Sabril® (vigabatrin) for Oral Solution for Infantile Spasms

United States Food and Drug Administration

Peripheral and Central Nervous System Drugs Advisory Committee

January 2009

OVATION PHARMACEUTICALS, INC.

Sabril® (vigabatrin) for Oral Solution for Infantile Spasms

Introduction

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Ovation Pharmaceuticals, Inc.

OVATION PHARMACEUTICALS, INC.

Summary of Yesterday's Meeting

- Committee recommended approval of Sabril for the adjunctive treatment of refractory complex partial seizures in adult patients who have failed to respond to several other AEDs
- Committee advised that approval be accompanied by a Risk Evaluation & Mitigation Strategy (REMS)
- Due to the potential for a clinically meaningful loss of vision, the Committee recommended that ophthalmologic assessments be performed at baseline, at 3-months prior to maintenance phase treatment, every 4-6 months thereafter and at a timepoint following drug discontinuation

Special Characteristics for IS Indication

- Orphan population in the US
  - 2,500 patients/year with IS
- Pediatric population: Infants ≤ 3 years of age
- No approved therapies for IS in the US
- Difficult to conduct clinical studies
- Treatment goal is complete cessation of spasms (vs reduction in seizure frequency)

Proposed Indication

NDA 22-006 (500 mg powder for oral solution)

- **Sabril is indicated as monotherapy for pediatric patients with Infantile Spasms (IS) for whom the potential benefits outweigh the potential risk of developing the peripheral visual field defect (pVFD).**

Worldwide Status

- Vigabatrin (VGB) currently available in more than 50 countries
  - North America: Canada and Mexico
  - Europe: Many countries within the EU
  - ROW: Certain 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

1989
1st CPS marketing approval in UK

1991
1st IS marketing approval in Germany

1997
1st reports of pVFD in Europe

1999
EMEA: benefit/risk profile positive
Article 12 studies requested

89 | **95** | **00** | **05**

1995
IS trial opens

2000
Orphan drug status for IS

2004
Ovation-NA rights

2006
Reports of MRI abnormalities in IS

2008
IS NDA and CPS amend. accepted

US

IS—Key Considerations (1)

- IS: Serious and catastrophic disease with unmet medical need
  - No approved therapies in the US
- VGB is effective for IS across etiologies and onset of effect is noted within 2 - 3 weeks
- Safety of VGB well characterized
  - > 4000 patients have received VGB in clinical trials, including 342 patients with IS
  - > 1.5 million patients have received VGB over past 19+ years

IS—Key Considerations (2)

- Many essential features of pVFD now better understood
  - Estimated prevalence in infants with IS is 31% (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 confrontation testing and/or ERG
- MRI abnormalities are transient, but long-term longitudinal studies required post-approval

IS—Key Considerations (3)

- Risk Evaluation and Mitigation (REMS) Plan
  - Labeling
  - Communication Plan/Education Programs
  - Elements to Assure Safe Use
    - Mandatory Sabril Registry
- Benefits of spasm cessation exceed risks for pVFD and MRI abnormalities

Today's Agenda

Unmet Medical Need and Disease Background	W. Donald Shields, MD Mattel Children's Hospital at UCLA
Efficacy and Safety	Stephen M. Sagar, MD Ovation Pharmaceuticals, Inc.
Intramyelinic Edema	D. Reid Patterson, DVM, PhD Reid Patterson Consulting, Inc.
Clinical MRI Abnormalities	James W. Wheless, MD The University of Tennessee Health Science Center
Risk Evaluation and Mitigation Plan	Tim Cunniff, PharmD Ovation Pharmaceuticals, Inc.
Benefit/Risk Assessment	John M. Pellock, MD Virginia Commonwealth University

Consultants

- **Richard M. Bittman, PhD**
  Bittman Biostat, Inc.
- **Robert H. Garman, DVM**
  Consultants in Veterinary Pathology, Inc.
- **Robert C. Sergott, MD**
  Wills Eye Institute
  Thomas Jefferson University
- **Carol Westall, PhD**
  University of Toronto Hospital for Sick Children

Sabril® (vigabatrin) for Oral Solution for Infantile Spasms

Unmet Need and Disease Background

W. Donald Shields, MD

Professor of Neurology and Pediatrics
Mattel Children's Hospital at UCLA

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Overview of Infantile Spasms

- Characteristics
- Etiology
- Treatment
- Outcome

Seizures in Young Children

Dichotomy

Benign

- Benign neonatal convulsions
- Benign infantile familial convulsions
- Benign infantile myoclonus
- Febrile seizures
- Absence epilepsy

EVERYTHING ELSE

Catastrophic

- **INFANTILE SPASMS (IS)**
- Severe myoclonic epilepsy in infancy (SMEI)
- Ohtahara syndrome
- Lennox-Gastaut syndrome
- Myoclonic/astatic epilepsy
- Sturge-Weber syndrome
- Rasmussen encephalitis

Catastrophic Childhood Epilepsy—Infantile Spasms Is a Rare Disorder

- Seizures start early in life, most often in first year
- Mental retardation is often a consequence (the catastrophe)
- Infantile spasms:
  - A relatively uncommon disorder, affecting ~ 2,500 children per year in the US
  - Seizures and EEG are clinically distinct
  - Seizures are difficult to control

West Description
Little Seizures, BIG Consequences

"The child is now near a year old; was a remarkably fine, healthy child when born, and continued to thrive till he was four months old. It was at this time that I first observed slight bobbings of the head forward,… these bobbings increased in frequency and strength… causing a complete heaving of the head forward towards his knees, these would be repeated alternately at intervals of a few seconds, and repeated from ten to twenty or more times at each attack, he sometimes has two, three, or more attacks in the day"

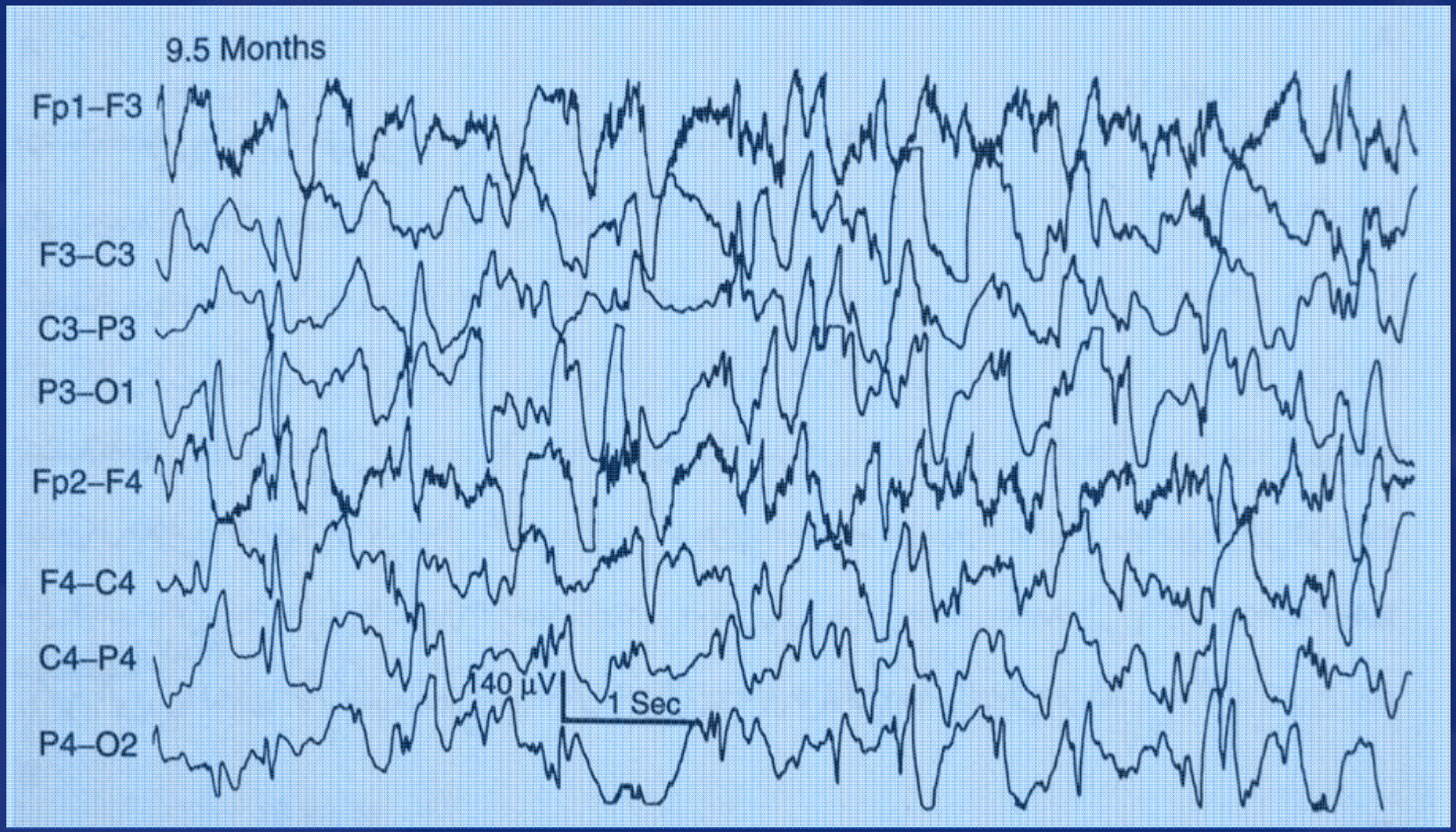
W.J. West: *On a peculiar form of infantile convulsions.* Letter. *Lancet*. 1840-1841, I: 724-725.

West Description
Little Seizures, BIG Consequences

"…and independent of this affliction is a fine grown child. But he neither possesses the intellectual vivacity or the power of moving his limbs of a child his age. He never cries at the time of the attacks, or smiles or takes any notice, but looks placid and pitiful. Yet, his hearing and vision are good."

W.J. West: O*n a peculiar form of infantile convulsions.* Letter. *Lancet*. 1840-1841, I: 724-725.

Infantile Spasms—Hypsarrhythmia



Etiologic Definitions

- Idiopathic
  - Entirely normal infant prior to onset of IS, no identifiable cause
- Cryptogenic
  - Suspected underlying CNS or metabolic abnormalities, but unable to identify
- Symptomatic
  - Structural lesion, metabolic disorder, previous CNS insult

Treatment of Infantile Spasms—Currently No FDA-Approved Medications for IS

- Medications considered effective (defined as 100% cessation of spasms)
  - ACTH/ Prednisone
  - Vigabatrin
- Some evidence of efficacy
  - Valproic acid
- Inconclusive, but try it anyway
  - Benzodiazepines
    - Nitrazepam, clonazepam, clobazam
  - Pyridoxine
  - Topiramate
  - Zonisamide
  - Lamotrigine
  - Felbamate
  - IVIG
  - Ketogenic diet

Initial Treatment of Infantile Spasms: ACTH and Vigabatrin—Administration/Side Effects

ACTH

- IM injections, 1 - 2 ×/day (parents administer)
  - Current recommendation: high initial dose for maximum efficacy, shorter duration for safety
    - 150 U/m^2 for 2 wk then taper over 6 - 8 wk (more rapid taper if no response)
  - Key side effects
    - Cushingoid appearance, stress ulcer, immunosuppression, hypertension, hyperglycemia, irritability, increased appetite, weight gain

Vigabatrin

- Soluble powder, oral administration
- Rapid titration to 125 - 150 mg/kg
  - 2-wk trial for efficacy
  - Duration of therapy: 3 - 12 mo or until age 1 year
- Key side effects
  - Drowsiness, risk of pVFD and MRI changes

Infantile Spasm Treatment Guidelines (Vigabatrin)

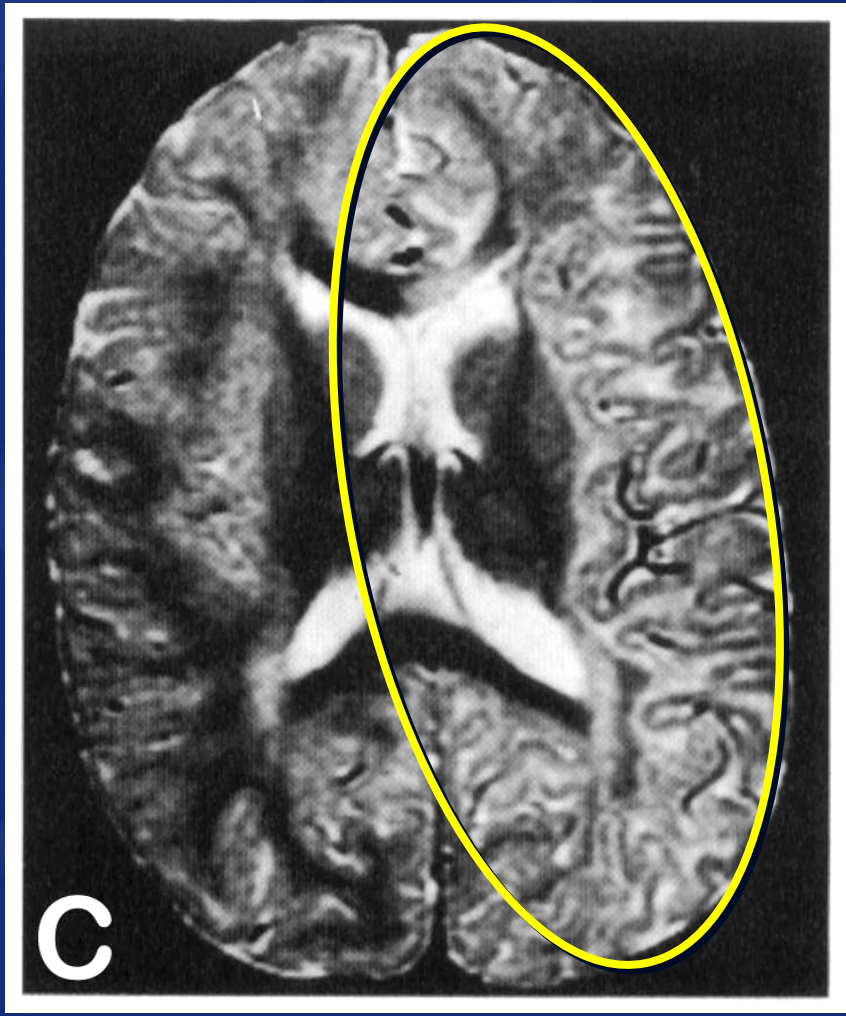
	AAN Practice Parameter	SIGN Epilepsies in Children and Young People	NICE (UK)
Infantile Spasms	Steroids probably effective VGB possibly effective for IS and IS with TS	Steroids first line, VGB "superior" when IS secondary to TS	VGB and Steroids first line therapy

	European Expert Opinion	US Expert Opinion
Infantile Spasms secondary to TS	VGB Rx of choice	VGB Rx of choice
Infantile Spasms – symptomatic	VGB Rx of choice, ACTH, prednisone also first-line	ACTH, topiramate Rx of choice, VGB sometimes appropriate

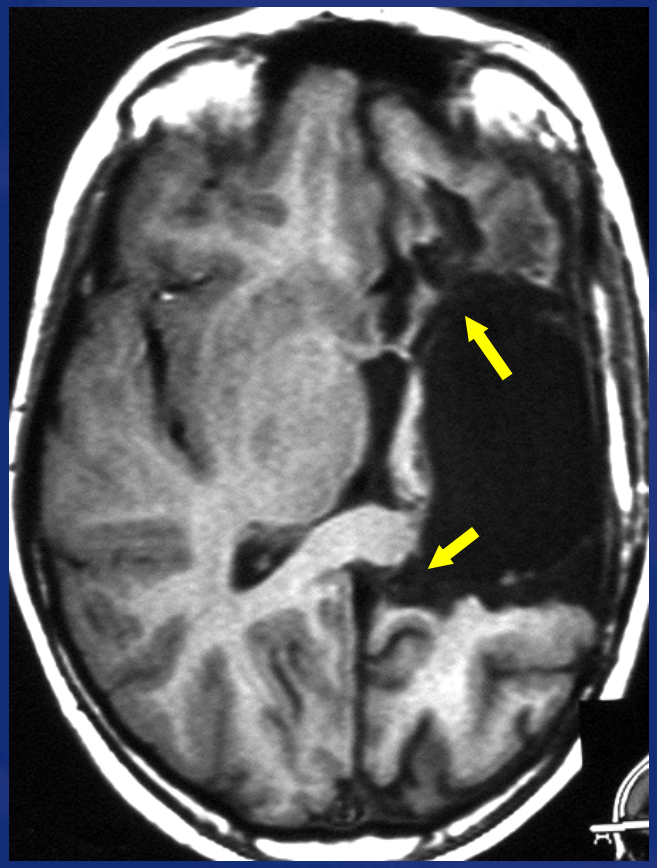
References:

NICE = National Institute for Health and Clinical Excellence; SIGN = Scottish Intercollegiate Guidelines Network.
Wheless, et.al. Epileptic disord. 2007, J Child Neurol. 2005

The Surgical Option if Medications Are Unsuccessful (The Issue of pVFD)



Modified Lateral Hemispherotomy



The Benefit: Excellent developmental outcome

The Cost: Right-sided weakness and visual field defect

Outcome of Infantile Spasms

- In children who are not controlled, the spasms generally evolve to other seizure types by 1 - 2 years of age
  - Most evolve to other catastrophic epilepsy syndromes such as Lennox-Gastaut syndrome or intractable partial seizures
- 6% - 33% die by age 3 years
- ~ 30% are autistic
- 70% - 90% are intellectually developmentally delayed

Does Treatment Affect Developmental Outcome?

Kivity S, et al. *Epilepsia*. 2004;45:255-262.

- **37 cryptogenic**

  IS patients (age at onset of spasm: 3 - 9 months)

- **Treatment**

  ACTH (tetracosactide depot) decreasing doses 10 - 12 weeks, followed by: Prednisone in decreasing doses for ≥ 6 months or to 1 year of age

Early treatment = within 1 month of onset of spasms

Treatment	Normal outcome (IQ > 70)	*p* value
Early treatment (22)	22/22 (100%)	< 0.001
Late treatment (15)	6/15 (40%)	

Does Treatment Affect Developmental Outcome?

Goh S, et al. *Neurology*. 2005;65:235-238.

50 TS patients (retrospective study)

- **Only 18/50 (36%) had IQ > 70**
- **3 Factors associated with poor developmental outcome**
  1. **Increased time from IS onset to cessation**

     OR 1.09/month (p = 0.004)
  2. **Increased time from treatment to cessation**

     OR 1.07/month (p = 0.020)
  3. **Poor control of other seizures after IS**

     OR 17.76 (p = 0.00004)

Catastrophic Childhood Epilepsy

- **Infantile Spasms is the archetypal catastrophic childhood epilepsy. But, children with IS often have the potential for normal, or at least improved, developmental outcome, if spasms are completely controlled early in the course**

Summary

- Severity of disease
  - Patients with IS are at significant risk for mortality and morbidity
  - The consequences go beyond the patient; parents and other family members are significantly affected
  - Very rare disorder; orphan disease status
  - Early, effective treatment is important for development
- Unmet medical need
  - All currently used therapies that are considered effective have potential or certain adverse effects/consequences
  - World wide and current US guidelines support Vigabatrin as an important therapeutic option
  - Risk:Benefit assessment favors aggressive therapy

Sabril® (vigabatrin) for Oral Solution for Infantile Spasms

Efficacy and Safety

Stephen M. Sagar, MD

Medical Director
Ovation Pharmaceuticals, Inc.

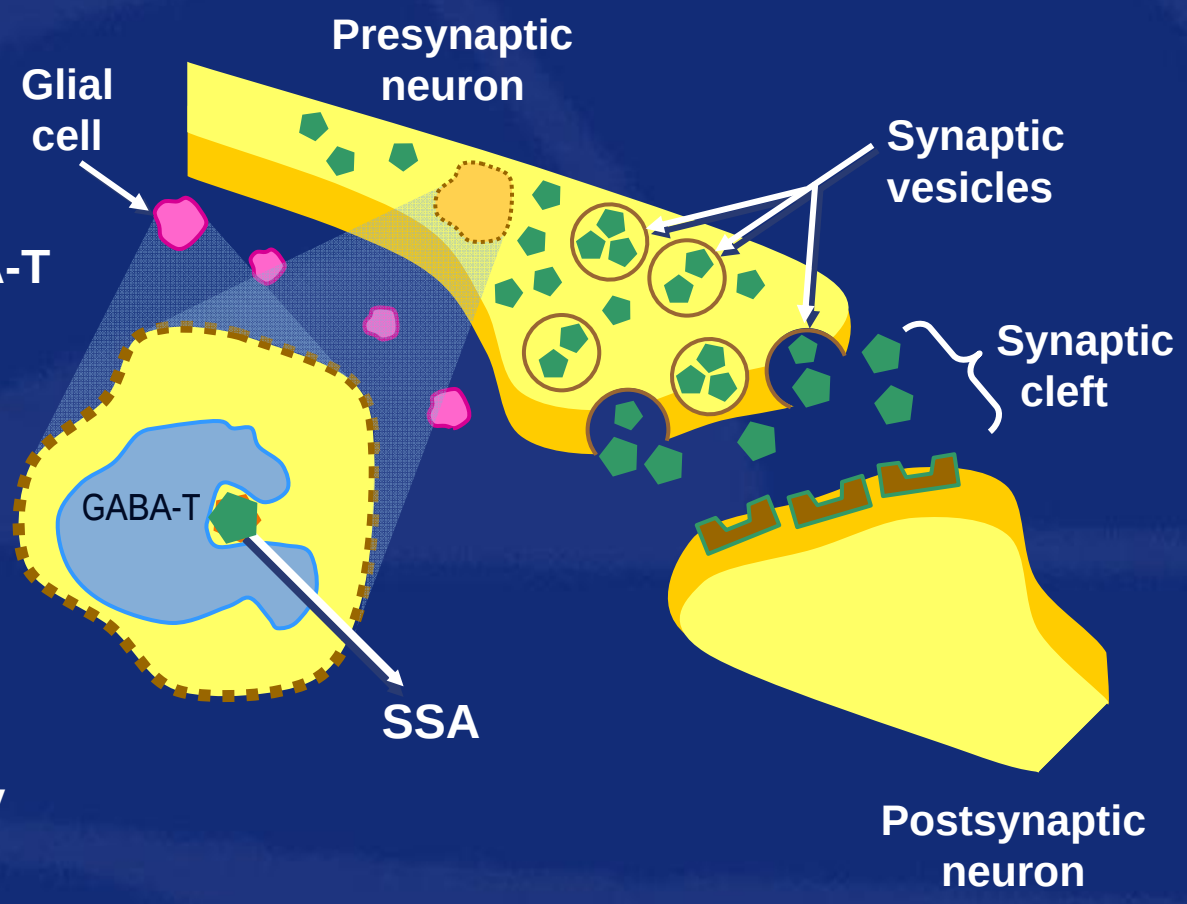
OVATION PHARMACEUTICALS, INC.

Vigabatrin—Unique Mechanism of Action

VGB selectively and irreversibly inhibits GABA-T

Increases number of GABA molecules at synapse

Decreases seizure activity



GABA GABA receptor VGB

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
- Plasma levels do not correlate with clinical effect

Overview

- IS clinical development program
  - Controlled trials
  - Uncontrolled trials
  - Supportive literature
- General safety
- Special safety
  - Retinal effects
  - MRI abnormalities

Clinical Trials in IS

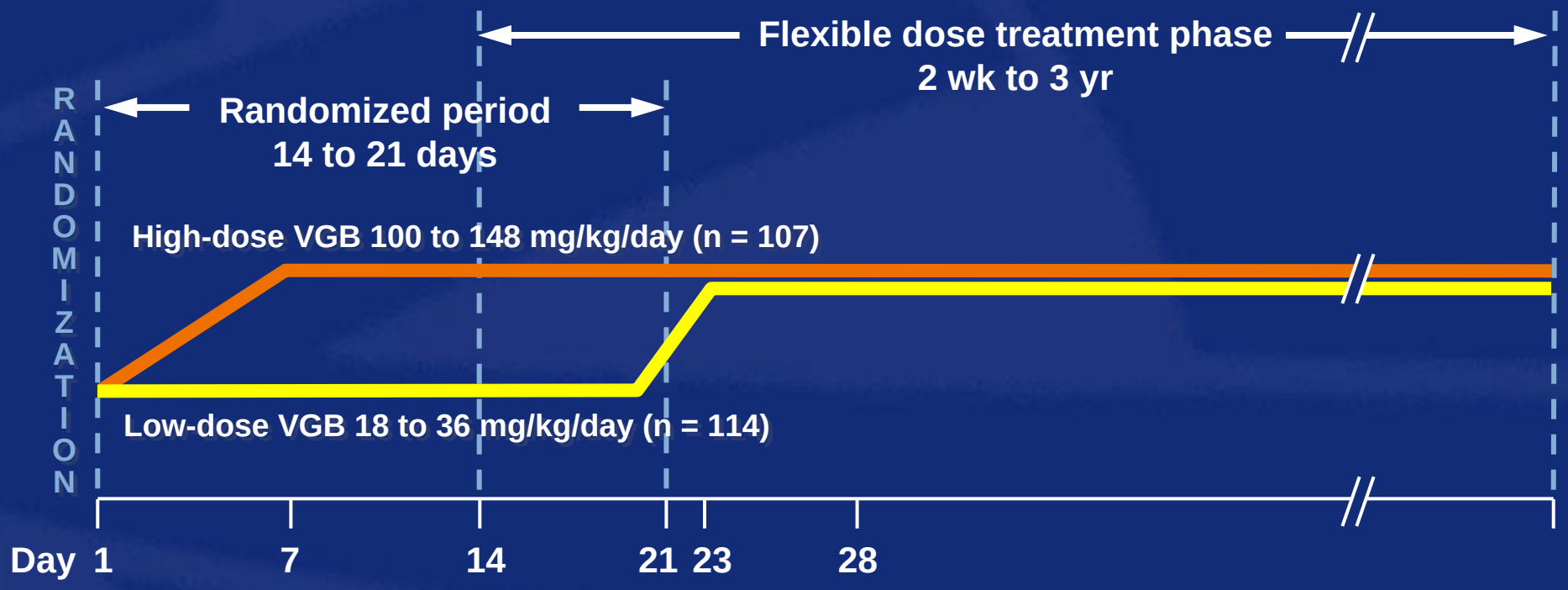
- Small patient population
- Prolonged placebo-controlled trials not feasible
- Monotherapy of IS
- Short observation period
- Spasm cessation is primary endpoint
- EEG confirmation

Summary of IS Controlled Trials
Studies 1A, FR03, W019

- **Spasm cessation was consistently observed in Study 1A, Study FR03, and Study W019**
- **Onset of efficacy within 2 - 4 weeks**
- **Consistent efficacy also demonstrated for other endpoints**

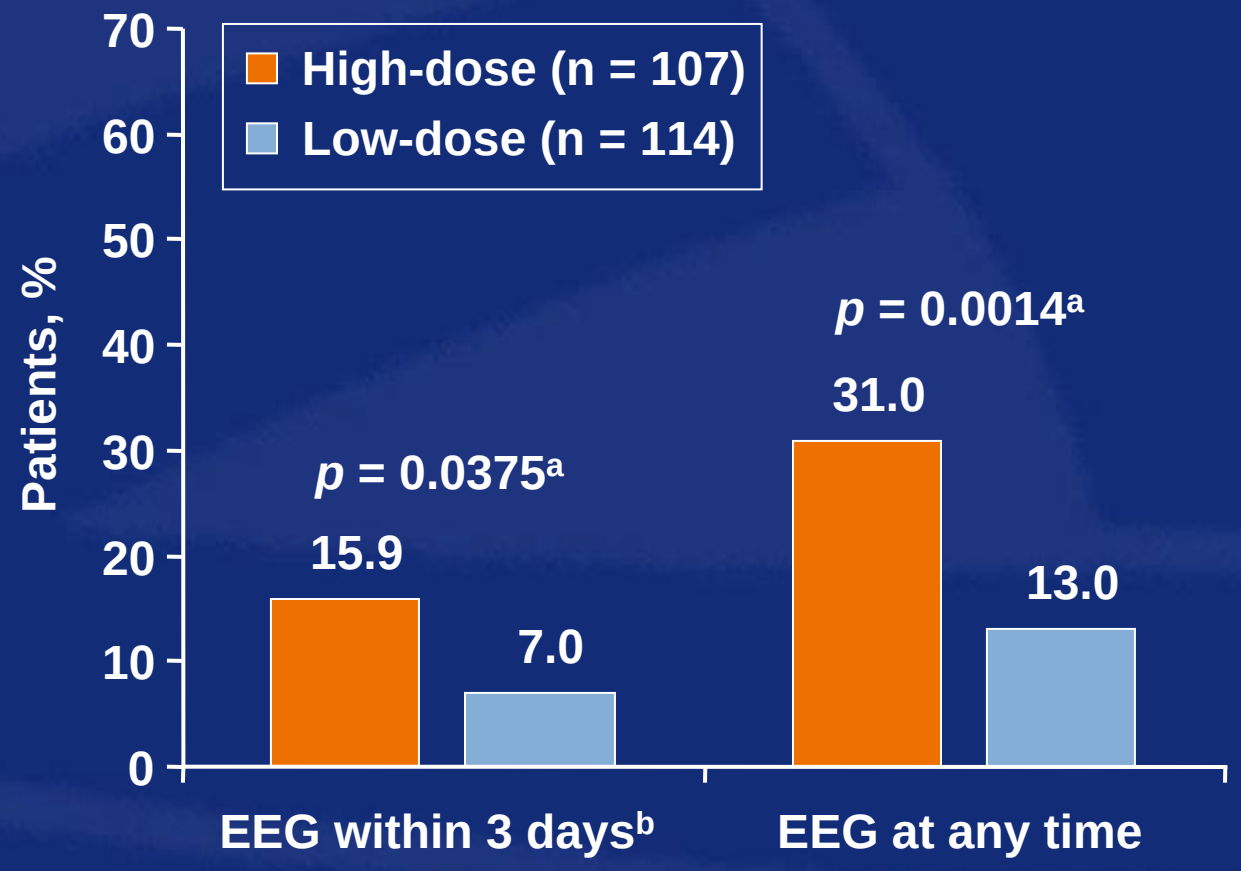
Study Design
Study 1A

Study 1A (N = 227 randomized, 221 MITT)



VGB Produces Spasm Cessation

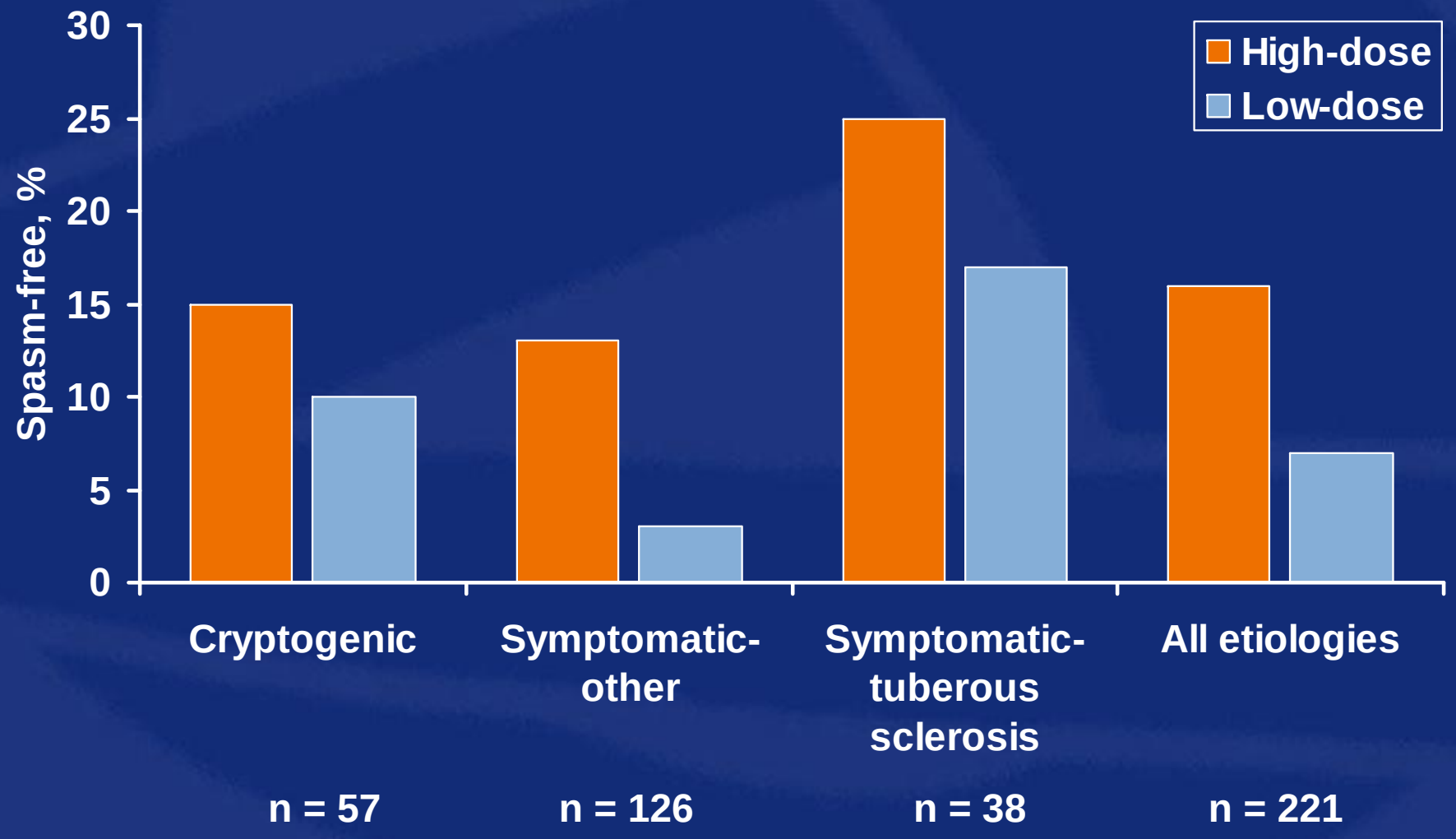
Study 1A



[a] Chi-square test.
[b] Based on CCTV EEG within 3 days of the spasm-cessation period.
Primary criteria based on caregiver assessment plus required CCTV EEG confirmation.

VGB is Effective Across Etiologies

Study 1A

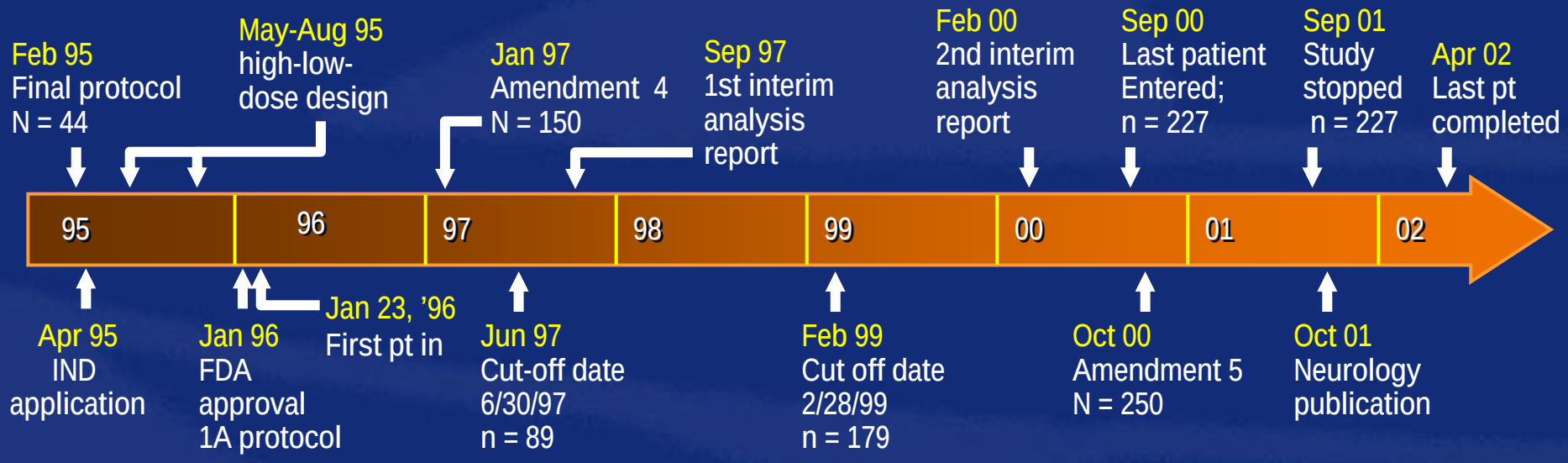


Summary
Study 1A

- VGB effective as monotherapy of IS
- Most effective dose > 100 mg/kg/day
- Rapid onset—within 2 - 3 weeks
- Effective across etiologies

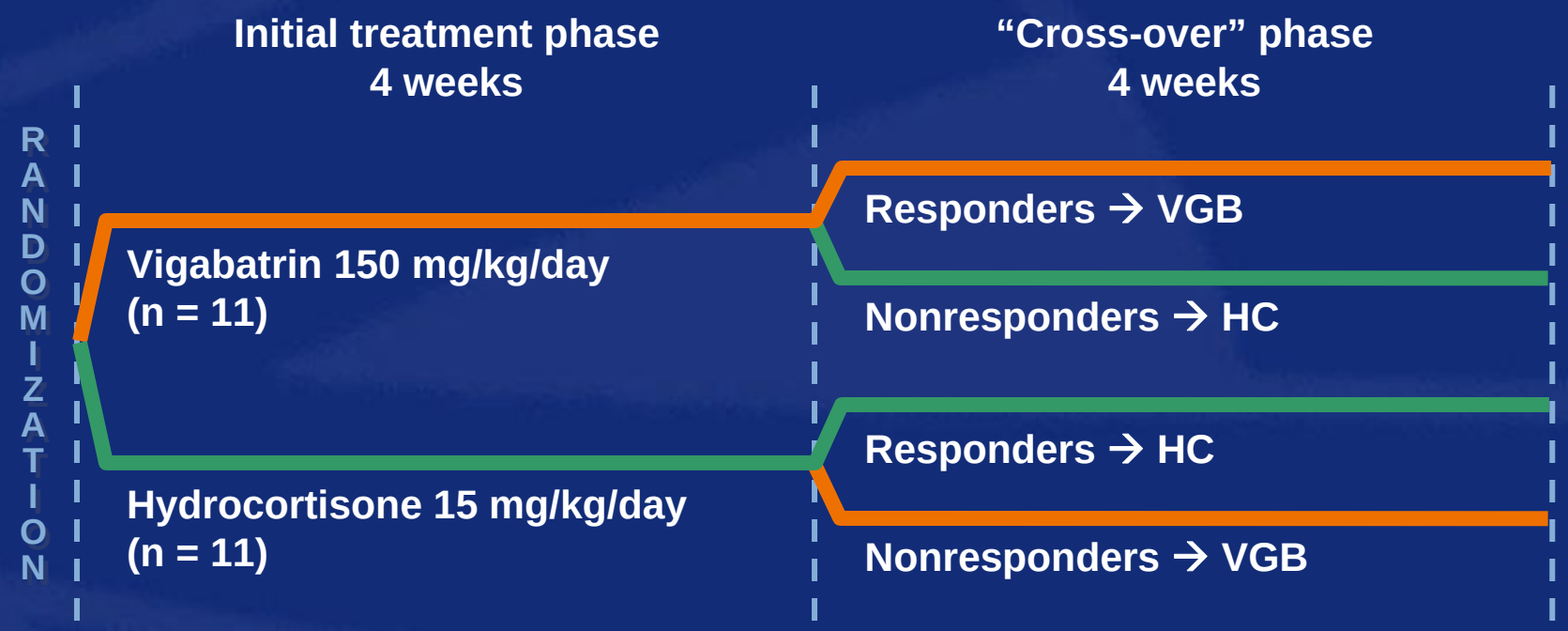
Timeline
Study 1A

- **Ovation acquired data 2004**
- **Performed independent source verification and data analysis**



Study Design
Study FR03

Study FR03 (N = 23 randomized, 22 evaluable)

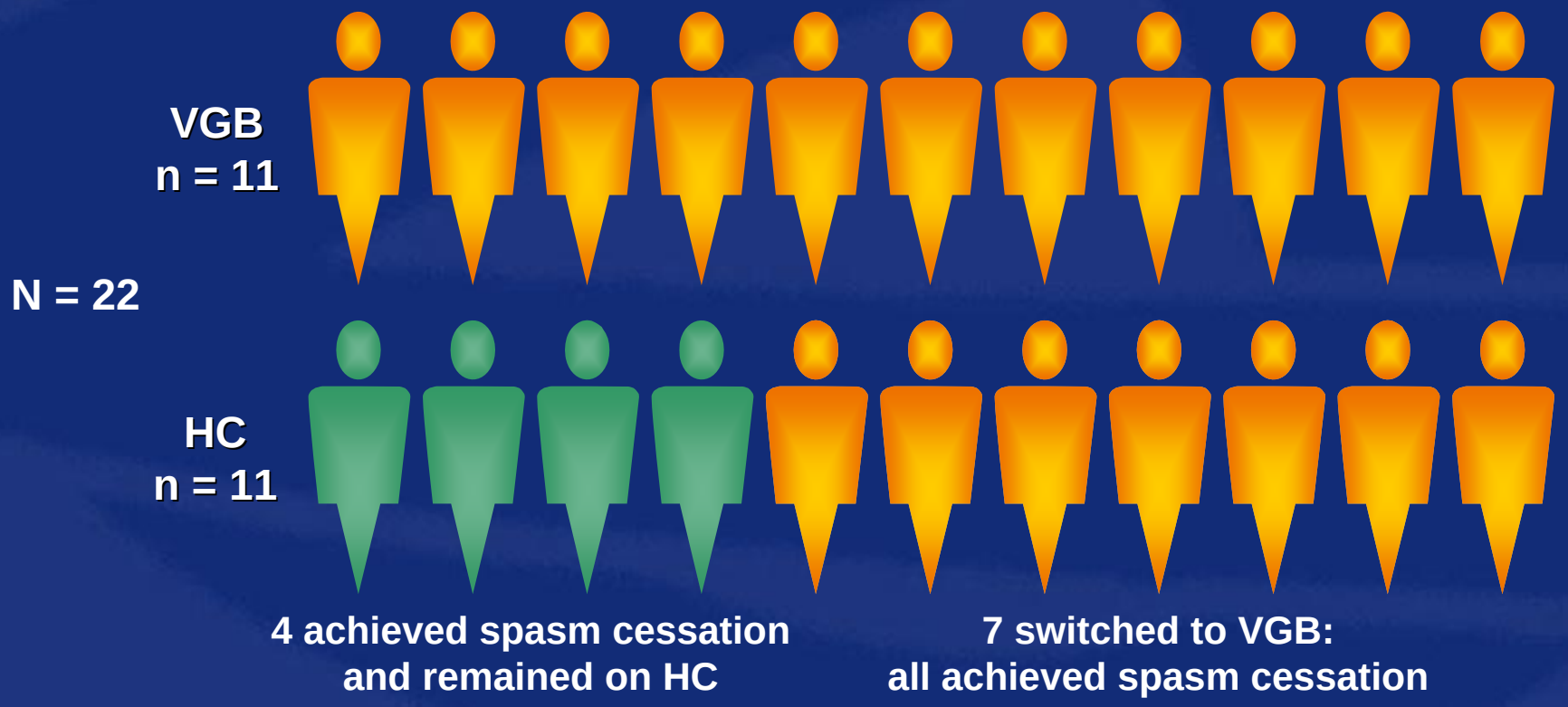


HC = Hydrocortisone.

All VGB-Treated Tuberous Sclerosis Patients Achieved Spasm Cessation

Study FR03

- **Protocol-specified primary endpoint showed statistically significant difference between the 2 treatment groups $p = 0.001$**



Efficacy—Secondary Endpoints[a]

Study FR03

	Patients improved,[a] n/N		
	VGB	HC	*p* value[b]
General well being	11/11	5/11	0.0124
Behavior	10/10	4/11	0.0039
EEG improved	8/10	4/4	

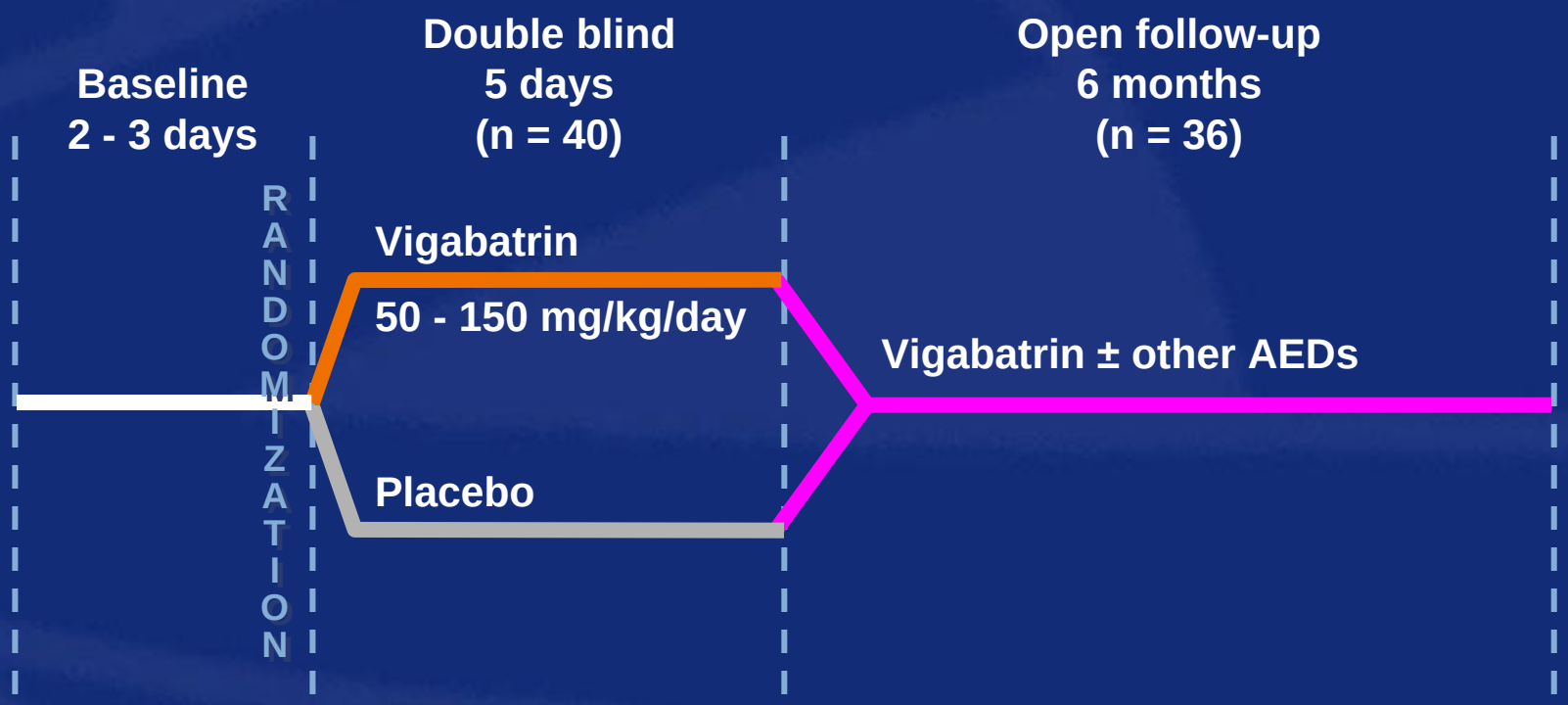
[a] Based on investigator assessment.
[b] Fisher's exact test.

Summary
Study FR03

- VGB effective as monotherapy in IS in subgroup of patients with tuberous sclerosis
- Onset of efficacy rapid—within 4 weeks
- Patients who did not respond to hydrocortisone responded to VGB
- Improvement in Physician's Global Assessment of function

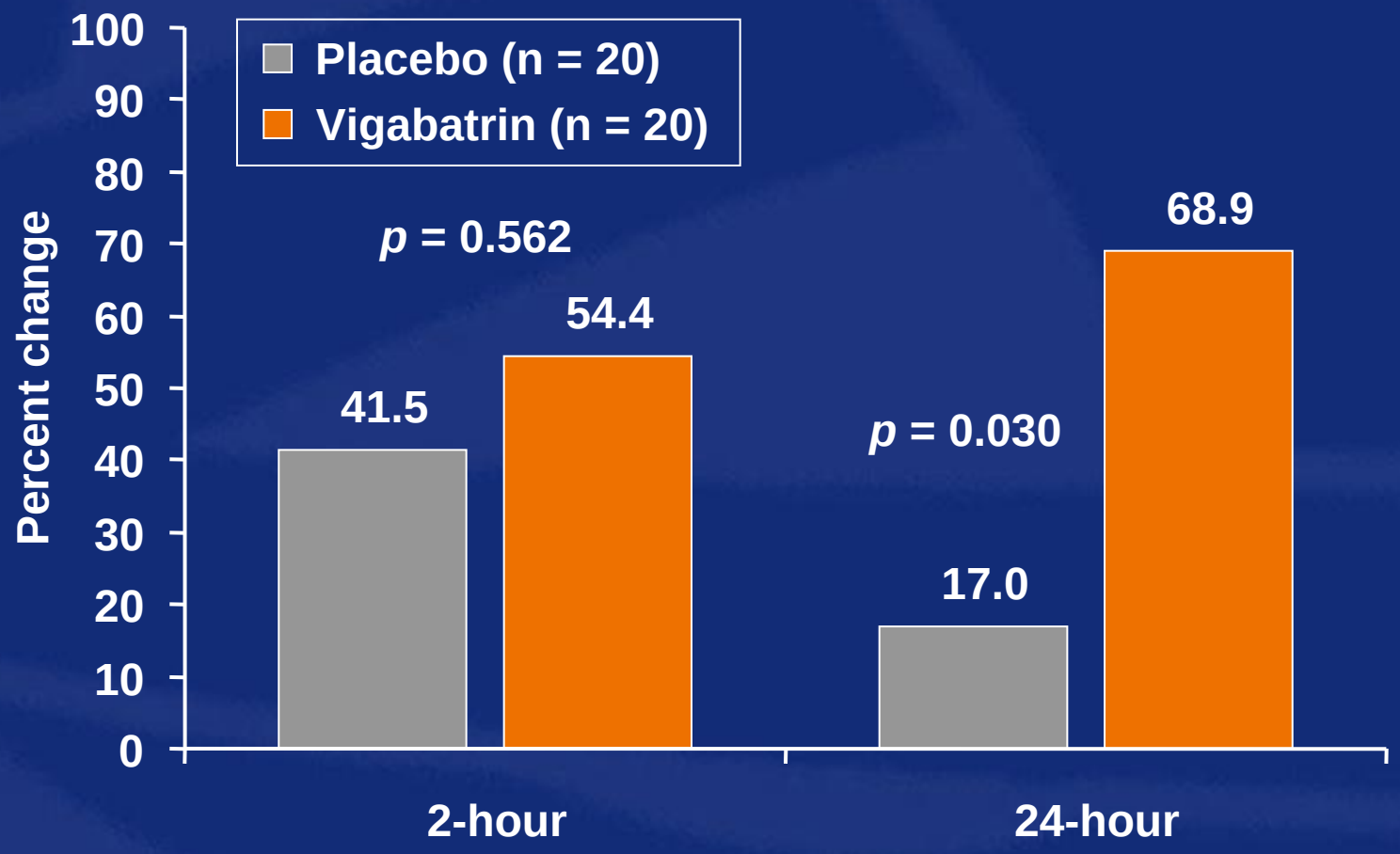
Study Design
Study W019

Study W019 (N = 40 randomized, 36 entered open label, 28 completed)



Percent Improvement in Average Frequency of Spasms in Final 2 Days

Study W019—ITT Population



Secondary Outcome Measures
Study W019

	Patients, %		
	Placebo	VGB	*p* value
Cessation of spasm (0 or 1 spasm)	15	45	0.036
Cessation of spasm (0 spasms)	10	35	0.063
Improvement in EEG	5	20	0.342

Summary
Study W019

- **Primary outcome: statistical significance not reached**
  - **Primary outcome measure inappropriate**
- **Secondary outcome: spasm cessation achieved**
- **Onset of efficacy < 2 weeks**

Long-term Benefit
Studies 1A, FR03, W019

- **Spasm cessation in open-label phase**
  - **Study 1A: 59.7% (132/221): up to 3 years**
  - **Study FR03: 78.6% (11/14): 2 years**
  - **Study W019: 30.6% (11/36): 6 months**
- **Developmental testing**
  - **Study FR03: 5/5 improved Brunet Lézine scores**
  - **Study W019: 4/25 improved Denver scores**
    - **21/25 unchanged**

Summary of IS Controlled Trials
Studies 1A, FR03, W019

- **Spasm cessation was consistently observed in Study 1A, Study FR03, and Study W019**
- **Onset of efficacy within 2 - 4 weeks**
- **Consistent efficacy also demonstrated for other endpoints**

Summary of Uncontrolled Trials

Study 332.5

- **Open-label, single-center study to evaluate safety and efficacy of VGB in infants and children with drug-resistant IS (N = 45)**
- **VGB used as adjunctive therapy**
- **46.5% achieved spasm cessation**

Summary of Uncontrolled Trials
Study 3E01

- Retrospective analysis of patients diagnosed with IS who received VGB as their initial treatment
- 59 centers in 11 European countries
- 68% of 192 “classic IS” patients (efficacy population) achieved complete cessation of spasm clusters
- Active across etiologies

Published Studies Demonstrating VGB Efficacy as Monotherapy of IS

	Study design	N	Spasm cessation
Siemes H and Brandl U 1998	Long-term follow study of vigabatrin	23	37.5%
Vigevano F and Cilio MR 1997	VGB vs ACTH as first-line therapy Newly diagnosed IS	42	48%
Villeneuve N, et al 1998	VGB as first-line therapy	70	54%
Lux AL, et al 2004	VGB vs prednisolone or tetracosactide 14 days	107	54%
Lux AL, et al 2005	Follow-up of 12 to 14 months	107	76%

Lux A, et al. (2004, 2005) UK Infantile Spasms Study (UKISS)

- 107 newly diagnosed IS patients (excluded patients with tuberous sclerosis) randomized to
  - Prednisolone 40 - 60 mg/day
  - Tetracosactide depot 0.5 - 0.75 mg (40 - 60 IU) QOD
  - VGB 100 - 150 mg/kg/day
- Spasm cessation by Day 14
  - Hormonal treatment 73%
  - VGB 54%
- Continued spasm freedom (14 mo of age)
  - Hormonal therapy 76%
  - VGB 75%

Efficacy Summary for Infantile Spasms
Controlled and Uncontrolled Trials, Literature

- **VGB as monotherapy**
  - **Significant spasm cessation**
  - **Effective across etiologies**
- **Rapid onset: efficacy observed in 2 - 4 weeks**
- **Spasm cessation maintained long-term**
- **Spasm cessation strongly associated with improved overall function**

Overview

- IS clinical development program
  - Controlled trials
  - Uncontrolled trials
  - Supportive literature
- General safety
- Special safety
  - Retinal effects
  - MRI abnormalities

Most Common Adverse Events ≥ 5% in VGB-treated Patients

Controlled Trial Safety Population (N = 261)

	VGB-treated patients, %
Upper respiratory tract infection	40.6
Otitis media	31.0
Pyrexia	20.7
Viral infection	16.9
Irritability	16.9
Somnolence	16.5
Sedation	15.3
Vomiting	14.2
Constipation	11.5
Pneumonia	11.1

	VGB-treated patients, %
Diarrhea	10.7
Insomnia	9.6
Ear infection	9.2
Rash	8.1
Nasal congestion	7.3
Decreased appetite	6.5
Sinusitis	6.1
Bronchitis	5.8
Lethargy	5.8
Convulsion	5.4

Studies 1A, W019 (double-blind period only), FR03.

Serious Adverse Events in ≥ 2 IS Patients
Controlled Trial Safety Population (N = 261)

System organ class SAE	Total VGB N = 261
Any system organ class, any event	75 (28.7)
Infections and infestations, any event	32 (12.3)
Pneumonia	10 (3.8)
Viral infection	4 (1.5)
Lobar pneumonia	3 (1.2)
Bronchitis	2 (0.8)
Infection	2 (0.8)
Urinary tract infection	2 (0.8)
Gastroenteritis	2 (0.8)
Pneumonia viral	2 (0.8)
Respiratory syncytial virus infection	2 (0.8)
Nervous system disorders, any event	22 (8.4)
Status epilepticus	11 (4.2)
Convulsion	5 (1.9)
Infantile spasms	3 (1.2)
Febrile convulsion	2 (0.8)
Hydrocephalus	2 (0.8)
Partial seizures	2 (0.8)

Studies 1A, W019 (double-blind period only), FR03.

Serious Adverse Events in ≥ 2 IS Patients
Controlled Trial Safety Population (N = 261)

System organ class SAE	Total VGB N = 261
Respiratory, thoracic, and mediastinal disorders, any event	18 (6.9)
Bronchospasm	4 (1.5)
Respiratory arrest	3 (1.2)
Pneumonia aspiration	2 (0.8)
Respiratory distress	2 (0.8)
General disorders and administration-site conditions, any event	13 (5.0)
Pyrexia	6 (2.3)
Death	3 (1.2)
Cyst	2 (0.8)
Unevaluable event	2 (0.8)

System organ class SAE	Total VGB N = 261
Gastrointestinal disorders, any event	9 (3.5)
Gastroesophageal reflux disease	3 (1.2)
Vomiting	3 (1.2)
Metabolism and nutritional disorders, any event	6 (2.3)
Dehydration	3 (1.2)
Surgical and medical procedures, any event	5 (1.9)
Hospitalization	2 (0.8)

Studies 1A, W019 (double-blind period only), FR03.

Deaths in Clinical Trials

- 4 deaths in controlled trials (N = 261)
  - 1 pneumonia
  - 1 hemorrhage secondary to congenital pulmonary angiomatosis
  - 1 cardiac arrest
  - 1 sudden death
- 4 deaths in retrospective Study 3E01 (N = 250)
  - 1 cardiac arrest; septic shock pneumonia
  - 1 bronchopneumonia
  - 1 sudden infant death
  - 1 renal infection, CMV infection, interstitial pneumonia

Postmarketing Safety Consistent With Clinical Trials

- Global safety database includes 132 AE reports from 1997 to 2007 in patients < 2 years of age
- Most common AE reports
  - MRI brain abnormal (11)
  - Agitation (6)
  - Hypotonia (5)
  - Somnolence (4)
  - Encephalopathy (4)

Summary of Safety

- VGB well tolerated
- General safety profile
  - Well characterized
  - Consistent with other AEDs

Overview

- IS clinical development program
  - Controlled trials
  - Uncontrolled trials
  - Supportive literature
- General safety
- Special safety
  - Retinal changes
  - MRI abnormalities

Retinal Function Testing in Infants

- Quantitative perimetry not feasible in infants
- Available tests for retinal testing in infants
  - Confrontation Visual Field Testing
  - ERG Testing

Confrontation Visual Field

Pathophysiology

- Most sensitive ERG measure of VGB retinal effect is 30 Hz flicker amplitude; cone b-wave amplitude[a,b] is less sensitive
- ERG abnormalities most marked in peripheral retina[c,d]
- VEP latencies normal
- No abnormalities of optic nerves or tracts on MRI
- The ERG matures with the retina until age 3 - 5.

[a] Westall CA, et al. *Doc Ophthalmol*. 2002;104:133-149.
[b] Krauss GL, et al. *Neurology*. 1998;50:614-618.
[c] McDonagh J, et al. *Neurology*. 2003;61:1690-1694.
[d] Harding GFA, et al. *Epilepsia*. 2000;41:1420-1431.

University of Toronto Hospital for Sick Children—Infantile Spasm (IS) Study

- Goal: Study vision in IS patients treated with VGB
- Design: Prospective (n = 117), Retrospective (n = 85) and Baseline without vigabatrin (n = 44)
  - To establish incidence, prevalence, and onset of VGB-induced retinal changes
- Methods
  - Serial ophthalmoscopic and electrophysiologic exams conducted before and/or after VGB treatment
  - Repeat exams q 3 - 6 months

Data cover 246 patients with ERG tests occurring between 1998 and 2007

Sustained Abnormal 30 Hz Flicker

		N
Period prevalence, %	31.1	177
Incidence, cases/100 pt-yr	15.3	63
Baseline abnormality, %	38.4	112

ERG Abnormalities in IS

ERG amplitude	Incidence	
	Any abnormality %	Sustained abnormality %
30 Hz flicker	53.6 n = 69	25.4 n = 63
Cone b-wave	31.5 n = 92	10.5 n = 86

Incidence = Patients who were free of abnormalities at Baseline.

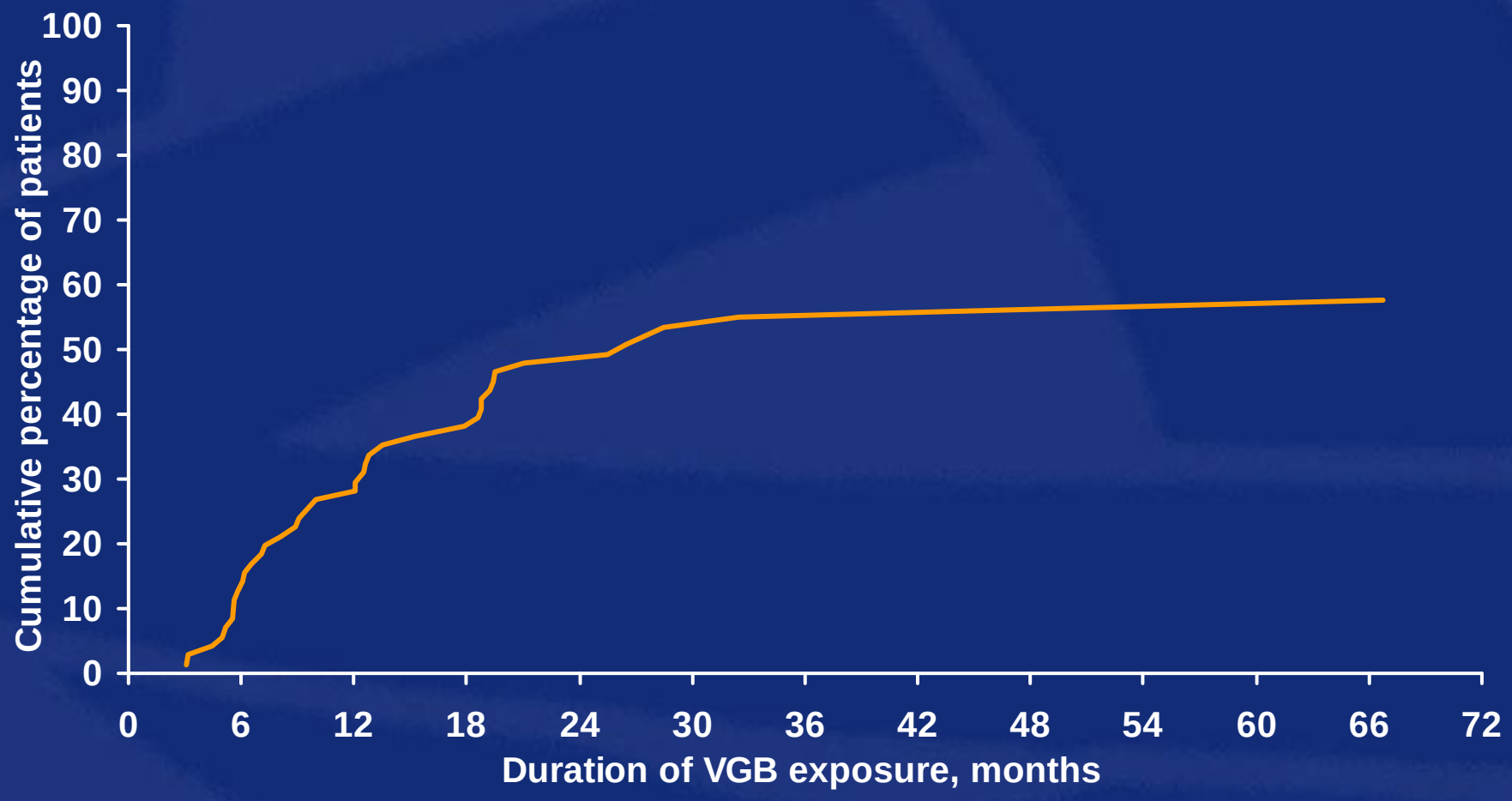
VGB Exposure at Time to First Abnormal Replicated[a] 30 Hz Flicker

n = 19	Months
Median	12.5
Mean	16.3
SD	16.6
Range	3.1 - 66.8

[a] Based on any two successive examinations.

Incidence of Abnormality—30 Hz Flicker Amplitude

Toronto IS Study



VGB-Induced Retinal Changes in Infants Summary

- ERG measures of cone pathway function correlate with extent of VGB-induced visual field constriction in adults
- Sustained ERG abnormality in infants treated with VGB for IS
  - Period prevalence: 31%
  - Incidence: 25% or 15.3 cases/100 pt-yr of exposure
- Earliest onset of abnormal ERG: 3 mo

Sedated Electroretinogram (ERG)—Ganzfeld Stimulator

VGB-Induced Retinal Changes in Infants Monitoring

- Routine confrontation testing
- When clinically indicated, vision in infants can be monitored by confrontation visual field testing or ERG
- Testing must be tailored to individual patients

Overview

- IS clinical development program
  - Controlled trials
  - Uncontrolled trials
  - Supportive literature
- General safety
- Special safety
  - Retinal changes
  - MRI abnormalities

Intramyelinic Edema: Knowledge From Animal Studies

D. Reid Patterson, DVM, PhD

Diplomate: ABT, ACVP, ACLAM;
Fellow: ATS, IATP
Reid Patterson Consulting, Inc.

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Overview

- Introduce the syndrome of IME
- Review prior research on IME associated with vigabatrin treatment
- Discuss the objectives, design, and results of 2 recent juvenile rat studies
  - OV-1007
  - OVNC-9004

Intramyelinic Edema (IME) in Animals

- Defined as edema within the myelin sheath
- With vigabatrin treatment in rats and dogs:
  - IME developed within several weeks
  - Stabilized, did not progress
  - Resolved 12-16 weeks after discontinuation
- General absence of residual pathology in brain tissue after resolution of vacuolar changes
- Monkeys with comparable exposures and GABA levels were unsusceptible to IME after 16 months or 6 years of treatment
- Magnetic resonance imaging (MRI) shown to be a valid non-invasive method to detect IME

Ovation-Initiated Vigabatrin Pediatric Rat Developmental Toxicity

Study OV-1007

- **Use of VGB in Infantile Spasms necessitated performance of juvenile developmental toxicity study**
- **Evaluated reproductive, neurological, auditory and behavioral development, retinal pathology, and neuropathology**
- **Rats dosed from neonatal age PND 4 to adult age PND 65 (62 consecutive days) at a MTD with recovery to PND 201**
- **No evidence for developmental deficits arising from vigabatrin treatment despite development of IME-like changes in the brains of high-dose rats**

Ovation-Initiated Vigabatrin Juvenile Rat Developmental Toxicity

Study OV-1007

- **Brain sections prepared from all regions to document neuropathologic alterations including vacuolation**
- **Brain sections prepared with special histochemical methods:**
  - **H&E for general histological changes**
  - **Luxol Fast Blue/Cresyl Violet for myelin, Nissel substance, neurons, cell nuclei**
  - **Fluro-Jade-B + DAPI counterstain to stain degenerating neurons and nucleic acid in viable cells**
  - **GFAP to characterize any gliosis**
- **Neuropathology results confirmed by an independent expert panel**

Ovation-Initiated Vigabatrin Juvenile Rat Developmental Toxicity

Study OV-1007

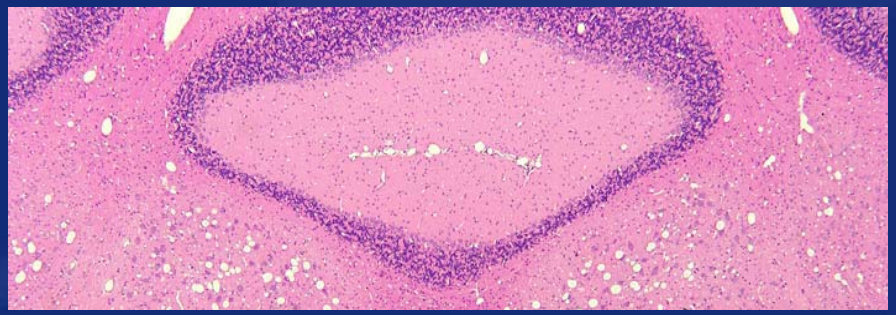
- Vacuoles were present in the neuropil, but did not involve neurons
- Vacuolar changes were reversible with discontinuation of VGB
- No histological or behavioral evidence for neuronal degeneration or post-degeneration gliosis
- Ultra-structural evaluations recommended for characterization of vacuoles

Use of Electron Microscopy to Define Cells With Vacuolar Change

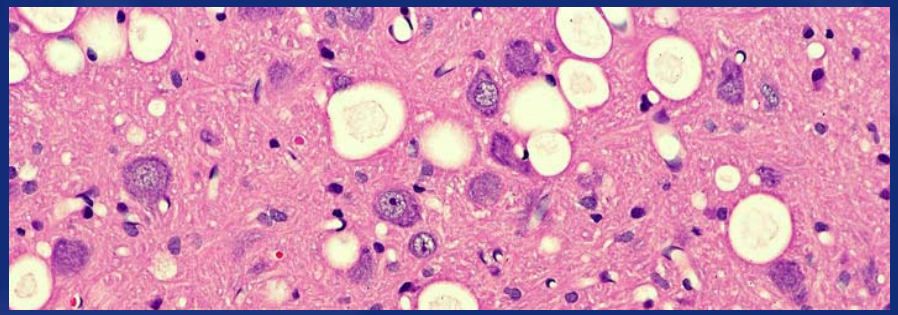
Study OVNC-9004

- **Rats treated with maximum tolerated dose of VGB**
  - **PND 4-25 (22 days)**
  - **PND 4-46 (43 days)**
  - **PND 4-65 (62 days)**
  - **PND 12-26 (15 days)**
- **Representative, prominent vacuoles in deep cerebellar nuclei and adjacent white matter selected for focus of EM study**
- **Ultrastructure micrographs used to confirm origin of vacuoles and assess impact of expanding vacuoles on surrounding parenchyma**

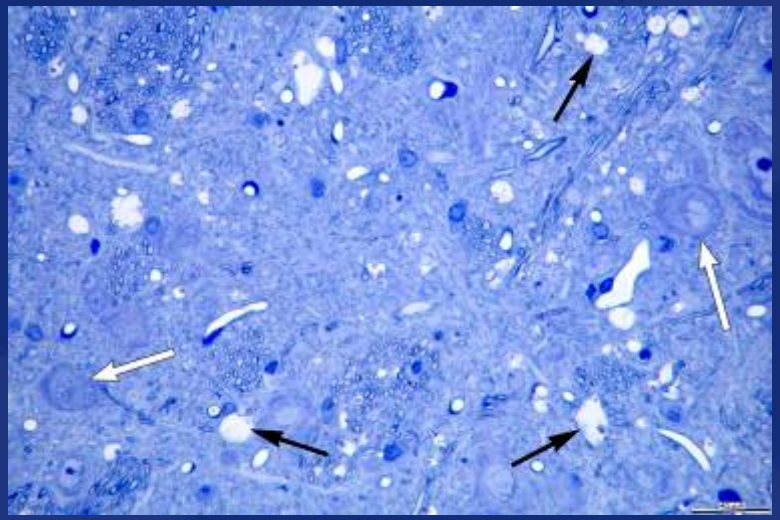
Light and Electron Microscopy Consistent With Vigabatrin-Induced IME in Animals



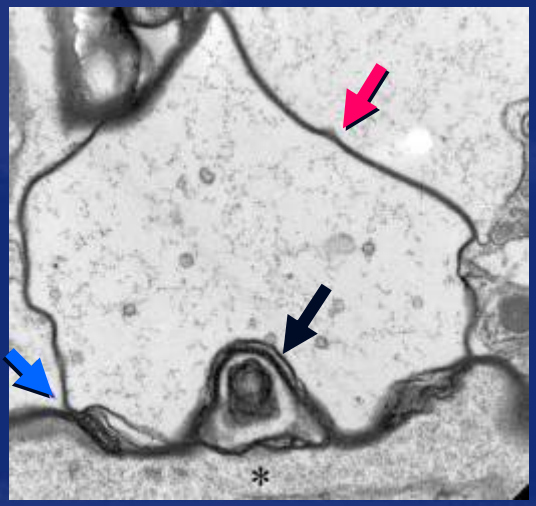
Low power (50x) light microscopic view of vacuoles in deep cerebellar nuclei of high dose rat in OV-1007 study (H&E)



Higher power (125x) view of vacuoles in same region surrounded by healthy, normal-appearing neurons (H&E)



Nucleus of trigeminal spinal tract in medulla contains multiple vacuoles, in contact with myelinated fibers (black arrows). Neurons in this region are histologically unremarkable (white arrows)



Ultrastructure (12,500x) of vacuole derived from split in myelin sheath, distended with flocculent material consistent with edema

Vacuolar Changes Identical Across Age and Species Despite Variation in CNS Distribution

- **Data confirmed that the vacuoles were:**
  - **Restricted to myelin sheaths**
  - **Absent from neurons or other CNS tissues**
  - **More prevalent in closer proximity to gray matter than reported with other classical IME-inducing chemicals**
  - **Absent after drug discontinuation**
  - **Not eliciting damage to adjacent neurons or neuropil**

Conclusions From Preclinical Data on IME

- IME is a reversible, non-progressive vacuolar change caused by edema within myelin sheathes surrounding neuronal axons in gray and white matter of the brain of mice, rats and dogs but not in non-human primates
- IME resolves with discontinuation of drug and not associated with neurological, behavioral or other developmental deficits
- No evidence for damage to or loss of neurons or gliosis indicative of earlier neuronal damage

Sabril® (vigabatrin) for Oral Solution for Infantile Spasms

Clinical MRI Abnormalities

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The University of Tennessee Health Science Center

Director, Neuroscience Institute & LeBonheur Comprehensive Epilepsy Program
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Historical Context

- Clinical trials in adolescents and adults showed no treatment-related MRI abnormalities
- Nearly 20 years of postmarketing experience in adolescents and adults with no reported MRI abnormalities
- Pearl reported MRI abnormalities in infants treated with VGB

Special Safety Categories—MRI Abnormalities

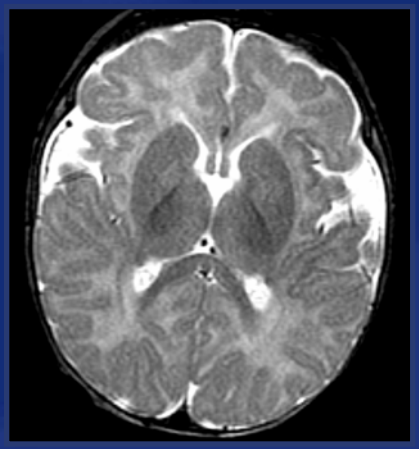
- 2006: Increased T2 MRI signal abnormality reported in 3/15 children
  - Case series
  - Limitations of findings: no control group, multiple confounders
  - No causal relationship could be established
  - The data resulted in FDA request for additional information to better characterize this issue

Pearl P, et al. *Epilepsia*. 2006;47(Suppl 4):14.

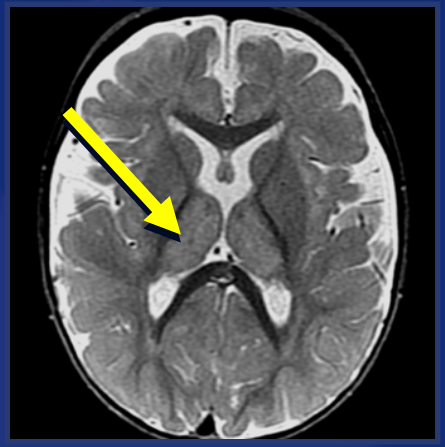
MRI Imaging: P. Pearl, 2006

T2 MRI

Pre-VGB

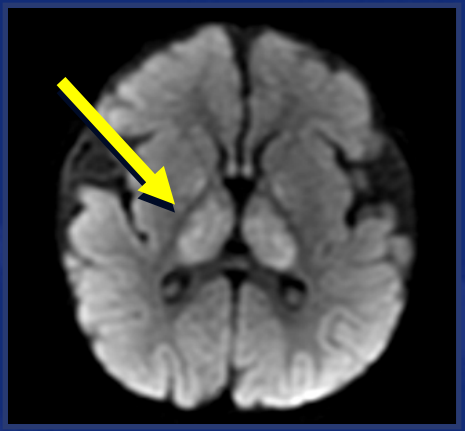


On VGB

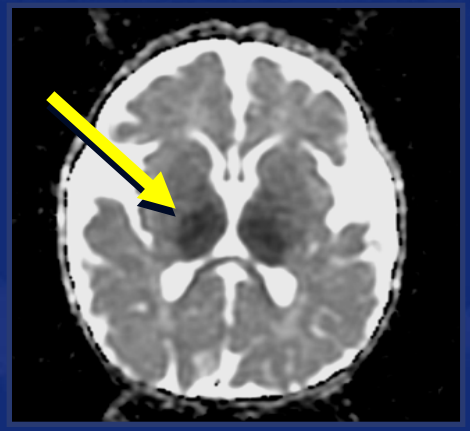


DWI MRI

On VGB



On VGB



ADC mapping MRI

Pearl P, et al. *Epilepsia*. 2006;47(Suppl 4):14.

2007—Ovation Addresses MRI Abnormality Concern

- Postmarketing search of Ovation AERS database (1989 - 2007) for VGB adverse events in IS patients
- Initiated study OV-1019
  - Retrospective assessment of cranial MRIs in IS patients

Postmarketing Reports of MRI Abnormalities Since 1989

- 71 AE reports in children ≤ 3 years
  - 20 reports of MRI abnormalities
    - Hyperintensities on MRI (n = 13)
      - 12 cases with same pattern as reported by Pearl
      - 3 children with transient motor signs
    - Miscellaneous lesions (n = 7)

Study Design—Retrospective MRI Review
Study OV-1019

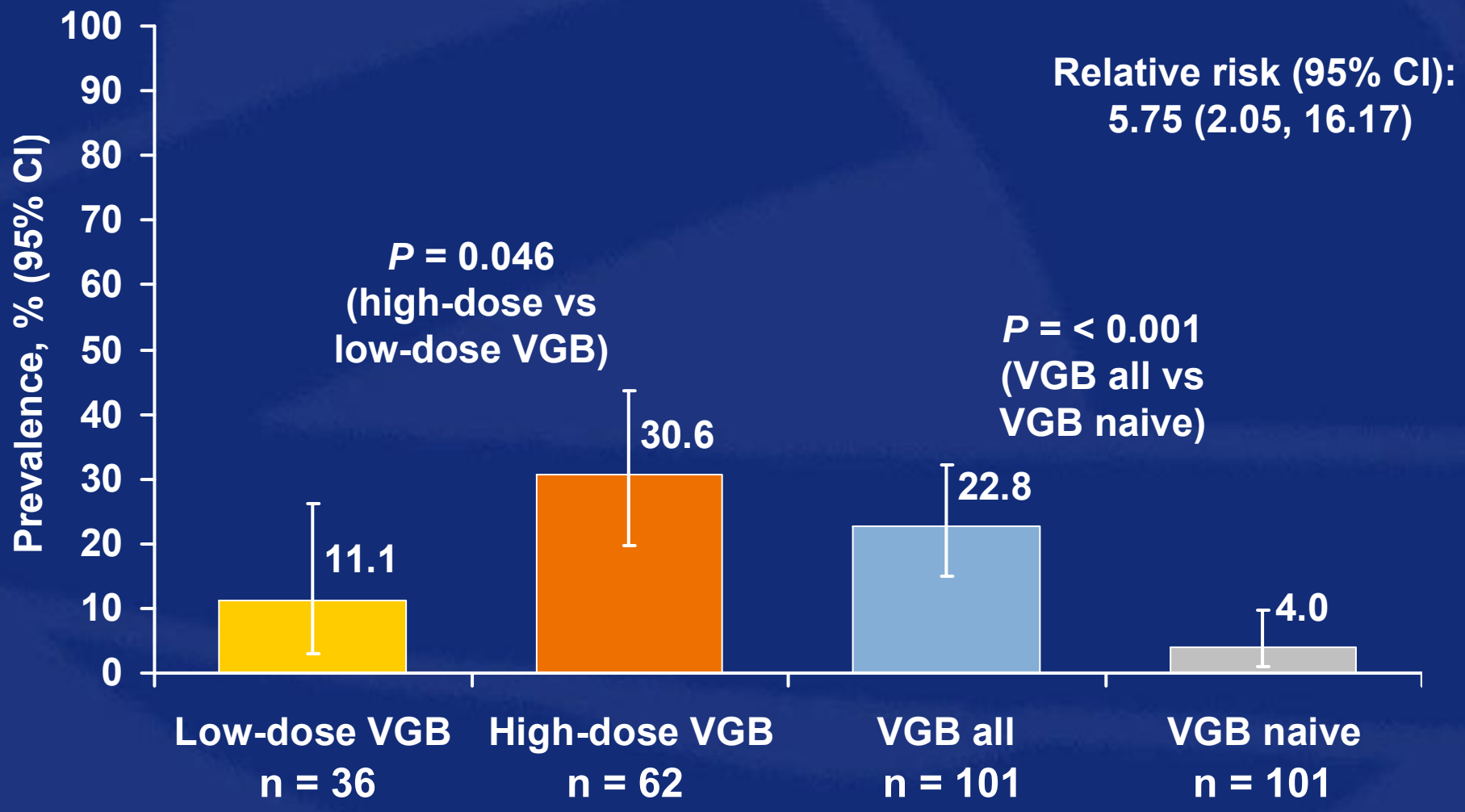
- Prespecified abnormalities include
  - Presence of increased T2 or FLAIR signal
  - Increased signal on DWI imaging
  - Not explainable by radiographically well-characterized pathologic process
- MRIs (digital or film) masked except for age of patient at time of MRI
- MRIs submitted to imaging core lab for central review and interpretation by 2 independent neuroradiologists with adjudication

Study Design—VGB Exposure
Study OV- 1019

- VGB exposed
  - Low-dose VGB (< 125 mg/kg/day)
  - High-dose VGB (≥ 125 mg/kg/day)
  - Unknown dose VGB
- VGB naive

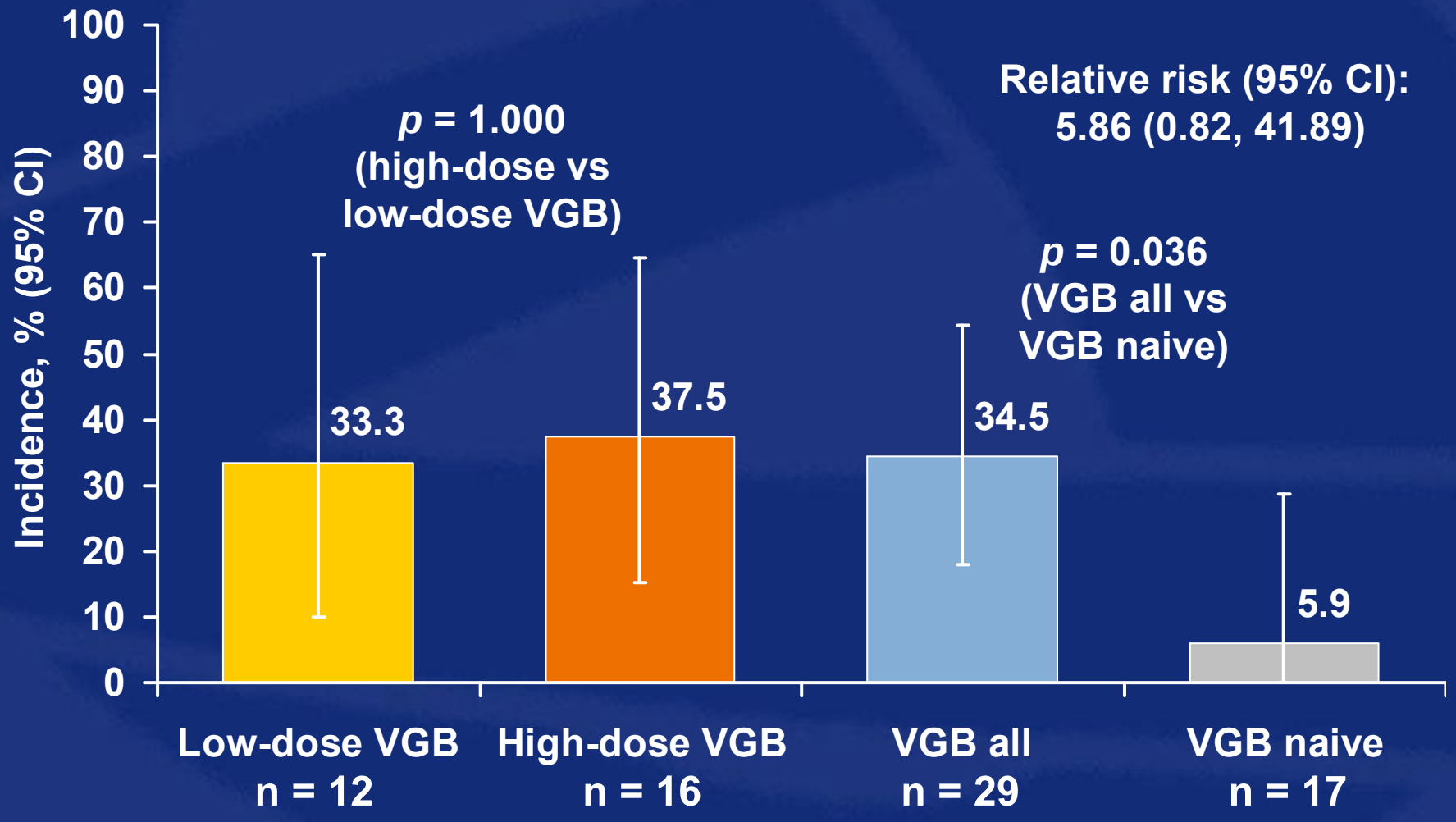
Prevalence of Cranial MRI Abnormalities

Study OV- 1019



Incidence of Cranial MRI Abnormalities

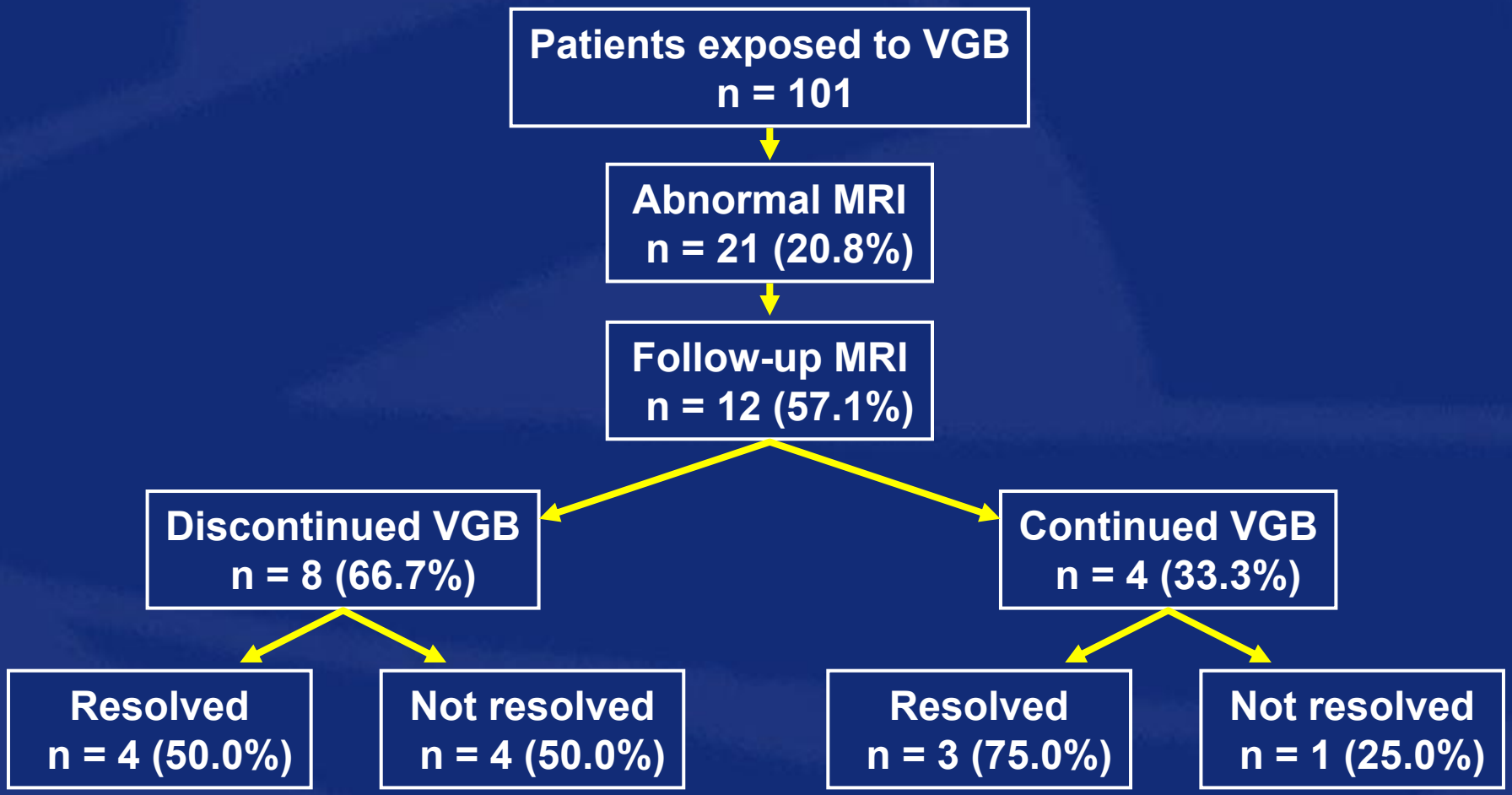
Study OV-1019



Results—Cranial MRI Abnormalities

Study OV-1019

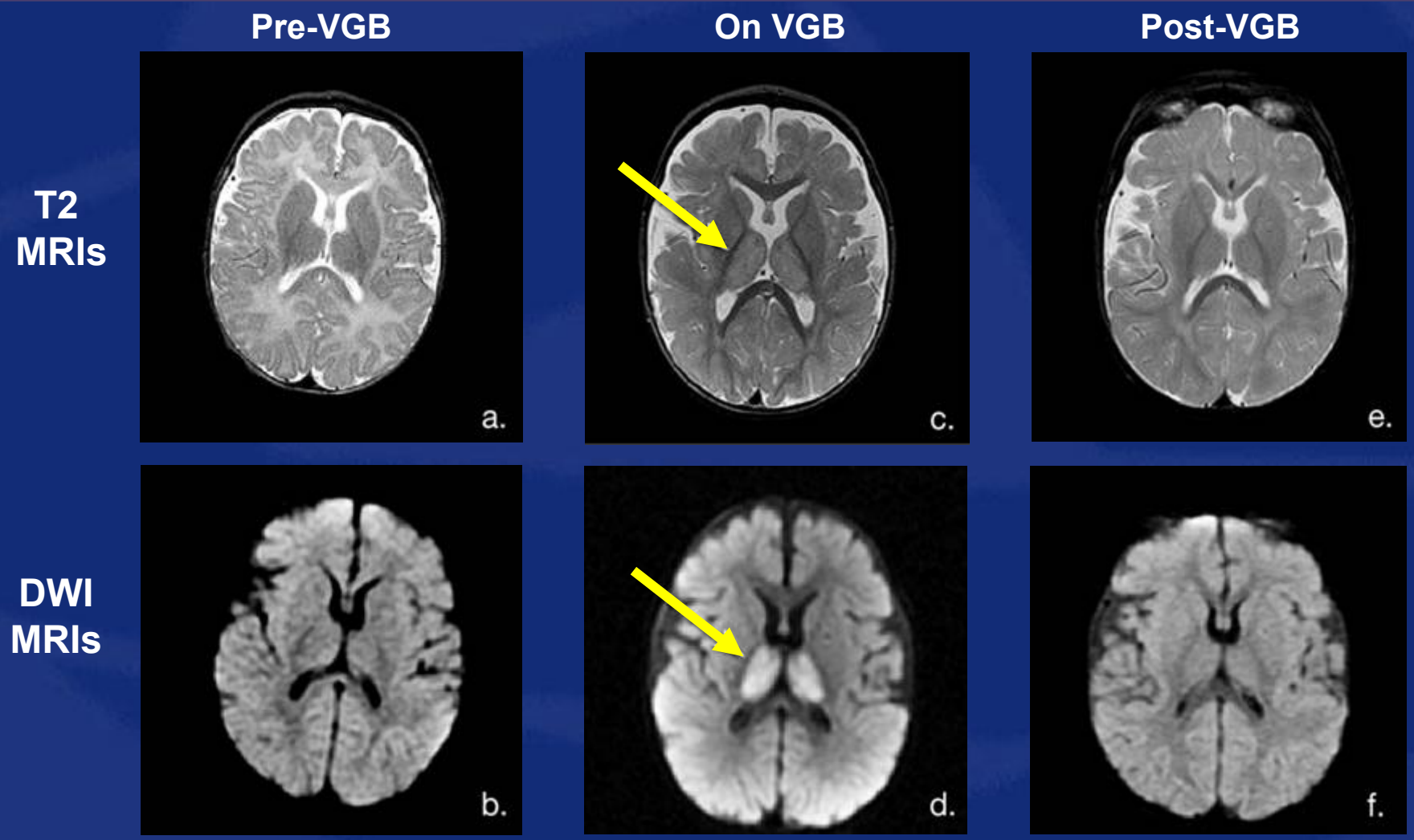
Resolution of MRI abnormalities



Patients in the prevalence population.

Resolution of Cranial MRI Abnormalities

Study OV-1019



Summary—MRI Abnormalities

- Characteristic location: brainstem, cerebellum, basal ganglia, and thalamus
- Approximately 6-fold greater relative risk with VGB exposure
- Possible dose-dependent effect
- No additional risk factors identified
- Resolved on follow-up MRI in 7 of 12 patients
  - After discontinuation or with ongoing VGB
- No associated clinical sequelae observed

Resolution of VGB-Associated MRI Changes

Pearl PL, et al. 2008

- 8/23 (36%) treated for IS had new abnormalities in basal ganglia, thalamus, brain stem, or dentate nucleus
  - All reversed with discontinuation of VGB
- 0/56 similar abnormal MRI in IS patients not treated with VGB

Desguerre I, et al. 2008

- 6/20 (30%) treated for IS with DWI abnormalities on MRI
  - 4 severely hypotonic, 1 dystonic movements, 1 no change
  - 5/6 resolved with follow-up MRI
    - 1 death; 4 still taking VGB; 1 high T2 in thalamus persisted

Pearl PL, et al. *Epilepsia.* 2008;epub; Desguerre I, et al. *Dev Med Child Neurol.* 2008;50:112-116.

Vigabatrin Use in Infants With IS—Conclusions

- Exposure to VGB is associated with increased incidence and prevalence of MRI abnormalities in infants with IS
- Exposure to high-dose VGB is associated with increased prevalence of MRI abnormalities compared to low-dose
- Majority of MRI abnormalities are reversible, whether or not patient continues taking VGB

Sabril® (vigabatrin) for Oral Solution for Infantile Spasms

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 Risk Evaluation and Mitigation Strategy (REMS)

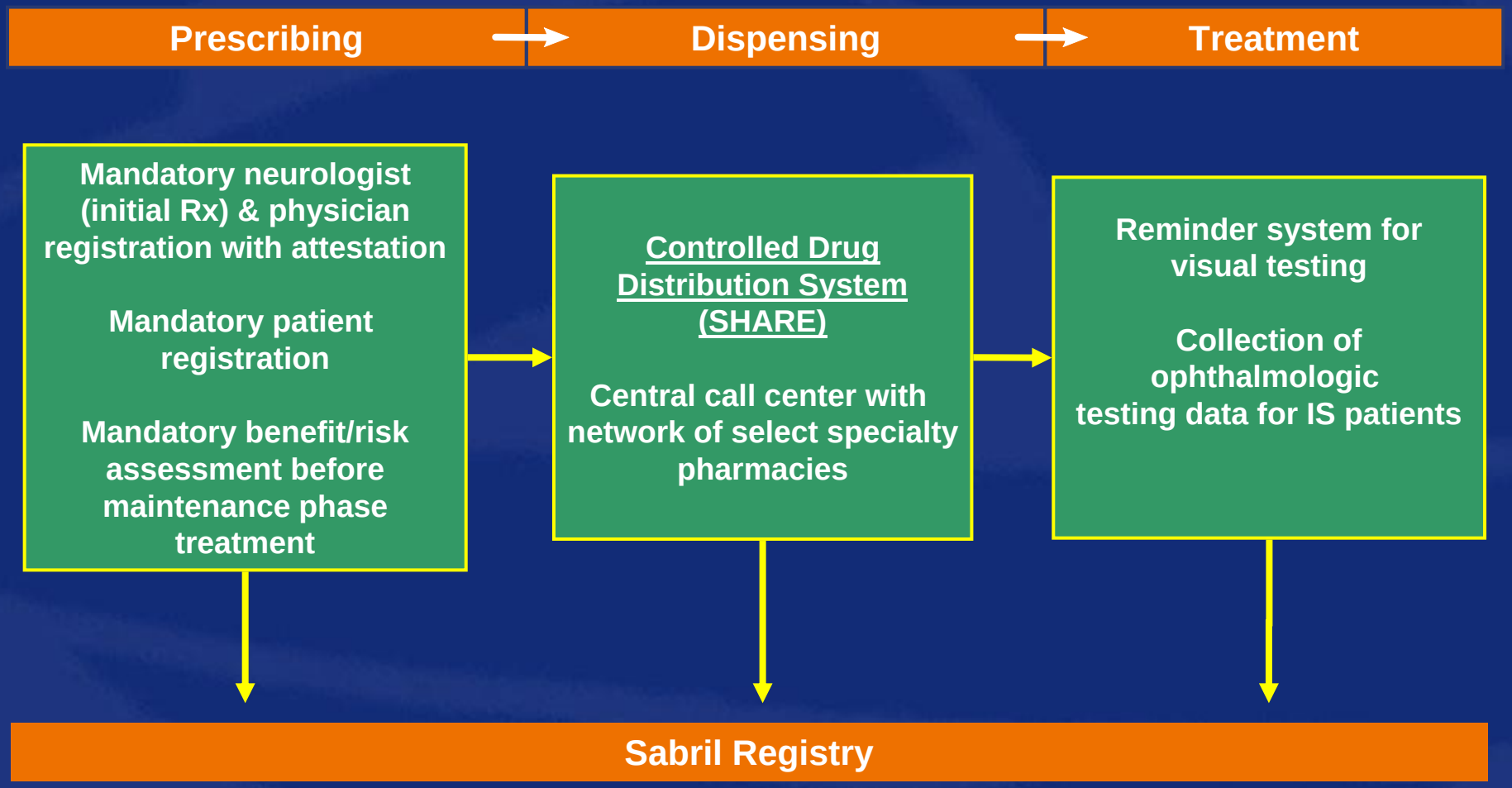
Labeling

- **Package Insert**
  - Black Box pVFD Warning and ophthalmologic monitoring
  - MRI Warning and consider monitoring if:
    - Treatment decisions will be impacted by MRI results
    - New findings on neurological exam
    - Motor abnormalities observed
- **Medication Guide**
  - pVFD
  - MRI abnormalities

Communication Plan

- **Physician education**
  - Dear Healthcare Professional (HCP) Letters
  - Sabril Benefit/Risk Slide Presentation
  - Visual Testing Guidance
- **Patient/Caregiver education**
  - Patient - Physician Agreement
  - Brochure(s) on Epilepsy, Sabril, and pVFD
  - Web-based Visual Field Simulator

Sabril REMS
Elements to Assure Safe Use



Sabril® (vigabatrin) for Oral Solution for Infantile Spasms

Benefit/Risk Assessment

John M. Pellock, MD

Professor and Chairman
Division of Child Neurology
Virginia Commonwealth University

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Uncontrolled Infantile Spasms Have Serious Consequences

- In children who are not controlled, the spasms generally evolve to other seizure types within 1 - 2 years
  - Most evolve to other catastrophic epilepsy syndromes such as Lennox-Gastaut syndrome or intractable partial seizures
- Mortality rate of up to 1/3 of patients
- Other catastrophic consequences:
  - Autism (~ 30%)
  - Developmentally delayed (70% - 90%)
- Rare, but devastating neurologic child emergency

Treating Infantile Spasm—Unmet Need

- No approved treatments in US
  - ACTH or corticosteroids (off-label use)
    - Efficacy Incomplete
    - Significant safety/tolerability issues
- Early, effective treatment is important for favorable developmental outcome
- Benefit/risk assessment favors aggressive therapy
  - Manageable risk

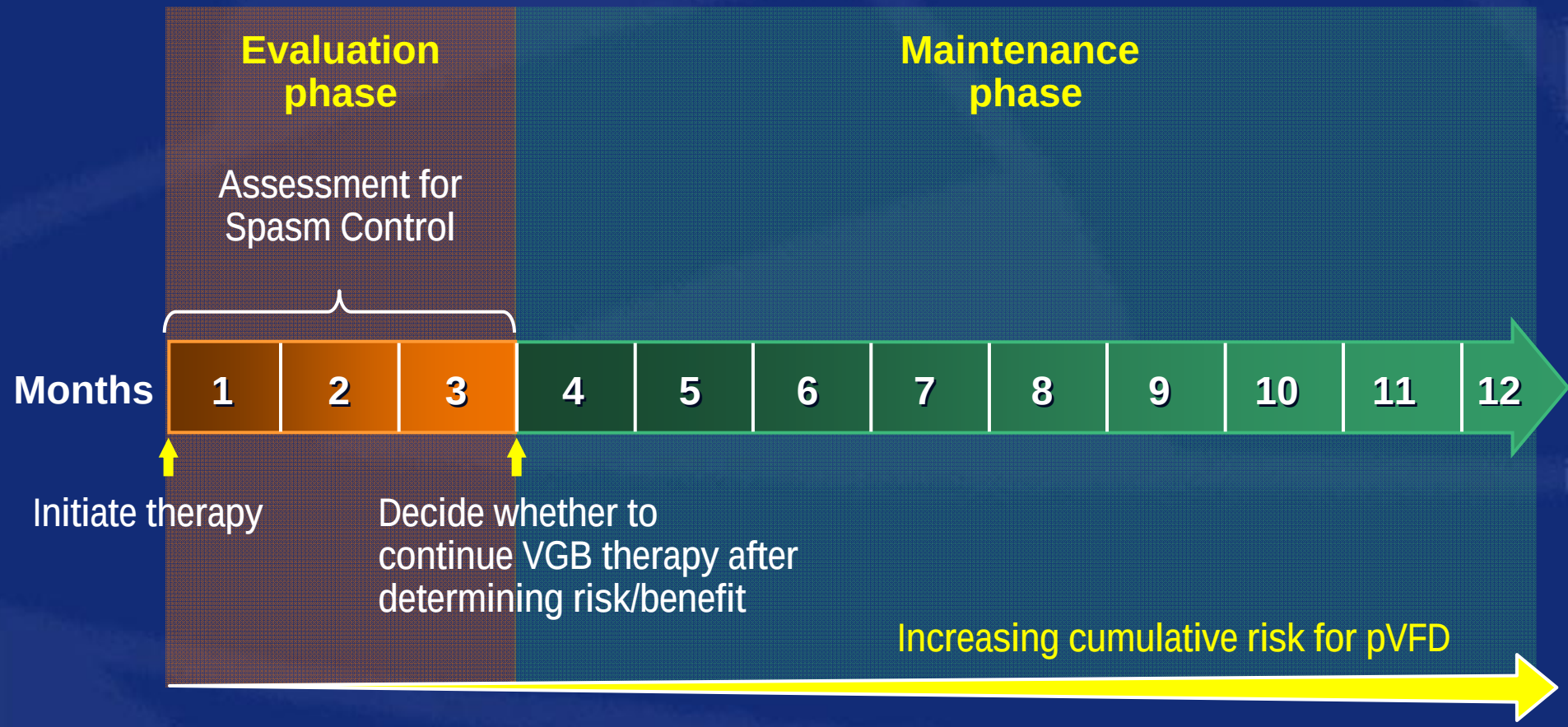
VGB Treatment Associated With Significant Improvement in Spasm Cessation

- **Spasm cessation observed in multiple studies, across all infantile spasm etiologies**
- **Rapid onset of spasm cessation (within 2 - 4 weeks of treatment)**
- **Generally well tolerated**
- **Accepted as first-line therapy around the world including the US**

VGB in IS—Associated Risks

- pVFD
  - Characterized by ERG
  - Can be monitored by confrontation testing or ERG
  - Challenges in monitoring this population
- MRI abnormalities
  - Changes generally resolve with
    - Discontinuation
    - Reduction of VGB dose
  - No known long-term clinical sequelae
  - MRI carries the risk of sedation in infants

Timeline to Evaluate Efficacy in Patients With IS



pVFD = Peripheral visual field defect.

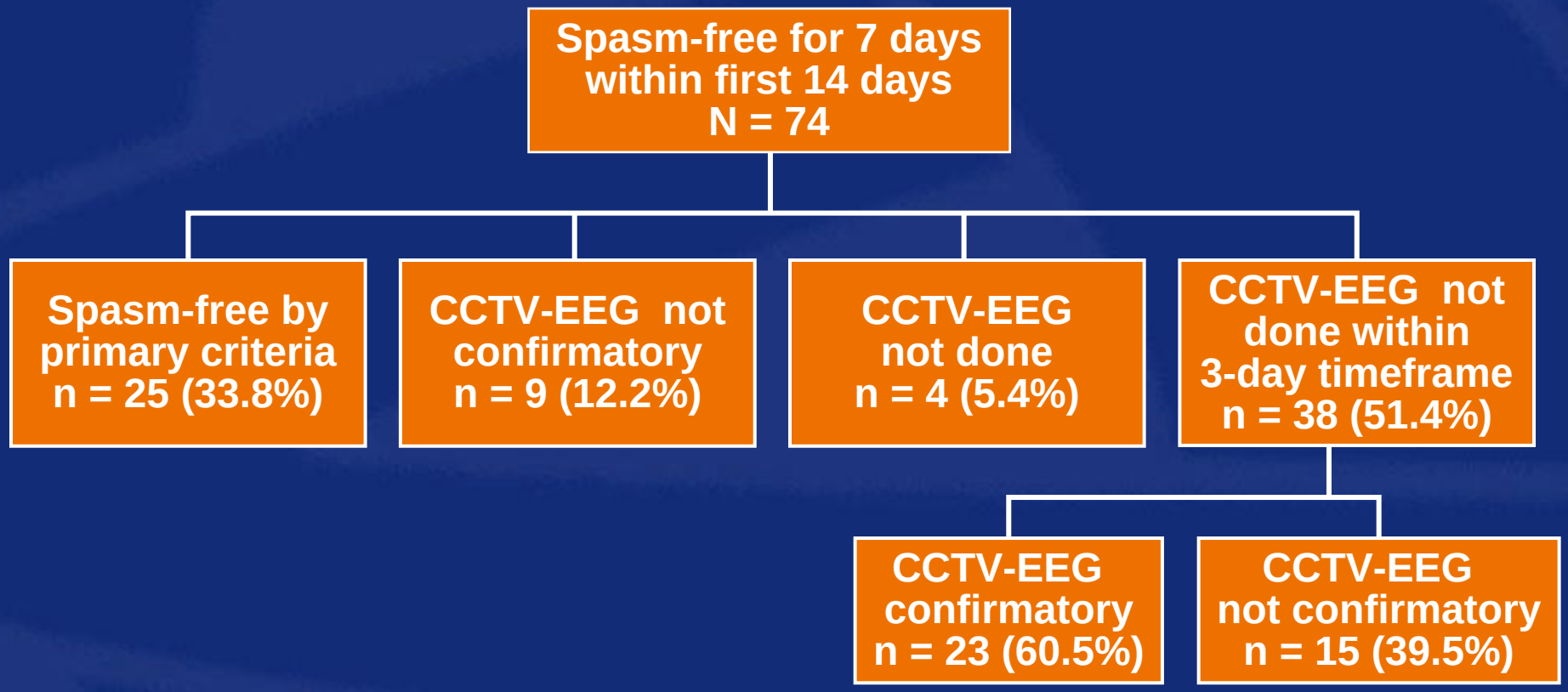
Positive Benefit/Risk Assessment of VGB Therapy in IS

- IS is a neurologic emergency; there are currently no approved therapies in US
- Treatment with VGB has produced spasm cessation in multiple studies across all IS etiologies
- VGB is recognized internationally and within the US in treatment guidelines as effective monotherapy for the initial treatment of IS (cryptogenic, symptomatic, and secondary to TS)
- In infants who respond to VGB, the benefit of spasm cessation exceeds the risks of pVFD and MRI changes

Summary

- Vigabatrin is recognized as 1st-line therapy worldwide for IS (West syndrome)
- Currently there is no regulated drug available to infants requiring treatment in US
- Currently infants in US are receiving VGB without proper safety instructions vs proposed REMs
- Children and their neurologists need VGB for IS treatment

CCTV-EEG Results/Availability—Spasm Cessation for 7 Days Within First 14 Days



[a] Subject must have confirmatory CCTV-EEG done within 3 days after the seventh day of spasm freedom.
[b] Counts and percentages presented are for results of CCTV-EEG not done within required timeframe.
Program: t_prim_eegres.sas (Date Generated: 05JUL2008)

Etiologically Diverse

Hypoxic-ischemic encephalopathy
- Near miss SIDS
- Cardiac arrest
- Near drowning
- PVL
- Post cardiac surgery

Maternal toxemia
Meningitis/encephalitis

Sturge-Weber syndrome
Tuberous sclerosis
Neurofibromatosis
Sebaceous nevus syndrome
Incontinentia pigmenti
Epidermal nevus syndrome
Miller-Dieker syndrome
Down syndrome

Idiopathic/Cryptogenic

Cortical dysplasias
Focal cortical dysplasia
Hemimegalencephaly
Hydranencephaly
Corpus callosum agenesis/dysgenesis
Septo-optico dysplasia
Schizencephaly
Holoprosencephaly
Multiple pineal cysts
Band heterotopia
Aicardi syndrome
Lissencephaly
Pachygyria
Hydrocephalus
Porencephaly

AVM
Stroke
Tumor
Cerebral abscess
Transplacental infections
Trauma

Pyridoxine dependent seizures
Phenylketonuria
Maple syrup urine disease
Biotinidase deficiency
Menkes disease
Hyperammonemia disorders
Non-ketotic hyperglycinuria
Leigh disease
Krabbe disease
ARX