Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures

United States Food and Drug Administration

Peripheral and Central Nervous System Drugs Advisory Committee

January 7, 2009

OVATION PHARMACEUTICALS, INC.

Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures

Introduction

Tim Cunniff, PharmD

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OVATION PHARMACEUTICALS, INC.

Proposed Indication

NDA 20-427 (500 mg tablet)

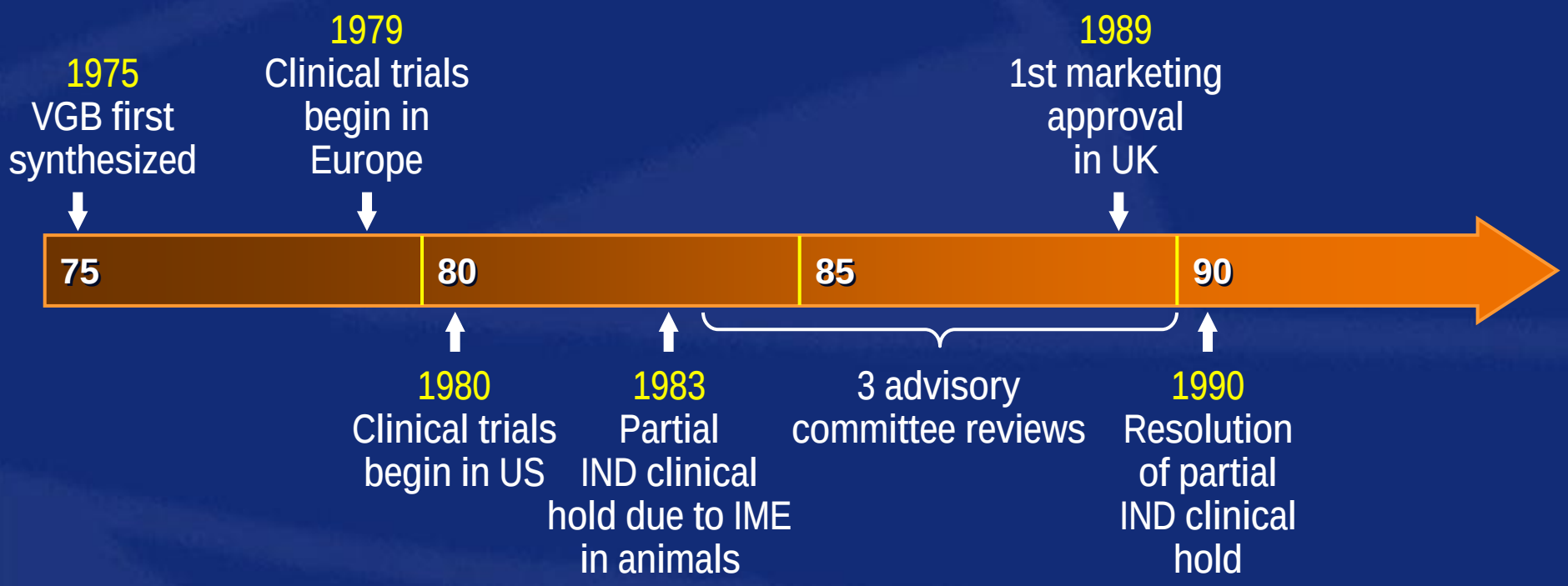
- **Sabril is indicated as adjunctive therapy for adult patients with refractory complex partial seizures (CPS) who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing the peripheral visual field defect (pVFD). Sabril is not indicated as a first-line agent for CPS.**

Worldwide Status

- Vigabatrin (VGB) currently available in more than 50 countries
  - North America: Canada, Mexico
  - Europe: Most countries within the EU
  - ROW: Many countries in Asia, Latin America, Africa/Middle East
- More than 1.5 million patients have received VGB over the past 19+ years

Vigabatrin Worldwide and US Development History

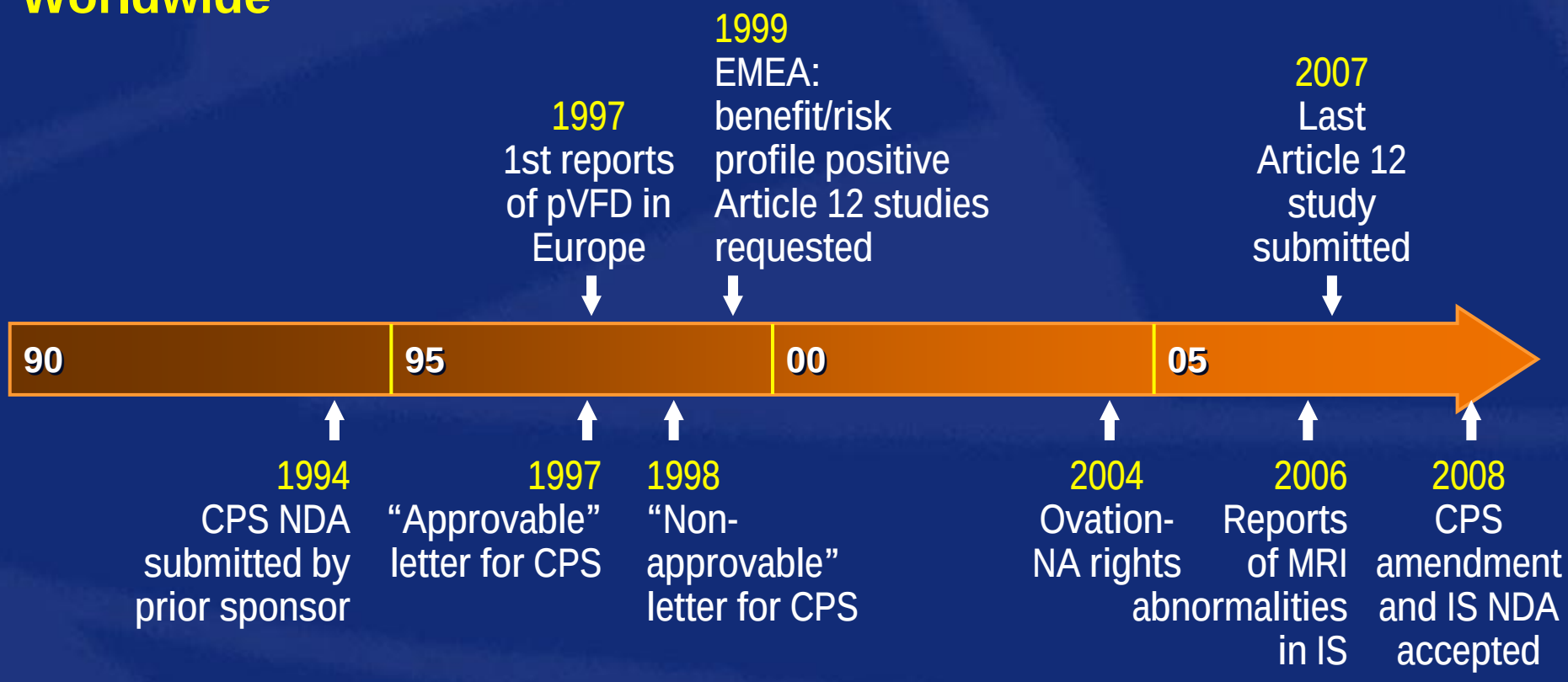
Worldwide



US

Vigabatrin Worldwide and US Development History

Worldwide



US

CPS—Key Considerations (1)

- Refractory CPS: Serious and life-threatening disease with unmet medical need
- Efficacy of VGB for CPS well established
  - Pivotal US clinical studies (025 and 024) meet FDA's statutory definition of adequate and well controlled
  - Therapeutic response observed within 4 - 6 weeks
- Safety of VGB is well characterized
  - > 4000 patients exposed to VGB in > 100 clinical trials
  - > 1.5 million patients have received VGB over past 19+ years

CPS—Key Considerations (2)

- Many essential features of pVFD now better understood
  - Estimated prevalence in adults with refractory CPS is 25% (range of 17% - 92% reported in the literature)
  - Typically occurs after prolonged VGB use, although there are infrequent reports prior to 6 months of VGB exposure
  - Most often mild or moderate, rarely severe
  - Appears to progress slowly while on drug
  - Irreversible if it occurs
  - Can be detected by age-appropriate ophthalmologic monitoring before becoming clinically meaningful

CPS—Key Considerations (3)

- Risk Evaluation and Mitigation (REMS) Plan
  - Labeling
    - Package Insert with prominent pVFD Black Box Warning
    - Patient Medication Guide
  - Communication Plan/Education Programs to reinforce key risk messages
  - Elements to Assure Safe Use
    - Restriction of initial prescription to board-certified neurologists
    - Restriction of dispensing to select specialty pharmacies (controlled distribution)
    - Enforced benefit/risk assessment after initial evaluation phase
    - Enforced ophthalmologic monitoring
    - Sabril registry

Today's Agenda

Unmet Medical Need	R. Edward Faught, MD University of Alabama School of Medicine University of Alabama at Birmingham
Efficacy and General Safety	Christopher Silber, MD Ovation Pharmaceuticals, Inc.
Peripheral Visual Field Defect Assessment and Monitoring	Robert C. Sergott, MD Wills Eye Institute Thomas Jefferson University, Philadelphia
Peripheral Visual Field Defect Characteristics	Stephen M. Sagar, MD Ovation Pharmaceuticals, Inc.
Risk Evaluation and Mitigation Strategy	Tim Cunniff, PharmD Ovation Pharmaceuticals, Inc.
Benefit/Risk Assessment	Roger J. Porter, MD University of Pennsylvania, Philadelphia Uniformed Services University of the Health Sciences, Bethesda

Consultants

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  Bittman Biostat, Inc.
- **D. Reid Patterson, DVM, PhD**
  Reid Patterson Consulting, Inc.
- **Carol Westall, PhD**
  University of Toronto Hospital for Sick Children
- **James W. Wheless, MD**
  The University of Tennessee Health Science Center

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An Unmet Need for Therapies

R. Edward Faught, MD

Professor and Vice Chair, Department of Neurology
University of Alabama School of Medicine
University of Alabama at Birmingham
Director, UAB Epilepsy Center

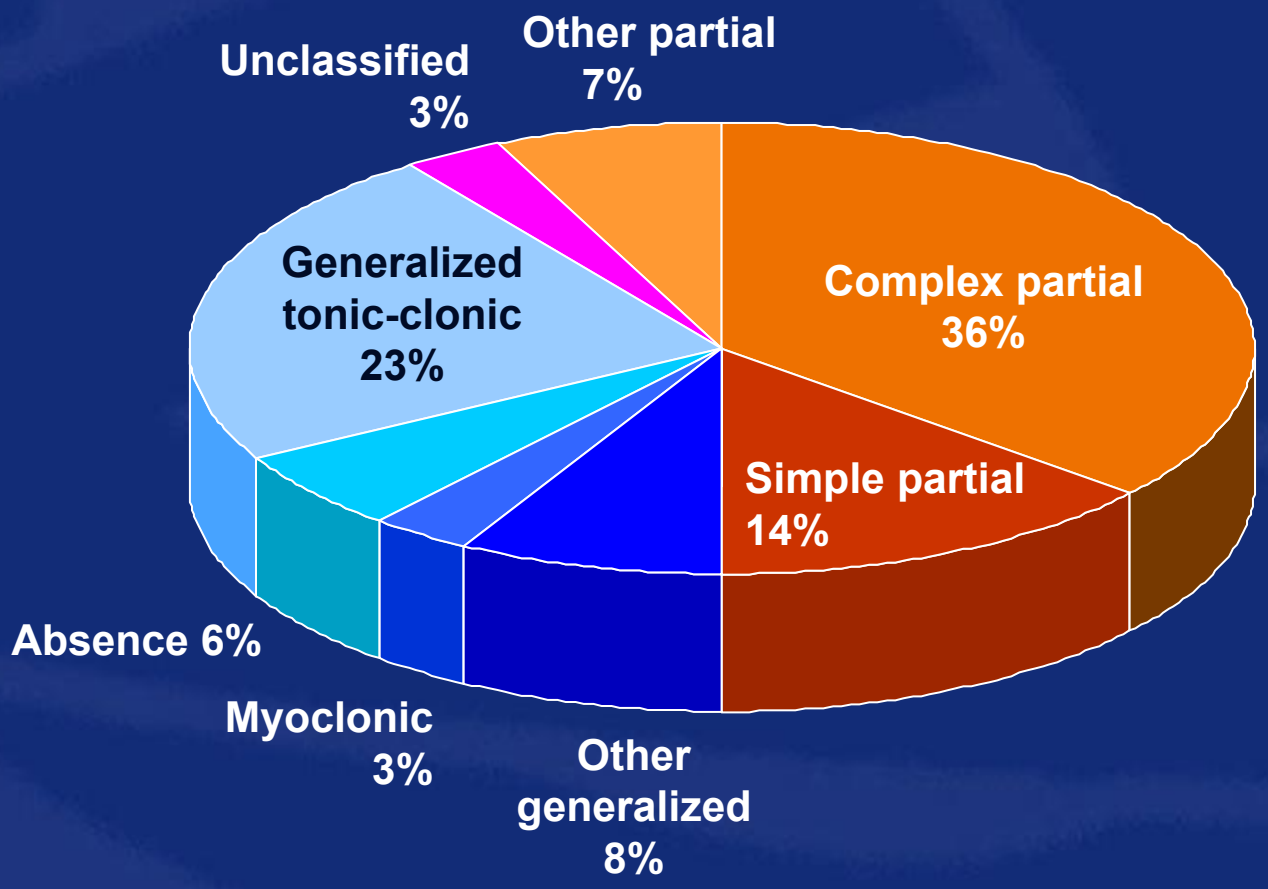
OVATION PHARMACEUTICALS, INC.

Seizures and Epilepsy

- Seizure: A brief, abnormal brain electrical discharge causing a change in behavior
- Epilepsy: A tendency to have repeated seizures
- Prevalence of epilepsy: 1% to 2% of population[a,b]
- Causes of epilepsy
  - Genetic
  - Biochemical
  - Traumatic
  - Neoplastic
  - Vascular
  - Degenerative
- The cause is unknown in 50% of patients

[a] Wheless JW, et al. *Epilepsy Behav*. 2006;8:756-764.
[b] Beghi E. *Lancet Neurol*. 2004;3:618-621.

Classification of Epileptic Seizures

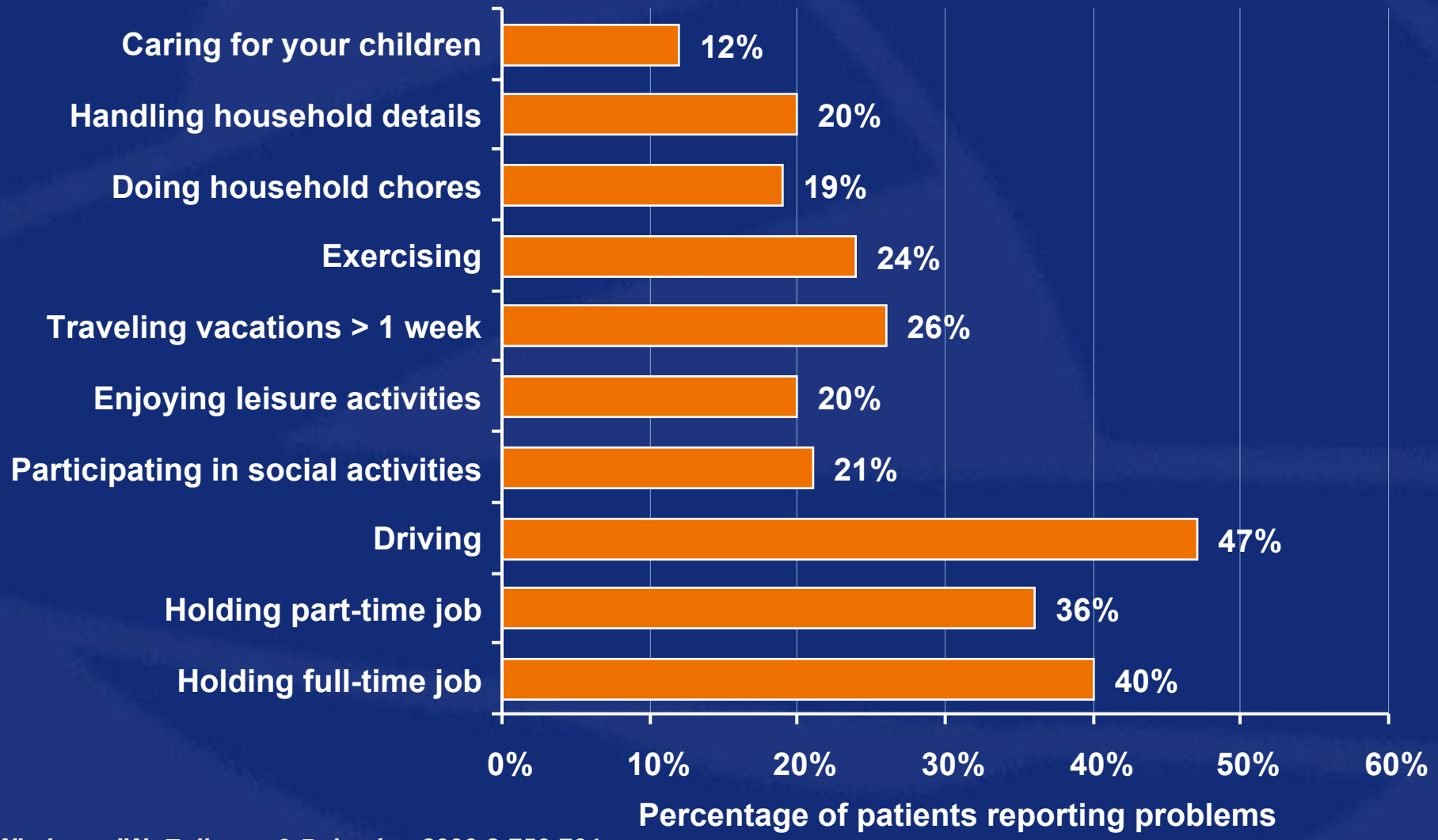


Hauser. *Epilepsia*. 1993.

What Is a Complex Partial Seizure?

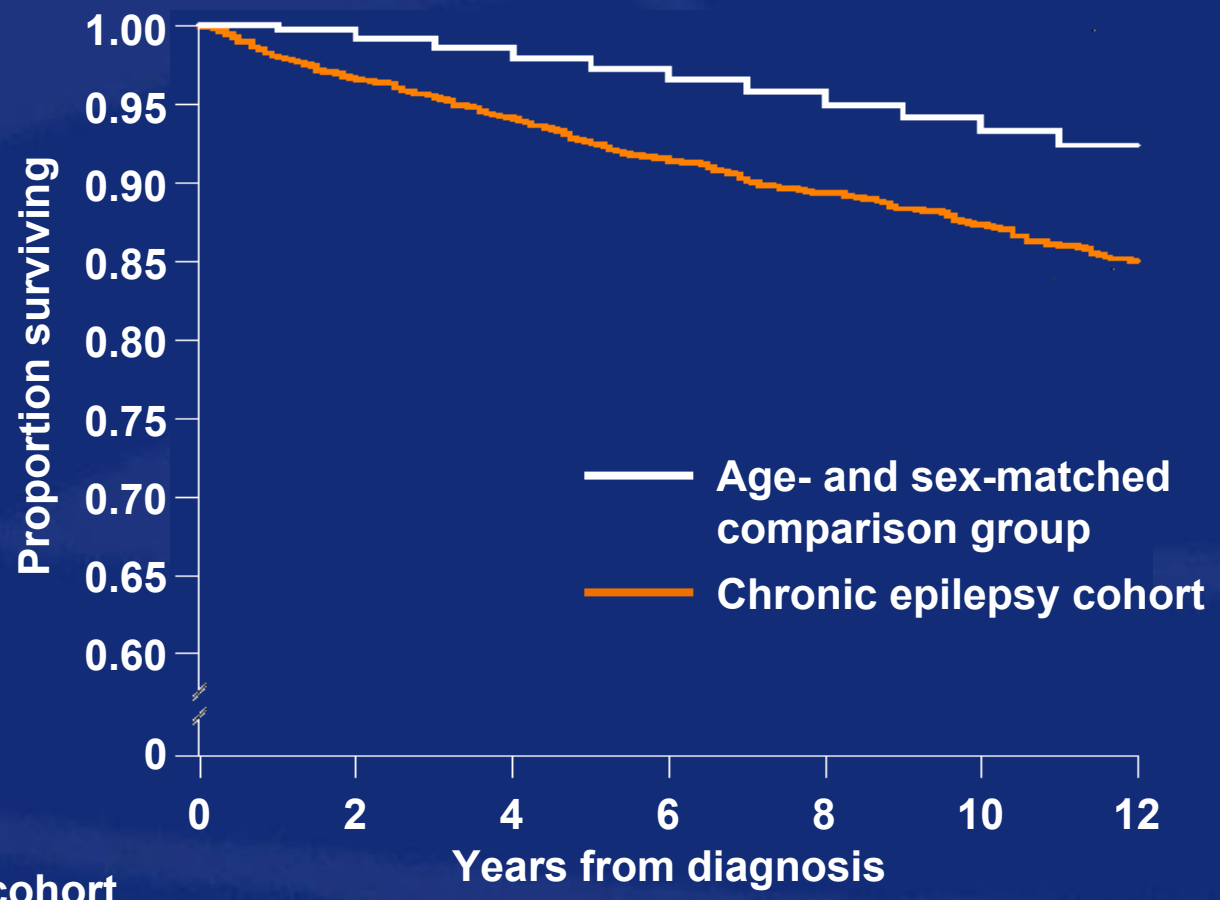
- Blank, unresponsive stare, often 1 to 2 minutes
- Automatisms: meaningless repetitive speech or movements
- Frequency varies widely: daily to monthly
- May progress to tonic-clonic convulsions in 50% of patients
- Period of confusion for minutes to hours after each seizure

Impact of Refractory Epilepsy on Quality of Life (N = 503)



Wheless, JW. *Epilepsy & Behavior.* 2006;8:756-764.

Uncontrolled Epilepsy May Be Fatal



Chronic epilepsy cohort							
Numbers at risk	2689	2603	2221	1766	1363	975	701
(number of deaths)	(0)	(86)	(148)	(208)	(244)	(269)	(290)

Mohanraj R, et al. *Lancet Neurol*. 2006;5:481-487.

Seizure Treatment Is Often Unsatisfactory

- 36% of patients with epilepsy are refractory, defined as having failed 2 monotherapies and at least one drug combination[a]
- In clinical trials for patients with refractory seizures[b]
  - Only 20% to 50% achieved a 50% reduction in seizure frequency
  - Fewer than 10% became seizure-free

[a] Kwan P and Brodie MJ. *N Engl J Med*. 2000;342:314-319.
[b] French JA. *Neurology*. 2004;62:1261-1273.

What is "Refractory" Epilepsy?

- Failure of ≥ 2 drugs and ≥ 1 drug combination
  - Indicates < 20% chance of control with any current drug[a,b]
- Best defined by numbers of drugs tried at adequate dosages without complete seizure control
- Not defined by either frequency or severity of seizures

[a] Kwan P and Brodie MJ. *N Engl J Med*. 2000;342:314-319.
[b] Callaghan BC, et al. Ann Neurol. 2007;62(4):382-389.

What Are the Treatment Options for Patients With Refractory Complex Partial Seizures?

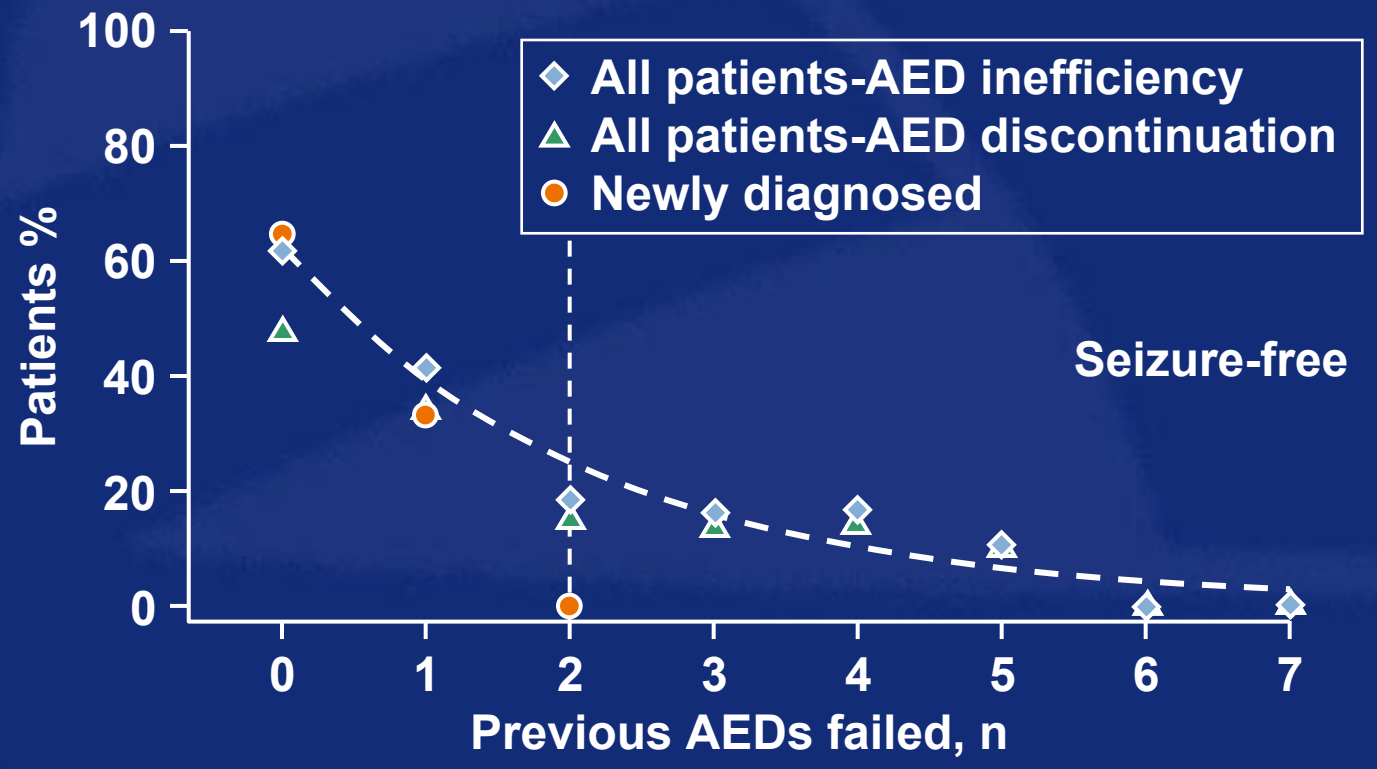
- Polytherapy combinations, 2 to 4 drugs
- Vagal nerve stimulator implantation
- Brain surgery to remove the seizure focus
- Less commonly used drugs with greater side-effect potentials

There Are 10 to 12 Commonly Used Antiseizure Drugs—Why Do We Need More?

- **There are multiple fundamental etiologies of epilepsy**
- **To address these varied etiologies, antiepileptic drugs differ in their mechanisms of actions**
- **Physicians cannot predict the most effective drug for a specific patient for refractory patients; several different drugs and combinations are often tried**
- **Every time a new drug becomes available, some refractory patients become seizure-free**

Lowenstein DH. Seizures and epilepsy. In: Fauci AS, et al, eds. *Harrison's Principles of Internal Medicine, 17th Ed.* McGraw-Hill Companies. 2008: chapt 363.

Is It Worthwhile to Keep Trying New Therapies in Refractory Epilepsy?



"…no matter how many AED therapies have failed, ***there is always hope*** of a meaningful clinical remission in this population."

Callaghan BC, et al. *Ann Neurol*. 2007;62(4):382-389.

Figure modified with permission from: Schiller Y and Najjar Y. *Neurology*. 2008;70:54-65.

Varied Mechanisms of Action of Antiseizure Drugs

- Sodium channel blockers
  - Phenytoin, carbamazepine, lamotrigine
- Postsynaptic GABA receptor facilitators
  - Benzodiazepines, barbiturates
- Modulators of neurotransmitter release
  - Levetiracetam, gabapentin, pregabalin
- Mixed actions
  - Valproate, topiramate, zonisamide, felbamate
- GABA metabolic blocker
  - Vigabatrin

Potentially Serious or Fatal Side Effects of Current Antiseizure Drugs

Phenytoin	Carbamazepine	Sodium valproate
Rash	Rash	Pancreatitis
Pseudolymphoma	Bone marrow suppression	Hepatic failure
Lupus syndrome	Cardiac dysrhythmia	Hyperammonemia

FBM	LTG	TGB	TPM	ZNS	LEV
Aplastic anemia	Rash	Rash	Metabolic acidosis	Rash	Depression
Hepatic failure	Multi-organ failure	Nonconvulsive status epilepticus	Cognitive slowing	Fever	Hostility

Felbamate—An Example of a Drug for Refractory Epilepsy

- 1993: FDA approved
- 1994: Discovery of ~ 1 in 5000 chance of liver failure or aplastic anemia; 1 in 10,000 chance of fatal outcome
  - FDA allowed continued use with more restrictive labeling
- Risk/benefit ratio still considered favorable for some patients with hard-to-control seizures: estimated 35,000 new patient starts 1996 - 2006[a]
- Illustrates the usefulness of a specific drug for a small but critical segment of patients

[a] Pellock J, Faught E, Leppik I, et al. *Epilepsy Res*. 2006;71:89-101.

A Potential Vigabatrin Candidate

A 35-yr-old woman had head trauma from an auto accident at age 22 then began to have staring spells lasting 2 minutes at age 23. At age 25, she had a convulsion. Phenytoin and carbamazepine therapies caused rash; topiramate caused confusion. Vagal nerve stimulation was ineffective. Oxcarbazepine reduced seizure frequency from 5/month to 2/month, but she eventually lost her job as a bank teller.

Evaluation for surgery included an MRI (normal) and a video-EEG (bilateral independent temporal lobe seizures onsets). Therefore surgery was not considered an option. Additional drug trials are planned.

Summary

- Refractory epilepsy is common, degrades quality of life, is dangerous, and may be fatal
- Complex partial seizures are often poorly controlled by current therapies
- Favorable drug response is unpredictable
- We need a wide variety of choices of drugs, especially those with different mechanisms of action and different side-effect profiles

Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures Efficacy and General Safety

Christopher Silber, MD

Vice President, Clinical Affairs
Ovation Pharmaceuticals, Inc.

OVATION PHARMACEUTICALS, INC.

Overview

- Clinical pharmacology
- Clinical development program
  - Efficacy in refractory complex partial seizures (CPS)
  - Safety

Summary of VGB in Refractory CPS

- Efficacy well established
- Rapid onset—within 4 to 6 weeks
- 2 pivotal studies meet FDA regulatory requirements for efficacy
- Safety profile well characterized
- Additional safety concerns
  - MRI abnormalities
  - Peripheral visual field defect (pVFD)

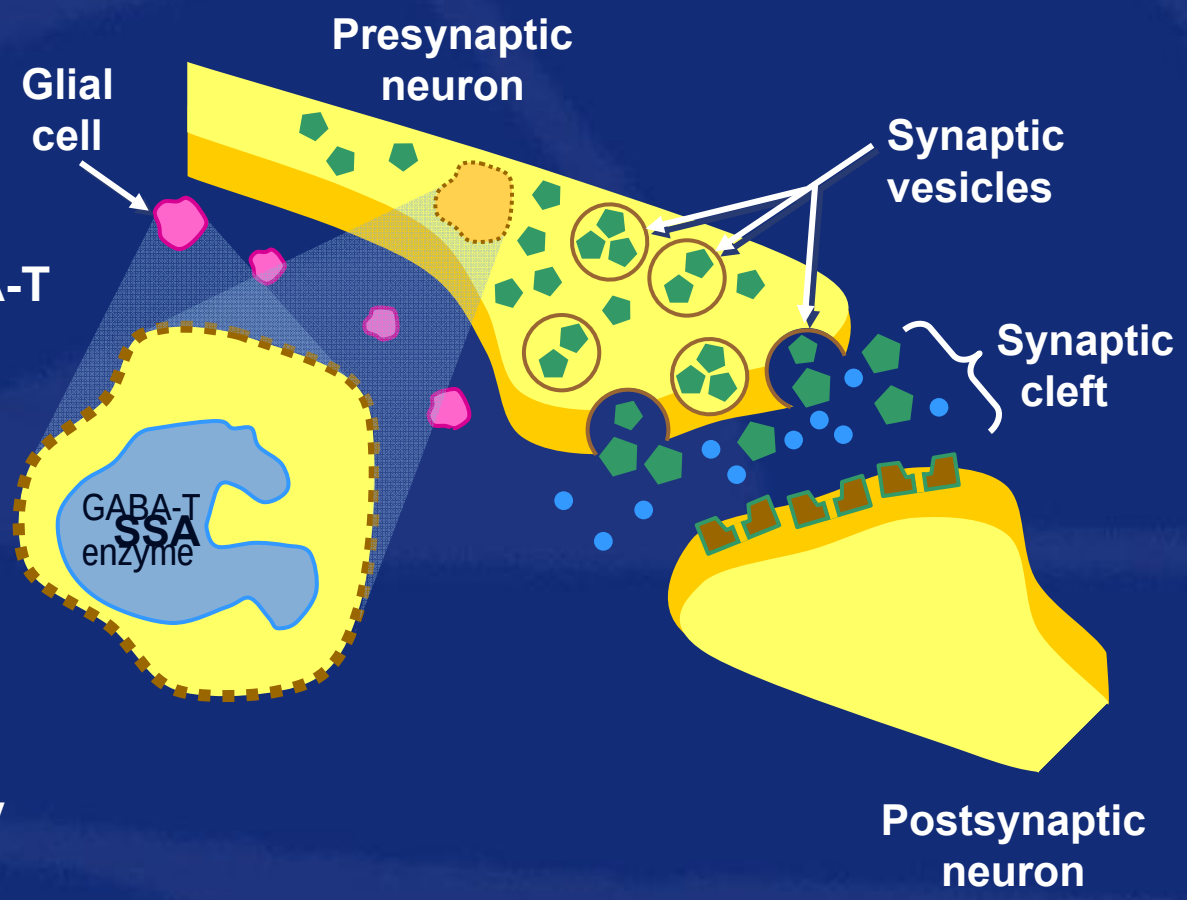
Vigabatrin—Unique Mechanism of Action

GABA is an inhibitory neurotransmitter

VGB selectively and irreversibly inhibits GABA-T (prevents breakdown of GABA molecules)

Increases number of GABA molecules

Decreases seizure activity



GABA | GABA A receptor | VGB | Cl^-

GABA-T = GABA-transaminase; SSA = Succinic semialdehyde.

Clinical Pharmacology Overview

- Orally absorbed, linear PK
- No clinically relevant effect of
  - Food, gender, race
- No clinically relevant drug-drug interactions
- Age-related $t_{1/2}$
  - Infants = 5.65 hr
  - Adults = 7.5 hr
- VGB plasma levels do not correlate with clinical effect

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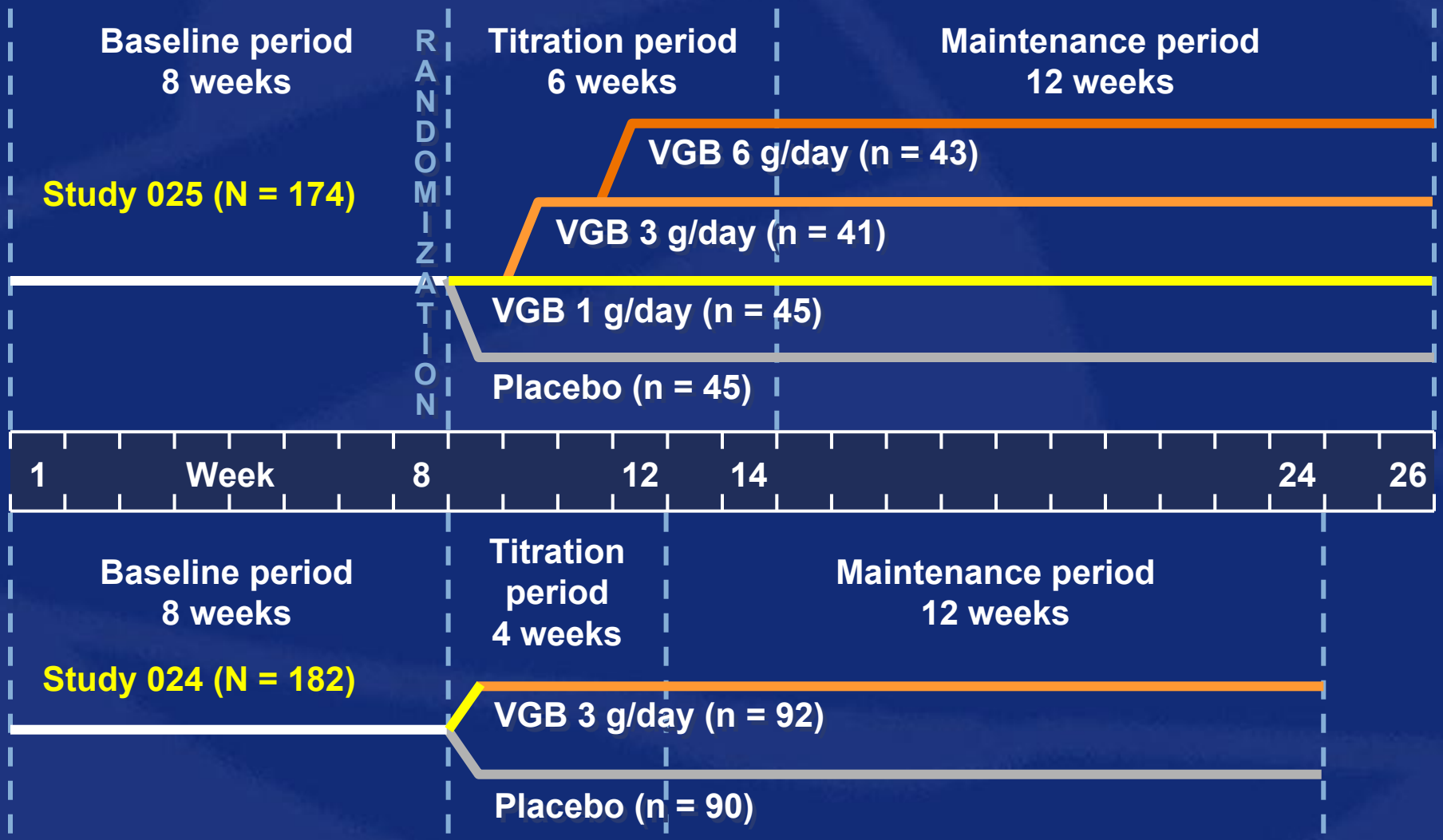
Study Design—Adjunctive Therapy for Refractory CPS

Studies 025 and 024



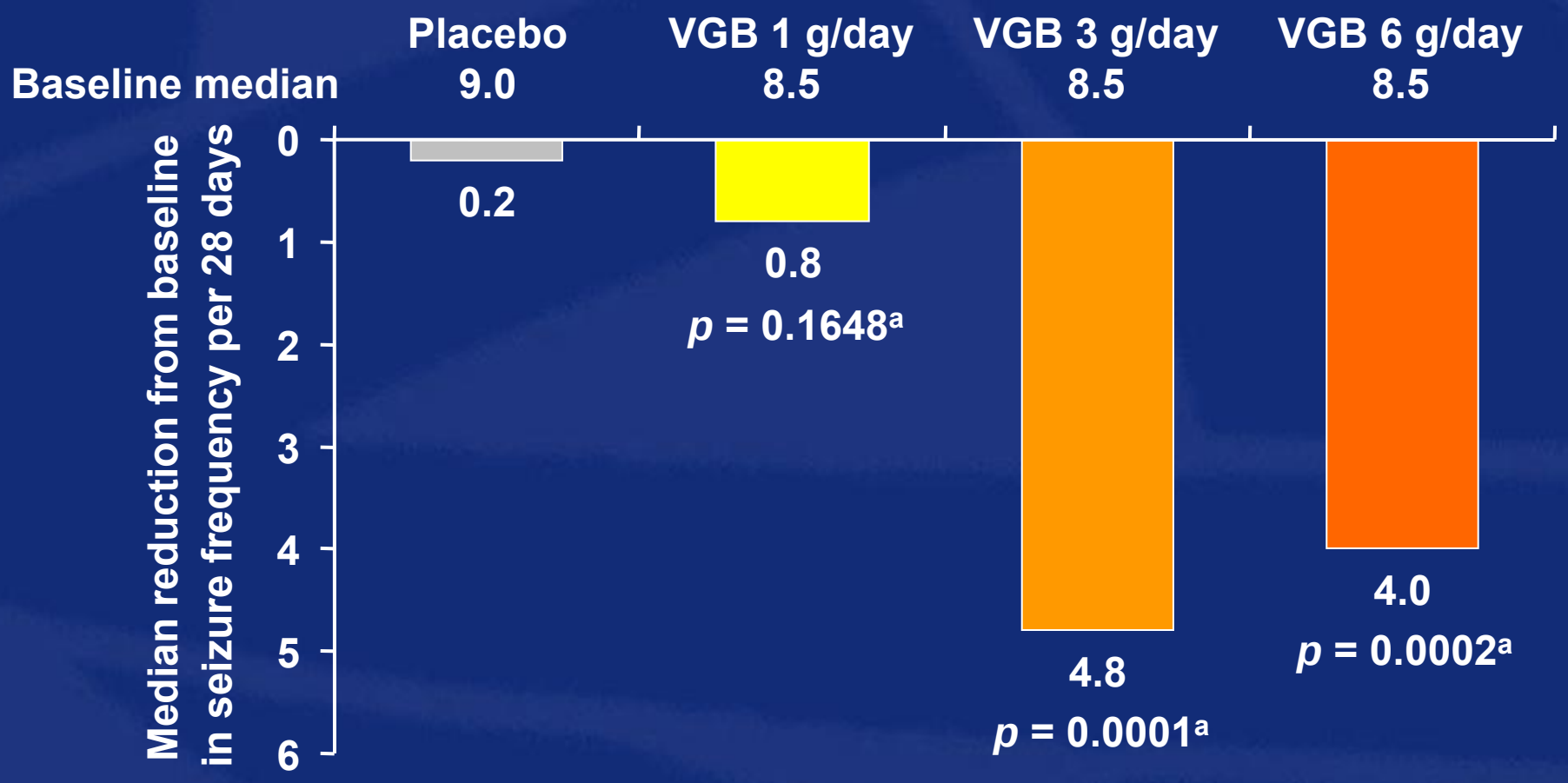
Refractory Patient Population
Studies 025 and 024

	Patients with prior AED[a] usage, %	
	Study 025 N = 174	Study 024 N = 182
≥ 1 AED	93.1	100.0
≥ 2 AEDs	87.9	96.7
≥ 3 AEDs	74.7	80.8
≥ 4 AEDs	48.3	51.6
≥ 5 AEDs	19.5	14.8
≥ 6 AEDs	1.7	1.6
No previous use indicated	6.9	0

[a] AEDs classified as barbiturate, benzodiazepine, carbamazepine, hydantoin, valproate, or other.

VGB Reduces Seizure Frequency (Protocol-specified Primary Endpoint)

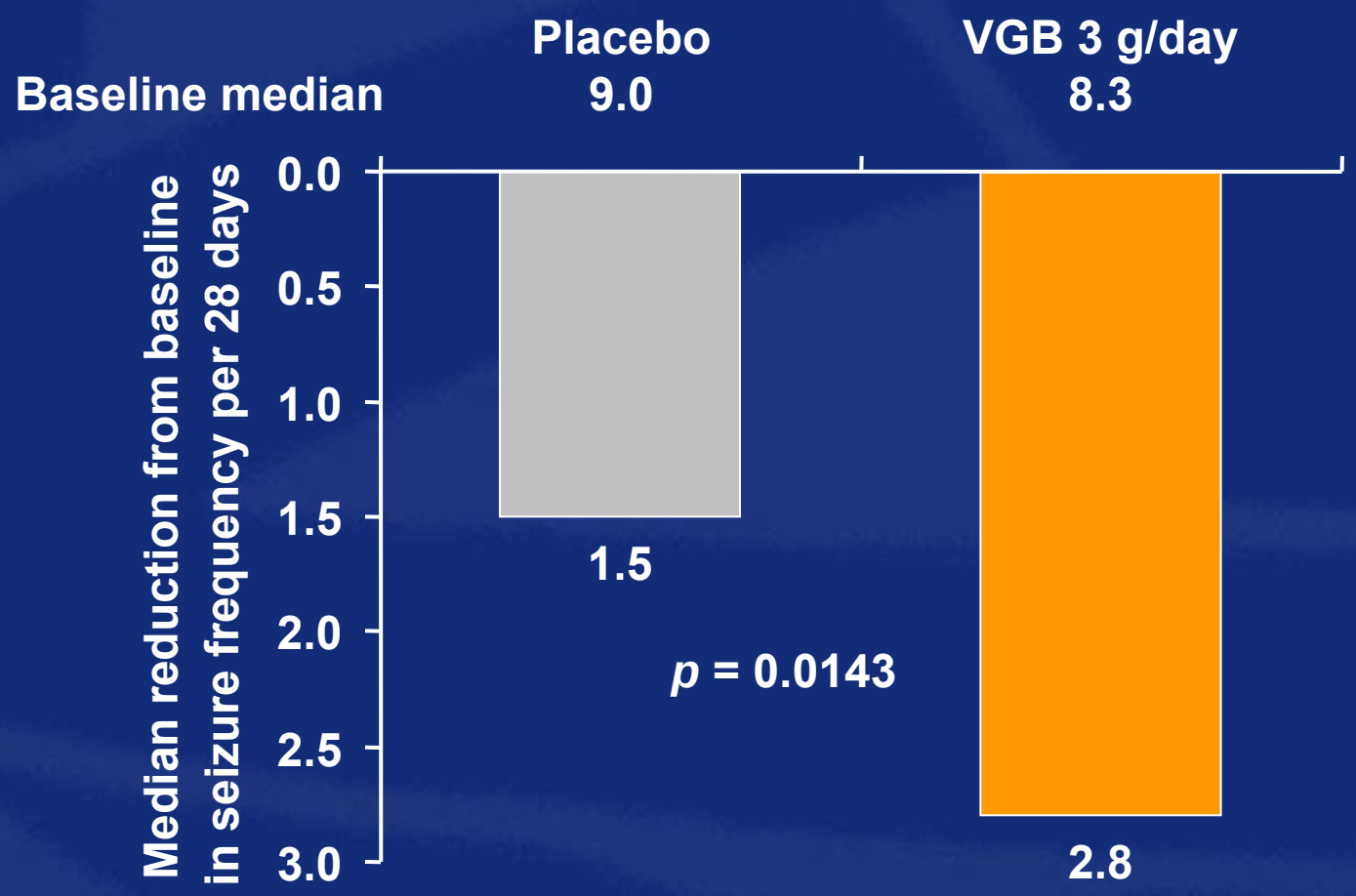
Study 025 (N = 174)



[a] *p* values vs placebo.

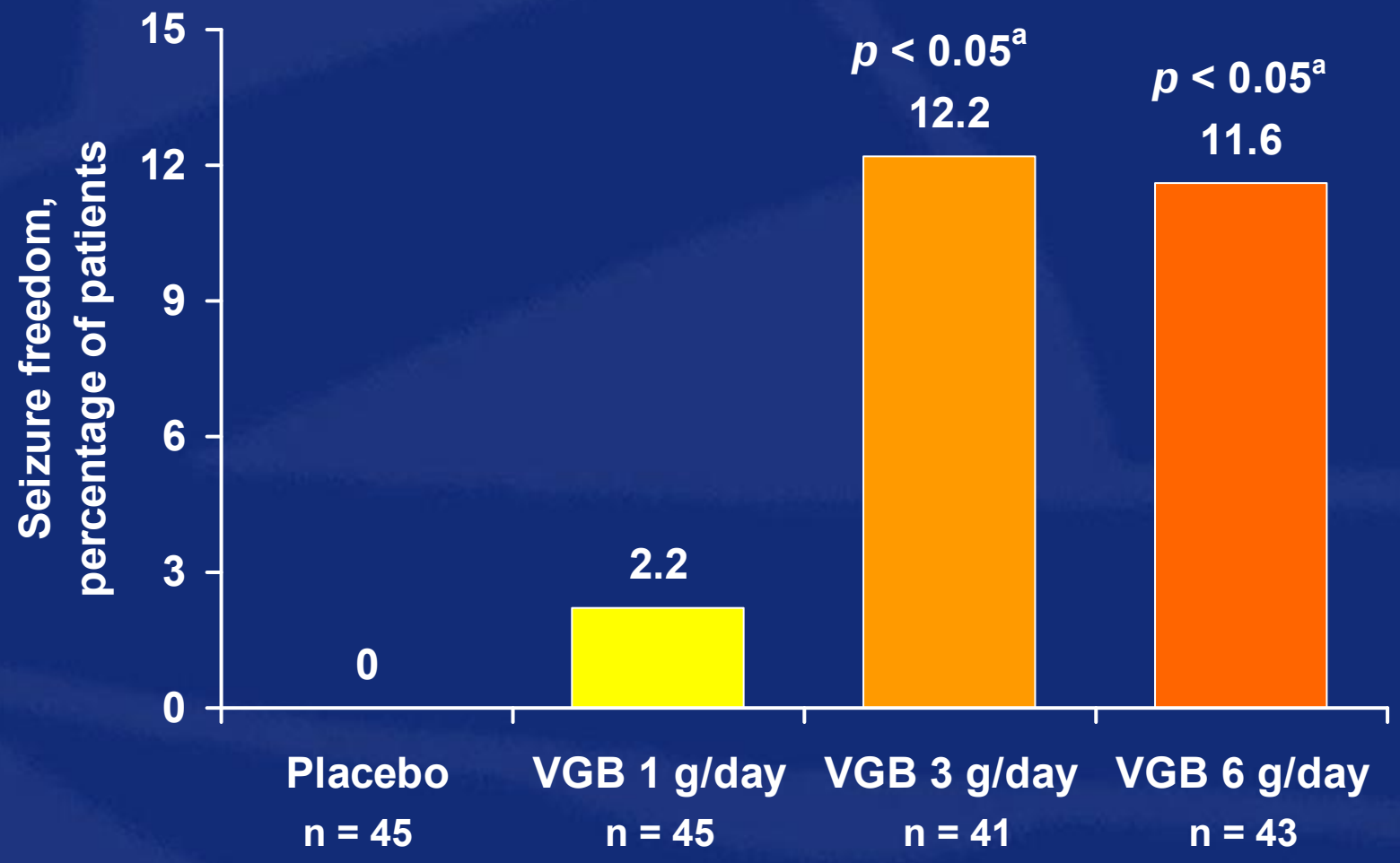
VGB Reduces Seizure Frequency (Protocol-specified Primary Endpoint)

Study 024 (N = 182)



VGB Can Produce Seizure Freedom

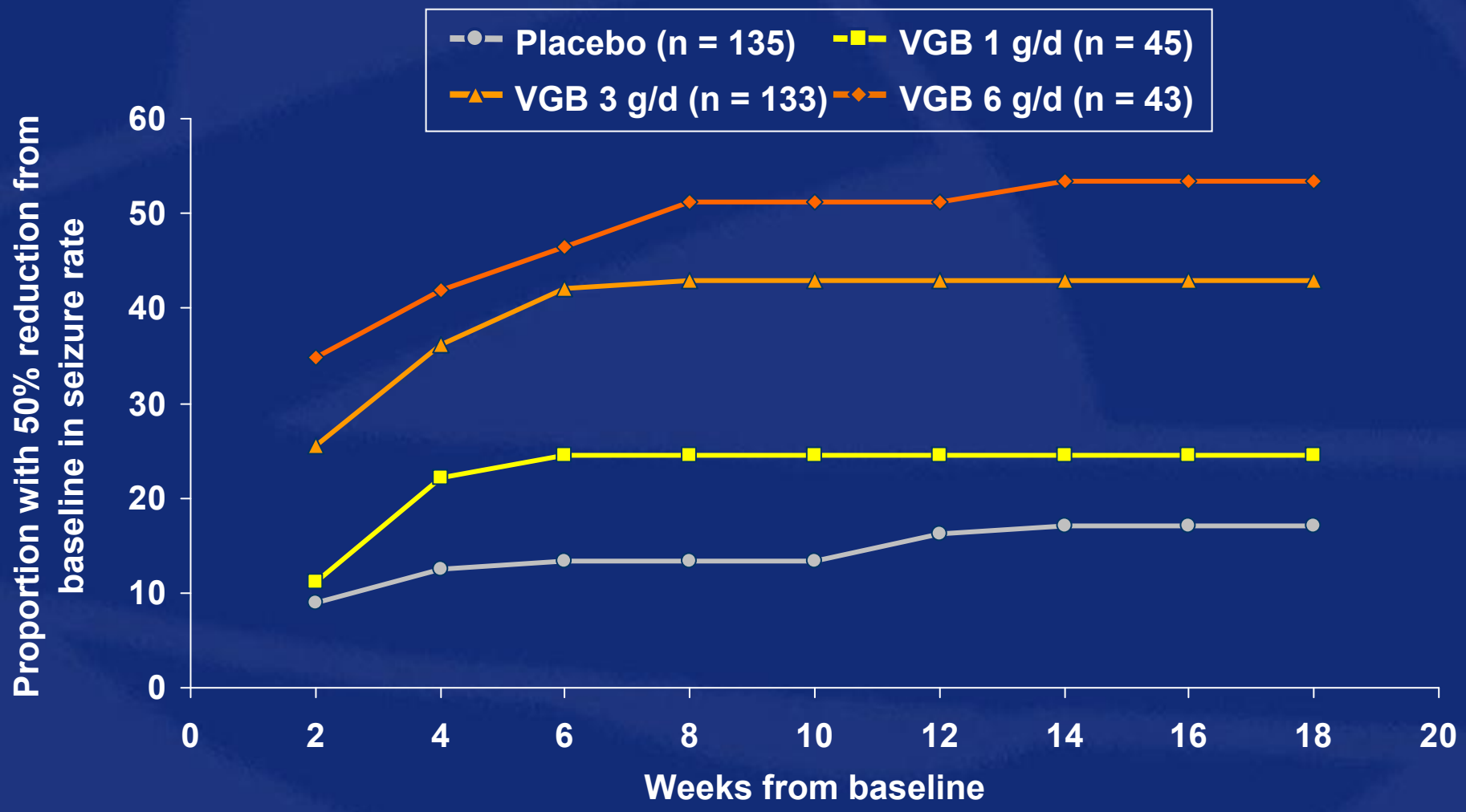
Study 025



[a] *p* values vs placebo.

VGB Efficacy Onset

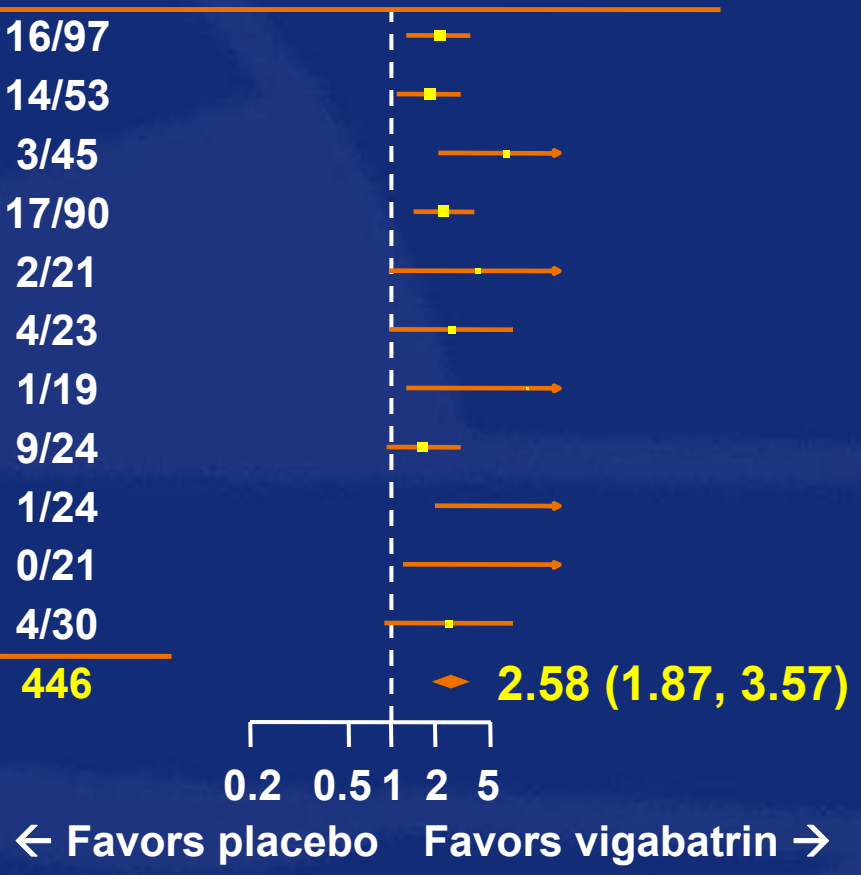
Pooled Studies 025 and 024



Multiple Studies Confirm VGB Efficacy

Cochrane Meta-analysis

Study or subgroup	Vigabatrin, n/N	Placebo, n/N
Beran 1996	34/97	16/97
Bruni 2000	28/58	14/53
Dean 1999/Dodrill 1995	55/129	3/45
French 1996/Dodrill 1993	40/92	17/90
Gram 1985	8/21	2/21
Grunewald 1994	10/22	4/23
Loiseau 1986	9/19	1/19
McKee 1993	15/24	9/24
Rimmer 1984	14/24	1/24
Tartara 1986	9/20	0/21
Tassinari 1987	10/30	4/30
Total (95% CI)	536	446



Hemming K, et al. *Cochrane Database of Systematic Reviews*. 2008, Issue 3. Art. No.: CD007302.

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Adverse Events in ≥ 5% of VGB-Treated Patients and More Frequently Than Placebo

Studies 025 and 024

Preferred term	Patients, n (%) VGB n = 222	Patients, n (%) Placebo n = 135
Fatigue	60 (27.03)	22 (16.30)
Somnolence	49 (22.07)	18 (13.33)
Dizziness	47 (21.17)	23 (17.04)
Nystagmus	34 (15.32)	12 (8.89)
Tremor	31 (13.96)	11 (8.15)
Nasopharyngitis	29 (13.06)	14 (10.37)
Vision blurred	25 (11.26)	7 (5.19)
Diarrhea	23 (10.36)	10 (7.41)
Irritability	23 (10.36)	10 (7.41)
Memory impairment	21 (9.46)	4 (2.96)
Upper respiratory tract infection	21 (9.46)	7 (5.19)
Coordination abnormal	19 (8.56)	3 (2.22)
Diplopia	19 (8.56)	4 (2.96)

Preferred term	Patients, n (%) VGB n = 222	Patients, n (%) Placebo n = 135
Nausea	19 (8.56)	11 (8.15)
Pharyngolaryngeal pain	19 (8.56)	7 (5.19)
Arthralgia	18 (8.11)	4 (2.96)
Weight increased	17 (7.66)	4 (2.96)
Vomiting	16 (7.21)	8 (5.93)
Depression	15 (6.76)	4 (2.96)
Dysmenorrhea	15 (6.76)	4 (2.96)
Gait disturbance	15 (6.76)	9 (6.67)
Constipation	14 (6.31)	4 (2.96)
Back pain	13 (5.86)	3 (2.22)
Confusional state	13 (5.86)	1 (0.74)
General symptom	13 (5.86)	4 (2.96)
Asthenia	12 (5.41)	2 (1.48)
Disturbance in attention	12 (5.41)	1 (0.74)

Serious Adverse Events Occurring More Frequently in VGB-Treated Patients

Studies 025 and 024

Preferred term	Patients, n (%) VGB n = 222	Patients, n (%) Placebo n = 135
Any serious adverse event	16 (7.21)	2 (1.48)
Status epilepticus	4 (1.80)	0
Convulsion	3 (1.35)	1 (0.74)
Pneumonia	3 (1.35)	0
Vomiting	1 (0.45)	0
Feeling drunk	1 (0.45)	0
Pyrexia	1 (0.45)	0
Urosepsis	1 (0.45)	0
Drug toxicity	1 (0.45)	0
Fall	1 (0.45)	0
Grand mal convulsion	1 (0.45)	0

Preferred term	Patients, n (%) VGB n = 222	Patients, n (%) Placebo n = 135
Simple partial seizures	1 (0.45)	0
Abnormal behavior	1 (0.45)	0
Completed suicide	1 (0.45)	0
Confusional state	1 (0.45)	0
Depression	1 (0.45)	0
Mood disorder due to a general medical condition	1 (0.45)	0
Personality disorder	1 (0.45)	0
Psychotic disorder due to a general medical condition	1 (0.45)	0
Suicide attempt	1 (0.45)	0
Hypertension	1 (0.45)	0

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MRI Assessment Overview

- 1983: Preclinical intramyelinic edema (IME)
  - Noted in rodents and dogs
- Late 1990s: Human concerns considered addressed
  - Prior sponsor review of MRIs
    - CPS: 7 trials in adults; 5 trials in pediatrics
  - No evidence of VGB-attributable MRI abnormalities
- 2006: Pearl - High T2 MRI signal abnormality reported in 3 patients with infantile spasms

2007: Ovation Repeat Review of MRIs

MRI Repeat review process

- Hard-copy MRIs for > 600 adult and pediatric patients
  - 2192 MRIs in database
  - 2024 MRIs were determinate
- Independent neuroradiologists
  - Masked double review with adjudication

Results of CPS MRI Repeat Review—Consistent With Epilepsy Population

MRI findings	VGB exposed	VGB naive
Prevalence (%)	14.2	13.1
95% CI	(11.5, 17.3)	(8.7, 18.7)
Incidence (%)	10.8	8.0
95% CI	(8.1, 13.9)	(4.2, 13.6)

Prevalence = Occurrence of ≥ 1 pre-specified MRI signal abnormality seen in a treatment period for T2, FLAIR, and/or diffusion-weighted imaging (DWI), irrespective of whether a baseline MRI was available.
Incidence = Occurrence of ≥ 1 pre-specified MRI signal abnormality on T2, FLAIR, and/or DWI among subjects with a determinate MRI at baseline which was free of pre-specified abnormalities

Wheless JW, et al. *Epilepsia*. 2008. DOI: 10.1111/j.1528-1167.2008.01896.x

Conclusion— VGB Does Not Cause MRI Abnormalities in Patients Treated for CPS

- No significant difference in prevalence or incidence of prespecified MRI abnormalities between VGB-exposed and VGB-naive
- Anatomic distribution of MRI abnormalities
  - Predominantly hemispheric white matter
  - Does not resemble pattern in IS patients or IME in animals
  - Consistent with literature reports of findings in epilepsy populations

Vigabatrin Efficacy and Safety Summary

- Unique MOA
- Effective with rapid onset
  - Decreases seizure frequency
  - Complete seizure freedom (7% - 12%)
  - Onset within 4 - 6 weeks
- Generally well tolerated
  - Common AEs (fatigue, dizziness, somnolence) similar to other AEDs
- MRI
  - No evidence of MRI abnormality or IME in refractory CPS patients

Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures

Peripheral Visual Field Defect (pVFD) Assessment and Monitoring

Robert C. Sergott, MD

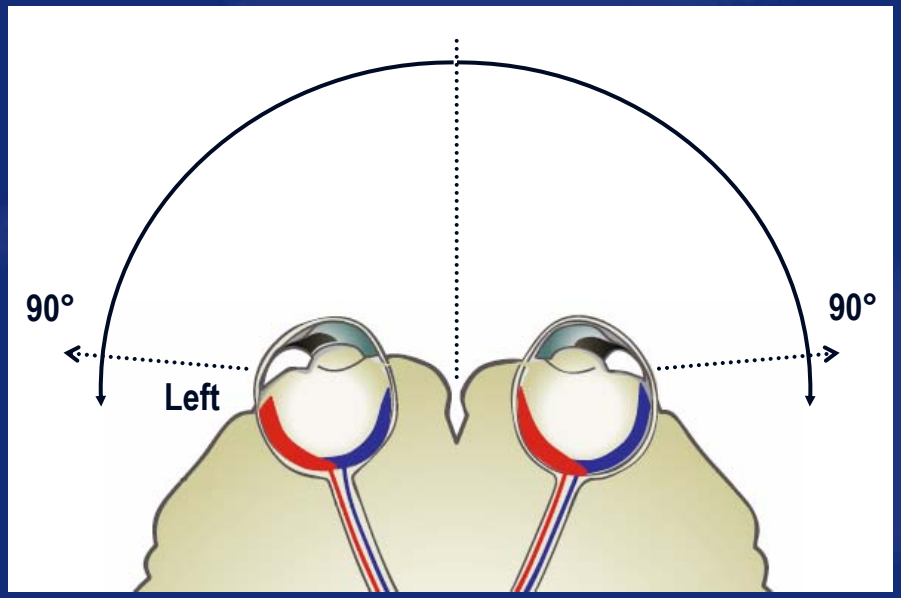
Director of Neuro-Ophthalmology
Professor of Ophthalmology and Neurology
Wills Eye Institute, Thomas Jefferson University

OVATION PHARMACEUTICALS, INC.

Vigabatrin pVFD

- Vigabatrin may produce a pVFD in some patients
- Detection and monitoring of pVFD requires regular assessments of visual function
- Will be able to detect peripheral defects comparable to glaucoma
  - Without loss of central vision
  - Tailor evaluation to patients' cognitive function and cooperation
    - Confrontation, static, and kinetic perimetry
    - Electroretinogram (ERG)
    - Optical coherence tomography (OCT)

The Normal Extent of Visual Field



What we see when we hold
our central vision steady on an object

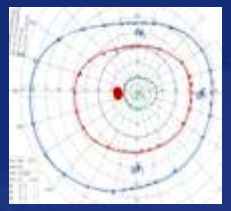
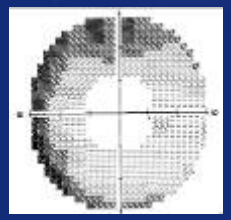
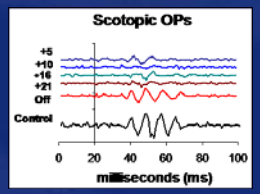
Largest dimension (isopter) of visual field extends
90 degrees temporally and
60 degrees nasally superiorly and inferiorly

Classifications of pVFD

Constriction –
concentric decrease in extent of field

- **Mild – not clinically significant (120° - 160°)**
- **Moderate – not clinically significant; can reliably detect change at the moderate level (60° - 120°)**
- **Severe – clinically significant (< 60°)**

Current Practice of Ophthalmology Can Detect a Moderate pVFD (Glaucoma & VGB)

Methodology		Age appropriateness[a]	Description
Confrontation visual field testing		All ages	Examiner interaction with patient; especially useful in young children and patients unable to perform formal perimetry
Kinetic target perimetry (Goldmann and automated)		≥ 9 yr	Suitable for patients who have shorter attention or poor visual acuity, but who can still cooperate and maintain fixation Tests both central and peripheral field
Static target Threshold perimetry		≥ 9 yr	Accurate, but threshold may vary in affected locations and requires good attention Stationary test object of constant size with variable intensity Tests both central and peripheral field
Electroretinogram (ERG) light-evoked potential		All ages	Fall-back option for a patient that cannot perform perimetry; usually requires sedation in children. Limited availability

[a] Cognitive age.

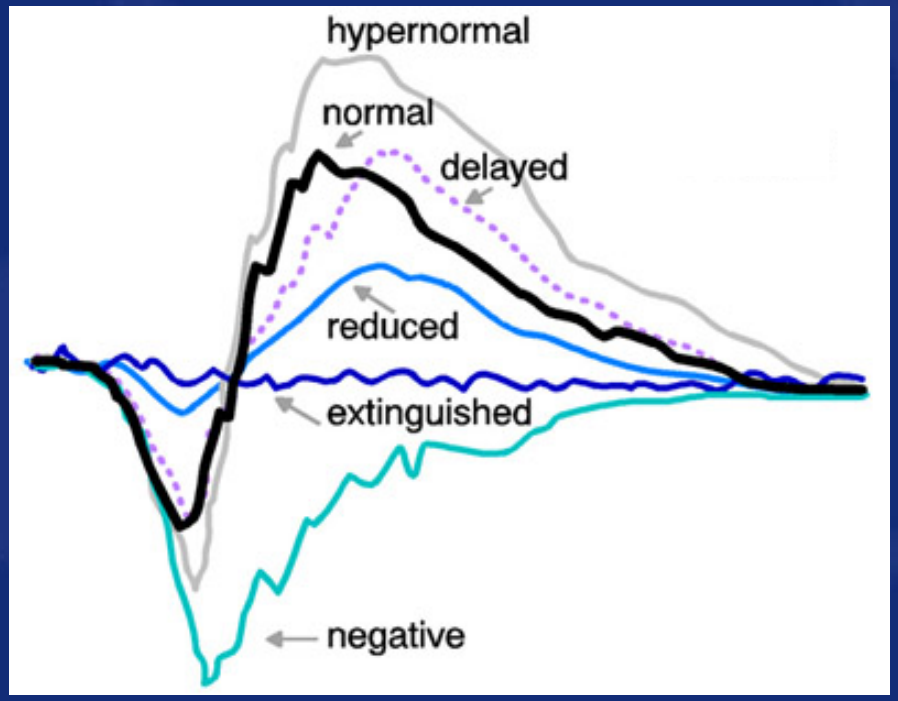
Reliability of Perimetry Testing in Epilepsy Patients Compared to Glaucoma Patients

- **Approximately 20% of epilepsy patients are unable to perform standard visual fields, according to Harding et al (2000)[a]**
- **Joint study from Detroit and Toronto demonstrated that only 25% - 34% of patients with glaucoma are unable to perform standard visual fields[b]**
- **Therefore, unreliable visual field testing in a small segment of patients is not a new or insurmountable problem for ophthalmologists**

[a] Harding GF, et al. *Neurology*. 2000;55(3): 347-352.
[b] Birt CM, et al. *Ophthalmology*. 1997;104(7):1126-1130.

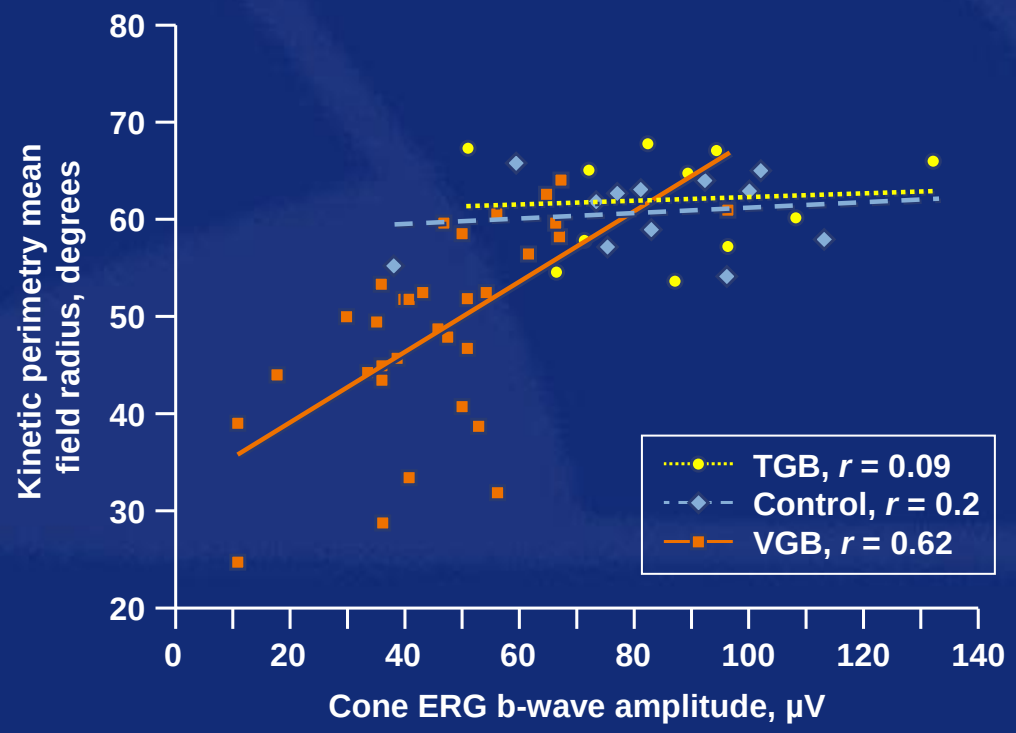
Electroretinogram Use for Infants and Adults Treated With Vigabatrin

- During ERG test, cells of retina (rods and cones) release tiny amounts of electricity in response to flashes of light
- If we know exactly how much light enters the eye and how much electricity comes out, we can determine how rods and cones are working
- To pick up electricity from retina, pupils are dilated, eyes dark-adapted, and a special contact lens is placed on surface of the eye



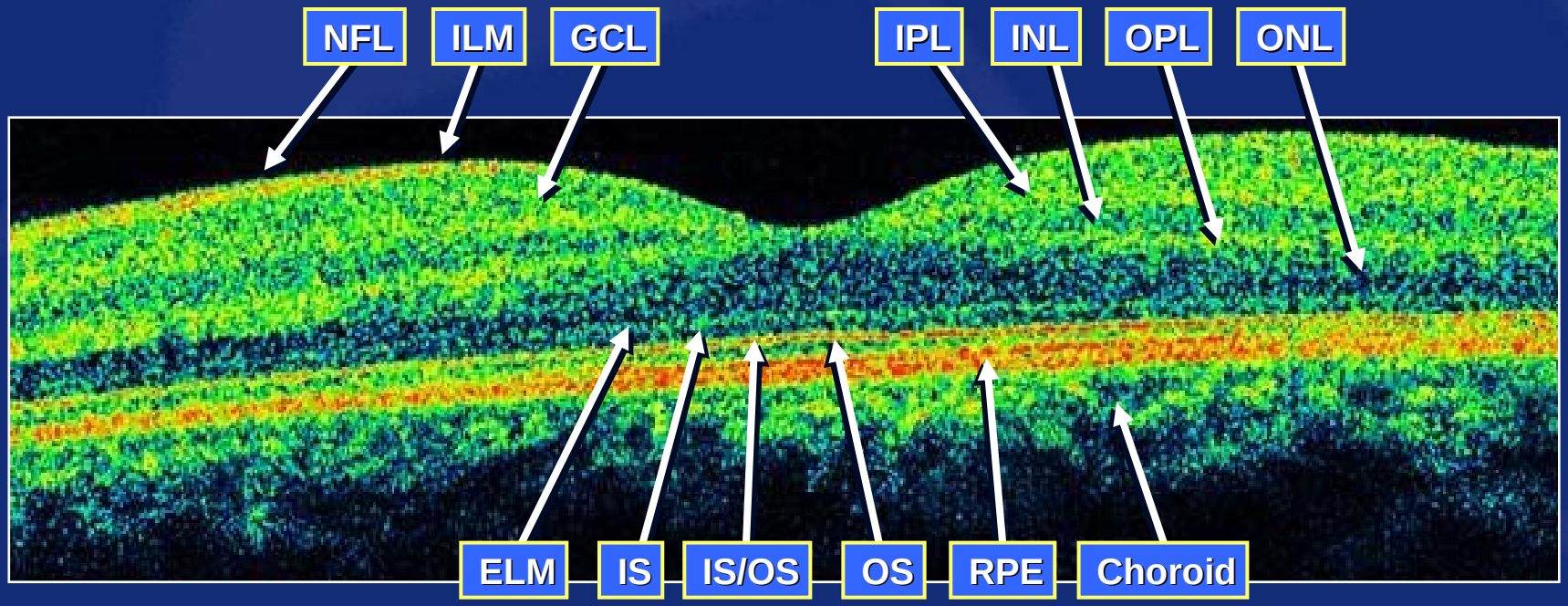
ERG as a Complementary Study for Possible Visual Field Constriction

- b-wave amplitude appears to correlate with peripheral field constriction
- Review of the literature discloses occasional discrepancies between visual field testing and ERG
- Discrepancies likely due to unreliable visual field testing



Krauss GL, et al. *J Neurol Neurosurg Psychiatry*. 2003;74:339-343.

Spectral Domain Optical Coherence Tomography



NFL = Nerve Fiber layer
ILM = Inner limiting membrane
GCL = Ganglion cell layer
IPL = Inner plexiform layer
INL = Inner nuclear layer

OPL = Outer plexiform layer
ONL = Outer nuclear layer
ELM = External limiting membrane
IS = Photoreceptor inner segment

IS/OS = Junction of inner and outer photoreceptor segments
OS = Photoreceptor outer segment
RPE = Retinal pigment epithelium

Use OCT to monitor retinal nerve fiber layer and macular thickness with vigabatrin use

Activities Retained After Onset of pVFD

✓ = Activities retained

+/– = May or may not be affected

Retained binocular field	Binocular Activities of daily living	Driving	Walking safely	Reading, watching TV, recognizing people
Mild (120° - 160°)	✓	✓	✓	✓
Moderate (60° - 120°)	✓	+/–	✓	✓
Severe (< 60°)	✓	—	Develop adaptive strategies such as scanning	✓

Ovation 2008 neuroophthalmologist panel.

Summary of Testing Reliability for VGB-Induced pVFD

✓ = Reliable test
+/– = May or may not be reliable

pVFD severity	Confrontation	Kinetic perimetry	Automated kinetic perimetry	Static perimetry	ERG	OCT
Mild (120° - 160°)	–	+/–	+/–	+/–	+/–	+/–
Moderate (60° - 120°)	✓	✓	✓	✓	✓	✓
Severe (< 60°)	✓	✓	✓	✓	✓	✓

Ovation 2008 neuroophthalmologist panel.

Approved Medications With Potential Retinal/ Optic Nerve Toxicity—Acceptable Risk/Benefit Ratio

Disruption of the retina and RPE

- Phenothiazines
  - Thioridazine
  - Chlorpromazine
- Chloroquine derivatives
  - Chloroquine
  - Hydroxychloroquine
- Quinine sulfate
- Clofazimine
- Deferoxamine/Desferrioxamine

Vascular occlusion

- Quinine sulfate
- Ergot alkaloids
- Oral contraceptives

Cystoid macular edema or retinal edema/folds

- Nicotinic acid
- Corticosteroids – central serous retinopathy
- Oral contraceptives

Crystalline retinopathy

- Methoxyflurane
- Tamoxifen
- Canthaxanthine
- Nitrofurantoin
- Talc

Miscellaneous

- Chemotherapeutic agents
- Amiodarone
- Rifabutin
- Ethambutol, rifampin, methotrexate
- Anti-TNF agents for RA

Adapted from American Academy of Ophthalmology (AAO) Focal Point Update Series.

Visual Acuity and Vigabatrin

- One study has been cited by the Agency that reports mild visual acuity changes with VGB
- Several issues make this finding difficult to interpret
  - Visual acuity was not reported to be done with standardized luminance
  - No refractions were performed as is required for standardized clinical trials. A pinhole test is not a reliable substitute for an expert refraction.
  - "Several older" patients were reported to have mild cataracts
  - No central scotomas (central visual deficits) were detected with visual field testing
- 12/32 had visual acuity ranging from 20/25 to 20/60, a level of vision that will permit those patients to read normal size type, recognize faces, and drive in many states
- 20/32 had visual acuity of 20/20 or better

[a] Miller NR, et al. *Neurology*. 1999;53(9):2082-2091.

Summary

- We understand that some patients treated with VGB will develop pVFD
- Currently available ophthalmologic testing methods can reliably detect moderate pVFD
- Periodic ophthalmologic examinations should be required in VGB treated patients to prevent clinically meaningful pVFD and to assess the benefit/risk ratio of this medication

Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures

Peripheral Visual Field Defect (pVFD) Characterization

Stephen M. Sagar, MD

Medical Director
Ovation Pharmaceuticals, Inc.

OVATION PHARMACEUTICALS, INC.

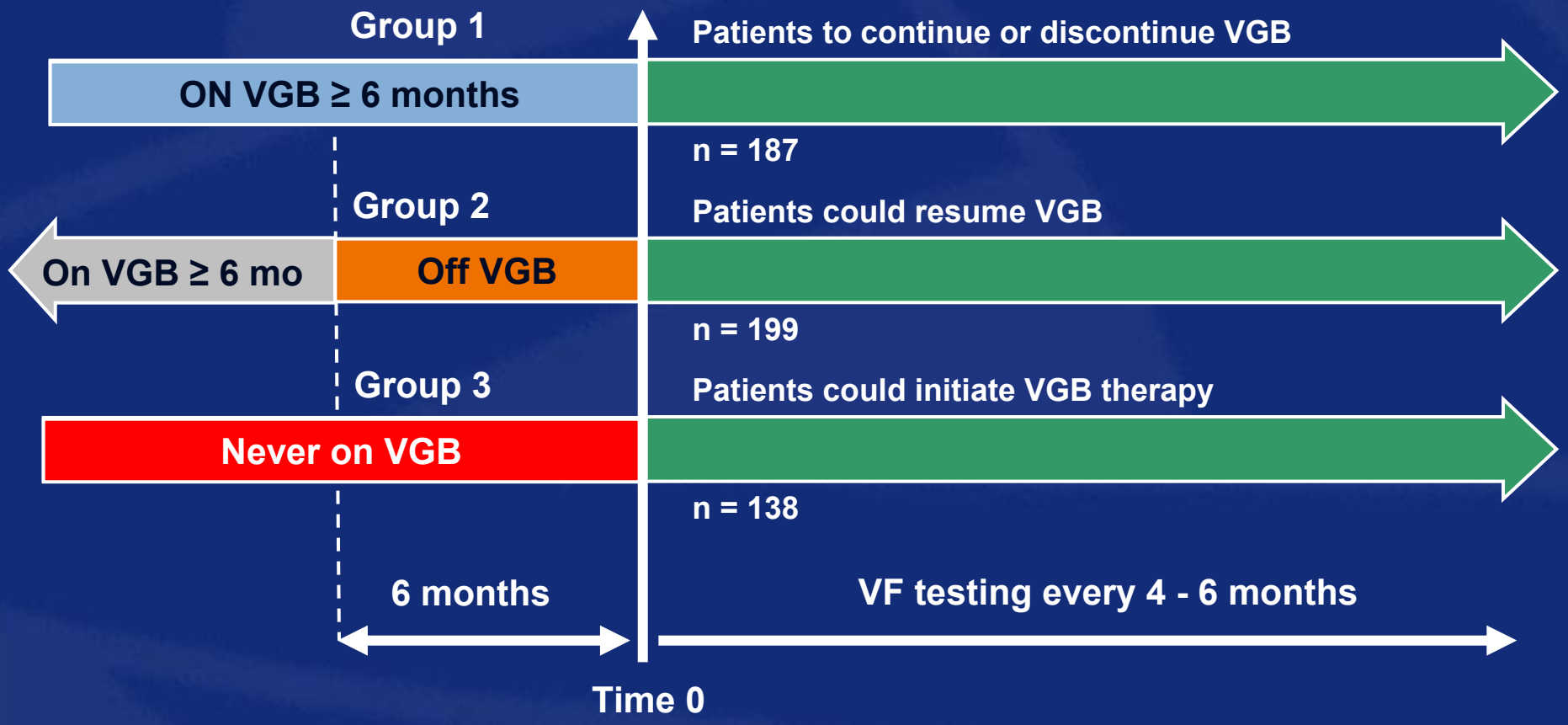
VGB-Induced pVFD

- Clinical features
- Study 4020 design and limitations
- Frequency of pVFD
- Severity and impact on the patient
- Risk factors
- Time course
- Visual acuity
- Conclusions and recommendations

VGB-Induced pVFD

- VGB can cause bilateral, concentric peripheral constriction of the visual fields, often more marked in the nasal than the temporal visual field
- Preponderance of the evidence supports no effect on visual acuity
  - Rare reports with confounding factors and minimal effect
- The retina is the site of injury

Schematic
Study 4020



Children: 8 - 12 years old (n = 126)
Adults: > 12 years old (n = 398)

Study Design
Study 4020

- Perimetries, either static or kinetic or both, every 4 to 6 months for up to 3 years
- Primary outcome measure, BCPC, was based on central review of perimetries by a single reader, Dr. John Wild, masked to treatment
- Ovation performed post-hoc, quantitative analysis based on 347/524 subjects who underwent Goldmann perimetry

Limitations
Study 4020

- BCPC determination based on overall clinical assessment of one reader
- Few Group III subjects began VGB on-study
- Few observations with short durations of drug exposure
- Specifications for perimetries relaxed during the study
- Subject selection and discontinuations may impact data interpretation

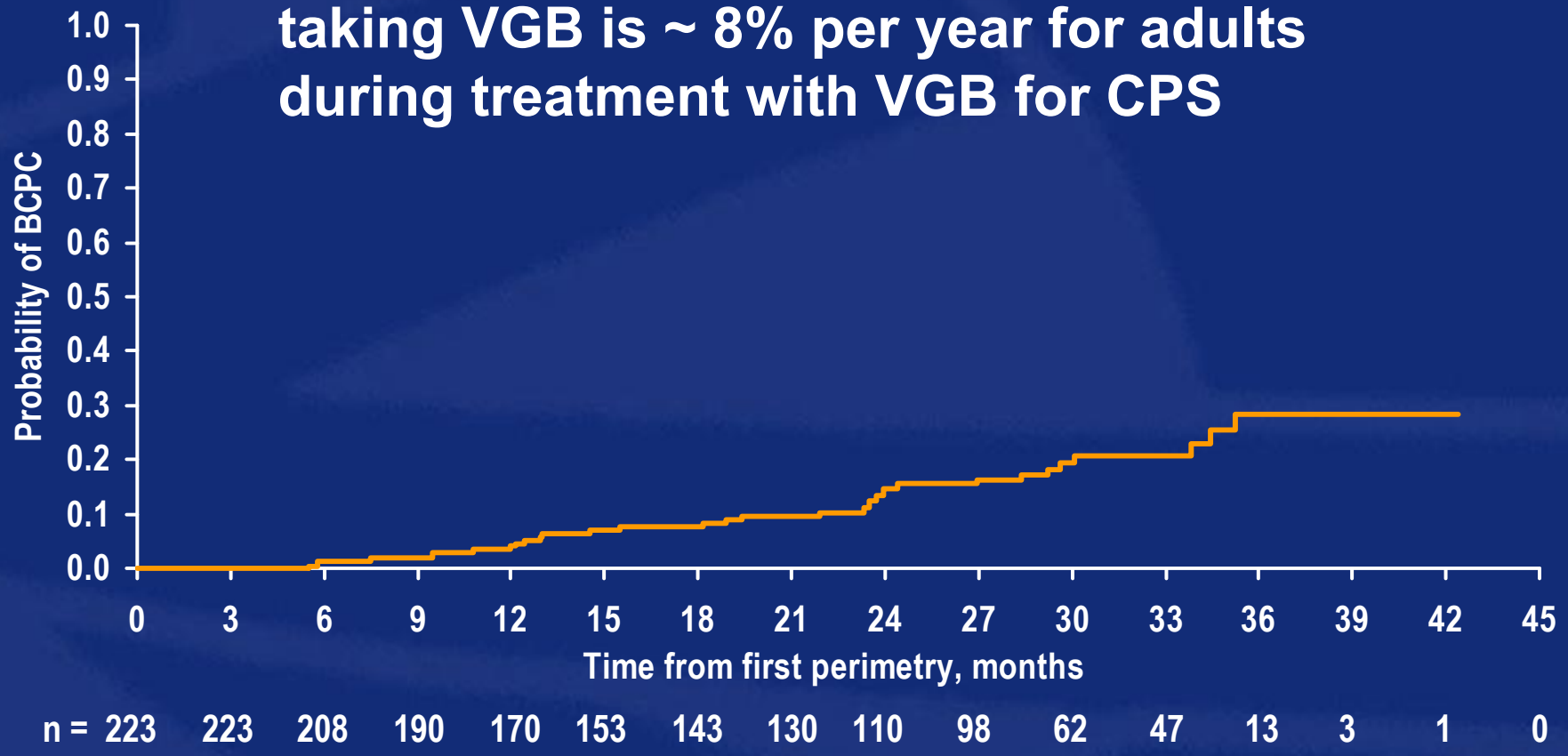
Prevalence of BCPC
Study 4020

Group	Prevalence, % (95% CI)	Median exposure, yr
Adult First conclusive perimetry	27.8 (20.2, 29.0)	3.2
Adult Confirmed BCPC	24.6 (19.8, 29.9)	4.7
Children Confirmed BCPC	15.3 (5.6, 19.9)	4.3
Highest prevalence		
Adult Group I ≥ 1 BCPC	45.6 (37.5, 54.0)	5.2
Adult Group I Confirmed BCPC	32.9 (25.4, 41.0)	5.4

Incidence of BCPC

Study 4020—Initially BCPC-free Cohort

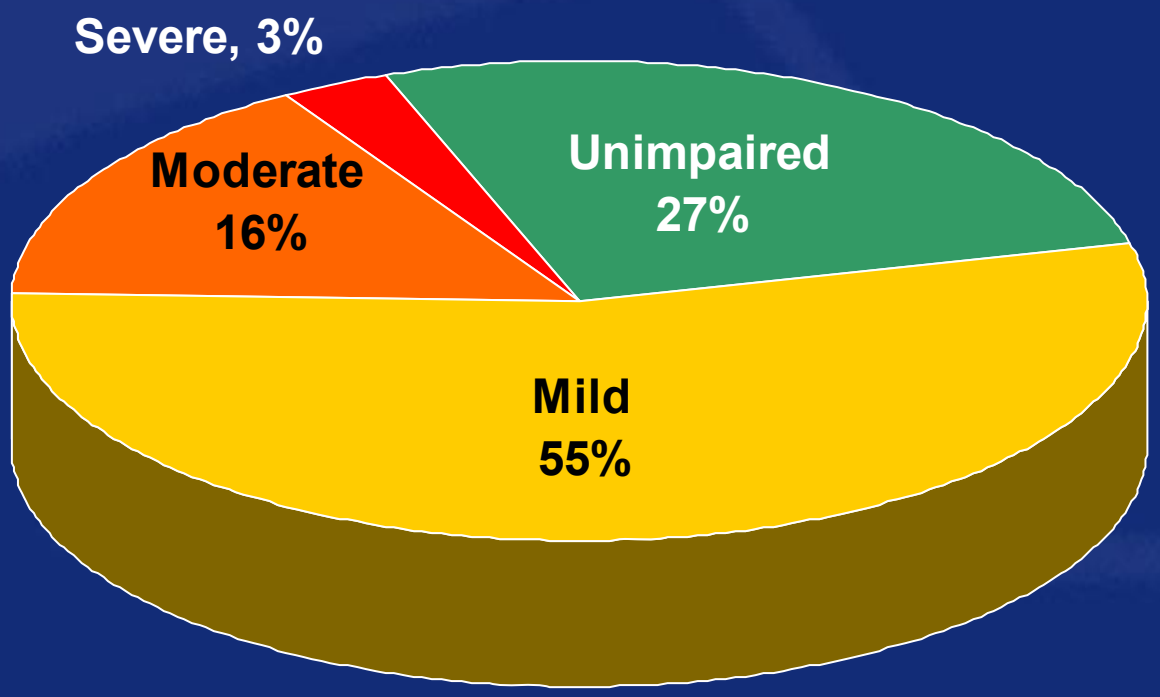
The risk of developing a new pVFD while taking VGB is ~ 8% per year for adults during treatment with VGB for CPS



Includes all evaluable patients exposed to VGB on or before their final perimetry.

Visual Field Impairment

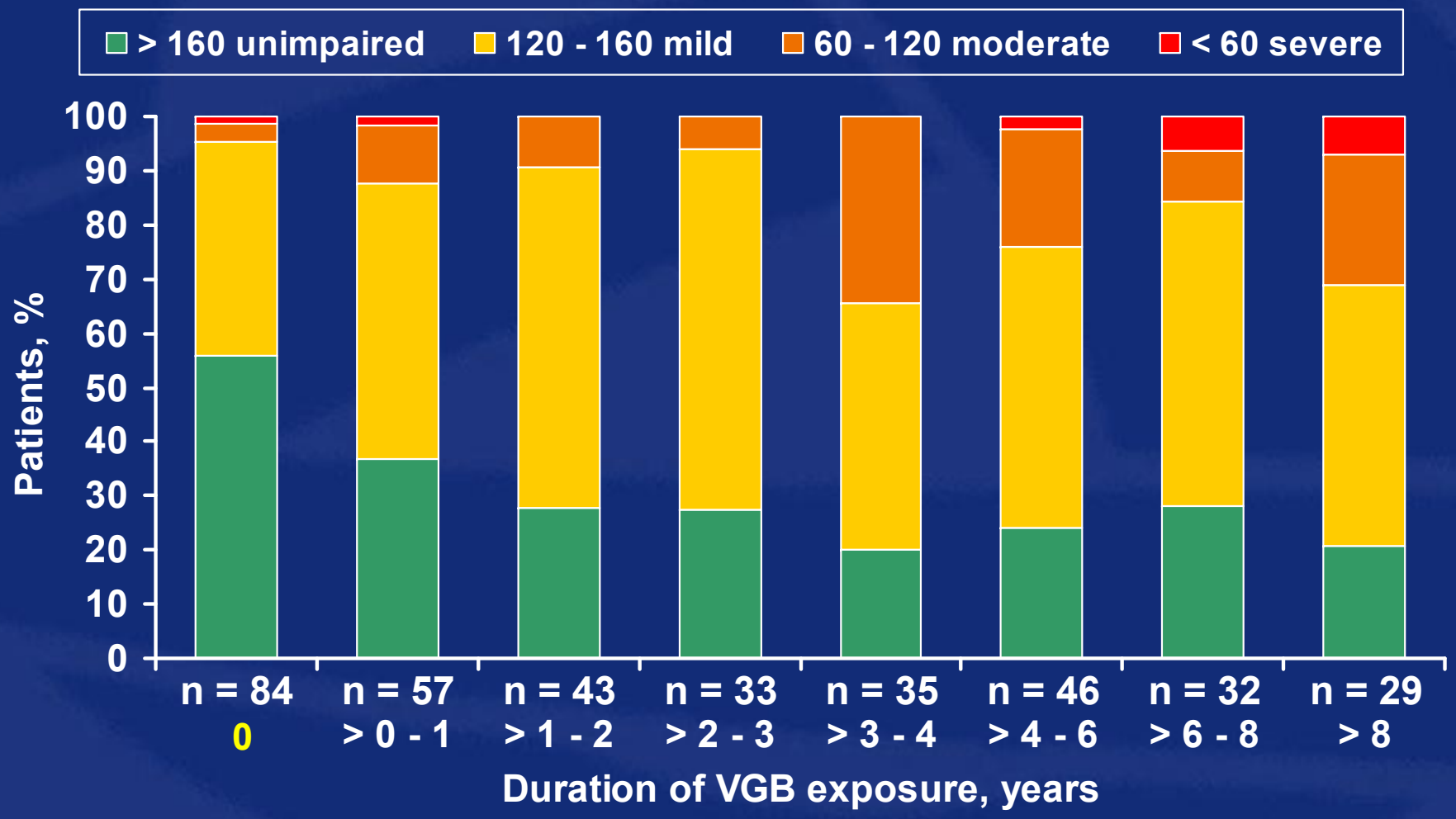
Study 4020 (N = 347)



- Unimpaired: > 160° binocular visual field, > 80° monocular temporal field retained
- Mild: 120 - 160° binocular visual field, 60 - 80° monocular temporal field retained
- Moderate: 60 - 120° binocular visual field, 30 - 60° monocular temporal field retained
- Severe: < 60° binocular visual field, < 30° monocular temporal field retained

Severity of pVFD—Retained Visual Field

Study 4020—Goldmann Perimetry



Impact on the Patient

Study 4020—Patients With Goldmann Perimetry

Answered Yes to ≥ 1 of 17 QOL questions

Population	Unimpaired (> 160), %	Mild (120 to 160), %	Moderate (60 to < 120), %	Severe (< 60), %
Adults	34.3 n = 99	36.8 n = 171	54.2 n = 48	66.7 n = 6
Children	12.5 n = 24	23.1 n = 52	47.1 n = 17	66.7 n = 3

Unless the pVFD becomes severe, it is generally asymptomatic and has minimal impact on quality of life

VGB-Induced pVFD—Risk Factors

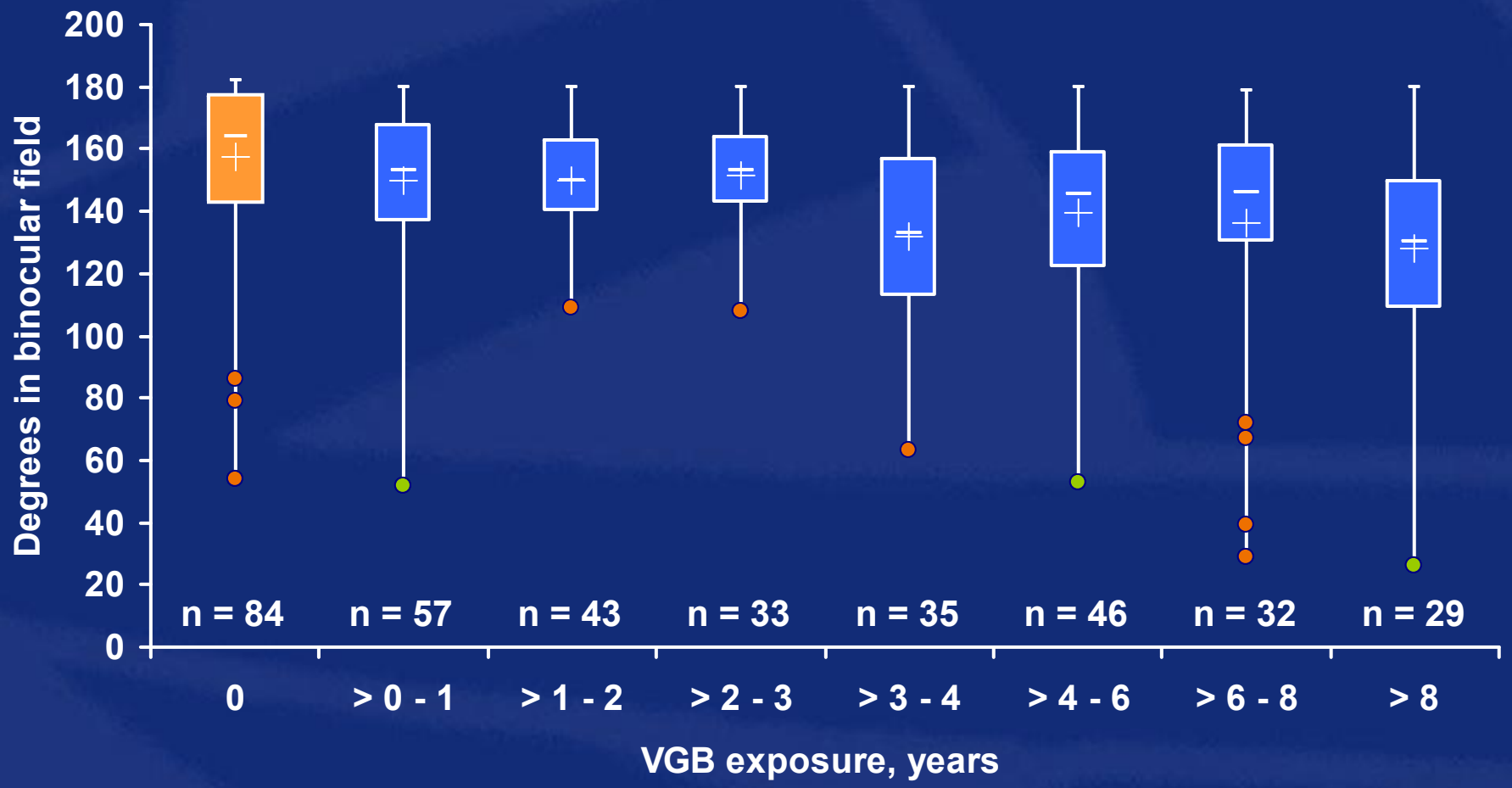
- Risk of pVFD increases with
  - Duration of exposure
  - Cumulative dose
  - Daily dose

VGB-Induced pVFD—Time Course

- In the majority of cases, VGB-induced pVFD is a slow process, generally becoming detectable by perimetry only after several years of exposure in adults
- Progression to a severe deficit (loss of < 60 degrees of temporal visual field) generally requires ≥ 3 years of exposure

All Patients With Goldmann Perimetry

Study 4020



Change of Temporal Field On VGB

Study 4020—Patients With Goldmann Perimetry

Cohort	VGB status	Subjects	Change, degrees/year of exposure	Standard error	*p* value
Adult I and III	On	91	–1.61	0.42	< 0.001
Adult I and II	Off	138	–1.65	0.45	< 0.001
Adult III	Off	66	NA	NA	NA
Child I and III	On	33	–0.94	0.95	0.330
– Child I and III	On < 7.5 years	29	–0.04	0.73	0.961
– Child I and III	On ≥ 7.5 years	4	–11.70	3.25	0.035
Child I and II	Off	43	–1.66	0.63	0.012
Child III	Off	17	NA	NA	NA

VGB-Induced pVFD—Time Course

- **Onset of pVFD detectable by perimetry is, with uncommon exceptions, after > 1 year of exposure**

VGB-Induced pVFD Onset < 1 Year—Clinical Studies

Source	Earliest onset	n/N	Comments
Study 4020	9 mo	5/58	Confirmed BCPC
R003	2 mo	1/25	Abnormal baseline exam
Pooled cohort analysis	< 1 yr	2/104	

Pooled Cohort Analysis

- Cross-sectional study
- Perimetry method and grading system not described
- Incidence analyses invalid
  - Wrong denominators used for subjects exposed
  - Only 2/104 subjects with VFD after ≤ 1 year VGB exposure

VGB-Induced pVFD Onset < 1 Year—Literature

Source	Earliest onset	n/N	Comments
Kiratli & Turkcuoglu (2001)	6 mo	1/1	No baseline, ERG normal
Malmgren et al. (2001)	4 mo	1/99	Abnl = < 80 deg temp, < 40 deg nasal
Riise et al. (2003)	1 yr	1/31	
Schmitz et al. (2002)	9 mo	1/29	Prospective study
Wild et al. (1999)	1 yr	1/42	
Fechtner et al. (2008)	NA	0/18	Prospective study, 8 week exposure

Kiratli & Turkcuoglu 2001 *Eye*; Malmgren et al 2001 *Epilepsia*; Riise et al 2003 *Weekly Journal for Doctors*; Schmitz et al 2002 *J Neurol*; Wild et al 1999, *Epilepsia;* Fechtner et al 2006 *Arch Ophthalmol*

VGB-Induced pVFD Onset < 1 Year—Postmarketing

- Database reviewed through 15 May 2008
- 'VFD' reported: 980 cases, 29 cases (6.4%) within 1 yr of VGB start
  - 23 had no documentation of a pVFD
  - 6 possible cases
    - 5 had inadequate documentation of the pVFD
    - 1 documented case: 19 yo female, normal baseline perimetry, pVFD at 5 weeks of VGB, resolved at 2 months after stopping VGB

VGB-Induced pVFD Time Course

- **With some possible exceptions, VGB-induced pVFD neither reverses nor progresses after drug is discontinued**

Change in Temporal Field Off VGB

Study 4020—Patients With Goldmann Perimetry

Cohort	Patients	Change, degrees/ year of exposure	Standard error	*p* value
Adult I and II	138	–0.15	0.50	0.773
Adult III	66	–1.32	0.65	0.050
Child I and II	43	2.05	1.24	0.108
Child III	17	1.44	1.36	0.317

Does VGB Affect Visual Acuity?

- The vast preponderance of the evidence indicates that VGB has no detectable long-term effects on visual acuity
- Few reports
  - Degree of impact minor
  - Confounded by other factors
  - Some fail to distinguish reversible pharmacologic effects while taking drug from permanent effects

Visual Acuity—Glasgow Data

	Visual acuity (logMAR units)			
Right eye	On VGB	Prior VGB	GABA AED	Non GABA AED
n	56	49	46	53
Median	0.00	0.05	0.08	0.00
Mean	0.07	0.08	0.04	0.10
Std Dev	0.15	0.14	0.35	0.42
Range	–0.1 - 0.8	–0.1 - 0.6	–2.0 - 0.7	–0.2 - 3.0

No differences between VGB and non-VGB treatment groups

Visual Acuity and Color Vision
Literature Reports

Author	Patient population	Results
Malmgren et al (2001)	99 VGB	19 w/VFD, VA WNL in all
Krauss et al (2003)	32 VGB, 12 TGB, 14 control	No difference between groups in VA
McDonagh et al (2003)	32 VGB (> 3 yr) 30 matched controls	No difference in VA, color vision
Kalviainen et al (1999)	32 VGB (mean 69 mos) 18 CBZ	40% VFD in VGB, 0 in CBZ (Goldmann), VA normal
Lawden et al (1999)	31 VGB	12 w/VFD (Humphries), VA and color WNL in 11
Wild et al (1999)	42 VGB	39 w/BCPC (Goldmann), VA, color vision unaffected
Miller et al (1999)	39 VGB 11 control	20 VGB w/ VA 20/20 or better; 12 VGB w/ VA 20/25 to 20/60, controls w/ NL VA, 19 VGB w/ color vision 3.5 to 8.5 (of 10)

Malmgren et al 2001 *Epilepsia;* Krauss et al 2003 *J Neurol Neurosurg Psychiatry*; McDonagh et al 2003 *Neurology*; Kalviainen et al 1999 *Neurology*; Lawden et al 1999 *J Neurol Neurosurg Psychiatry;* Wild et al 1999 *Epilepsia*; Miller et al 1999 *Neurology*

Implications for Monitoring Vision

- **Because the retinal effects may be asymptomatic, ongoing benefit/risk assessments for patients taking VGB require periodic ophthalmologic examinations**

Visual Function Monitoring
Mandatory Visual Testing

- Ophthalmological testing at baseline and then every 6 months while taking drug
- Increase in frequency to every 3 months if pVFD detected
- Use methods appropriate for cognitive ability
  - Confrontation
  - Kinetic and/or static perimetry
  - ERG
  - OCT

VGB-Induced pVFD Summary

- No effect on visual acuity
- VGB is associated with a distinctive bilateral constriction of the visual field (pVFD)
- Based on Study 4020, fewer than 3% will develop a severe restriction of peripheral vision over the first 4 - 5 years of exposure
- Generally progresses slowly, allowing effective monitoring of visual function
- Cognition and age-appropriate methods exist to monitor visual function

Sabril® (vigabatrin) Tablets and Powder for Oral Solution

Risk Evaluation and Mitigation Strategy (REMS)

Tim Cunniff, PharmD

Vice President, Global Regulatory Affairs, Pharmacovigilance & Clinical Quality Assurance
Ovation Pharmaceuticals, Inc.

OVATION PHARMACEUTICALS, INC.

Sabril REMS Goals

- To minimize the risk of Sabril-induced peripheral visual field defect (pVFD)
- To detect Sabril-induced pVFD before it results in a clinically meaningful restriction of the patient's peripheral vision
- To ensure regular ophthalmologic monitoring to facilitate ongoing benefit-risk assessments

Sabril REMS Elements

S·H·A·R·E™
Support, Help And Resources for Epilepsy

Medication Guide

- Risks explained in patient-friendly language via Medication Guide
  - pVFD
  - MRI
  - Suicidality
- Dispensed with every Rx

Communication Plan

- Dear Healthcare Provider Letter
  - pVFD
  - MRI
- Physician education
  - pVFD
  - MRI
- Patient/Caregiver education
  - pVFD
  - MRI

Elements to Assure Safe Use

- Mandatory SHARE registration
- Restriction of initial Rx to neurologists
- Controlled drug distribution
- Enforced benefit/risk assessment after evaluation phase
- Visual testing reminder system
- Enforced ophthalmologic monitoring
- Sabril registry

Medication Guide

- To provide information to the patient/caregiver about the risks (ie, pVFD, MRI, and AED suicidality) associated with Sabril therapy
- Written in patient-friendly language
- Reviewed and discussed with the patient/caregiver multiple times during the prescribing and dispensing process
- Provided with each prescription fill

MEDICATION GUIDE
Sabril® (vigabatrin) Tablet for Complex Partial Seizures in Adults
(Pronounced as Say-bril)

To use Sabril appropriately you should:

- Be aware that Sabril may cause a serious vision problem in some people.
- Read this Medication Guide to understand the potential benefits and potential risks of Sabril therapy.
- Discuss and sign the Patient-Physician Agreement if you agree.
- Report any side effects of Sabril to your doctor immediately.
- Visit your doctor regularly to re-evaluate if the benefits of Sabril continue to outweigh its risk.

Read this Medication Guide carefully. You doctor may require you to sign a Patient-Physician Agreement before you start taking Sabril. Read the Medication Guide you receive with each Sabril refill as it may contain new information. This Medication Guide does not take the place of talking with your doctor.

1. WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT Sabril?

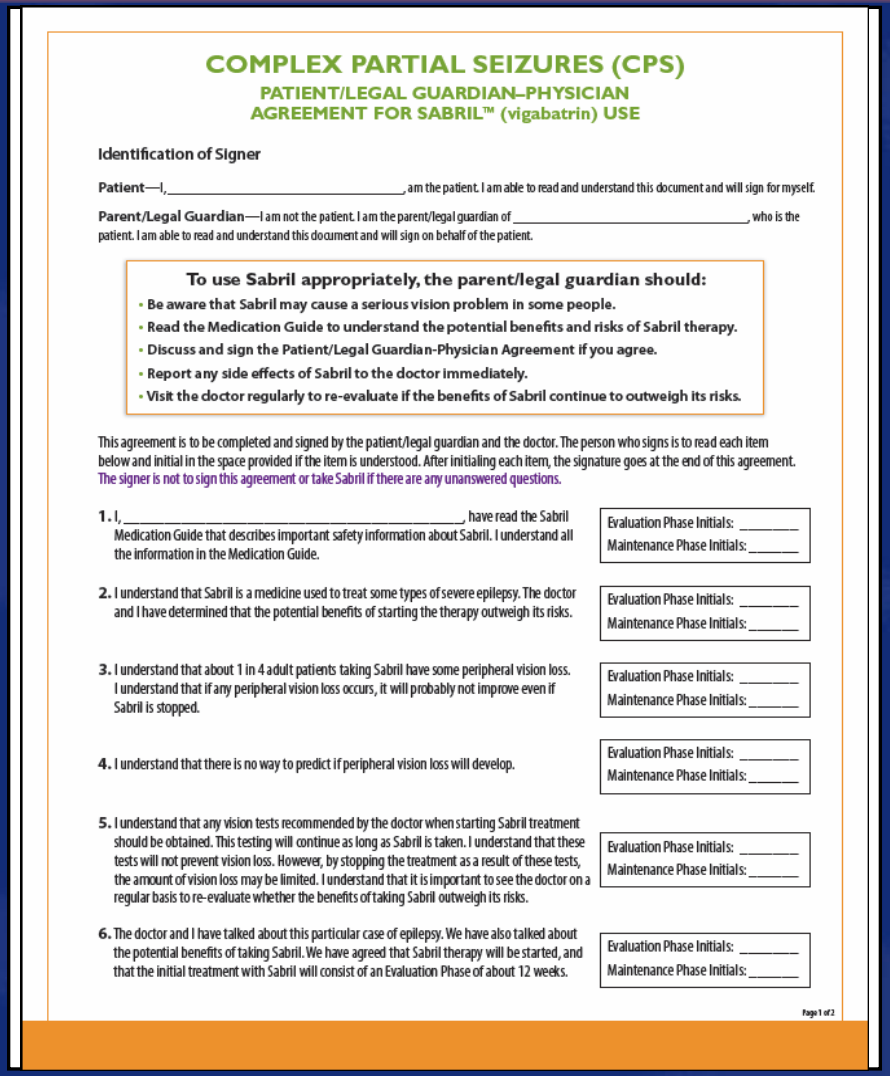
About one-quarter of adults (about 1 out of 4) and 15% of children (about 1 out of 7) who take Sabril may lose some peripheral vision. Peripheral vision is what you use to see out of the corner of your eye and at the very top or bottom. Sabril does not change central vision, which is the vision you use to read or watch television. People who have a peripheral vision problem may not be able to see things by their nose or an object to the side without turning their head.

In adults who got this vision problem after taking Sabril, the earliest it happened in clinical studies was after taking Sabril for 12 months. The amount of vision loss is different in everyone but usually, people who develop the problem may lose about one-fifth (1/5) of their side vision. The problem develops slowly over many weeks to months. If you get this vision problem, it does not go away. There is no way to treat this vision problem. If you stop taking Sabril, the chance of getting the vision problem goes away. You should tell your doctor immediately if you notice any changes to your vision.

Your doctor will recommend eye tests that should be done when you start taking Sabril and at certain times while you are still taking it.

Communication Plan

- **Physician Education**
  - Sabril Labeling with Black Box pVFD Warning and MRI Warning
  - Dear Healthcare Professional (HCP) Letters
  - Sabril Benefit/Risk Slide Presentation
  - Visual Testing Guidance
- **Patient/Caregiver Education**
  - Medication Guide with pVFD and MRI Warnings
  - Patient - Physician Agreement
  - Brochure(s) on Epilepsy, Sabril, and pVFD
  - Web-based Visual Field Simulator



COMPLEX PARTIAL SEIZURES (CPS)

PATIENT/LEGAL GUARDIAN–PHYSICIAN AGREEMENT FOR SABRIL™ (vigabatrin) USE

Identification of Signer

Patient—I,_____, am the patient. I am able to read and understand this document and will sign for myself.

Parent/Legal Guardian—I am not the patient. I am the parent/legal guardian of _____, who is the patient. I am able to read and understand this document and will sign on behalf of the patient.

To use Sabril appropriately, the parent/legal guardian should:

- Be aware that Sabril may cause a serious vision problem in some people.
- Read the Medication Guide to understand the potential benefits and risks of Sabril therapy.
- Discuss and sign the Patient/Legal Guardian-Physician Agreement if you agree.
- Report any side effects of Sabril to the doctor immediately.
- Visit the doctor regularly to re-evaluate if the benefits of Sabril continue to outweigh its risks.

This agreement is to be completed and signed by the patient/legal guardian and the doctor. The person who signs is to read each item below and initial in the space provided if the item is understood. After initialing each item, the signature goes at the end of this agreement. The signer is not to sign this agreement or take Sabril if there are any unanswered questions.

1. I, _____, have read the Sabril Medication Guide that describes important safety information about Sabril. I understand all the information in the Medication Guide.
   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____
2. I understand that Sabril is a medicine used to treat some types of severe epilepsy. The doctor and I have determined that the potential benefits of starting the therapy outweigh its risks.
   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____
3. I understand that about 1 in 4 adult patients taking Sabril have some peripheral vision loss. I understand that if any peripheral vision loss occurs, it will probably not improve even if Sabril is stopped.
   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____
4. I understand that there is no way to predict if peripheral vision loss will develop.
   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____
5. I understand that any vision tests recommended by the doctor when starting Sabril treatment should be obtained. This testing will continue as long as Sabril is taken. I understand that these tests will not prevent vision loss. However, by stopping the treatment as a result of these tests, the amount of vision loss may be limited. I understand that it is important to see the doctor on a regular basis to re-evaluate whether the benefits of taking Sabril outweigh its risks.
   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____
6. The doctor and I have talked about this particular case of epilepsy. We have also talked about the potential benefits of taking Sabril. We have agreed that Sabril therapy will be started, and that the initial treatment with Sabril will consist of an Evaluation Phase of about 12 weeks.
   Evaluation Phase Initials: _____
   Maintenance Phase Initials: _____

Page 1 of 2

Elements to Assure Safe Use

Prescribing → **Dispensing** → **Treatment**

Prescribing

Mandatory neurologist (initial Rx) & physician registration with attestation

Mandatory patient registration

Mandatory benefit/risk assessment before maintenance phase treatment

Dispensing

Controlled Drug Distribution System (SHARE)

Central call center with network of select specialty pharmacies

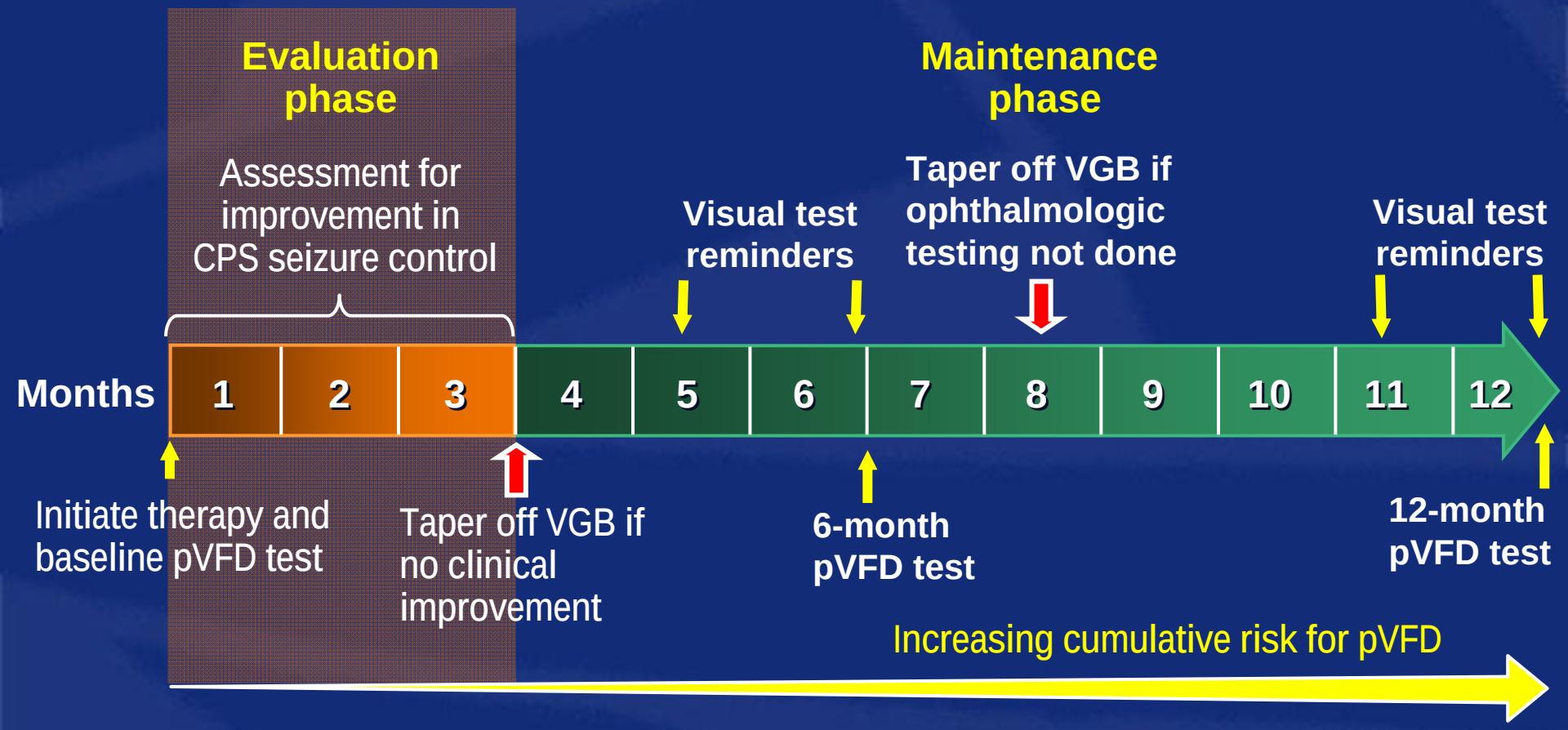
Treatment

Reminder system for visual testing

Enforced ophthalmologic monitoring for CPS patients

Sabril Registry

Enforced Benefit/Risk Assessment and Enforced Ophthalmologic Monitoring for Patients With CPS



pVFD = Peripheral visual field defect; CPS = Complex partial seizures.

Sabril Registry

- Data collection
  - Physician Attestation Form
  - Treatment Initiation Form
  - Treatment Maintenance Form
  - Ophthalmologic Assessment Form
- Annual reporting
  - Prescriber
    - Specialty, practice setting
  - Patient
    - Demographics, diagnosis, prior and current AEDs, dosing information, effectiveness (progression to treatment maintenance phase)
    - Ophthalmologic testing data (pVFD frequency, onset, severity, progression)

Assessment of Sabril REMS Effectiveness

- Data from Sabril Registry
- Physician and Patient/Caregiver Knowledge, Attitude and Behavior Surveys
  - 1 yr, 2 yr, 3 yr, 7 yr
- Pharmacovigilance Information
  - Periodic Adverse Event Reports: Quarterly × 3 years then annually
  - Expedited reporting of serious liver injury cases
- Assessment results will be discussed with FDA and REMS modifications implemented as appropriate

Sabril® (vigabatrin) Tablets for Refractory Complex Partial Seizures

Benefit/Risk Assessment

Roger J. Porter, MD

Adjunct Professor of Neurology
University of Pennsylvania, Philadelphia, PA

Adjunct Professor of Pharmacology
Uniformed Services University of the Health Sciences
Bethesda, MD

OVATION PHARMACEUTICALS, INC.

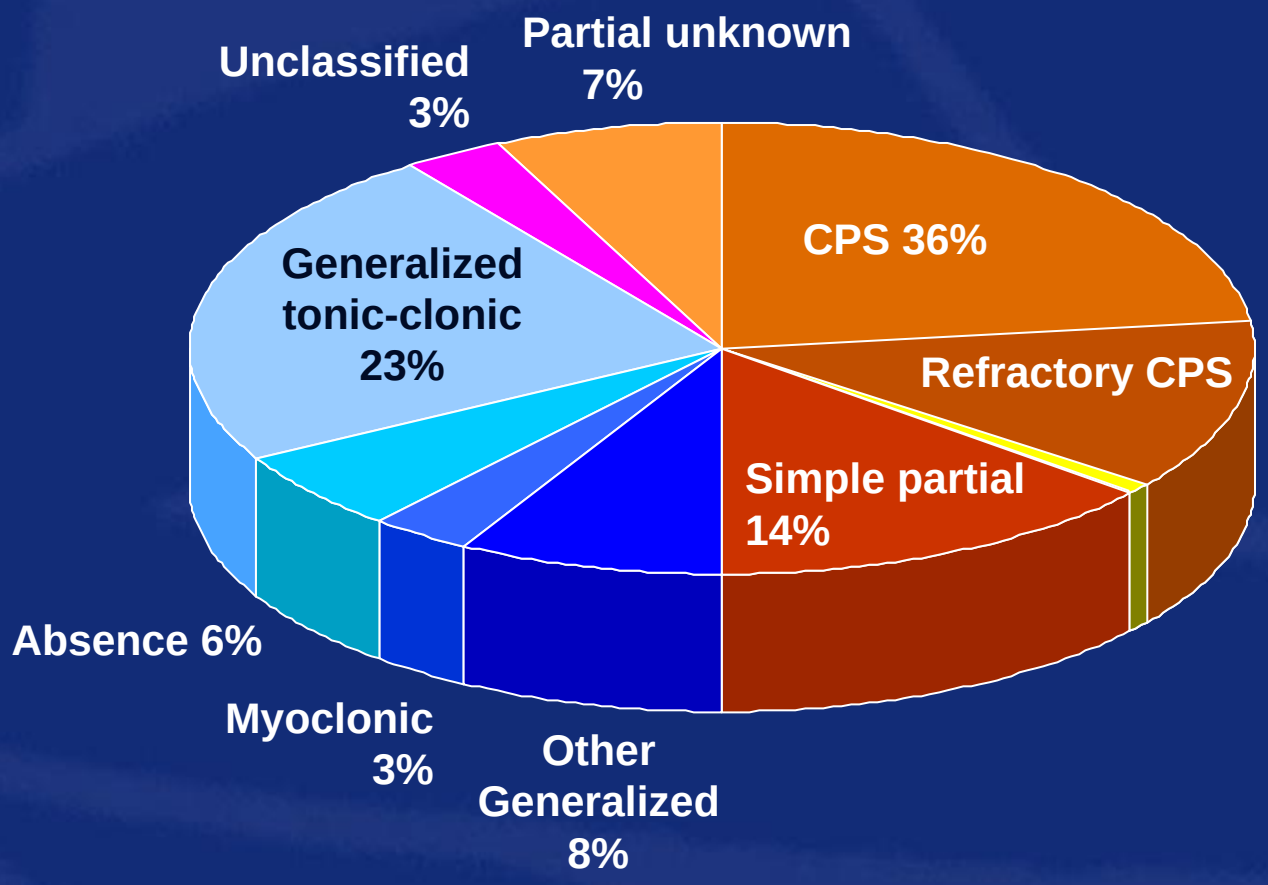
Sabril (vigabatrin) Tablets
CPS Benefit/Risk Assessment

I. **Patients with refractory complex partial seizures (CPS) have a devastating disorder**

II. **VGB has important benefits**

III. **VGB has some risks; these risks are manageable**

Complex Partial Seizures Are the Most Common Type of Seizure



Hauser. *Epilepsia*. 1993.

Morbidity/Mortality of Refractory CPS

- **Mortality rate** (in refractory seizures):
  - 4 - 7 times higher than general population
- **Injury rates**:
  - From 1 per 20 person-yr to 1 per 3 person-yr

Sperling MR. *CNS Spectr*. 2004;9:98-101, 106-109.

Morbidity/Mortality of Refractory CPS

- **Exacerbated by poor seizure control[a]**
  - **Frequent seizures = decreased quality of life[a]**
  - **Refractory CPS = increased risk of accidents and injuries vs general population[b]**
  - **Refractory epilepsy associated with SUDEP and suicide[b,c]**

SUDEP = Sudden unexpected death in epilepsy.

[a] Sperling MR. *CNS Spectr*. 2004;9:98-101, 106-109.
[b] Tomson T, et al. *Epilepsy Res*. 2004;60:1-16.
[c] Murro AM. Complex partial seizures. [Internet]. Updated October 11, 2006. Accessed January 12, 2007. Available at http://www.emedicine.com/NEURO/topic74.htm.

Treating Refractory Epilepsy Patients

- Some drugs work better in some patients
- Physicians cannot predict most effective drug for a specific patient
- Physicians use trial and error
  - Most drugs eventually attempted

Lowenstein DH. Seizures and epilepsy. In: Fauci AS, et al, eds. *Harrison's Principles of Internal Medicine, 17th Ed.* McGraw-Hill Companies. 2008: chapt 363.

Sabril (vigabatrin) Tablets
CPS Benefit/Risk Assessment

I. **Patients with refractory complex partial seizures (CPS) have a devastating disorder**

II. **VGB has important benefits**

III. **VGB has some risks; these risks are manageable**

Benefits of VGB as Add-on Therapy

- Substantial numbers of patients respond to VGB
- Demonstrated efficacy
  - Significant reduction in seizures
    - Clinical trial efficacy comparable to other AEDs
  - Freedom from seizures (7% - 12%)
  - Rapid onset of efficacy
- VGB generally well-tolerated
  - As with most other AEDs, the most common dose-related AEs are CNS-related

AED = Antiepileptic drug; AE = Adverse event; CNS = Central nervous system.

Dean C, et al. *Epilepsia*. 1999;40:74-82; Protocol 71754-3-C-025; NDA 20-427, v1.114.

Sabril (vigabatrin) Tablets
CPS Benefit/Risk Assessment

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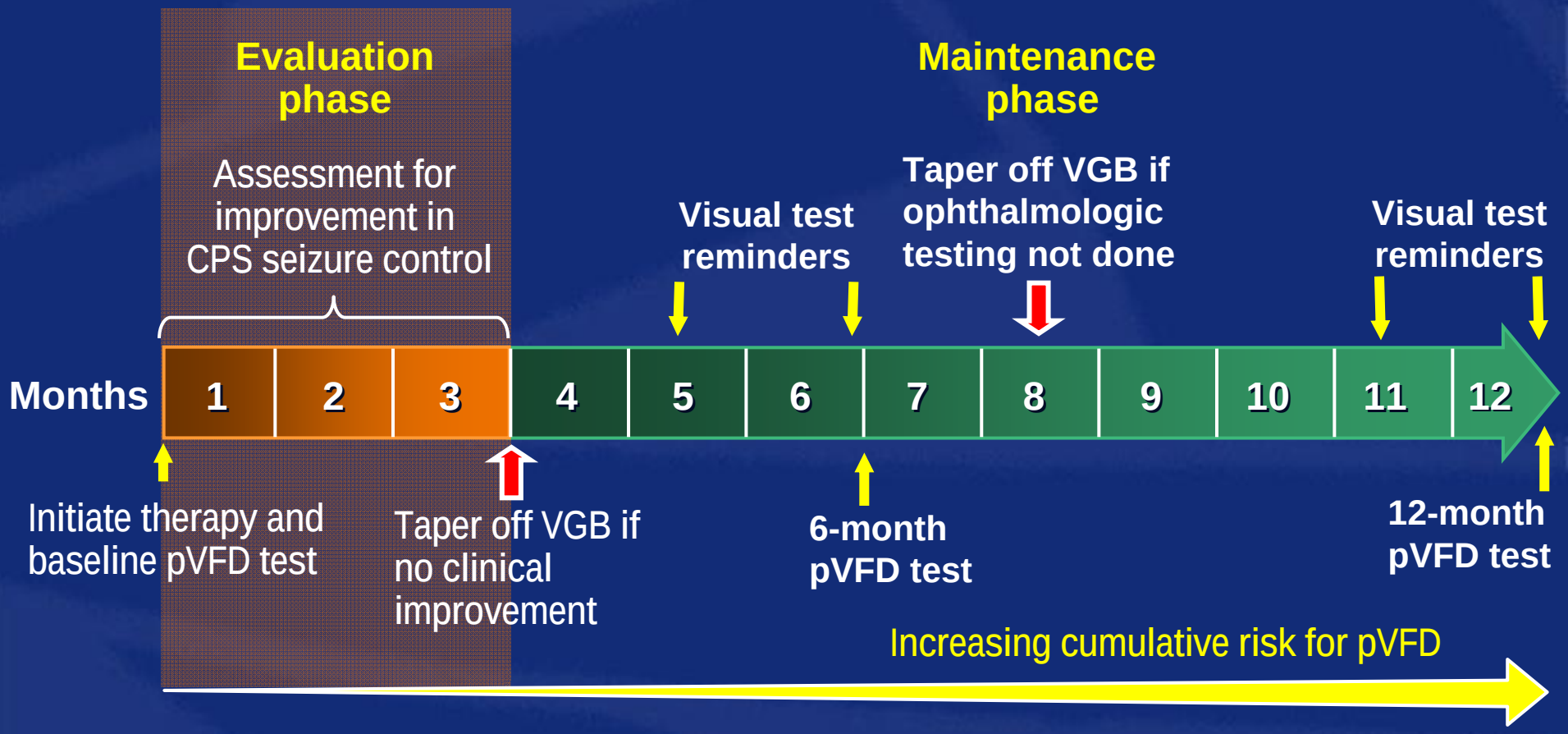
VGB in Refractory CPS—Risk of pVFD

- **Peripheral visual field defect (pVFD)**
  - **Well-characterized**
  - **Can be effectively monitored**
  - **Nonresponders can be discontinued early, thus limiting likelihood of exposure to risk**

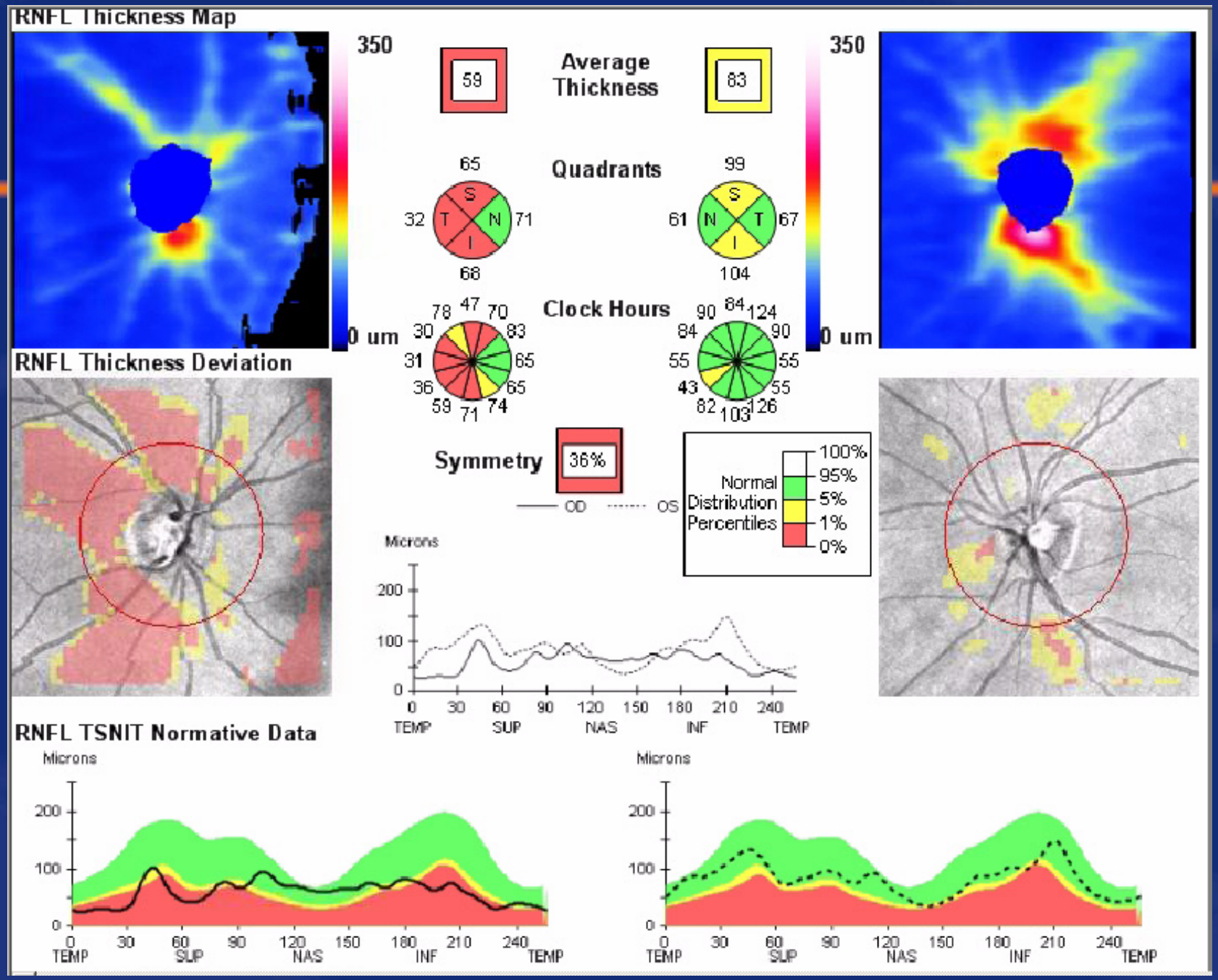
Enforced Benefit/Risk Assessment and Enforced Ophthalmologic Monitoring for Patients With CPS



pVFD = Peripheral visual field defect; CPS = Complex partial seizures.

Benefit/Risk of VGB Therapy in Adult Patients With Refractory CPS

- **Effective** option for decreasing/eliminating refractory CPS
- Opportunity exists to evaluate efficacy early, thus limiting exposure to pVFD risk
- Benefit:Risk **favors use of VGB** as adjunctive therapy for adult patients with refractory CPS who have inadequately responded to alternative treatments and for whom the potential benefits outweigh the potential risk of developing pVFD


RNFL Thickness Map
350
0 um
59
Average Thickness
83
350
0 um
Quadrants
65
S
32
T
N
71
I
68
99
S
61
N
T
67
I
104
Clock Hours
78
47
70
30
83
31
65
36
65
59
71
74
90
84
124
84
90
55
55
43
55
82
103
126
RNFL Thickness Deviation
Symmetry
36%
OD
OS
Normal Distribution Percentiles
100%
95%
5%
1%
0%
Microns
200
100
0
0
30
60
90
120
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210
240
TEMP
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NAS
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RNFL TSNIT Normative Data
Microns
200
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TEMP

Vigabatrin and OCT

- Cross-sectional, prospective observational design – right eye used
  - Group I – 13 patients VGB and field loss
  - Group II – 8 patients VGB, normal fields
  - Group III – 14 patients carbamazipine monotherapy
  - Group IV – 20 normal individuals, no epilepsy
  - Group V – 7 patients valporate montherapy
- Perimetry
  - 135 point full field screening followed by threshold 30-2 with and FASTPAC strategy

American Academy of Ophthalmology (AAO) Board Review Manuals, 2007-8.

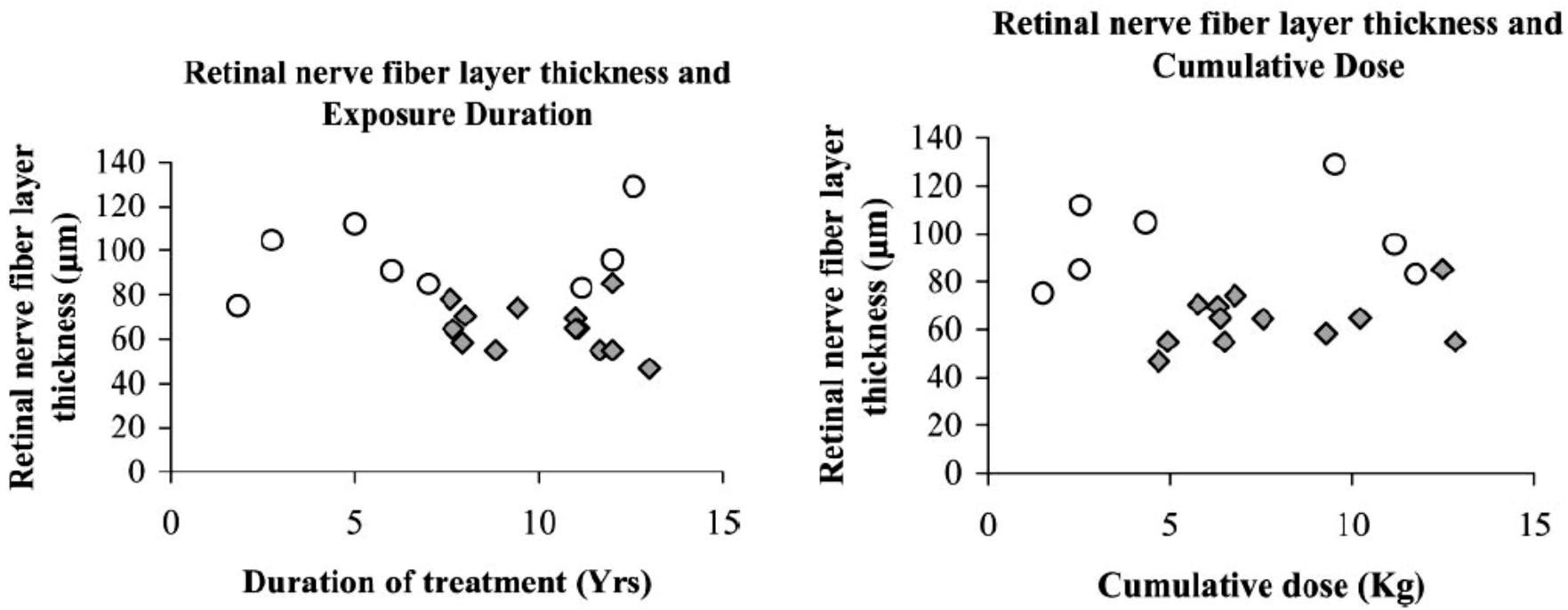


FIGURE 3. The average retinal nerve fiber layer thickness (in micrometers) for the complete 360° scan derived by OCT as a function of (*top*) duration of therapy (years) with vigabatrin and (*bottom*) cumulative dose of vigabatrin (kilograms) for the patients with vigabatrin-attributed visual field loss (Group I; *diamonds*) and for the patients exposed to vigabatrin but with normal fields (Group II; *circles*). Note that the cumulative dose could not be determined accurately in one patient in Group II, and the value has been omitted from Figure 3 (*bottom*).

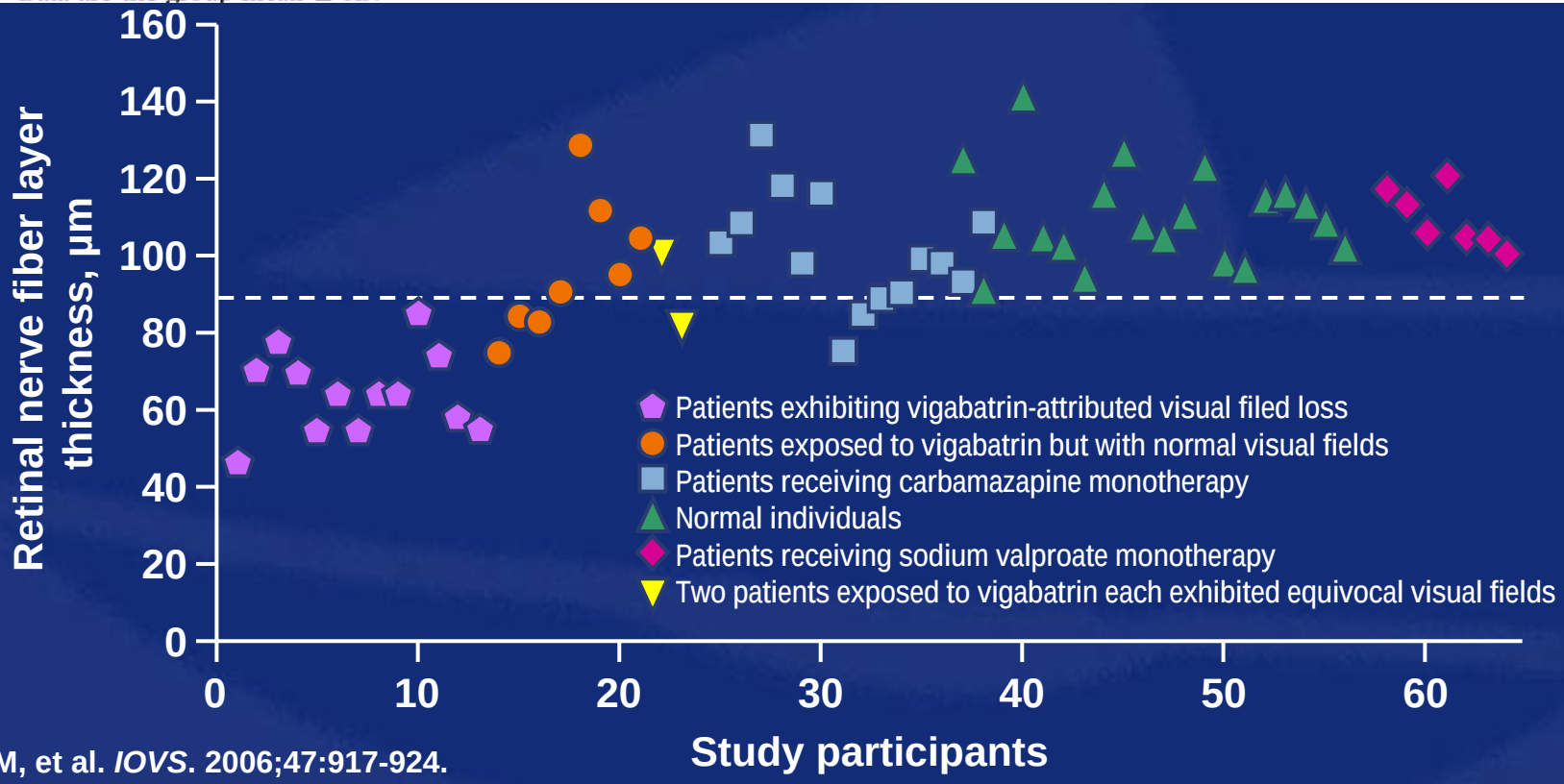
Wild JM, et al. *IOVS*. 2006;47:917-924.

Retinal Nerve Fiber Layer Thickness Derived by OCT

Wild JM, et al. (2006)

Group	Proportion Male: Female	Age (SD) (y)	Duration of Epilepsy (SD) (ys)	Duration of Vigabatrin Therapy (SD) (kg)	Cumulative Dose of Vigabatrin (SD) (kg)
I	7:6	42.9 (8.9)	27.3 (10.8)	10.1 (1.9)	7.8 (2.7)
II	8:0	40.1 (10.8)	25.9 (16.8)	7.3 (4.2)	6.1 (4.5)
III	3:11	41.2 (8.8)	19.5 (15.3)	Nil	Nil
IV	5:15	39.7 (12.3)	Nil	Nil	Nil
V	4:3	35.0 (11.2)	21.3 (14.8)	Nil	Nil

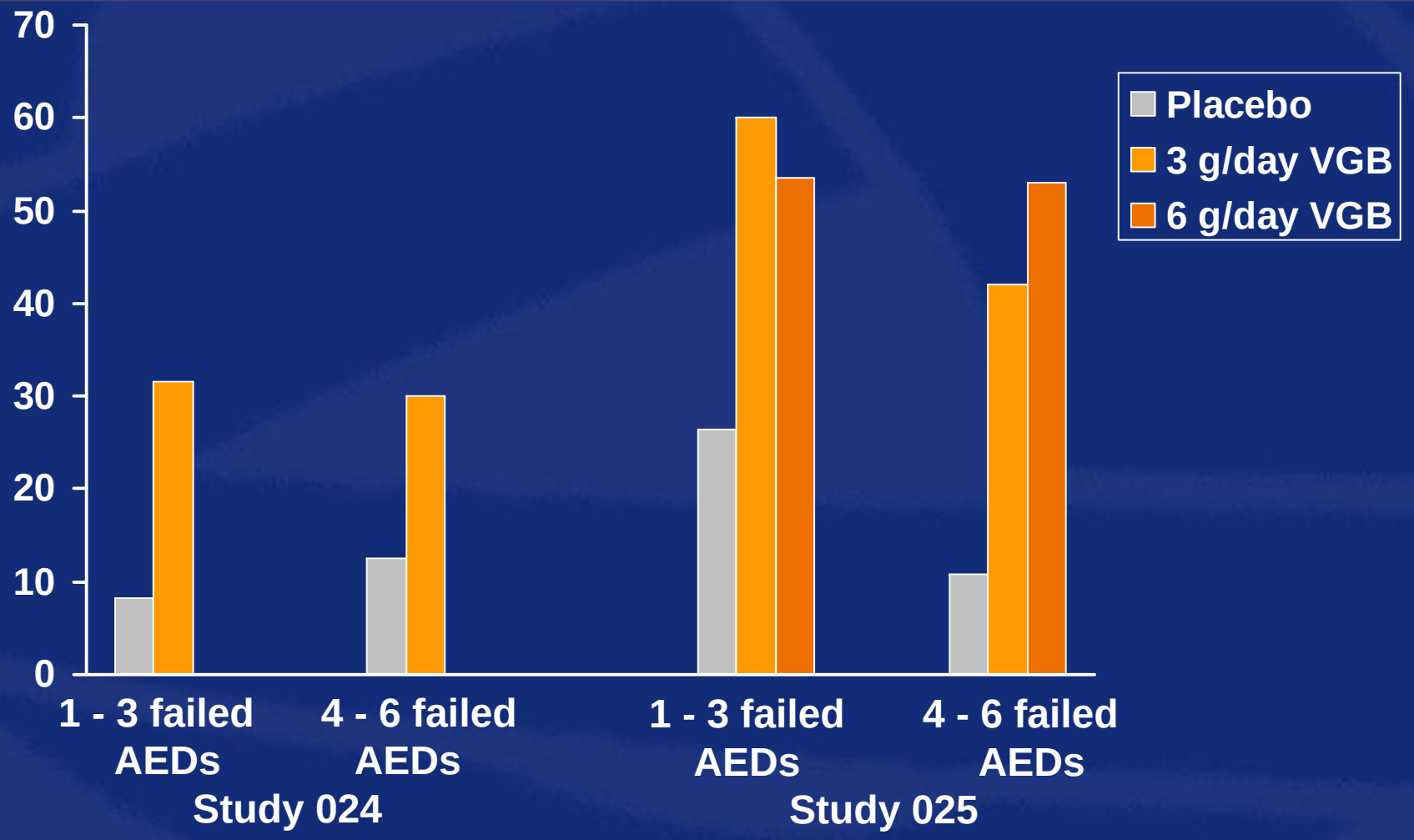
Data are the group mean ± SD.



Wild JM, et al. *IOVS*. 2006;47:917-924.

Percent of Patients Achieving ≥ 50% Reduction in Seizures by Number of Failed AEDs at Baseline[a]

Studies 024 and 025



[a] Failed for any reason.