range of medical specialties including urologists, ob-gyn specialists, geriatric specialists, internists, family practitioners, nurse practitioners and physician assistants
- **REMS letter for professional societies**

Conclusions

- **The proposed REMS for SER120 meets the following criteria**
  - Simple and comprehensible for patients and HCPs
  - Targeted and straightforward in focusing on hyponatremia and minimizing the potential risk
  - Practical and implementable within routine clinical practice
  - Effective communication to HCPs in identifying patients at risk for hyponatremia early in the course of treatment

Concluding Remarks

Steven Kaplan, MD

Professor of Urology
Icahn School of Medicine at Mount Sinai
Director, Benign Urologic Diseases and The Men's Health Program
Mount Sinai Health System

Concluding Remarks

- **Nocturia is an under recognized significant medical condition with substantive consequences and morbidities and a diminished quality of life**
- **In clinical practice, nocturia is treated ineffectively**
- **Patients and healthcare providers recognize the pressing need for a safe and clinically meaningful therapy for nocturia**

Concluding Remarks

- SER120 has been demonstrated to be effective in two well-controlled studies
- Benefit was shown to be clinically meaningful
- Shown to be safe and well tolerated in the target patient population
- Efficacy was shown to be durable and safety was documented in a large database with treatment up to 2 years

Concluding Remarks

- SER120 is effective for nocturia associated with the main etiologic factors including nocturnal polyuria, OAB and BPH
- Both proposed doses of 0.75 and 1.5 mcg demonstrate efficacy
- 0.75 mcg is an appropriate starting dose, and should be available for clinical use
- Desmopressin has been used for almost 40 years in all age groups in clinical practice
- SER120 is an improved dosage formulation with sustained efficacy and minimal side effects

Concluding Remarks

- **Proposed REMS plan mitigates risk, and is implementable in clinical practice**

- **SER120 fills the unmet medical need for an effective, safe, and clinically meaningful treatment for nocturia**

Additional Experts Available to the Committee

Tomas Berl, MD

Distinguished Professor of Medicine
Division of Renal Disease and Hypertension
University of Colorado
Denver, Colorado

James Longstreth, PhD

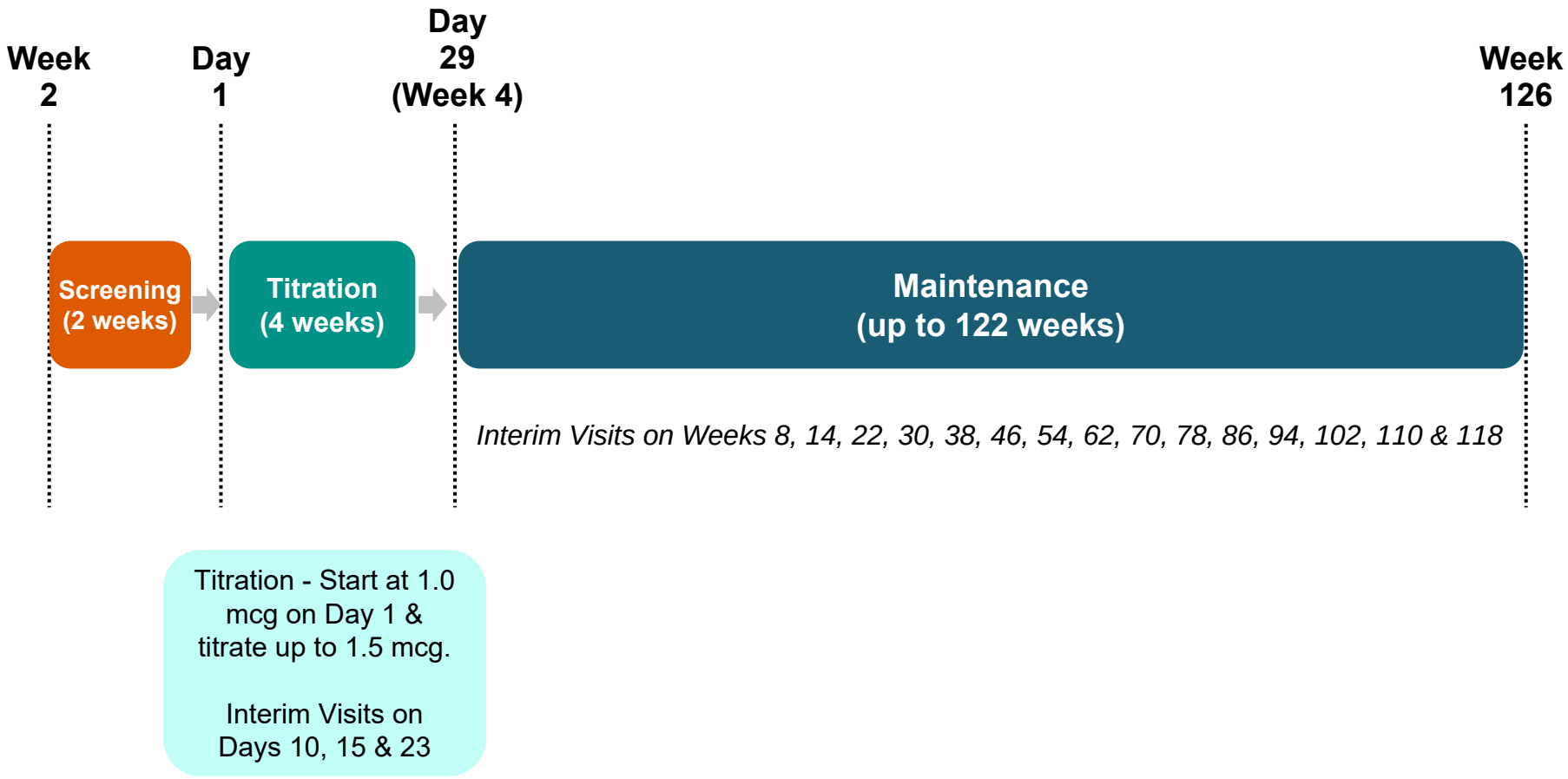
Founder and President
Longstreth & Associates, Inc.

J. Richard Trout, PhD

Professor Emeritus, Statistics
Rutgers University
New Brunswick, New Jersey

Backup Slides Shown at Meeting

Study Design
DB3-A2 Study



Co-primary Efficacy Variable 1: Reduction in Mean Number of Nocturic Episodes

ISE DB3/DB4 Studies, ITT Placebo Lead-in Responder Population

	Lead-in Placebo Responders		
Reduction in Nocturic Episodes	**Placebo N=120**	**SER120 1.5 mcg N=112**	**SER120 0.75 mcg N=114**
Screening[1] LSM (SE)	3.0 (0.08)	2.9 (0.08)	3.0 (0.08)
Treatment Period[2] LSM (SE)	1.3 (0.06)	1.0 (0.06)	1.1 (0.06)
Change from Screening LSM (SE)	-1.7 (0.06)	-1.9 (0.06)	-1.9 (0.06)
p-value (Treatment Comparison to Placebo)		0.0030[3]	0.0315[3]
95% CI – Change from Screening[4]		-0.4 to -0.1	-0.3 to 0.0

[1] Average of last 6 nights during screening
[2] Average of recorded diaries as specified by the protocol during the Treatment period.
[3] p-value for change from screening based on ANCOVA. Model is: chagne = Screening ncoturic voids/night + Treatment Group + Study + Study Center (Study) + Age Group + Gender
[4] 95% CI for treatment group difference based on L.S. Means: 2 active doses of SER120 to placebo

N-QOL Mean Change Scores

DB3 Study, ITT Population

Visit	Placebo N=186	SER120 1.5 mcg N=179	SER120 1.0 mcg N=183	SER120 0.75 mcg N=186	Treatment Group Comparison to Placebo: 1.5 mcg p-value	1.0 mcg p-value	0.75 mcg p-value
Screening							
LS Mean	53.7	53.8	56.7	52.4	0.9792[2]	0.1766[2]	0.5244[2]
SE	1.68	1.67	1.64	1.63			
Change from screening to week 8[4]							
LS	16.3	19.0	17.0	16.9			
SE	1.39	1.39	1.37	1.36	0.1352[3]	0.7266[3]	0.7349[3]
(95% CI[5])		(-0.8, 6.2)	(-2.9, 4.2)	(-2.9, 4.1)			
Change from screening to week 14							
LS	16.0	20.4	17.8	16.0			
SE	1.40	1.42	1.38	1.37	0.0161[3]	0.3380[3]	0.9956[3]
(95% CI[5])		(0.8, 8.0)	(-1.8, 5.3)	(-3.5, 3.5)			

[1]N-QOL item responses are totaled and transformed to a zero to 100 scale where higher scores indicate better HRQOL (less nocturia impact).
[2]P-Value for screening based on ANOVA. Model is: response = Treatment Group + Study Center + Age Group + Gender.
[3]P-Value for change from screening based on ANCOVA. Model is: change = Screening Score + Treatment Group + Study Center + Age Group + Gender.
[4]N-QoL collected at Day 57 during the Treatment Period.
[5]95% CI for treatment group difference: 3 active doses of SER120 to placebo based on LS means for both observed and change from screening data.

Co-primary Efficacy Variable 2: Percent of Responders (≥50% Reduction in Mean Number of Nocturic Episodes)
ISE DB3/DB4 Studies, ITT Placebo Lead-in Responder Population

	Lead-in Placebo Responders		
Percent of Responders	**Placebo N=120 n (%)**	**SER120 1.5 mcg N=112 n (%)**	**SER120 0.75 mcg N=114 n (%)**
Yes	82 (68.3)	92 (82.1)	86 (75.4)
p-value (Treatment Comparison to Placebo)		0.0221[1]	0.1912[1]

[1] p-value based on Cochran-Mantel-Haenszel test stratifying by Study, Age Group and Gender.

Summary of Falls
DB3/DB4 Study, Safety Population

Study	Placebo	SER120 1.5 mcg	SER120 1.0 mcg	SER120 0.75 mcg
DB3	N=187	N=184	N=186	N=188
	5	1	4	2
DB4	N=267	N=264	NA	N=266
	1	1	0	2
Total (DB3 + DB4)	6	2	4	4

Co-Primary Efficacy Variables: Change in Nocturic Episodes and Percent Responders by Baseline Mean Nocturic Episodes
ISE DB3/DB4 Studies, ITT Population

	≤3 Episodes/Night at Baseline			>3 Episodes/Night at Baseline		
Co-Primary Variables	**Placebo N=233**	**SER120 1.5 mcg N=220**	**SER120 0.75 mcg N=218**	**Placebo N=213**	**SER120 1.5 mcg N=219**	**SER120 0.75 mcg N=230**
Change in nocturic episodes, LSM (SE)	-1.0 (0.05)	-1.2 (0.05)	-1.2 (0.05)	-1.4 (0.07)	-1.9 (0.08)	-1.7 (0.07)
p-value		0.0067[1]	0.0776[1]		<0.0001[1]	0.0073[1]
% responders	31.3	52.3	44.5	29.1	45.2	31.7
p-value		<0.0001[2]	0.0021[2]		0.0008[2]	0.6333[2]

[1]p-value for change from screening based on ANCOVA. Model is: change = screening nocturic voids/night + treatment group + study + study center (study) + age group + gender

[2]p-value based on Cochran-Mantel-Haenszel test stratifying by study, age group and gender.

Nocturia Etiology – Percent of Patients with >1 Etiology and Only 1 Etiology

ISE DB3/DB4 Studies, ITT Population

Characteristic	Placebo N=446 n (%)	SER120 1.5 mcg N=439 n (%)	SER120 0.75 mcg N=448 n (%)	Overall N=1333 n (%)
>1 Etiology	299 (67)	263 (60)	297 (66)	859 (64)
Nocturnal Polyuria only	71 (16)	92 (21)	78 (17)	241 (18)
BPH Only	25 (6)	28 (6)	22 (5)	75 (6)
OAB Only	18 (4)	28 (6)	21 (5)	67 (5)
Polyuria Only	0	2 (1)	3 (1)	5 (0.4)
Unknown Only	33 (7)	26 (6)	27 (6)	86 (7)
Nocturnal Polyuria (based on 24 hour urine collection during screening)				
Present	349 (78)	342 (78)	354 (79)	1045 (79)
Absent	97 (22)	96 (22)	93 (21)	286 (21)

Standard Deviations for Change from Baseline at Treatment Phase for INTU and NQoL

ITT Population

	Placebo	SER120 1.5 mcg	SER120 0.75 mcg
INTU (DB4 Study), N	249	243	247
LS Mean ± SD	-11.5 ± 15.43	-14.1 ± 16.39	-12.4 ± 15.25
NQoL (DB3 Study)			
Day 57, N	175	166	172
LS Mean ± SD	16.3 ± 20.38	19.0 ± 19.33	16.9 ± 21.77
Day 99, N	182	168	179
LS Mean ± SD	16.0 ± 20.39	20.4 ± 21.33	16.0 ± 21.97

Co-Primary Efficacy Variables: Change in Mean Nocturic Episodes and Percent Responders

ISE DB3/DB4 Studies, ITT Population, OAB + BPH on Rx

	ITT Population		
Co-Primary Efficacy Variable	**Placebo N=103**	**SER120 1.5 mcg N=95**	**SER120 0.75 mcg N=118**
Change in nocturic episodes, LSM (SE)	-1.0 (0.13)	-1.4 (0.13)	-1.3 (0.11)
P-value		0.0073[1]	0.0814[1]
% Responders	20.4	44.2	29.7
P-value		0.0006[2]	0.1727[2]

[1]P-Value for change from screening based on ANCOVA. Model is: change = Screening Nocturic Voids/Night + Treatment Group + Study + Study Center (Study) + Age Group + Gender.
[2]P-Value based on Cochran-Mantel-Haenszel test stratifying by study, age group and gender.