Potiga™ (ezogabine) Tablets as Adjunctive Therapy for the Treatment of Partial Onset Seizures

Valeant Pharmaceuticals

Peripheral and Central Nervous System Drugs
Advisory Committee
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Introduction and Presentation Overview

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Valeant Pharmaceuticals North America

Epilepsy is Widespread, Chronic, and Serious

- Affects approximately 3 million people in U.S.
- 70% of adults with epilepsy have partial onset seizures
- Nearly 1/3 of patients with partial onset epilepsy are not adequately treated
- Goal of treatment is seizure reduction or elimination

Ezogabine (previously retigabine) Development History

- First neuronal potassium channel opener for epilepsy
- 1997: Clinical trials initiated
- 2005: Valeant acquired the molecule
- 2008: Valeant entered into development and commercialization agreement with GSK
- 2009: NDA submitted

Clinical Development Program

- Includes 45 studies across 2247 subjects:
  - 29 Ph I
  - 5 Ph II
  - 2 Ph III
  - 6 open label extension studies, 1 compassionate use, and 2 in other indications
- Three adequate and well-controlled studies provide evidence of effectiveness (205, 301, 302)

Adjunctive Therapy for Adults with Partial Onset Seizures

- Demonstrated efficacy in patients with inadequately controlled seizures under current therapy
- Intended Use:
  - Adjunctive treatment for patients 18 years of age or older with partial onset seizures
- Dosing / titration regimen:
  - Initial dose 100 mg TID (half-life of 6-10 hrs)
  - Titrate weekly- max increase 150 mg/day
  - Proposed dose range- 600 to 1200 mg/day

Clinical Safety and Benefit:Risk Profile

- Most AEs consistent with other AEDs
- Some AEs are related to the specific pharmacology of ezogabine
- Overall favorable benefit-risk profile as adjunctive treatment of partial onset seizures in adults
- Risk Management program proposed

Agenda

Introduction	**Susan T. Hall, Ph.D.** Valeant Pharmaceuticals NA
Unmet Medical Need and Efficacy	**John Messenheimer, M.D.** Epilepsy Expert Consultant
Safety Profile	**Neil Brickel, M.D.** GlaxoSmithKline
Risk Management Plan and Benefit:Risk Assessment	**Susan T. Hall, Ph.D.** Valeant Pharmaceuticals NA
A Clinician's Perspective: Urinary Retention	**Claus G. Roehrborn, M.D.** Professor and Chairman Department of Urology UT Southwestern Medical Center
A Clinician's Perspective: Treatment of Epilepsy	**Jacqueline A. French, M.D.** Professor, Neurology Epilepsy Center, NYU School of Medicine

Additional Participants

Eugene M. Laska, Ph.D.
Research Professor, Biostatistics
NYU Medical Center

Joel Morganroth, M.D.
Chairman and CSO
EResearch Technology, Inc.

Ezogabine* Efficacy Profile

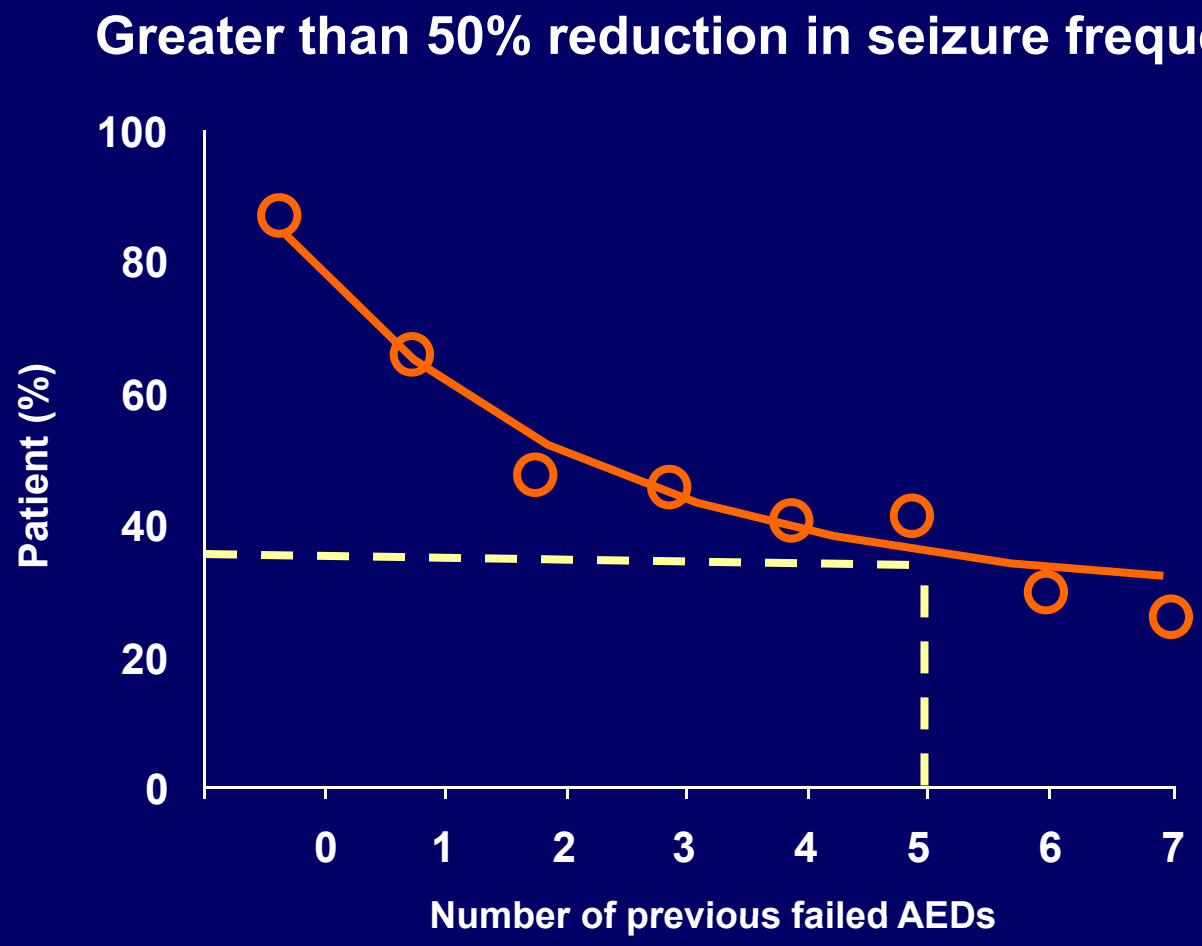
John Messenheimer, M.D.

*ezogabine (USAN)/ retigabine (INN)

Topics

- Ion channels in seizure pathophysiology
- Mechanism of action of ezogabine
- Clinical pharmacology and design of ezogabine pivotal clinical trials
- Key efficacy data for ezogabine

Challenge of Treating Patients Who Have Failed Multiple AEDs



Adapted from Schiller, Neurology 2008, 70:54-65.

EZOGABINE Mechanism of Action

Ion Channels Regulate Neuronal Excitability

- 4 key ion channels
  - Na^+, Ca^{++}, Cl^-, K^+
- Excitability: Na^+ and Ca^{++}
- Inhibition: Cl^- and K^+

Blum D. *BNI Quarterly.* 1999;15:42-48.

Ezogabine Targets Potassium KCNQ Channels

AED*	Decreased Excitation				Increased Inhibition	
	Na^+	Ca^{2+}	SV2A	Glutamate	Cl^- (GABA)	K^+ (KCNQ)
Ezogabine‡					●	●
Benzodiazepines					●	
Carbamazepine	●					
Felbamate				●	●	
Gabapentin		●				
Lacosamide	●					
Lamotrigine	●					
Levetiracetam			●			
Oxcarbazepine	●					
Phenobarbital		●		●	●	
Phenytoin	●					
Pregabalin		●				
Rufinamide	●					
Tiagabine					●	
Topiramate	●			●	●	
Valproate					●	
Vigabatrin					●	
Zonisamide	●	●				

* For treatment of partial-onset seizure
‡ In development

Ezogabine Targets
KCNQ 2-5 Channels

Subunit	Major Expression	Other expression	Effect Concentration
KCNQ1	Heart, cardiac myocytes, Cochlea	Bladder, vasculature, intestine, kidney, uterus	~ 100 uM
KCNQ2	Brain, spinal cord, peripheral nervous system including ganglia	Aortic baroreceptors	2.5 uM
KCNQ3	Brain, spinal cord, peripheral nervous system including ganglia	Aortic baroreceptors, bladder	0.6 uM
KCNQ4	Cochlea, vestibular hair cells	Brain, heart, vasculature, uterus	5.2 uM
KCNQ5	Brain, spinal cord, peripheral nervous system including ganglia	Bladder, aortic baroreceptors, vasculature, skeletal muscle, uterus	6.4 uM

References: Jentsch, 2000; Brown, 2009; Lerche, 2000; Schroeder, 2000; Kharkovets , 2000; Yeung, 2007; Wladyka, 2008; Passmore, 2003; McCallum, 2009.

Ezogabine Clinical Pharmacology

T_{max}	0.5-2 hours
Bioavailability	60%
$T_{1/2}$	6 – 10 hours
Protein Binding	80%
Metabolism	N-glucuronidation, N-acetylation
Metabolites	N2 and N4 glucuronides, N-acetyl metabolite and N2 and N4 glucuronides of the N-acetyl metabolite
Elimination	Renal and hepatic
Linearity	PK linear over dose range of 200 to 400 TID
Drug Interactions	Low potential for drug interactions (not metabolized via the P450 system)

EZOGABINE : Clinical Development

Summary of Ezogabine Clinical Development

Study	Design	Enrollment	Significance
200/201	Open-label, uncontrolled, randomized, parallel group	46	• 100 mg TID starting dose • 150 mg/week dose titration • 1200 mg/day as the MTD
202		60	
214	Double-blind, randomized, parallel group	73	• Explored faster titrations than 150 mg/week

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202		60	
214	Double-blind, randomized, parallel group	73	• Explored faster titrations than 150 mg/week
205	Double-blind, randomized, placebo-controlled, parallel group	396	Established dose response over 600 to 1200 mg dose range and efficacy at 900 and 1200 mg/day
301		305	Confirmed efficacy at 1200 mg/day
302		538	Confirmed efficacy at 600 and 900 mg/day

Pivotal Studies Were Similar in Design and Enrolled Similar Populations

	Study 205	Study 301	Study 302
Age	Age 16-70	Age 18-75	
Seizure Frequency	≥ 4 partial seizures/28 days with or without secondary generalization		
Concomitant AED Therapy	1-2 AEDs including VNS	1-3 AEDs ± VNS	
Treatment Groups	• 600 mg/day • 900 mg/ day •1200 mg/day	• 1200 mg/day	• 600 mg/day • 900 mg/day

Pivotal Studies Were Similar in Titration Method and Duration

	Study 205	Study 301	Study 302
Same Titration for All Studies	• Randomized titration to fixed doses • Starting dose = 300 mg • Increase 150 mg/day /week • All dosing TID		
Duration of Double blind	16 weeks	18 weeks	16 weeks
Duration of Titration	2 , 4 or 6 weeks (600, 900, 1200 mg/day)	6 weeks (1200 mg/day)	2- 4 weeks (600, 900 mg/day)
Maintenance Duration	8 weeks	12 weeks	12 weeks

Pivotal Studies Used Standard AED Primary and Key Secondary Endpoints

Primary Efficacy Endpoints

% reduction in total partial-seizure frequency per 28 days from baseline through double-blind period

Key Secondary Endpoints

Responder rate (i.e., ≥50% reduction in seizure frequency per 28 days) from baseline through double-blind period and maintenance period

Proportion of seizure free patients in double-blind and maintenance periods

Change in number of seizure free days in double-blind and maintenance periods

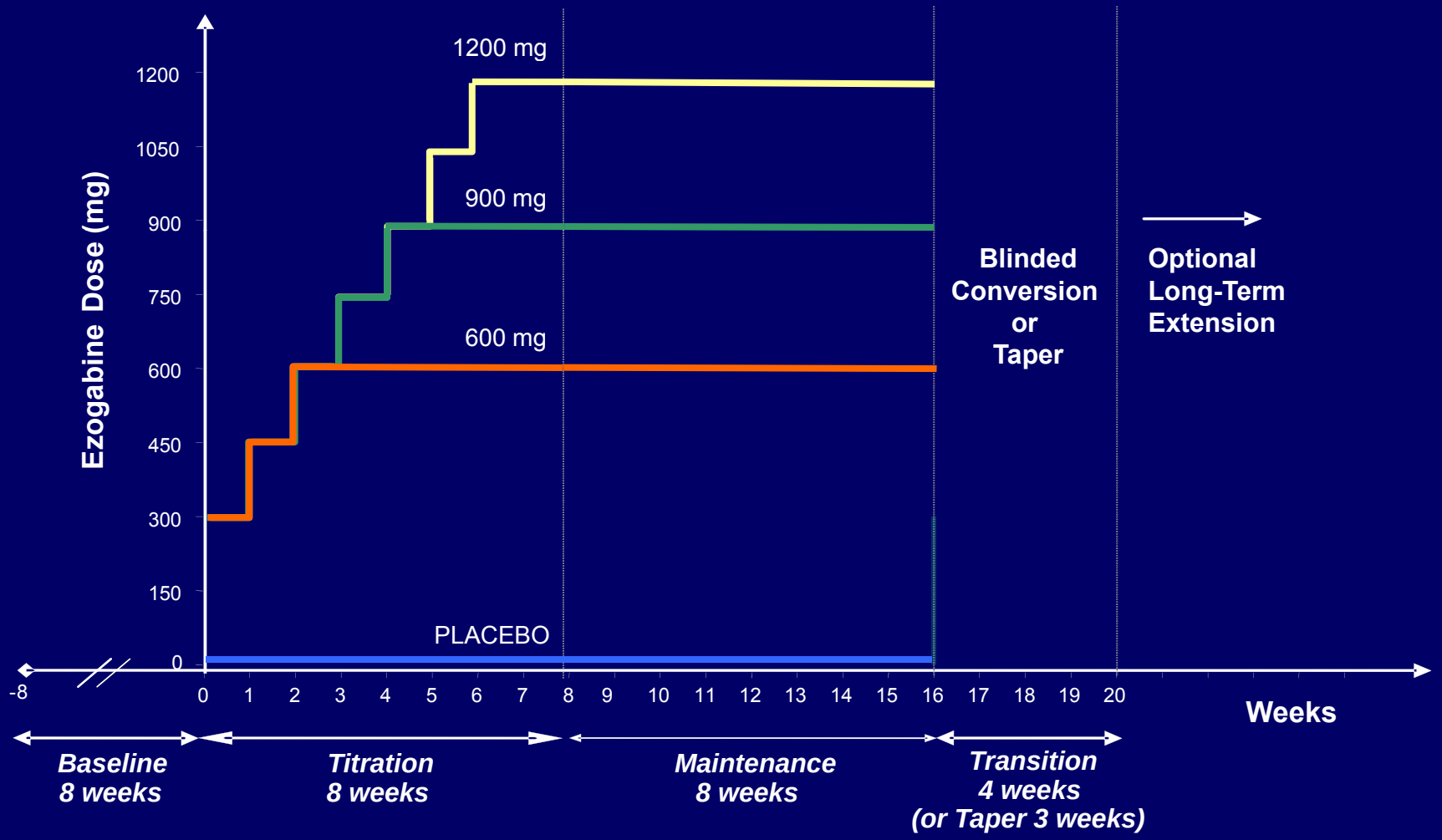
Baseline Characteristics of Subjects in Pivotal Trials Were Similar

	Study 205				Study 301		Study 302		
	PBO N=96	EZG 600mg N=100	EZG 900mg N=95	EZG 1200mg N=106	PBO N=152	EZG 1200mg N=153	PBO N=179	EZG 600mg N=181	EZG 900mg N=178
Age (years)	35	37	37	38	37	38	38	38	38
Gender (% Female)	50%	46%	49%	48%	53%	56%	50%	58%	48%
Race (%/Caucasian)	93%	98%	97%	97%	51%	59%	94%	96%	96%

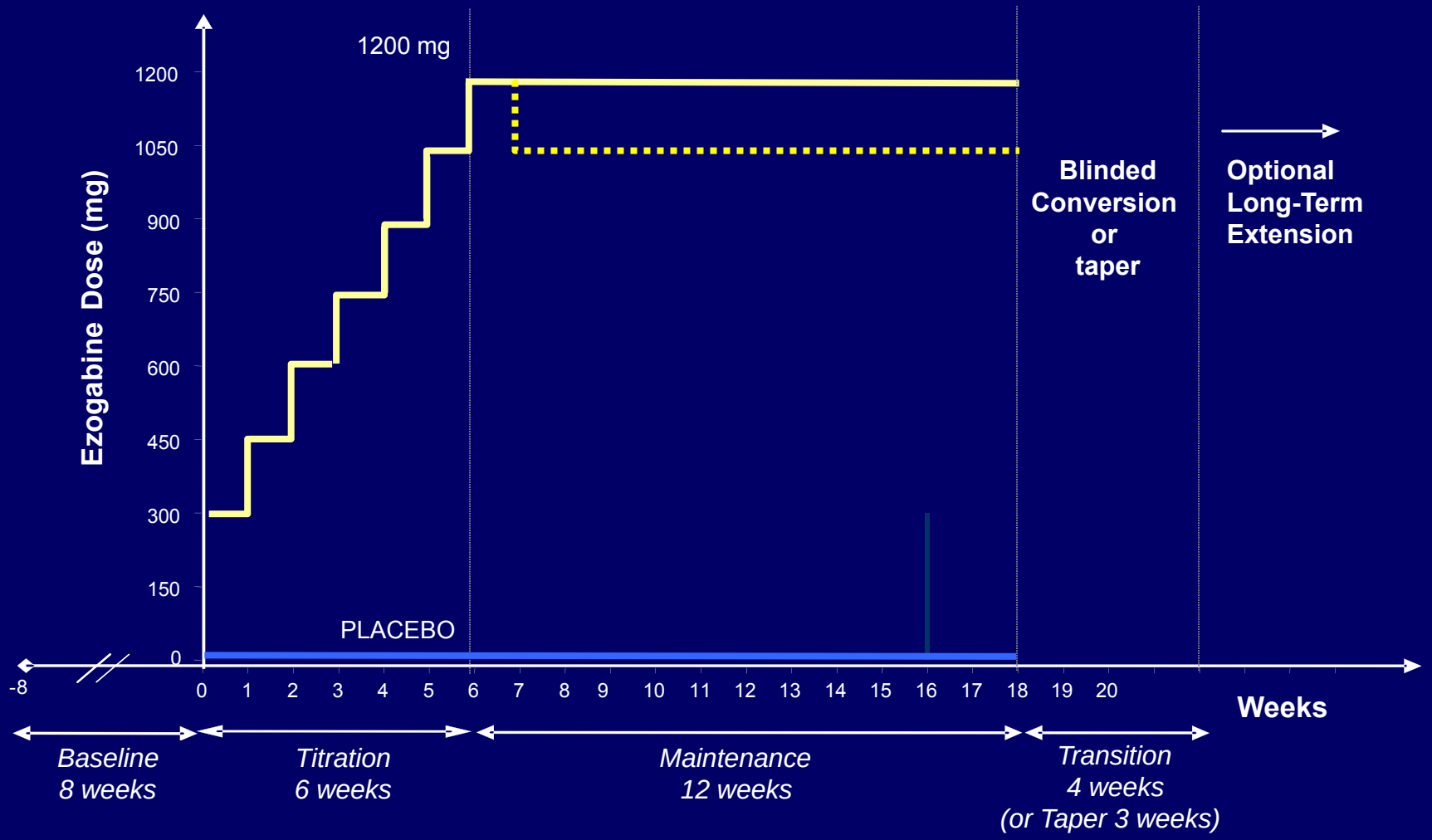
Baseline Characteristics of Subjects in Pivotal Trials Were Similar

	Study 205				Study 301		Study 302		
	PBO N=96	EZG 600mg N=100	EZG 900mg N=95	EZG 1200mg N=106	PBO N=152	EZG 1200mg N=153	PBO N=179	EZG 600mg N=181	EZG 900mg N=178
Median Seizure Frequency (monthly)	9	9	8	10	11	12	9	10	10
% Receiving ≥ 2 AEDs	66%	74%	73%	71%	86%	79%	78%	73%	80%
Epilepsy Duration (years)	21	21	20	20	23	24	23	23	23

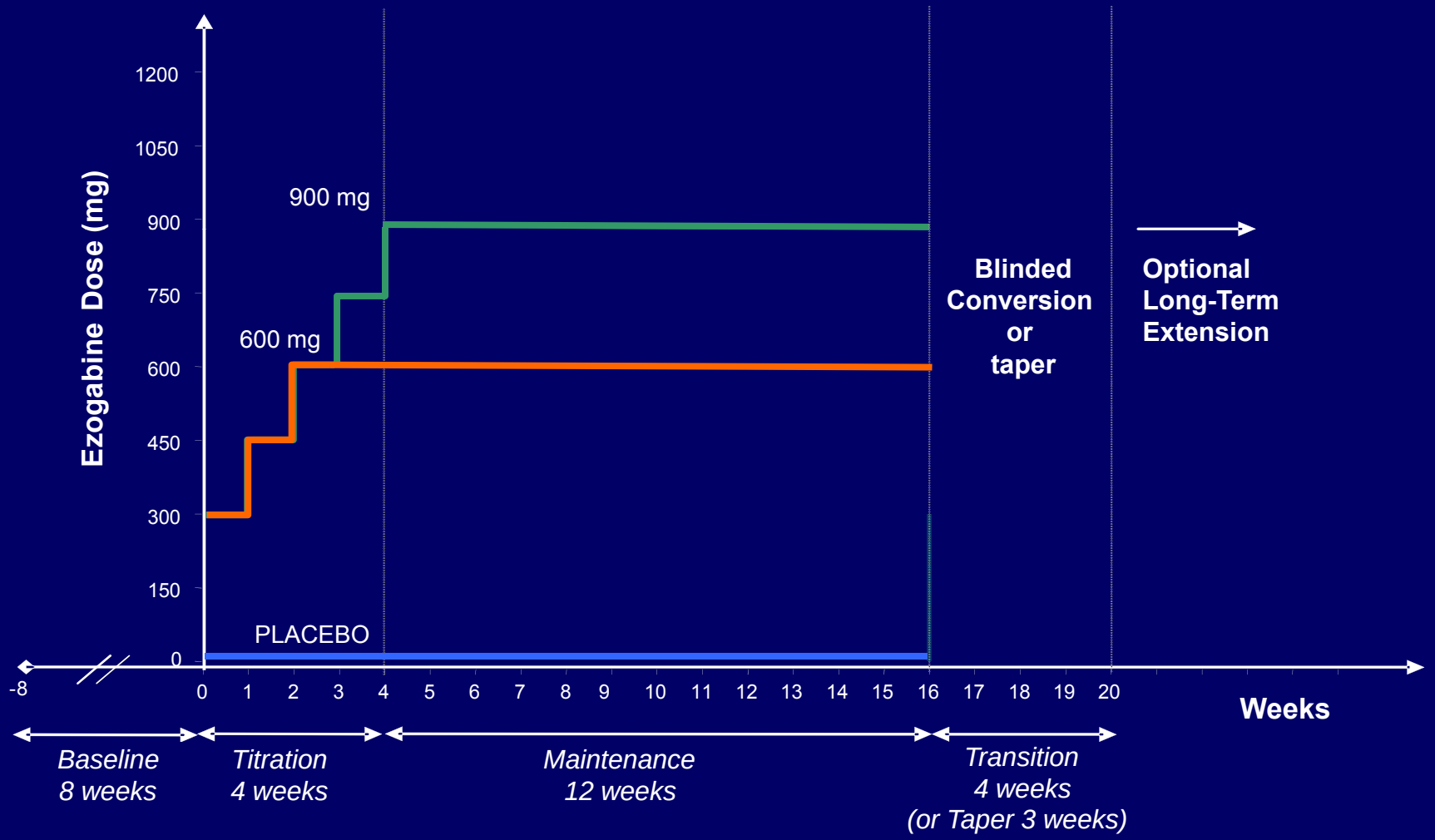
Study 205 Design Used Forced Titration Followed by 8 Week Maintenance



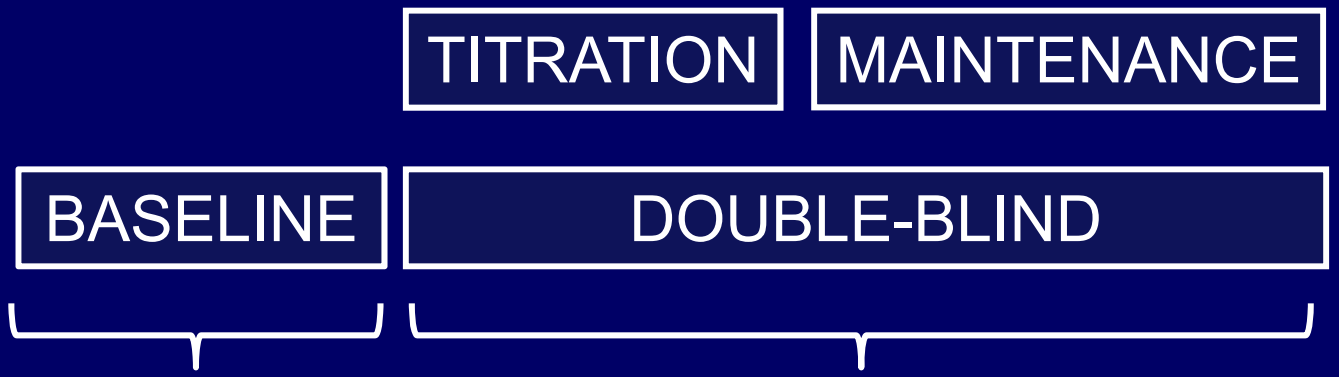
Study 301 Design Used 6 Week Forced Titration Followed by 12 Week Maintenance



Study 302 Design Used 4 Week Forced Titration Followed by 12 Week Maintenance



Calculation of Monthly Seizure Frequency



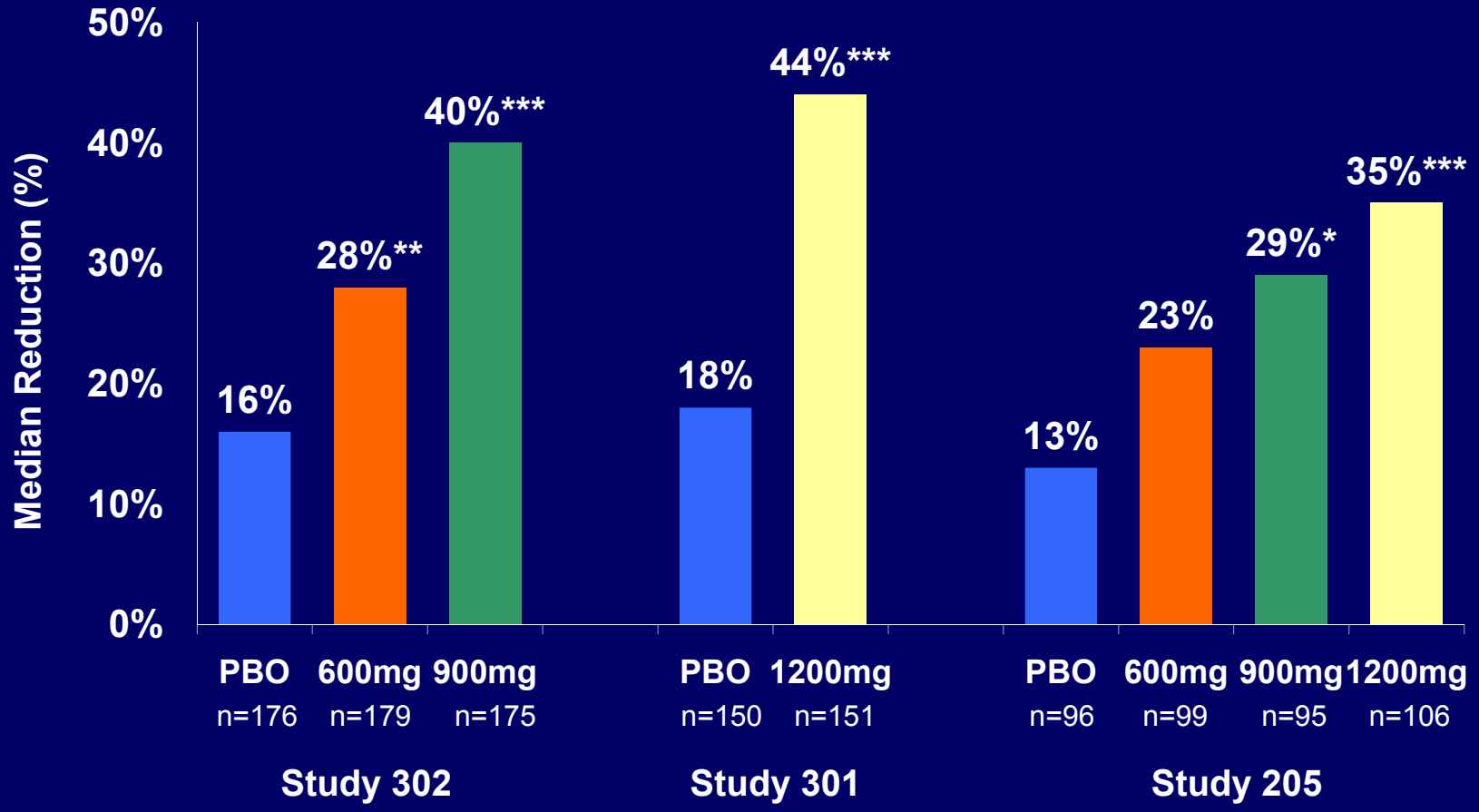
$$\frac{\text{Total partial seizures during each phase X 28}}{\text{Number of days in the phase}}$$

Randomized and ITT Populations Were Similar in the Pivotal Trials

	PBO	600	900	1200
Randomized	428	282	274	260
ITT Double-Blind	427	280	273	259
ITT Maintenance	379	241	223	187
Completed N (%)	353 (82%)	206 (74%)	185 (68%)	158 (61%)

EZOGABINE : Key Efficacy Data

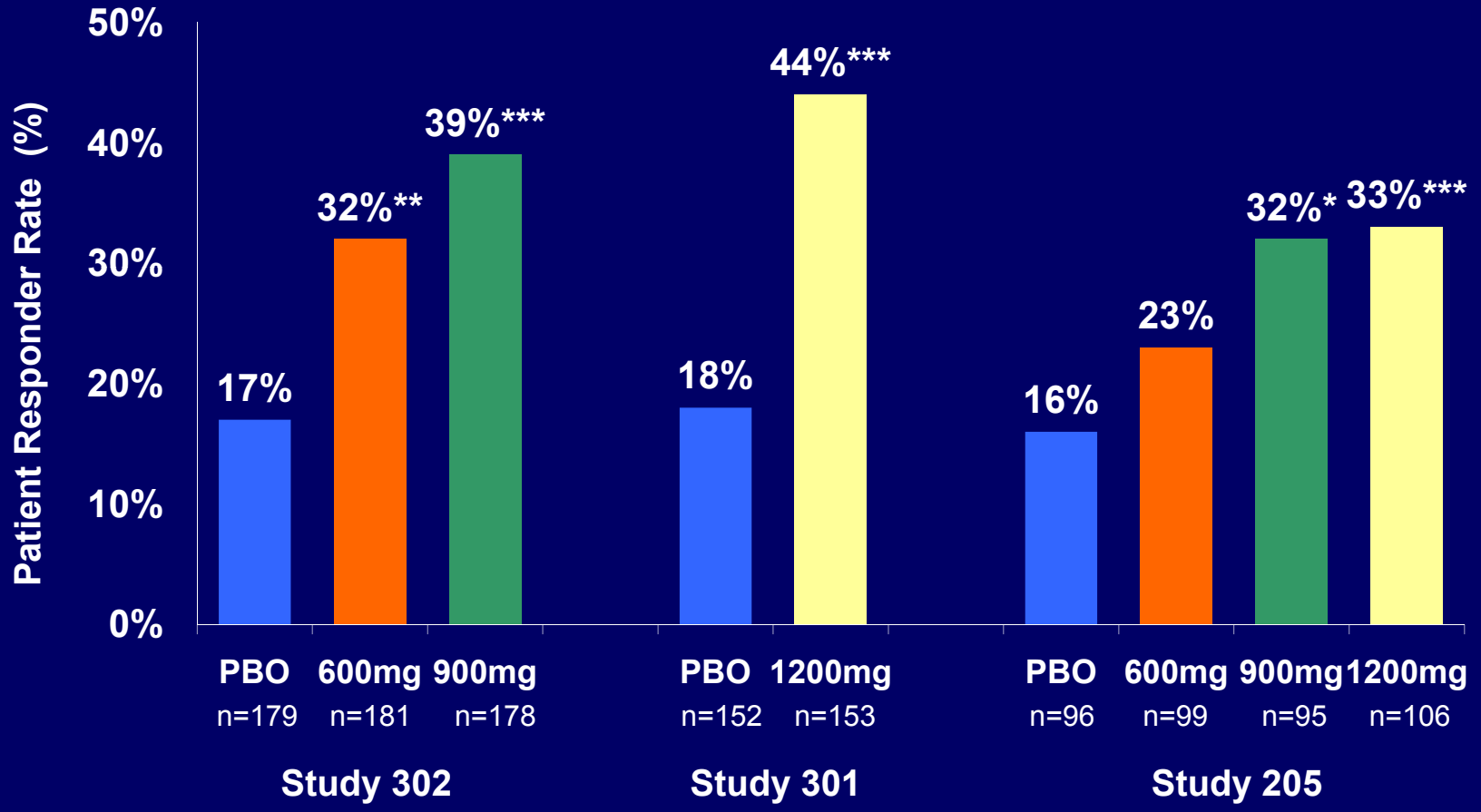
Significant Reductions in Partial Seizure Frequency Compared to Placebo



* p<0.05 vs. Placebo
** p<0.01 vs. Placebo
*** p<0.001 vs. Placebo

Placebo
Ezogabine 600 mg/day
Ezogabine 900 mg/day
Ezogabine 1200 mg/day

Responder Rates Significantly Higher Than Placebo



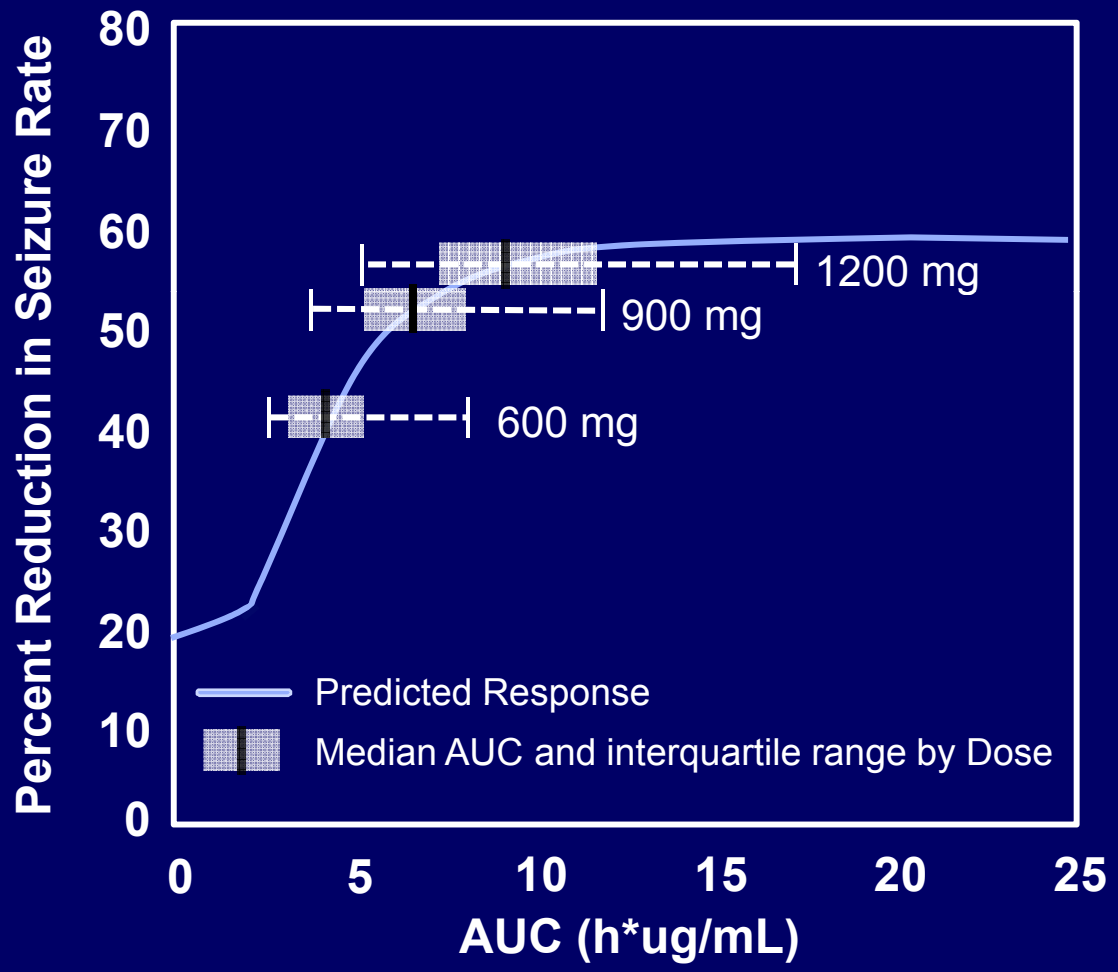
* p<0.05 vs. Placebo
** p<0.01 vs. Placebo
*** p<0.001 vs. Placebo

Placebo
Ezogabine 600 mg/day
Ezogabine 900 mg/day
Ezogabine 1200 mg/day

Efficacy During Open Label Continuation Studies

- 778 patients from the 3 pivotal trials entered into open label extension studies and received drug:
  - 77.5% were exposed to >6 mos ezogabine
  - 46.9% were exposed to >12 mos ezogabine
- Efficacy (median % reduction in seizure frequency) was maintained in the OLE studies with ranges of:
  - 49.3% to 55.7% at 3 mos
  - 50.4% to 59.3% at 6 mos
  - 49.3% to 63.4% at 12 mos

Ezogabine AUC and Efficacy by Dose in Studies 301 and 302 Maintenance Phase



Efficacy in Adjunctive Treatment of Patients with Uncontrolled Partial Seizures

- Ezogabine reduced seizure frequency in all 3 Pivotal Trials
  - Study 205
    - Demonstrated dose-response over 600 - 1200 mg/day
    - Established efficacy at 900 and 1200 mg/day
  - Study 301 and 302
    - Confirmed efficacy at 600, 900 and 1200 mg/day
- Efficacy maintained in open label extension trials

Efficacy Conclusions

- Ezogabine 600-1200 mg/day is effective adjunctive treatment for patients with uncontrolled partial-onset seizures
- The full dose range of 600-1200mg/day will allow physicians to individualize therapy

Ezogabine Safety Profile

Neil Brickel, M.D.

Ezogabine Shows Species-Sensitive Effects on Urinary Tract

- Inhibits urinary bladder smooth muscle contractility, causing bladder dilation and associated bladder /renal lesions due to increased urinary pressure
  - Pharmacologically mediated
  - Species sensitivity
    - Mouse > rat or dog
  - Higher sensitivity in rodents may be due to inability to exert central control over bladder musculature
  - Ezogabine does not totally block micturition
    - Rats and mice tolerated repeat dosing, 2 years and 13 weeks respectively

Preclinical Urological Findings Seen at Exposures Similar to 1200mg in Humans

- Mouse
  - Sufficient inhibition of micturition (bladder dilatation etc.) that kidney findings (tubular degeneration and necrosis, papilliary necrosis) were seen at exposures < 1200mg human dose
- Rat
  - Limited to bladder dilatation and vascular congestion
- Dog
  - Limited to the bladder (Focal mixed infiltration, Focal hemorrhage, smooth muscle proliferation and congestion) in one male and one female

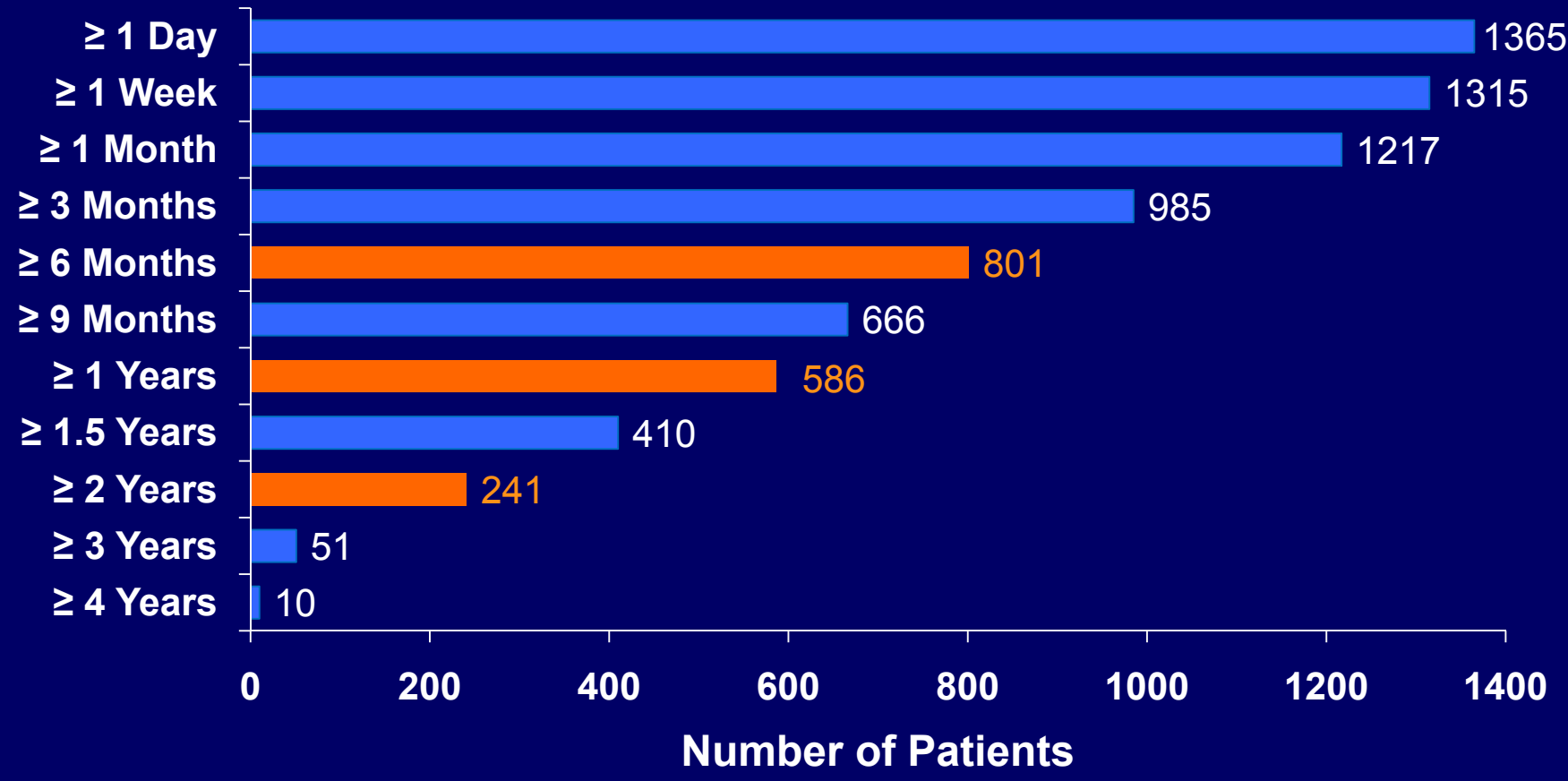
Safety Populations Presented to Provide Most Comprehensive AE Profile

- Pivotal Controlled Trials (PCTs)
  - 3 placebo controlled epilepsy trials
- All Phase II/III Combined (120 day safety update; 1365 patients)
  - PCTs (813 patients)
  - 4 other Phase II epilepsy studies
  - 6 long-term, open-label epilepsy extension studies
  - Includes 8 patients ≥ 65 years of age

Additional Studies Presented to Further Characterize Safety Profile

- PHN Study
  - Includes 61 patients aged 65 and over
- Thorough QT Study
  - Placebo-controlled
  - Healthy volunteers
- Phase I trial

586 Exposed to Ezogabine for at Least 1 Year



All Phase II/III Population: 1365 Patients

Up to cut-off based on the US 120-Day Safety Update.

Safety Presentation Overview

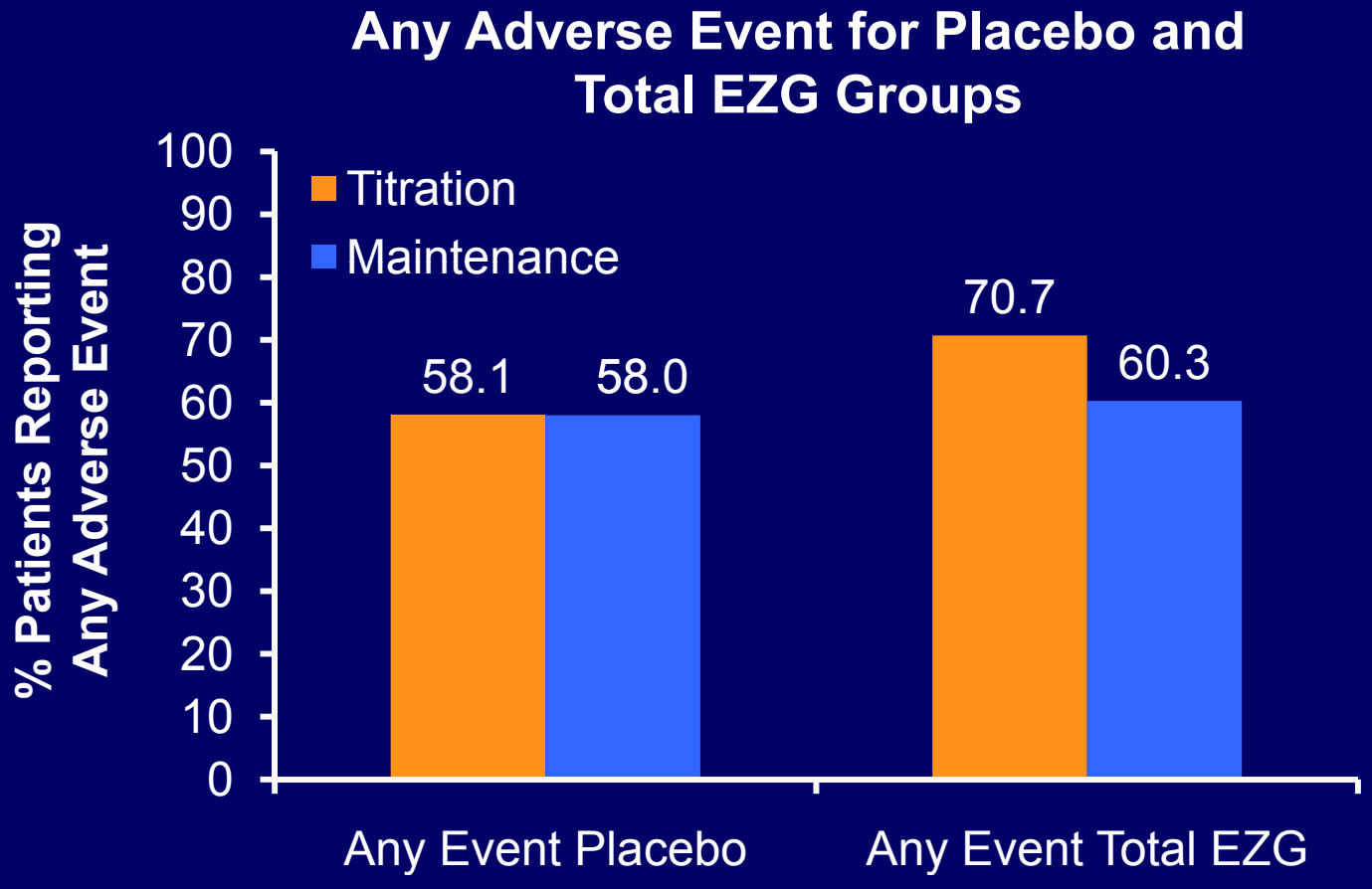
- Common adverse events
- Adverse events leading to discontinuation
- Serious adverse events
  - Non-fatal
  - Sudden Unexplained Death in Epilepsy Patients
- Adverse events of Special Interest
  - Urinary bladder dysfunction
  - Potential for cardiac arrhythmia
  - Hallucinations and psychosis
  - Liver function test abnormalities

Common AEs Were Generally Dose Related & Involved the Central Nervous System (PCT Population)

	Number (%) of Patients				
Preferred Term	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Any event	75%	74%	82%	88%	81%
Dizziness	9%	15%	23%	32%	23%
Somnolence	12%	15%	25%	27%	22%
Headache	16%	12%	17%	15%	15%
Fatigue	6%	16%	15%	13%	15%
Confusional state	3%	4%	8%	16%	9%
Tremor	3%	3%	10%	12%	8%
Coordination abnormal	3%	5%	5%	12%	7%
Vision blurred	2%	2%	4%	10%	5%

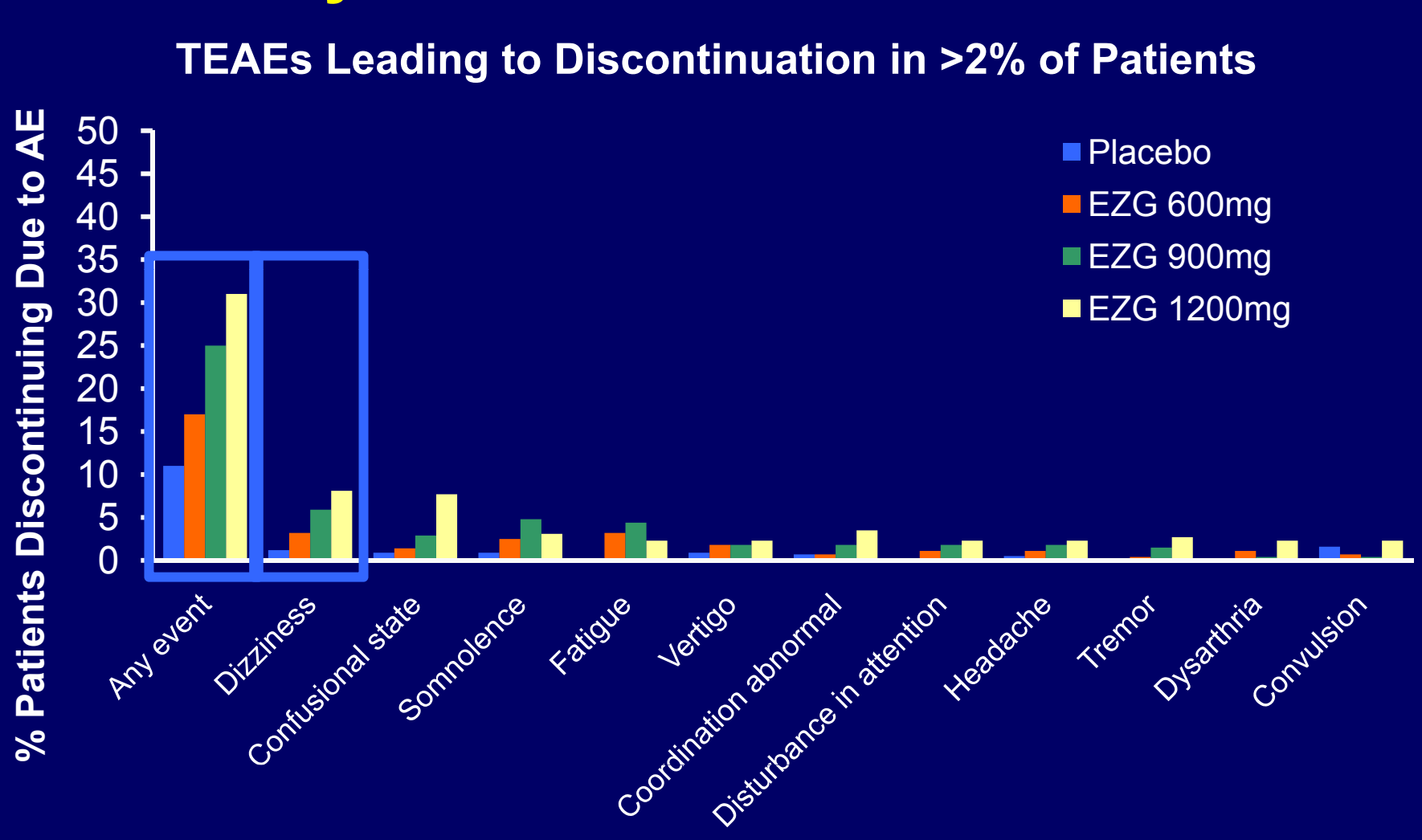
PCT Safety Population

AE Frequencies Were Similar to Placebo in the Maintenance Phase (PCT Population)



PCT Safety Population

AEs Leading to Discontinuation Were Generally CNS and Dose Related (PCT Population)



PCT Safety Population

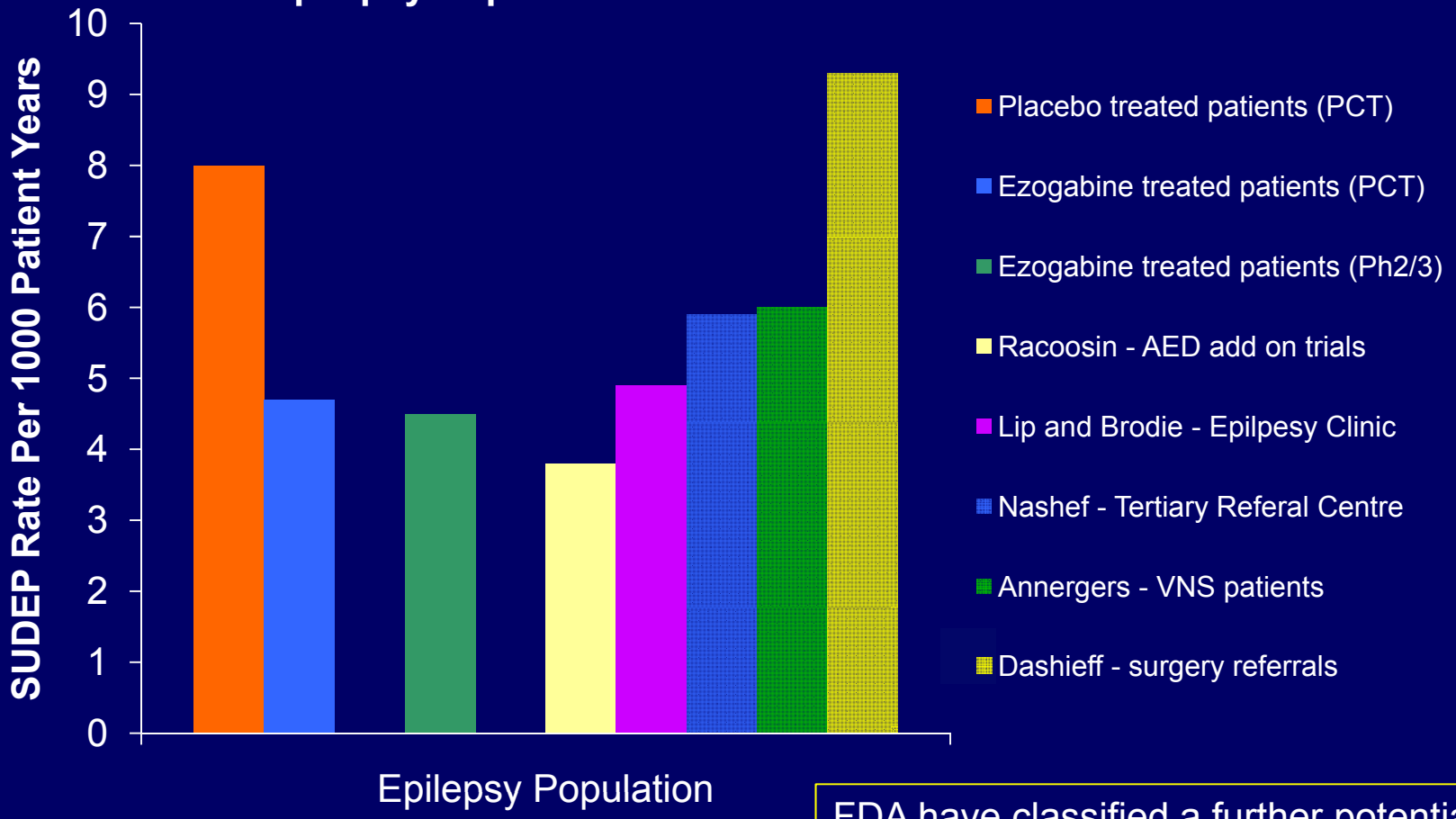
SAEs Were Infrequent and Typically CNS-Related
(PCT Population)

Preferred Term	Number (%) of Patients				
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Any event	25 (5.9%)	23 (8.2%)	18(6.6%)	29 (11.2%)	70 (8.6%)
Convulsion	5 (1.2%)	5 (1.8%)	2 (<1%)	5 (1.9%)	12 (1.5%)
Psychotic disorder	0	0	1 (<1%)	5 (1.9%)	6 (<1%)
Nausea	0	0	0	2 (<1%)	2 (<1%)
Fatigue	0	2 (<1%)	0	0	2 (<1%)
Drug toxicity	0	2 (<1%)	0	0	2 (<1%)
Encephalopathy	0	0	0	2 (<1%)	2 (<1%)
Dizziness	1 (<1%)	0	2(<1%)	0	2 (<1%)
Myoclonus	0	2 (<1%)	0	0	2 (<1%)
Confusional state	0	0	0	2 (<1%)	2 (<1%)
Suicidal ideation	0	0	0	2 (<1%)	2 (<1%)
Death	3 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)

PCT Safety Population

SUDEP Comparable to Published Rates for Uncontrolled Epilepsy

Comparison of Ezogabine SUDEP Rates Across Various Epilepsy Populations From The Medical Literature



FDA have classified a further potential SUDEP in the Phase 2/3 population

Adapted from Tomson et al, *Epilepsia* 2005;46(Suppl 11):54-61

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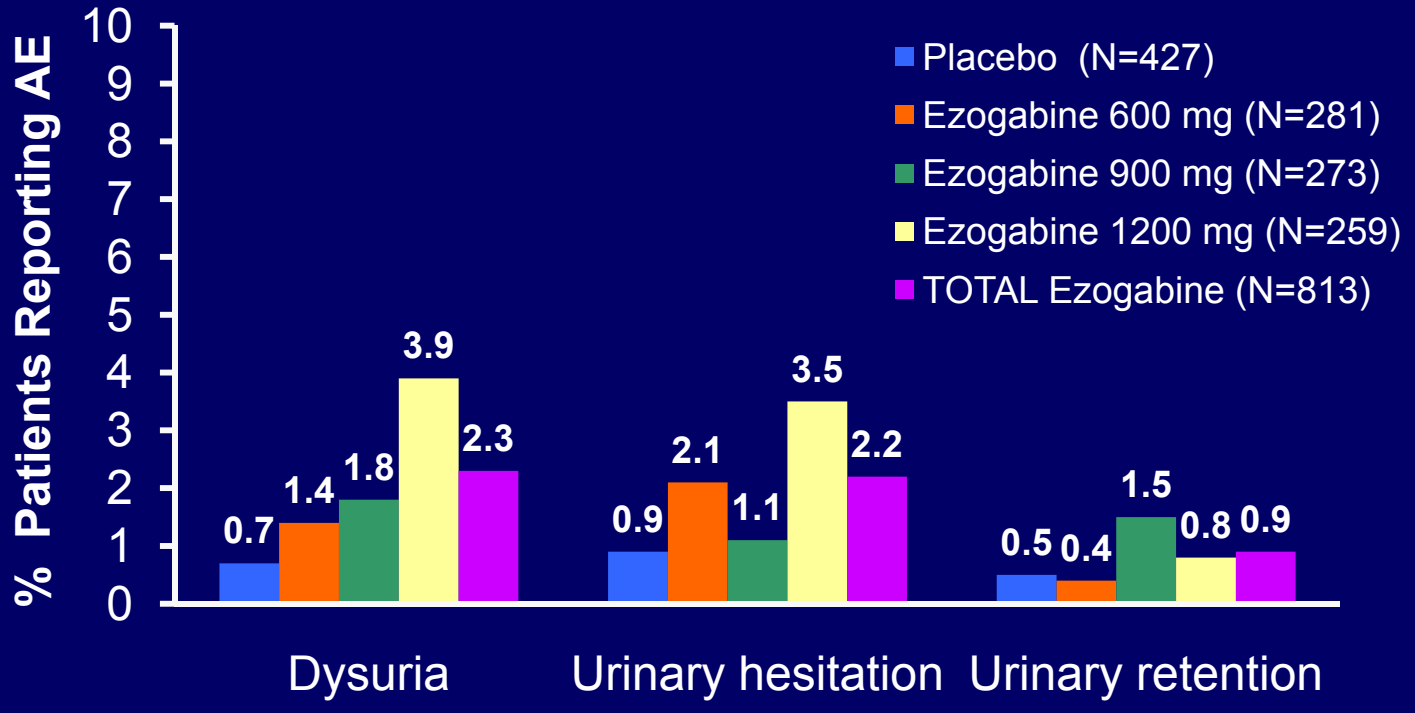
Urinary Retention-Related AEs Were Reported With Ezogabine Therapy (PCT Population)

Percentage of Patients Reporting Specific Urinary AEs by Dose – Pivotal Controlled Trials

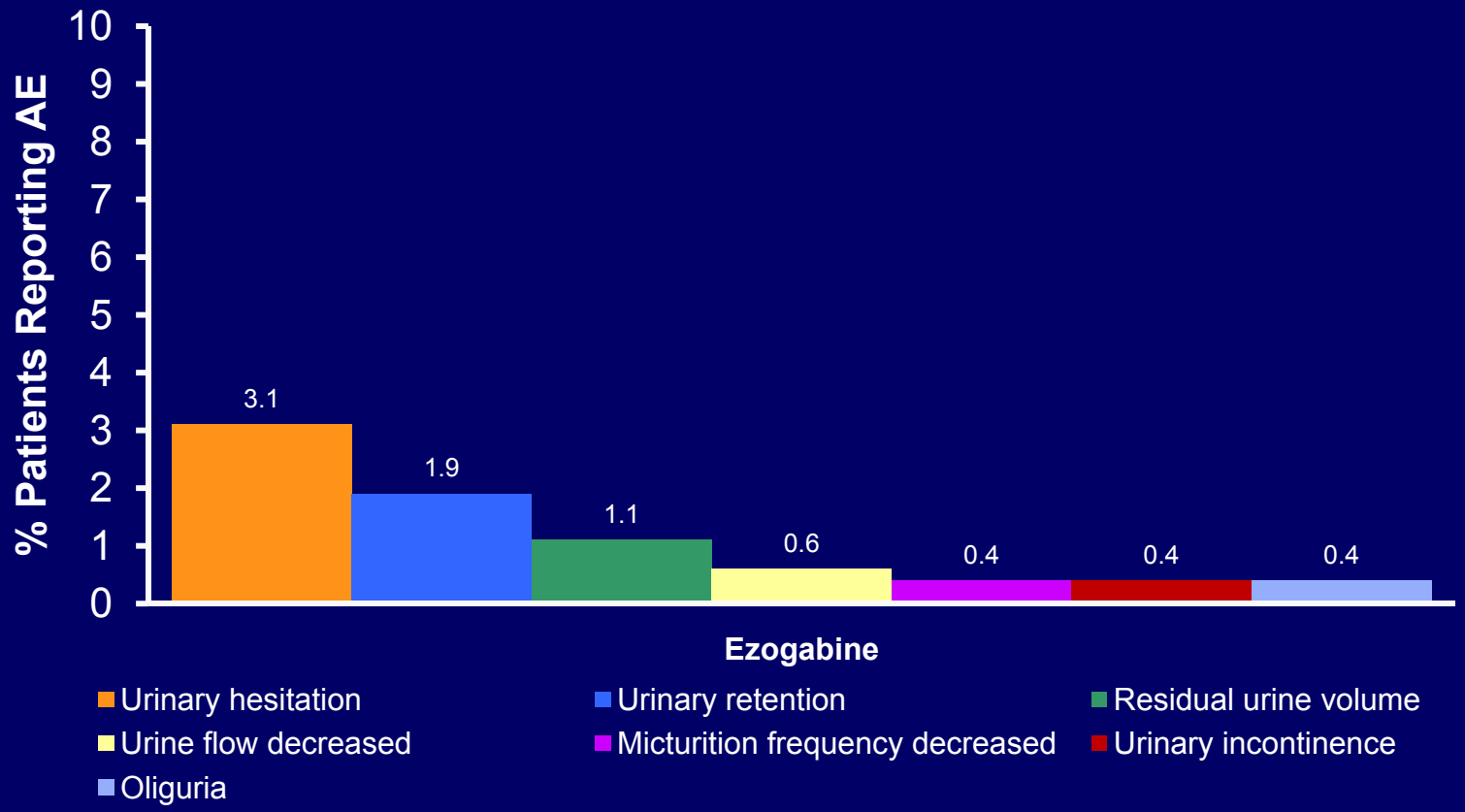


Lower Urinary Tract AE Preferred Terms

PCT Safety Population

Urinary Hesitation Was the Most Frequent Urinary Retention-Related AEs

(Phase II/III Population; N=1365)



Phase 2/3 Safety Population

Five Urinary Retention Events Required Catheterization (Phase II/III Population)

Study Number	Age/ Gender	Study Rx	TTO (day)	PVR: Baseline/ UR*	Comments	Discont.
205	53/F	EZG 600mg	~30	Not performed	Associated renal impairment and fluid overload	Yes
303	30/M	EZG 1050mg	81	Baseline: 24 mL Day81: 900 mL	Presented very agitated and was catheterised after 18 hours retention. Has required ongoing intermittent self catheterisation	Yes
304	46/F	EZG 900mg	57	Baseline: 7mL Day 57: 60 mL	Chose to intermittently self catheterise rather than discontinue because of benefit. Event resolved.	No
303	39/M	EZG 900mg	691	Baseline: 37 mL Day700: 699 mL	Event occurred post-ictal, patient had enlarged prostate. Prior PVRs all normal	No
301	55/M	Placebo	~29	Baseline: 20mL Day 29: N/A	Associated with increased seizures. Settled with one time catheterisation.	No

*UR: Urinary retention

Urinary Retention Resulting in Long-Term Intermittent Catheterization: Subject 303-03505

- 30 year old Caucasian male with partial epilepsy
  - History of urinary retention attributed to Lomotil
  - Post Void Residual volume (PVR) at baseline was 24 mL
- Day 81: Urinary retention first reported (ezogabine dose 1050mg/Day)
  - Presented to ER after 18 hrs urinary retention; PVR 900 mL
  - Catheterized and 1200 mL of urine released
- Day 82: Urodynamic test: able to void <50 mL of 250 mL sterile saline; taught self catheterization
- Day 83: Study drug discontinued

Urinary Retention Resulting in Long-Term Intermittent Catheterization: Subject 303-03505

- Bladder status at follow-up
  - **Day 116** (~ 30 days post study drug discontinuation): urodynamic study showed normal bladder compliance, sensation of fullness on filling. No leak with valsalva, but inability to void during exam. No EMG activity. Detrusor activity not sustained. Voided volume 0 mL; PVR 882 mL. Effects consistent with neurogenic bladder.
  - **Day 126:** CT lumbar spine and pelvis scan conducted: mild degenerative disc changes; mild dural sac indentation; no root sleeve involvement; no compression or mass
  - **Day 158:** PVR 91 mL
  - **Day 187:** intermittent self-catheterization; regular spontaneous voiding
  - **Day 691:** (20Oct 2009): Stable with ongoing requirement for intermittent self-catheterization

Post Void Residual (PVR) Volume Methodology

- Studies 301/302: PVRs measured at baseline, weeks 8 or 10; 16 or 18; end of study (week 20 or 22) or discontinuation
- Studies 303/304: measured ~1,3 and 12 months
- A PVR value >150 mL considered of potential clinical concern

American Urological Association Symptom Index (AUA SI)

- 7 questions, rated on a 0-5 scale (max score of 35)
- Assessment of symptoms includes incomplete emptying, straining and urgency
- Score of 0-7: mild; 8-18: moderate; 19-35: severe symptoms
- Administered in Phase II and III PCTs and extensions
- Studies 301/ 302: administered at baseline, weeks 4 or 6; 8 or 10; 16 or 18; end of study (weeks 20 or 22) or discontinuation

Urinary AEs Did Not Correlate with Objective Assessments of Urinary Function

- Independent urinary safety review was conducted
- Ezogabine can affect bladder function
- Poor association between AE reports and:
  - American Urological Association (AUA) Symptom Index
  - Post Void Residual Volume (PVR) assessments
- SAEs did not reveal a pattern

Identification of Urinary Tract Infections in PCTs

- UTIs diagnosed on signs and symptoms
- Urine cultures not protocol-specified
- Most UTIs not confirmed by urine culture

Percentage of UTIs by Individual PCT

Study	PBO	EZG 600	EZG 900	EZG 1200	Total EZG
205	4	2	4	3	-
301	9	-	-	12	-
302	2	2	3	-	-
Integrated	5	2	3	8	4

Nephrolithiasis and Renal Colic

- In PCTs:
  - Nephrolithiasis 4/813 ezogabine vs 0/427 placebo
  - Renal colic 3/813 ezogabine vs 1/427 placebo
- Across All Phase II/III studies:
  - Nephrolithiasis 10/1365
  - Renal colic 7/1365
- History of stones in 3 patients; 5 others taking topiramate; 1 patient treated for UTI 2 weeks earlier
- Onset ranged from 43-564 days of treatment initiation
- 2 hospitalizations, but no patient withdrew from treatment
- Stone analyzed in 1 patient (Ca Oxalate)
- Event resolved in all patients

Nephrolithiasis and Renal Colic

- 17 unique patients receiving ezogabine experienced nephrolithiasis, renal colic and/or calculus ureteric (Phase II/III)
- 1 patient receiving placebo experienced renal colic (PCT)

	Nephrolithiasis and Urolithiasis	Renal Colic
Number of Patients[a]	11	7
Stone Confirmed	3	1
Visualization (lithotripsy, CT)	2	1
"Passed stone"	1	0
No Confirmation[a, b]	8	6

a. One patient reported both nephrolithiasis and renal colic (208-00013)
b. Diagnostic data available for one case; iv pyelogram and ultrasound.

Summary of Urinary Safety Data

- Urinary AEs were reported more frequently in patients receiving ezogabine compared to placebo
  - Most patients able to continue on medication
  - Apart from one case, all resolved after discontinuation
- Urinary hesitation was the most frequently reported urinary retention-related AE
- No direct causal association with UTI
- Nephrolithiasis was uncommon

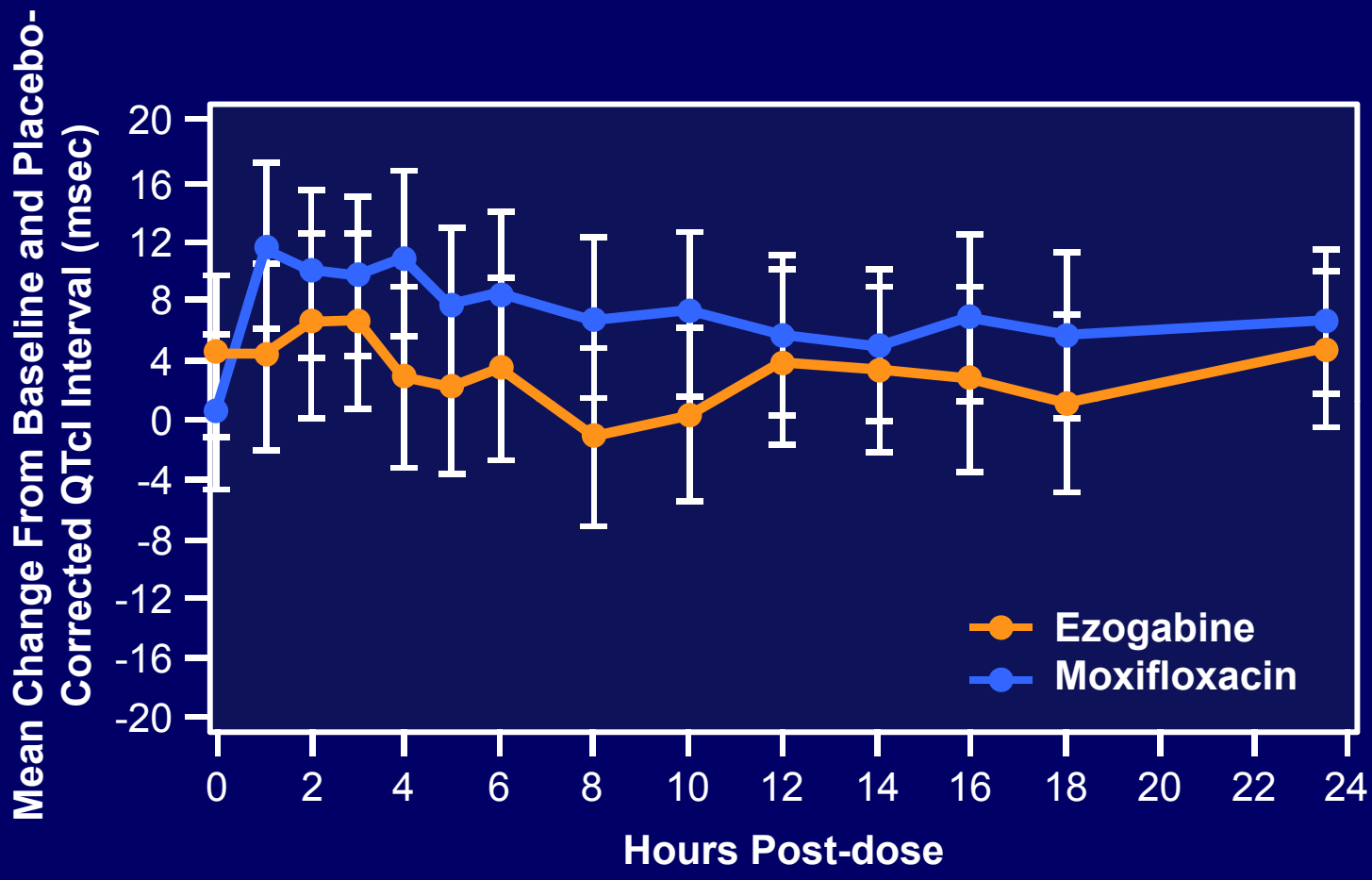
Thorough QT Study Conducted in Healthy Volunteers

- 40 subjects per arm
  - Placebo arm
  - Moxifloxacin as positive control
  - Ezogabine rapidly titrated to 1200mg
- High drop out rate due to lack of tolerability
  - 26 out of 40 completers
- Primary endpoint – aggregate of all patients at last completed dose

Primary Endpoint of the Study Did Not Demonstrate QTc Prolongation

- Analysis of the overall population did not demonstrate QTc prolongation
- The upper confidence interval crossed 10msec at one time point
  - 3 hours post dose

Transient QTc Prolongation



Completer analysis, 10msec crossed at three time points (1, 2 and 3h)

Note: Only subjects that are in “Completer” analysis population are included.
Data source: Study 103 CSR

No Cardiac Safety Signal from PCTs

- Placebo Controlled Trials
  - No significant cardiac AEs in PCTs
  - No clinically significant ECG changes
  - Cardiac AEs similar to placebo
  - 2 QT prolongation AEs on placebo, none on ezogabine
  - No Torsades de Pointes

No Consistent Pattern of Cardiac Arrhythmias From Non-Epilepsy Studies

- Non-epilepsy populations
  - 2 cardiac SAEs in abuse liability study (7 period cross over study; 36 subjects received at least one dose of drug)
  - Atrial Fibrillation was reported in 4/125 patients in a Post Herpetic Neuralgia (PHN) who received ezogabine and 0/62 who received placebo

Cardiac SAEs From Abuse Liability Study

Age	Sex	Study Rx	TTO	Comments	Discont.
36	F	Single dose EZG 900mg	~2 hrs	~25s period of asystole, spontaneous recovery. Baseline HR=44. Normal cardiology assessment, including stress echo before discharge.	Yes
41	M	Single dose EZG 900mg	~2.5 hrs	3 runs (longest 19 beats) of non-sustained asymptomatic ventricular tachycardia Normal ECG immediately after event	Yes

Atrial Fibrillation (AF) Cases From Post-Herpetic Neuralgia Study

Age	Sex	Study Rx	TTO	Comments	Discont. Due to AF	SAE
73	F	EZG 450mg	22	History of hypertension, Started amlodipine 1 week prior to onset.	Yes	Yes
77	M	EZG 450mg	16	C. diff colitis. Developed AF, congestive cardiac failure, pneumonia and pulmonary embolus.	No [a]	No [b]
84	M	EZG 600mg	~25	2 weeks of symptoms. Angiogram showed chronic total occlusion of LAD artery. Mild LVH	No [c]	No
84	F	EZG 600mg	23	History of diabetes. AF associated with cardiomegaly on CXR, spontaneously converted to sinus rhythm. Minimal LVH	No	No

a Patient discontinued due to SAE of C. diff colitis
b In relation to the diagnosis of AF
c Patient discontinued prior to Visit 4 without informing the site (reason unknown)

Low Potential of Ezogabine to Cause Cardiac Effects

- The potential effect of ezogabine on QT prolongation is likely to be small
  - Should not have important clinical significance except in patients who are at highest risk
- Adverse event reports of arrhythmia in the post herpetic neuralgia study were confounded by underlying conditions

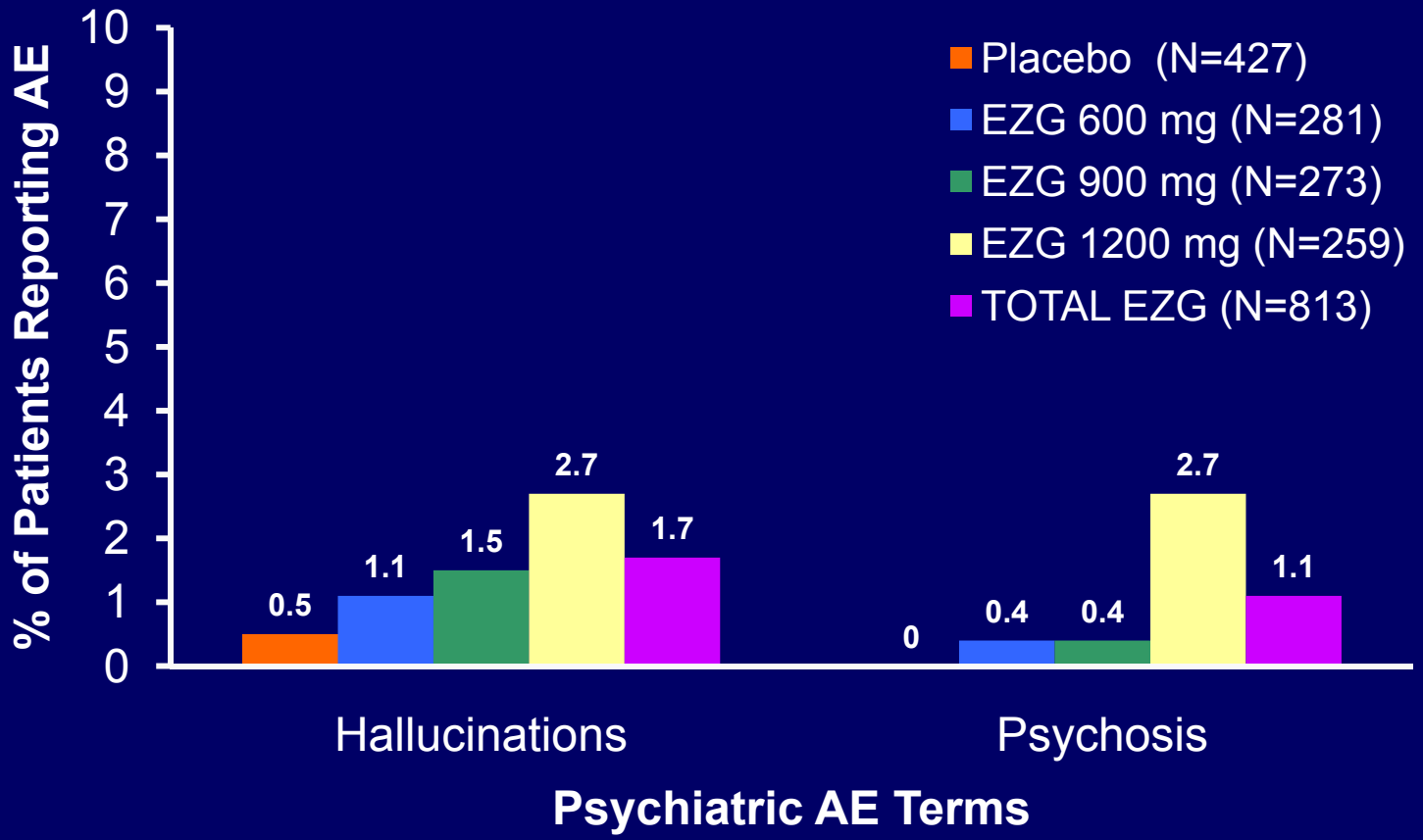
Psychotic Events Were Infrequent and Often Occurred With Seizures

- Psychiatric co-morbidities are common in epilepsy*
- In the PCTs, AEs occurred:
  - Early in treatment: 19 out of 32 reports during titration
  - Across the dose range, with evidence of a dose response
  - Seizures complicated some cases

*Gaitatzis et al. The Psychiatric Co morbidity of Epilepsy. Acta Neurol Scand 2004: 110: 207–220

Hallucination and Psychosis AEs Occurred More Commonly With Ezogabine (PCT Population)

Percentage of Patients Reporting Combined Hallucination and Psychosis AEs



PCT Safety Population

Effects on Liver Function

Non-Clinical

- No evidence of direct liver injury
  - Gall bladder distension seen in dogs
- Interference with billirubin assay

PCTs

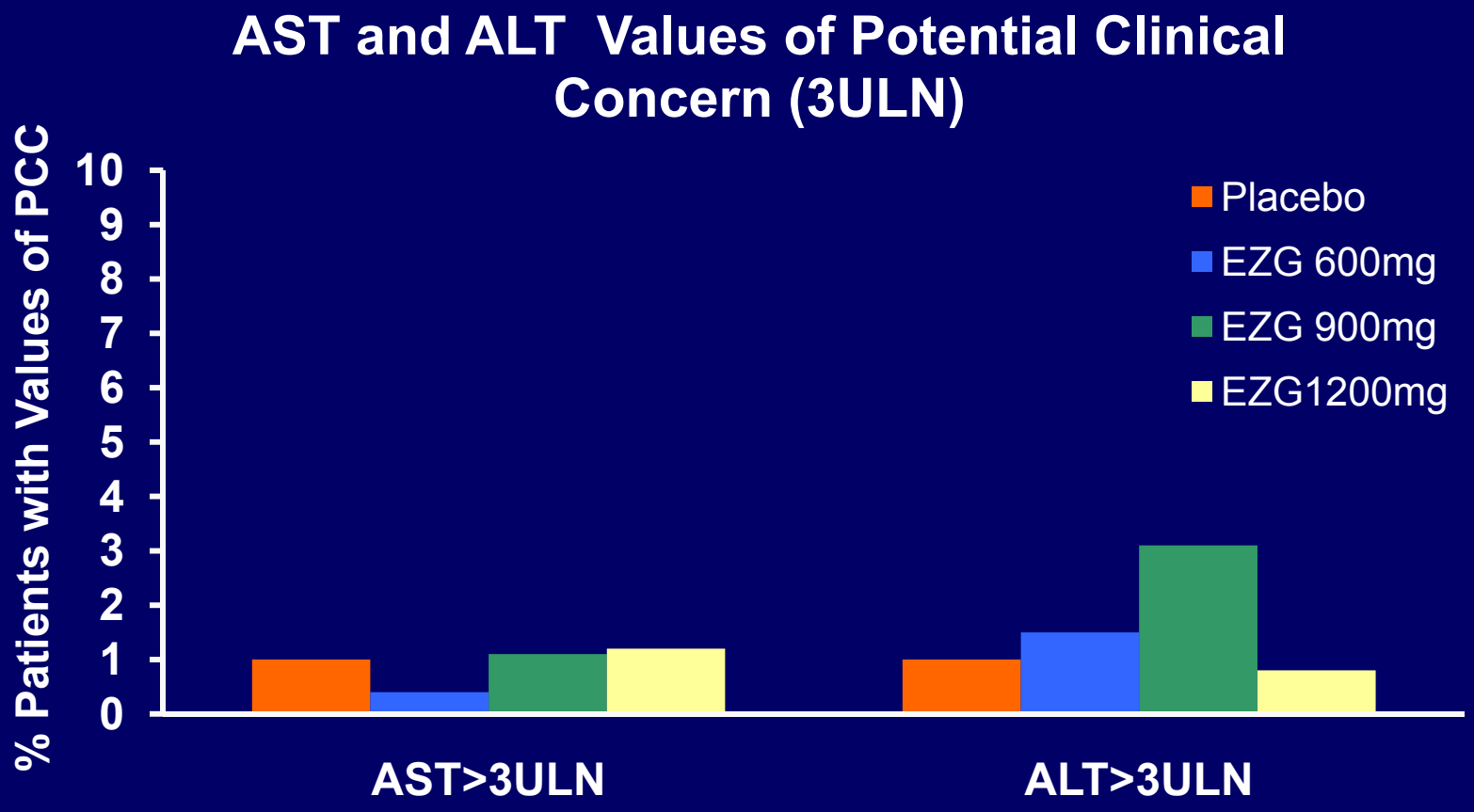
- 5 patients withdrew due to abnormal LFTs
  - 1 placebo, 4 ezogabine

Phase II/III Population

- 9/1365 patients withdrew due to abnormal LFTs

No cases met Hy's Law

Changes Were Seen in Liver Function Tests (PCT population)



PCT Safety Population

Summary/Conclusion

- CNS adverse events are the most common and consistent with other AEDs
  - Generally dose related: occurred early in treatment
- Urinary adverse events were uncommon
  - Most patients able to continue on medication
  - Apart from one case, all resolved after discontinuation
  - Can be managed in clinician-patient relationship
- Low potential for cardiac effects including QT prolongation
- Events relating to LFTs were uncommon
  - Resolved after discontinuation

Proposed Risk Management Plan

Susan T. Hall, PhD

Potential Risks of Interest

- Urinary retention
- Cardiac effects including QT prolongation
- Neuropsychiatric symptoms
- Liver function effects

Use of Ezogabine

- The prescriber should consider the potential effects on the bladder when deciding for whom the drug may be appropriate
- Ezogabine should be used with caution in:
  - Patients on concomitant medicines that impair bladder function (e.g., anticholinergics)
  - Patients with pre-existing risk for urinary dysfunction (e.g., BPH, neurogenic bladder)
  - Patients not able to communicate symptoms of urinary retention (e.g., cognitively impaired)

Risk Management Goals for Urinary Retention

- Communication of the risk of urinary retention to healthcare professionals, patients and caregivers
- Identification and prompt medical management should urinary retention occur
- Post marketing risk assessment of urinary retention through enhanced pharmacovigilance and a proposed observational study

Information and Educational Materials for Healthcare Providers

- Introductory letter to health care providers (HCP) highlighting the potential risks
  - e.g. epileptologists, neurologists, emergency room physicians, and pharmacists
- Company-sponsored ezogabine website
- Toll free response center
- Scientific communication

Information and Education for Patients and Caregivers

- A patient information packet to facilitate discussion between patient and HCP
  - Patient education brochure
  - Copy of the Medication Guide
  - Clear instructions on when to seek help
  - Medication alert card
- Medication Guide attached to each unit of use bottle and samples distributed to HCPs
- Company-sponsored ezogabine website
- Toll-free response center

Medication Guide: Current Draft Language for Urinary Retention

- POTIGA [ezogabine] can make it hard to urinate (empty your bladder) and could lead to your being unable to urinate. Call your healthcare provider right away if you:
  - Are unable to start urinating
  - Have trouble emptying your bladder
  - Have a weak urine stream
  - Or if you have pain with urination

Pharmacovigilance for Potential Safety Signals with Ezogabine

- Signal Detection
- Robust pharmacovigilance
  - Online Signal Management tool
  - SÆfetyWorks™ for data mining observational databases
- Review AEs monthly
- Actively investigate potential associations
  - e.g., abuse, overdose, age, drug interactions

Pharmacovigilance for Potential Safety Signals with Ezogabine

- Enhanced collection of safety information
  - Targeted follow up questionnaire for spontaneous AEs related to urinary events
  - eCRF page for urinary retention AEs in clinical trials
- Regular urinary retention reviews reported quarterly for 3 years and periodically thereafter

Targeted Follow Up of Urinary Retention AEs (Draft instrument)

Targeted Follow Up Questionnaire

EZOGABINE AND URINARY RETENTION

Patient/subject ID, DOB/initials: **Sex/weight (is patient obese if weight unknown):** **OCEANS CASE No:**

Description of the Event:	**Yes**	**No**
Prior to the event did the patient report any of the following?		
1. Dysuria	☐	☐
2. Urinary hesitation	☐	☐
3. Poor urinary stream	☐	☐
4. Nocturia	☐	☐
Was the event associated with?		
1. Urinary tract infection	☐	☐
2. Any change in background medication	☐	☐

Medical History	**Yes**	**No**
Does the patient have a history of any of the following conditions?		
1. Benign prostatic hypertrophy	☐	☐
2. Any other disorder associated with bladder outflow obstruction	☐	☐
3. Condition with potential bladder dysfunction, for example multiple sclerosis, diabetes	☐	☐
4. Renal calculi	☐	☐
If *yes*, please describe:		

Medication History	**Yes**	**No**
Has the patient take any of the following medicines prior the event?		
1. Anticholinergic drugs for detrusor instability, for example tolterodine.	☐	☐
2. Other drugs with anticholinergic properties, for example:	☐	☐
a. Amitriptyline	☐	☐
b. Loperamide	☐	☐
c. Chlorpheniramine	☐	☐
3. Sympathomimetic drugs, for example pseudoephidrine	☐	☐

Diagnostic Tests:	**Yes**	**No**
Please provide a summary of main results of abnormal laboratory values / investigations (or provide copies of relevant results):		
Were urea and electrolytes measured? If *yes*, please indicate dates and results:	☐	☐
Was a renal ultrasound performed? If yes, please describe result (or attach a copy of the report)	☐	☐

Outcome:	**Yes**	**No**
1. Did the patient require urinary bladder catheterisation?	☐	☐
2. Has the patient discontinued therapy with ezogabine?	☐	☐
3. Has bladder function returned to normal?	☐	☐
4. If continuing with ezogabine, are there ongoing urinary symptoms. If so please describe:	☐	☐

Proposed Study: Rate of Urinary Retention with Add-on AED Exposure in a Health Care Database

- **Aim:** Quantify urinary retention rate in epilepsy patients after add-on (EZG vs non-EZG)
- **Study Population:** Treated epilepsy patients in WellPoint Health Plans (estimated n ~ 100,000)
- **Prospective Study Cohorts**
  - EZG added to existing AED regimen
  - Non-EZG AED added to existing AED regimen
- **Outcome Definition:** Urinary retention and catheterization codes, confirmed by medical record review

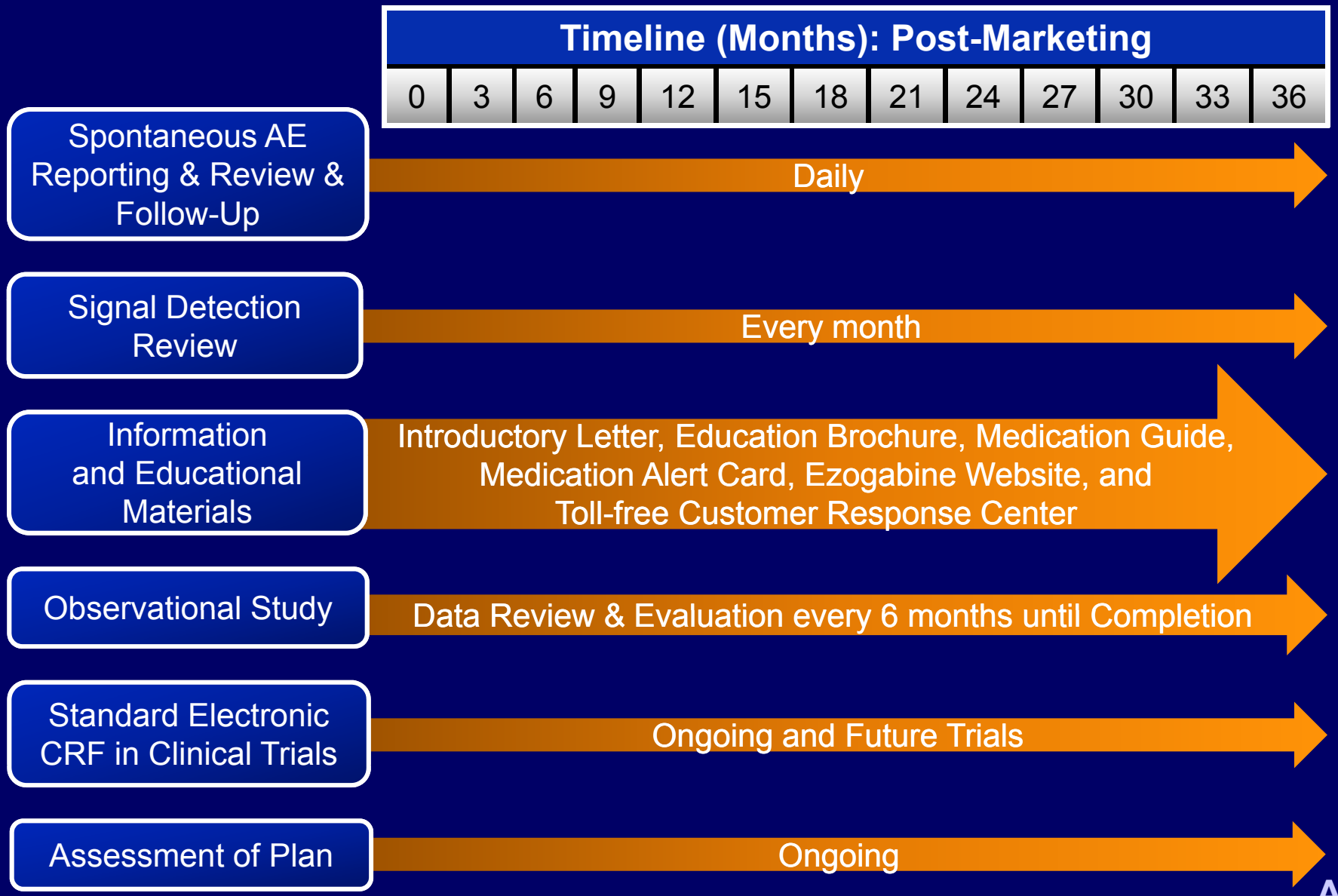
Proposed Study: Rate of Urinary Retention with Add-on AED Exposure in a Health Care Database

- **Primary Results:** Urinary retention Incidence overall and in subgroups every 6 months
  - Age (< 65 y, ≥ 65 y)
  - Sex
  - Co-morbid conditions associated with UR
  - Co-medications associated with UR
  - Other at risk subgroups (dementia, mental retardation)
- **Secondary Analysis:** Inferential analysis of EZG vs non-EZG

Risk Management Plan: Evaluation of Effectiveness

- Assessment of patient understanding of the Medication Guide
- Assessment of healthcare practitioners' knowledge of potential risks
- Assessment of postmarketing adverse events of interest

Pharmacovigilance: Urinary Retention



Summary of Risk Management Activities

- Comprehensive communication and education program for health care providers, patients, and caregivers
- Post-marketing risk assessment with enhanced pharmacovigilance
- Observational study to quantify real-world risk for urinary retention
- Assessment of RMP activities and updating of the RMP as needed

Benefit:Risk Summary

Susan T. Hall, PhD

Benefit

- Nearly one third of adult patients continue to have seizures despite treatment
- Ezogabine has a unique pharmacologic profile and offers an important new therapeutic option
- Efficacy has been demonstrated
  - Across the dose range of 600 to 1200 mg/day
  - In a patient population where 75% received ≥ 2 AEDs
  - Regardless of number or type AED
- Efficacy maintained in 3 open-label extension trials

Risks

- Common Adverse Events are CNS related and similar to other AEDs
- Potential risks that merit special attention:
  - Urinary retention
  - QT prolongation and arrhythmia
  - Psychosis and hallucinations
  - Liver function effects

Benefit:Risk Summary

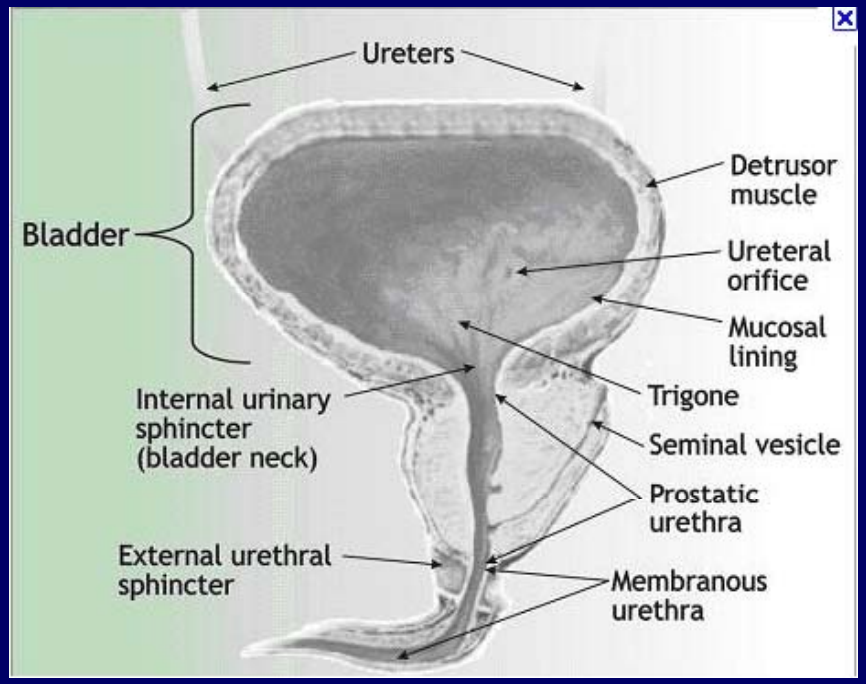
- Ezogabine has a favorable benefit:risk profile for adjunctive treatment of partial onset seizures in adult patients
- The proposed risk management plan will facilitate the safe and effective use of ezogabine

Urinary Tract Safety Assessment

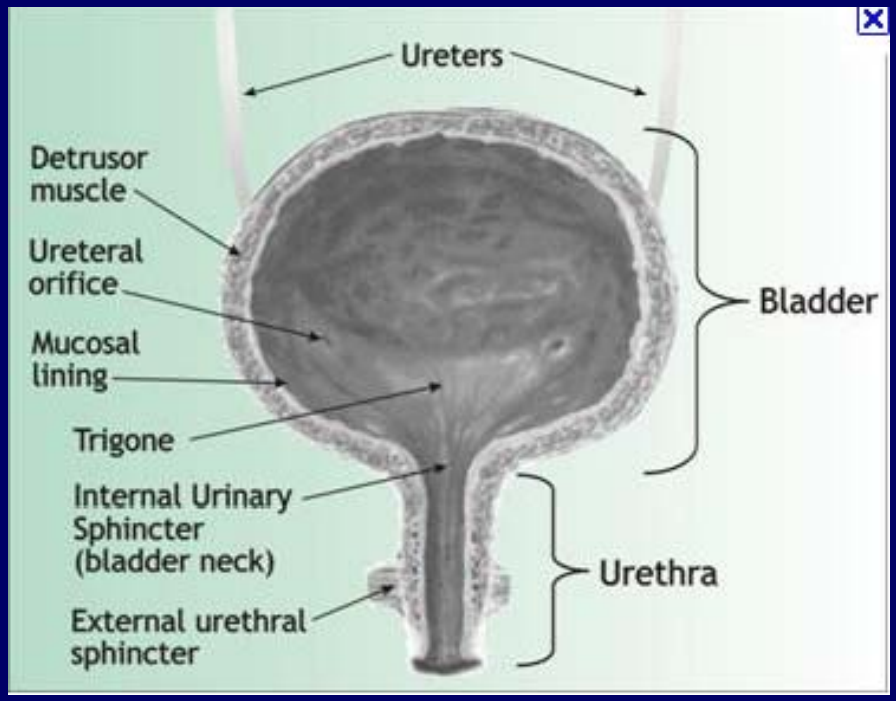
Claus G. Roehrborn, M.D.
Professor and Chairman
Department of Urology
UT Southwestern Medical Center at Dallas

Pathophysiology of Urinary Retention

Male

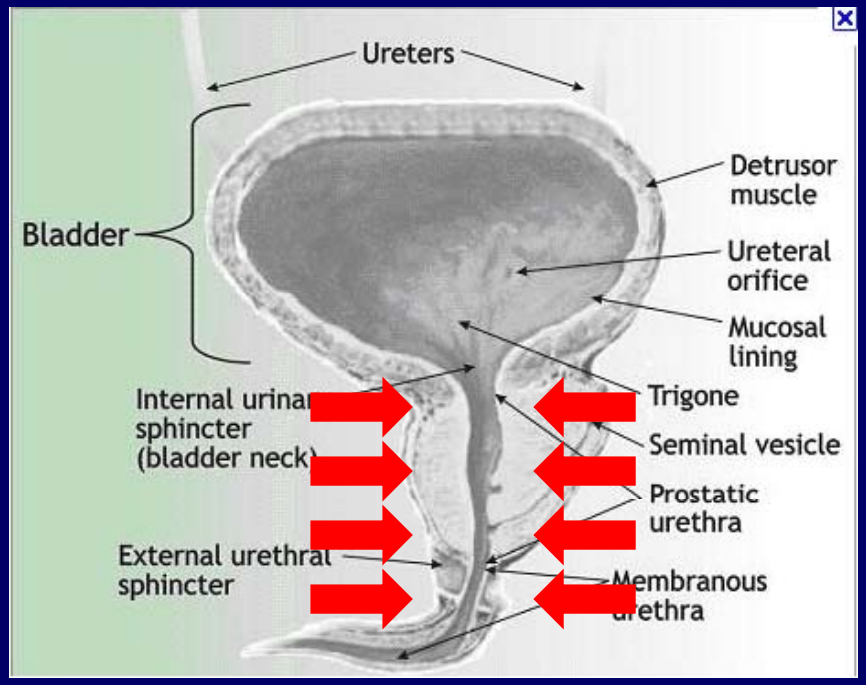


Female



Pathophysiology of Urinary Retention

Male



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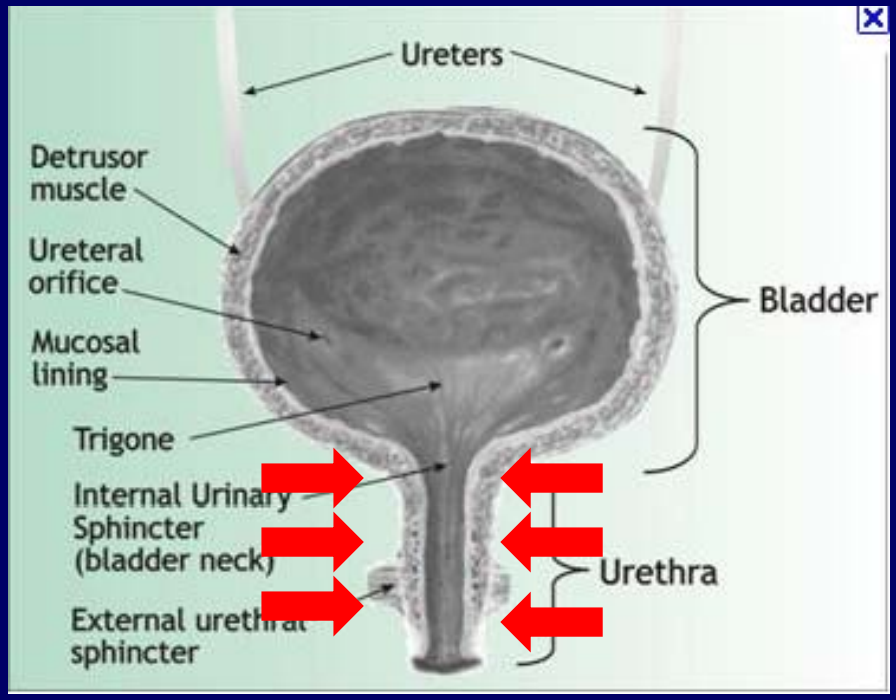
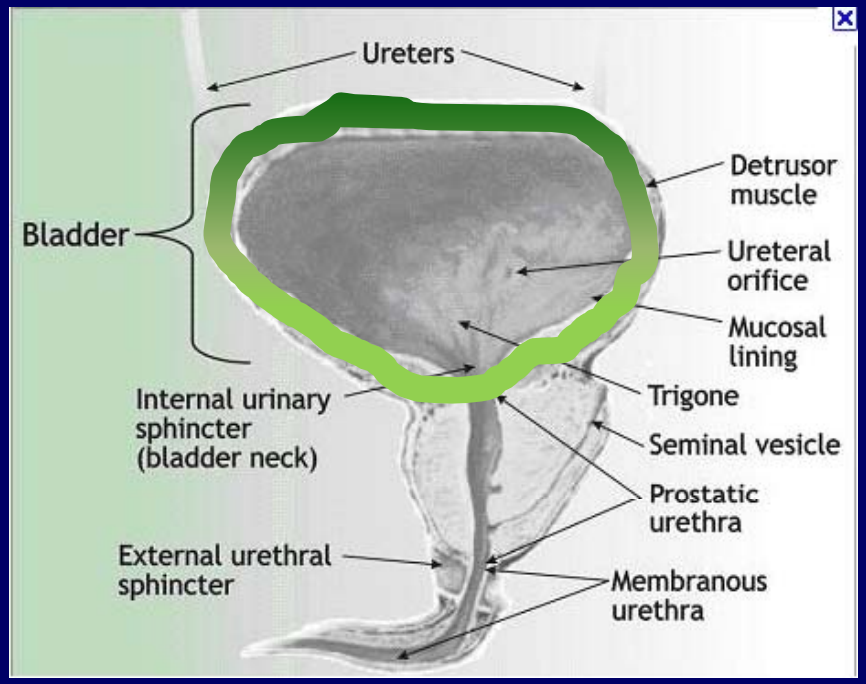


Pathophysiology of Urinary Retention

Male



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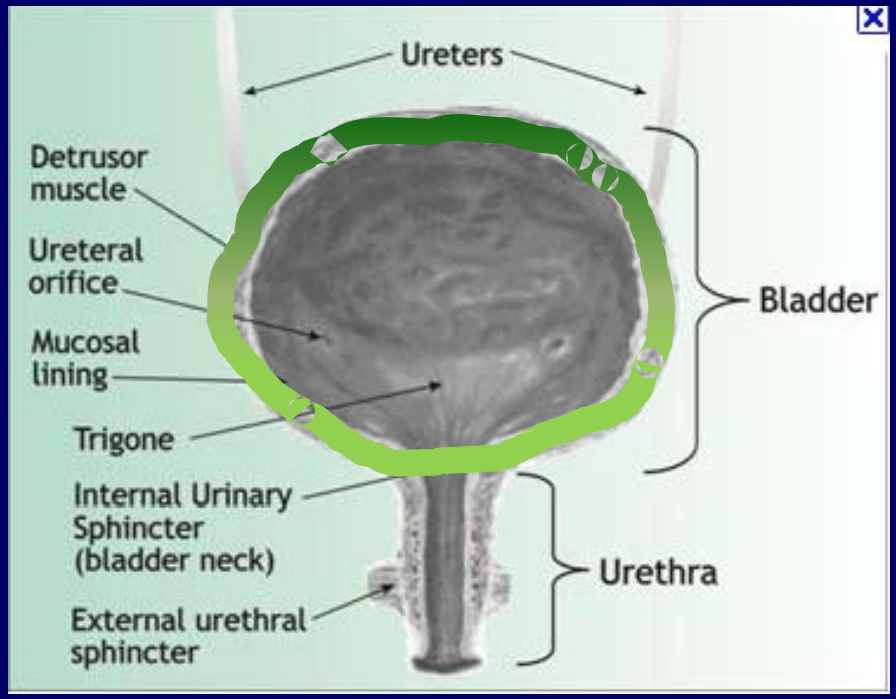


Definition of "Urinary Retention"

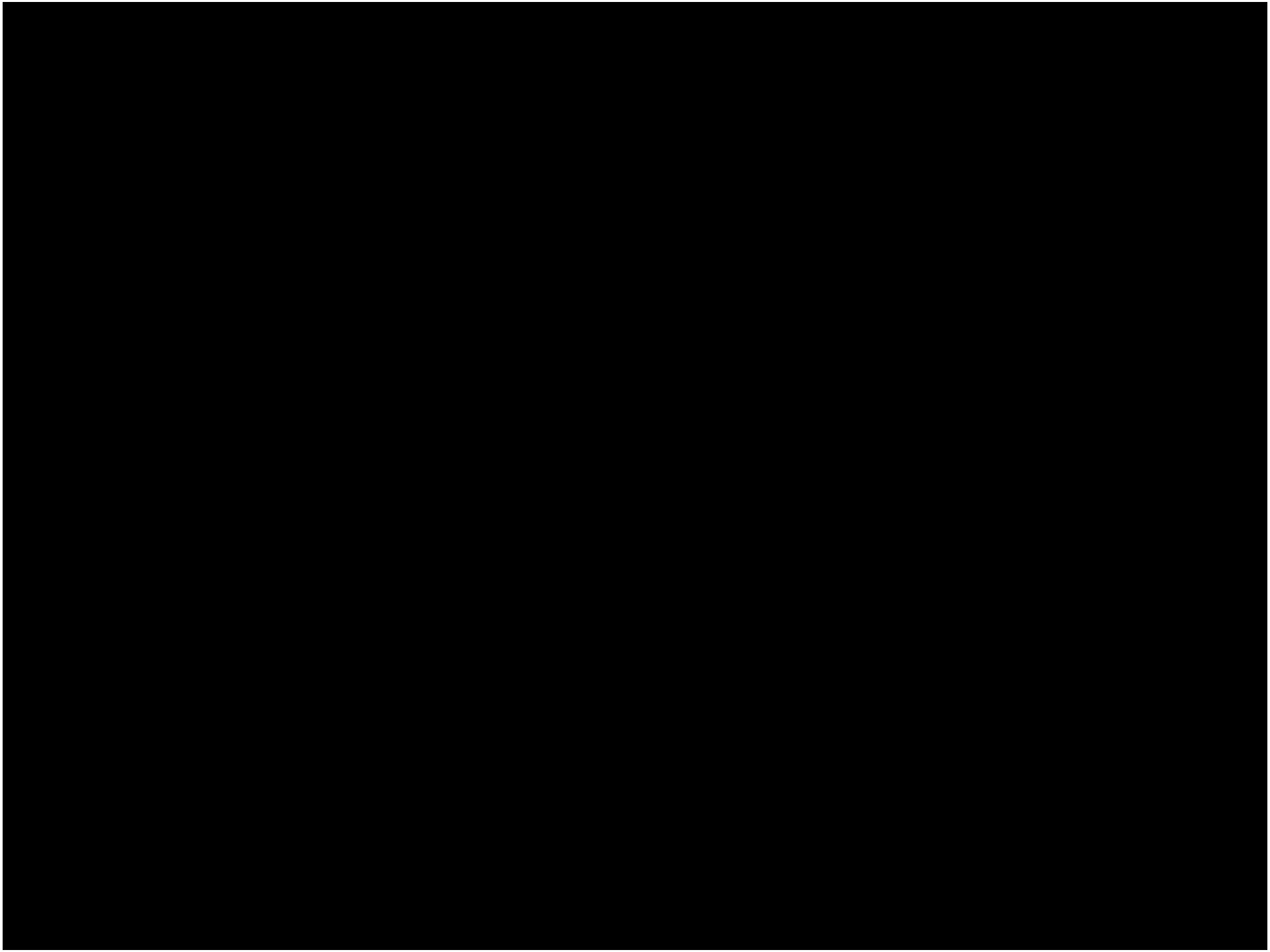
- Urinary Retention refers to a wide range of conditions:
  - Acute urinary retention – a "total" inability to urinate at all
  - Chronic urinary retention - which refers to a "partial" retention of urine in the bladder after voiding
    - Postvoid residual or PVR refers to the measurement of retained urine independent of type of urinary retention
- Only total urinary retention is of immediate consequence as it requires drainage by intermittent or continuous catheterization

General Principles for Management of Total Urinary Retention

- Requires:
  - Drainage by intermittent or temporary indwelling catheter
  - Address the underlying cause
- Most cases of Total Urinary Retention are reversible
  - Trial without catheter (TWOC) succeeds in nearly all cases with identifiable underlying cause

Consequences of Total Urinary Retention

- Prolonged unrecognized Total Retention may result in
  - Bladder overdistension
  - Secondary hydroureteronephrosis
  - Reduction in renal blood flow and GFR
  - Azotemia / uremia
- All of these events are reversible provided the retention episode is resolved with timely management

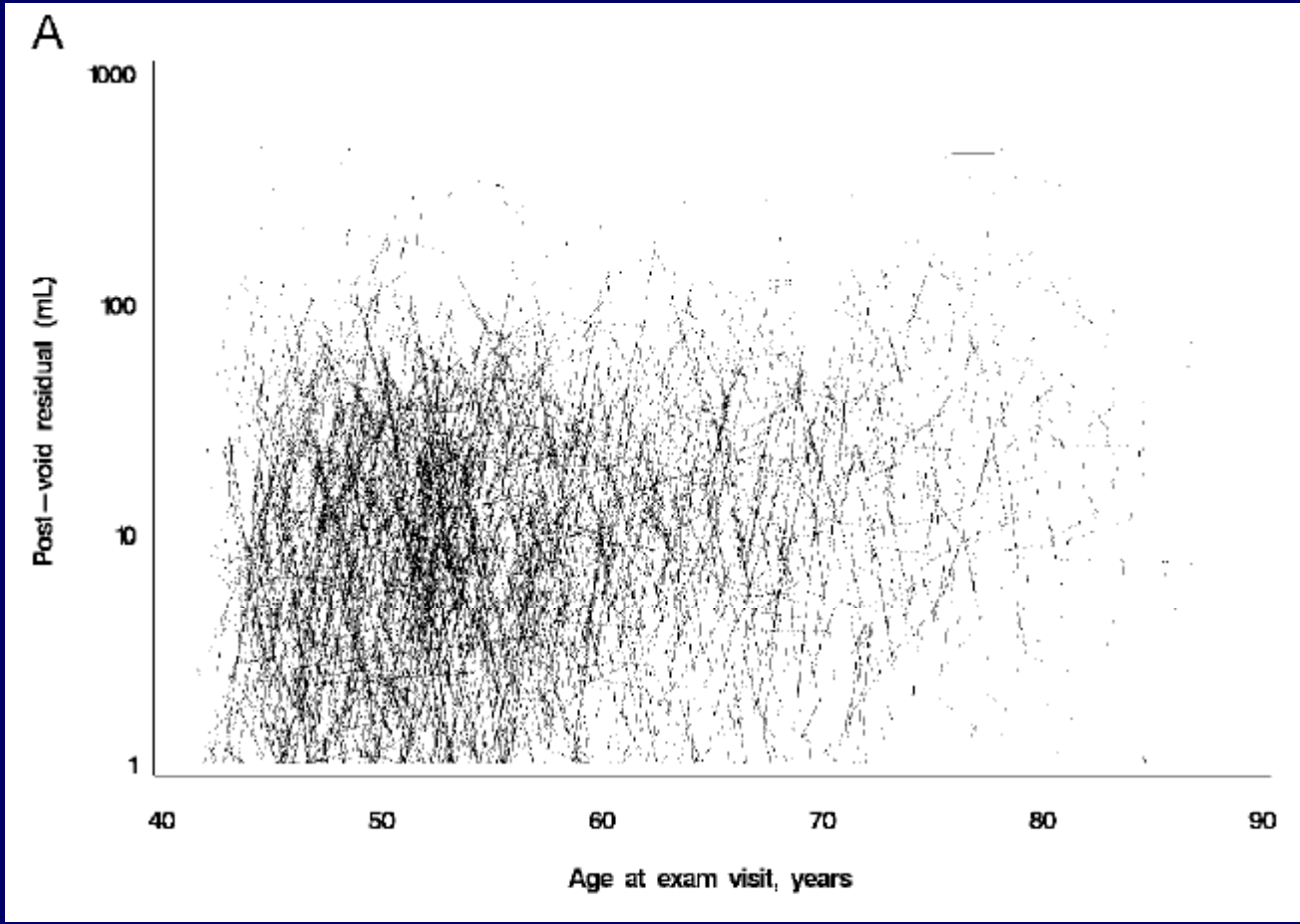


Large Within-Subject Variability of Partial Retention Volumes

The association between benign prostatic hyperplasia and chronic kidney disease in community-dwelling men

Plot of observed post-void residuals showing variability.

Each line represents individual subject with age



Rule et al : J Urol Vol. 174, 1317–1322, October 2005

Monitoring PVR Values is *Not* Predictive of Progression to Total Urinary Retention

- No documented progression of PVR values
  - Low to high
  - Low *or* high to acute urinary retention
- No accepted PVR thresholds in men or women
  - To predict imminent acute urinary retention
  - To indicate the need for therapeutic intervention
- PVR measurements optional even in those presumably at increased risk for total urinary retention
  - Lower urinary tract symptoms
  - Men with BPH

Summary

- "Urinary retention" refers to a range of conditions
- Total urinary retention
  - Requires therapeutic intervention
  - Cannot be predicted by PVR or AUA-SI monitoring
  - Generally reversible with timely treatment
- The sponsor's proposed risk management plan should be sufficient to minimize risk of urinary retention

Epilepsy: A Clinician's Perspective

Jacqueline A. French, MD
NYU Comprehensive Epilepsy Center

New Therapies Needed for Aggressive, Drug-Resistant Epilepsy

- *"Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom."*
  - No seizure frequency requirement

Kwan et al. Epilepsia 2010; 51:1067-1077

Penn Study Demographics

- "Aggressive" epilepsy – interferes with daily life on a regular basis
- 246 out of 3224 patients had aggressive, drug-resistant epilepsy

Male/Female	41%/59%
Mean age	40
Syndrome	
Partial epilepsy	81%
Generalized epilepsy	
Symptomatic generalized	11%
Primary generalized	7%
Duration of epilepsy (years)	25
Duration of intractability (years)	20

Consequences of Uncontrolled Seizures

- Shortened lifespan
  - Sudden unexplained death in epilepsy (SUDEP)
- Bodily injury, hospitalization
  - Status epilepticus
- Neuropsychological and psychiatric impairment
  - Depression
  - Reduced quality of life
- Social disability
  - Reduced employment
  - Reduced marriage rates

Current Options for Patients with Treatment-resistant Epilepsy

- 17 AEDs currently marketed
- Devices
- Epilepsy surgery evaluation
- Doing nothing

Serious Adverse Reactions with Current AEDs

- Carbamazepine
  - Aplastic anemia, hepatic failure, delayed hypersensitivity (TEN, SJS)
- Valproate
  - Hepatic failure, pancreatitis
- Lamotrigine
  - Delayed hypersensitivity
- Felbamate
  - Aplastic anemia, hepatic failure

SUDEP in Adjunctive Randomized Controlled Trials

Trials arms	Add-on AEDs	Placebo
Patient-years	2554	1879
# SUDEP*	2	12
	.08%/year	.64%/year

*p-value = 0.03

Ryvlin et al, Epilepsia 2009;50(Suppl 11):223.

Penn Study Follow Up – 10% Fatality Rate After 6 Years

- 24 of 246 patients died over 6 years observation
- Case fatality rate- 9.8% for this intractable cohort or an average of 1.5% per year
- Median age of death was 53

Risk vs Benefit Must be Assessed by Individual Patient

- AED benefits can take many forms
  - Decrease in seizure frequency, severity, timing, duration, etc.
  - Most not measurable, thus not captured in clinical trials
  - Commonly associated with improved seizure control

Clinician's Dilemma and Need for More Treatment Options

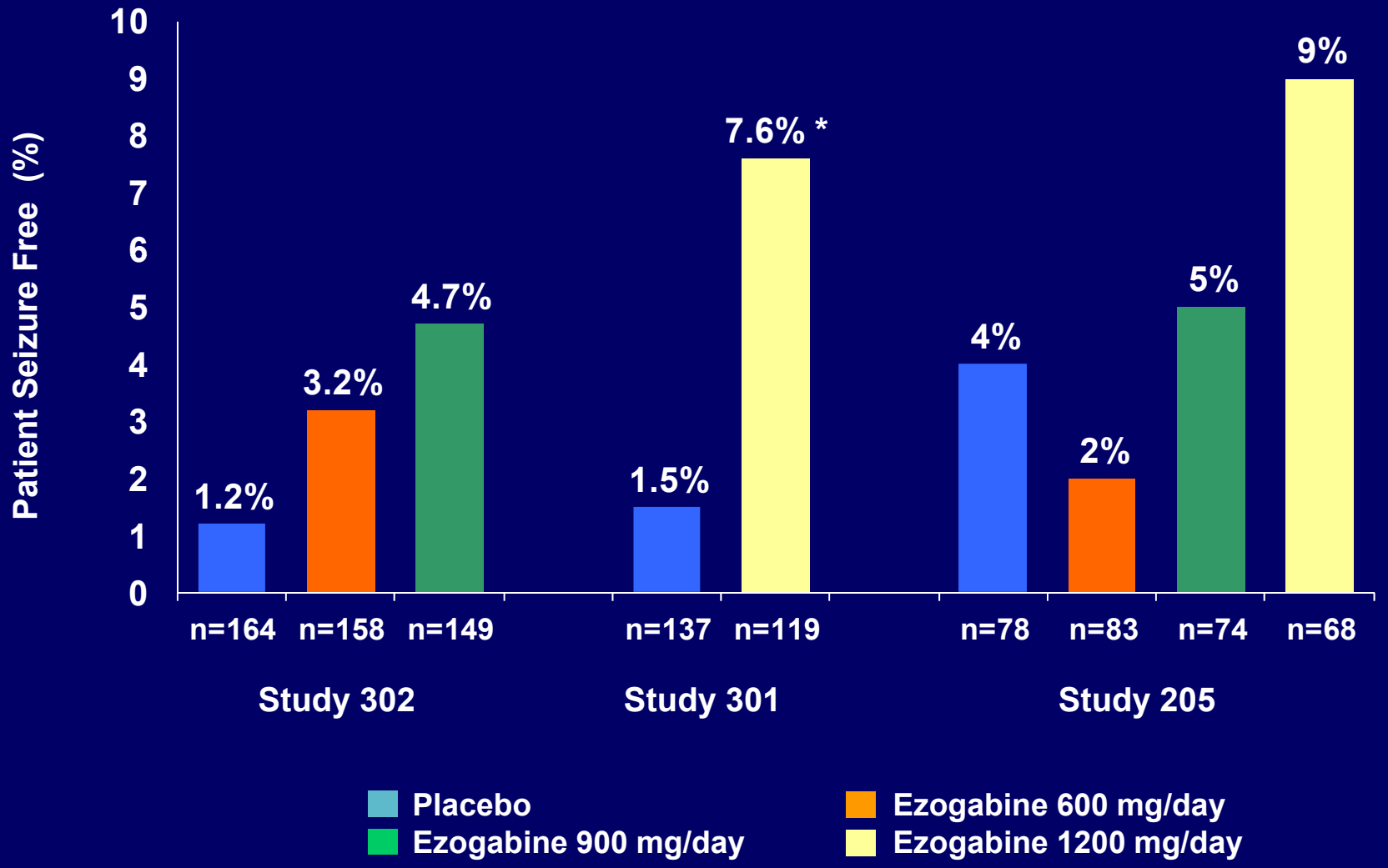
- No way to predict likely successful therapy
- Many AEDs necessary to search for individual improvements over time
- Patients need access to drugs with multiple pharmacologic MOAs

Conclusions

- All AED therapies have risks
- Risks of ezogabine are well within those accepted in a population of patients with partial onset seizures requiring adjunctive therapy
- Physicians can educate patients regarding benefit/risk of adverse event, and can manage them should they occur
- Clinicians and patients need access to as many therapies as possible to treat their epilepsy

BACKUPS

Percentage of Seizure Free Patients: Maintenance Phase Population by Study



*p < 0.05 vs placebo, Fisher's Exact Test

Estimated Median Monthly (number) Seizure Reduction and Incremental Improvement

	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day
Study 205	1.1	2.0	2.3	3.7
Study 302	1.5	2.7	4.1	-
Study 301	2.0	-	-	5.4

Calculated as BASELINE MEDIAN * median reduction (derived from Table 8 Valeant Briefing Document)

% Incremental effect from previous dose (derived from Table 8 Valeant Briefing Document)

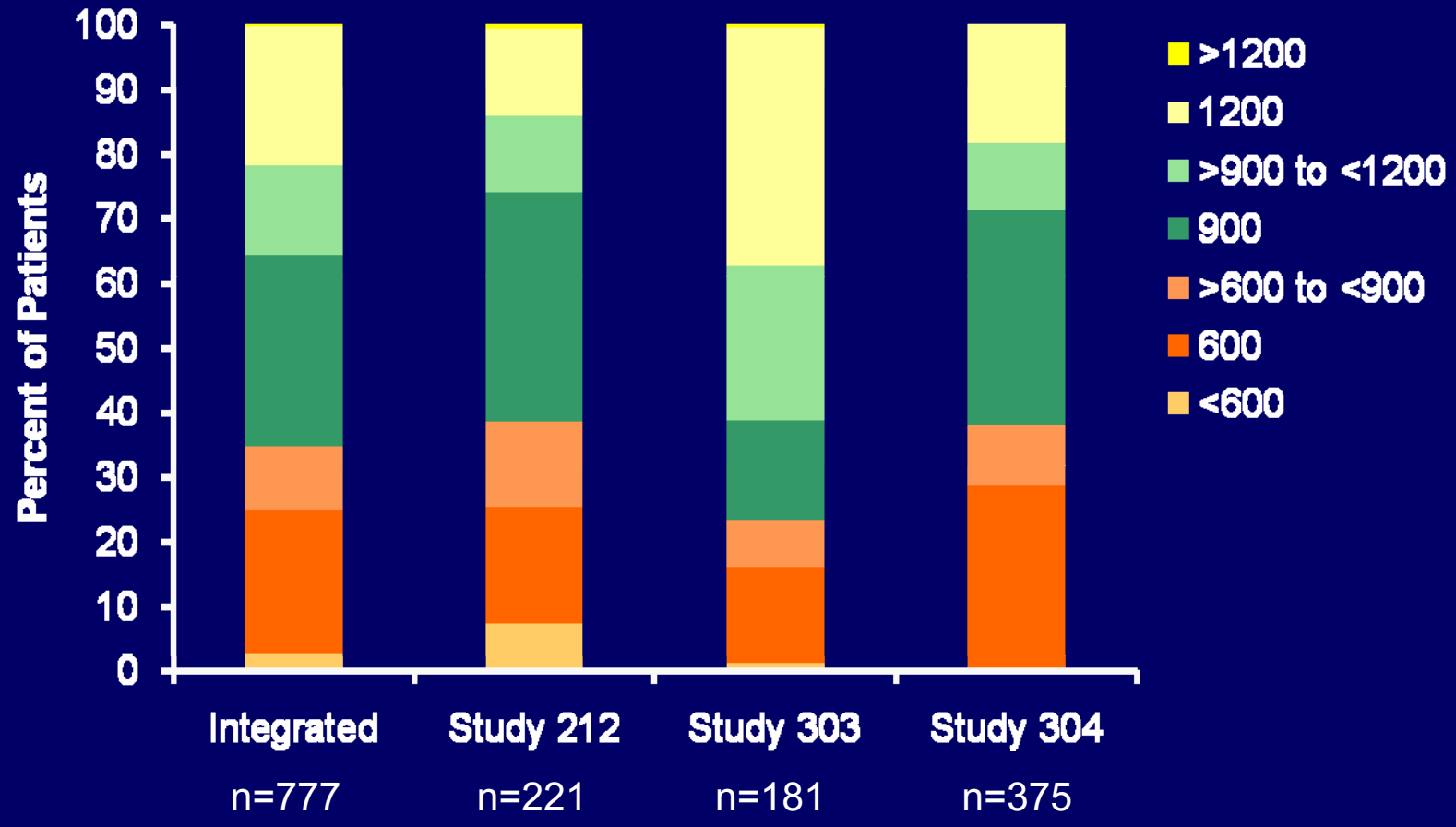
Incremental Improvement in Median % Reduction in Seizure Frequency

	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day
		A*	B*	C†
Incremental Improvement	**-**	**85%**	**42%**	**20%**

% Incremental improvement from previous dose calculated across studies with common adjacent doses (derived from Table 8 Valeant Briefing Document and Table 2.1 in the Integrated Summary of Efficacy)

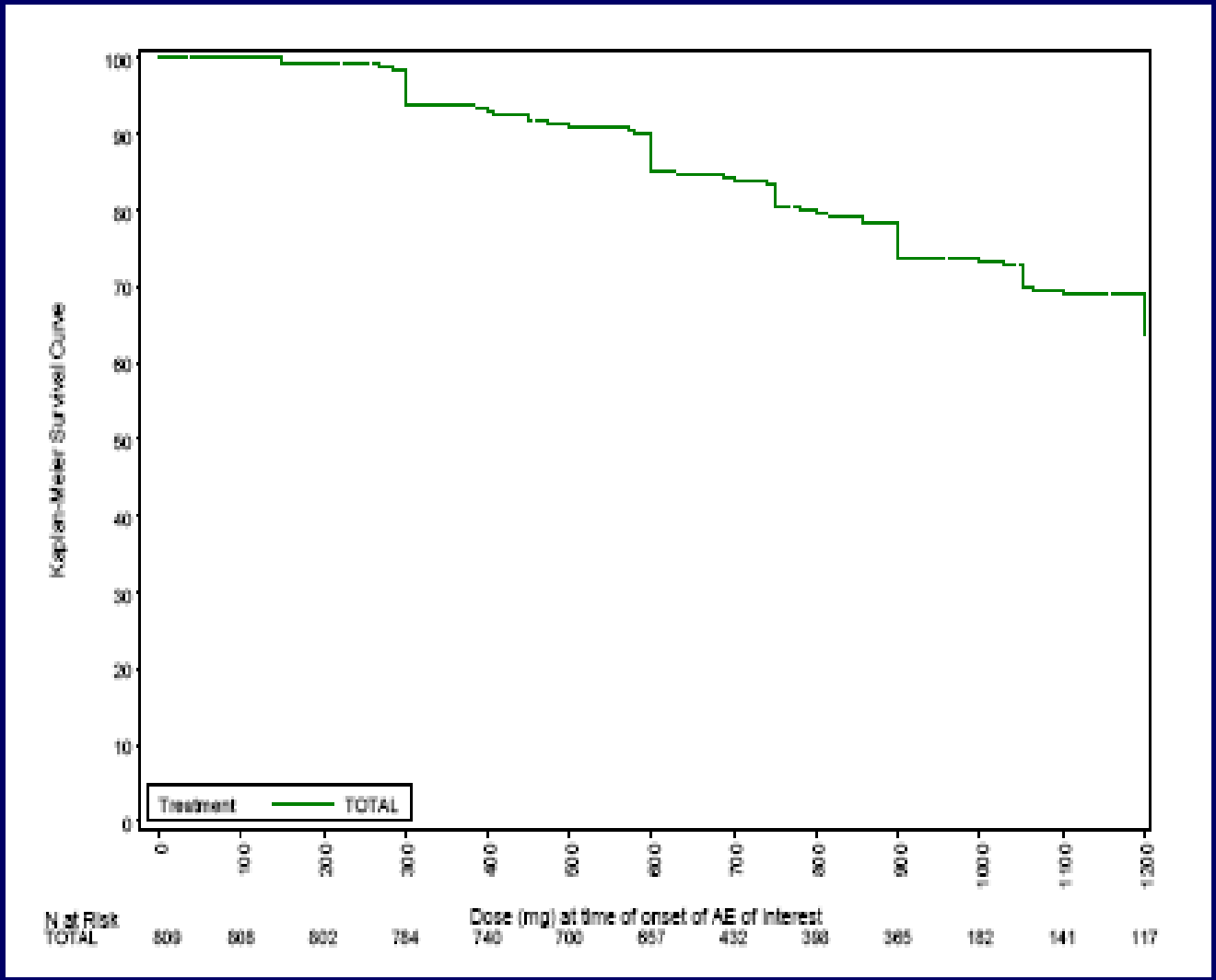
* Includes Study 205 and 302
† Includes Study 205

Summary of Prescribed Ezogabine Dose in the Open-Label Extension Studies (Integrated and by Study) (New Analysis)



Prescribed dose prior to taper phase or at last visit prior to October 2, 2009 data cut-off.

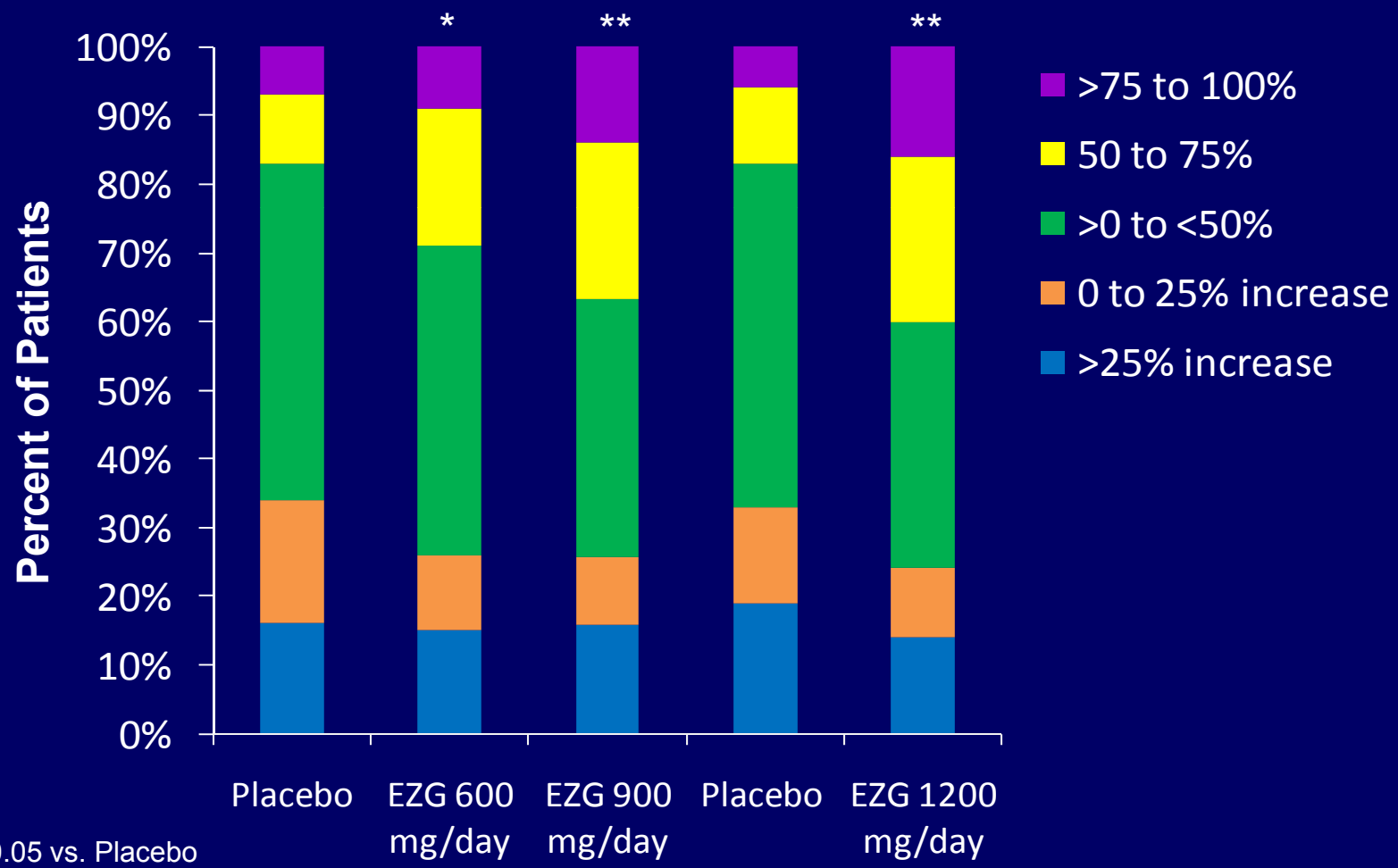
Dose to Onset of AEs Leading to Withdrawal



KM estimates:
600mg: 85%
900mg: 74%
1200mg: 64%

Incremental risk:
600→900mg: 11.5%
900 →1200mg: 9.7%

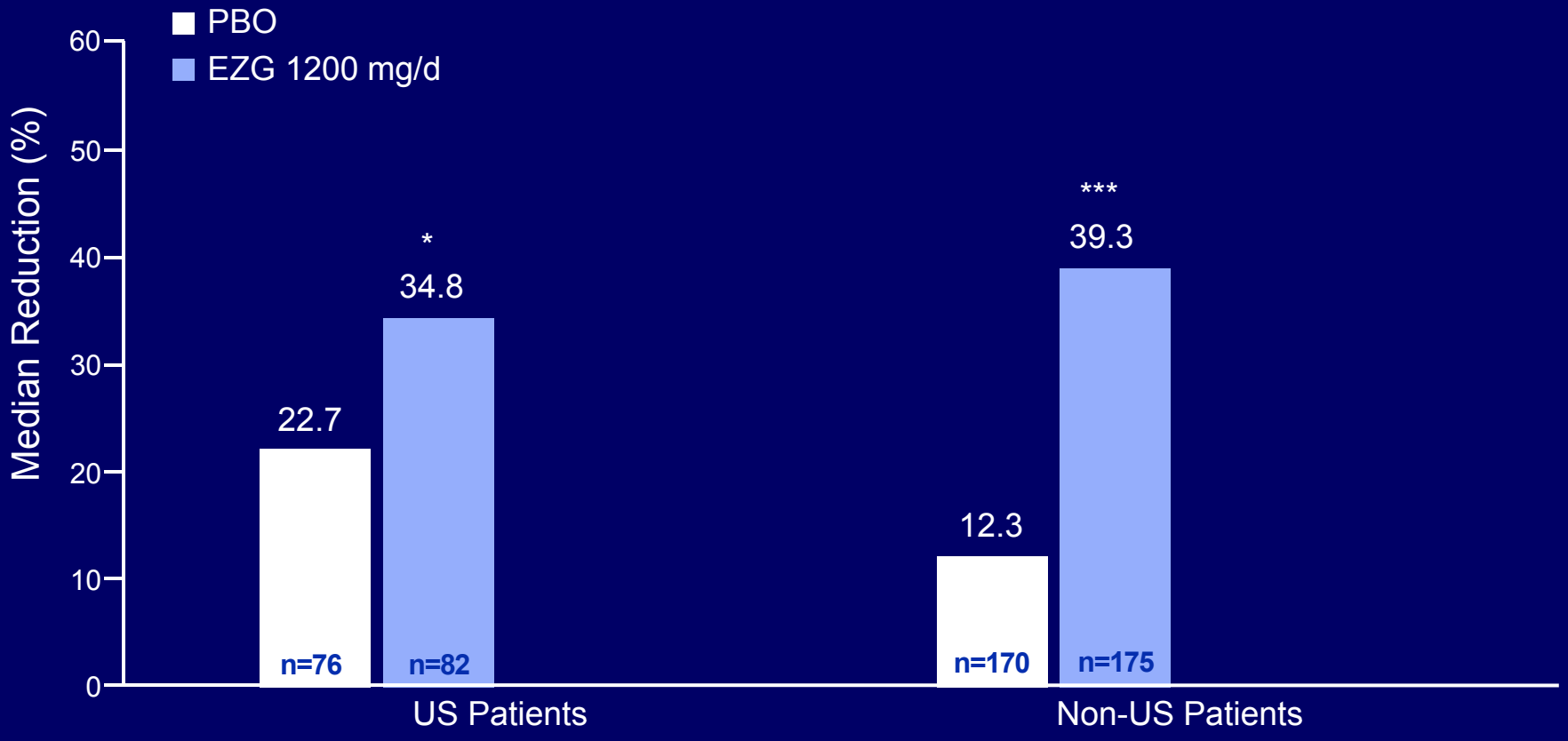
Percent Change in 28-Day Total Partial Seizure Frequency by Category (Double-Blind Phase) – ITT Double-Blind Population: Integrated Data from Studies 205, 301 and 302



* p<0.05 vs. Placebo
** p<0.01 vs. Placebo

Efficacy by US vs. non-US: Median Percent Reduction in Seizure Frequency per 28 Days: Double Blind Phase (1200 mg vs. Placebo)

Integrated Data from Studies 205 and 301



Treatment by region (US or Non-US) interaction comparison vs placebo: ezogabine 1200 mg/day vs placebo (p=0.303)

* p<0.05 vs. Placebo

*** p<0.001 vs. Placebo

Demographic and Baseline Characteristics by US and Non-US Subgroups in Pivotal Trials

- The disease burden was similar between US and Non-US subjects in the Pivotal Trials
  - Epilepsy duration
  - Median seizure frequency
  - Seizure subtypes
- Differences between the US and Non-US population in the Pivotal Trials
  - Weight (~10kg)
  - Older AEDs (carbamazepine and valproic acid) were used more frequently in Non-US than US
  - Both oxcarbazepine and levetiracetam were more frequently used in the US
  - However, the use of newer AEDs (topiramate and lamotrigine) was similar

Nephrolithiasis and Renal Colic

- 17 unique patients receiving exogabine experienced nephrolithiasis, renal colic and/or calculus ureteric
- 1 patient receiving placebo experienced renal colic

	Nephrolithiasis (and 1 calculus ureteric)	Renal Colic
Number of Patients[a]	11	7
Stone Confirmed	3	1
Visualization (lithotripsy, CT)	2 (212-000547, 301-00901)	1 (205-00125)
"Passed stone"	1 (301-00302)	0
No Confirmation	8	6

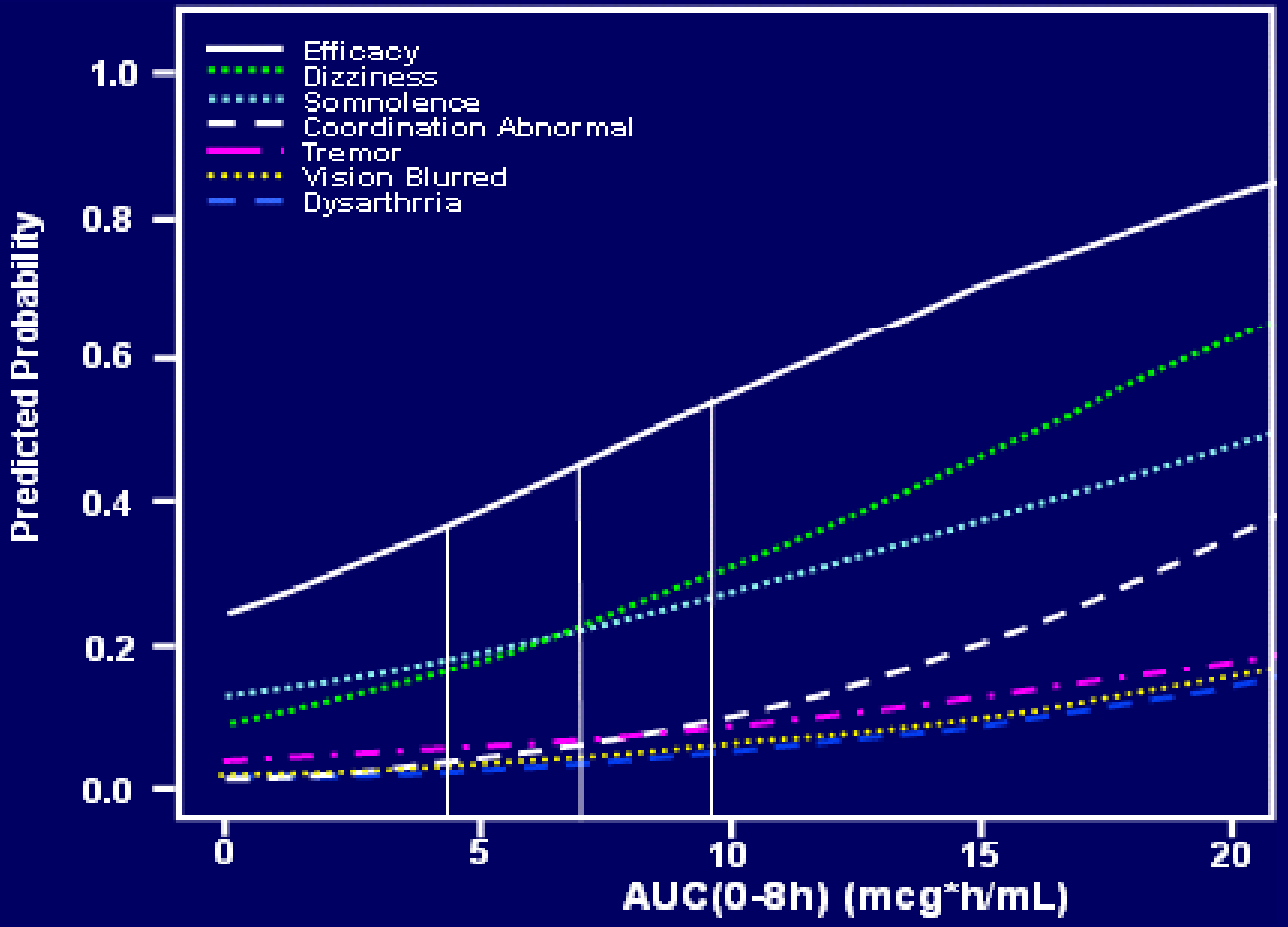
a. One patient reported both nephrolithiasis and renal colic (208-00013)

Anticholinergics and Urinary Retention

- Anticholinergic drugs were associated with cases of urinary retention and/or urinary hesitancy
  - In the Phase II/III group urinary retention and hesitation events were reported in:
    - 4/19 (21%) taking an anticholinergic
    - 114/1346 (8%) not taking an anticholinergic
- Caution is warranted in using anticholinergics with EZG

Retention/hesitancy terms combined
Numbers based on 2 Oct 09

PopPK/PD Modelling: Increases in Ezogabine Exposure Predict an Increase in Probability of Efficacy and AE

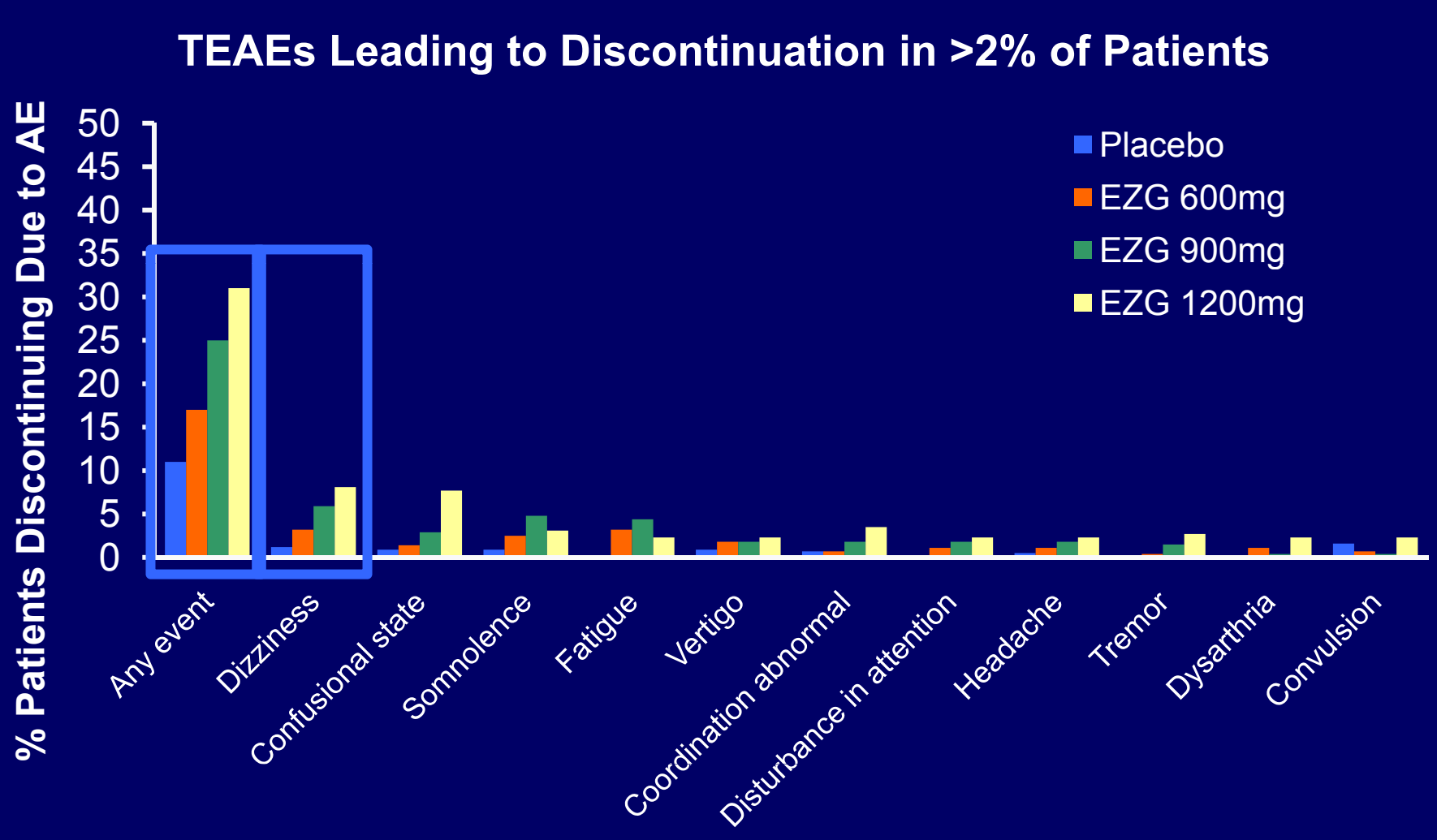


*Efficacy based on a patient having a >50% reduction from baseline in seizure frequency

Adverse Events Reported for Greater than or equal to 2 Patients in the Total EZG Group by Preferred Term for Patients with a Taper of >7 days (PCT)

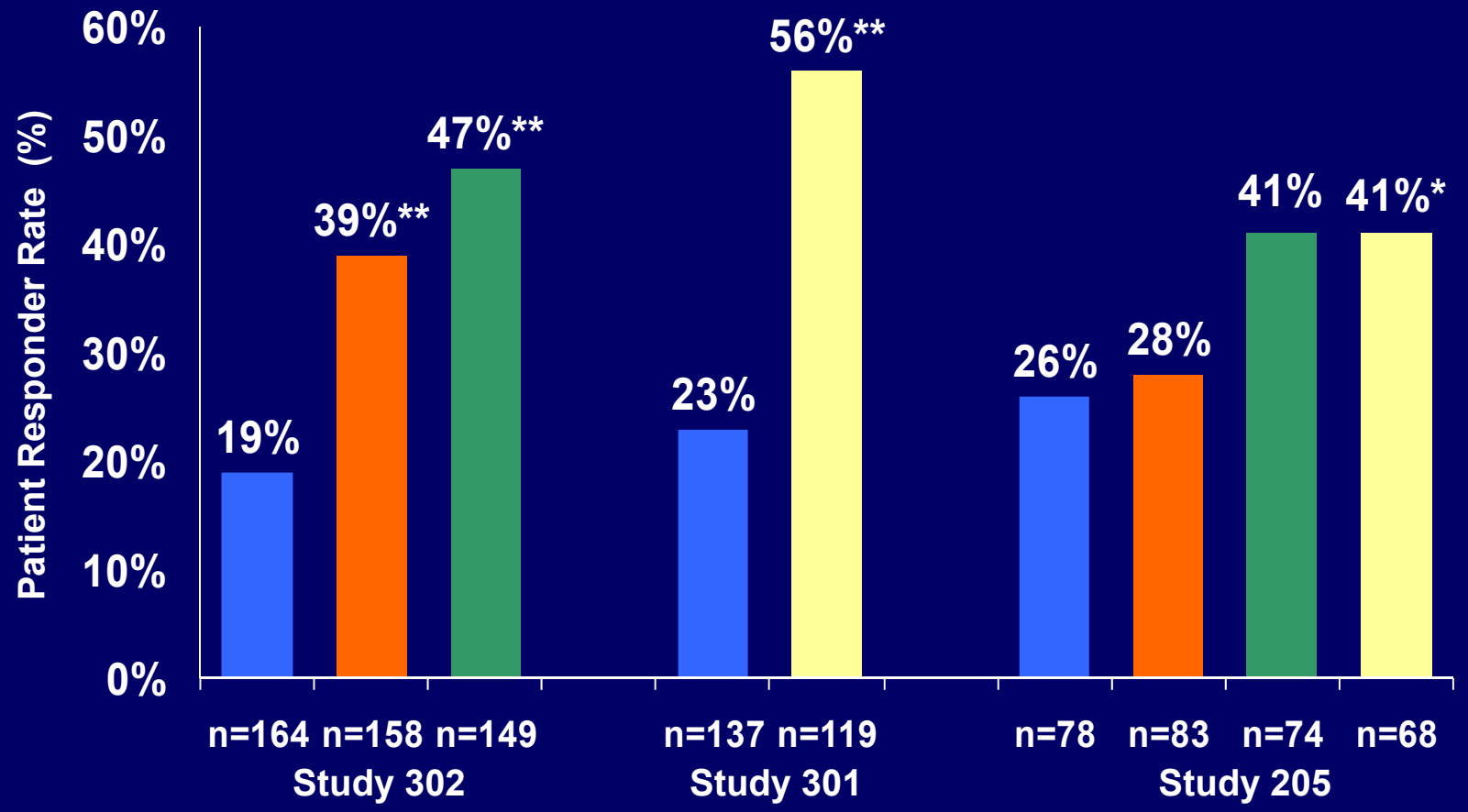
	% of Patients				
Preferred Term	Placebo (N=36)	EZG 600 mg/day (N=53)	EZG 900 mg/day (N=58)	EZG 1200 mg/day (N=60)	EZG Total (N=171)
Any AE	**17**	**28**	**21**	**28**	**26**
Headache	3	2	7	7	5
Dizziness	3	2	2	5	3
Nausea	0	4	0	2	2
Abdominal pain upper	0	4	0	2	2
Diarrhea	0	2	0	2	1
Gait disturbance	0	0	2	2	1
Influenza	0	4	0	0	1
Sinusitis	0	0	2	2	1
Disturbance in attention	0	2	0	2	1
Paraesthesia	0	0	2	2	1
Hematuria	0	2	0	2	1
Back pain	0	2	0	2	1
Depression	0	2	2	0	1

AEs Leading to Discontinuation Were Generally CNS and Dose Related (PCT Population)



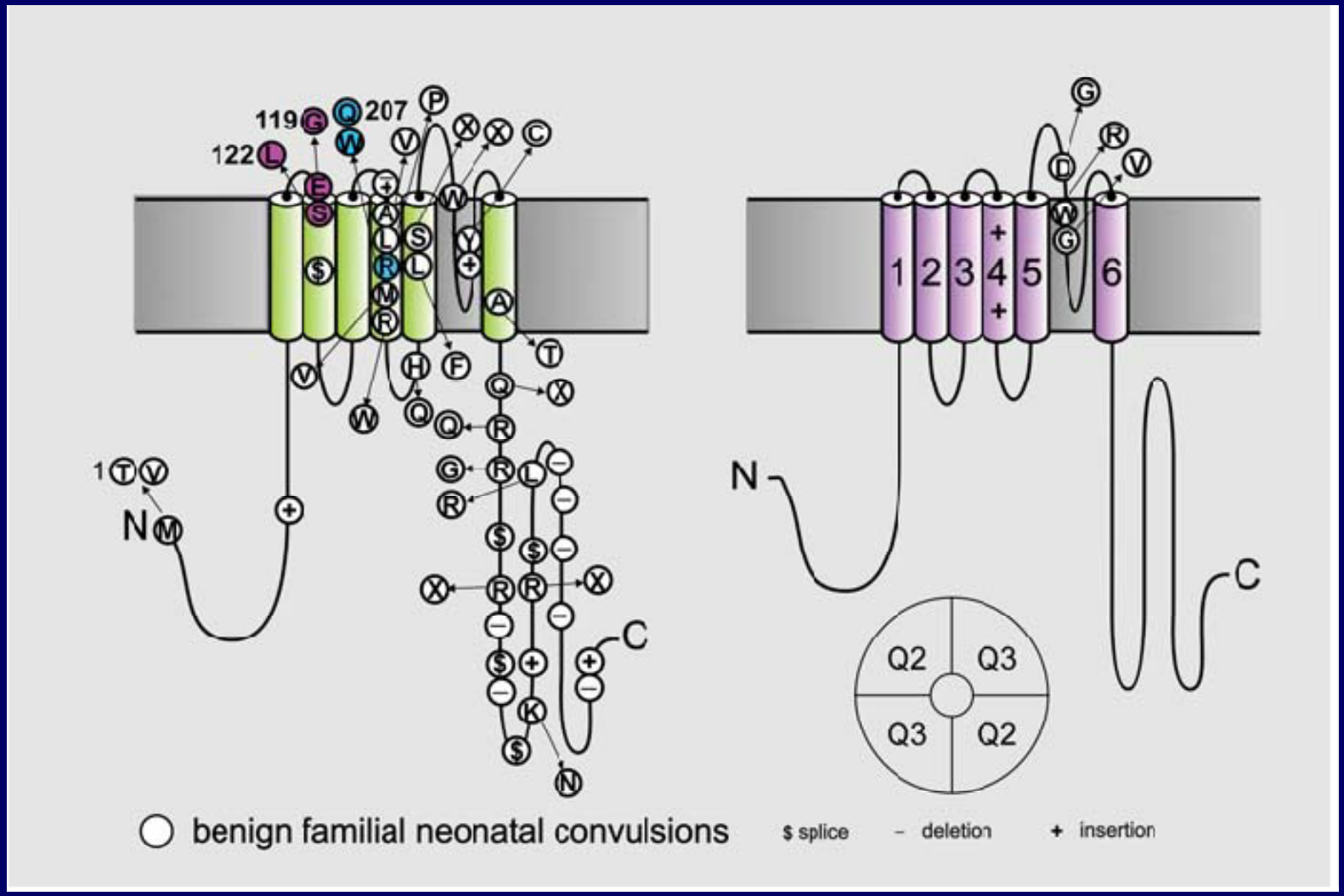
PCT Safety Population

Responder Rate (Maintenance Phase) – ITT Maintenance Population: Studies 205, 301 and 302



* p<0.05 vs. Placebo
** p<0.01 vs. Placebo

Mutations in human KCNQ2 and KCNQ3 genes linked to epilepsy (Benign Familial Neonatal Convulsions, BFNC)



- Impaired channel function leads to a loss of control of excitability

Maljevic et al 2008

Summary of Selected TEAEs from the Injury, Poisoning and Procedural Complications System Organ Class (PCT)

Preferred Term	Number of Patients	
	Placebo (N=427)	Total EZG (N=813)
Any event	51 (11.9)	53 (6.5)
Contusion	10	4
Skin laceration	7	7
Fall	7	5
Head Injury	5	2
Limb Injury	4	3
Clavicle fracture	2	0
Foot fracture	2	0
Joint dislocation	2	0
Rib fracture	2	0
Wrist fracture	2	0
Ankle fracture	1	1
Hand fracture	1	0
Mouth Injury	1	4
Stress fracture	1	0
Tibia Fracture	0	2
Lower limb fracture	0	1

Serious Adverse Events of Hallucination and Psychosis (Phase II/III 2 Oct 09)

Dose at which event was reported	300 – 450 mg	600 – 750 mg	900 – 1050 mg	1200 mg	Total EZG
Patients with SAE	2	4*#	9	4	19
Associated with seizure	0	2	5	3	10
History of psychosis or depression	0	1#	4	1	6

*one patient discontinued EZG 2 days before event
#one patient had déjà vu, myoclonic jerks, and history of anxiety

Preferred Terms Searched for Hallucinations and Psychosis

- Acute psychosis
- Agitation
- Déjà vu
- Delirium
- Delusion
- Delusional disorder (persecutory type)
- Depersonalization
- Elevated mood
- Epileptic psychosis
- Euphoric mood
- Hallucination
- Hallucination auditory
- Hallucination visual
- Hallucinations mixed
- Hypomania
- Illusion
- Mood altered
- Paranoia
- Psychotic disorder
- Schizoaffective

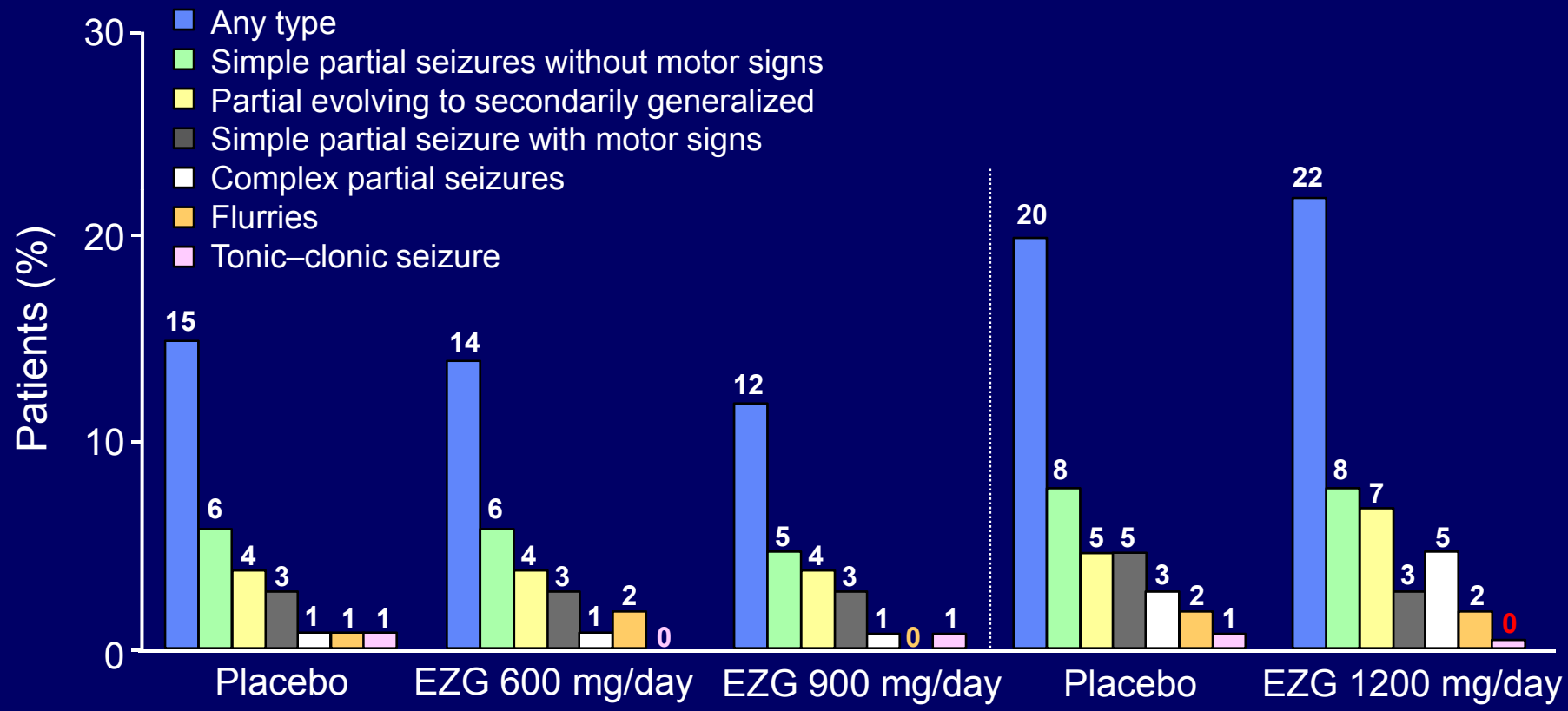
Prospective Observational Study: Epilepsy in WellPoint Healthcare Plan 2004-2009

- Unique members with a medical claim for epilepsy (ICD-9 codes 345.XX, 780.3, 780.39): ~ **244,000**

- Members with a medical claim for epilepsy and a claim for at least one AED: **~130,000**
  - <18 years old: ~ **22,000 (17%)**
  - 18 – 64 years old: ~ **91,000 (70%)**
  - 65+ years old: ~ **17,000 (13%)**

New Seizure Types Not Reported at Baseline: Double-Blind Phase: (New Analysis)

Integrated Data: Studies 205,302 and 301



Tonic seizure	1%	–	<1%	-	–
Atonic seizure	–	–	–	<1%	–
Unclassified	–	1%	–	-	–

ITT double-blind population; **205/302:** PBO, n= 272; EZG 600, n=278; EZG 900, n=270; **205/301:** PBO, n= 246; EZG 1200, n=257.

Proposed Labeling-Urinary Retention

- WARNINGS AND PRECAUTIONS
  - Urinary retention, dysuria, and urinary hesitation were reported in controlled clinical studies in patients treated with POTIGA, generally within the first 8 weeks of treatment. In these controlled studies, 7 of 813 patients (0.9%) treated with POTIGA reported urinary retention compared to 2 of 427 patients (0.5%) receiving placebo, with some cases requiring catheterization or hospitalization. POTIGA must be used with caution in patients at risk of urinary retention.

NOTE: Labeling is under review and not yet agreed with FDA

Proposed Labeling – QT Interval Effect

- WARNINGS AND PRECAUTIONS
  - A study of cardiac conduction demonstrated that ezogabine produced a slight and transient QT-prolonging effect in healthy volunteers titrated to 1,200 mg/day. The QT-prolonging effect occurred within 3 hours of dosing at 1,200 mg. Caution should be exercised when POTIGA is prescribed with medicines known to increase QT interval and in patients with congenital long QT syndrome, heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia.

NOTE: Labeling is under review and not yet agreed with FDA

Cardiac SAEs From Abuse Liability Study

Age	Sex	Study Rx	TTO	Comments	Discont.
36	F	Single dose EZG 900mg	~2 hrs	~25s period of asystole, spontaneous recovery. Baseline HR=44. Normal cardiology assessment, including stress echo before discharge.	Yes
41	M	Single dose EZG 900mg	~2.5 hrs	3 runs (longest 19 beats) of non-sustained asymptomatic ventricular tachycardia Normal ECG immediately after event	Yes

Subject 9077

- Lead II telemetry strip demonstrating:
  - Sinus rhythm prior to event
  - Period of asystole
  - Nodal rhythm post event