Advisory Committee Briefing Document

Sabril® (vigabatrin) Tablet and Powder for Oral Solution

For Adjunctive Treatment of Refractory Complex Partial Seizures in Adults (NDA 20-427)

For Monotherapy Treatment of Infantile Spasms (NDA 22-006)

Peripheral and Central Nervous System Advisory Committee

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Ovation Pharmaceuticals, Inc

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACTH	adrenocorticotropic hormone
AE	adverse event
AED	antiepileptic drug
AUC	area under the curve
BCPC	bilateral, concentric, peripheral constriction
BIBRA	British Industrial Biological Research Association
CBZ	Carbamazepine
CCTV EEG	closed-circuit television electroencephalogram
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CPS	complex partial seizures
CRF	case report form
CSF	cerebrospinal fluid
DWI	diffusion-weighted imaging
EEG	Electroencephalogram
EMEA	European Medicines Agency
EOS	ethanolamine-O-sulfate
EP	evoked potential
ERG	Electroretinogram
ETASU	elements to assure safe use
EU	European Union
FDA	Food and Drug Administration
FLAIR	fluid-attenuated inversion-recovery
GABA	gamma-aminobutyric acid
GABA-T	gamma-aminobutyric acid transaminase
GAD	glutamic acid decarboxylase
GADERS	Global Adverse Event Reports
GCP	good clinical practice
GFAP	glial fibrillary acidic protein
HC	horizontal cells
HIPAA	Health Insurance Portability and Accountability Act
IME	intramyelinic edema
IND	Investigational New Drug
IPL	inner plexiform layer

IS	infantile spasms
ISS	Integrated Summary of Safety
KAB	Knowledge, Attitude and Behavior
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mfERG	multifocal electroretinogram
MMD	Marion Merrell Dow
MRI	magnetic resonance imaging
NDA	New Drug Application
NMDA	N-methyl-D-aspartate
OCT	optical coherence tomography
OP	oscillatory potential
PEM	Prescription Event Monitoring
PND	post-natal day
PS	partial seizure
pVFD	peripheral visual field defect
PYs	patient-years
REMS	risk evaluation and mitigation strategy
RNFL	Retinal nerve fiber layer
SAE	serious adverse event
SD	standard deviation
SHARE	Support, Help, and Resources for Epilepsy
SSEP	somatosensory-evoked potentials
SUDEP	Sudden Unexplained Death in Epilepsy
TS	tuberous sclerosis
UK	United Kingdom
U.S.	United States
VEP	visual evoked potential
VFD	visual field defect
VGB	Vigabatrin
VPA	valproic acid
WF-mfERG	Wide field multifocal electroretinogram

1 INTRODUCTION AND BACKGROUND

Ovation Pharmaceuticals, Inc. ("Ovation") is seeking approval from the United States (U.S.) Food and Drug Administration (FDA) for the use of Sabril® (vigabatrin [VGB]) in the adjunctive treatment of adult patients with refractory complex partial seizures (CPS) and as monotherapy in patients with infantile spasms (IS). Two applications were submitted to support these indications respectively: an amended New Drug Application (NDA) 20-427 (500 mg tablet) for adult patients with refractory CPS and NDA 22-006 (500 mg powder for oral solution) for IS. As part of FDA's review process, Advisory Committee panels are being convened to review the benefit/risk profile of VGB in these two serious and life-threatening forms of epilepsy.

VGB is currently available in over 50 countries worldwide for these indications, including most countries of the European Union, Canada, and Mexico. Ovation has North American rights to VGB and is the marketing authorization holder in the latter two countries. Since initial marketing approval in the United Kingdom (UK) in 1989, more than 1.5 million patients have received VGB. In the U.S., the original NDA was submitted in 1994 for adult patients with CPS. FDA initially issued an Approvable Letter in 1997 prior to the emergence of reports of a peripheral visual field defect (pVFD). Due to the need for additional information on this safety issue, FDA issued a Non-Approvable Letter in 1998. Over the past decade, the features and clinical course of the pVFD have been studied extensively in multiple clinical and nonclinical studies. As a result, Ovation assembled the necessary data in order to respond to the 1998 Non-Approvable Letter via a December 2007 amendment to NDA 20-427 for adult patients with refractory CPS and at the same time submitted a new NDA 22-006 for patients with IS, an Orphan medical condition.

VGB is an irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), resulting in an increased level of GABA in the brain. As the only GABA metabolic blocker, VGB provides a unique mechanism of action in comparison to available antiepileptic drugs (AEDs). Multiple clinical studies conducted around the world including the U.S. have established the effectiveness and potency of VGB in the treatment of patients with refractory CPS and IS. Efficacy data for VGB in the treatment of adults with refractory CPS have been previously reviewed by the FDA as part of the original NDA submission. Efficacy data for VGB in the treatment of patients with IS have not been previously reviewed by FDA.

The use of VGB has been limited by the occurrence of a pVFD in some patients. This defect was first reported in 1997 [1], nearly 8 years after initial marketing authorization in the UK and led to a special safety review by the European Medicines Agency (EMEA) under Article 12 of the European Commission Directive 75/319/EEC (now known as Article 31). In 1999, The Committee for Medicinal Products for Human Use (CHMP) of the EMEA concluded that the benefit/risk for VGB remained favorable for a more narrow patient population than originally approved for, that is: 1) as adjunctive therapy for adult patients with resistant CPS who had inadequate response to alternate treatments and 2) as monotherapy in patients with IS, the same two indications currently under U.S. FDA review and the subject of this Advisory Committee meeting. In addition, the Marketing Authorization Holder (MAH) was

required to conduct a series of postmarketing clinical and nonclinical studies to further characterize pVFD as a condition of continued marketing approval.

More recently, following an October 2006 report (published in January 2007) of magnetic resonance imaging (MRI) abnormalities in 3 of 15 IS patients treated with VGB, Ovation initiated a comprehensive clinical and radiological investigation on this new finding. This review was requested by the FDA, due to the prior concern regarding intramyelinic edema (IME) noted in several animal species during the VGB development program. Results and conclusions from these investigations are presented in this briefing document.

This briefing document describes the unmet medical need that exists for refractory CPS and IS, two devastating and catastrophic forms of epilepsy and presents an evaluation of all available clinical and safety data describing VGB in its use as adjunctive treatment of refractory CPS in adults and monotherapy for IS. Also presented is a comprehensive Risk Evaluation & Mitigation Strategy (REMS) that is intended to 1) control distribution to facilitate prescribing VGB in accordance with its intended use in appropriate patients where an unmet medical need exists; 2) educate physicians, patients and parent/legal guardians about the risks of VGB treatment, in particular the risk of pVFD, and 3) provide guidance on how to actively assess and manage patients receiving VGB treatment.

Data presented in this document support the conclusions that:

- An unmet medical need exists for refractory CPS and IS, two serious and life-threatening forms of epilepsy. VGB provides a novel option for patients and has an important therapeutic role in the amelioration of these devastating and catastrophic conditions;
- Available clinical data support the use of VGB in the adjunctive treatment of refractory CPS for adults who have an inadequate response to alternative treatments and for whom the potential benefits outweigh the potential risk of developing pVFD; and as monotherapy for pediatric patients with IS for whom the potential benefits outweigh the potential risk of developing pVFD.
- The safety profile of VGB is well characterized and many features of the pVFD are now understood. The pVFD, if it occurs, generally appears after months of therapy, and is typically mild or moderate and rarely severe. Central visual acuity is not affected. The VGB-induced pVFD does not appear to begin, progress or reverse after the drug is discontinued, although the possibility cannot be rigorously excluded.
- An adequate REMS has been developed to manage the risk of pVFD and the overall safe use of VGB in appropriate patients where an unmet medical need exists.
- The benefits of VGB in the treatment of adult patients with refractory CPS and in patients with IS exceed the risks. Patients in the U.S. should have access to this important anti-epilepsy drug.

1.1. Unmet Medical Need in Refractory CPS

A significant unmet medical need exists for patients with refractory CPS who are at an increased risk for mortality and significant morbidity as compared to the general epilepsy

population [2]. Mortality rates in patients with epilepsy are 2 to 3 times higher than that in the general population [3], and, with uncontrolled epilepsy mortality rates are 4 to 7 times higher than in patients whose epilepsy is adequately controlled [4]. Neuropsychologic and psychiatric consequences of uncontrolled epilepsy include depression and reduced quality of life [4]. Social disabilities include less social interaction, reduced marriage rates, and reduced employment levels [4].

Although VGB has potential risks, most notably the pVFD, other available treatments have potential risks as well and all require careful benefit/risk considerations [5]. Toxicities caused by current treatments include: aplastic anemia, agranulocytosis, severe dermatologic reactions, including Stevens-Johnson Syndrome, hepatotoxicity, teratogenicity, and pancreatitis [6,7]. Despite the availability of numerous anti-epileptic drugs, about 1/3 of patients with epilepsy continue to have seizures and suffer the associated consequences of uncontrolled seizures [8]. For patients who have failed to respond to prior therapy, therapeutic success may be achieved for a subset of these patients with the introduction of additional agents [9,10]. Thus, there continues to remain an unmet medical need and Sabril is a valuable treatment option for patients with refractory epilepsy.

1.2. Unmet Medical Need in IS

In patients with IS, one of the most severe and refractory forms of epilepsy, uncontrolled and continuous seizures lead to impaired nervous system function, inability to attain critical developmental milestones and/or regression from previously established milestones. IS is frequently associated with neurological deficits such as mental retardation, occurring in 70% to 90% of patients,[11-17] with the majority developing severe-to-profound retardation. Approximately 30% to 50% of patients present other neurological deficits, such as static encephalopathy (cerebral palsy) [11,14,17]. The primary goal of any treatment program is complete suppression of spasms and hypsarrhythmia.

There are no approved treatments for IS in the U.S. The most commonly used off-label therapies are adrenocorticotropic hormone (ACTH) and prednisone. Although these treatments have at least initial efficacy in a sizable number of patients, they also have a relapse rate of approximately 40% in some studies, bringing overall efficacy to a much smaller number of patients [11,12,18-24]. Hormonal therapy such as ACTH may also have significant and potentially fatal side effects [19,25]. Other off-label therapies used less frequently include sodium valproate, benzodiazepines, and some newer AEDs. However, the safety and efficacy of these agents have not been established in controlled clinical studies, and they can be associated with significant side effects [26].

In the 1998 consensus guideline [27] for prescribing VGB in children, VGB remained the drug of choice for IS. These guidelines were revised after the reports of pVFD in VGB-treated adults to include specific recommendations for visual field monitoring [28, 29]; however, VGB has remained the drug of choice for IS among many treating physicians in Europe and Canada where the drug is approved, especially when IS is caused by tuberous sclerosis (TS) [28-34].

1.3. Regulatory Background

VGB was first approved in 1989 in the United Kingdom (UK) (International Birthdate). It is currently available in over 50 countries including most European Union (EU) Member States, Canada, Mexico and certain countries in Asia, Latin America and the Middle East for the treatment of resistant complex partial seizures and IS (West Syndrome).

The original NDA was submitted by Marion Merrell Dow (MMD), now Sanofi-Aventis, to the U.S. FDA in April 1994 for the adjunctive treatment of CPS in adults, based on two pivotal studies, 025 and 024. Following an initial Non-Approvable letter in April 1995 due to insufficient information to evaluate safety and effectiveness, subsequent submissions led to an Approvable letter in November 1997.

Around the same time, emerging postmarketing reports in the EU of pVFD associated with VGB ultimately led the FDA to issue a Non-Approvable letter in 1998, as the prevalence, severity, and mechanism of the defect were not fully understood.

In October 1998, EMEA initiated an Article 12 Referral to review the benefit/risk of VGB in light of its potential to cause pVFD. The CPMP of EMEA ultimately recommended to retain the marketing authorizations but recommended revisions to the labeling, including restriction to a more narrow patient population, initiation of treatment by a specialist, additional warnings regarding the occurrence of pVFD, recommendations for systematic visual screening examinations, and updates to the Undesirable Effects section to include wording on pVFD and its severity, onset, and prevalence. Additional nonclinical studies were requested to investigate the mechanism of VGB-induced retinal toxicity and to provide information on the possible differences in the severity of the defect in young and adult animals (see Section 2.2.2). Clinical studies were also required to evaluate the frequency, severity, progression and reversibility of pVFD. These clinical studies are described in further detail in Section 4.4.14.1 of this briefing document.

In March 2004, Ovation acquired the North American regulatory, distribution, and marketing rights for VGB from Aventis.

Ovation's first submission to FDA occurred in December 2005, when a complete response amendment to the Non-Approvable letter for NDA 20-427 for refractory CPS was submitted. Additional submissions were made in October 2006 and March 2007 to provide patient narratives. The original NDA 22-006 for IS was also submitted in March 2007. In April 2007, FDA refused to accept the NDA submissions for review due to a report of reversible MRI changes observed in 3 of 15 infants treated with VGB as described in the January 2007 issue of Clinical Neurology News [35]. FDA noted that these findings raised important new concerns given previous findings of IME in animals that needed to be addressed before review of the VGB NDAs could commence (see Section 4.4.14.2). Between 1983 and 1990 , patient enrollment into VGB clinical studies in the U.S. was suspended because of nonclinical findings of IME in rats and dogs. This issue was addressed in 3 closed-door Advisory Committee meetings, held in May 1984, October 1985, and November 1989, respectively, during which available data were reviewed to determine whether clinical studies in patients with uncontrolled epilepsy could proceed. After reviewing clinical data from

Europe which did not reveal any case of IME in humans or clinical or radiological data suggestive of IME in humans, the FDA allowed clinical studies in the US to proceed in patients with uncontrolled epilepsy in June, 1990. Subsequent U.S. clinical studies included prospective MRI monitoring, which again did not reveal evidence suggestive of IME in humans.

Based on the report of MRI abnormalities in 3 of 15 VGB-treated patients with IS, Ovation assembled new data from over 200 patients with IS who had cranial MRI evaluations and discussed findings with the FDA in June 2007. Based on this data, Ovation proposed and FDA agreed that a retrospective study of cranial MRIs in infants treated with VGB was required before NDA review could continue. Additionally, Ovation agreed to conduct a repeat review of MRI data collected in 12 prior CPS studies in adults and children conducted by the previous sponsor. Data from these reviews were included in December 2007 NDA submissions and are also presented in this briefing document (see Section 4.4.14.2). Finally, Ovation proposed and FDA agreed that a prospective study of cranial MRIs in patients with IS treated with VGB be required as a postmarketing study commitment following NDA approval.

1.4. Overview of Studies and Patient Populations in the Vigabatrin Clinical Development Program

This section presents an overview of the terminology used within this document to describe different populations and study types over the course of the entire VGB development program.

1.4.1 Non-IS and IS Patient Populations

For the purposes of presenting safety and efficacy for two separate patient populations, the terms non-IS patients (includes all adult and pediatric epilepsy patients and excludes IS patients) and IS patients are used throughout this document. Specifically for safety presentations, the non-IS population includes adult CPS patients and those with other types of epilepsy. It should be noted that pediatric CPS studies conducted to support a pediatric claim were stopped early due to reports of pVFD and FDA's subsequent non-approvable action.

1.4.2 U.S., Primary Non-U.S. and Secondary Non-U.S. Studies

Clinical development of VGB initiated in 1980 by the previous sponsors, who collected data from over 3000 patients treated with VGB in clinical studies. Although pivotal studies were conducted in the U.S., several supportive studies were conducted outside of the U.S., in the EU and elsewhere. For the purposes of submission to FDA, the previous sponsors described these non-U.S. studies as either primary or secondary, due to differing data collection methods, as follows:

- Primary non-U.S. studies describe those studies 1) in which data were supported by case report forms (CRFs), 2) which had a prospective protocol, and 3) in which data collection was conducted in accordance with the study protocol as written

- Secondary non-U.S. studies describe studies which were supported by CRFs, but did not have a prospective protocol and/or data was not collected in accordance with the study protocol

Because of the nature of the data collection, for the purposes of safety presentations to the FDA, the Agency requested that adverse events (AEs) be analyzed only for patients enrolled in U.S. and primary non-U.S. studies. Serious adverse events (SAEs), discontinuations due to AEs, and deaths were presented for all patients in all studies: U.S., primary non-U.S., and secondary non-U.S. studies. Deaths from compassionate use studies and other indications were also included.

1.4.3 Article 12 Studies

In addition to the studies conducted during the development program, the previous sponsor conducted 5 safety studies in response to the 1998 EMEA Article 12 Referral (see previous Section 1.3), investigating the relationship between pVFD and VGB therapy. These studies are labeled Article 12 Studies.

Table 1 provides an overview of studies conducted in non-IS patients with epilepsy (U.S., primary non-U.S., and secondary non-U.S.). Table 2 provides an overview of studies conducted in IS patients.

Table 1. Overview of Epilepsy Studies, Non-IS

Study	Location, Age	Epilepsy Type
Controlled and Uncontrolled Studies, U.S. and Primary Non-U.S.		
Placebo-Controlled Studies, U.S. and Primary Non-U.S.		
Studies Pertinent to Claimed Indication		
Pivotal Studies		
71754-3-C-024	U.S., Adult	Refractory CPS or PS 2nd generalized
71754-3-C-025	U.S., Adult	Refractory CPS or PS 2nd generalized
Supportive Studies		
097-444	Non-U.S., Adult	Refractory CPS or "grand mal"
097/W/AUS/01	Non-U.S., Adult	Uncontrolled CPS
0101	U.S., Adult	Non-refractory CPS
Studies not Pertinent to the Claimed Indication		
0118	U.S., Pediatric	CPS
0221	U.S., Pediatric	CPS
0192	Non-U.S., Pediatric	CPS
097-247	Non-U.S., Adult	Epilepsy
097-259	Non-U.S., Adult	Epilepsy
097-262	Non-U.S., Adult	Epilepsy
097-263	Non-U.S., Adult	Epilepsy
097-309	Non-U.S., Adult	Epilepsy
097-WUK04	Non-U.S., Adult	Epilepsy
71754-C-021	Non-U.S., Adult	Epilepsy
Other Controlled Studies, U.S. and Primary Non-U.S.		
0222: Active-controlled	U.S., Adult	CPS monotherapy
0223: Low-dose controlled, parallel-group	U.S., Adult	CPS monotherapy
71754-3-W-012: Active-controlled	Non-U.S., Adult	Epilepsy [resistant to CBZ] monotherapy
71754-3-W-007: Active-controlled	Non-U.S., Adult	Newly diagnosed epilepsy monotherapy
Uncontrolled Studies, U.S. and Primary Non-U.S.		
097-005	U.S., Adult	CPS
097-006	U.S., Adult	CPS
0242	U.S., Adult	CPS monotherapy
097-304	Non-U.S., Adult	CPS
0201	U.S., Pediatric	CPS
0294	Non-U.S., Pediatric	CPS
097-332	Non-U.S., Pediatric	Epilepsy
0098	U.S., Adult	Partial seizures
71754-3-C-020	U.S.	Epilepsy
71754-3-C-026	U.S.	Epilepsy

Table 1. Overview of Epilepsy Studies, Non-IS

Study	Location, Age	Epilepsy Type
71754-3-C-028	US, Adult	Epilepsy
097-212	Non-U.S., Adult	Epilepsy
097-215	Non-U.S., Adult	Epilepsy
097-236	Non-U.S., Adult	Epilepsy
097-237	Non-U.S., Adult	Epilepsy
097-244	Non-U.S., Adult	Epilepsy
097-254	Non-U.S., Pediatric	Epilepsy
097-255	Non-U.S., Pediatric	Epilepsy
097-312	Non-U.S., Adult	Epilepsy
097-315	Non-U.S., Adult	Partial seizures
097-315A	Non-U.S., Adult	Partial seizures
097-315LT	Non-U.S., Adult	Partial seizures
097-335	Non-U.S., Adult	Epilepsy newly diagnosed
097-WUK17	Non-U.S., Adult	CPS or “grand mal”
71754-3-C-022	Non-U.S., Adult	CPS
71754-3-W-002	Non-U.S., Adult	Epilepsy newly diagnosed
71754-III-ST-016	Non-U.S., Adult	Partial epilepsy [receiving CBZ]
9001/VGB	Non-U.S., Pediatric	Epilepsy
VIGA/4/ST/01	Non-U.S., Adult	Epilepsy
VIGA/4/ST06	Non-U.S., Adult	Epilepsy
VIGA-4-ST-03	Non-U.S., Adult	Refractory epilepsy
EMEA/CHMP Article 12 Referral Studies (Uncontrolled)		
R003	Non-U.S	Refractory partial epilepsy
4020	Non-U.S., Adult and Pediatric	Refractory partial epilepsy
4021	Non-U.S.	Epilepsy
4102	Non-U.S.	Refractory partial seizures
4103[a]	Non-U.S.	Epilepsy
Controlled and Uncontrolled Studies, Secondary Non-U.S. Epilepsy Studies		
Controlled		
097-230		Epilepsy
097-242		Epilepsy
097-253		Epilepsy
097-258		Epilepsy
Uncontrolled Studies		
097-233		Epilepsy
097-238		Epilepsy
097-240		Epilepsy
097-241		Epilepsy
097-258LT		Epilepsy
097-264		Epilepsy
097-300		Epilepsy

Table 1. Overview of Epilepsy Studies, Non-IS

Study	Location, Age	Epilepsy Type
097-305		Epilepsy
097-306		Epilepsy
097-307		Epilepsy
097-311		Epilepsy
097-314		Epilepsy
097-319		Epilepsy
097-320		Epilepsy
097-345		Epilepsy
097-W345A		Epilepsy
097-WEU02		Epilepsy
097-WUK14		Epilepsy

CBZ=carbamazepine; CPS=complex partial seizures; PS=partial seizures; CHMP=Committee for Medicinal Products for Human Use; EMEA=European Medicines Agency; U.S.=United States

[a.] Only serious adverse events were collected in this study

Table 2. Overview of IS Studies

Study (Location)	Design	IS Type
Controlled and Uncontrolled Studies		
Controlled Studies		
1A (U.S.)	Single-blind, high-dose, low-dose controlled with open-label follow-up	IS
7154-3-W-019 (Primary Non-U.S.)	Double-blind, placebo-controlled, parallel-group with open-label follow-up	Newly diagnosed and previously untreated IS
097-WFR03 (Primary Non-U.S.)	Open-label, comparative, cross-over	Newly diagnosed and previously untreated IS associated with TS
Uncontrolled Study		
097-332.5 (Secondary Non-U.S.)	Open-Label	Drug resistant IS
Retrospective Studies		
OV1019[a]	Cohort, comparative epidemiologic (MRI)	IS
3E01	Retrospective data collection in 11 European countries	Previously untreated IS

IS=infantile spasms, U.S.=United States

[a.] Study OV1019 is presented in Section 5.4.9.2.

2 NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

2.1. Pharmacology and Mechanism of Action

As the only GABA-T inhibitor in clinical use, VGB provides a unique mechanism of action in comparison to available AEDs, which include sodium channel blockers, postsynaptic GABA receptor facilitators, GABA reuptake inhibitors, and modulators of neurotransmitter release. The mechanism of VGB's anti-seizure effect is thought to be due to its potent action as a selective and irreversible inhibitor of GABA-T, which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter, GABA [36-39]. VGB prevents the breakdown of GABA molecules and therefore results in increased levels of GABA in the CNS. This increased level of GABA in the CNS leads to a reduction in seizure activity.

2.2. Toxicology

2.2.1 General Toxicology Studies and Intramyelinic Edema

VGB has a relatively low degree of acute toxicity, with the oral median lethal dose in rodents approximating 3 g/kg. Oral administration of VGB at 1 g/kg/day for 2-4 weeks caused reduced food consumption and retarded body weight gains, plus prostration and death in both rats and dogs. However, dosages of 200 mg/kg/day in dogs were tolerated for a year without toxicity. In rats treated for a year, 100 mg/kg/day elicited convulsions, but these abated after 3-4 months of treatment. Alopecia was observed only in rats and its relationship with VGB treatment was inconclusive. VGB was shown not to be genotoxic or carcinogenic.

The only consistent histopathologic finding in rats and dogs was microvacuolation of specific regions of the brain, predominantly within the white matter termed IME [40-46]. Ultrastructurally the vacuoles were seen to split the intraperiod line of the myelin producing fluid filled microvacuoles.

This edema developed over a period of several weeks, after which a relatively stable plateau occurred, and then regressed within 12-16 weeks after drug exposure was withdrawn. IME has not been seen in the spinal cord or peripheral nerves of any species. IME was further seen in the pups of dams given 50, 100 or 150 mg/kg/day, albeit without evidence for a dose response with respect to incidence or severity, nor other indication of impaired myelin development. Evoked potential (EP) and MRI proved to be sensitive non-invasive techniques to diagnose IME in rats and dogs and to support its absence in humans and other primates. No residual pathology was noted upon recovery in dogs, but rodents appeared to retain swollen axons and foci of microscopic mineralization within the cerebellum. Monkeys experienced no toxicity other than occasional loose stools despite dosing to 300 mg/kg/day for up to 6 years. After 16 months of treatment, these monkeys were evaluated for IME with no conclusive evidence for this lesion even at 300 mg/kg/day, providing maximum plasma concentrations of 38±4 μg/mL daily. This plasma level is consistent with that provided infants (Cmax=34.9 μg/mL) and near that provided young children (65.10 μg/mL) given 50 mg/kg/day of VGB [47]. Overall, IME was noted in both rodents and dogs, but no conclusive evidence was observed for monkeys.

Multiple toxicity studies in juvenile rats provide additional characterization of the IME observed in rodents. Ovation conducted a juvenile toxicity study to examine the adverse effects of VGB treatment on the physical and behavioral development of Crl:CD(SD) rats as they grew from neonates to adults (Study OV-1007) [48]. Treatment groups included controls (receiving only vehicle), and groups receiving VGB at daily doses of 5, 15, or 50 mg/kg/day. Treatment was provided by gavage daily from post-natal day (PND) 4 to PND 65 (61 days). A select group of 20 males and 20 females were sacrificed at the end of treatment; half were perfused with neutral buffered formalin for histopathologic assessment of the brain, while half were used for biochemical measurements. Microscopic evaluations revealed minimal to mild vacuolar change within the neuropil in select brain regions in rats treated with 50 mg/kg/day, irrespective of gender. Regions most affected were the gray matter in the central midbrain (tegmentum), substantia nigra, dorsal subiculum, deep cerebellar nuclei, posterior thalamus, basal forebrain (especially medial forebrain bundle), and medulla oblongata. While vacuoles were found in some white matter tracks, such as the medial longitudinal fasciculus and the medial forebrain bundle, most vacuoles were in or near the gray matter. The specific cell type containing these vacuoles could not be verified via light microscopy. There was no evidence for an associated gliosis, neuronal, or other cellular degeneration, for reduced myelination, or hypocellularity, all findings consistent with previous reports of older rats treated with VGB.

A pathology working group was assembled to review these neurological findings. This group agreed with the principal neuropathologist on the regional location of the vacuolar changes in both gray and white matter of the brain of neonatal/juvenile rats given 50 mg/kg/day, the highest dose. Similar lesions were not confirmed at lower dosages. While the panel could not determine by light microscopy which specific cells were vacuolated, they felt confident that neuronal cell bodies, blood vessel endothelium, and perivascular astrocytic end processes were not affected; further, ultrastructural investigations would be necessary to confirm the cell type vulnerable to this vacuolation. (This recommendation led to Study OVNC-9004, discussed below). The panel believed the morphologic appearance was consistent with IME, but that the distribution of lesions was somewhat different from that reported in adult rats, i.e., predominantly in subcortical gray matter in neonates but more so in major white matter tracts in adults. These experts did not find morphologic evidence for neuronal cell death (apoptosis), a reduction in neurons throughout the neuropil (hypocellularity), or a reactive gliosis. Withdrawal of VGB exposure for 19 weeks permitted virtual complete recovery of the neuropil. Based on the human clinical, imaging and pathology literature, the panel concluded that there was no evidence that the vacuolar changes in rats are relevant in humans receiving VGB [49].

Despite the considerable evidence for IME in rats exposed to VGB from the neonatal age of PND 4 to the adult age of PND 65 days, there was very little evidence for abnormal development in these rats (Study OV-1007) [48]. Representative subsets (minimum of 10/sex/group) of each treated group were evaluated for evidence of abnormal neurological, reproductive, ocular and general physical development as part of the study. Neurological development was assessed functionally by a comprehensive clinical observational battery, plus assessments for motor function, acoustic startle habituation and prepulse inhibition (auditory development), learning and memory, using both a simple spatial discrimination watermaze and a Morris watermaze, and morphologically by neuropathology. Reproductive

development was evaluated functionally by the onset of sexual maturation, estrus cycling, mating proficiency, male and female fertility, sperm count and motility, and morphologically by macroscopic and histologic pathology. Ocular development was assessed by ophthalmic examination, electroretinograms (ERG) and histopathology. General development was evaluated by body weight gain, food consumption, clinical behavior, laboratory findings (hematology, clinical chemistry, urinalysis) and anatomical changes. Whole body spasms were noted in 35% of the males and 29% of the females given the highest dose and developing evidence for IME. There was no evidence for convulsions or seizures, although approximately 4% of the females succumbed to this dose. Significant reductions in growth and food intake in rats given 15 or 50 mg/kg/day of VGB complicated the evaluation of certain motor function tests. Rats in these groups had a reduced forelimb and hindlimb grip strength and when dropped landed with reduced leg extension (splay), when compared to larger control rats. The neuropharmacologist attributed this finding to their smaller and weaker size rather than to a neurological deficit from VGB. None of the other assessments of motor function, including swimming in two watermazes, indicated a functional neurological deficit. All treated rats performed like control rats in the two watermaze assessments of learning and memory, with the sole exception of 3 of 18 (17%) of the high dose females that underperformed on a reversal learning phase of the Morris watermaze test, an assessment of learning. However, these findings were judged equivocal, because 1) the high dose group as a whole did not perform significantly differently from the concurrent control group, 2) a learning deficit was absent from the more difficult and complex Morris watermaze test, and 3) 2 of the same 3 rats were tested in the Morris test and performed comparably to untreated rats. Brain weights were lower than those in concurrent controls, but they were not abnormal for rats of the size in these treated groups. All other criteria assessed for the development were unaffected by treatment with VGB. Thus, the study did not demonstrate evidence for significant adverse consequences to IME in young developing rats.

As recommended by the pathology working group, subsequent ultrastructural characterization of microvacuolation in juvenile rats dosed with 50 mg/kg/day of VGB was performed using electron microscopy (Study OVNC-9004) [50]. Differential VGB dosing sequences of juvenile rats were employed in an attempt to delineate progression and/or severity of vacuole formation.

Neonatal and juvenile Sprague Dawley rats were exposed to daily gavage doses of 50 mg/day of VGB during PND days 4 through 25 (Group I), 4 through 46 (Group II), 4 through 65 (Group III), 12 through 26 (Group IV), and the vehicle during the same PND (controls). Transmission electron microscopy was performed on sections of the cerebellum in the region of the (roof) nuclei and adjacent white matter, and regions of the medullary nucleus of the spinal tract of cranial nerve V and reticular nuclear regions. These areas were identified from the initial light microscopy evaluations performed on these groups, which demonstrated vacuole formation in rats treated with VGB. The ultrastructural study revealed an evolution of vacuoles, which were initiated as splits of myelin sheaths (along the intra-period line). They expanded and evolved into large membrane-rich vacuoles, which were more prominent in later stages of dosing. More specifically, hypomyelination, demyelination, and some astrocytic swelling was noted in Group I (rats treated PND 4 through 25), likely related to test article exposure during the period of active myelination. There was compression of

adjacent neuropil by expanding vacuoles, but there was no associated neuronal injury or glial scarring. Cerebellar fibers from VGB-dosed rats in Group II (rats treated PND 4 through 46) demonstrated myelin sheaths that were thinner relative to axon caliber, consistent with retardation of myelination. However, hypomyelinated or unmyelinated fibers seen in Group I was not observed in Group II, despite similar exposures during the period of active myelination (approximately PND 4 through 20+).

Vacuoles derived from myelin splits, consistent with those described above, were present in rats from Group III (rats treated PND 4 through 65). A series of evolutionary events was seen as progressively larger vacuoles were examined. Rats dosed during PND 12 through 26 (Group IV) had vacuoles with a similar appearance and distribution, but were somewhat less extensive than those in rats with dosing beginning on PND 4. This was particularly true when comparing these animals to those dosed over PND 4 through 25 (Group I). Overall, there was progressive expansion of microvacuoles with continuing exposure to the test article by a process consistent with IME. There was compression of adjacent neuropil by expanding vacuoles, without significant associated neuronal injury. There was no evidence of swollen axons or mineralized residual bodies in the neuropil.

While IME affects myelinated nerve fibers or axons, the distribution of these vacuolar changes appears to vary with age, species, and potentially timing and duration of exposure in rodents and dogs. While studies in adult rats emphasized the presence of vacuoles in large white matter regions of the brain, neonatal and juvenile rats had lesions in white matter fibers traversing near or in the gray matter. The distribution of lesions is much broader in rats than in dogs or mice, although there are clearly more studies in rats than in other species. Lesions in the cerebellum appear before those developing in the reticular formation and other more rostral forebrain regions. While it is presumed that regions of most active myelination might be more directly affected, there are no data to explain these distributional patterns or temporal effects on lesion appearance and disappearance.

In conclusion, ultrastructural characterization in juvenile rats demonstrated that the cellular basis is the same between white and gray matter lesions: i.e., the same pathophysiology between lesions localized in gray and white matter was seen in young rats as well as those previously characterized in adult rats in earlier studies. The lesions are fluid-filled microvacuoles, with diffuse membranous material and with splitting of myelin sheaths and are exclusively located within oligodendrocyte-myelin processes. In mature animals, these lesions are found primarily in white matter tracts and in immature animals, they are found primarily in deep neuropil.

2.2.2 Retinal Toxicity

In recent years the clinical recognition of a pVFD in certain patients prescribed VGB has led to closer assessment of retinal toxicity in various animal models. One of the earliest reports of retinal toxicity in rats was reported in 1987 by Drs. Butler, Ford, and Newberne of the British Industrial Biological Research Association (BIBRA) and Merrell Dow Research [51]. Owing to known sensitivity of albino animals to photoretinopathy, these investigators provided 30, 100, and 300 mg/kg/day by both oral gavage and via the diet to the albino Sprague-Dawley rats but only 300 mg/kg/day by both routes to pigmented Lister-Hooded

rats. Ophthalmic examinations on treatment Day 86 failed to detect any abnormalities. However, after 90 days of treatment, histopathologic examinations revealed a disorganization of the outer nuclear layer with displacement of nuclei into the photoreceptor layer of the retina of select albino but not pigmented rats. Necrosis was not evident, although there was a subjective impression (but no objective data) of fewer nuclei per unit area. The peripheral regions of the retina appeared to be affected more than central regions.

While no retinal pathology was noted in rats given 30 mg/kg/day via the diet, one rat given the same dose via gavage developed retinopathy. Otherwise, the incidence and severity of the lesions within albino rats was reasonably dose-related. The method of dosing appeared to have little impact on the incidence or severity of the lesions. There were no retinal lesions in pigmented Lister-Hooded rats, despite comparable dosing and the presence of IME in brain sections from these rats. There were no lesions in the optic nerves despite changes in the retina.

The authors discussed the similarity of these retinal findings with those reported in albino but not pigmented rats after excessive exposure to environmental light [52-54]. Thus, they suggested that light-induced retinopathy might be necessary to permit the VGB-related lesions to develop. A similar dependence on environmental light was reported in the development of retinal lesions with clonidine [55]. Light can evoke GABA release in the retina, just as VGB can, providing a hypothesis to explain this additive or synergistic response [56]. The importance of phototoxicity in VGB-induced retinopathy was more recently presented by Yukitoshi Izumi and others at Washington University School of Medicine [57].

Paralleling early morphological reports were studies evaluating the biochemical changes in the retina following dosing with VGB. Cubells, et al from Albert Einstein College of Medicine reported in 1986 that γ-vinyl GABA (VGB) was found in very high concentrations of the retina of rats after oral dosing, causing markedly greater inhibition of the GABA-T in the retina compared to the brain, and inhibition of glutamic acid decarboxylase (GAD), the enzyme required for the synthesis of new GABA [58]. They reported that the estimated GABA turnover rate in normal retinas to be 0.51 μg/retina/min and that the rat retina contains approximately 0.32 mg of retinal protein. Thus the turnover rate would be approximately 93 nmol/mg of protein per hour. Based on turnover rates, they concluded that retinal GABA enzymes would be more affected than brain enzymes when exposed to VGB. They further recommended careful screening for retinal changes in patients given VGB, even though clinical concerns for the pVFD had yet to surface.

In 1989, Neal and others at St. Thomas University, London, confirmed the marked inhibition of retinal GABA-T by VGB and the resultant increase (5-fold) of retinal GABA content [59]. Using immunocytochemistry, they further revealed GABA immunoreactivity in glial Müller cells of the retinas only from VGB-treated rats and a reduction in the immunoreactivity of GABA-T in these same cells. Müller cell immunostaining was predominantly in the inner and outer nuclear layers and the outer limiting membrane. These data indicated that when GABA-T was inhibited, glial elements can no longer degrade GABA, permitting its accumulation. The apparent lack of altered pVFD in patients taking tiagabine, another GABA elevating anticonvulsant, was studied by Sills and others at Western Infirmary in Glasgow,

Scotland and reported in an abstract in 1999 [60]. Their data indicated that tiagabine did not lower GABA-T concentrations or elevate GABA levels in the retinas of treated rats, contrary to the action of VGB. They argue that the difference in GABAergic pharmacodynamics between these two agents may make the risk for GABA accumulation and toxicity in the retina different for these two agents. These data were later presented in greater detail as full manuscripts, wherein retinal concentrations of VGB were shown to be 18.5-fold higher than in brain tissues from the same animals [61-64].

In 2002, Hanitzsch and Küppers from the University of Leipzig (Germany) studied the role of GABA and the peripheral visual field loss using a rabbit model [65]. These investigators isolated the retinas and evaluated their electroretinographic response before and after in vitro exposure to 2 mM GABA. GABA significantly but reversibly reduced the light response of horizontal cells (HC) over 50%. VGB had no adverse effect on HC or the b-wave of the ERG, but reduced the PIII-component of the ERG by a significant 84%. The PIII-component of the ERG originates mainly from the Müller cells, a key site for GABA-T activity in catabolizing GABA. Thus, the PIII-component is a good indicator of Müller cell activity. GABA and VGB are rapidly transported into Müller cells by the glial GABA transporter (GAT 3) and more weakly by GAT 1. When VGB is transported into Müller cells, GABA-T is inhibited and GABA accumulates. HC cells appear to be GABAergic but lack $GABA_A$-receptors. The authors hypothesized that VGB increases the GABA content in Müller cells, and this high GABA acts on HC cells to influence the noxious stimuli from light. Benz and colleagues at Washington University School of Medicine used ex vivo rat retinal preparations to confirm that while VGB was not directly neurotoxic in the retina, it appeared to enhance the excitotoxic neuronal degeneration in the inner retina caused by neurotransmitters, glutamate, and N-methyl-D-aspartate (NMDA) [66].

An investigatory team in Lund Sweden, led by S. Kjellstrom, reported in 2003 that 5 rabbits given VGB for 1-8 months and evaluated every other week by ERG had evidence for reduced cone function in 2/5 (40%) of the rabbits [67]. Upon histopathological examination, they reported enhanced glial fibrillary acidic protein (GFAP) immunoreactivity of peripheral glial cells, weaker GAD staining in the inner plexiform layer (IPL) and amacrine cells, and short, stubby and broken Müller cells with swollen endfeet. These data indicated that the rabbit, as reported in the rodent in the literature, develop a cone b-wave amplitude deficit and histological evidence for pathology in the retina following exposure to VGB.

In 2004, Duboc, et al at the Laboratorire de Physiopathologie Cellulaire et Moléculaire de la Rétine in Paris, reported on investigations using ERG and morphological examinations to study the adverse effects on the retina of albino rats given 250 mg/kg VGB intraperitoneally for 45 days [68]. Two days after ending treatment, treated rats exhibited an irreversible decrease in photopic ERG, flicker response and oscillatory potentials. These functional deficits correlated well with a peripheral disorganization of the outer retina. Cone damage was not limited to these peripheral areas of disorganization, as the inner and outer segments of the cone layer were also injured in more central areas. Cone numbers appeared to be reduced 17-20%. Ultrastructural and immunocyotchemistry studies indicated enhanced photoreceptor apoptosis. The authors concluded that the visual field loss from VGB may begin with injury to the cone cells and extend throughout the photoreceptor layer.

In accordance with conditions of Article 12 imposed by the EMEA, a series of animal studies were conducted by Aventis Pharmaceuticals in 2001-2003 in an effort to determine species susceptibility and to investigate the pathogenesis of the pVFD reported in human patients given VGB. These investigations confirmed that oral administration of VGB to both pigmented (Long Evans) and non-pigmented, albino (Wistar) rats caused marked increases in GABA mean concentrations in the retina and vitreous in all VGB-treated rat groups, consistent with the GABAergic mimetic activity of VGB [69]. The concentrations were lower in rats given higher environmental light exposures versus non-illuminated rats. Excessive light resulted in degenerative retinal changes characterized by loss of photoreceptor and outer nuclear layers in albino rats, and mild decreases in the concentrations of most amino acids in albino and pigmented rats, likely to reflect a decreased activity of the retina. Similar findings were confirmed in pigmented 2-month old Long Evans rats treated for 3 months [70]. VGB-related changes in the eyes consisted of marked increases in GABA mean concentrations in the retina and vitreous, consistent with the GABAergic activity of VGB, and minimal increases in mean concentrations of taurine (both eyes), glutamate and glycine (males), and glutamine (females) in the vitreous. Likewise, non-epileptic and pilocarpin-induced epileptic Wistar rats had similar ocular findings, irrespective of the presence of the concurrent disease [71].

In a study evaluating the oral administration of VGB to Sprague-Dawley rats for 4 or 13 weeks, with a 4-week recovery arm, ophthalmic examinations and histopathologic assessments attempted to provide mechanisms to define the retinopathy [72]. Clinically, increased retinal luminescence and pallor and increased retinal vascular kinking were described, which correlated histologically with a peripheral retinal (nasal region especially) disorganization and loss of photoreceptor cells. These findings were dose-dependent in incidence and severity, nonprogressive but irreversible in 4 weeks after stopping drug, and more prominent in females. Amino acid concentrations in these retinas were not changed by VGB treatment. An amendment to this study, issued in 2003, presented data on the retinal concentrations of VGB in these rats, confirming a dose-response relationship, an inverse relationship to study duration, and higher concentrations in females [73]. In an attempt to determine whether young animals are more sensitive or resistant to VGB-induced retinopathy, oral doses of VGB were administered to Sprague Dawley-derived juvenile rats for 2 weeks [74]. While these young rats appeared to be more sensitive to the systemic toxicity of VGB, retinal histopathologic changes described in rats given the higher dosages may have been a function of the severe systemic toxicity rather than lesions induced by VGB. In a follow-on 4-week study in juvenile rats, a single unilateral focus of retinal degeneration was described and found to be of inconclusive etiology [75].

A juvenile toxicity study utilizing ERG and specialized ocular assessments both clinically and pathologically has recently been completed by Ovation (OV-1007) [48]. In this toxicity study in rats from PND 4 to 65, followed by an approximate 6-week recovery period, retinal changes were described as a variable incidence of focal retinal dysplasia, characterized by rosettes or inversions of the outer nuclear layer. Rosettes are a common incidental finding in very young untreated rats and one rosette was present in an untreated control. The Study Director for this study concluded that these rosettes were not related to treatment by VGB. Since the structure of the human retina is fully developed at the time of birth and prior to the initiation of VGB therapy, these findings were unlikely to be relevant for humans. There was

an absence of the more subtle retinal nuclear disorganization reported in older albino rats and in some humans [68].

Finally, Aventis secured a peer review of retinal histopathology from representative animals originally evaluated before the pVFD was recognized in humans. Kevin Issacs, an experienced British veterinary pathologist, reported the absence of retinal lesions in dogs treated for 6 or 12 consecutive months, sustained for 6 additional months without treatment and in dogs treated 7 months and held without treatment for 4 months and in cynomolgus monkeys treated for 3, 6 or 16 months [76,77]. However, during his evaluation of albino mice treated for 18 months, he found that all dosages (0, 50, 100, or 150 mg/kg/day) elicited retinal degenerative changes, with a slight predilection for females, as seen in rats [78]. The nasolateral lesions were somewhat dose-related with respect to the incidence and severity of retinal degeneration, again consistent with rats. For more central retinal lesions, there was a slight dose-response with respect to the severity of the lesions, but the incidence of lesions was not clearly dose-dependent. Thus, it appears that albino mouse, rat, and rabbit can serve as potential relevant models to further study the pathogenesis of VGB-related pVFD, although the validity of these models for the human remains under investigation.

3 CLINICAL PHARMACOLOGY

VGB exhibits ideal pharmacologic characteristics for an AED, including rapid and nearly complete absorption with dose-proportional and linear pharmacokinetics, wide distribution into the extravascular space without protein binding, less than 4% metabolism, and renal elimination of unchanged VGB [79-82].

3.1. Pharmacokinetics

Following oral administration, VGB is completely absorbed. Food did not have a significant effect on vigabatrin absorption (Cmax decreased by 33% and AUC decreased by 8%) and therefore VGB can be given without regard to meals [83].

VGB is widely distributed throughout the body with a volume of distribution at steady-state of 1.1 L/Kg [82]. VGB does not bind to plasma proteins [81].

The tablet formulation and powder for oral solution formulation are bioequivalent. VGB pharmacokinetics are dose proportional and linear following administration of single doses ranging from 0.5 g to 4 g, and after administration of repeated doses of 0.5 g and 2.0 g twice daily [79,80].

VGB is not metabolized and is eliminated primarily as parent drug by renal excretion. The t½, of VGB is approximately 8 hours; however plasma levels are not correlated with clinical effect [82]. Following administration of radiolabeled VGB ($^{[14]}$C-VGB) to healthy male volunteers, approximately 95% of the total radioactivity was recovered in the urine over a 72 hour collection interval [82]. *In vitro* metabolism studies show that there is low potential for drug-drug interactions with VGB due to enzyme induction of CYP2B6 or CYP3A4 and VGB may have the potential for induction of CYP2C9/CYP2C19 *in vivo* at concentrations of an order of magnitude greater that the therapeutic Cmax observed *in vivo* [84].

3.2. Drug Interactions

Drug interactions with VGB are few and generally modest in degree. These drug interactions are not clinically significant and do not require dose adjustment for VGB or concomitant medications. Based on population pharmacokinetics, carbamazepine (CBZ), clorazepate, primidone, and sodium valproate appear to have no effect on plasma concentrations of VGB [85-88].

VGB had no effect on plasma concentrations of clorazepate and primidone during controlled clinical studies [87]. Phenobarbital from phenobarbital or primidone was reduced by an average of 8% to 16%, and sodium valproate plasma concentrations were reduced by an average of 8% at end of study when compared to baseline [88].

Mean phenytoin pharmacokinetic parameters were not significantly altered by coadministration phenytoin and VGB. While there was a mean trend toward decreases in total phenytoin plasma AUC, Cmax and Cmin (approximately 20%) in most subjects, some subjects showed individual increases in maximum plasma phenytoin levels [85,86,89].

In a study of 12 healthy volunteers, clonazepam (0.5 mg) coadministration had no pharmacokinetic effect on VGB (1.5 g twice daily), nor did VGB produce detectable effects on the pharmacokinetics of clonazepam [90].

Coadministration of ethanol (0.6 g/kg) with VGB (1.5 g twice daily) indicated that neither drug influenced the pharmacokinetics of the other [91].

In a double-blind, placebo-controlled study using a combination oral contraceptive containing 30 µg ethinyl estradiol and 150 µg levonorgestrel, VGB (3 g/day) did not modify the *in vivo* indices of hepatic microsomal enzyme activity and did not interfere significantly with CYP3A-mediated metabolism of the contraceptive tested [92].

Additionally, no significant difference in pharmacokinetic parameters (AUC, Cmax, Tmax, t1/2, CL/F and Vd/F) between VGB and placebo were found for ethinyl estradiol and levonorgestrel.

3.3. Special Populations

3.3.1 Age

The renal clearance of VGB in healthy elderly patients (≥ 65 years of age) was 36% less than observed in healthy younger patients [93].

3.3.2 Gender

No gender differences were observed for the pharmacokinetic parameters of VGB in patients [87,88].

3.3.3 Race

A cross study comparison between 24 Caucasian and 8 Japanese patients who received 1, 2, and 4 g of VGB indicated that the AUC, Cmax, and t1/2 were similar for the two populations. Mean renal clearance of VGB in the Caucasian patient trial was slightly greater (16%) than that observed in the Japanese patient trial [94].

3.3.4 Renal Impairment

Mean AUC values increased approximately 32% and 253% and t1/2 increased 4.0 hours and 15.3 hours, respectively, in patients with mild to moderate (CLcr of 40-79 mL/min) and severe (CLcr of 10-39 mL/min) renal impairment [95]. These results indicate that accumulation of VGB may occur in patients with moderate or severe renal impairment and that therapy should be initiated at a lower dose with close monitoring for any dose-related side effects.

3.3.5 Hepatic Impairment

Since VGB is not metabolized and primarily excreted as unchanged drug; the pharmacokinetics of VGB in patients with impaired liver function has not been evaluated [82].

4 REFRACTORY COMPLEX PARTIAL SEIZURES IN ADULTS

4.1. Disease Description and Epidemiology

Estimates of epilepsy prevalence in the U.S. range from 1% to 2% in the general population [5,6]. Table 3 below lists the various types of seizures and the estimated proportion of incidence cases by seizure type [96-98]. Seizures are generally categorized into partial and generalized. Partial onset seizures may or may not lead to a loss of consciousness and occur due to a focal cortical lesion [97]. Partial seizures with secondarily generalized seizures are classified as simple partial and complex partial seizures that evolve to generalized seizures [96,97]. They can also be simple partial seizures that evolve to CPS and further evolve to generalized seizures [96,97]. Generalized seizures involve the entire brain and can range from brief absence seizures to severe convulsions [97]. Categorization of epilepsy type is often difficult and can produce variable estimates in incidence and prevalence rates of different seizure types [97].

Complex partial seizures causes impaired consciousness, a decrease in responsiveness, and decreased awareness of self and surroundings, usually lasting 30 seconds to 2 minutes [3]. Automatisms commonly accompany CPS and may be verbal (eg, moaning) or motor (eg, lip-smacking, picking) [3]. Complex partial seizures most often arise from the temporal lobe but are not limited to any cortical region [3].

Table 3. Classification of Epileptic Seizures

Seizure Types	Proportion of Incident Cases
Partial (Focal) Seizures	
Simple partial (consciousness not impaired)	14%
Complex partial (impairment of consciousness and often automatisms)	36%
Unknown partial	7%
Generalized Seizures (Convulsive or Nonconvulsive)	
Absence (impairment of consciousness alone or with mild clonic, atonic, or tonic components and automatisms)	6%
Generalized major motor (tonic, clonic, tonic-clonic)	23%
Myoclonic	3%
Other	8%
Unclassified	3%

4.2. Unmet Medical Need in Refractory CPS

Approximately 64% of all epilepsy patients achieve complete seizure control with minimal side effects on monotherapy or polypharmacy with 2 drugs. However, despite the availability of over 20 marketed AEDs and epilepsy surgery, the remaining 36% continue to have recurrent seizures and are classified as having refractory epilepsy [8].

CPS is a heterogeneous disease, and responses to individual AEDs vary widely from patient to patient. Unfortunately, there is currently no way of predicting the response of an individual patient to a given AED, so treatment is empirical. With the addition of each new AED to the clinical armamentarium, especially new agents acting through novel mechanisms, a subset of patients with refractory CPS experience clinically meaningful improvement with a substantial decrease in seizure frequency, and some patients become seizure-free. Consequently, even in patients with long-standing refractory CPS, gains can be made by undertaking treatment trials with new AEDs [9].

In addition to failing to respond to available AEDs, patients with epilepsy may also be intolerant or allergic to available agents. Cutaneous drug reactions are relatively common with AEDs and many patients cross-react to multiple agents [99]. Treatment and medication side effects also contribute to a reduced quality of life in patients with epilepsy. Common adverse effects of epilepsy, epilepsy treatments, or AEDs include difficulty thinking clearly, drowsiness, lethargy, memory loss, clumsiness, depression, and muscle twitches [5]. Importantly, available treatments carry risks that include severe toxicities, and all require careful benefit/risk considerations [5]. Severe toxicities caused by current treatments include: aplastic anemia, agranulocytosis, severe dermatologic reactions, including Stevens-Johnson Syndrome, hepatotoxicity, teratogenicity, and pancreatitis [6,100].

For patients with refractory CPS, recurrent and unpredictable episodes of altered consciousness (some of which may generalize to tonic-clonic seizures) have a major negative impact on occupational and social function as well as on quality of life [2]. Social disabilities

occurring in patients with refractory CPS include less social interaction, reduced marriage rates, and reduced employment levels [2]. In a survey of 503 respondents with epilepsy self-reporting on their condition and experiences, 46% and 50% of respondents reported that epilepsy limited their daily and future activities, respectively, and resulted in a reduced chance for work success (50%) [5]. Respondents often suffered from depression (46%) and felt they were a burden to others (47%) [5]. Respondents also reported being somewhat or completely unable to hold a part-time job (36%), hold a full-time job (40%), drive (47%), participate in social events (21%), enjoy leisure activities (20%), travel on vacation longer than 1 week (26%), exercise (24%), do household chores (19%), handle household details (20%), or care for their children (12%) as a result of their epilepsy [5].

Adult patients with refractory CPS are at increased risk for mortality and significant morbidity compared with the general epilepsy population [2]. The rate of mortality in individuals with epilepsy is 2 to 3 times that of the general population and most deaths are due to the underlying cause of epilepsy [3]. Moreover, mortality rates in patients with uncontrolled epilepsy are 4 to 7 times higher than in patients whose epilepsy is adequately controlled [2].

The incidence of SUDEP is considerably higher in patients with severe refractory seizures, 3 to 9 per 1000 person-years (PYs), than in patients with controlled seizures, 1-2 per 1000 PYs [7]. In addition, the suicide rate of patients with chronic epilepsy is approximately five times higher than that of the general population and as much as twenty-five times higher in patients with CPS [101]. In addition to the increased rates of SUDEP and suicide, impaired consciousness associated with CPS can lead to an increased risk of falls, burns, drowning, and accidents [4].

There remains a significant unmet need for patients who have failed multiple trials of AEDs, including polytherapy, and who have either failed or are not candidates for epilepsy surgery. They continue to suffer the multiple morbidities and risks of mortality associated with uncontrolled CPS. Additional drug trials may be undertaken with the hope that an untried drug or combination of drugs may reduce seizure frequency. For some patients a vagal nerve stimulator may reduce seizure frequency, but this only rarely produces seizure freedom. In some cases the doses of AEDs may be pushed as high as tolerated, but usually at the expense of increased side effects. As an example of the benefit/risk considerations for this refractory patient population, Felbamate an approved AED that is currently marketed with an indication limiting its use to only those patients who have responded inadequately to other treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or liver failure is considered acceptable. Therefore, there is a continuing unmet need for additional AEDs acting through novel mechanisms to provide epileptologists with as varied an arsenal as possible to combat this devastating disease.

4.3. Efficacy in Refractory Complex Partial Seizures

4.3.1 Overview of Clinical Studies in Adults with Complex Partial Seizures

VGB has been extensively studied in patients with epilepsy (Table 1). Two pivotal studies (025 and 024) as well as a number of supportive studies were conducted by the previous

sponsor. Based on the results of these 2 studies, the FDA issued an approvable letter on 26 November 1997 that stated VGB is effective adjunct therapy in the treatment of complex partial seizures (FDA, written communication, November 1997).

There were 5 placebo-controlled studies of VGB as adjunctive therapy in adults with CPS: Studies 025, 024, 097/W/AUS/01, 097-444, and 0101. Studies 025 and 024, double-blind, placebo-controlled, parallel-group studies in patients with refractory CPS, are the adequate and well-controlled U.S. pivotal studies for this indication. The other 3 studies are considered supportive studies. Study 097/W/AUS/01 was a double-blind, placebo-controlled crossover study in patients with uncontrolled CPS. Study 097-444 was a double-blind, placebo-controlled crossover study in patients with chronic, severe, uncontrolled, generalized grand ma1 seizures or severe CPS with or without secondary generalization. These 2 non-U.S. studies are considered supportive studies because their cross-over design has an inherent carryover effect that might complicate interpretation of the results. Study 0101, an adequate and well-controlled double-blind, placebo-controlled, adjunctive therapy study, assessed efficacy in epilepsy patients with non-refractory partial seizures. Because Study 0101 evaluated a slightly different population than in the indication being sought (patients with refractory CPS), it is considered a supportive study.

There were 3 uncontrolled studies in adult patients with CPS that assessed efficacy: Studies 097-005, 097-006, and 097-304. Study 097-006 was a long-term study that enrolled patients from Study 097-005.

A tabular description of the pivotal and supportive studies is presented in Table 4.

Table 4. Description of Pivotal and Supportive Refractory CPS Studies in Adults

Type of Study		Treatment Groups	
Study Number	Design and Duration	Dose	N Evaluated
Controlled Studies			
Pivotal Studies			
025	12-week baseline, double-blind parallel group 18-week treatment (6-week titration, 12-week maintenance)	Placebo	45
		1 g/day VGB	45
		3 g/day VGB	41
		6 g/day VGB	43
024	12-week baseline, double-blind parallel group 16-week treatment (4-week titration, 12-week maintenance)	Placebo	90
		3 g/day VGB	92
Supportive Studies			
097/W/AUS/01	8-week baseline, 20 week double-blind cross-over phase: 8-week treatment with placebo or VGB, 4-week washout period then 8-week treatment with alternate medication	Placebo	80
		2 or 3 g/day VGB	80
097-444	4-week baseline, 20 week double-blind cross-over phase: 12-week treatment with placebo or VGB, a 4-week washout period then 12-week treatment with alternate medication	Placebo	20
		2 or 3 g/day VGB	20
0101	12-week baseline, 28-week double-blind treatment (4-week titration, 24-week maintenance), 4-week taper or transfer to open-label extension	Placebo	58
		3 g/day VGB	119
Uncontrolled Studies			
097-005	8-week baseline, 4-week placebo run-in, 2 to 4-week titration, 12-week maintenance, 2-week taper	1-4 g/day VGB	83
097-006	1 day to 8.8 years	1-4 g/day VGB	63
097-304	8-week baseline, 12-week open 3 g/day treatment, 12-week double-blind 1.5 or 3 g/day treatment	1.5-3 g/day VGB	75

4.3.2 Design and Efficacy Assessments for the Pivotal Studies

The effectiveness of VGB as adjunctive therapy was established in two U.S. multicenter, double-blind, placebo-controlled, parallel-group clinical studies in 356 adults with refractory CPS, with or without secondary generalization (Studies 025 and 024). These studies were adequate and well-controlled and meet current criteria for studies in epilepsy. Studies 025

and 024 enrolled patients with frequent seizures and added the new agent (VGB) or placebo to each patient's individualized baseline AED regimen, a study design that remains the standard for testing new AEDs. The patient population evaluated in the 2 studies is consistent with the intended refractory epilepsy population for whom the benefit of VGB may outweigh the risks.

Study 025 (N=174) was a randomized, double-blind, placebo-controlled, dose-response study consisting of an 8-week baseline period followed by an 18-week treatment period. After establishing baseline seizure frequency, patients were randomized to receive placebo or 1, 3, or 6 g/day VGB administered daily in two divided doses. During the first 6 weeks following randomization, the dose was titrated upward beginning with 1 g/day and increasing by 0.5 g/day on days 1 and 5 of each subsequent week in the 3 g/day and 6 g/day groups, until the assigned dose was reached.

Study 024 (N=183 randomized, 182 evaluated for efficacy) was a randomized, double-blind, placebo-controlled, parallel-group study consisting of an 8-week baseline period and a 16-week treatment period. After establishing baseline seizure frequency, patients were randomized to receive placebo or 3 g/day VGB administered daily in two divided doses. During the first 4 weeks following randomization, the dose of VGB was titrated upward beginning with 1 g/day and increased by 0.5 g/day on a weekly basis to the maintenance dose of 3 g/day.

The protocol-specified primary endpoint in both studies was the patient's mean monthly frequency (mean number of seizures per 28 days) of CPS plus partial seizures secondarily generalized during the final 8 weeks of the maintenance phase compared to the final 8 weeks of the baseline phase. Secondary efficacy measures pre-specified in the protocols included therapeutic success (defined as a ≥50% reduction in mean monthly combined seizure frequency), and seizure freedom (proportion of seizure-free patients).

Because Studies 025 and 024 had identical inclusion and exclusion criteria and efficacy assessments, the results of these studies are presented together.

4.3.3 Patient Population in the Pivotal Studies

The patients enrolled had severe and chronic refractory CPS. Patients were required to have a documented history of CPS or partial seizures with secondary generalization and, during the last 8 weeks of baseline, to have had at least six CPS or partial seizures with secondary generalization and not to have a seizure-free interval exceeding 28 days. Patients were required to be on an adequate and stable dose of at least 1 but no more than 2 AEDs at baseline and have a history of failure of an adequate trial of CBZ or phenytoin. The patients enrolled had severe refractory CPS and were having frequent seizures, similar to the patients enrolled in other trials of adjunctive therapy for partial epilepsy.

Baseline demographic data for the populations across Studies 025 and 024 were balanced between treatment groups and generally comparable between studies. The median duration of epilepsy was 21 years in Study 025 and 22 years in Study 024. For CPS seizures plus partial seizures secondarily generalized, the median number of seizures per 28 days (monthly

seizure rate) during baseline was similar in Study 025 (8.8 seizures) and Study 024 (8.3 seizures). The majority of patients in both studies were Caucasian (95% in Study 025 and 91% in Study 024), with median ages of 33 years in Study 025 (age range of 18 to 63) and 33.5 years (age range of 18 to 60) in Study 024. In each study, similar percentages of males and females were enrolled (48% male and 52% female in Study 025, 44% males and 56% females in Study 024). In each study, similar percentages of patients were taking 2 AEDs at baseline (53% in Study 025, 62% in Study 024). Approximately 75% of patients had previously failed appropriate trials of either 3 or 4 AEDs from multiple classes.

4.3.4 Efficacy Results from the Pivotal Studies

4.3.4.1 Protocol-Specified Primary Efficacy: Reduction in Mean Monthly Seizure Frequency

Results for the primary measure of efficacy, median reduction in mean monthly (28 days) seizure frequency for CPS and partial seizures secondarily generalized, are shown for both studies in Table 5. In both studies, VGB was superior to placebo in reducing seizure frequency. In the 3 g/day (Studies 025 and 024) and 6 g/day (Study 025) dose groups, a statistically significant reduction in seizure rates was seen as compared to placebo. In Study 025, a statistically significant linear trend test was observed (p=0.0001), indicating the effect of VGB increased with increasing dose. However, when compared head-to-head, the 6 g/day dose was not statistically superior to the 3 g/day dose, nor was the 1 g/day dose statistically significantly different than placebo.

Table 5. Analysis of Seizure Frequency (Number/28 Days), CPS Plus Partial Seizures Secondarily Generalized

	Placebo	1 g/day VGB	3 g/day VGB	6 g/day VGB	Dose Trend p-Value[b]
Study 025	N=45	N=45	N=41	N=43	
Baseline Median	9.0	8.5	8.5	8.5	
End study Median[a]	8.8	7.7	3.7	4.5	
Median Reduction	0.2	0.8	4.8	4.0	0.0001
p-value vs placebo[b]		0.1648	0.0001	0.0002	
Study 024	N=90		N=92		
Baseline Median	9.0		8.3		
End study Median[a]	7.5		5.5		
Median Reduction	1.5		2.8		
p-value vs placebo[b]			0.0143		

a. Treatment duration of 18 weeks in Study 025 and 16 weeks in Study 024.

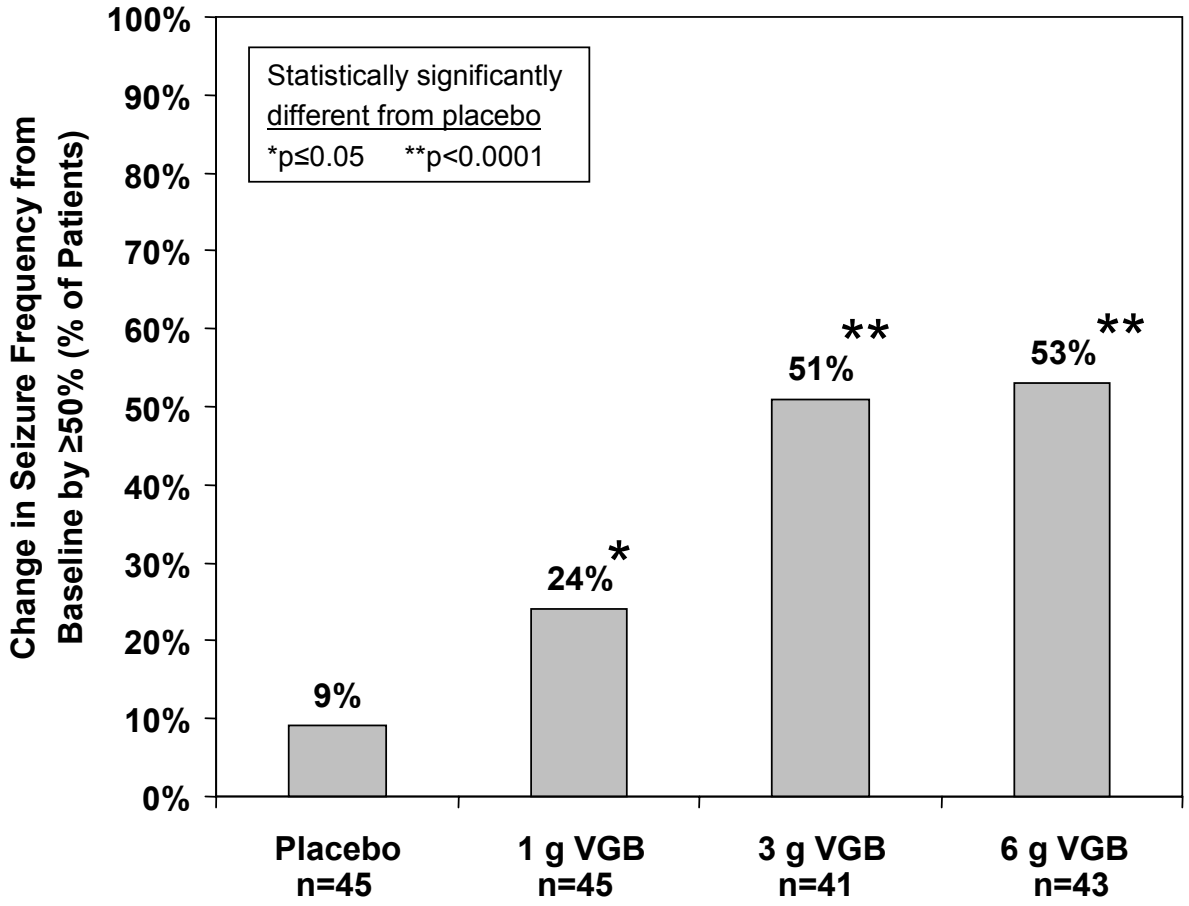
b. P–values from analysis of covariance of the ranked seizure frequencies adjusting for ranked baseline seizure frequency, treatment, site, and the interaction of site and treatment if appropriate.

4.3.4.2 Secondary Efficacy Measures

THERAPEUTIC SUCCESS

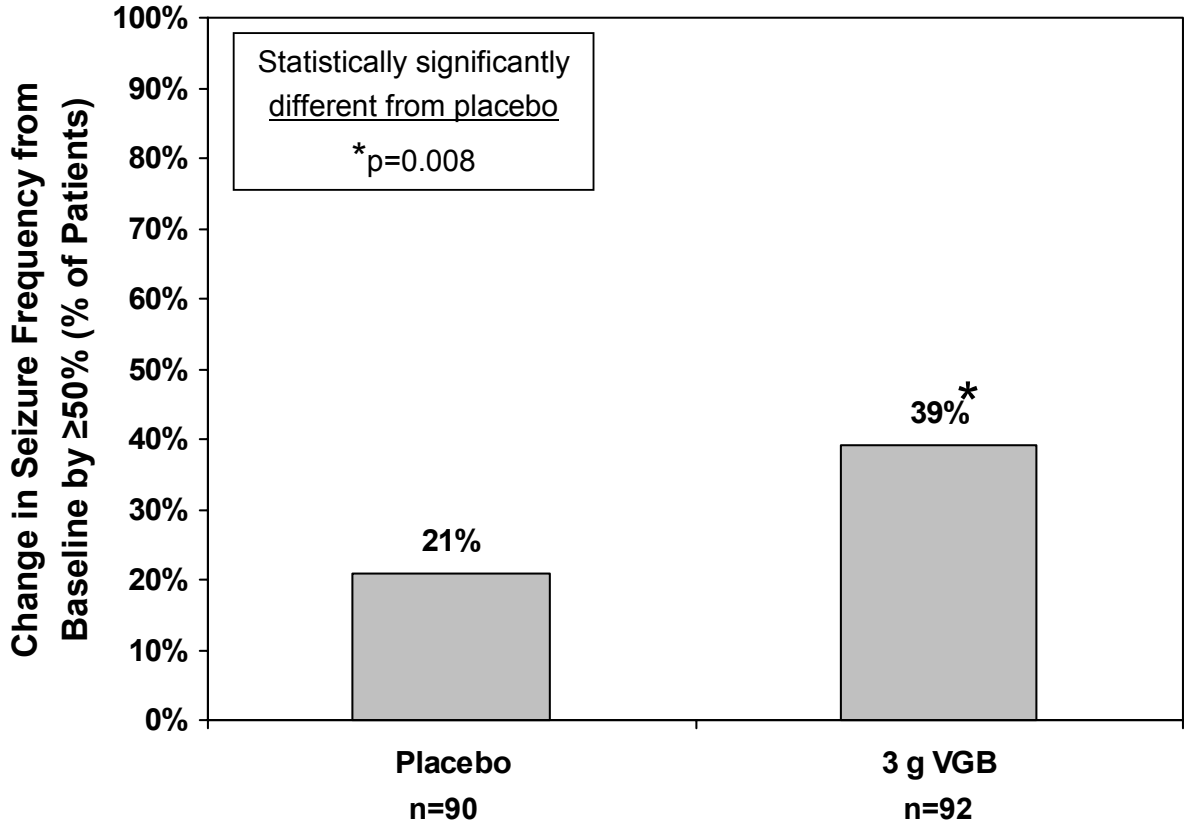
The percentage of patients who achieved therapeutic success (protocol defined as ≥50% decrease in seizure frequency) was significantly greater for all three VGB dose groups compared to placebo, with the 3 g/day dose common to Studies 025 and 024 showing a significant effect in both studies (Figure 1 and Figure 2). In Study 025 there was a statistically significant linear dose response (p<0.0001). However, the 6 g/day dose (53% of patients with therapeutic success) was not statistically superior to the 3 g/day dose (51% of patients with therapeutic success).

Figure 1. Therapeutic Success (≥50% Decrease in Seizure Frequency) –Study 025



P–value is from logistic regression model adjusted for ranked baseline seizure frequency and site.

Figure 2. Therapeutic Success (≥50% Decrease in Seizure Frequency) – Study 024



P–value is from Mantel–Haenszel test stratified by site.

SEIZURE FREEDOM

In Study 025, patients who either reported no seizures on their diaries during the final 8 weeks of the study or were evaluated on the End Study Physician's Evaluation of Therapeutic Effect as seizure-free met the criteria for seizure freedom. In Study 024, patients who had no partial seizures during the final 8 weeks of the study were classified as seizure-free by the investigator.

In Study 025, greater percentages of patients attained seizure freedom in the 3 g/day VGB treatment group (12.2%) and in the 6 g/day VGB treatment group in Study 025 (11.6%) than in the 1 g/day VGB treatment group (2.2%) or placebo group (0%) (Figure 3). In Study 024 a greater percentage of patients attained seizure freedom in the 3 g/day VGB treatment group (6.5% of patients) than in the placebo group (1.1%) (Figure 4), but the difference did not reach statistical significance.

Figure 3. Seizure Free Patients – Study 025

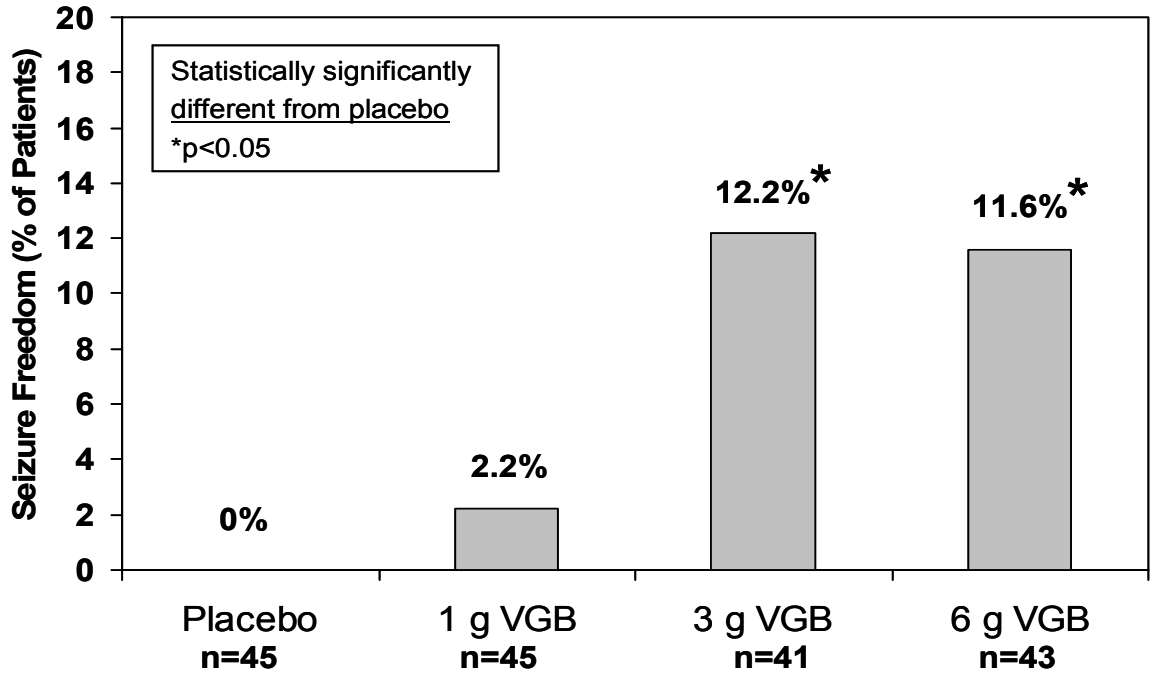
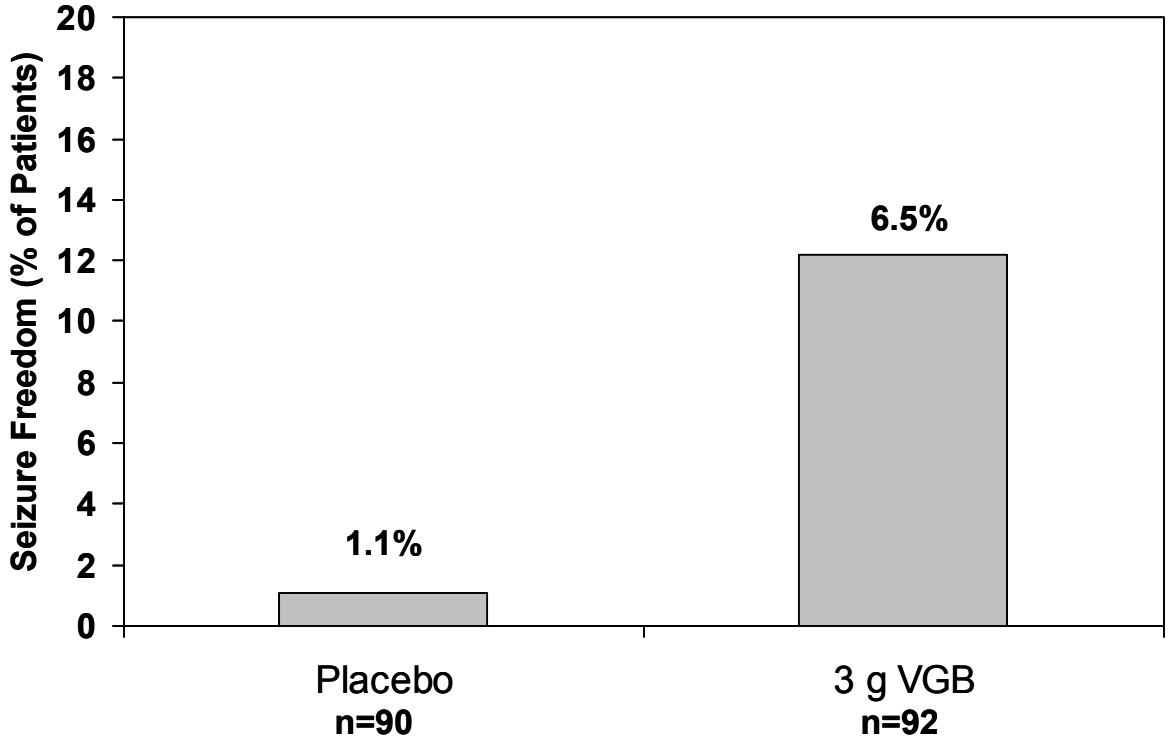


Figure 4. Seizure Free Patients – Study 024

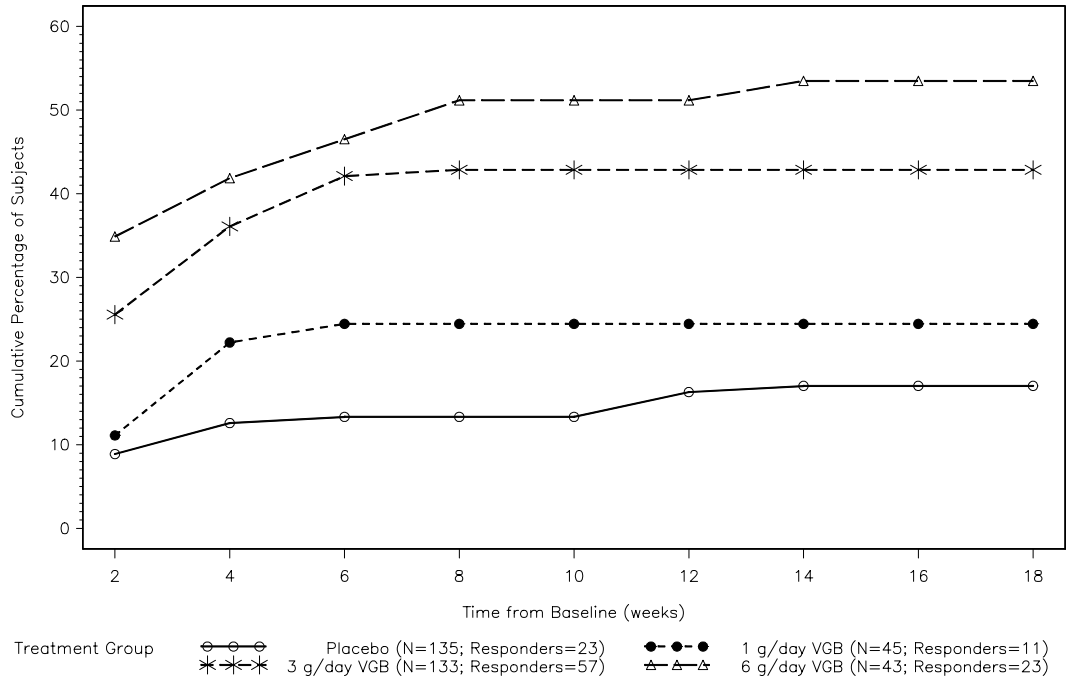


4.3.4.3 Time Course to Therapeutic Success (≥ 50% Decrease in Seizure Frequency)

Data were pooled from Study 025 and Study 024 to allow a descriptive analysis of the onset of efficacy among protocol-defined responders. At each timepoint after baseline it was determined how many patients ultimately achieving therapeutic success (50% reduction from baseline in seizure frequency during the 8-week maintenance period) first achieved a 50% reduction from baseline in seizure frequency at that time point. The cumulative percentage of these patients is shown in Figure 5.

Among patients achieving therapeutic success (ie, treatment 'responders'), a substantial proportion of patients achieved this response within 4 weeks, and nearly all are noted within 6 weeks of the initiation of treatment.

Figure 5. Time Course to Therapeutic Success (Responders) – Study 025 and Study 024



4.3.5 Efficacy Results from the Supportive Studies

4.3.5.1 Non-U.S. Cross-over Studies in Patients with Refractory CPS Seizures

There were 2 placebo-controlled non-U.S. studies that used a crossover design. A recognized problem with the crossover design is the inherent carryover effect that might complicate interpretation of the results.

Study 097/W/AUS/01 (N=80 evaluated for efficacy) and Study 097-044 (N=20 evaluated for efficacy) were randomized, double-blind, placebo-controlled, crossover non-U.S. studies. These studies evaluated the efficacy of VGB as adjunctive therapy in adults with refractory or uncontrolled CPS (both studies) and/or grand mal seizures (Study 097-044). In Study 097/W/AUS/01, patients received either VGB (at a dose of either 2 or 3 g/day) or placebo during the first 8-week treatment period, and received the alternate treatment during the second 8-week treatment period. In Study 097-044, patients received either VGB or placebo during the first 12-week treatment period, and received the alternate treatment during the second 12-week treatment period. In each treatment period, VGB-treated patients received 2 g/day VGB for the initial 6 weeks, then, if tolerability allowed, received 3 g/day VGB for the final 6 weeks.

In Study 097/W/AUS/01, the primary measure of efficacy in the study was the patients' reduction in mean monthly (number of seizures per 30 days) frequency of seizures during VGB treatment compared to placebo treatment. These data were calculated as the 'Mean Square Root' and then converted to the 'Mean Back-transformed Seizure Rate' which has been used as the efficacy seizure rate for all comparisons in the statistical methodology. There was a 34% reduction in the total mean back-transformed seizure rate during VGB treatment compared to placebo. There were 42 patients who received 2 g/day and placebo, and 38 patients who received 3 g/day and placebo. Similar efficacy was seen for both VGB doses in the total mean back-transformed seizure rate, with a 36% reduction in the 2 g/day group and a 31% reduction in the 3 g/day group relative to their placebo treatment periods. Thirty-four patients (42.5%) had a 50% or greater reduction of seizures during active treatment versus placebo period.

In Study 097-044, the primary measure of efficacy in the study was the patient's reduction in mean monthly (number of seizures per 28 days) frequency of seizures during VGB treatment compared to during placebo treatment. The estimated seizure rate for VGB-treated patients demonstrated an improvement of 24% when compared to placebo ($p<0.04$). There was no apparent improvement in seizure rates when VGB treatment was increased from 2 g/day to 3 g/day. Five patients (26.3%) showed a seizure reduction of at least 50% during VGB treatment when compared to placebo, and a beneficial effect was observed for partial seizures, but not for generalized tonic-clonic seizures.

4.3.5.2 U.S. Parallel Group Study in Patients with Non-Refractory CPS

Study 0101 (N=177 evaluated for efficacy) was a randomized, double-blind, placebo-controlled, parallel group adjunctive therapy study in non-refractory patients who experienced occasional complex partial seizures while on carbamazepine or phenytoin monotherapy. The study consisted of a 12-week baseline period followed by a 28-week

double-blind treatment period (4-week titration and 24-week maintenance period). During the maintenance period, patients received either 3 g/day VGB and a stable dose of carbamazepine or phenytoin, or placebo and a stable dose of carbamazepine or phenytoin. Patients who completed the double-blind maintenance period were given the option to continue in the study in an open-label continuation phase. Patients electing not to continue were tapered off study medication over a 4-week period.

Both patient enrollment and the duration of the study were terminated earlier than originally anticipated. Due to the early termination of enrollment, the number of patients in this study did not achieve the estimated sample size of 360 required to obtain 80% power at the two-sided 5% significance level to detect a difference of 8% in proportion of seizure-free patients between the VGB and the placebo groups. There were only 177 patients (49% of needed sample size) randomized to the study medication (119 VGB and 58 placebo).

The primary assessment of efficacy in the study was the proportion of patients who were seizure free during the last 20 weeks of the double-blind maintenance period (Endstudy). Patients who had no partial seizures (simple partial, complex partial, partial secondarily generalized) during the last 20 weeks of the double-blind maintenance period (based on their daily seizure records) were classified as seizure free. Patients who did not complete 20 weeks of the Maintenance Period were classified as not seizure free.

For the primary efficacy parameter, the proportion of patients who were seizure-free in the VGB group (9/119, 7.6%) was higher than in the placebo group (2/58, 3.4%), although no statistically significant difference was detected (p=0.51). As noted, due to early termination of enrollment the study was not adequately powered to detect a difference in the primary parameter.

Secondary efficacy parameters included therapeutic success, defined as achieving at least a 50% reduction from Baseline to Endstudy in the mean monthly frequency of complex partial seizures plus partial seizures secondarily generalized, and two global evaluations. The proportion of patients achieving therapeutic success in the VGB group was significantly greater than that in the placebo group (45.4% versus 25.9%, p=0.008). Patients receiving VGB had significantly greater improvement than placebo patients for both the Physician's Evaluation of Therapeutic Effect and the Physician's Global Evaluation (p=0.002 and p=0.012, respectively).

There was also a quality of life assessment using the Quality of Life in Epilepsy (QOLIE-89) instrument completed by the patient. There were no differences between the groups on any of the composite or summary measures.

4.3.6 Efficacy Results from Uncontrolled Studies

There were 3 uncontrolled studies in adult patients with CPS that assessed efficacy. Two were short-term studies that compared fixed dose(s) of VGB during a 12-week period to either placebo (Study 097-005) or 3 g/day VGB (Study 097-304) treatment in an initial lead-in period. Study 097-006, which enrolled patients from Study 097-005, assessed long-term efficacy.

Study 097-005 (N=83 evaluated for efficacy) consisted of a 12-week baseline (8-week untreated observation phase followed by a 4-week placebo treatment phase), a 2- to 4-week titration phase and a 12-week maintenance phase. Responders in Study 097-005 (defined as patients who, in the opinion of the investigator, demonstrated clinical improvement) were allowed to enroll in the long-term follow-up study, 097-006. Study 097-006 was a long-term (up to 8.8 years) study where patients received open-label VGB at doses of 1 g/day to 4 g/day.

Baseline seizure frequencies for both studies were calculated using the 12-week Baseline period of Study 097-005. For Study 097-005, the Endstudy period was the 12-week maintenance period. For Study 097-006, the Endstudy period was the last 3-month interval of study participation. Patients were considered to be therapeutic successes if they achieved at least a 50% reduction in seizures from Baseline to Endstudy.

The results from Studies 097-005 and -006 are consistent with those seen in the U.S. controlled studies. The median seizure frequency was reduced from a Baseline value of 10.3 to a VGB maintenance value of 5.3 in Study 097-005, and approximately half of the patients had a reduction of at least 50% from Baseline in both studies. This reduction in seizure frequency was maintained throughout the long term study, Study 097-006. These data indicate that the benefit of VGB in reducing seizure frequency is durable.

In Study 097-006, the reduction in seizures from the 12-week Baseline period of Study 097-005 was assessed monthly for the first 6 months and then every 3 months. In each 3-month interval, at least 50% of the patients evaluable for efficacy experienced at least a 50% reduction in complex partial seizure frequency versus Baseline. Of the 66 patients who entered this study, 23 completed (average study duration of 8.5 years). Of these 23 patients, 74% (17/23) experienced at least a 50% reduction in their complex partial seizures at Endstudy. Among efficacy evaluable patients who discontinued, 40% (16/40) experienced at least a 50% reduction in complex partial seizure frequency at Endstudy (defined to be the last 3-month interval of study participation).

Thirty-eight (60%) of the 63 patients evaluable for efficacy in Study 097-006 had at least a 50% reduction in the frequency of complex partial seizures during the maintenance phase of Study 097-005. Twenty-nine (76%) of those 38 patients averaged at least a 50% reduction in complex partial seizure frequency over all 3-month intervals in which they participated in Study 097-006, suggesting that patients who initially respond to VGB continue to respond.

Study 097-304 consisted of an 8-week baseline phase followed by a 12-week open-label treatment phase and a 12-week double-blind phase. Patients received 3 g/day VGB in the initial open-label phase. Those who either had ≥50% reduction in seizure frequency or showed a marked clinical improvement were randomized to either continue to receive 3 g/day or to have their dose reduced to 1.5 g/day in the double-blind phase.

For the 75 patients who completed the open-label phase, the median monthly seizure frequency was significantly decreased ($p<0.01$) in patients having complex partial seizures or secondary generalized seizures. Fifty-six of the 75 patients completing the open-label phase were judged to have shown sufficient response for entry into the dose reduction phase of the

study: 41 had ≥50% reduction in seizure frequency and 15 were considered by the investigator to have had a marked improvement in global performance.

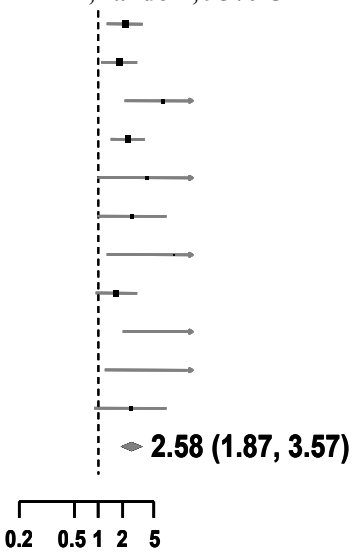
Of the 56 patients who entered the double-blind phase, 29 were allocated to continue on 3 g/day and 27 had their daily dose reduced to 1.5 g/day. This phase was completed by 53 patients, 28 on 3 g/day and 25 on 1.5 g/day. In the group taking the reduced dose, the median seizure frequency increased from 3.3 to 7.0 seizures/month, while in the group maintained on 3 g/day, there was no change. However, when the 25 patients in the 1.5 g/day group were compared with the baseline period they did show a clear improvement (7.0 seizures/month compared to 11 seizures/month), with the median percent reduction in seizures from baseline being 45%.

4.3.7 Summary of Efficacy in Controlled Studies Reported in Literature

In addition to data from the pivotal and supportive studies discussed previously, literature reports for other controlled studies evaluating the efficacy of vigabatrin in the treatment of refractory partial epilepsy are also available. In May of 2008, the Cochrane Collaboration published the results of a systematic review and meta-analysis of published data from randomized, double-blind, placebo-controlled studies of VGB as add-on treatment in refractory partial epilepsy [102]. The pivotal studies 024 and 025 are included in this analysis (ie, the French and Dean publications, respectively). As shown in Table 6, the patients randomized to VGB in each of these studies were more likely to achieve a 50% or greater reduction in seizure frequency than those randomized to placebo, with overall relative risk estimated as 2.58 (95% CI 1.87 to 3.57) favoring vigabatrin.

Table 6. Multiple Studies Confirm VGB Efficacy (Patients Achieving ≥50% Reduction in Seizure Frequency)

Study or Subgroup	VGB n/N	Placebo n/N	Weighted Risk Ratio M-H, random, 95% CI
Beran 1996	34/97	16/97	
Bruni 2000	28/58	14/53	
Dean 1999/Dodrill 1995[a]	55/129	3/45	
French 1996/Dodrill 1993[b]	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	**2.58 (1.87, 3.57)**
Total (95% CI)	536	446	



M-H = Mantel-Haenszel

Hemming et al., Cochrane Database Syst Rev 2008 Jul 16;(3):CD007302

a. Study 025

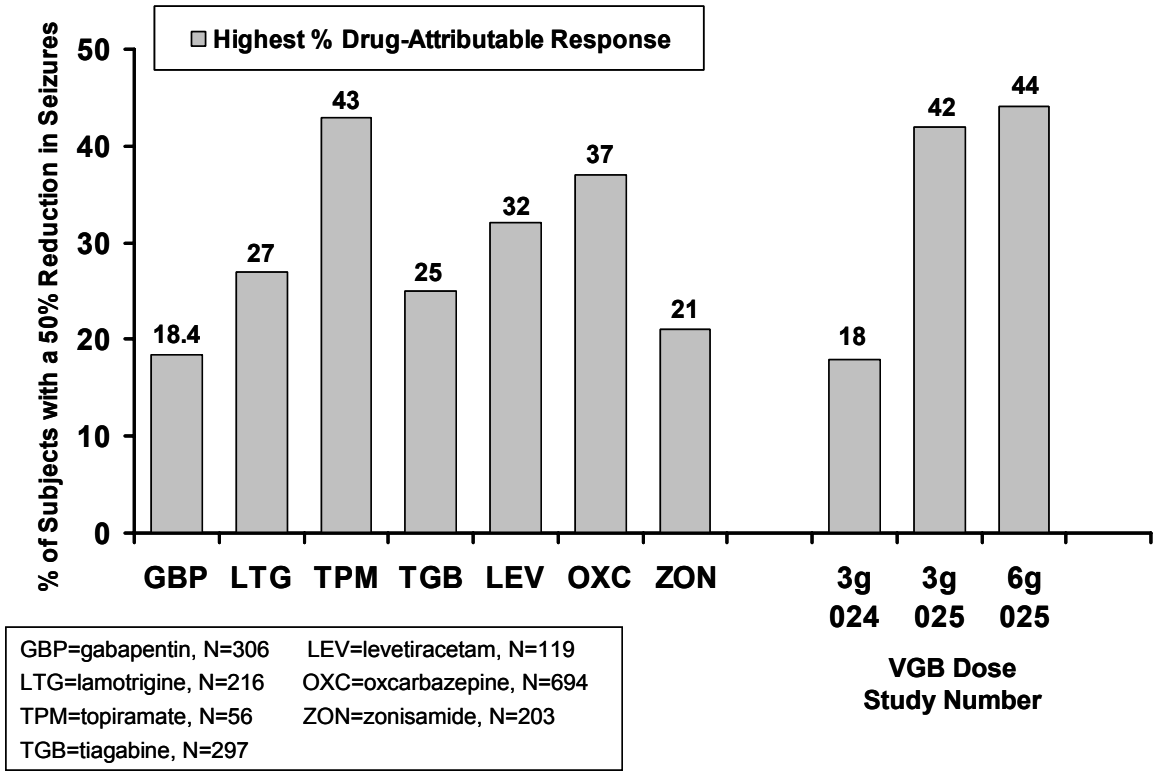
b. Study 024

The authors of this meta-analysis concluded that VGB reduces seizure frequency when used as an add-on treatment for refractory partial epilepsy.

We are unaware of published reports of randomized, controlled studies comparing adjunctive therapy with VGB to adjunctive therapy with other AEDs (including the newer agents), or of studies comparing any of the newer AEDs to each other. However, a review published by LaRoche and Helmers (2004) compared the results for available randomized, controlled studies of the AEDs approved for use in the United States as adjunctive therapy for the treatment of partial-onset seizures within the prior decade (felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, and zonisamide) [103]. In terms of reported patient demographics (eg, age, duration of epilepsy and frequency of seizures and prior and concomitant AEDs), the patients enrolled in these studies were similar both to each other and to the patients enrolled in pivotal studies 024 and 025. Figure 6 was derived from LaRoche & Helmers (2004) to show the percentage of patients achieving a 50% reduction in seizure frequency for each of these AEDs when used as adjunctive therapy in the treatment of partial-onset seizures (with placebo response subtracted). For AEDs where more than one study was available, the study with the highest response and associated sample size are reported in the graph.

For comparison, the placebo-subtracted percentages of patients achieving a 50% reduction in seizure frequency in both pivotal trials of VGB are shown on the right side of the graph.

Figure 6. VGB-Attributable Responder Rates are Consistent with Other 2nd Generation AEDs



Adapted from LaRoche & Helmers. JAMA 2004; 291:605-614

As shown above, VGB-responder rates compare favorably to those reported in the literature for other AEDs. Cross-study comparisons have significant limitations and only very limited conclusions can be drawn. However, these data support the efficacy of VGB when used as add-on therapy in the treatment of refractory CPS.

4.4. Safety in Refractory Complex Partial Seizures

4.4.1 Overview of Safety Database

A total of 4857 VGB-treated epilepsy and IS patients from 80 U.S., primary non-U.S., and secondary non-U.S. studies comprise the VGB safety database. All 4857 patients were included in the analyses of deaths and discontinuations due to AEs, while 4079 of 4857 patients were analyzed for AEs. This difference is due to the exclusion of secondary non-U.S. studies from analysis of AEs as described above (see Section 1.4.2). A total of 4740 of

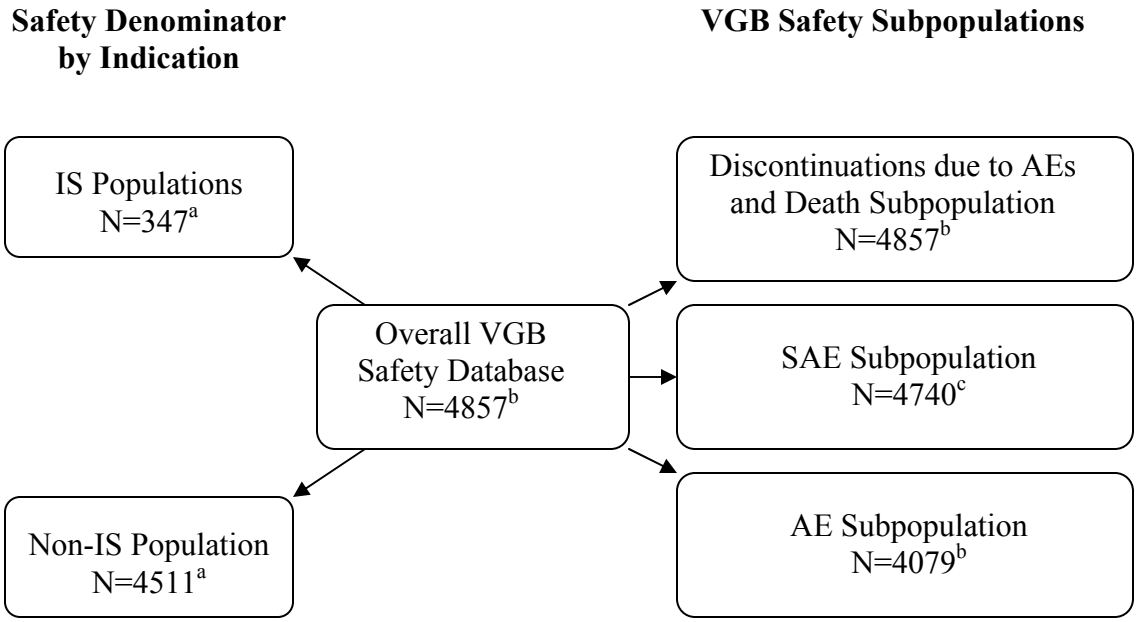
4857 patients were analyzed for SAEs. SAEs from 2 studies, 0098 and 4021, were entered into a separate database and reported independently. (see Section 4.4.3).

Analysis of safety for all 4857 VGB-treated patients is presented by indication for: 1) non-IS epilepsy population (N=4511) in Section 4.4 and 2) IS population (N=347) in Section 5.4. In addition to IS patients, the IS population also includes 21 infants (primarily <36 months of age) with other forms of epilepsy. One patient is counted twice, once in each indication, because the patient participated in an IS study and later in a non-IS study.

Data from both non-IS epilepsy and IS clinical studies were used for the reporting of SUDEP, psychiatric events, suicidality, and deaths (see Sections, 4.4.9, 4.4.10, 4.4.11, and 4.4.8.1, respectively). VGB deaths from all studies and sources are also presented in Section 4.4.8.

Figure 7 provides a schematic of the overall VGB safety database, as well as by indication.

Figure 7. Overall Integrated VGB Safety Database



a. One patient is presented in both the non-IS and IS populations.

b. Includes patients from all U.S., primary non-U.S., and secondary non-U.S. epilepsy studies. Excludes exposures from non-epilepsy/IS indications such as tardive dyskinesia, psychiatric disorders, ataxia and tremor, Huntington's Disease, spasticity, Parkinson's, dystonia and tort Collis, and clinical pharmacology studies (in epilepsy patients, healthy subjects, and renally impaired patients).

c. Includes patients from all U.S., primary non-U.S., and secondary non-U.S. epilepsy studies with the exception of some patients from Studies 0098 and 4021 which are presented separately in Section 4.4.6.4.

d. Includes patients from all U.S. and primary non-U.S. epilepsy studies.

4.4.2 Non-IS Epilepsy Safety Populations

A total of 4511 of 4857 patients from 76 clinical studies comprise the non-IS safety population. A listing of all studies included in this analysis is presented in Table 7.

Table 7. Studies Included in the Non-IS Epilepsy Safety Populations

U.S. Studies	Primary Non-U.S. Studies	Secondary Non-U.S. Studies
Adult Refractory CPS Pivotal Studies Population		
024		
025		
Controlled Non-IS Epilepsy Population		
024	097-WUK04	
025	71754-C-021	
0101	0192	
0118		
0221		
Controlled and Uncontrolled Non-IS Epilepsy Population		
024	097-444	097-230
025	097/W/AUS/01	097-242
0101	0192	097-253
0222	097-247	097-258
0223	097-259	097-233
0118	097-262	097-238
0221	097-263	097-240
097-005	097-309	097-241
097-006	097-WUK04	097-258LT
71754-3-C-020	71754-C-021	097-264
71754-3-C-026	71754-3-W-012	097-300[a]
0098	71754-3-W-007	097-305
71754-3-C-028	097-212	097-306
0242	097-215	097-307
0201	097-236	097-311
	097-237	097-314[a]
	097-244	097-319
	097-254	097-320
	097-255	097-345
	097-304	097-W345A[a]
	097-312	097-WEU02
	097-315	097-WUK14
	097-315A	
	097-315LT	
	WIT01 (9001/VGB)[a]	
	097-332[a]	
	097-WUK17	
	VIGA/4/ST/01	
	VIGA/4/ST06	
	71754-3-C-022	
	097-335	
	71754-3-W-002	

Table 7. Studies Included in the Non-IS Epilepsy Safety Populations

U.S. Studies	Primary Non-U.S. Studies	Secondary Non-U.S. Studies
	VIGA-4-ST-03	
	71754-III-ST-016	
	4020	
	4021	
	4103	
	R003	
	0294	

[a.] From these 5 studies, 21 patients who were primarily <36 months of age were excluded from the non-IS epilepsy safety populations and are presented with IS safety.

The non-IS population (N=4511) is further divided into 3 subgroups: 1) Controlled and Uncontrolled Non-IS Epilepsy Population, 2) Controlled Non-IS Epilepsy Population, and 3) Adult Refractory CPS Pivotal Studies Population (Table 8).

- The *Controlled and Uncontrolled Non-IS Epilepsy Population* (VGB N=4511) comprises patients who received at least 1 dose of VGB from all U.S., primary non-U.S., and secondary non-U.S. non-IS epilepsy studies and is used to detect less-frequently occurring AEs as well as those occurring with long-term therapy.

- The *Controlled Non-IS Epilepsy Population* (VGB N=588, placebo=373) comprises patients from all placebo-controlled, double-blind, parallel-group non-IS epilepsy studies and provides an overall assessment of the safety of VGB relative to placebo. Studies with a crossover design are excluded.

- The *Adult Refractory CPS Pivotal Studies Population* (VGB N=222, placebo=135) comprises patients from the 2 pivotal controlled U.S. studies, 025 and 024.

Exposure and safety data from 21 patients enrolled in the uncontrolled refractory epilepsy studies 097-300, 097-314, 097-332, 097-W345A, and WIT01, who were primarily <36 months of age are not included in the analysis of non-IS safety. Exposure and safety data for these 21 patients are presented with IS patients in order to provide a complete safety profile of the effect of VGB in the intended age range for IS treatment (Section 5.4).

Table 8. Non-IS Safety Populations

Non-IS Safety Population	Studies Included	N
Controlled and Uncontrolled Non-IS Epilepsy[a]	All epilepsy non-IS studies (see Table 7)	VGB=4511
Controlled Non-IS Epilepsy	024, 025, 021, 0101,WUK04, 0118, 0221, and 0192	VGB=588 placebo=373
Adult Refractory CPS Pivotal Studies	025 and 024	VGB=222 placebo=135

[a.] Excludes 21 infants (primarily <36 months of age) who are presented with IS safety.

Controlled and Uncontrolled Non-IS Epilepsy Population

Patients in the Controlled and Uncontrolled Non-IS Epilepsy Population (N=4511) were analyzed for AEs, SAEs, and discontinuations due to AEs as follows:

- *AE Subpopulation*: (N=3783)

This subpopulation includes 3783 VGB-treated patients from U.S. and primary non-U.S. studies only. Secondary non-U.S. studies were excluded per agreement with FDA due to the nature of the data collection or lack of a prospective protocol in these secondary studies (Section 1.4.2).

- *SAE Subpopulation* (N=4394)

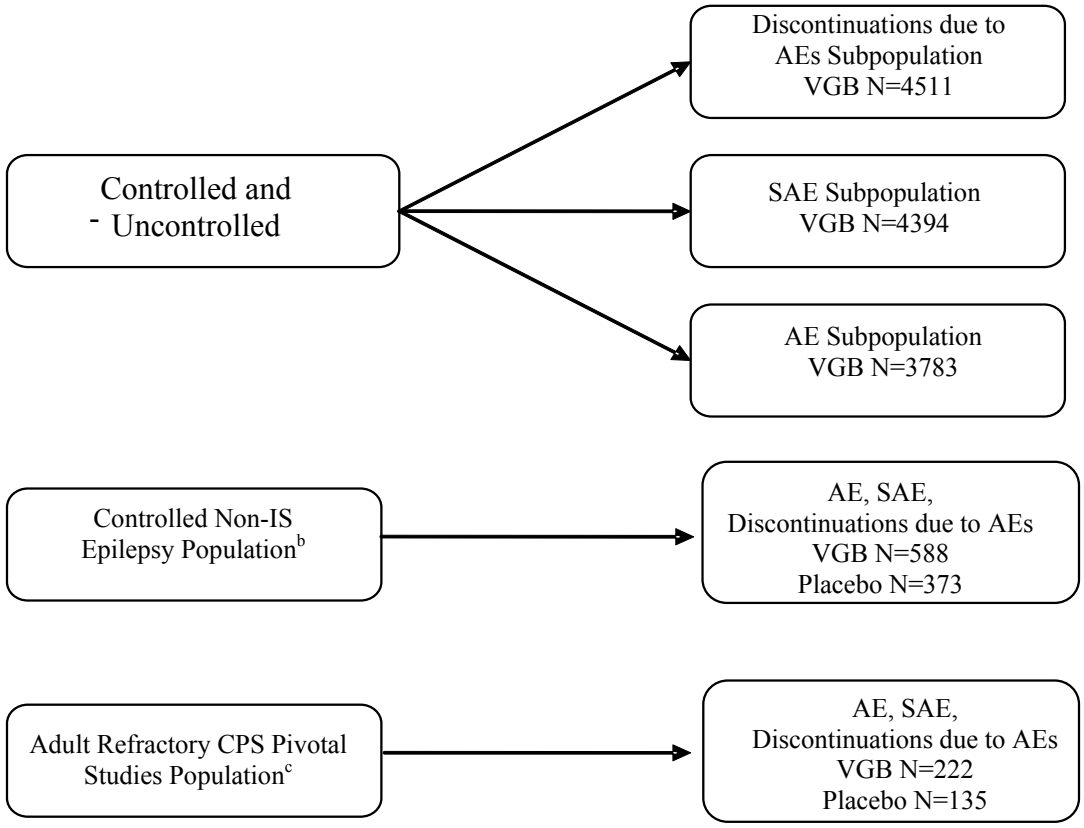
This subpopulation includes 4394 VGB-treated patients in all U.S., primary non-U.S., and secondary non-U.S. studies. SAEs for patients enrolled in Studies 0098 and 4021 were entered into a separate database, accounting for the difference in N from the *Discontinuations due to AEs Subpopulation.* These SAEs are presented separately in Section 4.4.6.4.

- *Discontinuations due to AEs Subpopulation* (N=4511)

This subpopulation includes 4511 VGB-treated patients in all U.S., primary non-U.S., and secondary non-U.S. studies.

A schematic of these subpopulations is provided in Figure 8.

Figure 8. Non-IS Epilepsy Safety Populations and Subpopulations



a. Includes patients from all (Table 7) U.S., primary non-U.S., and secondary non-U.S. studies.

b. Includes patients from studies 024, 025, 021, 0101, WUK04, 0118, 0221, and 0192; all are U.S. or primary non-U.S. studies.

c. Includes patients from pivotal studies 025 and 024.

4.4.3 Non-Integrated Safety Data

As noted above, SAEs from Studies 0098 and 4021 have not been integrated into the VGB safety database, and were analyzed separately. These SAEs are reported in Section 4.4.6.4.

4.4.4 Exposure in Non-IS Epilepsy Studies

Total exposure to VGB is summarized in Table 9 for non-IS epilepsy studies and overall for all epilepsy studies, including IS.

Total exposure to VGB in all epilepsy studies was 8780 patient-years (PYs) (approximately 3.2 million days). The majority of these exposures occurred in non-IS epilepsy studies (8424 PYs). Over 70% of patients in non-IS epilepsy studies were treated with VGB for more than

6 months. Of these 3234 patients, 2608 were exposed for over 1 year. A total of 403 patients were exposed for over 5 years, including 67 patients who were exposed for more than 10 years. The duration of exposure in non-IS epilepsy studies was similar to the overall epilepsy population.

Table 9. VGB Exposure: Non-IS Epilepsy Studies and All Epilepsy Studies

	Non-IS Epilepsy Studies[a,b]	All Epilepsy Studies[b,c]
	VGB [N=4511]	**VGB [N=4857]**
Number of patients exposed	4511	4857
Total patient days of exposure	3076974	3206984
Total patient years of exposure	8424	8780
Mean patient days of exposure	n=4370	n=4715
Mean (SD)	704.1 (791.66)	680.2 (771.60)
Median	474	461
Range	1, 6173	1, 6173
Number of patients dosed, n (%)		
1–14 days	44 (1.0)	51 (1.1)
>14–30 days	77 (1.7)	86 (1.8)
>30–60 days	196 (4.3)	228 (4.7)
>60–90 days	279 (6.2)	295 (6.1)
>90 days–6 months	540 (12.0)	599 (12.3)
>6 months–1 year	626 (13.9)	703 (14.5)
>1–2 years	1028 (22.8)	1123 (23.1)
>2–3 years	890 (19.7)	926 (19.1)
>3–5 years	287 (6.4)	301 (6.2)
>5–10 years	336 (7.4)	336 (6.9)
>10 years	67 (1.5)	67 (1.4)
Missing	141 (3.1)	142 (2.9)

a. Exposure for all U.S., primary non-U.S., and secondary non-U.S. studies in the *Controlled and Uncontrolled Non-IS Epilepsy Population* is presented. Includes all non-IS epilepsy studies. Excludes IS studies and 21 patients primarily <36 months of age from non-IS studies who are included in analysis of IS exposure and safety.

b. Percentages are with respect to the number of patients exposed for each population.

c. Exposure for all U.S., primary non-U.S., and secondary non-U.S. epilepsy studies (including non-IS and IS studies). Excludes exposures from non-epilepsy/IS indications such as tardive dyskinesia, psychiatric disorders, ataxia and tremor, Huntington's Disease, spasticity, Parkinson's, dystonia and torticollis, and clinical pharmacology studies (in epilepsy patients, healthy subjects, and renally impaired patients).

4.4.5 Adverse Events in Non-IS Epilepsy Safety Populations

A total of 3783 non-IS epilepsy patients were analyzed for AEs.

4.4.5.1 Adult Refractory CPS Pivotal Studies Population

In the pivotal controlled studies, 024 and 025, 97.3% of VGB-treated patients reported at least 1 AE, similar to the incidence observed in patients treated with placebo (94.1%)

(Table 10). The most common AEs (≥10%) occurring more frequently in VGB-treated patients were the following: fatigue (27.0% VGB, 16.3% placebo), somnolence (22.1%, 13.3%), dizziness (21.2%, 17.0%), nystagmus (15.3%, 8.9%), tremor (14.0%, 8.2%), nasopharyngitis (13.1%, 10.4%), vision blurred (11.26%, 5.2%), diarrhea (10.4%, 7.4%), and irritability (10.4%, 7.4%).

Table 10. Adverse Events Occurring in ≥5% of VGB-Treated Patients and More Frequently Than Placebo: Adult Refractory CPS Pivotal Studies Population[a]

Body System Preferred Term	VGB [N=222] n (%)	Placebo [N=135] n (%)
Any Adverse Event	216 (97.30)	127 (94.07)
Eye Disorders		
Vision blurred	25 (11.26)	7 (5.19)
Diplopia	19 (8.56)	4 (2.96)
Gastrointestinal Disorders		
Diarrhea	23 (10.36)	10 (7.41)
Nausea	19 (8.56)	11 (8.15)
Vomiting	16 (7.21)	8 (5.93)
Constipation	14 (6.31)	4 (2.96)
General Disorders and Administration Site Conditions		
Fatigue	60 (27.03)	22 (16.30)
Gait disturbance	15 (6.76)	9 (6.67)
General symptom	13 (5.86)	4 (2.96)
Asthenia	12 (5.41)	2 (1.48)
Infections and Infestations		
Nasopharyngitis	29 (13.06)	14 (10.37)
Upper respiratory tract infection	21 (9.46)	7 (5.19)
Investigations		
Weight increased	17 (7.66)	4 (2.96)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	18 (8.11)	4 (2.96)
Back pain	13 (5.86)	3 (2.22)
Nervous System Disorders		
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)
Memory impairment	21 (9.46)	4 (2.96)
Coordination abnormal	19 (8.56)	3 (2.22)
Disturbance in attention	12 (5.41)	1 (0.74)
Psychiatric Disorders		

Table 10. Adverse Events Occurring in ≥5% of VGB-Treated Patients and More Frequently Than Placebo: Adult Refractory CPS Pivotal Studies Population[a]

Body System Preferred Term	VGB [N=222] n (%)	Placebo [N=135] n (%)
Irritability	23 (10.36)	10 (7.41)
Depression	15 (6.76)	4 (2.96)
Confusional state	13 (5.86)	1 (0.74)
Reproductive System and Breast Disorders		
Dysmenorrhea	15 (6.76)	4 (2.96)
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	19 (8.56)	7 (5.19)

[a] Studies 024 and 025.

Cognitive Outcomes

Cognitive outcomes were evaluated in both pivotal studies using a battery of 8 standardized cognitive tests (Lafayette Pegboard Test, Stroop Test, Benton Visual Retention Test, Controlled Oral Word Association, Symbol Digit Modalities Test, Rey Auditory Verbal Learning test, Wonderlic Personnel Test, Digit Cancellation Test). There were no significant differences between treatment groups in any measure of cognition in Study 024. In Study 025, scores on the Digit Cancellation test decreased with increasing doses of vigabatrin ($p<0.05$). No other differences were seen. Based on these results, treatment with vigabatrin appears to have little effect on cognitive function [85,86].

4.4.5.2 Controlled Non-IS Epilepsy Population

In the *Controlled Non-IS Epilepsy Population*, 95.6% of VGB-treated patients reported at least 1 AE, similar to the incidence observed in patients treated with placebo (93.6%) (Table 11). The most common AEs (≥10%) occurring more frequently in VGB-treated patients were the following: fatigue (22.3% VGB, 15.3% placebo), dizziness (18.9%, 15.6%), somnolence (16.3%, 9.9%), and weight increased (11.1%, 7.2%).

Table 11. Adverse Events Occurring in ≥5% of VGB-Treated Patients and More Frequently Than Placebo: Controlled Non-IS Epilepsy Population[a]

Body System Preferred Term	VGB [N=588] n (%)	Placebo [N=373] n (%)
Any Adverse Event	562 (95.58)	349 (93.57)
Eye Disorders		
Diplopia	51 (8.67)	18 (4.83)
Vision blurred	39 (6.63)	14 (3.75)
Gastrointestinal Disorders		
Diarrhea	50 (8.50)	28 (7.51)
Nausea	46 (7.82)	27 (7.24)
Vomiting	43 (7.31)	26 (6.97)
Constipation	31 (5.27)	11 (2.95)
General Disorders and Administration Site Conditions		
Fatigue	131 (22.28)	57 (15.28)
Infections and Infestations		
Upper respiratory tract infection	56 (9.52)	32 (8.58)
Influenza	44 (7.48)	23 (6.17)
Investigations		
Weight increased	65 (11.05)	27 (7.24)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	31 (5.27)	9 (2.41)
Nervous System Disorders		
Dizziness	111 (18.88)	58 (15.55)
Somnolence	96 (16.33)	37 (9.92)
Nystagmus	52 (8.84)	20 (5.36)
Tremor	51 (8.67)	23 (6.17)
Coordination abnormal	46 (7.82)	10 (2.68)
Memory impairment	39 (6.63)	15 (4.02)
Psychiatric Disorders		
Depression	46 (7.82)	17 (4.56)
Confusional state	32 (5.44)	6 (1.61)
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	32 (5.44)	19 (5.09)
Skin and Subcutaneous Tissue Disorders		
Rash	31 (5.27)	19 (5.09)

[a] Studies 024, 025, WUK04, 021, 0101, 0118, 0221, 0192.

4.4.5.3 Controlled and Uncontrolled Non-IS Epilepsy Population: Adverse Events Subpopulation

In the *Controlled and Uncontrolled Non-IS Epilepsy Population*, almost all patients (97.0%) reported at least 1 AE (Table 12). The most common AEs in VGB-treated patients were the following: headache, fatigue, somnolence, dizziness, convulsion, weight increased, and nasopharyngitis, each occurring in ≥10% of patients. These events would not be considered unusual for this population.

Table 12. Adverse Events Occurring in ≥5% of VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	**VGB** **[N=3783]** **n (%)**
Any Adverse Event	3669 (96.99)
Eye Disorders	
Vision blurred	255 (6.74)
Diplopia	251 (6.63)
Gastrointestinal Disorders	
Nausea	282 (7.45)
Diarrhea	244 (6.45)
Vomiting	209 (5.52)
General Disorders and Administration Site Conditions	
Fatigue	670 (17.71)
Infections and Infestations	
Nasopharyngitis	409 (10.81)
Upper respiratory tract infection	296 (7.82)
Influenza	234 (6.19)
Investigations	
Weight increased	413 (10.92)
Musculoskeletal and Connective Tissue Disorders	
Back pain	187 (4.94)
Nervous System Disorders	
Headache	743 (19.64)
Somnolence	645 (17.05)
Dizziness	622 (16.44)
Convulsion	438 (11.60)
Visual field defect	359 (9.49)
Tremor	288 (7.61)
Nystagmus	286 (7.56)
Memory impairment	272 (7.19)
Coordination abnormal	260 (6.87)

Table 12. Adverse Events Occurring in ≥5% of VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	**VGB [N=3783] n (%)**
Psychiatric Disorders	
Depression	334 (8.83)
Insomnia	245 (6.48)
Irritability	221 (5.84)
Skin and Subcutaneous Tissue Disorders	
Rash	207 (5.47)

a. *AE Subpopulation*; includes U.S. and primary non-U.S. studies; excludes 280 patients from U.S. and primary non-U.S. IS studies and 15 patients from U.S. and primary non-U.S., non-IS studies who are included in IS safety.

4.4.6 Serious Adverse Events in Non-IS Epilepsy Safety Populations

A total of 4394 non-IS epilepsy patients were analyzed for SAEs.

4.4.6.1 Adult Refractory CPS Pivotal Studies Population

In the pivotal controlled studies, 024 and 025, 7.2% of VGB-treated patients reported at least 1 SAE, compared with 1.5% of patients treated with placebo (Table 13). All SAEs occurred in less than 2% of each treatment group. SAEs that occurred in more than 1 patient were the following: status epilepticus (1.8% VGB, 0% placebo), convulsion (1.4%, 0.7%), and pneumonia (1.4%, 0%). Status epilepticus and convulsion are not unexpected events in the epilepsy population.

Table 13. Serious Adverse Events Occurring More Frequently in VGB-Treated Patients Than Placebo: Adult Refractory CPS Pivotal Studies Population[a]

Body System Preferred Term	VGB [N=222] n (%)	Placebo [N=135] n (%)
Any Serious Adverse Event	16 (7.21)	2 (1.48)
Gastrointestinal Disorders		
Vomiting	1 (0.45)	0 (0.00)
General Disorders and Administration Site Conditions		
Feeling drunk	1 (0.45)	0 (0.00)
Pyrexia	1 (0.45)	0 (0.00)
Infections and Infestations		
Pneumonia	3 (1.35)	0 (0.00)
Urosepsis	1 (0.45)	0 (0.00)
Injury, Poisoning and Procedural Complications		
Drug toxicity	1 (0.45)	0 (0.00)
Fall	1 (0.45)	0 (0.00)
Nervous System Disorders		
Status epilepticus	4 (1.80)	0 (0.00)
Convulsion	3 (1.35)	1 (0.74)
Grand mal convulsion	1 (0.45)	0 (0.00)
Simple partial seizures	1 (0.45)	0 (0.00)
Psychiatric Disorders		
Abnormal behavior	1 (0.45)	0 (0.00)
Completed suicide	1 (0.45)	0 (0.00)
Confusional state	1 (0.45)	0 (0.00)
Depression	1 (0.45)	0 (0.00)
Mood disorder due to a general medical condition	1 (0.45)	0 (0.00)
Personality disorder	1 (0.45)	0 (0.00)
Psychotic disorder due to a general medical condition	1 (0.45)	0 (0.00)
Suicide attempt	1 (0.45)	0 (0.00)
Vascular Disorders		
Hypertension	1 (0.45)	0 (0.00)

[a] Studies 024 and 025.

4.4.6.2 Controlled Non-IS Epilepsy Population

In the *Controlled Non-IS Epilepsy Population*, 16.2% of VGB-treated patients reported at least 1 SAE, similar to the incidence observed in patients treated with placebo (13.4 %) (Table 14). The majority of SAEs were related to nervous system disorders, psychiatric disorders, and infections and infestations. SAEs that occurred in approximately 1-2% of the VGB-treatment group and more frequently than placebo were the following: status

epilepticus (1.7% VGB, 0.5% placebo), depression (1.2%, 0.5%), confusional state (1.0%, 0%), dizziness (1.0%, 0.5%), and injury (1.0%, 0.3%).

Table 14. Serious Adverse Events Occurring in ≥2 VGB-Treated Patients and More Frequently Than Placebo: Controlled Non-IS Epilepsy Population[a]

Body System Preferred Term	VGB [N=588] n (%)	Placebo [N=373] n (%)
Any Serious Adverse Event	95 (16.16)	50 (13.40)
Eye Disorders		
Visual disturbance	2 (0.34)	0 (0.00)
Gastrointestinal Disorders		
Diarrhea	2 (0.34)	1 (0.27)
General Disorders and Administration Site Conditions		
Fatigue	4 (0.68)	0 (0.00)
Infections and Infestations		
Pneumonia	5 (0.85)	0 (0.00)
Bronchitis	4 (0.68)	0 (0.00)
Candidiasis	2 (0.34)	0 (0.00)
Sinusitis	2 (0.34)	1 (0.27)
Injury, Poisoning and Procedural Complications		
Injury	6 (1.02)	1 (0.27)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	2 (0.34)	1 (0.27)
Nervous System Disorders		
Status epilepticus	10 (1.70)	2 (0.54)
Dizziness	6 (1.02)	2 (0.54)
Somnolence	4 (0.68)	0 (0.00)
Coordination abnormal	3 (0.51)	0 (0.00)
Tremor	3 (0.51)	0 (0.00)
Disturbance in attention	2 (0.34)	0 (0.00)
Partial seizures	2 (0.34)	0 (0.00)
Psychiatric Disorders		
Depression	7 (1.19)	2 (0.54)
Confusional state	6 (1.02)	0 (0.00)
Agitation	3 (0.51)	0 (0.00)
Anxiety	2 (0.34)	0 (0.00)
Delirium	2 (0.34)	0 (0.00)
Skin and Subcutaneous Tissue Disorders		
Rash	4 (0.68)	1 (0.27)
Vascular Disorders		
Hypertension	2 (0.34)	0 (0.00)

[a] Studies 024, 025, WUK04, 021, 0101, 0118, 0221, 0192.

4.4.6.3 Controlled and Uncontrolled Non-IS Epilepsy Population: Serious Adverse Events Subpopulation

In the *Controlled and Uncontrolled Non-IS Epilepsy Population*, 19.6% of VGB-treated patients reported at least 1 SAE (Table 15). The highest incidences of SAEs were nervous system disorder related, with pVFD reported in 338 patients (7.7%). This high incidence of pVFD represents the inclusion of events from the EMEA/CHMP Article 12 studies, which primarily focused on the detection and evaluation of the visual defect. Other nervous system-related SAEs reported in ≥1% of patients were convulsion (2.9%) and status epilepticus (1.5%), events which are not unexpected in the epilepsy population. No other SAEs were reported with an incidence ≥1%.

Table 15. Serious Adverse Events Occurring in ≥3 VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	**VGB** **[N=4394]** **n (%)**
Any Serious Adverse Event	862 (19.62)
Blood and Lymphatic System Disorders	
Anemia	3 (0.07)
Cardiac Disorders	
Myocardial infarction	3 (0.07)
Eye Disorders	
Scotoma	4 (0.09)
Gastrointestinal Disorders	
Vomiting	10 (0.23)
Abdominal pain	6 (0.14)
Diarrhea	5 (0.11)
Dyspepsia	3 (0.07)
General Disorders and Administration Site Conditions	
Pyrexia	14 (0.32)
Chest pain	6 (0.14)
Fatigue	6 (0.14)
Drug interaction	4 (0.09)
Asthenia	3 (0.07)
Hepatobiliary Disorders	
Cholecystitis	5 (0.11)
Infections and Infestations	
Pneumonia	13 (0.30)
Influenza	6 (0.14)
Upper respiratory tract infection	6 (0.14)
Cellulitis	5 (0.11)
Bronchitis	4 (0.09)
Gastroenteritis	4 (0.09)

Table 15. Serious Adverse Events Occurring in ≥3 VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	VGB [N=4394] n (%)
Osteomyelitis	4 (0.09)
Sinusitis	4 (0.09)
Urinary tract infection	4 (0.09)
Appendicitis	3 (0.07)
Infection	3 (0.07)
Injury, Poisoning and Procedural Complications	
Injury	10 (0.23)
Overdose	7 (0.16)
Fall	6 (0.14)
Ankle fracture	4 (0.09)
Hip fracture	4 (0.09)
Head injury	3 (0.07)
Joint dislocation	3 (0.07)
Metabolism and Nutrition Disorders	
Hyponatraemia	3 (0.07)
Musculoskeletal and Connective Tissue Disorders	
Back pain	6 (0.14)
Osteoarthritis	5 (0.11)
Intervertebral disc protrusion	3 (0.07)
Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)	
Basal cell carcinoma	3 (0.07)
Nervous System Disorders	
Visual field defect	338 (7.69)
Convulsion	128 (2.91)
Status epilepticus	66 (1.50)
Hemianopia	32 (0.73)
Complex partial seizures	15 (0.34)
Grand mal convulsion	15 (0.34)
Headache	14 (0.32)
Postictal state	12 (0.27)
Dizziness	11 (0.25)
Somnolence	10 (0.23)
Epilepsy	8 (0.18)
Partial seizures	7 (0.16)
Coordination abnormal	6 (0.14)
Hemianopia homonymous	6 (0.14)
Tremor	6 (0.14)
Cerebrovascular accident	5 (0.11)

Table 15. Serious Adverse Events Occurring in ≥3 VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	**VGB [N=4394] n (%)**
Hemiparesis	4 (0.09)
Lethargy	4 (0.09)
Amnesia	3 (0.07)
Disturbance in attention	3 (0.07)
Simple partial seizures	3 (0.07)
Psychiatric Disorders	
Depression	21 (0.48)
Confusional state	20 (0.46)
Aggression	13 (0.30)
Psychotic disorder	13 (0.30)
Suicidal ideation	12 (0.27)
Suicide attempt	10 (0.23)
Abnormal behavior	7 (0.16)
Anxiety	7 (0.16)
Agitation	5 (0.11)
Acute psychosis	4 (0.09)
Disorientation	4 (0.09)
Affect lability	3 (0.07)
Conversion disorder	3 (0.07)
Delusion	3 (0.07)
Hallucination, auditory	3 (0.07)
Irritability	3 (0.07)
Mental status changes	3 (0.07)
Respiratory, Thoracic and Mediastinal Disorders	
Pneumonia aspiration	10 (0.23)
Dyspnea	6 (0.14)
Hypoxia	5 (0.11)
Aspiration	3 (0.07)
Asthma	3 (0.07)
Skin and Subcutaneous Tissue Disorders	
Rash	4 (0.09)

Table 15. Serious Adverse Events Occurring in ≥3 VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	VGB [N=4394] n (%)
Surgical and Medical Procedures	
Brain lobectomy	6 (0.14)

a. *SAE Subpopulation*; includes U.S., primary non-U.S., and secondary non-U.S. studies; includes 1 patient from pediatric study 097-332 who also has data for IS Study 097-332.5 included in the IS safety section; excludes 325 patients from IS studies and 21 patients from non-IS studies who are included in IS safety; excludes SAEs from Studies 0098 and 4021 which were not integrated (see Section 4.4.6.4).

4.4.6.4 Serious Adverse Events: Studies 0098 and 4021

Non-integrated SAEs from Studies 0098 and 4021 are presented separately in Table 16. This analysis calculates frequency of events based on the total number of patients from these 2 studies who reported SAEs (N=161), not the total number of patients receiving vigabatrin. Therefore, although data from these studies are included for completeness, the frequency of specific SAEs appearing in this analysis cannot be directly compared to the SAEs reported for the 3 non-IS safety populations presented above.

The highest incidence of SAEs reported in Studies 0098 and 4021 were nervous system disorder related (99 patients, 61.5%). Visual field defect was reported for 43 patients (26.7%). Other nervous system disorder-related SAEs reported in at least 5 patients were convulsion (28 patients, 17.4%) and status epilepticus (14 patients, 8.7%). These SAEs are not considered unexpected in the epilepsy population.

Table 16. Serious Adverse Events Occurring in ≥3 VGB-Treated Patients: Studies 0098 and 4021[a]

Body System Preferred Term	VGB Patients Reporting Any SAE [N=161[b]] n (%)
Any Serious Adverse Event	161
Cardiac Disorders	
Myocardial infarction	4 (2.5)
Eye Disorders	
Retinopathy	4 (2.5)
Gastrointestinal Disorders	
Vomiting	3 (1.9)
General Disorders and Administration Site Conditions	
Chest pain	8 (4.8)
Pyrexia	4 (2.4)
Infections and Infestations	
Pneumonia	7 (4.3)

Table 16. Serious Adverse Events Occurring in ≥3 VGB-Treated Patients: Studies 0098 and 4021[a]

Body System Preferred Term	VGB Patients Reporting Any SAE [N=161[b]] n (%)
Injury, Poisoning and Procedural Complications	
Fall	4 (2.5)
Investigations	
Retinogram abnormal	3 (1.9)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Basal cell carcinoma	3 (1.9)
Breast cancer	3 (1.9)
Nervous System Disorders	
Visual field defect	43 (26.7)
Convulsion	28 (17.4)
Status epilepticus	14 (8.7)
Ataxia	4 (2.5)
Complex partial seizures	3 (1.9)
Dysarthria	3 (1.9)
Somnolence	3 (1.9)
Psychiatric Disorders	
Major depression	4 (2.5)
Depression	3 (1.9)
Psychotic disorder	3 (1.9)
Suicide attempt	3 (1.9)
Respiratory, Thoracic and Mediastinal Disorders	
Pneumonia aspiration	4 (2.5)
Asthma	3 (1.9)

a. All serious and fatal cases with event onset date between 16 March 1997 and 17 June 2005 (inclusive) or initial case received between 16 March 1997 and 17 June 2005. Cases with unknown report date are also included.

b. N=total number of patients with at least 1 SAE.

4.4.7 Discontinuations due to Adverse Events

A total of 4511 non-IS epilepsy patients were analyzed for AEs leading to discontinuation.

4.4.7.1 Adult Refractory CPS Pivotal Studies Population

In the pivotal controlled studies, 025 and 024, 10.8% of VGB-treated patients discontinued due to an AE compared with 2.2% of placebo-treated patients (Table 17). The most common AE leading to study discontinuation for the VGB treatment group was headache (1.4% VGB, 0% placebo). All other AEs leading to discontinuation occurred in less than 1% of each treatment group.

Table 17. Discontinuations due to Adverse Events Occurring in ≥2 VGB-Treated Patients and More Frequently Than Placebo: Adult Refractory CPS Pivotal Studies Population[a]

Body System Preferred Term	VGB [N=222] n (%)	Placebo [N=135] n (%)
Any Adverse Event Causing Withdrawal	24 (10.81)	3 (2.22)
General Disorders and Administration Site Conditions		
Fatigue	2 (0.90)	0 (0.00)
Pain	2 (0.90)	0 (0.00)
Nervous System Disorders		
Headache	3 (1.35)	0 (0.00)
Balance disorder	2 (0.90)	1 (0.74)
Dizziness	2 (0.90)	0 (0.00)
Somnolence	2 (0.90)	1 (0.74)
Psychiatric Disorders		
Abnormal behavior	2 (0.90)	0 (0.00)
Depression	2 (0.90)	0 (0.00)
Expressive language disorder	2 (0.90)	1 (0.74)
Mental status changes	2 (0.90)	0 (0.00)
Thinking abnormal	2 (0.90)	0 (0.00)
Skin and Subcutaneous Tissue Disorders		
Pruritus generalized	2 (0.90)	0 (0.00)

[a] Studies 024 and 025.

4.4.7.2 Controlled Non-IS Epilepsy Population

In the *Controlled Non-IS Epilepsy Population*, 14.0% of VGB-treated patients discontinued from a study due to an AE compared with 4.6% of placebo-treated patients (Table 18). The most common AEs leading to study discontinuation for the VGB treatment group were depression (1.7% VGB, 0.5% placebo), convulsion (1.2%, 0.5%), disturbance in attention (1.0%, 0%), headache (1.0%, 0.5%), and agitation (1.0%, 0%). All other AEs leading to discontinuation occurred in less than 1% of the VGB treatment group.

Table 18. Discontinuations due to Adverse Events Occurring in ≥3 VGB-Treated Patients and More Frequently Than Placebo: Controlled Non-IS Epilepsy Population[a]

Body System Preferred Term	VGB [N=588] n (%)	Placebo [N=373] n (%)
Any Adverse Event Causing Withdrawal	82 (13.95)	17 (4.56)
Eye Disorders		
Vision blurred	3 (0.51)	1 (0.27)
General Disorders and Administration Site Conditions		
Fatigue	3 (0.51)	1 (0.27)
Nervous System Disorders		
Convulsion	7 (1.19)	2 (0.54)
Disturbance in attention	6 (1.02)	0 (0.00)
Headache	6 (1.02)	2 (0.54)
Somnolence	4 (0.68)	2 (0.54)
Balance disorder	3 (0.51)	1 (0.27)
Dizziness	3 (0.51)	0 (0.00)
Status epilepticus	3 (0.51)	0 (0.00)
Psychiatric Disorders		
Depression	10 (1.70)	2 (0.54)
Agitation	6 (1.02)	0 (0.00)
Confusional state	4 (0.68)	0 (0.00)
Irritability	4 (0.68)	0 (0.00)
Abnormal behavior	3 (0.51)	1 (0.27)
Aggression	3 (0.51)	0 (0.00)
Anxiety	3 (0.51)	1 (0.27)
Delirium	3 (0.51)	0 (0.00)
Thinking abnormal	3 (0.51)	0 (0.00)
Skin and Subcutaneous Tissue Disorders		
Rash	5 (0.85)	0 (0.00)

[a] Studies 024, 025, WUK04, 021, 0101, 0118, 0221, 0192.

4.4.7.3 Controlled and Uncontrolled Non-IS Epilepsy Population: Discontinuations due to Adverse Events Subpopulation

Despite the fact that almost all VGB-treated patients (97.0%, see Table 12) experienced at least 1 AE, only 14.2% of patients discontinued from a study due to an AE (Table 19). The primary reasons for discontinuation were depression (1.6%) and convulsion (1.5%). Discontinuations due to AEs that occurred in ≥0.5% and <1% of patients included fatigue (0.9%), somnolence (0.9%), dizziness (0.7%), headache (0.7%), confusional state (0.7%), weight increased (0.7%), aggression (0.6%), irritability (0.6%), abnormal behavior (0.6%), status epilepticus (0.5%), and coordination abnormal (0.5%).

Table 19. Discontinuations due to Adverse Events Occurring in ≥5 VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	**VGB [N=4511] n (%)**
Any Adverse Event Causing Withdrawal	642 (14.23)
Ear and Labyrinth Disorders	
Vertigo	9 (0.20)
Eye Disorders	
Vision blurred	15 (0.33)
Diplopia	11 (0.24)
Gastrointestinal Disorders	
Nausea	15 (0.33)
Constipation	10 (0.22)
Vomiting	9 (0.20)
Diarrhea	8 (0.18)
Abdominal pain	6 (0.13)
Abdominal pain upper	5 (0.11)
General Disorders and Administration Site Conditions	
Fatigue	40 (0.89)
Gait disturbance	6 (0.13)
Feeling abnormal	5 (0.11)
Edema peripheral	5 (0.11)
Investigations	
Weight increased	30 (0.67)
Metabolism and Nutrition Disorders	
Anorexia	5 (0.11)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	6 (0.13)
Nervous System Disorders	
Convulsion	68 (1.51)
Somnolence	42 (0.93)
Dizziness	31 (0.69)
Headache	30 (0.67)
Status epilepticus	23 (0.51)
Coordination abnormal	21 (0.47)
Memory impairment	19 (0.42)
Tremor	18 (0.40)
Visual field defect	14 (0.31)
Disturbance in attention	11 (0.24)

Table 19. Discontinuations due to Adverse Events Occurring in ≥5 VGB-Treated Patients: Controlled and Uncontrolled Non-IS Epilepsy Population[a]

Body System Preferred Term	**VGB [N=4511] n (%)**
Lethargy	11 (0.24)
Balance disorder	8 (0.18)
Paraesthesia	7 (0.16)
Sedation	7 (0.16)
Amnesia	6 (0.13)
Myoclonus	6 (0.13)
Nystagmus	6 (0.13)
Dyskinesia	5 (0.11)
Grand mal convulsion	5 (0.11)
Partial seizures	5 (0.11)
Psychiatric Disorders	
Depression	71 (1.57)
Confusional state	30 (0.67)
Aggression	28 (0.62)
Irritability	28 (0.62)
Abnormal behavior	26 (0.58)
Psychotic disorder	17 (0.38)
Insomnia	16 (0.35)
Agitation	11 (0.24)
Anxiety	11 (0.24)
Paranoia	10 (0.22)
Suicidal ideation	10 (0.22)
Expressive language disorder	8 (0.18)
Mental disorder	8 (0.18)
Hallucination	7 (0.16)
Affect lability	6 (0.13)
Hallucination, auditory	5 (0.11)
Mood swings	5 (0.11)
Suicide attempt	5 (0.11)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea	6 (0.13)
Skin and Subcutaneous Tissue Disorders	
Rash	11 (0.24)

a. *Discontinuations due to AEs Subpopulation*; includes U.S., primary non-U.S., and secondary non-U.S. studies; includes 1 patient from pediatric study 097-332 who also has data for IS Study 097-332.5 included in the IS safety section; excludes 325 patients from IS studies and 21 patients from non-IS studies who are included in IS safety.

4.4.8 Deaths

A total of 112 VGB deaths have been reported through 30 June 2007 (the cut off date for safety reporting for the December 2007 NDA submission), including 63 deaths in primary or secondary epilepsy and IS clinical studies (Section 4.4.8.1) and 49 deaths from additional studies and sources, including postmarketing studies, non-U.S. non-CRF studies, Japanese studies, non-U.S. compassionate use and miscellaneous sources (Section 4.4.8.2). A listing of these 112 patients who died while receiving VGB with the corresponding investigator terms for cause of death is presented in Table 20.

Sixty-seven deaths were reported during postmarketing surveillance through 30 June 2007 that are not included in the 112 total VGB deaths. (Section 4.4.8.2) For purposes of this Briefing Document, the postmarketing database was searched from 01 July 2007 to 17 June 2008 for additional deaths. The search revealed one spontaneous report of death, a 59-year-old male patient that committed suicide after being on VGB for more than 22 years. (Section 4.4.8.2) Additionally, 140 patients died in the UK Prescription Event Monitoring (PEM) Study (Section 4.4.8.2)

4.4.8.1 Deaths in Epilepsy and IS Studies

Sixty-three patients across all age groups died during a primary or secondary epilepsy/IS clinical study (U.S. studies, n=44; non-U.S. primary studies, n=8; non-U.S. secondary studies, n=9; EMEA/CHMP Article 12 referral studies, n=2). The 2 most common reported causes of death were seizure (n=22) and SUDEP (n=18). The remaining events reported in >1 and <5 patients were respiratory events, aspiration, cancer, cardiovascular events, coronary artery atherosclerosis, drowning, hypoxia, myocardial infarction, and trauma. For several patients, there were multiple listed events contributing to that patient's death. Additionally, some deaths were categorized in multiple ways for summarization. For example, Patient 071-009 from Study 7154-3-C-026 had a single cause of death of drowning (investigator term). However this cause of death was summarized under "Seizure (all)" and "SUDEP".

4.4.8.2 Deaths from Additional Sources and Studies

Forty-nine patients across all age groups died during non-U.S. non-CRF studies (n=8), non-epilepsy/IS studies (n=2; tardive dyskinesia study, clinical pharmacology study), Japanese studies (n=11), postmarketing studies (n=5), non-U.S. compassionate use (n=17), and miscellaneous sources (n=6). The 6 deaths from miscellaneous sources include 2 patients who died during an independent Investigational New Drug (IND) study and 4 cases reported as deaths during a retrospective review of data in IS patients in Europe. The most common cause of death in these 49 patients receiving VGB was seizure or seizure-related causes which occurred in 36.7% (18/49) of deaths. Other less frequently reported causes of death included infectious disease (20.4%; 10/49), suicide (16.3%; 8/49), and drowning (14.3%; 7/49). For several patients, there were multiple listed events contributing that patient's death.

Sixty-seven deaths were reported during postmarketing surveillance through 30 June 2007 that are not included in the 112 total VGB deaths. Forty-nine deaths were spontaneously reported through 15 March 1997 and 18 deaths were spontaneously reported from 15 March

1997 through 30 June 2007 and are summarized in the December 2007 NDA submission. For purposes of this Briefing Document, the postmarketing database was searched from 01 July 2007 to 17 June 2008 for additional deaths. The search revealed one spontaneous report of death, a 59-year-old male patient that committed suicide after being on VGB for more than 22 years.

Additionally, 140 patients died in the UK Prescription Event Monitoring (PEM) Study. This study was a postmarketing surveillance epidemiology survey with limited data collection and unknown patient compliance. More importantly, some of the deaths described in the UK PEM Study may be duplicate reports of deaths also included in the spontaneous sources, but with the limited information provided by the UK PEM Study group, duplicate patients cannot be identified. The rate of death in the UK PEM Study was 1.4% (140/10178), similar to that observed in completed VGB clinical studies. The most common cause of death was seizure, which accounted for 22% of the deaths.

Table 20. Patient Listing of Deaths Through 30 June 2007

Patient ID/Study #	Database or Other Source of Data	Non-IS Epilepsy or IS Study?	Sex	Age at death	VGB Dose (last dose prior to death)	Cause of Death
006-003 / 097-006	U.S.	Non-IS Ep	M	36	4 g/day	Coronary atherosclerosis / seizures
012-007 / 097-006	U.S.	Non-IS Ep	M	49	2 g/day	Atherosclerotic heart disease
012-009 / 097-006	U.S.	Non-IS Ep	M	37	3 g/day	Asphyxiation / seizures
012-013 / 097-006	U.S.	Non-IS Ep	M	29	3 g/day	Multiple traumatic injuries secondary to blunt force trauma
067-010 / 7154-3-C-024	U.S.	Non-IS Ep	F	35	3 g/day	Suicide by CBZ intoxication
070-010 / 7154-3-C-026	U.S.	Non-IS Ep	F	20	3 g/day, d/c 5 days prior	Seizure
071-009 / 7154-3-C-026	U.S.	Non-IS Ep	M	41	3 g/day	Drowning
058-001 / 71754-3-C-028	U.S.	Non-IS Ep	M	34	5 g/day	Seizure disorder (epilepsy)
1193-0014 / VGPR0098	U.S.	Non-IS Ep	M	34	4 g/day	Intracranial hemorrhage
1204-0003 / VGPR0098	U.S.	Non-IS Ep	M	34	3 g/day	Epileptiform seizure disorder
1219-0006 / VGPR0098	U.S.	Non-IS Ep	M	35	2 g/day	Seizure disorder and drowning
1225-0013 / VGPR0098	U.S.	Non-IS Ep	M	23	3 g/day	Cerebral hypoxia due to a seizure
1228-0001 / VGPR0098	U.S.	Non-IS Ep	F	69	0.25 g/day (d/c 6 wks prior)	Lung cancer
1230-0006 / VGPR0098	U.S.	Non-IS Ep	M	25	6 g/day	Suspected status epilepticus
1241-0012 / VGPR0098	U.S.	Non-IS Ep	M	38	3 g/day	Aspiration
1247-0004 / VGPR0098	U.S.	Non-IS Ep	M	32	3 g/day	Possible grand mal seizure
1189-0013 / VGPR0098	U.S.	Non-IS Ep	M	38	4 g/day	Prolonged hypoxia due to seizure
1199-0013 / VGPR0098	U.S.	Non-IS Ep	F	45	3 g/day	Intracerebral hemorrhage
1206-0001 / VGPR0098	U.S.	Non-IS Ep	F	44	6 g/day	Status epilepticus
1237-0020 / VGPR0098	U.S.	Non-IS Ep	M	45	5 g/day	Sudden unexpected death due to severe chronic epilepsy
1238-0016 / VGPR0098	U.S.	Non-IS Ep	M	52	3 g/day	Sudden cardiac death
1238-0018 / VGPR0098	U.S.	Non-IS Ep	F	25	2.5 g/day	Seizure
1246-0002 / VGPR0098	U.S.	Non-IS Ep	F	37	3.5 g/day	Seizure disorder
1247-0010 / VGPR0098	U.S.	Non-IS Ep	F	47	5 g/day	Acute myocardial infarction, ventricular fibrillation
1224-0007 / VGPR0098	U.S.	Non-IS Ep	M	34	3.5 g/day	Chronic seizure disorder resulting in cardiac arrest

Table 20. Patient Listing of Deaths Through 30 June 2007

Patient ID/Study #	Database or Other Source of Data	Non-IS Epilepsy or IS Study?	Sex	Age at death	VGB Dose (last dose prior to death)	Cause of Death
13490007 / 0101	U.S.	Non-IS Ep	F	43	VGB; dose not available	Possible seizure and pulmonary edema
13440002 / 0101	U.S.	Non-IS Ep	M	34	3 g/day	Cerebral hypoxia due to a seizure
15071001 / 0242	U.S.	Non-IS Ep	M	41	4 g/day	Head injury secondary to motor vehicle accident
15410003 / 0242	U.S.	Non-IS Ep	M	36	3 g/day	Seizure disorder
15450004 / 0242	U.S.	Non-IS Ep	M	24	4 g/day	Myocardial infarction
11920014 / 0098	U.S.	Non-IS Ep	F	48	5.5 g/day	Seizure
12040015 / 0098	U.S.	Non-IS Ep	F	30 @ entry	5 g/day	Pneumonia, respiratory arrest
12110008 / 0098	U.S.	Non-IS Ep	M	38 @ entry	not available	Grand mal seizure, sudden death
12300010 / 0098	U.S.	Non-IS Ep	M	46 @ entry	6 g/day	Pneumonia, pulmonary carcinoma, multiple organ failure
12340002 / 0098	U.S.	Non-IS Ep	M	52 @ entry	not available	Myocardial infarction
12370012 / 0098	U.S.	Non-IS Ep	M	54 @ entry	not available	Carcinoma
13030106 / 0098	U.S.	Non-IS Ep	M	63	not available	Myocardial infarction
13040002 / 0098	U.S.	Non-IS Ep	M	53 @ entry	3.5 g/day	Myocardial infarction
13040004 / 0098	U.S.	Non-IS Ep	M	35	3 g/day until patient self-reduced	Seizure
15400001 / 0242	U.S.	Non-IS Ep	M	59 @ entry	4 g/day	Adenocarcinoma
16210007 / 0201	U.S.	Non-IS Ep	F	17	1 g/day	Hepatic necrosis with multisystem organ failure
W-148-007 / 71754-3-W-007	Non-U.S. primary	Non-IS Ep	M	64	1 g/day, d/c 5 days prior	Valvular cardiac failure
W-101-038 / 71754-3-W-007	Non-U.S. primary	Non-IS Ep	F	69	3.5 g VGB, d/c 2 days prior	Myocardial infarction, stomach ulcer and gastrointestinal bleeding
068-049 / 097-335	Non-U.S. primary	Non-IS Ep	M	61	3 g/day	Drowning
W-101032 / 71754-3-W-007(LT)	Non-U.S. primary	Non-IS	F	50	2 g/day	Malignant glioma
068-046 / 097335(LT)	Non-U.S. primary	Non-IS	M	52	3 g/day	Cardiomyopathy and heart failure
125701-P3 / VIGA/4/ST/01	Non-U.S. primary	Non-IS	F	35	4 g/day	Bronchial pneumonia

Table 20. Patient Listing of Deaths Through 30 June 2007

Patient ID/Study #	Database or Other Source of Data	Non-IS Epilepsy or IS Study?	Sex	Age at death	VGB Dose (last dose prior to death)	Cause of Death
125701-P22 / VIGA/4/ST/01	Non-U.S. primary	Non-IS	M	44	0.5 g/day	Subdural hematoma secondary to fall
21202 / 097-306	Non-U.S. secondary	Non-IS	M	60	4.5 g/day, d/c 5 days prior	Heart failure secondary to metastatic small cell lung carcinoma
25310 / 097-306	Non-U.S. secondary	Non-IS	M	38	3 g/day	Status epilepticus following general aesthetic for knee surgery
25816 / 097-306	Non-U.S. secondary	Non-IS	F	60	3 g/day	Acute pulmonary edema and cardiogenic shock
30330006 / 097-306	Non-U.S. secondary	Non-IS	F	32	4.5 g/day	Generalized seizure
30330028 / 097-306	Non-U.S. secondary	Non-IS	M	45	4.5 g/day	Colonic adenocarcinoma with hepatic metastases
30430415 / 097-306	Non-U.S. secondary	Non-IS	M	36	4 g/day	Coronary artery disease
30330048 / 097-345	Non-U.S. secondary	Non-IS	F	23	4 g/day	Thought to have died during a seizure
32330925 / 097-345	Non-U.S. secondary	Non-IS	F	28	2 g/day	Drowned in bathtub following a seizure
41931404 / 094-345	Non-U.S. secondary	Non-IS	M	42	2.75 g/day, d/c ~3 wks prior	Aspiration pneumonia - vomited during tonic-clonic seizure
00340014 / 4020	non-U.S.; EMEA/CHMP Article 12 referral study	Non-IS	F	56 @ entry	500 mg/day	Not reported
0405010 / R003	non-U.S.; EMEA/CHMP Article 12 referral study	Non-IS	M	58 @ entry	not available	Convulsion
702103 / 71754-3-W-019	Non-U.S. primary	IS	F	1	0.43 g/day	Cardiac arrest
461 / 1A	U.S.	IS	F	10.7 months	not available; d/c ≥3 weeks prior to death	Pneumonia
559 / 1A	U.S.	IS	F	3 months	148.8 mg/kg	Pulmonary hemorrhage secondary to pulmonary angiomatosis
911 / 1A	U.S.	IS	F	7 months	195 mg/kg	Sudden death
24173 / 097-241	Non-U.S., non-CRF	No	M	15	1.5 g/day, d/c 2.5 months prior	Progression of disease (familial myoclonic epilepsy)

Table 20. Patient Listing of Deaths Through 30 June 2007

Patient ID/Study #	Database or Other Source of Data	Non-IS Epilepsy or IS Study?	Sex	Age at death	VGB Dose (last dose prior to death)	Cause of Death
533300024 / 097-300	Non-U.S., non-CRF	No	F	35	4 g/day	Seizure
533300045 / 097-300	Non-U.S., non-CRF	No	F	46	Unknown, d/c 6 months prior	Unknown
33131405 / 097-314	Non-U.S., non-CRF	No	M	51	4 g/day	Myocardial infarction
36631403 / 097-314	Non-U.S., non-CRF	No	M	25	2 g/day	Suicide
36731401 / 097-314	Non-U.S., non-CRF	No	M	44	2 g/day	Died as passenger in car accident
124701-P5 / SAB 0190/5	Non-U.S., non-CRF	No	M	39	2 g/day	Suicide
20204 / 097-202	Non-U.S., non-CRF	No	M	41	2 g/day	Suicide
015-007 / 7154-1-C-014	Non-U.S. primary	No	M	24	2 single doses: 0.5 g (9 days prior) and 1 g (5 days prior)	Trauma secondary to motorcycle accident
22407 / 097-224	Non-U.S. primary	No	F	73	2 g/day (but had taken placebo for 5 days prior to death)	Occult infection and respiratory insufficiency
30330052 / 097-300	Non-U.S. compassionate use	No	F	38	6 g/day	Astrocytoma
30330090 / 097-300	Non-U.S. compassionate use	No	M	59	3.5 g/day	Cardiac disease
36130001 / 097-300	Non-U.S. compassionate use	No	F	16	2 g/day	Metastatic malignant brain tumor
40630001 / 097-030	Non-U.S. compassionate use	No	M	21 months	0.75 g/day	Severe epilepsy
30733301 / 097-333	Non-U.S. compassionate use	No	F	15	3 g/day	Suicide
31533301 / 097-333	Non-U.S. compassionate use	No	M	44	2 g/day	Suicide
34033399 / 097-333	Non-U.S. compassionate use	No	F	9.5 mos	0.5 g/day	Prolonged infection

Table 20. Patient Listing of Deaths Through 30 June 2007

Patient ID/Study #	Database or Other Source of Data	Non-IS Epilepsy or IS Study?	Sex	Age at death	VGB Dose (last dose prior to death)	Cause of Death
39933301 / 097-333	Non-U.S. compassionate use	No	M	34	1.5 g/day	Pneumonia following seizure
40133328 / 097-333	Non-U.S. compassionate use	No	M	7	Unknown	Asphyxiation - choked on a toy
43533301 / 097-333	Non-U.S. compassionate use	No	F	25	3 g/day	Status epilepticus
45433301 / 097-333	Non-U.S. compassionate use	No	M	10	1 g/day	Pneumonia following prolonged status epilepticus
32334551 /	Non-U.S. compassionate use	No	F	33	2.5 g/day	Seizure possibly precipitated by bronchopneumonia
31730707 /	Non-U.S. compassionate use	No	M	39	3.5 g/day	Acute liver insufficiency
VGST-AU16-0001 / IPU	Non-U.S. compassionate use	No	M	46	3 g/day	Partial status epilepticus following surgery for recurring oligodendroglioma
VGST-AU17-0001 / IPU	Non-U.S. compassionate use	No	M	28	3 g/day	Suicide or accidental drowning
VGST-SW03-00PY /	Non-U.S. compassionate use	No	F	58	4 g/day, d/c 1.5 months prior	Metastatic breast carcinoma
VGST-F101-0001 /	Non-U.S. compassionate use	No	M	40	1 g/day	Seizure while eating
202-180-05 / JGVG-CL-202	Japanese studies	No	F	46	4 g/day	Drowned in bathtub, possibly following seizure
202-06Y-06 / JGVG-CL-202	Japanese studies	No	F	34	3 g/day, d/c 1.6 months prior	Fulminant hepatitis
202-15M-02 / JGVG-CL-202	Japanese studies	No	F	59	3 g/day	Drowned in bathtub, secondary to seizure
26T-01 / JGVG-CL-202	Japanese studies	No	F	23	2 g/day, d/c 1 month prior	Acute heart failure
25K-05 / JGVG-CL-401	Japanese studies	No	M	36	4 g/day	Drowning due to seizure
01A-02 / JGVG-CL-401	Japanese studies	No	M	35	3 g/day	Drowning due to seizure
13J-04 / JGVG-CL-401	Japanese studies	No	M	23	3 g/day	Suicide

Table 20. Patient Listing of Deaths Through 30 June 2007

Patient ID/Study #	Database or Other Source of Data	Non-IS Epilepsy or IS Study?	Sex	Age at death	VGB Dose (last dose prior to death)	Cause of Death
12-4 / JGVG-CL-302A,B	Japanese studies	No	M	18	not available	Drowning due to a seizure
63-2 / JGVG-CL-302A,B	Japanese studies	No	M	37	not available	Suicide-hanging
71-02 / JGVG-CL-302A,B	Japanese studies	No	M	21	not available	Cerebral hypoxia due to pneumonia following status epilepticus
17-2 / JGVG-CL-302A	Japanese studies	No	F	39	not available; VGB d/c 1 yr prior	Drowning
2401 / 71754-3-F-2	Postmarketing studies	No	M	39	2 g/day	Head injury secondary to fall from complex partial seizure
3141 / 71754-3-F-2	Postmarketing studies	No	M	30	2 g/day	Generalized seizure resulting in fall from bed with facial impact and probable suffocation
4181 / 71754-3-F-2	Postmarketing studies	No	M	64	2 g/day, d/c 3 weeks prior	Relapse of oligodendroglioma; intracranial hypertension
0004 / 097-WFR-01	Postmarketing studies	No	M	22	2 g/day	Injuries from bicycle collision with car
0008 / 097-WFR-01	Postmarketing studies	No	M	26	2 g/day	Injuries from motorcycle accident
VGSD-0005-5023 / 95-N-0008	Miscellaneous	No	F	39	4.75 g/day	Possible seizure complicated by aspiration, asphyxiation, or cardiac arrhythmia
07-07-07 / 71754/III/E/01	Miscellaneous	No	M	28 months	147 mg/kg/day	Cardiac arrest; septic shock pneumonia
11-03-22 / 71754/III/E/01	Miscellaneous	No	F	17 months	80 mg/kg/day	Bronchopneumonia
02-02-02 / 71754/III/E/01	Miscellaneous	No	M	33 months	200 mg/kg/day	Sudden infant death
08-02-01 / 71754/III/E/01	Miscellaneous	No	M	5 months	64 mg/kg/day	Renal infection, CMV infection, interstitial pneumonia
VGSD-0006-0005 / VGSC0006	Miscellaneous	No	F	17	3.75 g/day	Pneumonia, respiratory failure
TOTAL Vigabatrin Deaths Through 30 June 2007 = 112						

4.4.9 SUDEP

In U.S. and primary non-U.S. clinical studies of 4079 VGB-treated patients**,** 18 patients were reported to have sudden and unexplained deaths (estimated minimum 7091 PYs of exposure). This represents an incidence of 1.9 deaths per 1000 PYs. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of SUDEP in patients with epilepsy not receiving VGB (ranging from 0.5 per 1000 PYs for the general population of epilepsy patients, to 4 per 1000 PYs for recently studied clinical trial populations similar to the population in the clinical development program for VGB, to 5 per 1000 PYs for patients with refractory epilepsy). The estimated SUDEP rate in patients receiving VGB was similar to that observed in patients receiving other AEDs who underwent clinical testing in a similar population at about the same time.

4.4.10 Psychiatric Events

In U.S. and primary non-U.S. clinical epilepsy and IS studies of 4079 VGB-treated patients, the most common psychiatric event was depression, reported in 8.2% (334 of 4079) of VGB-treated patients. Insomnia and irritability were each reported by 6.6% of VGB-treated patients. Less than 1% of patients reported either psychotic disorder or hallucination as an AE and no deaths were attributed to these events in any U.S., primary non-U.S., or secondary non-U.S. study. Confusional state was related to patient death in 1 VGB-treated patient.

In the *Controlled Non-IS Epilepsy Population* of 588 VGB-treated patients and 373 placebo-treated patients, more placebo-treated than VGB-treated patients reported AEs of irritability or insomnia. Depression and confusional state were reported more frequently in VGB-treated patients (7.8% and 5.4%, respectively) than in placebo-treated patients (4.6% and 1.6%, respectively). The rates of these events that met the criteria for serious events were: 1.2% VGB vs 0.5% placebo for depression, and 1.0% VGB vs 0% placebo for confusional state (Table 14). The rates of discontinuation due to depression or confusional state for VGB-treated patients compared with placebo were: 1.7% VGB vs 0.5% placebo for depression, and 0.7% VGB vs 0% placebo for confusional state (Table 18).

In the *Controlled IS Patients Population* of 261 VGB-treated patients and 20 placebo-treated patients, AEs of irritability and insomnia were reported by 16.9% and 9.6% of VGB-treated patients, respectively, compared with 0% of placebo-treated patients. This difference could be attributed to a shorter duration of exposure to placebo compared with VGB (see Section 5.4.3.1). None of the events were considered serious. One VGB-treated patient discontinued a study due to irritability.

A review of the postmarketing database of spontaneous reports received from 15 March 1997 through 30 June 2007 revealed a total of 3202 AEs reported in 1791 reports for patients treated with VGB. The most commonly reported AEs in the psychiatric disorders system organ class during this time period were agitation, reported in 28 (1.6%) of all reports, confusional state (23 reports, 1.4%), psychotic disorder (23 reports, 1.3%), depression (21 reports, 1.2%), aggression (18 reports, 1.0%), abnormal behavior (13 reports, 0.7%), anxiety (9 reports, 0.5%), and hallucinations (9 reports, 0.5%). Suicide-related events are discussed in Section 4.4.11.

A search of terms in the postmarketing database (15 March 1997 through 30 June 2007) including psychosis, agitation, aggression, confusion, behavioral change, and hallucinations identified 56 reports containing sufficient information for analysis. Of these, 17 were reports of patients 17 years of age or younger, 10 were of patients 60 years of age or older, and 29 were of patients ranging from 25 to 59 years, inclusive. Of the majority of reports in which concomitant AEDs were listed (and there was at least 1 concomitant AED), 13 reports listed 1 additional AED (concomitant with VGB), 10 reports described 2 concomitant AEDs, and 4 patients were on more than 2 concomitant AEDs. Patients were on a range of VGB doses and there was no consistent trend between dose and severity of AEs.

4.4.11 Suicidality

Studies in FDA Request: In March 2005 FDA requested that all sponsors of AEDs submit data from placebo-controlled studies to assess a possible association between AEDs and suicidality events. For VGB, 9 studies (including 634 VGB patients and 418 placebo patients) met the criteria for inclusion in the assessment. In these studies, 5 (0.79%) VGB patients and 1 (0.24%) placebo patient were classified as having suicidality events. Among the VGB patients, the suicidality events included 1 completed suicide, 2 suicide attempts, 1 patient with preparatory acts toward imminent suicidal behavior, and 1 suicidal ideation; for placebo patient, the event was suicidal ideation. The completed suicide was Patient 067-010 from Study 024, who died of carbamazepine intoxication.

Overall SAE Population: In controlled and uncontrolled studies that comprise the overall SAE population (including the above 9 studies in the FDA assessment) of 4740 patients, there were a total of 24 SAEs related to suicidality. This corresponds to a frequency of 0.5%, or 4.1 events per 1000 PYs (based on total exposure of 5849 PYs). In studies 0098 and 4021, which were summarized separately and not included in the SAE population, there were 3 SAEs of suicide attempt and 1 SAE of suicide ideation.

Overall Deaths: As noted in Section 4.4.8, there were a total of 112 VGB deaths from prospective and retrospective clinical studies and compassionate use through 30 June 2007, 9 of which were suicides. One suicide occurred in a clinical study in the integrated database; this is the completed suicide referred to in the FDA request paragraph above. The remaining 8 suicides were from additional non-integrated studies and sources, as follows: 3 from non-U.S., non-CRF studies, 3 from non-U.S. compassionate use studies, and 2 from Japanese studies.

Postmarketing: The previous sponsor reported 3 successful suicides through 15 March 2007. A search of the postmarketing database for reports received from 15 March 1997 through 30 June 2007 (with over one million patients exposed to VGB during this timeframe) revealed 9 additional suicide-related reports: 3 reports of suicidal ideation, 4 reports of suicide attempt and 2 reports of completed suicide. Time on VGB was 6 months or less in 4 of the 9 cases, 4 to 10 years in 3 cases, and not specified in 2 cases. One of the 2 fatal reports included information on past medical history; that patient had significant depressive history and alcohol abuse.

For purposes of this Briefing Document, the postmarketing database was searched from 01 July 2007 to 17 June 2008 for additional cases of completed suicides. The search revealed one 59-year-old male patient that committed suicide after being on VGB for more than 22 years.

4.4.12 Drug Abuse and Dependence

VGB has not been formally evaluated in a human abuse liability study. However, an evaluation of AEs from human clinical studies and international postmarketing data show no evidence of abuse potential, nor is there evidence of psychological or physical dependence in humans. No reports of abuse or diversion of VGB were reported in several open label substance abuse treatment studies in high risk methamphetamines and/or cocaine-dependent patients.

Animal studies in the literature designed to predict human abuse and dependence did not demonstrate potential of VGB for human abuse and dependence.

4.4.13 Postmarketing Safety

Since the first marketed use of VGB in 1989, there has been extensive, cumulative postmarketing safety data from various nonclinical trial sources: spontaneous reports, literature, and from reports to regulatory authorities that establishes a well-defined safety profile in >1.5 million patients exposed. The general safety profile that has emerged is consistent with that observed in clinical studies of VGB.

4.4.14 Safety Issues of Special Concern

4.4.14.1 Peripheral Visual Field Defect (pVFD)

In 1997, nearly 8 years after initial marketing approval in the UK, the first accounts of the association of VGB with a characteristic pVFD were reported from Europe [1]. Wild et al [104] provided a detailed description of its clinical features. The pVFD was described as a slowly progressive bilateral concentric peripheral constriction (BCPC) of visual fields, generally more marked nasally than temporally, beginning after years of VGB exposure. Other investigators have agreed on this description of BCPC, but not all found the nasal predominance [105, 106]. Because only far peripheral vision was affected and central vision and color vision were spared, the pVFD was almost always asymptomatic. Patients could use head turning and other scanning maneuvers to compensate for the deficit. The typical latency of years between beginning VGB therapy and the onset of the pVFD along with its generally asymptomatic character likely contributed to the long delay between initial marketing and the recognition of the problem.

The causal relation of VGB and the pVFD was initially equivocal. However, Kalviainen et al [106] provided strong evidence of a causal relationship. They performed visual field testing on 32 VGB exposed patients from a prior randomized clinical trial of VGB monotherapy and compared them to 18 control, carbamazepine-treated patients from the same trial. Forty percent of the VGB exposed patients and none of control patients exhibited the characteristic BCPC, providing support to a causal relationship between VGB and this effect. No dose

effect could be demonstrated and the earliest onset in this series was after 29 months of VGB exposure. And, consistent with the results of Wild et al [107], visual acuity was normal in all VGB exposed patients.

In response to these and other reports, a series of postmarketing nonclinical and clinical studies were initiated, as mandated by the EMEA as a condition of continuing marketing approval under Article 12 of the European Commission Directive 75/319. Five EMEA clinical studies were initiated (Study 4020, Study 4021, Study 4102, Study 4103, Study R003); however, not all studies met intended objectives (Study 4103, R003) or led to meaningful conclusions because of limited sample sizes (Study 4021). Nevertheless, Study 4020 provided important new data, which will be discussed in detail.

Numerous investigations have added to the current knowledge of the relationship between VGB and pVFD and there is now a considerable body of information characterizing pVFD, examining pathophysiology, methods to diagnose and monitor the pVFD associated with VGB, and the incidence, prevalence, and functional impact of the defect. Available evidence varies widely in assessment methods employed and includes: case reports, retrospective studies, cross-sectional and longitudinal studies, prospective controlled studies, and postmarketing surveillance. While no single data source addresses all questions surrounding the relationship of pVFD associated with VGB treatment, in the aggregate they characterize the key issues related to pVFD.

Each data source has specific strengths and limitations in the type and level of evidence provided, and the available evidence should be considered to best characterize pVFD. Table 21 summarizes the key clinical issues that will be discussed in this section, and the specific supportive data source referenced.

A subset of 6 data sources is most relevant in addressing the key issues regarding the characterization of pVFD: Study 4020 [108], Malmgren et al [105], Kinirons et al [109], the University of Glasgow Study, the University of Toronto Study, and the Postmarketing Database. Of the available literature, these studies were considered to be most informative based on the quality of study design and methodology used. Other studies are referenced as appropriate.

Study 4020 conducted at the request of EMEA was the largest and most comprehensive study of prevalence, incidence, clinical course, and quality of life consequences of the pVFD. Malmgren et al conducted a careful study of patients undergoing epilepsy surgery with perimetry performed by an expert; this study provides information concerning prevalence and rate of progression. Kinirons et al carried out a cross-sectional study of 93 patients from an epilepsy clinic taking VGB and has good dosing information and expertly performed perimetry. The University of Glasgow study has detailed information on visual acuity and color vision. The University of Toronto study is the only extensive database on retinal function in infants, using ERG as a measure. These data sources are covered in detail in order to demonstrate the range and variety of data available. Four of the 5 studies of interest are briefly summarized below. The University of Toronto Study is further covered in Section 5.4.9.1.

Table 21. Overview of Key Issues for pVFD

Characteristic	Supportive Data
Pathophysiology	Nonclinical studies, ERG data from Clinical Studies
Prevalence	Study 4020, University of Toronto Study, Malmgren et al
Incidence	Study 4020, University of Toronto Study
Severity	Study 4020, Kinirons et al
Time to Onset	Kinirons et al, Study 4020, Postmarketing, University of Toronto
Long-Term Prognosis	
Rate of Progression	Study 4020, Kinirons et al, Malmgren et al
Reversibility	Study 4020, Kinirons et al
Color Vision	University of Glasgow Study
Visual Acuity	University of Glasgow Study
Risk Factors	Study 4020, Kinirons, et al, Malmgren et al
Visual Function	Study 4020

PATHOPHYSIOLOGY OF THE VGB-INDUCED PVFD

Nonclinical studies, along with ERG studies in humans [110], demonstrated that the site of injury is the retina, and visual evoked potential and brain imaging demonstrated that optic nerve and central visual pathways are unaffected. Although in albino rodents, the initial site of injury appears to be the photoreceptors, ERG observations in humans indicate that the inner retina, especially post-receptor cone responses, is most affected. A single post-mortem examination of human retina found cell loss in all retinal layers [111]. Ophthalmoscopic observations demonstrating nerve fiber layer atrophy in some patients with VGB retinal changes [112] as well as measurements of nerve fiber layer thickness measurements with OCT [107] provide additional evidence of involvement of the inner retina.

The pathophysiological mechanism of the pVFD is unknown. One hypothesis is that elevated GABA levels contribute to retinal effects. VGB is more effectively transported into retina than into brain and consequently elevations of tissue GABA concentrations in retina are even greater than in brain [63]. Moreover, there is some evidence for retinal effects by other AEDs operating through GABAergic mechanisms, although only in rare case reports [63, [113-127]. Tiagabine, an inhibitor of GABA reuptake, has not been associated with pVFD in most investigations, [105,109,113-116,128-132] although one study was inconclusive [116] and another study reported a single asymptomatic, reversible pVFD [133].

CHARACTERISTICS OF THE VGB-INDUCED PVFD— DATA SOURCES

Study 4020

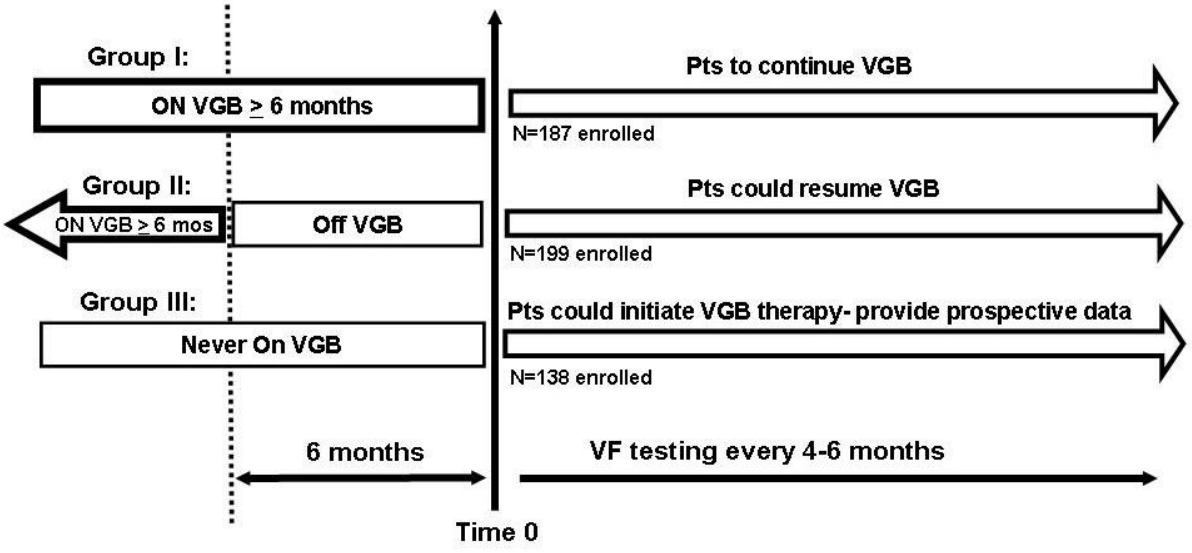
The largest and most comprehensive longitudinal study of pVFD induced by VGB is Aventis Study 4020, which formed part of the Article 12 commitment to the EMEA. Study 4020 was designed to resolve some of the inconsistencies in the literature, in particular to better define the incidence, prevalence, rate of progression and risk factors of the pVFD. Study 4020 provides comprehensive data for multiple variables for over 500 adults and children with

refractory partial epilepsy. This Good Clinical Practice (GCP)-compliant study was conducted at 46 clinical study sites in France, South Korea, Italy, Spain and Australia. The first patient was enrolled on 15 March 1999 and the last patient was enrolled on 28 April 2003. All patients completed the study by 16 June 2006.

The primary objective of Study 4020 was to determine the prevalence of the pVFD in refractory partial epilepsy treated with AEDs and with VGB in particular [1, 34]. Secondary objectives included determination of the incidence, clinical course, and impact of the pVFD on daily living. The primary study objective and many of the secondary objectives were met; however, clinical course of pVFD could not be rigorously characterized because few VGB-naive patients initiated VGB treatment during the study. The results of the analyses of the primary and secondary objectives were summarized in interim and final study reports issued by Sanofi-Aventis through June 2006. The interim analysis was summarized in a publication [1] and the final Aventis Study 4020 Clinical Study Report has been completed [108].

Additional analyses of data from the final Sanofi-Aventis database (after study closure, 16 June 2006) were undertaken by Ovation Pharmaceuticals, Inc. between 2006 and 2007. The main objectives of the Ovation analyses were: (1) to analyze quantitative information concerning the extent of visual loss in the subset of patients who underwent Goldmann perimetry; (2) to more thoroughly analyze the visual quality of life data gathered in Study 4020; and (3) to estimate prevalence and incidence of the pVFD by analyzing the occurrence of BCPC, the specific visual field abnormality induced by VGB exposure, and to apply a stringent definition of a finding of an abnormal visual field. Because of intrapatient variability in perimetry results, confirmation of an abnormal perimetry result by a second examination is generally required for research purposes. Therefore, this criterion was applied to some estimates of prevalence and incidence. Additional objectives of the Ovation analysis included characterization of the time to BCPC onset and the relationship between BCPC and duration of VGB dosing. The design of Study 4020 is illustrated in Figure 9.

Figure 9. Study 4020 Design Schematic



In order to qualify for participation in Aventis Study 4020, patients were required to be at least 8 years of age with a history of refractory partial epilepsy for a minimum of 1 year. Three groups of patients were included, with varying exposure to VGB prior to, and at the time of study entry as follows:

1. Group I: Patients who were taking VGB at the time of study entry and had been taking it for at least 6 months prior to entry.
2. Group II: Patients who had taken VGB for at least 6 months in the past but who discontinued VGB at least 6 months prior to entry.
3. Group III: Patients who had no prior VGB treatment.

Those with identified ophthalmologic pathology of known etiology were excluded from the study.

For the prospective component of the study, from the time of study entry, Group I patients were to continue VGB at the discretion of their physician and Group II patients could resume VGB at the discretion of their physician. The expectation when the study was designed was that many Group III patients would begin VGB therapy during the course of the trial and provide prospective data. However, changes in VGB prescribing patterns precluded this from happening, and in fact only 7 of the 138 Group III patients actually started taking VGB during the study, and none developed a BCPC.

The primary outcome measure of the study was perimetry. From the time of study entry, patients were to have perimetry performed every 4-6 months for 3 years. The perimetry was carried out at the individual sites using the methods available, which included static perimetry with the Humphries or Octopus systems or kinetic perimetry using the Goldmann device.

Static perimetry is performed on an automated device by testing each point in the visual field with flashing lights of varying sizes and intensity to determine the patient's threshold of detection at each point. The most widely used protocol in clinical practice tests from the fixation point out to 30 degrees of the visual field, but in Study 4020 a protocol testing between 30 and 60 degrees from the fixation point was frequently used. Kinetic perimetry is a manual method in which a technician moves a spot of light projected onto a bowl from the far periphery into the patient's visual field until the patient indicates that she or he first sees the light. Using varying sizes and intensities of lights, the perimetry of detection of each stimulus, termed an isopter, is drawn on a radial grid. Both methods of perimetry require patient attention and are subject to artifacts.

In Study 4020, many patients were tested using both methodologies. In the Aventis analysis, static perimetry was preferred over kinetic perimetry when both were available. The rationale for this choice was not stated. In general, kinetic perimetry is regarded as a more sensitive method of detecting peripheral visual field defects than static perimetry. In addition, for the method of static perimetry frequently employed in Study 4020 (testing a torus of the visual field between 30 and 60 degrees from the fixation point), normative data are not available.

In order to systematize and analyze perimetry data from these exams, which had been performed by many different individuals using varied perimetry techniques during the study, perimetries were sent by Aventis to a visual field expert (Dr. J. Wild, Cardiff School of Optometry and Vision Sciences, Cardiff University, Cardiff, United Kingdom) who conducted an independent and masked review of each patient case. Perimetry results were first classified as normal or abnormal. Abnormal examinations consisted of two categories: abnormal with identified aetiology (IAe) in which the visual field abnormality was explained by the clinical findings reported on the CRF; and abnormal with non-identified etiology (NIAe) in which BCPC and other NIAe patterns were observed. BCPCs were defined as bilateral peripheral visual field constriction most marked nasally. Dr. Wild examined the reports for the presence or absence of BCPC and these data were used to establish BCPC prevalence and period prevalence. Point prevalence was defined by Aventis in several ways (and reported as frequency): As the number and percentage of patients with BCPC at study entry, on first conclusive examination, and on last conclusive examination. Point prevalence was defined by Ovation at first conclusive perimetry, period prevalence of at least one occurrence of BCPC, and confirmed BCPC upon entry into and over the course of the study.

Of the enrolled population of 735 patients in the final locked database, 733 (99.7%) were classified and 524 (71.3%) were evaluable for analysis (ie., provided at least one conclusive perimetry outcome during the course of the study). Of the 524 evaluable patients, 126 (24%) were children (between 8 and 12 years of age) and 398 (76%) were adults (defined as over age 12). Of the evaluable population, 187 (35.7%) were enrolled in Group I, 199 (38.0%) were enrolled in Group II and 138 (26.3%) were enrolled in Group III. Children represented 20.3%, 23.6% and 29.7% of these groups, while adults comprised 79.7%, 76.4% and 70.3%, respectively.

The findings are discussed in detail in subsequent sections of this document.

Malmgren et al (2001) [105]

This study investigated the prevalence, prognosis, and possible relationship to cumulative dose in VGB-treated epilepsy patients and compared them to similar patients not exposed to VGB. To this end, 155 patients who underwent epilepsy surgery were studied. All patients had undergone pre-operative Goldmann perimetry by an expert perimetrist; 99 had been treated with VGB prior to their initial examination. Nineteen of 99 (19%) VGB-treated patients had a pVFD on initial examination, compared to 6 of 56 (11%) VGB non-exposed patients. The 19 VGB-treated patients with pVFD had been treated with VGB for a mean of 52 months (range 4-152 months), compared to 14.6 months (range 1-90 months) for those without pVFD. Moreover, there was a correlation of frequency of pVFD reported with cumulative dose, with a prevalence of 4% in those exposed to ≤ 1 kg VGB and 75% in those exposed to 3-5 kg. However, there were patients without pVFD exposed to > 7 kg.

Sixteen of 19 VGB-treated patients with pVFD were re-examined 31-124 months later. Twelve of these 19 had conclusive examinations and 5 (42%) had progressed, 7 were unchanged and none were improved. Of the 5 who progressed, 3 had continued to take VGB and 2 had discontinued the drug.

Kinirons et al (2006) [109]

This was a retrospective study of 93 patients from an epilepsy clinic treated with VGB for at least 6 months. All underwent Goldmann perimetry and the primary objective was to determine if VGB retinal effects are correlated with daily dose, duration of therapy or cumulative dose. Perimetry results were analyzed quantitatively by calculating mean radial degrees (MRD) by averaging the visual field at 12 intervals, 30 degrees apart. The normal in a control population was 53.67 degrees and an abnormal result was defined as being less than 2 standard deviations below this value (i.e., below 49.29 degrees). Forty-nine (52.7%) of patients had a pVFD by this definition, of which 15 were rated as severe (MRD < 30 degrees). In contrast to the findings of Malmgren et al, however, no correlation was found with maximum dose of VGB, duration of exposure or cumulative dose.

University of Glasgow Study

Investigators at the University of Glasgow have carried out a long-term study of visual function in epilepsy patients treated with VGB. This study has been partially supported by Ovation [129]. The University of Glasgow study was designed as a longitudinal cohort study, matching 204 adult patients with focal epilepsy on age, sex, duration of epilepsy and seizure control. A large subset of patients (n=109) had serial examinations during the study, including brain MRIs, color vision testing, acuity testing, Humphries 120 point static perimetry, ISCEV standard ERGs, dilated fundus exams, wide field multifocal ERGs, extensive quality of life and vision defect questionnaires and advanced laser retinal scanning.

Tests were performed from April 13, 1999 through June 19, 2007. Four groups of patients were studied:

- Group I: Those on VGB (n=56, average exposure 7.8 years)
- Group II: Those previously on VGB (n= 49; a minimum of two years on VGB and off drug for two years)
- Group III: Those on GABAergic drugs but not VGB (n=46)
- Group IV: Those never on GABAergic drugs (n=53).

The results of the color vision and acuity testing are that no differences were found between the four groups in color vision or visual acuity assessments. Data for visual acuity are presented below.

Postmarketing Data

Peripheral VFD was the most commonly reported adverse event in the postmarketing database through 30 June 2007. A total of 959 (53.5% of all reports) reports contained 1359 (42.4% of all adverse events) events that were specifically designated as ‘visual field defect’. An additional assessment was recently conducted on postmarketing data available through 15 May 2008 to review cases with onset of pVFD with < 1 year exposure to VGB. Of 980 total reports of pVFD (959 through 30 June 2007 and 21 from 1 July 2007 to 15 May 2008), there was one confirmed case found and that will be discussed below.

CHARACTERIZATION OF THE PVFD

Frequency of pVFD

Prevalence

A summary of pVFD prevalence values from Study 4020 and Malmgren et al are presented in Table 22. Further details on prevalence results for Study 4020 and Malmgren et al study are provided below. Because of variability in perimetry and ERG data, confirmation of an abnormal finding on a subsequent exam provides a more rigorous definition of persistent abnormality than a single abnormal finding and prevalence values are therefore provided for that criterion as well as for a single abnormal examination. Prevalence results for the University of Toronto Study are covered in detail in Section 5.4.9.1 since this data pertains to the Infantile Spasms population.

Table 22. Summary of Prevalence of pVFD

	Study 4020	Malmgren et al
Period Prevalence		
At least one BCPC occurrence	Adults: 36.5% Children: 20.0%	Adults: 19%
At least two BCPC occurrences[a]	Adults: 24.6% Children: 15.3%	--

[a.] Confirmed pVFD

The summary of pVFD period prevalence for Study 4020 is presented in Table 23. The results indicated that the prevalence of a single finding of BCPC in adults treated with VGB (Groups I and II combined) was 36.5% (45.6% of Group I, 27.6% of Group II), while the prevalence in children treated with VGB (Groups I and II combined) was 20.0% (26.3% of Group I, 14.9% of Group II). Because of inconsistencies in visual field mapping over time, a confirmed diagnosis required 2 examinations (not necessarily consecutive) demonstrating the characteristic findings of BCPC. Using this criterion, the prevalence of confirmed BCPC in adults treated with VGB (Groups I and II combined) was 24.6% (32.9% of Group I, 16.4% of Group II) and 15.3% in children (18.4% of Group I, 12.8% of Group II).

Table 23. Period Prevalence of BCPC and Confirmed BCPC – Study 4020

BCPC Endpoint	Children (N=126)				Adults (N=398)			
	I [N=38]	II [N=47]	I+II [N=85]	III [N=41]	I [N=149]	II [N=152]	I+II [N=301]	III [N=97]
At least one BCPC Occurrence	26.3 %	14.9%	20.0%	0.0%	45.6%	27.6%	36.5%	2.1%
At least two BCPC Occurrences	18.4%	12.8%	15.3%	0.0%	32.9%	16.4%	24.6%	2.1%

Incidence

As mentioned above, little information on true incidence of BCPC was available from study 4020, because few patients who were VGB-naïve at study entry initiated VGB during the study. Two approaches to assessing incidence were examined. The first considered all evaluable patients and measured surveillance from time of first dose of VGB for those who had been exposed to VGB at study entry, and from study entry for those who had not been exposed at study entry. In this approach, patients exposed to VGB did not actually come under perimetric surveillance until some time after first dose, and the time attributed to an occurrence of BCPC that had occurred prior to study entry was the time from first dose to the examination that detected the BCPC. The second approach considered a more pristine cohort, only those evaluable patients whose first conclusive perimetry examination showed them to be free of BCPC, and measured surveillance time from the first conclusive perimetry.

The summary of BCPC incidence in Study 4020 is presented in Table 24. The incidence estimates are based on PY since first exposure to VGB. For the group I patients, who were taking VGB at entry into the study, these values give an estimate of incidence of BCPC per year of exposure to VGB. Over the entire course of VGB treatment (Groups I and II combined), the incidence was 5.5 cases (7.8 cases in Group I and 3.7 cases in Group II) per 100 patient-years of treatment in adults and 3.5 cases (4.7 cases in Group I and 2.5 cases in Group II) per 100 patient-years of treatment in children. The incidence of confirmed BCPC was 3.6 cases (5.4 cases in Group I and 2.2 in Group II) per 100 patient-years in adults and 2.6 cases (3.3 cases in Group I and 2.2 cases in Group II) per 100 patient-years in children.

Table 24. Incidence of BCPC and Confirmed BCPC – Study 4020

BCPC Endpoint	Children (N=126)				Adults (N=398)			
	I [N=38] n (*)	II [N=47] n (*)	I+II [N=85] n (*)	III [N=41] n (*)	I [N=149] n (*)	II [N=152] n (*)	I+II [N=301] n (*)	III [N=97] n (*)
At least one BCPC Occurrence[a]	10/211.0 (4.7)	7/276.4 (2.5)	17/487.4 (3.5)	0/69.7 (0.0)	68/874.9 (7.8)	42/1129.1 (3.7)	110/2004.0 (5.5)	2/169.2 (1.2)
At least two BCPC Occurrences[b]	7/214.9 (3.3)	6/279.6 (2.2)	13/494.5 (2.6)	0/69.7 (0.0)	49/904.9 (5.4)	25/1144.0 (2.2)	74/2040 (3.6)	2/170.2 (1.2)

* Cases per 100 PYs of patient follow-up. In Groups I and II, patient follow-up is measured from first dose of VGB to time of event, for patients with events, or to time of last conclusive perimetry for patients without events. In Group III patient follow-up is measured from study entry to time of event, for patients with events, or to time of last conclusive perimetry for patients without events. Note that the same absolute count of BCPC events may entail different incidence rates because times at risk may vary depending on the nature of the event.

a. Unconfirmed pVFD

b. Confirmed pVFD

The second incidence analysis is limited to those patients who were free of BCPC at their first conclusive perimetry, hence represent the appearance of a new determination of BCPC during the study. There is also a difference in choice of the time origin for computing duration of exposure. In Table 24 the time origin is the first dose of VGB for those exposed

and time of enrollment for those not exposed. For Table 25 and Table 26 the time origin is the first conclusive perimetry examination. There is also a difference in the patients assumed to be at risk for the incident event. In Table 24, all 524 evaluable patients were considered at risk for BCPC and all with 2 conclusive examinations were at risk for confirmed BCPC. In Table 25 and Table 26, all patients with 2 conclusive perimetry examinations, the first being non-BCPC, were considered at risk for incidence of BCPC. Patients with 3 conclusive examinations, the first being non-BCPC, were considered at risk for incidence of confirmed BCPC. The incidence rates are somewhat different using the 2 methods, but the overall picture is similar. BCPC has a higher incidence in those continuing to take VGB during the study than in those who had stopped VGB prior to enrollment, but in the second incidence analysis the difference between children and adults is less marked. Two Group III patients, both adults, developed a BCPC during the study but neither was exposed to VGB.

Table 25. Incidence Rate (Events per 100 Patient Years) of BCPC (Patients Free of BCPC at First Perimetry Exam)-Study 4020, Children

	Patient Strata			
	I	**II**	**I+II**	**III**
With at least 2 conclusive exams, the first showing lack of BCPC	22	30	52	31
With at least one BCPC	16.2 (5.9, 35.2)	1.7 (0.0, 9.5)	7.4 (3.0, 15.2)	0.00 (NA, NA)
With at least 2 assessments of BCPC	12.6 (4.1, 29.3)	1.7 (0.0, 9.5)	6.1 (2.2, 13.3)	0.0 (NA, NA)

Note: Includes only patients who have at least 2 conclusive perimetry exams and for whom the first conclusive perimetry is free of BCPC. BCPC endpoint implies exams in addition to the first conclusive perimetry free of BCPC. Results are stated as y.y (l.l, u.u) where y.y is the resulting incidence rate as events per 100 patient years and (l.l, u.u) is the 95% confidence interval around the rate. Years of patient observation is calculated relative to date of first conclusive perimetry exam. Confidence intervals are based on the assumption that new-onset events occur as a Poisson distribution.

Program: ah_bcpc_ir_wCI.sas

Source Data: Data from Aventis Study M071754/4020 (APR2006) (Date Generated: 15OCT2008)

Table 26. Incidence Rate (Events per 100 Patient Years) of BCPC (Patients Free of BCPC at First Perimetry Exam)-Study 4020, Adults

	Patient Strata			
	I	**II**	**I+II**	**III**
With at least 2 conclusive exams, the first showing lack of BCPC	70	95	165	70
With at least one BCPC	10.3 (5.7, 17.3)	6.8 (3.5, 11.9)	8.4 (5.5, 12.2)	0.7 (0.0, 3.9)
With at least 2 assessments of BCPC	6.4 (2.9, 12.1)	2.8 (0.9, 6.5)	4.4 (2.4, 7.3)	0.7 (0.0, 3.9)

Note: Includes only patients who have at least 2 conclusive perimetry exams and for whom the first conclusive perimetry is free of BCPC. BCPC endpoint implies exams in addition to the first conclusive perimetry free of BCPC. Results are stated as y.y (l.l, u.u) where y.y is the resulting incidence rate as events per 100 patient years and (l.l, u.u) is the 95% confidence interval around the rate. Years of patient observation is calculated relative to date of first conclusive perimetry exam. Confidence intervals are based on the assumption that new-onset events occur as a Poisson distribution.

Program: ah_bcpc_ir_wCI.sas

Source Data: Data from Aventis Study M071754/4020 (APR2006) (Date Generated: 15OCT2008)

Based on the data of Study 4020, the largest study of its kind, using confirmation of an abnormal visual field examination, the estimated prevalence of confirmed BCPC in VGB exposed patients is 25% in adults and 15% in children. If one accepts only one observation of a BCPC, the prevalence is as high as 46% in Group I adults and 26% in Group I children. This range of estimates is consistent with the literature. The incidence rates assume a uniform rate of occurrence of BCPC, which may not be the case if patients are relatively

resistant to the toxicity for a period of months or, in some cases years. Nevertheless, if one uses the more conservative numbers and requires confirmation of the finding of BCPC, the estimates of risk vary from 1.6-12.7 occurrences per 100 patient years of exposure for children and 2.6-5.4 occurrences per 100 patient years in adults.

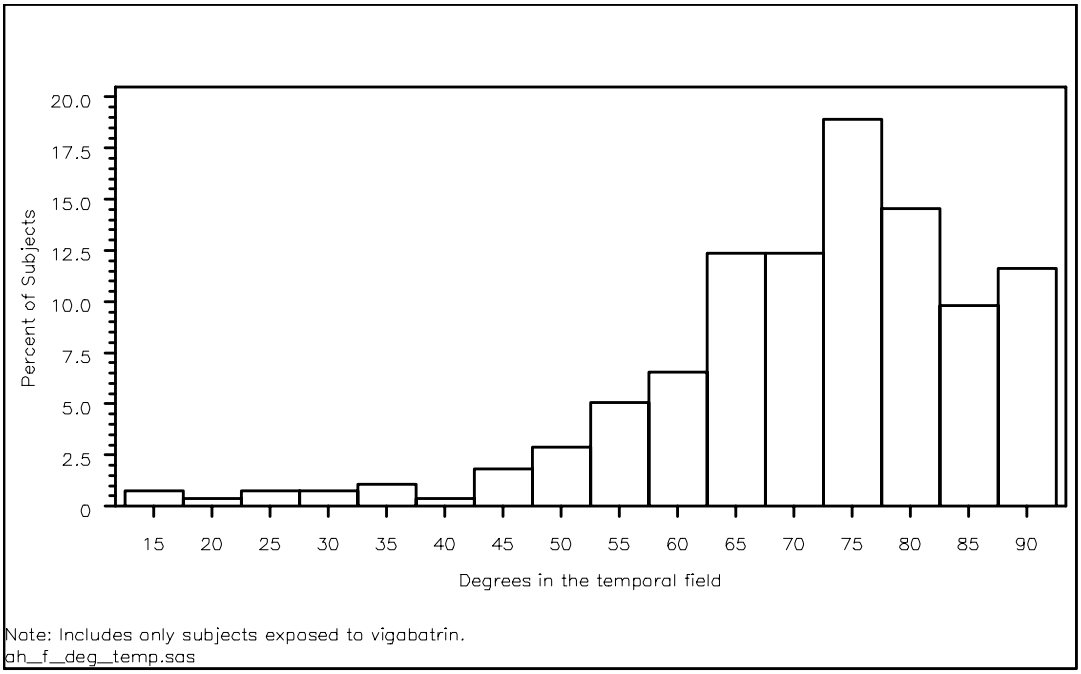
The literature has varying estimates of the prevalence and incidence of VGB-induced pVFD, as well as inconsistent observations on the correlation with maximum or cumulative dose and the influence of other risk factors. Prevalence estimates have ranged from 17% [134] to 92% [135]. The findings are summarized by Kinirons et al. [109]. This variability reflects the different populations subjected to visual field testing, differing testing methods and differing definitions of a visual field defect. Prevalence estimates in the literature mainly cluster between 40 and 60%.

Severity of pVFD

In Study 4020, both static and kinetic perimetry were performed in the majority of patients; To obtain quantitative measurements of retained vision, Goldmann visual fields were assessed by ORA Clinical Research & Development, Inc., which quantified degrees of temporal and nasal fields. Reviewers were blinded as to patient strata; all fields were viewed by two board-certified ophthalmologists with extensive experience in perimetry. They scored the extent of the patients' temporal fields to a maximum of 90 degrees. In general, there was little difference between the left and right eye extent of temporal field and the two readings were averaged within patient at each visit for further analysis.

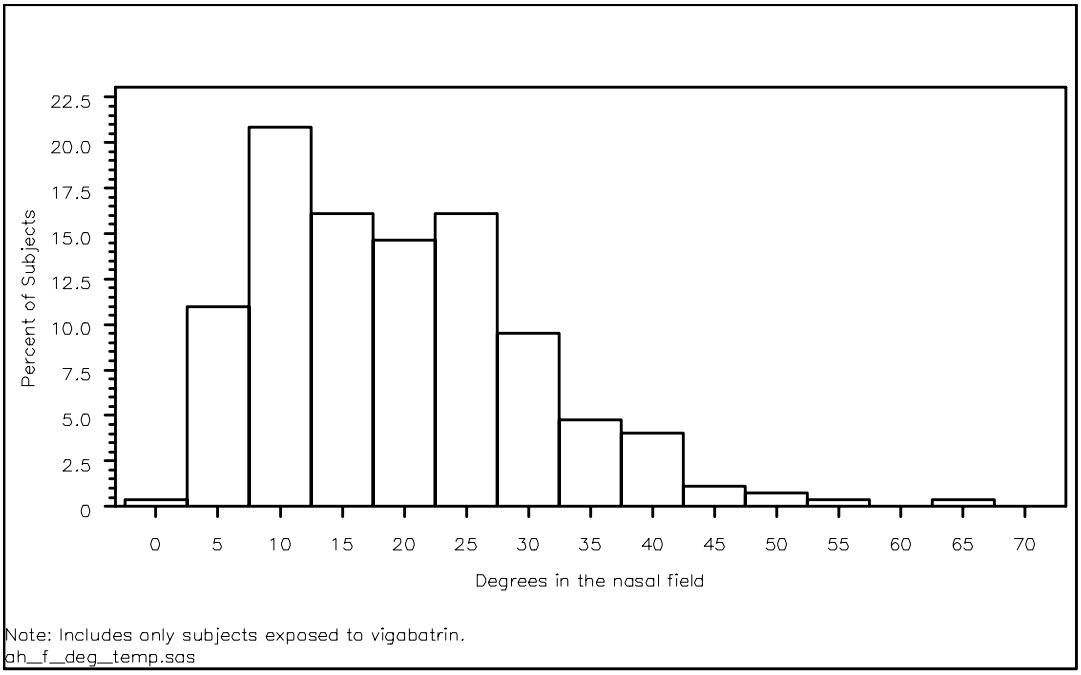
Figure 10 illustrates the Goldmann visual field data, representing the degrees of temporal field remaining at the final Goldmann perimetry examination for VGB-exposed patients. Data is presented as monocular visual field measurements. The full binocular field is the sum of the retained temporal visual fields for both eyes. At the final Goldmann examination, monocular temporal fields averaged 71.1 degrees (median 73.0 degrees), range: 13.0 to 90.0) in the VGB-exposed patients. As shown in Figure 11, the mean preserved nasal field was 19.1 degrees (median 18.0 degrees) with a range of 0 to 63.5 degrees. For reference, the normal nasal visual field is about 50 degrees in extent.

Figure 10. Distribution of Degrees Remaining in Monocular Temporal Visual Field in Vigabatrin Exposed Patients



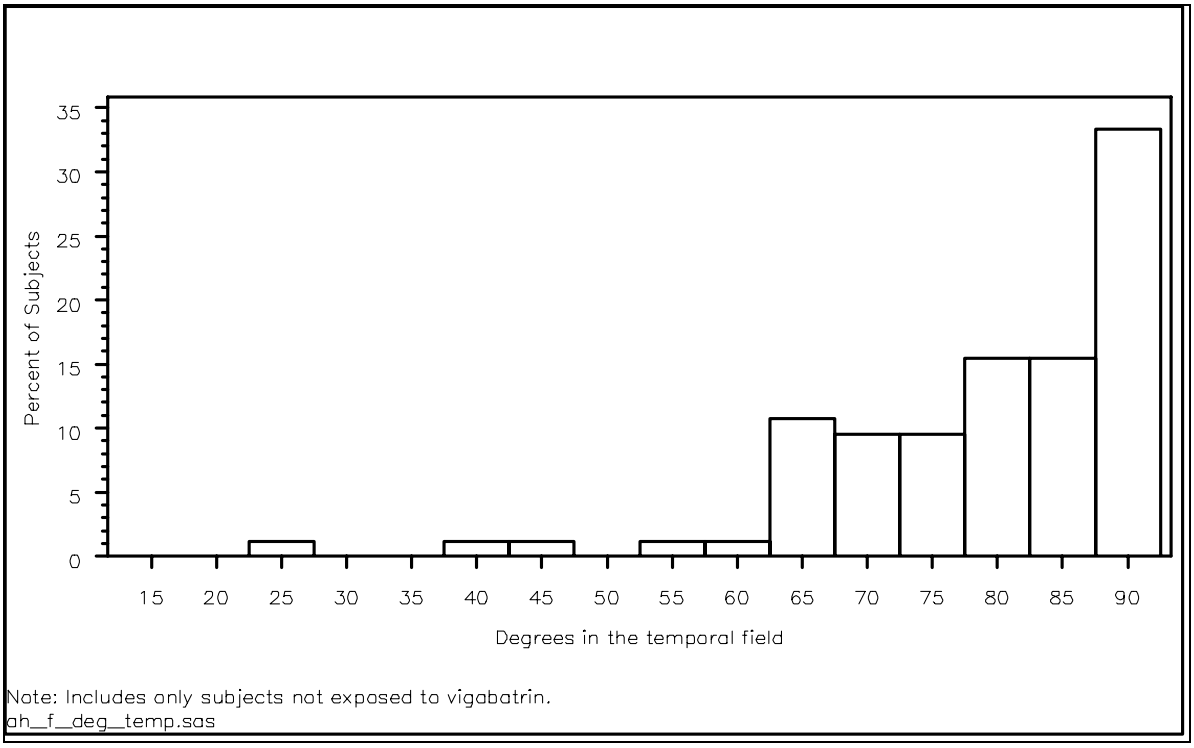
For those patients who developed BCPC, the mean retained monocular temporal visual field averaged 64.7 degrees (median 65.0 degrees, range 14.5 to 90.0). The mean retained monocular nasal field of patients with BCPC was 18.0 degrees (median 15.5 degrees, range 3.5 to 63.5).

Figure 11. Distribution of Degrees Remaining in Monocular Nasal Visual Field in Vigabatrin Exposed Patients



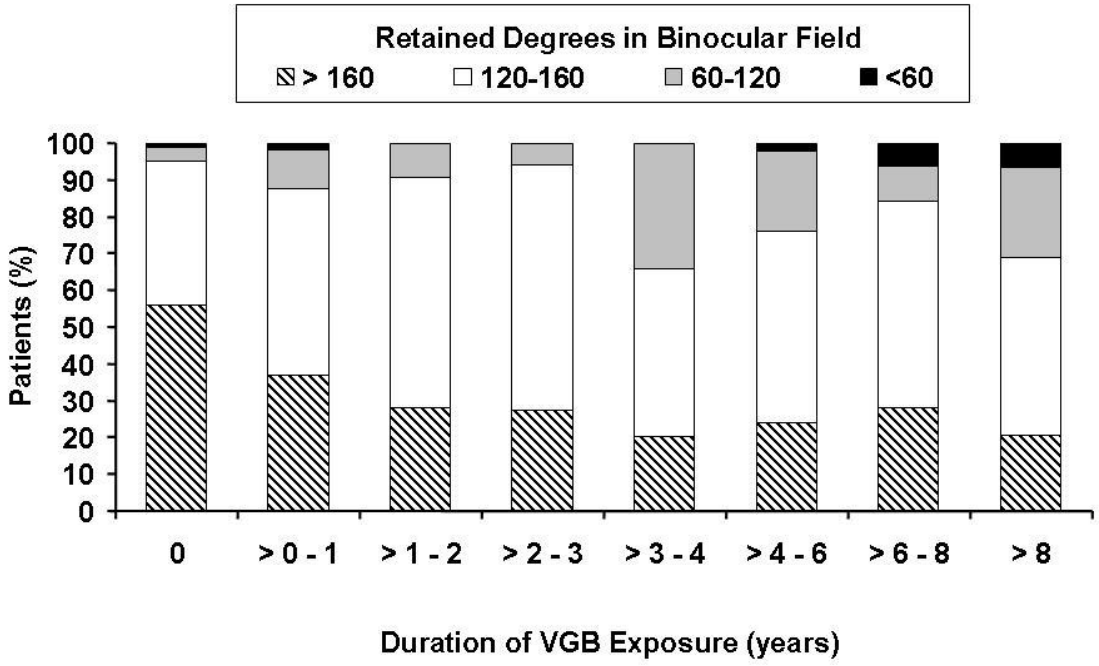
For comparison, the histogram of retained monocular temporal visual field is shown in Figure 12 for VGB-naïve patients.

Figure 12. Distribution of Degrees Remaining in Monocular Temporal Visual Field in Vigabatrin Naïve Patients



Defining a severe defect as < 30 degrees of retained temporal field (< 60 degrees binocular field), 2.4% of patients have a severe defect (Figure 13). By comparison, using a different definition of severity, in the study of Kinirons et al. [109], of 49 VGB-treated patients with a pVFD, 15 (31%) were rated as severe (MRD < 30 degrees). In the Study 4020 data, 27% of patients had unimpaired visual fields (>160 degrees of binocular visual field retained, > 80 degrees of monocular temporal field) at their final conclusive perimetry, 55% had mild impairment 120-160 degrees of retained binocular visual field, 60-80 degrees of monocular temporal field), and 16% had a moderate impairment (60-120 degrees retained binocular visual field, 30-60 degrees of monocular temporal field).

Figure 13. Severity of pVFD in Study 4020 (Goldmann Perimetry)

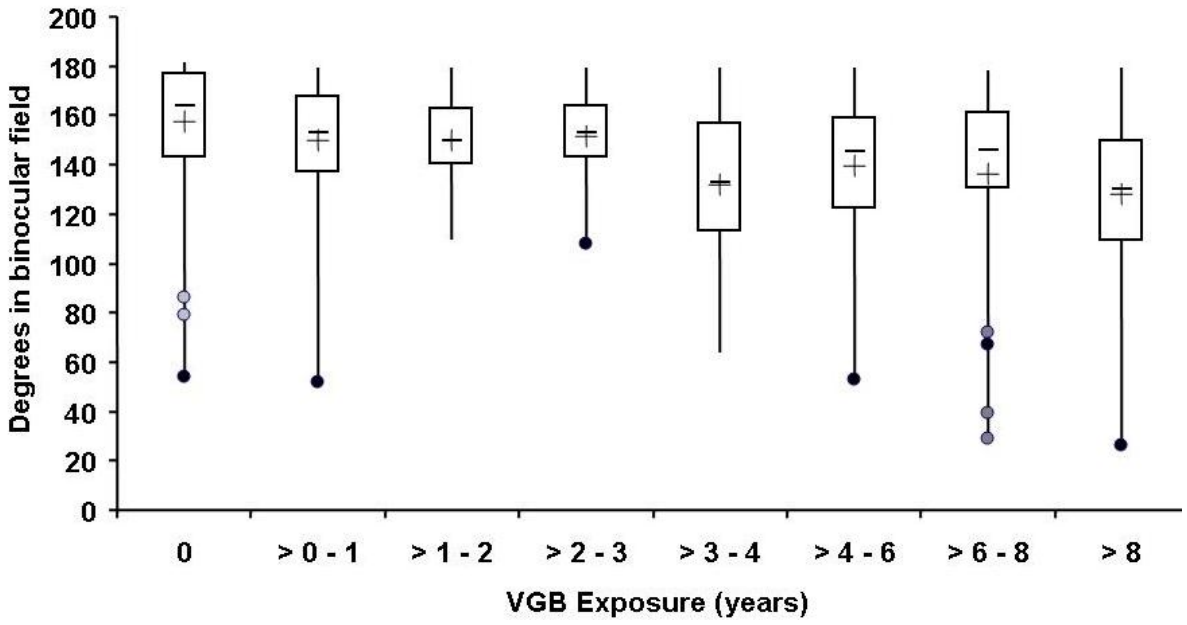


Time to Onset of pVFD

In Study 4020, the time from first VGB dose to the first observed BCPC was examined and summarized. It should be noted that ophthalmologic monitoring was performed at 4-6 month intervals and 6 months of prior exposure was required for patients in Groups I and II of the study. This limits the ability of the study to precisely determine the very earliest time to onset of pVFD. The time to onset for the entire group of patients ranged from less than 1 year to 15.1 years. The earliest detection of a BCPC occurred at 11 months in children and 9 months in adults, with the median time to onset of the first observation of BCPC ranging from 4.3 to 4.7 years, respectively. Among patients who had a confirmed BCPC, the time from the first VGB dose to the second of 2 or more observations ranged from 1.5 to 13.9 years. The mean onset to confirmed BCPC ranged from 6.5 to 8.5 years in children and 6.3 to 7.2 years in adults. Patients with BCPC generally had a longer duration of VGB dosing than those without BCPC occurrence; however, there were children and adults in the study with more than 10 years of exposure to VGB without a diagnosis of BCPC.

Another way to analyze this issue is to assess the risk of demonstrating a pVFD as a function of duration of VGB exposure. Figure 14 displays box and whisker plots of the retained binocular field for VGB-exposed and VGB non-exposed patients of Study 4020 who obtained Goldmann perimetry. The box gives the interquartile range, the horizontal line the median, the "+" the mean and the whiskers the range. As can be seen even with 0 exposure to VGB there is a wide range of quantitative visual fields and there is very little demonstrable change in the distribution for at least 3 years of drug exposure.

Figure 14. Retained Binocular Field for VGB-Exposed and VGB Non-Exposed Patients – Study 4020



The literature is consistent in reporting that pVFD occurs only after months and, in most cases, years of VGB exposure. In most reports, the earliest onset was at 1 year or greater. [104, 106, 109, 136-139] These studies are limited by their cross-sectional design as well as the time gap between patients' first exposure to VGB, and entry into the study.

In the study of Kinirons et al [109], the majority of patients had been taking VGB for a number of years prior to visual testing, and therefore little data was available to determine how quickly constriction developed. Of 3 the patients who had visual fields measured within the first year of VGB treatment, none demonstrated evidence of constriction or developed constriction during the course of the study. Of the 9 patients who had visual fields measured within 2 years of initiating VGB treatment, 4 demonstrated evidence of constriction. Of these, the shortest exposure time was 1.1 years. None of the other 5 patients demonstrated any constriction during the follow-up assessments. In the study of Malmgren et al, the earliest onset of pVFD was after 4 months of VGB exposure, but the mean duration of exposure was 52 months.

In addition there are 2 published prospective studies that had visual field and ophthalmologic assessments and initiation of VGB treatment simultaneously and that provide information regarding onset of pVFD. Fechtner et al [140] reported visual field and visual acuity results of a group of 18 patients who completed a clinical trial of VGB for cocaine and methamphetamine abuse. All patients were treated with VGB for 8 weeks, which included a 2 week dose escalation phase, a maintenance dose of 3 g/day for 4 weeks and a 2 week period of drug taper. All patients received visual acuity (Snellen chart) assessments and Humphries automated perimetry (HFA 60-4 protocol) at baseline and at 1, 4 and 8 weeks of

treatment and at a follow-up visit 4 or more weeks after stopping drug. There was no change in either visual fields or visual acuity in any patient.

Schmitz et al [141, 142] prospectively followed patients treated with VGB for CPS, predominantly with Goldmann perimetry. These investigators state that they found pVFD as early as 6 weeks after starting VGB in their study, although this is stated only in an abstract [141] and no details are provided. Moreover, they also found constriction of the visual fields in patients taking carbamazepine and without exposure to VGB, raising the question of whether a reversible pharmacologic effect or a true toxic effect was being observed. In a cross-sectional follow-up of the same patients [142], it is stated that the earliest onset reported was after 9 months of VGB exposure.

In the literature, there are rare cases of apparent onset before 6 months of exposure reported to date. In cross-sectional studies of VGB exposed patients, the minimum duration of VGB exposure associated with a well-characterized pVFD is a case of Malmgren et al [105] who developed a pVFD after 4 months of exposure. Dr. Carol Westall of the Hospital for Sick Children in Toronto, in a study of patients treated for IS (Section 5.4.9.1) examined an infant with an abnormal ERG, which was subsequently confirmed by a second abnormal ERG, after 3 months of exposure. Krauss et al (2003) reported that abnormalities in the ERG cone responses could occur in adults after as little as 6 months of VGB exposure [110].

The postmarketing database was searched for the term “visual field defect” through 15 May 2008. There were 980 cases identified. Of these, twenty nine (6.4%) were noted to have been reported within 1 year of initiation of VGB exposure. Of these, 23 either did not actually have a pVFD when the information was scrutinized, the report did not have any further description, supportive evidence or documentation of pVFD, or the event date or date of VGB treatment was missing. Of the six remaining cases, 5 had inadequate documentation of the nature of the pVFD to draw any conclusions about causality, but 1 case was well characterized and documented

This report was that of a 19-year-old woman with a confirmed pVFD after 5 weeks of taking VGB for CPS. However, the defect had recovered completely on a follow-up perimetry examination 2 months after stopping drug, so this is not a case of permanent toxicity. No other well documented case of a treatment emergent pVFD with less than 1 year of exposure was identified in the postmarketing database.

PROGRESSION/RISK FACTORS

A summary of long-term effects from Study 4020, and Kinirons et al [109], are presented in Table 27.

Table 27. pVFD Progression and Reversibility: Rate of Change of Monocular Temporal Visual Field

	Study 4020	Kinirons et al
Progression	Adults: -1.50±0.40 degrees/year of exposure Children: -0.04±0.73[a] degrees/year of exposure	Adults: 4/41 patients had progression of constriction
Reversibility[b]	Adults: -0.11±0.47 degrees/year of exposure Children: 2.05±1.24 degrees/year of exposure	Adults: 6/14 patients displayed improvement on follow-up testing[c]

a. Values for rate of progression in children are for children with less than 7.5 years of exposure.

b. Reversibility representing change in visual fields after stopping VGB.

c. Improvement was observed after discontinuation of VGB in 6 out of 14 patients who developed constriction while on VGB (out of all 24 patients who had follow-up examinations).

In Study 4020, the rate of progression of pVFD following onset was evaluated for the temporal and nasal fields of those patients who received Goldmann perimetry. The mean decrease in temporal field over time was less than 2 degrees per year in adults with current or previous exposure to VGB (-1.50±0.40 degrees/year of exposure) and less than 1 degree in children with exposure less than 7.5 years of exposure (-0.04±0.73 degrees/year of exposure). A sharp decrease is observed in the 4 children who had exposure of VGB of greater than 7.5 years (-11.70 degrees/year of exposure). This may represent a real phenomenon or the difficulty in performing perimetry in children.

Investigators have generally found that the pVFD induced by VGB neither progresses nor resolves after exposure to the drug discontinues [134, 136, 143, 144] although there are exceptional cases that appear to progress or recover [109, 143].

Additionally in Study 4020, there were two observations that suggest that it is possible that there was some loss of peripheral vision after stopping VGB, although that loss appeared to be relatively minor. One piece of evidence is the quantitative estimates of visual field loss over time. In Group I and II patients after the discontinuation of VGB; these show an average loss of 0.11 degrees per year. However, the standard error of the 0.11 result is 0.47, and Group I and II children gained an average of 2.05 degrees per year after stopping VGB. The other piece of evidence is that 1/30 children and 12/95 adults in Group II, who were no longer taking VGB went from normal visual fields to BCPC during the course of the study.

The presence of 12 adult and 1 child incident cases in Group II, i.e., patients who had discontinued taking VGB prior to entering Study 4020, raises the question of whether the pVFD can begin or progress after drug is stopped. Ovation therefore asked 2 neuro-ophthalmologists (R. Sergott MD, Director of Neuro-Ophthalmology, Thomas Jefferson

University and R. Kardon MD, Director of Neuro-Ophthalmology Service, University of Iowa) to review all incident cases of BCPC for which Goldmann perimetries were available to determine the degree of change in the visual fields after VGB was discontinued.

There were 34 incident cases of BCPC during Study 4020, that is, patients who were free of BCPC at first conclusive perimetry but who had a determination of BCPC at a later examination. Of these, there were 18 (15 adults and 3 children) for whom the first determination of BCPC occurred after the date of the last VGB dose. Goldmann perimetries were available for 24 of the 34 incident cases. From these 24, the neuro-ophthalmology reviewers identified a total of 6 cases of possible incident BCPC, all 6 of which had stopped VGB prior to the determination of BCPC. For 5 of the 6 cases, the determination of BCPC was based on a small indentation in the nasal field. The sixth case had a concentric constriction of the visual field, but the reliability of the perimetry was questioned by both neuro-ophthalmology reviewers. The other 18 cases of incident BCPC identified by the Aventis analysis were felt to be based on unreliable findings on static perimetries and were not borne out by the Goldmann visual fields.

Based on this reanalysis of the incident cases of BCPC, it is not possible to rigorously exclude the possibility that a new BCPC can occur after stopping VGB. However, any field changes that were detected after stopping drug were minor in degree and would not be expected to impact visually guided behaviors in everyday life.

In the study of Kinirons et al (2006) [109], of the 93 patients, 41 had visual field examinations while taking VGB, 24 had follow-up examinations following discontinuation of VGB, and 28 patients only had one visual field assessment. Of the 41 patients who had visual field examinations while taking VGB, 24 had normal fields on initial assessment and none showed evidence of progressive constriction on any follow-up visit. Seventeen patients had evidence of constriction at the initial assessment. Of these, 10 patients had stable fields on follow-up while still taking VGB, 3 patients had mixed results (demonstrating both worsening and improvement on follow-up), 3 patients had progressive constriction of <10%, and 1 patient had definitive progression.

Additionally in Kinirons et al, after discontinuation of VGB, 24 patients had follow-up visual field assessments. Of these 24 patients, 14 had previously developed constriction on VGB. Of these, 6 displayed improvement on follow-up testing, although none completely returned to normal. In 5/6, the degree of recovery was <10% [109]. None of the 24 progressed.

Risk Factors

Although several cross-sectional studies have failed to detect a correlation of pVFD with cumulative VGB dose or duration of exposure [104,106,109,138], others have reported a clear correlation [105, 134, 137, 138, 142]. Lawden et al reported a statistically significant correlation of extent of visual field defect and maximum daily dose, but not with cumulative dose in a cross-sectional study of 31 patients [145]. See Table 28 below. In a univariate logistic regression analysis of Study 4020, duration of VGB treatment, cumulative VGB dose, and average daily vigabatrin dose were all associated with the occurrence of BCPC.

Age and smoking were also associated, but these have not been consistently borne out in the literature.

Table 28. Relationship Between Vigabatrin Dose and Risk of Developing a Peripheral Visual Field Defect

Studies	No. of patients	Mean age, years	VGB dose, mean (range)		Frequency of VGB-induced pVFD, %	Correlation between pVFD and VGB dose
			Cumulative, kg	Daily, g		
Malmgren [105]	84	34.8	0.4 (0.02–0.9) 4.3 (3.8–4.8) 8.0 (5.9–11.4)	-- -- --	4 75 67	Prevalence of pVFD increased with increasing cumulative dose (P<0.0001)
Lawden [145]	31	32.8	4.4 (1.3–8.9)	3.1 (1.5–5.0)	39	Cumulative dose may be factor in development of pVFD
Wild [107]	432	27.5	2.3 (0.0–11.8)	--	29.8	Compared with cum. dose < 1kg, cum. dose ≥ 3kg was assoc with 8.5-fold increased incidence of pVFD
Hardus [136]	92	38.7	1.8 (SD, 1.9)	1.5 (SD, 0.6)	--	Cum: 0.49 (P<0.001) Daily: 0.67 (P<0.001)
Conway [138]	31	37.9	--	--	56	Daily: P=0.020 (right eye); P=0.012 (left eye)

Cum = cumulative; pVFD = peripheral visual field defect; VGB = vigabatrin

In Study 4020 BCPC was approximately 1.5 times more frequent in males than females. Patients with BCPC generally had a longer duration of VGB dosing than those without BCPC occurrence. However, there are children and adults in Study 4020 with more than 10 years of exposure to VGB without a diagnosis of BCPC.

Visual Acuity and Color Vision

The Glasgow data, as well as the literature, provides evidence that any effect of VGB on central vision, as measured by visual acuity and color vision, is at most very slight. Some of the early literature concerning visual function in VGB-treated patients does not clearly distinguish reversible pharmacologic effects of VGB on color vision, which are observed

while patients are taking the drug and which are shared by other AEDs, from irreversible toxic effects which persist after the drug is discontinued.

The Glasgow study provides detailed longitudinal data of visual acuity and color vision and finds no persistent abnormality on either measure. Logmar visual acuity data from the Glasgow study is given in Table 29 and demonstrates no significant differences between the 4 groups. Data on color vision are not presented in detail, but also demonstrate no significant differences. The literature has been quite consistent on the lack of effect of VGB on visual acuity when investigators have distinguished long-term toxic effects from reversible pharmacologic effects. The asymptomatic nature of the VGB-induced pVFD is further evidence of the lack of effect on central vision.

Table 29. Minimum Left and Right Eye Visual Acuity Data from Glasgow Study

	Visual Acuity (logmar units)					
Minimum Left and Right Eye	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Groups 1 & 2**	**Groups 3 & 4**
Visit 1						
n	56	49	46	53	105	99
Median	0.00	0.00	0.00	0.00	0.00	0.00
Mean	0.04	0.00	-0.00	0.03	0.02	0.01
Std Dev	0.12	0.30	0.33	0.15	0.22	0.25
Range	-0.2 : 0.5	-2.0 : 0.3	-2.0 : 0.7	-0.5 : 0.4	-2.0 : 0.5	-2.0 : 0.7
Visit 2						
n	28	20	18	24	48	42
Median	0.00	0.00	0.10	0.00	0.00	0.04
Mean	0.01	0.03	0.05	0.05	0.02	0.05
Std Dev	0.10	0.08	0.14	0.19	0.09	0.17
Range	-0.2 : 0.2	-0.2 : 0.2	-0.3 : 0.3	-0.2 : 0.7	-0.2 : 0.2	-0.3 : 0.7
Change from Visit 1 to Visit 2						
n	28	20	18	24	48	42
Median	0.00	0.00	0.00	0.00	0.00	0.00
Mean	-0.01	0.08	0.16	0.01	0.03	0.07
Std Dev	0.05	0.41	0.48	0.12	0.26	0.33
Range	-0.1 : 0.1	-0.1 : 1.8	-0.1 : 2.0	-0.2 : 0.5	-0.1 : 1.8	-0.2 : 2.0
Minimum of Visit 1 and Visit 2						
n	56	49	46	53	105	99
Median	0.00	0.00	0.00	0.00	0.00	0.00
Mean	0.03	0.00	-0.01	0.02	0.02	0.00
Std Dev	0.12	0.30	0.33	0.15	0.22	0.25
Range	-0.2 : 0.5	-2.0 : 0.3	-2.0 : 0.7	-0.5 : 0.4	-2.0 : 0.5	-2.0 : 0.7

Note: Groups are defined as follows: 1=On VGB at least two years 2=On VGB at least two years and off VGB at least two years 3=Took GABA-ergic AEDs but not VGB 4=Did not take VGB or any other GABA ergic AEDs 1 & 2=Took VGB at any time 3 & 4=Never took VGB
t_4_visual_min.rtf

Visual Function

Patients in Study 4020 were asked to fill out questionnaires concerning visual symptoms that one might expect to result from constricted visual fields (e.g., bumping into objects, difficulties walking in the street). There was a high frequency of positive responses in all groups, but in the original Aventis analysis no correlation with presence or absence of BCPC was demonstrated. The Aventis investigators questioned whether the questionnaire was adequately sensitive. If one restricts the analysis to patients with Goldmann perimetry, however, and divides the patients into those with normal temporal fields (> 160 degrees remaining binocularly), and mild (120-160 degrees), moderate (60-120 degrees) and severe (< 60 degrees) impairment, there is a weak (r = 0.16) but statically significant (p = 0.005) correlation of answering positively to at least one item on the questionnaire and degree of impairment. This substantiates the Aventis conclusion that there was not a strong correlation of BCPC and visual symptoms but does indicate that the questionnaire was in fact sensitive enough to detect differences. Overall the conclusion is consistent with the literature, which consistently reports that the pVFD is asymptomatic in the large majority of patients. See Table 30 below.

Table 30. Visual Disability at First Goldmann Perimetry by Level of Visual Impairment (All Patients)

	Visual Impairment (Degrees in Binocular Field)			
Visual Disability	**Unimpaired (>160) (N=115)**	**Mild (120-160) (N=194)**	**Moderate (60-<120) (N=44)**	**Severe (<60) (N=6)**
Difficulty in lateral vision	6 / 114 (5.3)	16 / 190 (8.4)	9 / 41 (22.0)	3 / 6 (50.0)
Need to turn head to see to the side	11 / 115 (9.6)	26 / 190 (13.7)	8 / 42 (19.0)	3 / 5 (60.0)
Worsening vision for shapes	9 / 115 (7.8)	17 / 193 (8.8)	5 / 44 (11.4)	2 / 6 (33.3)
Worsening vision for colors	6 / 114 (5.3)	6 / 193 (3.1)	0 / 44 (0.0)	0 / 6 (0.0)
Worsening vision for positions	0 / 113 (0.0)	9 / 191 (4.7)	4 / 42 (9.5)	2 / 5 (40.0)
Does not notice steps of stairs	5 / 113 (4.4)	16 / 193 (8.3)	4 / 43 (9.3)	2 / 6 (33.3)
Does not notice footpath	9 / 113 (8.0)	12 / 192 (6.3)	4 / 43 (9.3)	3 / 6 (50.0)
Does not notice other things	1 / 110 (0.9)	4 / 188 (2.1)	1 / 43 (2.3)	1 / 5 (20.0)
Bump into people from the left	11 / 113 (9.7)	15 / 190 (7.9)	5 / 39 (12.8)	3 / 6 (50.0)
Bump into people from the right	9 / 113 (8.0)	11 / 190 (5.8)	6 / 39 (15.4)	3 / 6 (50.0)
Bump into doors	13 / 115 (11.3)	15 / 194 (7.7)	10 / 44 (22.7)	2 / 6 (33.3)
Bump into wall-cupboards	8 / 115 (7.0)	14 / 194 (7.2)	6 / 44 (13.6)	2 / 6 (33.3)
Bump into walls	6 / 115 (5.2)	6 / 194 (3.1)	5 / 44 (11.4)	2 / 6 (33.3)
Bump into other things	6 / 113 (5.3)	7 / 190 (3.7)	0 / 42 (0.0)	1 / 6 (16.7)
Difficulties when walking in street	3 / 115 (2.6)	17 / 191 (8.9)	5 / 41 (12.2)	1 / 6 (16.7)
Difficulties for sport practice	2 / 104 (1.9)	5 / 171 (2.9)	0 / 35 (0.0)	1 / 5 (20.0)
Difficulty catching ball[a]	1 / 22 (4.5)	5 / 48 (10.4)	2 / 10 (20.0)	1 / 2 (50.0)
At Least One Item	34 / 115 (29.6)	64 / 194 (33.0)	25 / 44 (56.8)	5 / 6 (83.3)

[a.] Difficulty catching a ball was intended to be answered only by children. Only responses from children are included.

Program: ah_temp_vs_qol.sas
Source Data: Data from Aventis Study M071754/4020 (APR2006) (Date Generated: 27JUN2008)

These observations provide evidence that there is a mild effect of the pVFD on visual quality of life, but it generally only impacts patients with more than mild degrees of pVFD. It may be surprising that a loss of peripheral vision does not have a greater impact on daily function. However, the binocular nature of human vision renders nasal visual field defects innocuous in everyday activities. Therefore, it is more meaningful in detecting impact of quality of life to assess binocular visual fields, which depend on the temporal field vision of each eye.

Defects of the temporal visual field are more likely to affect daily function, but can be compensated by head turning and visual scanning strategies, and, unless severe, also do not have major impact on daily activities.

Other Drugs Causing Retinal Changes

Apart from AEDs, other drugs such as ethambutol, hydroxychloroquine and thioridazine can cause retinal effects [146, 147]. These latter drugs are approved for use with periodic visual monitoring recommended in their labeling.

Ethambutol, which is indicated for susceptible pulmonary tuberculosis, has been related to decreased visual acuity which can be characterized by scotoma, color blindness and/or decreased acuity. The visual monitoring recommended on the label includes visual acuity testing before beginning treatment, and then periodically during drug administration. Patients receiving doses of more than 15 mg/kg/day should have visual testing conducted monthly. The label also recommends that patients should be periodically questioned about blurred vision and other subjective eye symptoms. Recovery of visual acuity can occur over a period of weeks to months after discontinuation of ethambutol.

Hydroxychloroquine is an agent indicated for the treatment of malaria, lupus erythematosus, and acute or chronic rheumatoid arthritis. It has been found to be associated with irreversible retinal damage when taken for long-term treatments or at high doses. If prolonged treatment is contemplated, the label recommends conducting initial ophthalmologic exams, including visual acuity, expert slit-lamp, fundoscopic and visual field testing, and for testing to be repeated every 3 months. Visual symptoms may progress following discontinuation of hydroxychloroquine.

Thioridazine hydrochloride is indicated for the treatment of refractory schizophrenia. Pigmentary retinopathy has been observed in a small number of patients receiving long-term treatment with daily doses above the recommended maximum of 600 mg/day, and is rarely seen in patients taking less than that. The pigmentary retinopathy is characterized by decreased visual acuity, usually brown-tinted chromatopsia, impairment of dark adaptation, and progressive loss of vision. The label recommends that patients should be told to report changes in vision, and, if high doses are envisaged, then full ophthalmologic exams should be carried out at appropriate intervals.

Discussion and Conclusions

Based on the available evidence, the following conclusions may be drawn:

- VGB, in prolonged use, may be associated with a distinct pVFD. When the pVFD occurs, it is most often mild or moderate in degree and rarely severe. Of the patients in Study 4020 who developed BCPC, the mean retention of monocular temporal visual field was 64.7 degrees and only 2.4% of patients retained < 30 degrees monocular visual field (< 60 degrees binocular visual field retained).
- The pVFD does not impact visual acuity or color vision, hence is generally asymptomatic. However, the pVFD can cause modest disability when it is severe in degree.
- In clinical studies specifically designed to evaluate prevalence of pVFD, the estimated prevalence of confirmed VGB-induced pVFD are 25% of adult patients and 15% of children receiving long-term VGB therapy. A wide range of prevalence estimates is reported in the literature (17-92%), depending on the criteria and methodology applied to define a pVFD.
- For those who develop a pVFD, the median duration of VGB exposure at the time that the pVFD is first detected is 4.3 years (children) to 4.7 years (adults). The earliest onset seen in the long-term study conducted to evaluate pVFD was 11 months in children and 9 months in adults, however, reports of pVFD prior to 1 year of exposure to VGB are infrequent.
- The risk of developing a pVFD is associated with dose and cumulative exposure to VGB.
- The VGB-induced pVFD does not appear to begin, progress or reverse after the drug is discontinued, although the possibility cannot be rigorously excluded.

Given the above, it is prudent to attempt to detect a developing pVFD as early as possible. If a mild pVFD is detected, the evidence indicates that discontinuing the drug at that point will avoid progression of the defect and any impact on daily function. However, because pVFD does not generally have a major impact on daily function, there will be patients who choose to continue taking VGB despite evidence of an early pVFD. In those patients monitoring of visual function including patient-specific, age-appropriate visual field testing will be essential in informing ongoing discussions between the physician and patient concerning benefit-risk assessments.

Table 31 represents an overview of available visual tests based on age appropriateness and cognitive ability.

Table 31. Available Age- and Cognitive-Appropriate Tests

Methodology	Age Appropriateness[a]	Description
Confrontation testing	All	Readily performed, requires no specialized equipment.
Goldmann perimetry (kinetic)	≥9 yr	Reliable and accurate for assessing far peripheral fields, but not universally available and requires experienced operator.
Humphries perimetry (static)	≥9yr	Reliable and accurate. Widely available, not significantly operator-dependent. Not as robust in assessing far peripheral fields as central fields.
Electroretinogram (ERG)	All ages	Option for any patient that cannot perform any of the other tests. Sensitive and specific. Wide-field, multifocal ERG is under development.

[a.] Cognitive age

Standard methods of assessing visual fields in older children and adults include Goldmann kinetic perimetry and Humphries static automated perimetry [148]. Kinetic perimetry utilizes a moving stimulus of fixed intensity light around the perimeter of the visual field to determine where the light is visible by the patient. The current standard test is the Goldmann Bowl Perimeter Test.

The advantages of the Goldmann kinetic perimetry include assessment of both the peripheral and central fields, ease of interpretation, and flexibility of the procedure. Isopters, which are lines where a given size and intensity light is detectable, provide a zone of "similar visual thresholds" for the patient; the lower the light intensity, the smaller the isopter. Goldmann kinetic perimetry requires manual measurement by a technician. Fatigue and inattention of the patient can increase the number of errors.

Static perimetry including the Humphries Visual Field Analyzer Computerized Perimeter Test and similar techniques, utilize a fixed light stimulus at a specific location to determine the threshold intensity that permits perception of the light by the patient at that location in the visual field. In this type of test, the size of the stimulus light ranges from the smallest (0.25 mm^2), designated Roman numeral I, to the largest (64.0 mm^2) or Roman numeral V. The intensity of the light is designated by a combination of numbers 1 through 4 and letters a through e.

Both static and kinetic perimetry methods are operator and patient-dependent; the literature differs on which is more sensitive [149,150]. Kinetic testing is preferable in detecting lesions in the far periphery; however, kinetic methods can usually only be used in children over 9 years of age. The static method provides more information on the threshold for various areas of retinal perception [151]. Rarebit perimetry, which uses an automated microdot assessment, is reported to correlate well with injury and dose over time (cumulative dose) effects [152]. An automated kinetic method, which is now available in Humphries and Octopus systems, has been shown to provide data equivalent to the Goldmann [153]. Either static or kinetic methodology is sufficiently sensitive and specific to establish a baseline and to monitor

peripheral vision. However, in a neurologically impaired population, static perimetry may be more reproducible than kinetic perimetry, even though with an attentive patient and experienced operator, the latter is more sensitive to subtle peripheral field deficits.

Electrophysiologic measurements of retinal function can be used to assess pVFD. ERG is widely available, although it may require sedation or even anesthesia in young children and the cognitively impaired. The 30 Hz flicker response has been reported to be the most predictive of the presence and severity of VGB-induced pVFD [154,155]. Other parameters, such as cone b-wave amplitude and late OPs, are also held to be highly sensitive measures of VGB injury. Alterations of 30 Hz flicker amplitude and cone b-wave parameters which show sustained abnormality over time have been shown by Harding [154,155] to correspond to the VGB-induced peripheral field defect.

Standard visual evoked potential (VEP) methods are not useful in assessing VGB retinal changes, as VEP assesses the function of the optic nerve and central visual pathways, which are not affected by VGB.

OCT is an imaging modality which is undergoing rapid technological development and which is highly promising as a method for assessing VGB retinal effects. It is widely available, quantitative and can be used in patients with limited ability to participate in examination techniques, such as perimetry, which require prolonged periods of attention. Wild et al (2007) reported that OCT was reliable in detecting advanced VGB retinal changes. The data is not yet available comparing OCT with perimetry and ERG in detecting early toxicity. It is highly likely that OCT will be the primary modality of assessing VGB retinal effects within 5 years.

In conclusion, VGB has been associated with the occurrence of a distinct pVFD. However, patients rarely sustain a severe degree of peripheral visual field impairment sufficient to impact daily function. Moreover, the available evidence indicates that the onset of pVFD is sufficiently delayed after starting VGB to permit an early assessment of the efficacy of VGB with minimal risk of pVFD. For patients with refractory CPS who continue to derive a major benefit from VGB in managing their epilepsy, age-appropriate methods are widely available to monitor visual fields and retinal function and reliably inform an ongoing assessment of benefit and risk.

4.4.14.2 Brain MRI

Although there are no known cases of VGB-induced MRI abnormalities in patients treated for CPS, concern for such was raised initially by the finding of IME in adult rodents and dogs and by the report of Pearl et al [156] of treatment emergent MRI signal changes in infants treated with VGB for IS. The nonclinical findings of IME in animal species are discussed in Section 2.2.1 and the report of Pearl et al. [156] is summarized in Section 5.4.9.2. Evidence specifically addressing the CPS population is discussed here.

ABSENCE OF CLINICAL FINDINGS OF IME

Clinical studies of VGB conducted by the prior sponsor in adults and children with CPS included prospective surveillance with MRI. Contemporaneous review by the previous

sponsor of the original MRI reports as well as subsequent central review of the original MRI images by subspecialty experts provided no evidence of IME in these populations. The absence of IME in monkeys and humans on histologic examination and the lack of electrophysiological or imaging evidence of IME in humans led to the tentative conclusion that IME did not occur in primates.

Examinations of human brain autopsies and surgical specimens from 23 and 53 VGB-treated patients, respectively, failed to provide histologic evidence of IME. In most autopsy cases, the cerebrum, cerebellum, brain stem, hippocampus, fornix, and optic tract were inspected. Routine examinations, as well as immunohistochemical and neurofilament protein assessments, were conducted. No instances of IME-related changes, such as astrocytosis or axonal alterations, associated with VGB treatment were detected. While gliosis was found in the brains of several patients, the pattern of this abnormality did not resemble that seen in animal models and was similar to patients with chronic CPS not exposed to VGB. Furthermore, gliosis also appeared in 11 patients who had not been treated with VGB. In a review of the data by the prior sponsor, three neurologists agreed that structural brain changes normally seen in animals treated with VGB were not identified in the human population.

REPEAT REVIEW OF CPS STUDIES

The prior NDA sponsor conducted prospective MRI examinations in 7 adult and 5 pediatric trials of VGB for epilepsy. These include both randomized, controlled trials and open-label follow-up studies (Table 32). The MRIs were read locally at the individual sites and then were centrally reviewed independently by 2 neuroradiologists specifically looking for abnormalities suggestive of IME as had been seen on MRIs of VGB-exposed rats and dogs. No indication of MRI abnormalities suggestive of IME was found. However, at the Type A Meeting of Ovation with the FDA in June, 2007, the Agency expressed concern that by focusing narrowly on IME, radiologists in the prior review may have overlooked other abnormalities in the MRI images. Therefore, in contrast to the original review of the CPS studies, the repeat review by Ovation used a broad definition of abnormality. The pre-specified abnormalities were defined as high T2 or fluid-attenuated inversion-recovery (FLAIR) signal, with or without associated diffusion restriction and not otherwise explainable by a radiologically diagnosable pathological process (ie, mesial temporal sclerosis or remote ischemia). During the repeat review, two neuroradiologists conducted a masked review of all available images, with adjudication in cases of disagreement.

The studies included in the repeat retrospective imaging review are presented in Table 32. All studies were multi-center, with sites in the U.S., Canada, and Europe. Seven studies were conducted in adult patients with CPS and 5 studies were conducted in pediatric patients with CPS. Studies included both placebo-controlled and open-label studies; most patients participated in more than one trial. The primary objectives in these studies were evaluation of safety and efficacy of VGB as adjunctive therapy with difficult-to-control CPS. In all studies, MRI was a pre-specified assessment due to potential safety concern of development of IME.

Table 32. Studies Included in Repeat Review of Adults and Children with CPS Conducted by Ovation

Study Number	Indication	Population	Design
020	CPS	Adult	Open-label
021	CPS	Adult	Placebo-controlled
022	CPS	Adult	Open-label
024	CPS	Adult	Placebo-controlled
025	CPS	Adult	Placebo-controlled
026	CPS	Adult	Open-label
028	CPS	Adult	Open-label
118	CPS	Pediatric	Placebo-controlled
192	CPS	Pediatric	Placebo-controlled
201	CPS	Pediatric	Open-label
221	CPS	Pediatric	Placebo-controlled
294	CPS	Pediatric	Open-label

Reviewers assessed whether the images were of sufficient technical quality to be interpretable. For assessments of pre-specified signal abnormalities, each reviewer provided an overall assessment for that time point, as well as an assessment of the pre-specified signal abnormalities by brain region/anatomic structure and brain hemisphere, where applicable. On images where the reviewer could not determine whether or not an abnormality was present in a particular anatomical region or sequence, a reading of "indeterminate" was given. Thus, images had to have been both interpretable and determinate in order to be evaluable.

In the repeat analysis, to maintain objectivity the independent reviewers (all practicing neuroradiologists) were blinded to patient name, patient identifier, patient date of birth, investigative site identifiers, investigative site assessments, examination dates, and VGB or other AED treatment, and were asked to identify the pre-specified imaging abnormalities in any region of the brain. Each image was read by 2 reviewers, with a total of 11 reviewers participating in the study. In the event of discrepant results for any examination between the two primary reviewers, a third reviewer (adjudicator) was presented with the results of the examination from the primary reviewers and determined the final assessment for the time point. Reviewers assessed whether the images were of sufficient technical quality to be interpretable. For assessments of pre-specified signal abnormalities, each reviewer provided an overall assessment for that time point, as well as an assessment of the pre-specified signal abnormalities by brain region/anatomic structure and brain hemisphere, where applicable. On images where the reviewer could not determine whether or not an abnormality was present in a particular anatomical region or sequence, a reading of "indeterminate" was given. Thus, images had to have been both interpretable and determinate in order to be evaluable.

Of the 2192 MRI examinations listed in the datasets from the previous sponsor, 2074 were located. Of these, 89 were excluded from analysis: 37 were judged to be of inadequate technical quality, and 52 scans could not be assigned to a particular patient, had unresolvable conflicting identifying data, or had insufficient data. Following exclusions, 90.6% of scans

performed in the 12 studies contributed to the Ovation repeat analysis. Table 33 summarizes the available MRI scans by treatment group. VGB-exposed referred to the time period during which patients received VGB in any of the CPS studies being reviewed. VGB-naïve referred to the time period during which the patient received placebo prior to receiving VGB as well as patients who received placebo only. Note that an individual patient who received placebo followed by VGB may be represented in both the VGB-exposed as well as the VGB-naïve groups.

Across all eligible patients, the number of MRI examinations in any treatment period ranged up to 5. For the VGB-only group (n=422), 37 (8.8%) patients had 1 MRI examination, 94 (22.3%) had 2, 148 (35.1%) had 3, 100 (23.7%) had 4, and 43 (10.2%) had 5. For the placebo-VGB group (n=236), during placebo treatment, 4 (1.7%) had no MRI examinations, 49 (20.8%) had 1, 177 (75.0%) had 2, and 6 (2.5%) had 3; during VGB treatment, 38 (16.1%) had 1 MRI examination, 93 (39.4%) had 2, 68 (28.8%) had 3, 34 (14.4%) had 4, and 3 (1.3%) had 5. In the placebo-only group (n=13), 4 (30.8%) had 1 MRI examination, and 9 (69.2%) had 2. The median time from baseline until the last determinate MRI examination was 17.51 months for the VGB-only group, 4.27 months for the placebo-VGB group during placebo treatment, 7.00 months for the VGB-only group during VGB treatment, and 4.27 months for the placebo-only group.

Table 33. Summary of MRI Examinations by Group

Group	Total MRI	Interpretable MRI	Determinate MRI
VGB only	1284	1271	1264
Placebo-VGB during placebo	421	412	408
Placebo-VGB during VGB	579	567	565
Placebo only	22	17	17
VGB exposed	1863	1838	1829
VGB naïve	443	429	425

Prevalence was defined as the occurrence of at least 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. Six hundred thirty-five patients were included in the prevalence population. Of these, 103 had a pre-specified signal abnormality and 532 did not. Note that a single patient can be represented in both VGB-exposed and VGB-naïve groups. Among the VGB-exposed group, 84 of 592 had a pre-specified abnormality, as did 25 of 191 patients in the VGB naïve group. Among the VGB-exposed group, 84/592 patients had a pre-specified abnormality (14.2%, 95% CI: 11.5, 17.3). Among the VGB-naïve group, 25/191 patients had a pre-specified abnormality (13.1%, 95% CI: 8.7, 18.7). The relative risk for all patients in the prevalence population, or the ratio of risk of abnormality between the two groups was 0.88 (95% CI: 0.57, 1.37). There was no statistically significant difference between VGB-exposed and VGB-naïve patients with respect to the prevalence of pre-specified MRI abnormalities (p=0.579).

Incidence was defined as the occurrence of at least 1 pre-specified MRI signal abnormality on T2, FLAIR, and/or DWI among patients with a determinate MRI at baseline which was free of pre-specified abnormalities. Of the 515 patients in the incidence population, 63 had a

pre-specified MRI abnormality and 452 had no pre-specified abnormalities. By treatment group, 51 of 474 (10.8%, 95% CI: 8.1, 13.9) VGB-exposed patients had an abnormality, compared with 12 of 150 (8.0%, 95% CI: 4.2, 13.6) VGB-naïve patients. Note that a single patient can be represented in both VGB-exposed and VGB-naïve groups. The relative risk for all patients in the incidence population, or the ratio of risk of abnormality between the two groups was 1.34 (95% CI: 0.74, 2.45). There was no statistically significant difference between VGB-exposed and VGB-naïve patients with respect to the incidence of pre-specified MRI abnormalities (p=0.437).

The anatomical distribution of the high T2 signal abnormalities seen in both VGB-exposed and VGB-naïve CPS patients was not suggestive of the pattern of abnormality seen in the nonclinical studies or IS patients. The predominant localization of the findings was in cerebral white matter and is consistent with reports of MRI abnormalities in patients with epilepsy.

The repeat review used a broad definition of abnormality. This analysis in isolation may be subject to the risk of missing infrequent cases of abnormality caused by VGB because the underlying rate of abnormalities is relatively high. Therefore, an additional analysis using a more narrow definition of abnormality was conducted by Ovation (bilateral increased T2 or FLAIR signal in the globus pallidus, caudate, putamen, thalamus or cerebellum or abnormal signal in the midbrain or pons). The results for both analyses are shown in Table 34.

Although the prevalence and incidence of abnormal MRI examinations are much lower using the narrow than the broad definition, the conclusions are the same. There is no difference between VGB-exposed and VGB-naive patients in either the prevalence or incidence of abnormal MRI examinations in the 12 studies reviewed. These results, combined with the negative results of MRI interpretations carried out by the previous sponsor, provide no evidence that VGB used to treat CPS is associated with MRI abnormalities.

Table 34. Calculation of Prevalence and Incidence of Abnormal MRI Examinations Using Narrow Definition

	VGB-Exposed N=594	**VGB Naïve N=193**
Prevalence (%)	3.0	3.1
(95% CI)	(1.8, 4.7)	(1.1, 6.6)
Relative risk 0.66 (0.16, 3.9)		
VGB vs. non-VGB p=0.556		
	VGB-Exposed N=538	**VGB Naïve N=171**
Incidence (%)	2.8	2.9
(95% CI)	(1.6, 4.6)	(1.0, 6.7)
Relative risk 0.95 (0.35, 2.59)		
VGB vs. non-VGB p=1.000		

SUMMARY OF MRI IN CPS

Based on all information available, clinical, histopathological, electrophysiological, and radiological, there is no evidence of IME occurring in children or adults treated with VGB for CPS. The anatomic distribution of MRI findings in adults and children with CPS is not suggestive of a VGB associated effect, and there is no difference detected in the frequency of MRI abnormalities between VGB-treated patients and VGB-naïve patients.

The clinical implications of these findings are that routine MRI surveillance of patients with CPS who are treated with VGB is not warranted. Moreover, no recalculation of benefit/risk is required for this indication.

4.5. Benefit/Risk Assessment in Refractory CPS

Data presented in the preceding sections of this briefing document support the following:

- Although approximately 64% of patients with epilepsy achieve complete seizure control with minimal side effects on monotherapy or polytherapy with 2 drugs, the remaining 36% remain refractory to treatment. Refractory CPS is a serious and life-threatening disease and an unmet medical need exists.
- Uncontrolled epilepsy is associated with considerably higher rates of mortality and SUDEP than controlled seizures.
- The efficacy of VGB for refractory CPS, as add-on therapy, was established in 2 adequate and well-controlled pivotal studies, in a design that remains the current standard for testing AEDs. Statistically significant and clinically meaningful reductions in seizure frequency were observed. Among responders, onset for these improvements was generally noted within 6 weeks of the initiation of treatment.
- The binocular pVFD, if it occurs, is typically mild (120-160 degrees binocular field remaining) or moderate (60-120 degrees binocular field remaining) and rarely (2.4%) severe (<60 degrees remaining), and central visual acuity is not affected.
- Prevalence estimates reported in the literature of the distinctive pVFD vary widely (17-92%) but studies designed to specifically evaluate this issue have estimated the prevalence of confirmed VGB-induced pVFD in 25% of adult patients and 15% of children receiving long-term VGB therapy.
- Although infrequent reports have been noted within the first 12 months of treatment, the defect does not generally appear to manifest early following initiation of therapy. For those who develop a pVFD, the median duration of VGB exposure at the time the pVFD is detected is 4.3 years in children and 4.7 years in adults.
- The VGB-induced pVFD does not appear to begin, progress or reverse after the drug is discontinued, although the possibility cannot be rigorously excluded. The pVFD can be reliably detected and monitored by patient-specific and age appropriate methods in most adult patients with refractory CPS

- Although VGB therapy is associated with potential risks, particularly pVFD, the benefits of VGB-treatment outweigh the potential risks in adult patients with refractory CPS who have a clinically meaningful response to the addition of VGB to their AED regimen.

5 INFANTILE SPASMS

5.1. Disease Description and Epidemiology

Infantile spasms (IS) constitutes a rare and refractory type of childhood epilepsy that is characterized by spasms, arrested psychomotor development, and an abnormal electroencephalogram (EEG) characterized by hypsarrhythmia which constitutes high amplitude slow waves and spikes that are asynchronous, nonrhythmic, and variable in duration and topography [157-159]. This syndrome is also referred to as West syndrome. Children with IS may also have other EEG manifestations showing multifocal spikes with normal or nearly normal background [157-158,160]. Spasms are typically characterized by symmetric, salaam-like contractions of the trunk followed by a more sustained tonic phase. An individual spasm typically lasts for less than 1 second, but may last up to 5 seconds [161]. Spasm clusters of 3 to 20 spasms typically occur several times per day, most commonly upon awakening.

IS is an uncommon disorder with approximately 2500 cases per year in the U.S.[162]. The incidence of IS is estimated to be between 2 to 5 per 10,000 live births [159,163-165]. The lifetime prevalence of IS at age 10 years has been estimated at 1.5 to 2 per 10,000 children [14,163], with 85 to 90% of cases occurring in children less than 1 year of age [166]. The lower prevalence of IS in older children compared with the incidence may likely be attributed to the progression of untreated IS into other seizure types and the relatively high mortality rate.

Relatively little is known about the pathophysiology of IS, however, a commonly accepted hypothesis is that IS is a nonspecific, age-dependent reaction of the immature brain to injury. Although most injuries resulting in spasms are diffuse in nature, focal damage to the brain may also cause IS. Other hypotheses focus on abnormal function in subcortical structures, such as the brainstem, as the central mechanism for causing IS and hypsarrhythmia. It is conjectured that abnormal brainstem activity could influence the cerebral hemispheres diffusely through cortical projections.

Consistent with this, several case reports have identified pathologic changes in the brainstem of patients with IS [167-168]. The involvement of the brainstem, however, has not been consistently demonstrated to be the site of genesis [169]. Other subcortical structures, such as the hypothalamus, have also been implicated because of the effects of ACTH and glucocorticosteroids on the resolution of IS. However, no comprehensive mechanism for the pathophysiology of IS has been established.

5.2. Unmet Medical Need in IS

IS is a catastrophic form of epilepsy beginning within the first year of life. IS has a devastating effect on neurological development of the child. Children with uncontrolled spasms suffer impaired nervous system development and may never attain critical developmental milestones and frequently regress from previously established milestones. The primary goal of any treatment for IS is complete suppression of spasms and hypsarrhythmia to allow neurological development to resume.

The prognosis for patients with IS is poor. Although IS "resolves" in the majority of patients during childhood, this means that the clinical semiology of the epilepsy changes [11,15-19]. In the past, various studies have estimated that 50% to 70% of patients develop other seizure types [16,17]. In patients with IS who were followed long-term, approximately 50% of patients developed chronic refractory epilepsy, of which 20% to 50% developed Lennox-Gastaut Syndrome [12,14,19,165,170].

Patients with IS frequently have neurological deficits. Mental retardation is present in 70% to 90% of patients [11-17], with the majority having severe-to-profound retardation. In addition, approximately 30% to 50% of patients have other neurological deficits, such as static encephalopathy (cerebral palsy) [11,14,17]. Mortality rates are high; estimates range from 5% to 30% [11,14,15,16,163] with approximately 10% to 33% of deaths occurring before age 3 [11,15,171].

There are no approved treatments for IS in the U.S. The most commonly used off-label therapies are adrenocorticotropic hormone (ACTH) and prednisone. Although these drugs have at least initial efficacy in a sizable number of patients, they also have a relapse rate of up to 40% in some studies, bringing overall efficacy to a much smaller number of patients [11,12,18-24]. Additionally, hormonal therapy such as ACTH may also have significant and potentially fatal side effects [19,25]. Other therapies have also been used off-label to treat IS, including sodium valproate, benzodiazepines, and some newer AEDs. However, the safety and efficacy of these agents has not been established in controlled clinical studies, and they can have significant side effects [26]. A ketogenic diet also has demonstrated success in treating refractory epilepsy in children, with seizure freedom rates of 30.5% to 55% in patients with refractory childhood epilepsy and 36% to 43% in patients with IS [172]. However management is often difficult and nutritional needs must be closely monitored [173].

The long-term outcome of children who experienced IS early in life is highly dependent on the underlying etiology of IS. In those with symptomatic IS, their prognosis is the prognosis of their underlying disease. For cryptogenic cases, there is substantial evidence from retrospective studies that a favorable cognitive and behavioral outcome after IS is strongly associated with achieving early and complete control of spasms by whatever therapy is adopted. Kivity et al. (2004) [174] performed cognitive testing on 37 children who had been treated with hormonal therapy as infants for cryptogenic IS. All of 22 infants who had a response to therapy within 1 month of onset of IS had a favorable outcome, whereas only 40% of those infants who did not achieve rapid spasm cessation had a favorable outcome. Moreover, those infants who achieved spasm cessation before the occurrence of marked or severe developmental regression had a uniformly favorable outcome. In those who experienced developmental regression, a favorable outcome was achieved in only 25%. Other studies support these conclusions [11], [175-177].

These observations have led to the view by pediatric epileptologists that IS is a neurological emergency, requiring rapid confirmation of the diagnosis and institution of effective therapy if the child is to be given the maximum chance of normal development. There are no FDA approved therapies for this catastrophic form of epilepsy and institution of treatment is frequently delayed by reimbursement issues and limits to access to effective therapy.

In the 1998 UK consensus guideline [27] for prescribing VGB for children, VGB remained the drug of choice for IS. These guidelines were revised after the discovery of pVFD in VGB-treated adults to include specific recommendations for monitoring visual fields [28,29] however, VGB has remained the drug of choice for IS among many treating clinicians in Europe and Canada, especially when IS is caused by tuberous sclerosis (TS) [28,30-34].

5.3. Efficacy in Infantile Spasms

5.3.1 Overview of Clinical Studies in Infantile Spasms

The effectiveness of VGB as monotherapy treatment for IS was established in 3 adequate and well-controlled studies: one U.S. study (Study 1A) and 2 ex-U.S. studies (71754/3/W/019 [hereafter designated Study W019] and 097/W/FR/03 [hereafter designated Study FR03]). All 3 studies were similar in terms of disease characteristics and prior treatment and all enrolled infants who had a confirmed diagnosis of IS. FR03 was restricted to patients with TS. Two studies were blinded and all 3 used EEG or video EEGs as part of the efficacy evaluations. Study 1A, the pivotal trial and the largest with 222 patients (221 evaluated), required closed-circuit television electroencephalogram (CCTV EEG) confirmation of spasm cessation or hypsarrhythmia as the primary endpoint. Since the efficacy of VGB had been demonstrated in prior studies, and because of the belief that rapid control of spasm is associated with a favorable outcome, it was not considered ethical to utilize prolonged placebo-controlled periods.

Efficacy data were also evaluated in Study 097-332.5, an uncontrolled study of VGB as adjunctive therapy in infants and children with drug-resistant IS. In addition, efficacy data were evaluated in Study 3E01, a retrospective data collection from patients diagnosed with IS who had been treated with VGB as their first drug.

A total of 279 patients from the 3 controlled studies received VGB and were evaluable for efficacy. Patients were all younger than 2 years at the time of enrollment and of either sex. Initial doses of VGB ranged from 18 to 150 mg/kg/day, were subject to protocol-allowed titration, and were increased to a maximum dose of 369.5 mg/kg/day in the long-term follow-up periods.

A tabular description of the IS studies is presented in Table 35.

Table 35. Description of IS Studies

Type of Study		Treatment Groups	
Study Number	**Duration**	**Dose (mg/kg/day)**	**N Evaluated**
Controlled Studies			
1A	Controlled: 14 to 21 days single-blind phase followed by open-label phase up to 3 years	Low dose VGB (18 -36) High dose VGB (100-148) Total VGB	114 107 221
W019	2 to 3-day baseline, 5-day double-blind treatment, 6-month open-label follow-up	DB: Placebo DB: 50-150 VGB OL New VGB (Placebo in DB) Total VGB DB + OL	20 20 20 40
FR03	8-week comparator phase: Initial 4-weeks VGB or hydrocortisone treatment Next 4 weeks: • Non-responders crossed over to receive alternate therapy for 4 weeks. • Hydrocortisone responders tapered off, • VGB responders received VGB Long-term follow-up ≥2 years	Month 1: 15 hydrocortisone Month 1: 150 VGB Month 2: 15 hydrocortisone Month 2: 150 VGB Hydrocortisone only Total VGB	11 11 0 7[a] 4 18
Uncontrolled Studies			
097-332.5	2- to 4-week baseline phase, 3-month evaluation phase, long-term phase ≥1 year	50 to 150 VGB	43
3E01	Median 7.6 months (range: 0.5 to 28.6 months)	14 to 400 VGB	192

[a] Cross-over patients, received hydrocortisone during Month 1

Cessation of spasms was the primary endpoint for documenting VGB efficacy in all studies except W019. Uncontrolled seizures can cause loss of function and can also cause irreparable harm to cognition and development. Infants with IS lose acquired developmental milestones and may suffer permanent developmental delay unless spasms and the underlying electrographic characteristic of hypsarrthymia are completely eliminated. Two of the controlled studies (Study 1A and FR03) assessed behavior via a physician assessment. Two of the controlled studies (Study W019 and FR03) assessed cognitive and motor development using the objective psychomotor tests of Denver and Brunet Lézine instruments. Study W019 assessed psychomotor development during the controlled and the uncontrolled long-term follow-up periods. An overview of the efficacy parameters in the controlled IS studies is presented in Table 36.

Table 36. Summary of Efficacy Measures in Controlled IS Studies

Parameter	1A	FR03	W019
Primary Efficacy			
Proportion of patients free of spasms for 7 consecutive days after 14 days of VGB treatment based on CCTV EEG within 3 days of end of 7-day spasm-free period[a]	X		
Proportion of patients with total disappearance of spasms and time to response		X	
Percentage reduction in average frequency of spasms (assessed during 2-hour monitoring window) from baseline to end of DB period			X
Ad Hoc Sensitivity of Primary Efficacy			
Primary analysis, CCTV EEG at next visit after end of 7-day spasm-free period[a]	X		
Primary analysis, CCTV EEG within 10 days of end of 7-day spasm-free period, beginning on 7th spasm-free day[a]	X		
Primary analysis, CCTV EEG within 10 days of end of 7-day spasm-free period, beginning prior to end of 7-day spasm-free period[a]	X		
Secondary Efficacy			
Spasm Cessation (Response)			
Time to Response	X		
Proportion of Responders	X		X
Frequency of Spasm Clusters	X		X
Percentage reduction in average frequency of spasms (assessed during 24-hour monitoring window) from baseline to end of DB period			X
EEG Assessments		X	X
Physician Global Assessment	X	X	
Caregiver Global Assessment	X		
Investigator's Overall Assessment Of Efficacy			X
Psychomotor Development			
Brunet Lézine test		X	
Denver developmental test			X
Long Term Follow-up			
Relapse	X	X	X
Up-Titration of VGB Dose	X		
Use of AEDs	X	X	
Occurrence of Partial Seizures		X	
Spasm Count			X
Time to Response and Proportion of Responders			X
Time to Therapeutic Success and Proportion of Patients			X
Investigator's Overall Assessment Of Efficacy			X

[a] Caregiver deemed patient to be spasm-free

Subgroup analyses included age at onset of IS, use of AEDs at baseline, duration of IS, and, in Studies 1A and W019, disease etiology (symptomatic or cryptogenic).

5.3.2 Patient Population in Controlled Studies

Overall, the populations of the 3 controlled studies were similar in terms of disease characteristics and prior treatment. All 3 controlled studies enrolled infants with a confirmed diagnosis of IS, with Study FR03 enrolling only patients with IS due to TS. The U.S. study (Study 1A) specified a diagnosis of 3 months or less prior to study entry, whereas the non-U.S. studies (Studies W019 and FR03) specified that only newly diagnosed patients be enrolled. Study 1A also allowed prior treatment with other AEDs, except corticosteroids, ACTH, or VPA, as long as patients had been on a stable dose prior to study enrollment. Study W019 specified that patients must be newly diagnosed and previously not have received IS treatment with ACTH, corticosteroids, benzodiazepines, sodium valproate, phenobarbitone, or VGB; however, any investigational new drug or medication deemed "anticonvulsant" was allowed up until 2 months prior to study entry. Study FR03 excluded patients who were previously treated for IS or who had been treated with other AEDs for other types of seizures.

Each study had similar numbers of males and females, and overall (combining all 3 studies), there were 138 males and 144 females (information regarding gender for 2 patients in Study 1A was not recorded). The large majority of patients in these studies were Caucasian.

5.3.3 Study 1A

5.3.3.1 Study 1A Design and Efficacy Assessments

Study 1A was an investigator-initiated, multi-center, randomized, parallel group clinical trial of 2 dose ranges of VGB, 18-36 mg/kg/day vs. 100-148 mg/kg/day. The study was originally designed in 1995 as a compassionate use study to make VGB available to patients with IS while the FDA completed its review of the NDA for VGB use in refractory CPS. However, the original investigator-sponsored IND was not approved by the FDA. After discussion with the Agency, the investigators redesigned the study as a randomized trial of 2 dose ranges of VGB with a 2-3 week randomized trial period followed by an open-label, flexible-dose follow-on period. The first version of the protocol planned enrolling 44 patients, but the protocol was amended twice to increase the sample size, first to 150 and subsequently to 250 patients. Both increases were motivated by the desire on the part of the investigators to continue to make VGB available to patients. The first increase had a secondary goal of increasing the power of the study from 80% to 99% to detect a difference in efficacy between the 2 dose ranges. In 2001, after the prior NDA sponsor decided not to pursue approval of VGB, the study was stopped at the request of the FDA with 228 patients enrolled.

Two interim analyses of the study were performed at the request of the previous NDA sponsor, in order to compile safety and efficacy data to submit to NDA 20-427. Neither interim analysis was performed with the intention of either stopping the study or changing its conduct. The second interim analysis achieved a statistically significant result but the study was continued nonetheless.

During the first, randomized phase of the study, patients were randomized to receive either 18-36 mg/kg/day or 100-148 mg/kg/day VGB given orally in 2 divided doses. The dose ranges were chosen based on the VGB formulation of 500 mg tablets, which could be divided in halves or quarters. The tablets have been subsequently demonstrated to be bioequivalent to the powder for oral administration. The dose was titrated over 7 days, followed by a constant dose for 7 days. If the patient became spasm-free on or before day 14, another 7 days of constant dose were administered. During the open-label, dose-ranging, long-term follow-up (up to 3 years), VGB dose could be increased or decreased at the discretion of the investigator. IS etiology was categorized as symptomatic-TS, symptomatic-other, or cryptogenic.

The primary endpoint of this study was the proportion of patients who were free of spasms for 7 consecutive days beginning within the first 14 days of VGB therapy. Patients considered spasm-free must have remained free of spasms for 7 consecutive days according to caregiver response to direct questioning regarding spasm frequency, and have had no indication of spasms or hypsarrhythmia during 8 hours of CCTV EEG recording that included at least 1 sleep-wake-sleep cycle. In order to be considered a treatment responder, the CCTV EEG must have been conducted within 3 days of the end of the 7-day period during which the patient was deemed to be free of spasms by caregiver observation. This short time window was chosen when the study was designed because of concern that the low-dose VGB might prove to be inadequate treatment for IS, and investigators did not want to deny infants effective therapy while awaiting a confirmatory laboratory test. As noted below, the 72 hour window proved too restrictive.

Because of the difficulty of obtaining CCTV EEG within 72 hours, 2 ad hoc analyses were conducted to determine the sensitivity of the endpoint definitions for the primary analysis. These analyses allowed EEG confirmation of spasm cessation:

1. At a subsequent visit,
2. A day-by-day extension of the visit window to day 10 after the seventh day of spasm freedom, including EEGs taken:
   - On the seventh spasm-free day
   - Prior to the seventh spasm-free day.

The secondary efficacy endpoints of the study assessed spasm freedom without the use of a CCTV EEG, based on caregiver assessment of spasm frequency in response to direct questioning regarding spasm frequency or as recorded in the seizure diary. The secondary endpoints are presented in Table 36.

5.3.3.2 Study 1A Efficacy

PROTOCOL SPECIFIED PRIMARY EFFICACY ENDPOINT

The protocol specified primary efficacy endpoint was the proportion of patients who were spasm-free for 7 consecutive days beginning within the first 14 days of VGB therapy, based on caregiver assessment and confirmed by a CCTV EEG recording within 3 days of the seventh day of spasm freedom. Seventeen patients in the high dose group achieved spasm

freedom compared with 8 patients in the low dose group. This difference was statistically significant (p=0.0375). Primary efficacy results are shown in Table 37.

Table 37. Spasm Freedom by Primary Criteria[a] – Study 1A

Treatment Group	Patients with Spasm Cessation n (%)	Patients with Spasm Non-cessation n (%)	p-value
High-dose (N=107)	17 (15.9)	90 (84.1)	
Low-dose (N=114)	8 (7.0)	106 (93.0)	0.0375
Total (N=221)	25 (11.3)	196 (88.7)	

[a] Primary criteria were based on caregiver assessment plus required CCTV EEG confirmation.

AD HOC SENSITIVITY ANALYSIS OF PRIMARY ENDPOINT

Attainment of CCTV EEGs was frequently impossible in the protocol-mandated 3-day window for a variety of reasons: the low numbers of available video monitoring beds and transportation or other family issues. Thus, ad hoc analyses were performed to determine efficacy outcome with various sensitivities.

Relaxing the EEG timing criterion to allow confirmation at a subsequent clinic visit, rather than only within 3 days, resulted in cessation rates for the high- and low-dose treatment groups of 31% (33/107) and 13% (15/114), respectively (chi-square test, p=0.0014) (Table 38).

To further explore the sensitivity of cessation rates to timing of the video EEG, analyses were performed for a variety of EEG visit windows. In the analyses where the visit window began on the seventh spasm-free day (Day 0), as the visit window broadened from 3 days to 10, not only did the total number of responders increase in both high-and low-dose, but the separation between high and low-dose also increased (Table 38). Statistical significance was maintained between the high and low-dose at Day 4 (19% [20/107] high-dose; 7% [8/114] low-dose, p=0.0091) and continued to be present throughout. The difference by Day 9 was 26% [28/107] high-dose and 11% [12/114] low-dose (p=0.0025). An important point is that this extended period of clinical spasm-freedom prior to video EEG confirmation is more stringent than the primary endpoint. In other words, this is actually a more conservative evaluation of spasm cessation since it requires a longer period of spasm-freedom prior to video EEG confirmation than the primary efficacy window of 3 days.

In the analyses where the visit window began prior to the seventh spasm free day (Days −1, −2), a significant difference was also attained. For example when the EEG confirmation occurred between 1 day prior to and 3 days after the seventh day of clinical spasm-freedom (visit window Day −1, 3) there was a statistically significant difference between the high-dose 17% (18/107) and the low-dose 7% [8/114] groups (p=0.0238).

Therefore, the conclusion that the high-dose group achieved a higher rate of spasm cessation than the low-dose group is robust and does not depend on the timing of the confirmatory CCTV EEG recording. However, the inclusion of CCTV EEG confirmation in the efficacy measures reinforces the strength of the conclusion.

Table 38. Responder Analysis – Sensitivity to EEG Visit Windows

EEG Visit Window[a]	Responders (n) High-dose N = 107	Responders (n) Low-dose N = 114	Total n of Responders N = 221	χ2 test p-value
Subsequent Visit	33	15	48	0.0014
0,3[b]	17	8	25	0.0375
0,4	20	8	28	0.0091
0,5	22	9	31	0.0067
0,6	22	11	33	0.0229
0,7	25	12	37	0.0106
0,8	26	12	38	0.0067
0,9	28	12	40	0.0025
0,10	28	12	40	0.0025
-1,3	18	8	26	0.0238
-1,4	21	8	29	0.0055
-1,5	23	9	32	0.0041
-1,6	23	11	34	0.0147
-1,7	26	12	38	0.0067
-1,8	27	12	39	0.0042
-1,9	29	12	41	0.0015
-1,10	29	12	41	0.0015
-2,3	19	8	27	0.0148
-2,4	22	8	30	0.0033
-2,5	24	9	33	0.0024
-2,6	24	11	35	0.0093
-2,7	27	12	39	0.0042
-2,8	28	12	40	0.0025
-2,9	30	12	42	0.0009

a. The values of the visit window are relative to the day 7 of the 7-day spasm-free period. Negative values correspond to visits occurring before the end of the period. For example, -1,3 represents the window from one day before to 3 days after last day of the end of the 7-day spasm-free period.

b. The 0,3 window is that of the primary endpoint definition.

SECONDARY EFFICACY ANALYSIS

Responders and Time to Response (Spasm-free Status for 7 Consecutive Days)

The results of the secondary analyses of spasm-free status for 7 consecutive days are shown in Table 39 for the group of patients who remained spasm-free during the entire study period and patients who were spasm-free for 7 consecutive days but not necessarily for the duration of the study. In the group who did not relapse, a significant difference was seen between the treatment groups, with more responders in the high-dose VGB group than in the low-dose VGB group.

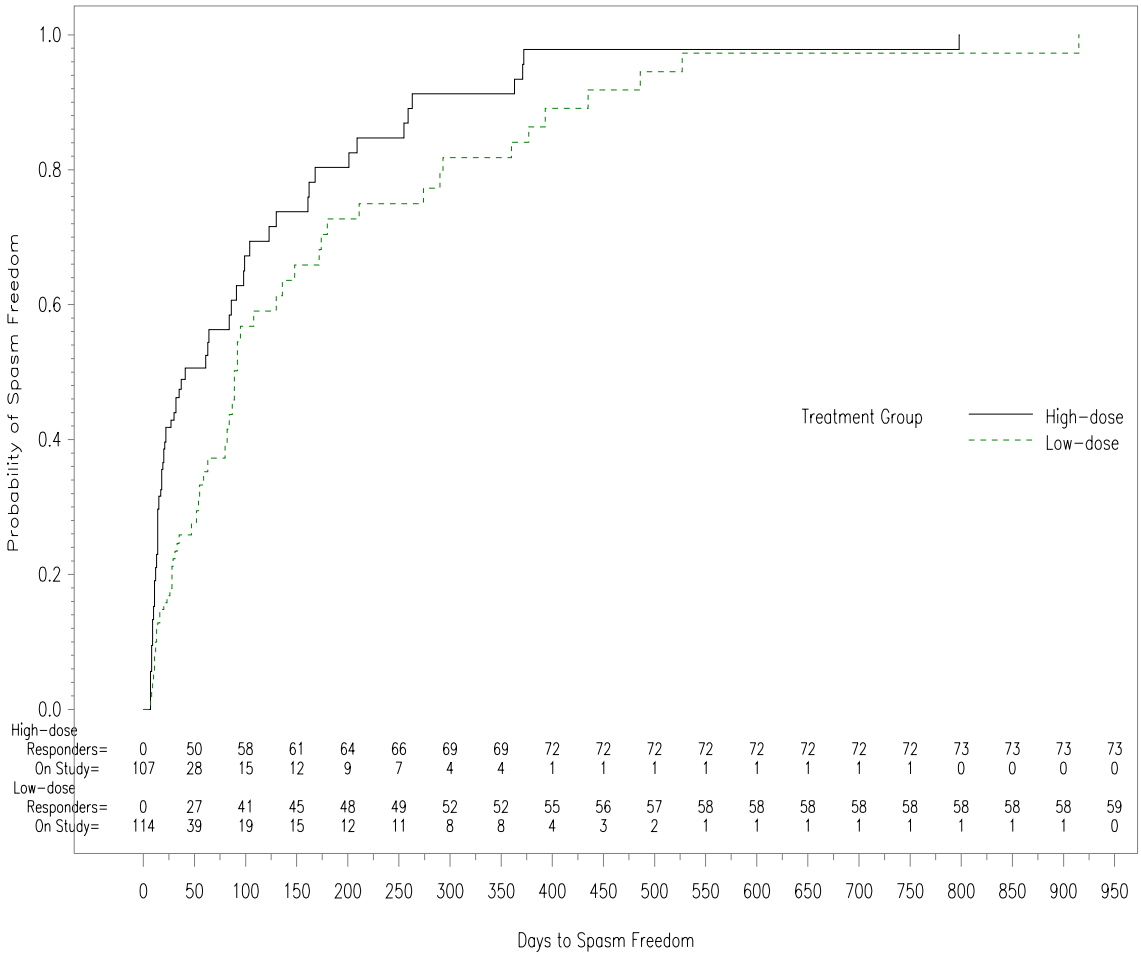
Table 39. Spasm Cessation for 7 Consecutive Days During the Study Period by Secondary Criteria[a] – Study 1A

Treatment Group	Patients with Spasm Cessation n (%)	Patients with Spasm Non-Cessation n (%)	p-value
Spasm cessation for 7 consecutive days and remained spasm-free for the duration of the study			
High-dose (N=107)	73 (68.2)	34 (31.8)	
Low-dose (N=114)	59 (51.8)	55 (48.3)	0.0126
Total (N=221)	132 (59.7)	89 (40.3)	
Spasm cessation for 7 consecutive days, allowing for relapse			
High-dose (N=107)	84 (78.5)	23 (21.5)	
Low-dose (N=114)	87 (76.3)	27 (23.7)	0.6975
Total (N=221)	171 (77.4)	50 (22.6)	

[a.] Secondary criteria were based on caregiver assessment, without electroencephalographic confirmation.

The time-to-response data for patients who attained spasm cessation for 7 consecutive days and maintained spasm cessation for the duration of the study Kaplan-Meier techniques are shown in Figure 15 for each of the 2 treatment groups. There was a clear separation between the high- and low-dose Kaplan-Meier curves (p=0.0016), beginning at week 2 of VGB exposure, showing a greater response in the high-dose group. High-dose and low-dose groups achieved the majority of their maximum spasm-free percentages by approximately week 6 and week 13, respectively. With increasing time, the curves in approach each other, because the low dose patients entered the open-label phase and titrated to higher doses, and because approaching probability 1.0 is a characteristic of Kaplan-Meier curves when most dropouts (censoring) occurred before other patients achieved spasm freedom.

Figure 15. Kaplan-Meier Curves Comparing High- and Low-Dose Treatment Groups on Time to Spasm Cessation for 7 Consecutive Days and Remained Spasm-free During the Study Period by Secondary Criteria (Caregiver Assessment) – Study 1A



Spasm Cluster Frequency over Time – Study 1A

The comparison of the patient-specific number of spasm clusters in the high- and low-dose VGB treatment groups over the course of the study period was completed using negative binomial regression techniques with repeated measures to model the spasm frequency over time. Although the frequency of spasm clusters decreased over time in both groups (Table 40) (chi-square test, p=0.0013), there was no significant difference in the number of spasm clusters in the high- and low-dose groups (chi-square test, p=0.6425). In Table 40, the adjusted mean number of spasm clusters is shown based on the full regression model, which includes a time by treatment interaction. One treatment has a smaller number of clusters than the other, depending on month, but this apparent interaction is not statistically significant (p=0.53).

Table 40. Spasm Frequency Over Time – Study 1A

Time Point	Dose Group	Adjusted Mean (SE) Number of Spasm Clusters
Baseline	High-dose	5.8 (1.1)
	Low-dose	5.8 (1.1)
Week 2	High-dose	6.7 (1.6)
	Low-dose	6.6 (1.3)
Month 1	High-dose	3.0 (1.3)
	Low-dose	3.9 (1.2)
Month 2	High-dose	2.9 (1.5)
	Low-dose	3.0 (1.3)
Month 3	High-dose	4.2 (1.6)
	Low-dose	1.6 (1.4)

Standard descriptive statistics (means and medians) for the number of clusters per day show a similar pattern. The median number of spasm clusters per day decreased from baseline at each visit through month 3 in both groups, with the median count lower in the high-dose group compared with the low-dose group at each visit. The mean numbers of clusters also show a decrease and are both larger and more variable than the median numbers, owing to large counts observed in a small number of patients. At baseline, the median numbers of clusters were similar in the high dose (3.5) and low dose (3.6) groups. By week 2, the median numbers of clusters had decreased by half in the high-dose group, versus an approximate 25% reduction in the low-dose group. By month 1, median clusters in the high-dose group had decreased to 0.5 and by month 2, to zero, while at each of these times the low-dose group had improved, but far less than the high-dose group. Table 41 summarizes the distributions of clusters per day from baseline to month 3.

Table 41. Distribution of Clusters per Day – Study 1A

Visit	Dose Group	Mean Clusters	SD	Median Clusters
Baseline	High-dose	5.6	7	3.5
	Low-dose	5.8	7.2	3.6
Week 2	High-dose	6.8	31.7	1.6
	Low-dose	6.6	15.6	2.4
Month 1	High-dose	3	7.4	0.5
	Low-dose	3.9	8.8	1.5
Month 2	High-dose	2.8	12.1	0
	Low-dose	3	7	0.5
Month 3	High-dose	3.4	18.4	0
	Low-dose	1.6	5.3	0

Subgroup Analyses of Spasm-Free Status by IS Etiology

On the primary outcome measure, the 3 IS etiology groups, cryptogenic, symptomatic-other, and symptomatic-TS, did not differ significantly (logistic regression, Wald $\chi 2$ test statistic $\chi 2[2]=5.22$, $p=0.0736$), after adjusting for the treatment factor. Twenty-one percent (8/38) of

the patients in the symptomatic-TS group, 7.9% (10/126) of the symptomatic-other group, and 12% (7/57) of the cryptogenic etiology group achieved spasm-free status.

Response rates were higher in the high-dose treatment group for all etiologies: symptomatic-TS (high-dose, 25%; low-dose, 17%); symptomatic-other (high-dose, 13%; low-dose, 3%); and cryptogenic (high-dose, 15%; low-dose, 10%). This observed dose effect was similar among the etiology groups, consistent with the non-significant interaction between treatment and etiology (logistic regression, Wald $\chi 2$ test statistic $\chi 2[2]=1.25$, p=0.5340).

Physician and Caregiver Global Assessment of VGB Efficacy

The comparisons of physician and caregiver global assessments over time in the high- and low-dose VGB treatment groups were completed using repeated measures analysis of variance techniques. The following assessment scale was used for both the physician and caregiver assessments: 1=Marked Deterioration; 2=Moderate Deterioration; 3=Mild Deterioration; 4=No Change; 5=Mild Improvement; 6=Moderate Improvement; and 7=Marked Improvement.

For both assessments, scores increased from "mild improvement" to "moderate improvement" over a 3-month period (p=0.0008 for physician assessment and p=0.0018 for caregiver assessment). For physician global assessment, the high-dose group had significantly higher scores than the low-dose group overall (chi-square test, p=0.0285). The high-dose group achieved a higher average score than the low-dose group at week 2 and on average maintained the difference throughout the study period. There were no significant differences between the treatment groups for caregiver global assessment.

Long Term Follow-up

Relapse

Thirty-nine (23%) of the 171 patients who became spasm-free for 7 consecutive days during the course of the study relapsed, 11/84 (13.1%) in the high dose group, 28/87 (32.2%) in the low dose group (p=0.0035). Twenty-eight (72%) of the 39 patients who relapsed achieved subsequent spasm-free status, while 11 (28%) of the 39 patients who relapsed did not achieve spasm-free status again. Twenty-two (79%) of the 28 patients who achieved spasm freedom again remained spasm-free for the remainder of their follow-up. The average follow-up time for all 39 patients who relapsed was 22 months, ranging from 2 to 43 months. Spasm freedom was regained with changes in AED regimen, including increased dose of VGB or adding an additional AED. During the open-label phase of Study 1A, patients were managed at the discretion of their local physicians.

Among patients who relapsed, the average time from initial spasm-free status to relapse was 126 days and the median was 64 days, ranging from 28 to 619 days. Twenty patients had their VGB dose increased 1 to 625 days after their relapse. Fifteen patients had their VGB dose decreased 8 to 601 days after their relapse. Four patients did not have sufficient dose data past the relapse date to assess any change.

Up-titration of Dose and Response (Spasm Cessation)

Table 42 shows the response rates for patients whose dose was increased after 14 days of VGB therapy (ie, responders as defined by the secondary efficacy criteria, allowing relapse). When VGB dosage was increased, more patients in the high-dose group (38%) compared to the low-dose group (34%) were responders. More patients in the low-dose group (11.3%) compared to the high-dose group (9.5%) were not responders when VGB dosage was increased. The same percentage of patients in both groups (high-dose, 1%; low-dose, 1%) who did not receive increased VGB dosage were non-responders. The titration range in the high-dose group of responders (N=84) was 54 to 207 mg/kg/day; in the low-dose group of responders (N=74) the range was 32 to 158 mg/kg/day.

Table 42. Up-titrated Dose (Responder vs Non-Responder) – Study 1A

	Low Dose VGB N=114	High Dose VGB N=107
Patient's Dose Up-titrated		
Responder[a]	74 (33.5)	84 (38.0)
Non-Responder	25 (11.3)	21 (9.5)
Patient's Dose Not Up-titrated		
Responder	13 (5.9)	0
Non-Responder	2 (0.9)	2 (0.9)

a. To that dose increase

Use of Other AEDs and Response (Spasm Cessation)

The relationship between VGB dose and use of AEDs in the flexible dosing period was examined. These analyses did not adjust for use of other AEDs at baseline. One hundred and seven patients received AEDs after 14 days and prior to 3 months: 49 patients in the high-dose group, 5 patients in the low-dose group and 53 patients in the low to high-dose group. The low to high-dose category comprises those patients who were randomized to the low dose group and who received a higher dose of VGB at some point after 14 days than they did during the initial 14 days (Table 43). The use of other AEDs did not seem to interact with dosing categories in their effects on spasm cessation, that is, persistent spasm freedom was not influenced by the presence of other AEDs. It is important to note that in the flexible-dosing period, these VGB dose categories, rather than predicting cessation, are determined by the patient's cessation status and the investigators' decisions to modify dose. For example, the cessation rates in the low-dose category, either with or without other AEDs, generally reflect the investigators' decisions not to increase VGB dose in those patients whose spasms were controlled on the low dose.

Table 43. Use of Other AED and Percentage of Responders – Study 1A

	Low Dose	High Dose	Low to High Dose
Received other AEDs after the initial 14 days			
N	5	49	53
Responder	2 (40%)	34 (69%)	28 (53%)
Did not receive other AEDs after the initial 14 days			
N	14	58	42
Responder	12 (86%)	39 (67%)	17 (40%)

Conclusions

The primary conclusion from Study 1A is that VGB can achieve complete spasm cessation in about 30% of patients with IS within 2-3 weeks and in about 75% over the course of the study. The higher dose employed in Study 1A, 100-148 mg/kg/day, was more effective than the low dose, 18-36 mg/kg/day.

5.3.4 Study FR03

5.3.4.1 Study FR03 Design and Efficacy Assessments

Study FR03 (N=23) was a multicenter, open-label, randomized, comparative, response-mediated, 2-month crossover study designed to compare the efficacy and safety of VGB (150 mg/kg/day without titration) and hydrocortisone (15 mg/kg/day) as first-line monotherapy in the treatment of infants with newly diagnosed IS due to TS. Patients were evaluated every 2 weeks during the study. After 1 month (4 weeks) of therapy, patients who had an incomplete response to the first treatment or had signs of intolerance crossed over to the other treatment, whereas patients who responded (became spasm-free) were not crossed over. Hydrocortisone responders were tapered off treatment (over a 15-day period) after 1 month of treatment in order to limit steroid-induced adverse effects, whereas for VGB responders, a stable VGB dose was maintained throughout. At the end of 2 months (8 weeks), responders to VGB could be maintained on VGB on a long-term basis.

The primary efficacy endpoint in this study was based on the number spasms and the proportion of patients with a total disappearance of IS. Seizure counts were determined each day by the nurse and/or the investigator (if the patient was hospitalized) and/or by the parents (guardian) at home. The proportion of responders and time to response were both primary efficacy parameters. The primary efficacy was assessed at 1 month and 2 months.

The secondary efficacy endpoints were:

- Counting of other types of seizures (if any)
- EEG pattern variations
- Global efficacy assessment, performed by the physician and focusing on the variations of seizure frequency/severity, the patient's general well-being, and the patient's behavior

- Assessment of psychomotor development, performed using the Brunet Lézine test

Following the completion of the 2-month study period, a long-term follow-up was carried out in most of the patients. During the follow-up, relapse of IS and the occurrence of other types of seizures were assessed.

5.3.4.2 Study FR03 Efficacy

PROTOCOL SPECIFIED PRIMARY EFFICACY ENDPOINT

All 11 patients who received VGB as the first treatment achieved a complete response; therefore, no patients were crossed over to the hydrocortisone group (Table 44). Four of 11 patients randomized to receive HC became spasm-free by the 1 month assessment. All 7 hydrocortisone non-responders achieved spasm-freedom when crossed over to VGB therapy for the second month. The proportions of patients with total spasm cessation were significantly different between the 2 treatment groups (p=0.001).

Table 44. Response to Treatment (Freedom from Spasms) – Study FR03

	Month 1 Treatment		Month 2 Treatment	
	VGB [N=11]	**Hydrocortisone [N=11]**	**Hydrocortisone [N=0]**	**VGB [N=7]**
Patients who achieved spasm freedom	11	4	--	7
p-value vs hydrocortisone		0.001		--

The time to response for the responders was significantly shorter for the patients who received VGB as the first treatment (4 days) compared to the patients who received hydrocortisone (13 days) (p=0.058) (Table 45). In a comparison of overall treatment, the time to response was also significantly shorter in first or second line treatment with VGB (3 days) compared to hydrocortisone treatment (13 days) (p=0.01).

Table 45. Time to Response (Freedom from Spasms) – Study FR03

Parameter	Treatment		p-value
	VGB First	Hydrocortisone First	
	N=11	N=11	
Time to response (days)			
Mean (SD)	4.0 (5.1)	12.8 (11.9)	0.058
	VGB Second	Hydrocortisone Second	
	N=7	N=0	
Time to response (days)			
Mean (SD)	2.4 (1.3)	--	
	VGB Overall	Hydrocortisone Overall	
	N=18	N=4	
Time to response (days)			
Mean (SD)	3.48 (4.08)	12.8 (11.9)	0.01

SECONDARY EFFICACY

Other Types of Seizures

One patient (in the VGB-first group) had other types of seizures, specifically, minor partial seizures; however, these seizures did not justify the prescription of concomitant AEDs.

Improvement in EEG

A total of 16 patients received EEG examinations after the 8 week treatment phase. Although EEG data were missing for some patients, an improvement was observed after 8 weeks of treatment in 8 of 10 patients initially randomized toVGB. In the hydrocortisone-first group, the influence of hydrocortisone was more difficult to evaluate since most patients had been crossed over to the VGB group (the effect of each drug separately was therefore impossible to assess). However, the 4 patients who remained on hydrocortisone had an EEG pattern assessed as improved.

Physician Global Assessment of VGB Efficacy

In the physician's global efficacy assessment, 11/11 VGB patients had seizure frequency/severity classified as markedly improved, and 9/11 had general well-being classified as markedly improved. Marked improvement in behavior was also observed for 6/11 VGB patients, and 4/11 patients had moderate improvement in behavior. The results in the hydrocortisone group were less clear, particularly in the 4 patients maintained with hydrocortisone; there was no apparent correlation between marked improvement in seizure frequency/severity and the lack of improvement in general well-being and/or behavior in 2 of these patients.

Statistical analyses of the physician global assessments were performed using Fisher's exact test to compare the 2 treatments in the first treatment period. Given the small numbers of patients, the response categories were aggregated to improvement (marked or moderate) versus no improvement (unchanged or worse). Statistically significant differences in improvement were seen in general well-being (11/11 VGB versus 5/11 hydrocortisone, p=0.0124) and behavior (10/10 VGB versus 4/11 hydrocortisone, p=0.0039). There was also a trend favoring VGB in seizure-frequency severity scores (11/11 VGB versus 7/11 hydrocortisone, p=0.0902).

Psychomotor Development

In the assessment of psychomotor development, the evaluation of a developmental quotient (assessed with the Brunet Lézine test) was performed in 11 patients before and after treatment, precluding any statistical testing. Patients initially receiving VGB who underwent this test twice had an improvement in developmental quotient, although it appeared to be mild in some cases. Three of the 4 patients maintained on hydrocortisone (and not crossed over to VGB) were tested both before and after treatment, and all 3 exhibited a stable or improved developmental quotient. The 2 patients crossed over from HC to VGB had mild decreases in developmental quotient (53 to 32 and 76 to 64).

Long Term Follow-up

In the efficacy evaluations for the post-study follow-up, only patients who were followed for at least 2 years were included (14/18 VGB patients and 4/4 hydrocortisone patients). These evaluations included relapse of spasms, occurrence of other types of seizures, and the use of concomitant AEDs. The results are shown in Table 46.

Table 46. Efficacy Results During Long-term Follow-up – Study FR03

Parameter	VGB (N=14)	Hydrocortisone (N=4)	p-value
Duration of follow-up (years), mean (SD)	2.41 (0.90)[a]	2.13 (0.75)	NS
Number of patients with relapse of IS	3	0	
Time to relapse (months), mean (range)	3.7 (3.5-5)	--	
Number of patients with occurrence of partial seizures	11	3	
Number of patients maintained on monotherapy (%)	3 (21)	1 (25)	NS

[a] N for VGB group is 13 for duration of follow-up.

Relapse was observed in 3 patients, all of whom had received VGB as their first therapy. Relapse occurred after a mean period of control of IS of 3.7 months (range: 3.5 to 5 months). No relapse was reported in the 4 hydrocortisone patients. Statistical analysis was not performed owing to the small sample size of the hydrocortisone group.

The occurrence of partial seizures was reported for 11/14 VGB patients and for 3/4 hydrocortisone patients. These seizures generally occurred within the first 6 months following the end of the initial study. Following the occurrence of partial seizures, concomitant antiepileptic therapy had to be initiated in most patients. One patient received no

concomitant therapy for clinically minor partial seizures. All other patients received CBZ; 4 patients also received clobazam, and one patient also received stiripentol.

5.3.5 Study W019

5.3.5.1 Study W019 Design and Efficacy Assessments

W019 (N=40, between 4 and 20 months of age) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study consisting of a pre-treatment (baseline) period of 2-3 days, followed by a 5-day double-blind treatment phase during which patients were treated with VGB (initial dose of 50 mg/kg/day with titration allowed to 150 mg/kg/day) or placebo. Patients were then followed for a period of 6 months, during which all patients continuing in the study were treated with VGB in an open-label fashion.

Efficacy was assessed by spasm count (spasm frequency and number), seizure count, EEG-determined hypsarrhythmia, physician global rating scale, and testing of psychomotor development. For the purposes of this study, a "spasm" was defined as a sudden, generally bilateral and symmetrical contraction of muscles of the neck, trunk, and extremities (flexor, extensor, or mixed). A number of these spasms occurring together (≥5) was classified as a "cluster." The primary efficacy endpoint in this study was the average percent change in daily spasm frequency, assessed during a pre-defined and consistent 2-hour window, from baseline to the end of the double-blind study period, where end of the double-blind study period was defined as the final 2 days of the period.

Secondary efficacy parameters during the double-blind period included:

- The average percent change in daily spasm frequency, assessed over the whole 24-hour period, from baseline to the end of the double-blind period, where end of the double-blind period was defined as the final 2 days of the period.
- The number of patients achieving cessation of spasms on the final day of the double-blind period, as assessed over the whole 24-hour period.
- The average percent change in frequency of clusters from baseline to the end of the double-blind period, assessed during a pre-defined 2-hour window and over the whole 24-hour period.
- The average percent change in the duration of clusters from baseline to the end of the double-blind period.
- EEG findings (proportion of patients showing disappearance of hypsarrhythmia at the final study visit.
- The investigator's assessment of efficacy on the final day of the double-blind period.

The data from the open-label phase of the study were investigated as an integral part of the entire study (ie, the double-blind and open-label phases combined). For the open-label phase data, the baseline was taken as the double-blind phase baseline. The following efficacy endpoints were investigated:

- Percentage change from baseline in spasm counts.
- Number of responders to VGB therapy. A responder:
  - Was spasm-free for a continuous 4-week period at any stage in the open-label phase, irrespective of whether the patient completed the study;
  - Did not receive, at any time before the end of the responder-defining period, any antiepilepsy or antispasm concomitant medication (ie, a medication indicated for "infantile spasm" or a medication not indicated for "infantile spasm" but with potential for antispasm activity, taken for more than 48 hours).
- Number of therapeutic successes. Therapeutic success patients:
  - Completed the open-label phase to the end;
  - Were spasm-free for the last 12 weeks of the open-label phase (complete data being required);
  - Did not receive, at any time, any antiepilepsy or antispasm concomitant medication (as defined above).
- Time to response for responders and for therapeutic successes.
- EEG findings (presence of hypsarrhythmia at the final study visit [ie, week 24 or whenever the patient withdrew from the study]).
- Psychomotor development (Denver test results at the final study visit).
- The investigator's assessment of efficacy at the final study visit (efficacy for spasm, seizure, and overall benefit).

5.3.5.2 W019 Efficacy Results during Double-Blind Period

PROTOCOL SPECIFIED PRIMARY EFFICACY ENDPOINT

The primary efficacy variable was the percentage change in the average frequency of spasms as assessed from the 2-hour intensive monitoring window, from baseline to the end of the double-blind period, where the end of the double-blind period was defined as the last 2 days of that treatment period. The difference in reduction of spasms between VGB and placebo was not statistically significant, 54.4% vs 41.5% (p=0.562). Unfortunately, the sampling window of 2 hours per day was poorly chosen since, 1) it provided an inadequate observation window to detect spasms, and 2) it assumed constancy of spasms at the same time each day; therefore treatment effects could not be discerned.

The results in the 2 treatment groups were similar, with 8 patients in each group (40% placebo group and 47% VGB group) achieving greater than 70% improvement (ie, reduction in spasm frequency), and 3 patients in each treatment group (15% of placebo and 18% of VGB patients) achieving 40% to 69% improvement during the 2-hour time window. However, in the placebo group, 8 patients (40%) had no improvement or worsened as compared with 4 patients (24%) in the VGB group.

In an analysis of the primary endpoint, using a log analysis, least squares means (ie, the estimates of the percentage of baseline spasms still present after treatment) in the 2-hour sampling window were 45.6% (95% CI: 24% to 88%) in the VGB group and 59.5% (95% CI: 30% to 117%) in the placebo group, indicating a relative ratio benefit of VGB over

placebo of 0.766 (95% CI: 0.305-1.929). In this case, a relative ratio benefit of VGB over placebo exists if this ratio is less than 1. Equivalently, this means that the percentage reduction in spasms in the VGB group was 54.4% (95% CI:, 12% to 76%) compared with 41.5% (95% CI: 17% to 70%) in the placebo group. This treatment difference was not statistically significant (p=0.562).

SECONDARY EFFICACY

Percentage Change in the Average Frequency of Spasms (24-Hour Intensive Monitoring Window)

In the secondary efficacy analysis of the 24-hour monitoring window, the differences between the treatment groups were much greater than for the 2-hour window (Table 47), with 8 patients (40%) in the VGB group and 3 patients (15%) in the placebo group achieving greater than 70% improvement. LS means (i.e., the estimates of the percentage of baseline spasms still present after treatment) (95% CI's) were, in the VGB group 31.1% (17 to 58%) and in the placebo group 83.0% (43% to 159%). Equivalently, this means the overall percent reduction in spasms in the VGB group in this analysis was 68.9% (95% CIs: 42% to 83%) compared with 17.0% (95% CI: 59% to 57%) in the placebo group; this difference was statistically significant (p=0.030). This measure of spasm frequency is considered a more clinically appropriate and more rigorous measure.

Table 47. Percentage Change in Average Frequency of Spasms at the 24-Hour Timepoint, Double-blind Phase (over Final 2 Days) – Study W019

	Treatment Group			
Percent Improvement	**Placebo [N=20] n (%)**	**VGB [N=20] n (%)**	**Total [N=40] n (%)**	**p-value[a]**
≥70%	3 (15)	8 (40)	11 (28)	
40-69%	3 (15)	3 (15)	6 (15)	
1-39%	4 (20)	5 (25)	9 (23)	
≤0%	10 (50)	4 (20)	14 (35)	
Mean % improvement (95% CI)	17% (-59%-57%)	69% (42%-83%)		0.030
Percentage (%) of Baseline Spasms Still Present after Treatment				
Mean[b]	83.0%	31.1%	0.374[c]	
95% CI[b]	(43%-159%)	(17%-58%)	(0.155-0.902)[c]	0.030

a. P-value taken from final model from log analysis.

b. The mean and 95% CIs for this primary variable are taken from the final log model over the complete distribution.

c. Relative risk with corresponding CIs of VGB/placebo from the final log model.

Spasm Freedom

For the secondary efficacy analyses on cessation of spasms, the percentage of patients achieving complete cessation of spasms (0 or 1 spasm) on the final day of the double-blind period was 45.0% in the VGB group compared with 15.0% in the placebo group (p=0.036).

When cessation of spasm was taken to mean no spasm at all on the final day of the double-blind period, 7 (35%) of patients in the VGB group compared with 2 (10%) patients in the placebo group showed complete cessation of spasms (p=0.063).

Spasm Clusters

The results of the secondary efficacy analyses on spasm clusters (frequency and duration) were similar to those of overall spasm frequency in that no statistically significant differences between treatment groups were observed for the 2-hour monitoring window for either cluster frequency or duration. For the 2-hour window, 11 (55%) of patients in the VGB group had a 40% or greater reduction in cluster frequency compared with 10 (50%) in the placebo group (p=0.820). For the 24-hour window, also in the double-blind phase of the study, the differences between treatment groups for cluster frequency were greater, with 13 (65%) of patients in the VGB group achieving 40% or greater reduction in cluster frequency compared with 8 (42%) patients in the placebo group (p=0.068).

For the 24-hour window for cluster duration, 8 patients (42%) in the VGB group had a 70% or greater reduction in the duration of spasm clusters compared with 4 patients (22%) in the placebo group. Nine patients (50%) in the placebo group compared with 3 patients (16%) in the VGB group had no reduction or an increase in the duration of spasm clusters. These treatment differences were statistically significant (p=0.023).

Subgroup Analyses of Spasm-Free Status by IS Etiology and Age at Onset

The overall effect of treatment (i.e., cessation of spasms, some decrease in number of spasms, or no reduction or increase in number of spasms) for all patients (in the ITT population) was examined by 2 IS etiologies (cryptogenic or idiopathic versus symptomatic). The overall effectiveness, regardless of etiology, was greater in the VGB-treated patients than in the placebo-treated patients, although the number of patients in each category was small. In the cryptogenic + idiopathic category, 3 of 6 VGB treated patients achieved complete spasm cessation, compared to 2 of 6 placebo patients. In the symptomatic category 4 of 14 VGB treated patients achieved complete spasm cessation compared to 0 of 14 placebo patients.

This study examined efficacy by age at onset. All age groups (≤4 months, 5 to 8 months, 9 to 12 months, ≥12 months) treated with VGB had better response than did the analogous age groups treated with placebo; however, the number of patients in each age group category was too small to determine any definitive trends in efficacy based on age of IS onset.

Improvement in EEG

In the secondary analysis of the effect of study treatment on hypsarrhythmia, the results showed that more VGB-treated (20.0%) than placebo-treated (5.0%) patients had complete disappearance of hypsarrhythmia by day 8, although this difference did not achieve statistically significance (p=0.342).

Investigator's Overall Assessment of Efficacy

In the investigator's overall assessment of efficacy (double-blind phase), the differences between treatment groups were statistically significant in favor of VGB treatment ($p<0.001$) (Table 48). In addition, the investigator recorded whether or not the patient had benefited from study treatment. In the VGB group, 16 patients (84%) were considered to have benefited from treatment compared with 3 patients (15%) in the placebo group.

Table 48. Investigator's Overall Assessment of Efficacy on Final Day of Double-blind Phase – Study W019

	Treatment Group		
Changes Observed	**Placebo [N=20] n (%)**	**VGB [N=20] n (%)**	**Total N=40 n (%)**
Marked improvement	2 (10)	9 (45)	11 (28)
Moderate improvement	1 (5)	7 (35)	8 (20)
Minimal improvement	2 (10)	1 (5)	3 (8)
Unchanged	11 (55)	3 (15)	14 (35)
Minimally worse	1 (5)	0 (0)	1 (3)
Much worse	3 (15)	0 (0)	3 (8)
p-value	<0.001		

5.3.5.3 W019 Efficacy Results during Open-Label

SPASM COUNT

For spasm count, of the 25 patients with spasm data at week 24, 22 demonstrated a decrease in their spasm count of at least 70% compared with baseline. The remaining 3 patients all had an increased spasm count compared with baseline; these 3 patients had all received VGB plus other anti-spasm medication during the study.

RESPONDERS

A total of 15 patients were classified as responders to VGB, representing 38% of all patients who entered the study and 42% of those who entered the open-label phase. Response was defined as a spasm-free period of 4 weeks or more. Of the patients who responded, 9 (60%) did so within 2 weeks of the initiation of treatment; the mean (± SD) time to response was 1.5±1.1 weeks (range: 0 to 4 weeks).

THERAPEUTIC SUCCESS

Eleven patients could be classified as therapeutic successes with VGB first-line monotherapy. Therapeutic success was defined as complete absence of spasms in the final 12 weeks of the open-label phase in patients taking no other anti-spasm medications. Time to response for therapeutic successes was the same as that for all responders (ie, mean of 1.5 weeks).

PSYCHOMOTOR DEVELOPMENT

Thirty six patients underwent the Denver Developmental test at the end of the open label phase. Seven patients achieved a normal Denver test result at the end of the study; all 7 were classified as therapeutic successes. Three patients who were suspect at baseline became normal at end of study. All patients who had a normal Denver test by the end of study had responded to VGB monotherapy. No patients had normal Denver tests in the non-responder group. Five patients were untestable, and 6 had incomplete testing. Of the untestable patients, none were responders. This is consistent with the need to have complete response, that is, elimination of spasms and hypsarrythmia, to improve psychomotor development. Unfortunately, 6 patients had missing baseline or end of study tests, including both responders and nonresponders. This precluded a more rigorous analysis of therapeutic effect on development. No patients rated as normal at baseline worsened, i.e., were rated as suspect, at the end of the study. This demonstrates that VGB did not lead to worsening of mental development. These findings support the importance of achieving complete spasm control in order to allow normal development. It also demonstrates that patients who did not respond to therapy did not attain normal development.

INVESTIGATOR'S OVERALL ASSESSMENT OF EFFICACY

The percentages of patients (N=36) with improvement in the open-label period investigator's assessment of spasms were 65% (marked improvement), 12% (moderate improvement), and 6% (minimal improvement). Seventy-six percent of patients (26/36) were considered by the investigator to have benefited from their treatment as either VGB monotherapy or in combination with other AEDs.

For the investigator's assessment of seizures other than spasms during the open-label period, the percentage of patients (N=36) marked "not applicable" (meaning this percentage of patients had no other seizures during the open-label follow-up) was 69% (22/36); the remaining patients were classified as having marked improvement (9%), moderate improvement (3%), minimal improvement (6%), no change (9%), or worsened (3%).

5.3.6 Uncontrolled Studies: 332.5 and 3E01

5.3.6.1 Study Design and Efficacy Assessments

Study 332.5 was an open-label, single-center study designed to evaluate the safety and efficacy of VGB as adjunctive therapy in infants and children with drug-resistant IS. The study was composed of 3 phases. During the 2- to 4-week baseline phase, patients maintained a stable dose of their usual AEDs. During the 3-month evaluation phase, VGB was to be added to the usual AED regimen, and the dose of VGB (50 to 150mg/kg/day) was optimized. During the long-term phase, patients who had achieved >50% reduction in spasm frequency continued on long-term VGB treatment. Efficacy endpoints included spasm frequency and severity and physician and patient overall assessment.

Study 3E01 was a retrospective data collection in 11 European countries involving records of patients diagnosed with IS who had been treated with VGB as their first drug. Data were collected on a paper CRF from original case records. Diagnosis and etiology of IS were

confirmed by EEG (and video EEG, if available), MRI and/or CT scans, and clinical records. All source data were verified during on-site monitoring visits. All patient data were subsequently presented before a peer review committee to confirm diagnosis. Efficacy assessments included the number of spasm clusters per day occurring before and after treatment, occurrence of relapse, and response to treatment at the final visit.

5.3.6.2 Efficacy Results

In these 2 studies, a total of 235 patients were evaluable for efficacy. Initial VGB doses ranged from 50 to 161 mg/kg/day, and doses during long-term treatment ranged from 25 to 400 mg/kg/day. In Study 3E01, the initial mean dose was 61 mg/kg/day and mean steady-state dose was 99 mg/kg/day. In Study 332.5, the average dose was not reported across the study population as a whole.

In the uncontrolled Study 332.5, response to VGB was defined as a greater than 50% reduction in spasms. This reduction was observed in 31/43 patients (72%) and complete suppression was achieved in 20 patients (46.5%) at the end of the evaluation phase.

In the uncontrolled, retrospective Study 3E01, 131 patients (68.0%) were classified as having complete cessation of spasm clusters after initiation of VGB. An additional 37 patients (19.3%) were reported as having a decrease in the frequency of clusters. Twenty-four patients (12.5%) showed no improvement in spasm frequency and 1 patient (0.5%) was reported to have deteriorated following VGB treatment.

Time to response was only reported for patients in Study 332.5 who had TS (8 patients). Of these 8 patients, 6 achieved complete suppression of spasms within 1 month of starting VGB therapy at daily doses ranging from 40 to 120 mg/kg/day (mean=68 mg/kg/day). Eventually, all 8 had complete cessation of spasms with follow up periods of 7 to 23 months. In both studies, improvement with VGB therapy was more pronounced in patients with symptomatic IS, especially in those with TS, compared with patients who had cryptogenic IS. In Study 332.5, subgroup analyses showed that efficacy of VGB was greater in patients whose duration of spasms was <12 months prior to study entry, and in Study 3E01, efficacy was more pronounced in patients whose age of IS onset was <3 months.

The incidence of relapse for those who attained initial complete cessation of spasms on VGB was 21% in Study 3E01. In Study 332.5, 5/33 patients (15%) had a recurrence of spasms after an initial decrease and 22/23 maintained the level of spasm control obtained in the evaluation phase which included complete and partial control of spasms. Twenty of 33 were spasm-free at the time of last visit with a duration of treatment from 4 to 23 months. Thus, in the uncontrolled studies, long-term treatment with VGB (ranging from 3 months to 29 months) resulted in continued spasm control for the majority of treated patients.

In Study 332.5, formal neurological examinations including mental status and psychomotor function were performed before, during and after VGB treatment in 45 patients. Changes in neurologic and mental status were noted in 34 patients. An improvement in psychomotor function was reported in 30 patients, ranging from an increase in alertness to the reappearance of mental development: language, motor coordination and social behavior.

These improvements were noted as early as the second study visit, which corresponded to approximately 30 days of VGB treatment, and the changes continued to be present for the duration of the long-term follow-up period (up to 23 months). In 4/8 patients in whom developmental or intellectual quotient was assessed before and after VGB treatment, there were objective signs of these children catching up to their age appropriate mental development. Deterioration was noted in 1 patient with transient hypotonia without recurrence upon reintroduction of VGB treatment. In 3 patients, little or no change in psychomotor function occurred.

Study 332.5 concluded that VGB effectively reduced seizure frequency in patients with refractory IS. Study 3E01 concluded that the efficacy of VGB as first treatment for IS and for long-term treatment seemed comparable to that of ACTH and valproate and better than that of benzodiazepines.

5.3.7 Summary of Efficacy in Uncontrolled Studies Reported in Literature

A review of published literature reveals 33 uncontrolled or retrospective studies of VGB in the treatment of patients with IS. The uncontrolled studies reported in the literature included approximately 900 patients who received VGB. Nineteen studies reported exclusively on patients under the age of 28 months, 13 were in IS and 6 in West syndrome. VGB doses of 10 to 250mg/kg/day were administered. Patients were followed for up to 5 years, with 1 retrospective study following patient for a median of 10 years [178]. As with the controlled studies in the literature, reports from uncontrolled studies showed that VGB was effective in treating IS and that it could be used as first-line therapy and/or as monotherapy. For the majority of the studies, response rates (spasm cessation) were between 30% and 80%, and response occurred within 2 weeks for the majority of those that specified a time period [160, 179-189]. For those studies in which a relapse rate was reported, rates ranged from 0% to 23.5% [160,179,180,182,187,189,190-196]. Most of the VGB articles (both controlled and uncontrolled studies) reported better response in patients with symptomatic IS than in those with those cryptogenic IS, although 2 of the uncontrolled studies reported better VGB efficacy in patients with spasms of cryptogenic etiology [197, 198].

5.4. Safety in Infantile Spasms

5.4.1 IS Safety Populations

A total of 347 patients from 9 clinical studies were analyzed for safety. A list of all studies included in the safety analysis is presented in Table 49. Four IS studies were included in the analysis in addition to 21 patients primarily <36 months of age from 5 non-IS studies. Safety in IS was analyzed for 3 populations: 1) *Controlled IS Population*, 2) *Uncontrolled IS Population*, and 3) *Infant Epilepsy Non-IS Population*.

Controlled IS Population
The *Controlled IS Population* includes all IS patients with available data, regardless of age, from Study 1A, Study W019 (double-blind period only), and Study FR03. Data from Study 1A includes 2 patients >36 months of age (3.1 and 3.9 years) and 4 patients of unknown age.

Uncontrolled IS Population

The *Uncontrolled IS Population* includes all patients with available data, regardless of age, from Study W019 (open-label period only) and Study 097-332.5. Data from Study 097-332.5 includes 8 patients >36 months of age (37, 46, 62, 88, 90, 98, 119, and 150 months old). An additional uncontrolled study in patients with IS (Study 3E01) was not included in this analysis because its retrospective construction from case records did not ensure appropriate surveillance for and reporting of untoward events. Although not presented in the summary tables below, AEs, SAEs, discontinuations due to AEs, and deaths in Study 3E01 are described in text.

Infant Epilepsy Non-IS Population

The *Infant Epilepsy Non-IS Population* includes all patients <36 months of age with available data who were enrolled in the uncontrolled refractory epilepsy studies 097-300, 097-314, 097-332, 097-W345A, and WIT01. One exception was Study WIT01 which included 2 patients >36 months of age (40 and 118 months). Although these patients were not from IS studies, they are included in order to provide a complete safety profile of the effect of VGB in the intended age range for IS treatment.

Table 49. Studies and Patients Included in the IS Safety Populations

	Hydrocortisone [N]	Placebo [N]	VGB [N]
Controlled IS Population			**261**
1A	--	--	223[a,b]
W019 (double-blind period only)	--	20	20[c]
FR03	12	--	18
Uncontrolled IS Population			**81**
W019 (open-label period only)	--	--	36[c]
097-332.5	--	--	45[d]
Infant Epilepsy Non-IS Population (all uncontrolled)			**21**
097-300	--	--	2
097-314	--	--	1
097-332	--	--	4
097-W345A	--	--	3
WIT01	--	--	11[a]

a. Includes 2 patients >36 months of age.

b. Includes 4 patients of unknown age.

c. Forty patients in W019 were exposed to VGB (20 double-blind + 36 open-label minus 16 exposed in both double-blind and open-label).

d. Eight patients were >36 months of age.

e. Includes all patients <36 months of age with available data who were enrolled in refractory epilepsy studies 097-300, 097-314, 097-332, 097-W345A, and WIT01.

5.4.2 Exposure

Exposure to VGB is summarized in Table 50 for IS and infant epilepsy non-IS patients. VGB exposure in all epilepsy studies (previously displayed in Table 9), is also presented.

Total exposure to VGB in all epilepsy studies was 8780 years (3,206,984 days). Over half of epilepsy patients were treated with VGB for more than 1 year. Approximately 4% of VGB exposures in all epilepsy studies occurred in patients analyzed for IS safety (130,013 days). A total of 221 patients in the total IS population (IS + infant epilepsy non-IS patients) were treated with VGB for more than 6 months. Of these 221 patients, 145 patients received more than 1 year of treatment with VGB.

Table 50. VGB Exposure: Total IS Safety (IS Patients + Infant Epilepsy Non-IS Patients) and All Epilepsy Studies

	Total IS (IS Patients + Infant Epilepsy Non-IS Patients)[a] VGB [N=347]	All Epilepsy Studies[b] VGB [N=4857]
Number of patients exposed	347	4857
Total patient days of exposure	130013	3206984
Total patient years of exposure	356	8780
Mean patient days of exposure	n=346	n=4715
Mean (SD)	375.8 (315.52)	680.2 (771.62)
Median	290	461
Range	2, 1759	1, 6173
Number of patients dosed, n (%)[c]		
1–14 days	7 (2.0)	51 (1.1)
>14–30 days	9 (2.6)	86 (1.8)
>30–60 days	32 (9.2)	228 (4.7)
>60–90 days	16 (4.6)	295 (6.1)
>90 days–6 months	61 (17.6)	599 (12.3)
>6 months–1 year	76 (21.9)	703 (14.5)
>1–2 years	95 (27.4)	1123 (23.1)
>2–3 years	36 (10.4)	926 (19.1)
>3–5 years	14 (4.0)	301 (6.2)
>5–10 years	0	336 (6.9)
>10 years	0	67 (1.4)
Missing	1 (0.3)	142 (2.9)

a. Includes patients from IS studies and 21 patients primarily <36 months of age from non-IS studies (see Table 49).

b. Exposure for all U.S., primary non-U.S., and secondary non-U.S. epilepsy studies (including non-IS and IS studies). Excludes exposures from non-epilepsy/IS indications such as tardive dyskinesia, psychiatric disorders, ataxia and tremor, Huntington's Disease, spasticity, Parkinson's, dystonia and torticollis, and clinical pharmacology studies (in epilepsy patients, healthy subjects, and renally impaired patients).

c. Percentages are with respect to the number of patients exposed for each population.

5.4.3 Adverse Events in Infantile Spasms Safety Populations

5.4.3.1 Controlled IS Population

In the controlled studies of IS, 84.7% of VGB-treated patients experienced at least 1 AE, similar to the incidence observed with hydrocortisone (83.3%) (Table 51). The incidence of AEs was lower in placebo-treated patients (35.0%). It should be noted that this finding could be attributed to the fact that the only placebo patients were the 20 in W019 whose duration of exposure to placebo was much shorter (1–8 days). VGB patients in Study 1A were exposed to VGB for up to 3 years. In comparison, patients randomized to hydrocortisone in Study FR03 could have had a maximum exposure to hydrocortisone of approximately 6 weeks (1 month of treatment followed by a 15-day taper).

The most common AEs (≥5%) in VGB-treated patients were: 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%), 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%), and convulsion (5.4%). A majority of these events are not uncommon pediatric medical conditions and are not unexpected in long-term observation of a group of infants and children.

Table 51. Adverse Events Occurring in ≥5% of VGB-Treated Patients (Controlled IS Population)

System Organ Class Preferred Term	Placebo [N=20] n (%)[a]	Hydrocortisone [N=12] n (%)[a]	VGB [N=261] n (%)[a]
Any System Organ Class			
Any event	7 (35.00)	10 (83.33)	221 (84.67)
Infections and Infestations			
Any event	3 (15.00)	2 (16.67)	174 (66.67)
Upper respiratory tract infection	1 (5.00)	0 (0.00)	106 (40.61)
Otitis media	0 (0.00)	0 (0.00)	81 (31.03)
Viral infection	0 (0.00)	0 (0.00)	44 (16.86)
Pneumonia	0 (0.00)	0 (0.00)	29 (11.11)
Ear infection	0 (0.00)	0 (0.00)	24 (9.20)
Sinusitis	0 (0.00)	0 (0.00)	16 (6.13)
Bronchitis	0 (0.00)	0 (0.00)	15 (5.75)
Nervous System Disorders			
Any event	2 (10.00)	4 (33.33)	122 (46.74)
Somnolence	1 (5.00)	1 (8.33)	43 (16.48)
Sedation	0 (0.00)	0 (0.00)	40 (15.33)
Lethargy	0 (0.00)	0 (0.00)	15 (5.75)
Convulsion	0 (0.00)	0 (0.00)	14 (5.36)
Gastrointestinal Disorders			
Any event	2 (10.00)	4 (33.33)	92 (35.25)
Vomiting	1 (5.00)	1 (8.33)	37 (14.18)
Constipation	0 (0.00)	0 (0.00)	30 (11.49)
Diarrhea	1 (5.00)	0 (0.00)	28 (10.73)
Psychiatric Disorders			
Any event	0 (0.00)	7 (58.33)	82 (31.42)
Irritability	0 (0.00)	1 (8.33)	44 (16.86)
Insomnia	0 (0.00)	1 (8.33)	25 (9.58)
General Disorders and Administration Site Conditions			
Any event	1 (5.00)	2 (16.67)	83 (31.80)
Pyrexia	1 (5.00)	0 (0.00)	54 (20.69)
Respiratory, Thoracic and Mediastinal Disorders			
Any event	0 (0.00)	0 (0.00)	73 (27.97)
Nasal congestion	0 (0.00)	0 (0.00)	19 (7.28)
Skin and Subcutaneous Tissue Disorders			
Any event	2 (10.00)	0 (0.00)	55 (21.07)
Rash	1 (5.00)	0 (0.00)	21 (8.05)

Table 51. Adverse Events Occurring in ≥5% of VGB-Treated Patients (Controlled IS Population)

System Organ Class Preferred Term	Placebo [N=20] n (%)[a]	Hydrocortisone [N=12] n (%)[a]	VGB [N=261] n (%)[a]
Metabolism and Nutrition Disorders			
Any event	0 (0.00)	0 (0.00)	39 (14.94)
Decreased appetite	0 (0.00)	0 (0.00)	17 (6.51)

[a] Percentage is with respect to N, the total number of patients.

5.4.3.2 Uncontrolled IS Population

In uncontrolled studies of IS, 50.6% of patients experienced at least 1 AE (Table 52). The most common AEs (≥5%) included somnolence (12.4%), bronchitis (11.1%), and rhinitis (6.2%).

In the uncontrolled study 3E01 not included in this population due to its retrospective nature, a total of 33/250 patients (13.2%) experienced 42 AEs. The most frequently experienced AEs were: somnolence (15/42 events; 35.7%), hyperkinesia (8/42 events; 19.0%), insomnia (5/42 events; 11.9%), hypotonia (4/42 events; 9.5%), and nervousness (3/42 events; 7.1%). All other events were experienced only once each (agitation, asthenia, coma, laryngitis, myoclonus, diarrhea, and weight increase).

Table 52. Adverse Events Occurring in ≥2% of VGB-Treated Patients (Uncontrolled IS Population)

System Organ Class Preferred Term	VGB [N=81] n (%)[a]
Any System Organ Class	
Any event	41 (50.62)
Infections and Infestations	
Any event	20 (24.69)
Bronchitis	9 (11.11)
Rhinitis	5 (6.17)
Otitis media	3 (3.70)
Ear infection	2 (2.47)
Lower respiratory tract infection	2 (2.47)
Pharyngitis	2 (2.47)
Nervous System Disorders	
Any event	19 (23.46)
Somnolence	10 (12.35)
Hypotonia	4 (4.93)
Hypertonia	2 (2.47)
Psychiatric Disorders	
Any event	10 (12.35)
Insomnia	3 (3.70)
Irritability	3 (3.70)
Agitation	2 (2.47)
Gastrointestinal Disorders	
Any event	8 (9.88)
Constipation	3 (3.70)
Diarrhoea	2 (2.47)
Vomiting	2 (2.47)
General Disorders and Administration Site Conditions	
Any event	6 (7.41)
Pyrexia	2 (2.47)
Investigations	
Any event	5 (6.17)
Weight increased	2 (2.47)
Blood and Lymphatic System Disorders	
Any event	2 (2.47)
Anemia	2 (2.47)

[a] Percentage is with respect to N, the total number of patients.

5.4.3.3 Infant Epilepsy Non-IS Population

For the *Infant Epilepsy Non-IS Population*, 33.3% of patients experienced at least 1 AE, and the only AE that occurred in more than 1 patient was hyperkinesia (2 of 21 patients; 9.5%) (Table 53).

Table 53. Adverse Events Occurring in Any VGB-Treated Patient (Infant Epilepsy Non-IS Population)

System Organ Class Preferred Term	VGB [N=21] n (%)[a]
Any System Organ Class	
Any event	7 (33.33)
Nervous Systems Disorders	
Any event	5 (23.81)
Hyperkinesia	2 (9.52)
Psychomotor hyperactivity	1 (4.76)
Sedation	1 (4.76)
Somnolence	1 (4.76)
Investigations	
Any event	1 (4.76)
Weight increased	1 (4.76)
Metabolism and Nutrition Disorders	
Any event	1 (4.76)
Increased appetite	1 (4.76)
Psychiatric Disorders	
Any event	1 (4.76)
Bulimia nervosa	1 (4.76)
Irritability	1 (4.76)

[a] Percentage is with respect to N, the total number of patients.

5.4.4 Serious Adverse Events in Infantile Spasms Safety Populations

5.4.4.1 Controlled IS Population

It is important to note the differential exposures reflected in this safety dataset, as previously noted in Section 5.4.3.1. In the controlled studies of IS, 28.7% of VGB-treated patients experienced at least 1 SAE (Table 54). SAEs with the highest incidence in VGB-treated patients were status epilepticus (4.2%) and pneumonia (3.8%). As mentioned in Section 5.4.3.1, SAEs of infectious nature, such as pneumonia, are common in this age group.

All SAEs occurred in Study 1A, which is not unexpected considering the longer duration of the study (up to 3 years). No SAEs were reported for hydrocortisone- or placebo-treated patients.

Table 54. Serious Adverse Events Occurring in ≥2 VGB-Treated Patients (Controlled IS Population)

System Organ Class Preferred Term	Placebo [N=20] n (%)[a]	Hydrocortisone [N=12] n (%)[a]	VGB [N=261] n (%)[a]
Any system organ class			
Any event	0	0	75 (28.74)
Infections and Infestations			
Any event	0	0	32 (12.26)
Pneumonia	0	0	10 (3.83)
Viral infection	0	0	4 (1.53)
Lobar pneumonia	0	0	3 (1.15)
Bronchitis	0	0	2 (0.77)
Gastroenteritis	0	0	2 (0.77)
Infection	0	0	2 (0.77)
Pneumonia viral	0	0	2 (0.77)
Respiratory syncytial virus infection	0	0	2 (0.77)
Urinary tract infection	0	0	2 (0.77)
Nervous System Disorders			
Any event	0	0	22 (8.43)
Status epilepticus	0	0	11 (4.21)
Convulsion	0	0	5 (1.92)
Infantile spasms	0	0	3 (1.15)
Febrile convulsion	0	0	2 (0.77)
Hydrocephalus	0	0	2 (0.77)
Partial seizures	0	0	2 (0.77)
Respiratory, Thoracic, and Mediastinal Disorders			
Any event	0	0	18 (6.90)
Bronchospasm	0	0	4 (1.53)
Respiratory arrest	0	0	3 (1.15)
Pneumonia aspiration	0	0	2 (0.77)
Respiratory distress	0	0	2 (0.77)
General Disorders and Administration Site Conditions			
Any event	0	0	13 (4.98)
Pyrexia	0	0	6 (2.30)
Death	0	0	3 (1.15)
Cyst	0	0	2 (0.77)
Unevaluable event	0	0	2 (0.77)

Table 54. Serious Adverse Events Occurring in ≥2 VGB-Treated Patients (Controlled IS Population)

System Organ Class Preferred Term	Placebo [N=20] n (%)[a]	Hydrocortisone [N=12] n (%)[a]	VGB [N=261] n (%)[a]
Gastrointestinal Disorders			
Any event	0	0	9 (3.45)
Gastroesophageal reflux disease	0	0	3 (1.15)
Vomiting	0	0	3 (1.15)
Metabolism and Nutritional Disorders			
Any event	0	0	6 (2.30)
Dehydration	0	0	3 (1.15)
Surgical and Medical Procedures			
Any event	0	0	5 (1.92)
Hospitalization	0	0	2 (0.77)

[a.] Percentages are with respect to N, the total number of patients in each study type.

5.4.4.2 Uncontrolled IS Population

In the uncontrolled IS studies, 4.9% of VGB-treated patients experienced at least 1 SAE (Table 55). The SAEs reported for this population, bronchitis, infection, lower respiratory tract infection, pneumonia, urinary tract infection, cardiac arrest, gastroesophageal reflux disease, and agitation, were each experienced by only 1 patient.

Table 55. Serious Adverse Events (Uncontrolled IS Population)

System Organ Class Preferred Term	VGB [N=81] n (%)[a]
Any System Organ Class	
Any event	4 (4.94)
Infections and Infestations	
Any event	3 (3.70)
Bronchitis	1 (1.23)
Infection	1 (1.23)
Lower respiratory tract infection	1 (1.23)
Pneumonia	1 (1.23)
Urinary tract infection	1 (1.23)
Cardiac Disorders	
Any event	1 (1.23)
Cardiac arrest	1 (1.23)
Gastrointestinal Disorders	
Any event	1 (1.23)
Gastroesophageal reflux disease	1 (1.23)
Psychiatric Disorders	
Any event	1 (1.23)
Agitation	1 (1.23)

[a] Percentage is with respect to N, the total number of patients.

5.4.4.3 Infant Epilepsy Non-IS Population

No SAEs were reported in the Infant Epilepsy Non-IS Population.

5.4.5 Discontinuations due to Adverse Events

5.4.5.1 Controlled IS Population

It is important to note the differential exposures reflected in this safety dataset, as previously noted in Section 5.4.3.1. AEs resulting in withdrawal from the controlled IS studies are summarized in Table 56. A total of 6.5% of VGB-treated patients in the *Controlled IS Population* withdrew from a study due to an AE. No placebo-treated patient and 33.3% of hydrocortisone-treated patients discontinued a study due to an AE.

Five AEs led to study withdrawal in ≥2 patients. These included status epilepticus, convulsion, infantile spasms, pneumonia, and death.

Two hydrocortisone-treated patients in Study FR03 experienced more than 1 event which led to study withdrawal. Patient 407012 withdrew from the study due to AEs of agitation, hypertension, opisthotonus, and sleep disorder, and Patient 407016 discontinued due to events of agitation, hyperkinesia, insomnia, and vomiting.

Four VGB-treated patients in Study 1A experienced more than 1 event which led to study withdrawal. Patient 280 withdrew from the study due to AEs of convulsion and rash; Patient 303 withdrew from the study due to AEs of gastrointestinal infection and postoperative infection; Patient 352 withdrew from the study due to events of pneumonia and status epilepticus; and Patient 406 experienced IS and hypertension and withdrew.

Table 56. Adverse Events Causing Withdrawal From Study Occurring in ≥2 VGB-Treated Patients (Controlled IS Population)

System Organ Class Preferred Term	Placebo [N=20] n (%)[a]	Hydrocortisone [N=12] n (%)[a]	VGB [N=261] n (%)[a]
Any system organ class			
Any event	0	4 (33.33)	17 (6.51)
Nervous System Disorders			
Any event	0	2 (16.67)	9 (3.45)
Status epilepticus	0	0	3 (1.15)
Convulsion	0	0	2 (0.77)
Infantile spasms	0	0	2 (0.77)
Infections and Infestations			
Any event	0	0	4 (1.53)
Pneumonia	0	0	2 (0.77)
General Disorders and Administration Site Conditions			
Any event	0	0	2 (0.77)
Death	0	0	2 (0.77)

[a] Percentages are with respect to N, the total number of patients in each study type.

5.4.5.2 Uncontrolled IS Population

AEs resulting in withdrawal from the uncontrolled IS studies are summarized in Table 57. A total of 4.9% of VGB-treated patients in the *Uncontrolled IS Population* withdrew from a study due to an AE. No AE leading to study withdrawal occurred in more than 1 patient.

Two patients in Study 097-332.5 experienced more than 1 event which led to study withdrawal. Patient 407332656 withdrew from the study due to AEs of hypertonia and insomnia, and Patient 407332628 discontinued due to events of developmental coordination disorder and hypotonia.

Two patients in Study 3E01 (retrospective uncontrolled study not included in the integrated analysis) had AEs leading to discontinuing VGB (Patient 07-06-05, severe myoclonic status; Patient 08-02-01, severe irritability). Patient 08-02-01 subsequently died of pneumonia, cytomegalovirus, hepatitis, and renal infection, 2 months after discontinuation of VGB.

Table 57. Adverse Events Causing Withdrawal From Study (Uncontrolled IS Population)

System Organ Class Preferred Term	**VGB** **[N=81]** **n (%)[a]**
Any System Organ Class	
Any event	4 (4.94)
Nervous System Disorders	
Any event	3 (3.70)
Developmental coordination disorder	1 (1.23)
Dystonia	1 (1.23)
Hypotonia	1 (1.23)
Hypertonia	1 (1.23)
Investigations	
Any event	1 (1.23)
Weight increased	1 (1.23)
Psychiatric Disorders	
Any event	1 (1.23)
Insomnia	1 (1.23)

[a.] Percentage is with respect to N, the total number of patients.

5.4.5.3 Infant Epilepsy Non-IS Population

One patient out of the 21 patients in the *Infant Epilepsy Non-IS Population* discontinued from a study due to an AE (hyperkinesia).

5.4.6 Deaths

Three deaths were included in the integrated safety database presented in the December 2007 NDA, all of which occurred in Study 1A. Another death, which occurred 2 days after completing vigabatrin treatment, was reported in the CSR for Study W019. Because this event occurred after study completion and in compliance with the reporting requirements at the time, it was not captured as a study event and therefore it was not included in the integrated safety database.

One death (sudden death of Subject 911 in Study 1A) occurred in a patient following a well baby visit and standard immunizations. The investigator indicated on the Adverse Event case report form that the relationship to vigabatrin was "Unknown", however, on the Serious Adverse Event case report form, the investigator reported that the event was "Unlikely" related to vigabatrin, therefore the death was characterized as unrelated to vigabatrin therapy. The sponsor believes this death would be considered a SUDEP (Sudden Unexplained Death in Epilepsy). The other deaths in the safety database were considered not related to vigabatrin treatment.

Further information on these 4 deaths is presented in Table 58.

Table 58. Deaths in IS Clinical Studies

Study	Subject Number Age[1]/Gender/Race	Reported Cause(s) of Death	Relationship to Vigabatrin	Other Reported Adverse Events
1A	461 7/Female/Black	Pneumonia, urinary tract infection	Not related	candidiasis, urinary tract infection, convulsion, status epilepticus
1A	559 1/Female/Caucasian	Pulmonary hemorrhage secondary to congenital pulmonary angiomatosis	Not related	pulmonary hemorrhage, vomiting
1A	911 5/Female/Black	Sudden death	Not related[2]	None
W019	103[3] 7/Female/Caucasian	Cardiac arrest	Not related	amaurosis, bronchitis, candidiasis, depressed level of consciousness, diarrhea, hypoacusis, hypotonia, infection, nervous system disorder, neurological examination abnormal, edema, pneumonia, rhinitis

[1] Age in months at time of entry into study.

[2] For this event of death in Subject 911, the investigator indicated on the Adverse Event case report form that the relationship to vigabatrin was "Unknown", however, on the Serious Adverse Event case report form, the investigator reported that the event was "Unlikely" related to vigabatrin, therefore the death was characterized as unrelated to vigabatrin therapy.

[3] This event for Study W019 Subject 103 occurred after study completion and was not captured as a study event; it is therefore not included in the integrated safety database but is discussed in the clinical study report.

Source: ISS

Four deaths were reported in the CSR of the uncontrolled study (Study 3E01) but were not included in the integrated safety database given the retrospective nature of the study. The causes of death were spinal motor atrophy (Subject 02-02-02); pneumonia, shock, and cardiac arrest (Subject 07-07-07); pneumonia, cytomegalovirus, hepatitis, and renal infection (Subject 08-02-01); and bronchopneumonia (Subject 11-03-02). None of the deaths were considered related to vigabatrin therapy. In 2 of these patients (Subjects 07-07-07 and 08-02-01), death occurred after vigabatrin therapy had been discontinued (7 months and 2 months, respectively, after stopping therapy.

Section 4.4.8. presents overall deaths for all clinical studies.

5.4.7 Psychiatric Events

For a summary of psychiatric events in all epilepsy studies as well as the *Controlled IS Population*, see Section 4.4.10.

5.4.8 Postmarketing Safety

Since the first marketed use of VGB in 1989, there has been extensive, cumulative postmarketing safety data from various nonclinical trial sources: spontaneous reports, literature, and from reports to regulatory authorities that establishes a well-defined safety profile in >1.5 million patients exposed. The overall safety profile that has emerged is generally consistent with that observed in clinical studies of VGB.

Reports of MRI abnormalities in patients with IS contained in the postmarketing database are discussed below.

5.4.9 Safety Issue of Special Concern

5.4.9.1 Peripheral Visual Field Defect

Information regarding the evidence of a causal relationship between VGB and peripheral pVFD, the clinical features of VGB-induced pVFD, and a summary of clinical studies conducted in adults and children with CPS are presented in Section 4.4.14.1.

TESTING VISION IN YOUNG INFANTS AND CHILDREN

Since the determination of effects on vision in infants and young children under 3 years of age cannot be accomplished by methods such as static and kinetic perimetry, which can be utilized to confirm retinal effects in adults [199], patient-specific and age-appropriate methods, including confrontation testing and full field ERG, may be used to monitor retinal function in infants. While informative, confrontation testing is not quantitative or extremely sensitive. While quantitative and sensitive, the performance of ERG requires sedation which carries some risk in the infant population.

As infants and young children grow, changes occur in retinal electrophysiology while the retina develops and matures, requiring comparison of electrophysiologic measures to age-appropriate normal patients. Alterations in certain ERG patterns specifically related to VGB have been identified. Among these, cone responses, particularly 30 Hz flicker and cone b-wave amplitudes, have been verified to be sensitive indicators of retinal effects in infants and children [154].

Developmental differences in patterns of ERG in infants and children have been noted [200]. In reporting on the evolution of retinal development in young infants, Westall and colleagues [201] noted that dark and light-adapted ERG a- and b-wave amplitudes reached adult levels by 3-5 years of age, although scotopic rod-mediated responses were slower to develop than photopic cone-mediated activity. They further reported that in infancy, the oscillatory potentials were least developed but matured rapidly by age 2 in most children. Morong et al [202] found that within about 6 months of initiation of VGB therapy, children developed a

reduction in the summed early photopic oscillatory potential (OP); suggesting that the earliest effect is on the depolarizing retinal pathways. Later work by this group demonstrated that alterations in the early OPs associated with VGB are reversible, that is, are not toxic effects. Alterations of some late OPs, in particular OP4 [201], may be correlated to VGB toxicity. Although similar to changes in other parameters, abnormalities even in the most sensitive parameters, do not develop in all infants [200-204]. Analysis of longitudinal data from a subset of 71 children prospectively assessed with the use of ophthalmoscopy and full flash ERG [201,202] showed that cone system ERGs demonstrate the greatest change from initial recordings. Sustained changes in 30 Hz flicker and cone b-wave amplitude indicate evidence of retinal effects and support similar findings by Harding et al [155]. Most of the alterations of early and late OPs and flicker implicit times are likely associated with a reversible drug effect and not with permanent retinal changes.

Electrophysiologic measurements of retinal function can be used to assess retinal effects using standard evoked potentials (EP) equipment which is widely available. It has particular value in testing patients who are cognitively-impaired. The Harding H-field stimulus test has been shown to be useful in children as young as a few years of age and therefore can also be used in testing adults who are severely cognitively-impaired. However, it is not widely available.

Standard VEP appears to be least correlated with accurate assessment of pVFD. Several investigators have concluded that the ERG is better than VEP and electrooculography for testing [152, 205]. The 30 Hz flicker response has been reported to be the most predictive of the presence and severity of VGB-induced pVFD [154,155]. Other parameters, such as cone b-wave amplitude and late OPs, are also held to be highly sensitive measures of VGB injury. Alterations of 30 Hz flicker amplitude and cone b-wave parameters which show sustained abnormality over time have been shown by Harding [154,155] to correspond to the VGB-induced peripheral field defect.

UNIVERSITY OF TORONTO IS STUDY

A study was initiated in 2001 by Dr. Carol Westall, a vision scientist who heads the vision testing laboratory of the Hospital for Sick Children in Toronto, to understand the potential for retinal injury in infants who are treated with VGB for IS. Ovation Pharmaceuticals has supported this ongoing study since 2005. The database has been provided to Ovation with the objective of establishing prevalence and incidence of ERG abnormalities in this population.

The following analysis is based on a comprehensive assessment of ERGs performed on 246 infant patients, nearly all with IS and all exposed to VGB with or without other AEDs, between 17 April 1998 and 28 June 2007 [206]. A large normative database was established from healthy infants and children with a variety of other diseases. Dr. Westall, et al have developed a considerable database on the evolution of the ERG from infancy to adulthood [201] and have monitored children who have been treated with a wide variety of AEDs, including VGB. This database is used to study the effects of AED exposure reflected in ERG alterations.

The study included retrospective and prospective arms.The term "prospective" is used to refer to patients with both baseline and post-baseline ERG data. Patients with post-baseline data only comprise the “retrospective” cohort. Additionally, there were some patients who only had baseline data. These "baseline only" patients were excluded from most analyses but were included in demographic summaries. A patient’s baseline for an ERG parameter was defined to be the examination results obtained closest to, but no later than 7 days after the first dose of VGB. Of the 246 patients with ERG tests, 44 (17.8%) had only a baseline measurement taken, 117 (47.6%) had baseline and at least one post-baseline measurement, and 85 (34.6%) had no baseline but at least one post-baseline measurement taken. The majority of patients (76%) had 2 or more ERG tests.

Age-specific normal ranges were developed for each ERG parameter, based on data collected on a cohort of patients with nystagmus and no retinal problems, all naïve to VGB. For amplitude measures, results below the 95% lower normal limit were considered clinically significant and were identified as abnormal. More than one examination was required for confirmation of abnormal results due to the high frequency of baseline abnormalities and post-natal developmental changes in the developing retina in infants. Repeat examinations were conducted every 3 to 6 months.

The median age in the prospective and retrospective cohorts at the time of their most recent ERG test was 2.2 years, with a range from 0.5 years to 22.5 years. Fifty-six percent (56%) of the patients were male and 44% were female. Most patients (55%) were taking both VGB and other AEDs. The median duration of VGB therapy was 13 months, with 49% of the patients having been treated for a year or less, and 74% having been treated for less than 2 years. Eight percent (8%) had been treated for 5 years or more. The median age at initiation of treatment was approximately 8 months and 90% were on VGB by their third year. Over half of the patients (58%) received their first ERG test by the age of 1 year and over 80% were evaluated by their second year.

The incidence of a new ERG abnormality based on 30 Hz flicker amplitude in prospectively examined patients with a normal baseline was 53.6%; the incidence of a sustained abnormality (those observed on the last 2 examinations) was 25.4%. The incidence rate of a sustained abnormality based on 30 Hz flicker amplitude was 15.3 cases/100 patient-years. Based on cone b-wave amplitude, the incidence of a new abnormality was 31.5%; the incidence of a sustained abnormality was 10.5%. The incidence rate of a sustained abnormality based on cone b-wave amplitude was 6.2 cases/100 patient-years.

While it is most informative to assess emergence of ERG abnormalities in patients known to be normal before their first dose of VGB, the available data included a large patient subgroup without available baseline results. Therefore, the period prevalence of ERG abnormalities was examined in all patients taking VGB, regardless of whether or not they had baseline data available. The period prevalence based on 30 Hz flicker amplitude among infants who had at least one abnormal result was 63.4%; the period prevalence for a sustained abnormality was 31.1%. The period prevalence based on cone b-wave amplitude abnormalities among infants who had at least one abnormal result was 37.1%; the period prevalence for a sustained abnormality was 14.7%.

Table 59 presents data regarding the time to onset for the first abnormality and to sustained abnormality. A sustained abnormality is one present on at least 2 examinations including the final examination, implying that it represents a permanent defect. The median duration of VGB exposure at the time of first abnormal 30 Hz flicker amplitude was 12.50 months. The earliest detection of a new ERG abnormality based on the 30 Hz flicker amplitude occurred 3.1 months after VGB treatment was initiated (in patients receiving VGB). The overall range was 3.1 months to 66.8 months with a mean of 15.59±13.15 months. The earliest detection of a new ERG abnormality based on the cone b-wave amplitude occurred 2.8 months after VGB treatment was initiated (in patients receiving VGB). The overall range was 2.8 months to 55.8 months with a mean of 18.10±15.14 months. The median duration of VGB exposure was 12.50 months.

Table 59. Time to Abnormality

Assessment	First Abnormality	Sustained Abnormality
30 Hz Flicker amplitude		
N	37	15
Mean (SD), months	15.59 (13.15)	18.53 (15.59)
Median, months	12.50	18.63
Range, months	3.1 to 66.8	3.1 to 54.4
Cone b-wave amplitude		
N	29	9
Mean (SD), months	18.10 (15.14)	22.22 (19.14)
Median, months	12.50	18.73
Range, months	2.8 to 55.8	2.8 to 54.4

Visual field data were available for 63 patients who had been exposed to VGB as infants and who were examined after they were 10 years of age or greater. Time of exposure to VGB was known for 42 patients; these patients were exposed to VGB for a median of 20.8 months. Visual field abnormalities potentially related to VGB were found in 5 (7.9%) of the children in the study. No VGB-induced reductions in central vision acuity were found, although many patients were unable to perform acuity testing.

BOSTON CHILDREN'S HOSPITAL STUDY

A retrospective study was sponsored by Ovation at Boston's Children's Hospital Medical Center of 49 pediatric patients, aged 3 to 52 months, who had received VGB therapy and all of whom had a diagnosis of IS. ERG examinations were classified into two groups: those performed within 6 months of the patients' exposure to VGB and those performed after 6 months of exposure to VGB. Very few children had repeat examinations; therefore the analysis compares average changes between time periods rather than changes for individual patients, and longitudinal analyses were not conducted. The incidence and background rates for retinal effects could not be established from this dataset because baseline data were available for only a few patients. The study design and small sample of patients permit only tentative conclusions to be drawn from these analyses.

Of the 49 children, 47 had at least one ERG evaluation after their first dose of VGB. The results indicated that responses differed between patients treated with VGB for <6 months and patients treated with VGB for >6 months. Children with more than 6 months of exposure to VGB had (on average) lower 30 Hz flicker and cone b-wave amplitudes than children with less than 6 months exposure. The mean amplitude of the 30 Hz flicker response before starting VGB was 68.00 ± 40.57 μV (n=3). With 6 months or less of VGB exposure, the mean was 77.63 ± 24.49 μV (n=16), and with more than 6 months exposure 54.65 ± 20.37 μV (n=13). For cone b-wave amplitude, the means were 91.00 ± 44.26 μV (n=5) pre-VGB, 97.49 ± 38.66 μV (n=34) with less than 6 months exposure, and 77.45 ± 29.60 μV (n=22) with more than 6 months exposure. These results were consistent with the findings of the Toronto study and reinforced the importance of obtaining baseline and serial ERG examinations to adequately assess retinal status and changes over time.

These data support the findings of other laboratories in that the most sensitive and robust ERG measures of VGB retinal changes are cone b-wave amplitude and 30 Hz flicker amplitude. Only tentative conclusions may be drawn from this analysis due to the small number of patients and high proportion of children in the data set who lacked baseline exams. While further research must be undertaken to confirm these findings, this analysis demonstrates the value of obtaining baseline ERG exams for patients with IS. The analysis also suggests that periodic exams, particularly within the first 6 to 12 months of VGB treatment, are necessary in order to monitor the effects of VGB on visual fields and determine the most appropriate course of treatment for patients.

VISUAL FUNCTION DATA FROM VGB EFFICACY STUDIES IN IS

At the request of the FDA, data were obtained from investigators who had conducted three efficacy studies: Study FR03, Study W019 and Study 1A. Investigators participating in the three studies were asked to report whether each patient who had been enrolled in their study had been followed after study exit and whether follow-up vision exams and exam methodology had been conducted and documented. In addition, the results of vision testing, with particular attention to severe visual disabilities and the timing and etiology of any disability, were documented. Since the underlying pathology contributing to the development of IS can also lead to severe visual disabilities in some patients, the status of visual function at birth, when known, was recorded. Examples of severe vision disorders, which may have been present at baseline, include retinopathy of prematurity, cortical blindness and micropsia.

All investigators who enrolled patients in the three studies responded to the inquiries. Most investigators enrolled patients from outside their own clinical practice, with many caregivers driving long distances to participate in the study and then returning to a primary caregiver for follow-up once the patient exited the study.

Seven study sites followed some patients after completion of the clinical study. Of 279 patients who participated in the three studies, follow-up data were available for 127 patients from these seven centers. Vision testing in the follow-up period was performed in 55 patients. Absence of testing occurred due to several factors, including severe retardation, presence of blindness from birth, lack of interest in participation or lack of insurance being the most frequently cited reasons. The majority of patients for whom there

was testing data, had confrontation field tests, although a small number had Goldmann perimetry tests. Of the 55 patients with vision follow-up data, 48 were judged by pediatric neurologists as having normal vision and 24 had abnormal vision unrelated to VGB. At least 15 patients were blind at birth. No patients were found to have severe visual disability due to VGB.

pVFD IN POSTMARKETING DATABASE

Peripheral VFD was the most commonly reported adverse event in the postmarketing database through 30 June 2007. A total of 959 (53.5% of all reports) reports contained 1359 (42.4% of all adverse events) events that were specifically designated as 'visual field defect'. Patient age was included in 693 (72.3%) of the 959 reports that contained a pVFD. In the younger age ranges, there were 3 reports (0.3% of all pVFD reports, and 2.7 % of reports in age grouping) in patients <3 years old, 1 of which was considered serious, and 61 reports (6.4% of all pVFD reports, 38.4% of reports in age grouping) in patients 3 to <12 years old. Six of the 61 pVFD reports (9.8%) in the 3 to <12 year old group were considered serious.

SUMMARY OF RETINAL FUNCTION IN IS

Based on the Toronto Study, the following conclusions may be drawn:

- The ERG abnormalities which have been proven to underlie the VGB pVFD in adults are also seen in infants. These are the 30 Hz flicker amplitude and cone b-wave amplitude correlate with persistent retinal changes.
- In the Toronto study, the median duration of VGB exposure at the first ERG abnormality was 12.5 months (range 3 to 67 months). The incidence of a sustained ERG abnormality in patients with a normal baseline ERG was 25.4%, with an overall prevalence of 31%.
- In 63 patients in the Toronto Study, visual field examinations were performed with confrontation perimetry. For the 42 patients whose date of visual field examination was known, the median duration of VGB exposure was 20.8 months (range 3.1-61.7). Five (7.9%) had abnormal visual fields attributed to VGB.

5.4.9.2 IME and Abnormal Brain MRI

Information regarding the lack of clinical and radiological findings suggestive of IME from clinical studies conducted in adults and children with CPS are presented in Section 4.4.14.2.

ABNORMAL MRI AND ASSOCIATION WITH VGB THERAPY

Based on a January 2007 report of MRI abnormalities in 3 of 15 patients with IS treated with VGB [35], Ovation initiated a comprehensive clinical and radiological investigation of patients exposed to VGB. This review was requested by FDA due to the issue of IME previously described and characterized in several animal species that was reported during the clinical development of VGB.

IME FINDINGS IN NONCLINICAL STUDIES

Human studies with VGB were temporarily suspended in the U.S. in 1983 when data from mice, rats, and dogs demonstrated histopathologic findings termed IME following prolonged VGB administration. Microvacuoles were found histologically, with the predominant localization of histopathologic abnormalities in the midline and deep hemispheric structures, including brainstem, cerebellum, basal ganglia, and white matter tracts, such as the anterior commisure of rats and the fornix of dogs. IME has not been seen in the spinal cord or peripheral nerves of any species. Ultrastructurally, the vacuoles were seen to split the intraperiod line of myelin, hence the name intramyelinic edema. Additional nonclinical pharmacology associated with IME is described in Section 2.2.1.

The absence of vacuolar changes in primates [207-217] and the absence of MRI changes in children and adults with CPS taking VGB tested with sensitive methodologies [218,219] suggested that IME did not occur in developmentally mature primates. After extensive research, the US FDA permitted clinical studies to continue in 1990 once the sponsor had demonstrated that VEP and MRI could detect lesions in animals, and confirmed the absence of similar pathology during or after therapy in humans with CPS aged 3 to 70 years [218].

MRI Abnormalities in IS

Dr. Philip Pearl of Children's National Medical Center reported MRI signal changes, consistent with IME, in 3 infants treated with VGB for IS. These findings were presented at a national meeting in October 2006 and have subsequently been published [35]. These new data again raised the question of whether VGB could induce IME in humans and, if so, whether there were clinical accompaniments or sequelae. This concern was reinforced by the reports of 12 additional cases of MRI abnormalities in children under 36 months of age associated with VGB captured through postmarketing safety surveillance and by a report of 6 possible cases in a draft manuscript, since published [219], provided to Ovation by Dr. Olivier Dulac of Necker-Enfants Malades University Hospital, Paris, France.

In response to this issue, Ovation convened an expert review panel composed of pediatric epileptologists and neuroradiologists in February 2007. This expert panel advised that a retrospective study in IS patients should be conducted to define incidence and prevalence of such abnormalities.

In addition to this retrospective study in patients with IS (Study 1019, described below), Ovation conducted a repeat review of prospectively-collected MRIs from 12 studies in adults and children with CPS (Section 4.4.14.2).

RETROSPECTIVE REVIEW OF MRIS FROM PATIENTS WITH HISTORY OF IS

In order to follow-up on the initial reports by Dr. Philip Pearl of MRI signal changes in 3 infants treated with VGB for IS, Ovation collected information from institutions which either had ongoing, approved studies of IS, or who could provide such de-identified data as was appropriate under ethics/privacy rules. Available data were collected on diagnosis, seizure etiology, age at onset of IS, age at onset of other seizures, age at VGB start, age and weight at time of MRI, VGB dose at time of MRI, total duration of VGB treatment, other

AEDs or ketogenic diet at time of MRI, and IS and other seizure types responses at time of MRI. Table 60 outlines the institutions included in the retrospective analysis.

Table 60. Sites Included in the Retrospective Review of MRI Data in Infants with IS

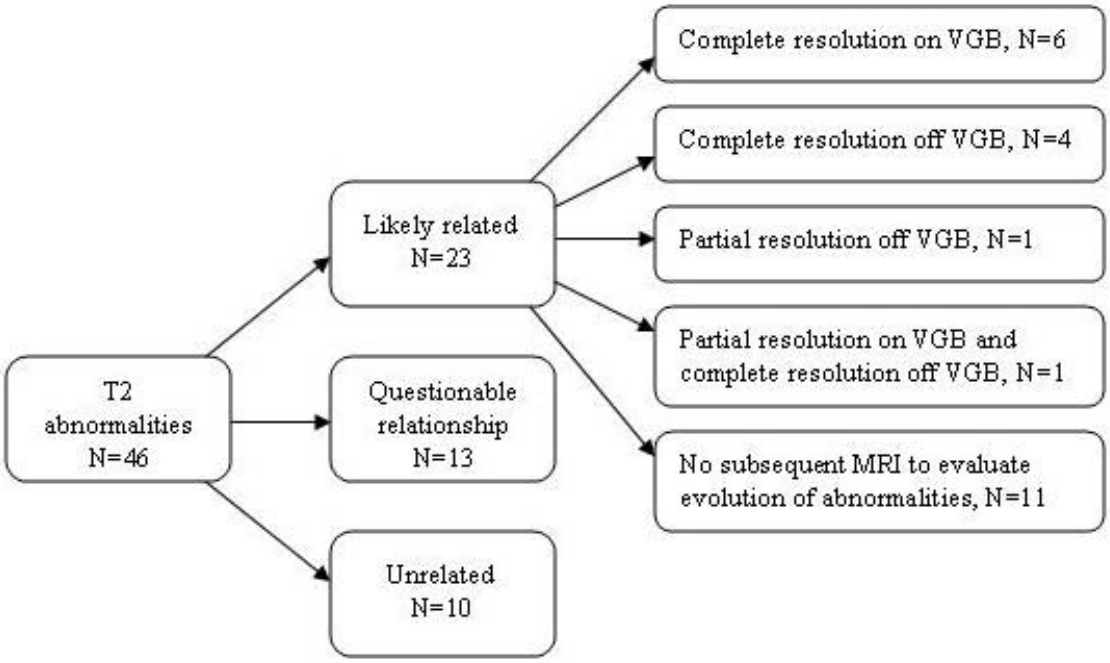
Site Identifier	Institution	Patients with MRI Data Included N=213
002 Bourgeois	Children's Hospital Medical Center, Boston, MA	1
003 Carmant	Hopital Ste. Justine, Montreal, Que.	89
004 Chiron	Hopital Enfants Malades, Paris, France	35
005 Thiele	Massachusetts General Hospital, Boston MA	34
007 Westall	Hospital for Sick Children, Toronto, Ont.	54

A total of 213 patients were reported, 204 of whom had MRI results. Of these, 46 had T2 abnormalities on at least on MRI, and 158 had no T2 abnormalities on any scan (see Figure 16).

The 46 patients with T2 abnormalities were divided into 3 categories to define the potential relationship of the MRI findings to VGB. The categories were, 1) likely related: typical topographic distribution involving bilateral deep gray matter structures and occurring while on VGB; 2) questionable relationship: the MRI abnormality was atypical in terms of topography but occurred while on VGB, a typical MRI abnormality occurred while off VGB, an underlying pathology could explain the MRI abnormality, or the timing of exposure to VGB in relation to the MRI was unknown; or 3) unrelated: only the MRI abnormality was present on a baseline MRI or when the MRI abnormality was atypical in terms of topography or occurred while off VGB. By these criteria, 23/213 (11%) of infants had likely treatment-related MRI abnormalities.

A summary of the 46 patients with T2 abnormalities are presented in Figure 16. Of the patients with subsequent MRI examinations, all abnormalities had either completely or partially resolved. Based on these data, the estimated incidence of IS patients treated with VGB with MRI abnormalities was 10% to 20%.

Figure 16. Summary of T2 Abnormalities, Outcome and Relationship to VGB



POSTMARKETING REVIEW OF ABNORMAL MRI FINDINGS IN IS

The Ovation Oracle AERS database was searched for all VGB adverse event reports received since 1989, when VGB was first marketed in the UK, through 30 June 2007, which described abnormal MRI findings in patients receiving the drug for any indication. The Medical Dictionary for Regulatory Activities (MedDRA) 9.1 preferred terms used in the search were brain edema, brain scan abnormal, nuclear magnetic resonance imaging brain abnormal, nuclear magnetic resonance imaging abnormal, nuclear magnetic resonance imaging brain, computerized tomogram head, computerized tomogram abnormal, scan brain, scan abnormal, and demyelination. A total of 20 reports were identified and divided into 2 categories: cytotoxic edema/hyperintensities (n=13) and miscellaneous lesions (n=7).

Seven reports were identified in the miscellaneous MRI lesions category. Overall, the patients represented a heterogeneous group with diverse findings. There was no consistent pattern of lesion and the majority of the reports described complicating factors for the events.

Thirteen reports were identified in the cytotoxic edema/hyperintensities category. Twelve patients were <36 months in age and 1 patient was 56 years of age (multifocal periventricular white matter T2 lesions suggestive of small vessel ischemic disease). Eleven patients were taking VGB for IS and the other 2 were taking VGB for other epilepsy/convulsions. Dose per body weight was determined for 9 of the infants to be 130-200 mg/kg/day. Time to onset of MRI findings ranged from 26 to 2316 days, with a median of 90 days (n=13). The summary for the cases of cytotoxic edema/hyperintensities that occurred in infants (n=12) is provided in Table 61.

The most commonly described T2 hyperintensities were found in the basal ganglia (11 of 12 reports), thalamus, globus pallidus, and cerebellum. Ten of the 12 patients had been exposed to high doses of VGB (>125 mg/kg/day) prior to the MRI changes. Many of these reports provided incomplete information with regard to baseline MRI or follow-up MRI. Three of the patients were described as having changes in muscle tone or dystonic movement that coincided with abnormal MRIs. Based on these reports, the EMEA has recently requested a Risk Management Plan for VGB in Europe addressing cytotoxic edema and related dystonia/movement disorders.

Table 61. Postmarketing Cases of Cytotoxic Edema/Hyperintensities in Infants

Pt.[a]	Baseline MRI	T2 Hyperintensity on MRI	Normal Follow-up Scan
1	Normal	Abnormal basal ganglia	Resolved after VGB discontinued
2	Post-infarction state due to cerebral artery occlusion; no basal ganglia changes. MRI performed after starting VGB	Basal ganglia and other changes on T2 and DWI; previous findings unchanged	Resolved after VGB discontinued
3	None	Brainstem and dendate nucleus	Resolved after VGB discontinued
4	None	Basal ganglia and elsewhere	Not reported
5	Normal	Basal ganglia and elsewhere	Resolved after VGB discontinued
6	Normal	Basal ganglia and elsewhere	Resolved after VGB discontinued
7	Normal	Basal ganglia and elsewhere	Resolved after VGB discontinued
8	Normal	Basal ganglia and elsewhere	Normal 14 days after VGB discontinuation and a few weeks after VGB reintroduction (100 mg/kg/day)
10	Normal	Basal ganglia and elsewhere	Not yet performed
11	Normal	Basal ganglia and elsewhere	Not yet performed
12	Normal except slight cortical atrophy	Basal ganglia and elsewhere	Not yet performed
13	Normal except slight cortical atrophy	Basal ganglia and elsewhere	Not yet performed; patient lost to follow-up

[a] Patient #9 was a 56-year old female and therefore not included in the summary of infants.

RETROSPECTIVE ASSESSMENT (STUDY OV-1019 AND ADDITIONAL MRIS COLLECTED POST STUDY-CLOSURE)

The purpose of the retrospective MRI study was to obtain estimates of the prevalence and incidence of MRI abnormalities in infants with IS who were treated with VGB compared with those treated with other modalities. The primary objective in this trial was to compare incidence of pre-specified abnormalities on cranial MRI between VGB-exposed and VGB naïve cohorts of pediatric patients treated for IS. Secondary objectives included the following:

- Comparison of the prevalence between VGB-exposed and VGB-naïve cohorts of pediatric patients treated for IS;
- Comparison of the prevalence between infants treated with high-dose VGB (≥125 mg/kg/day) to those treated with a low dose (<125 mg/kg/day);
- Quantification of the transient occurrences;
- Assessment of the risk factors;
- Understanding of the time course of the abnormalities.

Participating centers were instructed to screen up to 200 patients and to enroll as many patients as possible who had been treated for IS and for whom MRI images were available. Sites were instructed to begin with their most recent patients and screen in reverse chronological order in 5 year increments. Patients enrolled included those who had IS (West syndrome) as a primary or secondary diagnosis, who were ≤24 months of age at the time of their diagnosis, and who had cranial MRIs (including at least 1 cranial MRI with any T2, FLAIR, or DWI sequence available for evaluation) performed at or before the age of 35 months, but subsequent to the date of onset of IS. All patients were to have been treated with VGB or another anti-epileptic therapy, including ketogenic diet, corticosteroids, or other AEDs. Image processing and review was similar to that for the CPS population (see Section 4.4.14.2).

The initial data collection was terminated on 31 October 2007. The original NDA 22-006 included data from 226 patients which were summarized in a final clinical study report. Subsequent to this, retrospective MRI data from an additional 30 patients, termed the Current Patients, were received and included in the 120 Day Safety Update. Because the criteria for selecting the Current Patients and reviewing their MRI results were identical to study OV-1019, the data was combined into an integrated dataset and will be presented here.

A number of analysis populations were employed to reflect MRI findings related to the timing of patients' MRI in relationship to the use of VGB. The populations are described below:

- VGB-initial therapy: patients started on VGB at the time of diagnosis of IS are analyzed in this treatment category for the duration of their follow-up in the study. They contribute data to the VGB-exposed category.
- VGB-subsequent therapy: patients were treated with VGB only after a period of treatment with other modalities. Therefore, these patients may contribute data to both VGB-naïve and VGB-exposed treatment categories during different treatment periods.
- Never VGB: patients were never treated with VGB, and therefore contribute data only to the VGB-naïve category.
- VGB-exposed: all patients after their first exposure to VGB, including VGB-initial therapy and VGB-subsequent therapy after starting VGB. Patients were still considered VGB-exposed after discontinuation of VGB. VGB-exposed were also divided by low-dose (<125 mg/kg/day), high dose (≥125 mg/kg/day).

- VGB-naïve: patients who never received VGB plus the VGB-subsequent therapy group before starting VGB.

Prevalence was defined as the occurrence of at least 1 pre-specified MRI signal abnormality in a treatment period on T2, FLAIR, and/or DWI; a baseline was not required. The prevalence for the integrated data (Study 1019 patients + Current Patients) is presented in Table 62. The prevalence of pre-specified MRI signal abnormalities during or after treatment was 11.1% (4/36) in the low-dose group, 30.6% (19/62) in the high-dose group, and 22.8% (23/101) for all VGB-exposed patients. The corresponding prevalence for VGB-naïve patients was 4.0% (4/101). The relative risk for all VGB-exposed vs VGB-naïve was 5.75 (95% CI: 2.05, 16.17). Statistically significant differences were observed for the comparisons between low, high, and VGB-naïve groups ($p<0.001$) and between high- and low-dose groups ($p=0.046$).

Table 62. Prevalence of MRI Signal Abnormalities – Study 1019 Patients + Current Patients

	VGB Exposed				
	Low-dose N=36	High-dose N=62	All N=101	Never VGB N=79	VGB Naïve N=101
Prevalence (%)	11.1	30.6	22.8	5.1	4.0
95% CI	(3.1, 26.1)	(19.6, 43.7)	(15.0, 32.2)	(1.4, 12.5)	(1.1, 9.8)

Incidence was defined as the occurrence of at lease 1 pre-specified MRI signal abnormality post-baseline on T2, FLAIR, and/or DWI among patients with a determinate MRI at baseline that was free of pre-specified abnormalities. The incidence for the integrated data (Study 1019 patients + Current Patients) is presented in Table 63. The incidence of pre-specified MRI abnormalities following a normal baseline MRI was 33.3% (4/12) in the low-dose group, 37.5% (6/16) in the high-dose group, and 34.5% (10/29) for all VGB-exposed patients. The relative risk for all VGB-exposed vs. VGB-naïve was 5.86 (95% CI: 0.82, 41.89). A statistically significant difference was observed for the comparisons between all VGB-exposed and VGB-naïve groups ($p=0.036$). The relative risk indicates that the incidence of MRI abnormalities were more likely with VGB treatment; however, the confidence intervals for both groups were high.

Table 63. Incidence of MRI Signal Abnormalities – Study 1019 Patients + Current Patients

	VGB Exposed				
	Low-dose N=12	High-dose N=16	All N=29	Never VGB N=14	VGB Naïve N=17
Incidence (%)	33.3	37.5	34.5	7.1	5.9
95% CI	(9.9, 65.1)	(15.2, 64.6)	(17.9, 54.3)	(0.2, 33.9)	(0.1, 28.7)

Additional analyses of incidence were performed with consideration of duration of drug exposure and include an analysis for eligible patients in both the incidence and prevalence populations (Table 64) and for eligible patients in the incidence population (Table 65). These results are presented in the following tables and are expressed in event rates per patient-year. Although the event rates are higher in VGB-exposed than in VGB-naïve patients, the differences do not quite reach statistical significance in this analysis.

Table 64. Rate of MRI Signal Abnormalities (Eligible Patients in Study 1019 plus Current Patients Incidence and Prevalence Populations With at Least Two MRIs and the First Without Abnormality)

	VGB-Exposed	VGB Naive
# of Patients	46	38
# of Patients with Signal Abnormalities	12	2
Total Patient Years of Observation[a]	69.8	38.6
Event Rate (per patient year)[b]	0.17	0.05
P-value[c]	0.079	

Note: Includes all patients in incidence population and patients in prevalence population who have at least two determinate MRIs, with no signal abnormality at the first determinate MRI. First determinate MRI may or may not be a true baseline MRI for patients in the prevalence population only.
Note: A patient who received VGB subsequent to non-vigabatrin initial therapy for IS may be counted as at risk for a pre-specified MRI signal abnormality in both the initial non-VGB period and later in the VGB period.
At most one incident of pre-specified MRI signal abnormality is counted per patient.

a. Years of observation is derived as time from the earlier of date of baseline and first determinate MRI for VGB-Naive and from the earlier of date of first VGB and first determinate MRI for VGB-exposed to date of first signal abnormality for patients with abnormality and to date of last determinate MRI for patients without abnormality.

b. Event rate is defined as number of abnormalities divided by total patient years of observation.

c. P-value from log-rank test.

Program: ah_rate_event.sas
Source Data: core, endpoint.sas7bdat (Date Generated: 23JUN2008)

Table 65. Rate of MRI Signal Abnormalities (Eligible Patients in Study 1019 plus Current Patients Incidence Population)

	VGB Exposed	VGB Naive
# of Patients	29	17
# of Patient with Signal Abnormalities	10	1
Total Patient Years of Observation[a]	36.1	19.5
Event Rate (per patient year)[b]	0.28	0.05
P-value[c]	0.071	

Note: A patient who received VGB subsequent to non-VGB initial therapy for IS may be counted as at risk for a pre-specified MRI signal abnormality in both the initial non-VGB period and later in the VGB period.
At most one incident of pre-specified MRI signal abnormality is counted per patient.

a. Years of observation is derived as time from the earlier of date of baseline and first determinate MRI for VGB-Naive and from the earlier of date of first VGB and first determinate MRI for VGB-exposed to date of first signal abnormality for patients with abnormality and to date of last determinate MRI for patients without abnormality.

b. Event rate is defined as number of abnormalities divided by total patient years of observation.

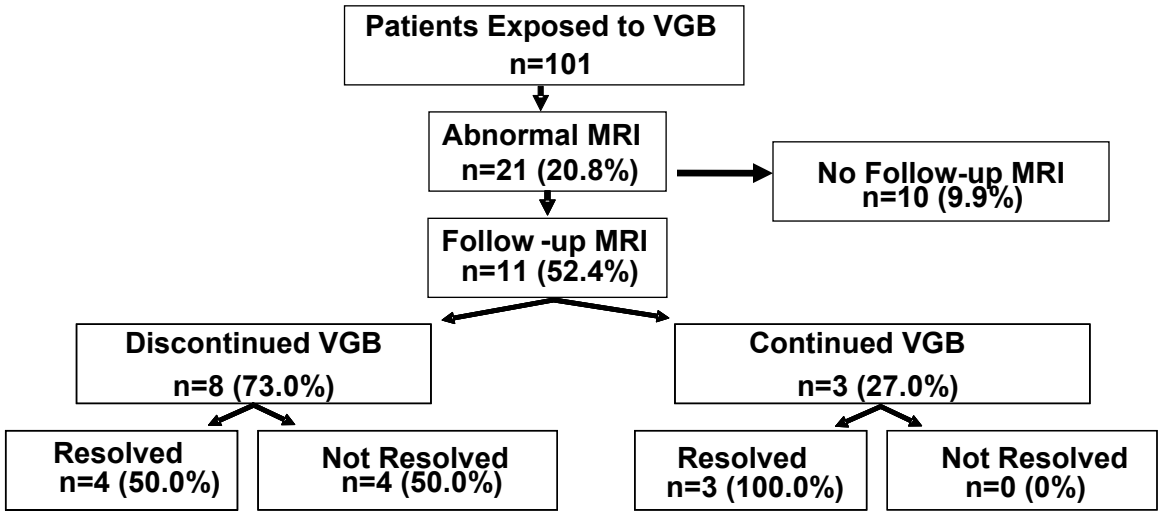
c. P-value from log-rank test.

Program: ah_rate_event.sas
Source Data: core, endpoint.sas7bdat (Date Generated: 23JUN2008)

Of 101 patients in the Study 1019 plus Current Patients prevalence population, 21 had a pre-specified MRI abnormality while taking VGB (Figure 17). Of these 21, 11 had follow-up, determinate MRI examinations and of these 11, the abnormalities resolved on 7 (63.6%). As there is no systematic follow-up information available on the patients, it is not known if the remaining abnormalities also resolved over time.

No risk factors other than VGB for the development of MRI signal abnormalities were identified. In particular, in this series there was no detectable relationship between the etiology of IS and the prevalence of pre-specified MRI abnormalities.

Figure 17. Radiographic Resolution of MRI Signal Abnormalities



CONCLUSIONS

These results provide evidence that VGB exposure is associated with characteristic high T2 signal abnormalities in brain MRI of infants with IS. These results are consistent with the observations of Dr. Pearl and with observations of a recent publication from the pediatric epileptology group at Hopital Necker Enfants in Paris [220]. This group reported MRI abnormalities on DWI in 6 of 20 infants referred for medically refractory IS. All were taking VGB at the time of the index MRI demonstrating the abnormality. Five of those 6 patients had follow-up MRI examinations and the DWI abnormalities had resolved in all. Of note, for each of these reports the anatomic pattern of findings is similar.

To date, a clinical correlation with the imaging abnormalities has not been established. The Ovation retrospective data do not identify clinical correlates of the MRI abnormalities, which are noted during exposure to a high dose of VGB. The publication of Desguerre et al [220] comments that their patients were hypotonic or dystonic, and 3 postmarketing reports comment on motor findings in infants which correlate with the appearance of the MRI changes.

Importantly, the MRI changes were noted to resolve whether VGB was continued or stopped. Longitudinal clinical observations, which would be necessary to establish whether the MRI changes have long term clinical sequelae have not been performed.

5.5. Benefit/Risk Assessment for IS

Data presented in the preceding sections of this briefing document support the following:

- IS is a rare but catastrophic type of childhood epilepsy, with an estimated incidence to be between 2 to 5 per 10,000 live births in the U.S.
- Mortality rates are high; Up to one-third of infants with IS will die before the age of 3.
- Severe to profound mental retardation is also common in this patient population and approximately half the population suffers from other neurological disorders, such as static encephalopathy (cerebral palsy). Patients with IS also experience severe developmental delay or regression from previously attained milestones.
- There are no currently approved treatments for IS in the U.S. Commonly used off-label therapies such as ACTH and prednisone, while demonstrating initial efficacy in patients, are characterized by a high relapse rate (up to 40% in some studies), bringing efficacy to a much smaller number of patients. Other off-label therapies such as VPA, benzodiazepines and some newer AEDs, have been used, but efficacy has not been established in controlled studies, nor are they without potential risk.
- The efficacy of VGB in patients with IS is established and supported by 3 prospective controlled studies, 2 uncontrolled studies, and additional uncontrolled clinical studies reported in the literature. Pivotal clinical Study 1A is the largest prospective study ever conducted in patients with IS. Findings from this study are supported by multiple controlled and uncontrolled clinical studies that in aggregate demonstrate that spasm cessation is achieved in 30-80% of VGB treated patients.
- Onset of VGB efficacy is within 2-4 weeks and the drug is effective across etiologies of IS. In those infants who achieve spasm cessation, the response is maintained in over 75%.
- VGB is the drug of choice for IS for physicians in countries where it is readily available.
- Retinal changes are a risk for infants treated with VGB as well as adults. Because therapeutic response to VGB can be assessed within 2-4 weeks in patients with IS, and retinal toxicity typically manifests after longer exposures (earliest onset 3.1 months; median onset 16.2 months), non-responders can be removed from the drug without significant risk of permanent retinal injury. In those infants who respond to VGB with cessation of spasms and resumption of neurological development, visual function can be

monitored with confrontational testing and/or ERG to inform ongoing benefit-risk discussions between physicians and caregivers.

- VGB is associated with the development of MRI abnormalities in infants. These MRI changes have been reported to resolve, whether VGB is continued or stopped. The only clinical findings reported to date are transient motor abnormalities in several patients; however, longitudinal clinical observations are lacking to establish whether the MRI changes have long-term clinical sequelae.
- The benefits of VGB exceed the risks in patients with IS who achieve a substantial clinical response.

6 RISK EVALUATION & MITIGATION STRATEGY (REMS)

6.1. Identification of Risks

6.1.1 Background

One specific risk associated with VGB use has been identified and well-characterized: a distinctive pVFD. In addition, T2 MRI abnormalities in patients with IS can occur during Sabril therapy.

In a large multinational study (Study 4020), the prevalence of a confirmed VGB-induced pVFD was approximately 25% in adults and 15% in children (see Section 4.4.14.1). The prevalence of a confirmed Sabril-induced retinal abnormality of the most sensitive ERG parameter in infants was approximately 31% (see Section 5.4.9.1). Those who do develop a defect generally experience a decrease in lateral vision from presumably normal at 90 degrees to, on average, 65 degrees. The peripheral VFD does not appear to reverse after discontinuation of Sabril, although the possibility cannot be excluded. Therefore, it should be expected that if this defect occurs, it is permanent. With possible rare exceptions, the peripheral VFD does not begin or progress after discontinuation of Sabril. The risk of developing a pVFD increases with total dose and duration of use. However, some patients have had long-term exposure without developing this defect. While the defect has an impact on vision, that impact is very rarely on the central field of vision, and the great majority of patients do not demonstrate significant functional problems with the loss of peripheral vision.

Concern about the possible occurrence of IME in humans as a result of VGB therapy for epilepsy was primarily based on 2 observations: 1) the occurrence of IME in rodents and dogs treated chronically and subchronically with VGB; and 2) case reports of MRI signal abnormalities in a reproducible anatomical distribution in infants treated with VGB for IS. These data include case reports in the literature [206, 220] and reports by individual physicians captured by postmarketing safety surveillance. These reports are of infants with IS treated with VGB, typically at a dose above 125 mg/kg/day, who were found to have symmetric regions of diffuse high T2 and FLAIR signal and restricted diffusion in the globus pallidus and thalamus. In some cases the abnormalities extended into brainstem and deep cerebellar nuclei. The imaging abnormalities resolve over weeks to months with discontinuation or a dose reduction of VGB. Some of the most pressing questions to the practicing clinician include whether there are any clinical signs associated with the imaging

abnormalities, and most importantly, whether there are any long-term sequelae. Long-term prospective studies will be required to address these questions. Moreover, with no histopathological data from infants treated with VGB and developing MRI signal abnormalities, the MRI findings cannot definitely be equated with histologic findings of IME.

6.1.2 Evaluation of Detection and Prevention Potential

6.1.2.1 Peripheral Visual Field Defect

In adequate and well-controlled studies, the efficacy of vigabatrin was established in adults within 12 weeks of initiating therapy. In a long-term clinical study specifically designed to evaluate the pVFD, this defect was not detected until 9 months of therapy in adults and 11 months in children. An opportunity exists to evaluate the efficacy of Sabril in individual patients early during Sabril therapy since the risk of peripheral VFD increases over time.

For adults with refractory CPS, the EMEA has recommended visual field testing at baseline and every 6 months and the incidence data from Study 4020 (see Section 4.4.14.1) supports this frequency recommendation. Therefore, Ovation is proposing visual field testing at baseline and every 6 months in adults with refractory CPS receiving Sabril. These recommendations are included in the draft U.S. package insert. Depending on patient age and cognitive status, a variety of ophthalmologic testing modalities can be used; including confrontation, perimetry, and electrophysiologic testing. A pVFD detected during ophthalmologic testing should be confirmed in a timely fashion by additional testing. If confirmed and the patient and physician decide to continue therapy, ophthalmologic testing should be increased in frequency to 3 month intervals with ongoing benefit/risk assessments.

Since children with IS are unable to engage in quantitative perimetry testing, age appropriate visual testing, such as confrontation or electrophysiologic testing, is needed for detection. It is recommended that ophthalmologic testing be performed in children receiving Sabril at baseline and at 3 month intervals for the first 18 months and then every 6 months thereafter. A retinal abnormality detected during ophthalmologic testing should be confirmed by additional testing. If confirmed and the parent/legal guardian and physician decide to continue therapy, ophthalmologic testing should be conducted at 3 month intervals with ongoing benefit/risk assessments.

6.1.2.2 MRI Abnormality

For children and adults treated with VGB for refractory CPS, routine MRI surveillance is not required, as there is no evidence that VGB causes MRI changes in this population. MRI examinations should be performed as clinically indicated.

For infants treated with VGB for IS, MRI examination requires sedation and hence carries risk. Moreover, the clinical sequelae of the VGB-induced MRI changes are unknown [5]. Therefore, routine MRI surveillance of this population is not recommended. In cases where treatment decisions would be dependent on the MRI findings, an MRI one month after starting treatment and again at 3 months will have a high probability of detecting any VGB-induced MRI changes based on known time course of the abnormalities.

If infants with IS develop new findings on neurological examination while taking Sabril, especially motor abnormalities, the clinician should strongly consider an MRI examination if there are potential alternative treatment modalities available to control the epilepsy. If MRI signal changes characteristic of VGB effects are seen, a decision should be made whether to continue or modify therapy taking into account the benefit of Sabril to the patient.

6.2. REMS Elements

6.2.1 Goals and Objectives

The REMS goals are the following:

- To minimize risk of the Sabril induced peripheral visual field defect (pVFD) while delivering maximum benefit to the appropriate patient populations.
- To detect and monitor Sabril induced pVFD to facilitate ongoing benefit-risk assessments between physicians and patient/parent or legal guardian.

The REMS objectives are the following:

- Prescribing physicians will be knowledgeable regarding approved clinical indications, the risk of Sabril induced pVFD and visual testing methods.
- Prescribing physicians will be knowledgeable regarding the findings of treatment emergent T2 MRI changes in infants with IS on Sabril therapy.
- Prescribing physicians will understand the process by which to assess individual patient's benefits and risks of continuing Sabril therapy.
- Patient/parent or legal guardian will be knowledgeable regarding approved clinical indications, the risk of Sabril induced pVFD and visual testing methods.
- Patient/parent or legal guardian will be knowledgeable regarding the findings of treatment emergent T2 MRI changes in infants with IS on Sabril therapy.

6.2.2 REMS Elements

The proposed Sabril REMS includes the following elements;

- A Medication Guide for patients/parent or legal guardian
- A Communication Plan with physician and patient/parent or legal guardian education to reinforce key risk messages
- Elements to Assure Safe Use (ETASU) of Sabril in patients including: mandatory registration of physicians and patients into a controlled distribution program, mandatory benefit-risk assessment prior to the beginning of maintenance treatment, and visual testing reminder system.

The REMS program will impact both physicians and patients, as it is integral to initiating a Sabril prescription and evaluating the benefit-risk proposition. To facilitate familiarity with

the REMS and all of its components, we will brand the REMS and the associated services under the acronym S.H.A.R.E that stands for Support, Help and Resources for Epilepsy. Our intent is that physicians and patients become familiar with the SHARE acronym and logo so that they recognize the importance of materials or communications that are branded. All physicians who prescribe Sabril and all patients who take Sabril will be enrolled in the SHARE program. This will aid in meeting our objective of educating key stakeholders about the benefits and risks associated with Sabril.

6.2.2.1 Medication Guide

The objective of this tool is to provide information to the patient/parent or legal guardian about the risks associated with Sabril therapy. The medication guide will be reviewed and discussed multiple times in the prescription process and will be included in the Sabril Starter Kit and reviewed with the patient/parent or legal guardian by the physician prior to starting the patient on Sabril therapy. The medication guide will be provided to the patient/parent or legal guardian by the specialty pharmacies at each refill and will be included at the end of each product insert.

6.2.2.2 Communication Plan

The communication plan includes activities in Physician and Patient/Parent or Legal Guardian Education and implementation of the Sabril Product Website.

PHYSICIAN EDUCATION

The objectives of this tool are to ensure that physicians with experience in treating epilepsy are properly educated regarding appropriate patient selection for Sabril; clearly understand the risks and benefits associated with Sabril therapy in patients with uncontrolled seizures; are aware of available patient tools and resources; and are aware of the recommendations for visual field testing.

Several tools will be employed to educate physicians including:

- Product Labeling - Sabril Package Insert (PI) with Black Box Warning (BBBW)
  - The objective of this tool is to clearly highlight the potential risk of the Sabril induced pVFD. A boxed warning will convey the prevalence, onset, severity, and risk factors associated with the Sabril induced pVFD. Information presented in the boxed warning will also be incorporated into all promotional and other applicable materials with the appropriate level of prominence.
- Visual testing guidance
  - The objective of this tool is to provide guidance to ophthalmologists on appropriate visual testing methods to be used in monitoring for pVFD.
- Dear Healthcare Professional letter
  - The objective of this tool is to inform appropriate physicians of Sabril availability, reinforce the key safety messages related to pVFD, inform appropriate physicians of current understanding of the treatment emergent T2 MRI findings in infants with IS, and highlight the appropriate product indication. This correspondence would be

distributed at product launch to the appropriate healthcare professional audiences (e.g., pediatric neurologists, and epileptologists).

- Sabril Benefit Risk Slide Presentation
  - The objective of this tool is to provide information on Sabril benefits and risks
- Newsletters
  - The objectives of this tool are to educate physicians and communicate updated information regarding visual field testing to physicians promptly.
- Sabril Product Website
  - The objective of this tool is to provide information to both patients and physicians regarding the product and disease states. All REMS components will be available on the website including a Sabril educational presentation and the Physician Attestation Form. The website will provide information on visual testing, and provide links to related websites including advocacy groups. Email links and other company contact information will also be made available on the website.

These tools will be updated as necessary in order to assure physicians are well informed of the Sabril REMS.

PATIENT/PARENT OR LEGAL GUARDIAN EDUCATION

The objective of the Sabril Starter Kit is to provide physicians and healthcare providers with a set of materials to facilitate education and discussion with a Patient/Parent or Legal Guardian prior to initiating Sabril therapy. The Sabril Starter Kit will be distributed to physicians and healthcare practitioners by representatives to facilitate the initiation of Sabril therapy. Components of the kit include:

- Medication Guide
  - The objective of this tool is to provide information to the Patient/Parent or Legal Guardian about the risks associated with Sabril therapy. The medication guide will be reviewed and discussed multiple times in the prescription process and will be included in the Sabril Starter Kit and reviewed with the patient by the physician prior to starting the patient on Sabril therapy. The medication guide will also be provided to the patient by the specialty pharmacies at each refill and will be included at the end of each product insert.
- Patient/Parent or Legal Guardian – Physician Agreement
  - The objective of this tool is to provide prescribing physicians with a Patient/Parent or Legal Guardian - Physician Agreement Form they can use as needed with their patients to document the patients' understanding of the risks associated with Sabril therapy. Instead of using the Patient/Parent or Legal Guardian - Physician Agreement provided by Ovation, prescribing physicians may use their own similar Patient/Parent or Legal Guardian - Physician Agreement if required by their institution or practice. Due to the unique risk profile of Sabril, this tool has a biphasic sign-off process. The patient/parent or legal guardian and physician should each sign the document after reviewing the Medication Guide and deciding to initiate therapy (Evaluation Phase Agreement). After the evaluation phase (approximately 12 weeks), the patient/parent

or legal guardian and physician must discuss the degree of seizure improvement that was observed. If no meaningful improvement was observed, Sabril therapy should be discontinued. However, if meaningful seizure improvement was observed, the patient/parent or legal guardian and physician must discuss the risks and benefits of Sabril maintenance therapy. If the decision is made to proceed with maintenance therapy, the patient/parent or legal guardian and physician must sign the Maintenance Phase Agreement. The signed agreement must be filed at SHARE so that patient may enter the maintenance treatment.

- Brochure(s) on Epilepsy, Sabril and the pVFD
  - The objective of this tool is to provide information on epilepsy, Sabril and pVFD.
- Seizure Diary
  - The objective of this tool is to track/assess seizure improvement in patients.
- SHARE Program Information
  - The objective of this tool is to provide information on the SHARE program and its requirements.
- Web based Visual Field Simulator
  - The objective of this tool is to help a patient/parent or legal guardian understand the potential Sabril induced peripheral vision problem. This interactive simulator allows them to experience a possible peripheral vision problem and how it affects someone's vision.
- Sabril Product Website
  - The objective of this tool is to provide information to both patients and physicians regarding the product and disease states. All REMS components will be available on the website. The website will include information on visual testing, and provide links to related websites including advocacy groups. Email links and other company contact information will be made available on the website. Patients will be able to register for the SHARE Program which will be designed to proactively provide patients reminders about the product, visual field testing and information about epilepsy.

These tools will be updated as necessary in order to assure patients/parents or legal guardians are well informed of the Sabril REMS.

6.2.3 Elements to Assure Safe Use (ETASU)

6.2.3.1 Mandatory Registration of Physicians and Patients into a Controlled Distribution Program

In order to prescribe and/or receive Sabril, both physician and patient/parent or legal guardian must be registered in the controlled drug distribution system called SHARE (Support Help And Resources for Epilepsy) which comprises a Call Center which acts as the hub for a network of select specialty pharmacies. The SHARE program will serve to ensure that Sabril is only prescribed by physicians with experience in treating epilepsy and that physicians and patients/parent or legal guardian have been properly educated on Sabril's clinical indications, benefits and risks and associated visual testing requirements. Only

physicians with experience in treating epilepsy and who have registered and attested to receiving and understanding Sabril informational material may prescribe Sabril. Patients will only be registered in SHARE to receive Sabril treatment if they have prescriptions written by physicians who are registered in SHARE.

6.2.3.2 Mandatory Benefit-Risk Assessment

The initial treatment evaluation phase with Sabril may last up to approximately 12 weeks duration. Prior to maintenance treatment with Sabril, a mandatory benefit-risk assessment is required to be performed which will be documented on a Treatment Maintenance Form. The benefit risk assessment will comprise assessment of seizure response to treatment and occurrence of any Sabril side effects including pVFD. Sabril will be discontinued in patients who do not demonstrate a clinically meaningful improvement in seizure control thereby minimizing risk for occurrence of pVFD.

6.2.3.3 Visual Testing Reminder System

Visual testing is required to detect and monitor Sabril induced pVFD to facilitate ongoing benefit risk assessments in patients.

The labeling will contain requirements for periodic visual testing and the recommended testing methods.

A reminder system in SHARE will facilitate visual testing in patients treated with Sabril. Patients will be reminded (direct telephone contact) by SHARE call center to attend scheduled visual testing appointments.

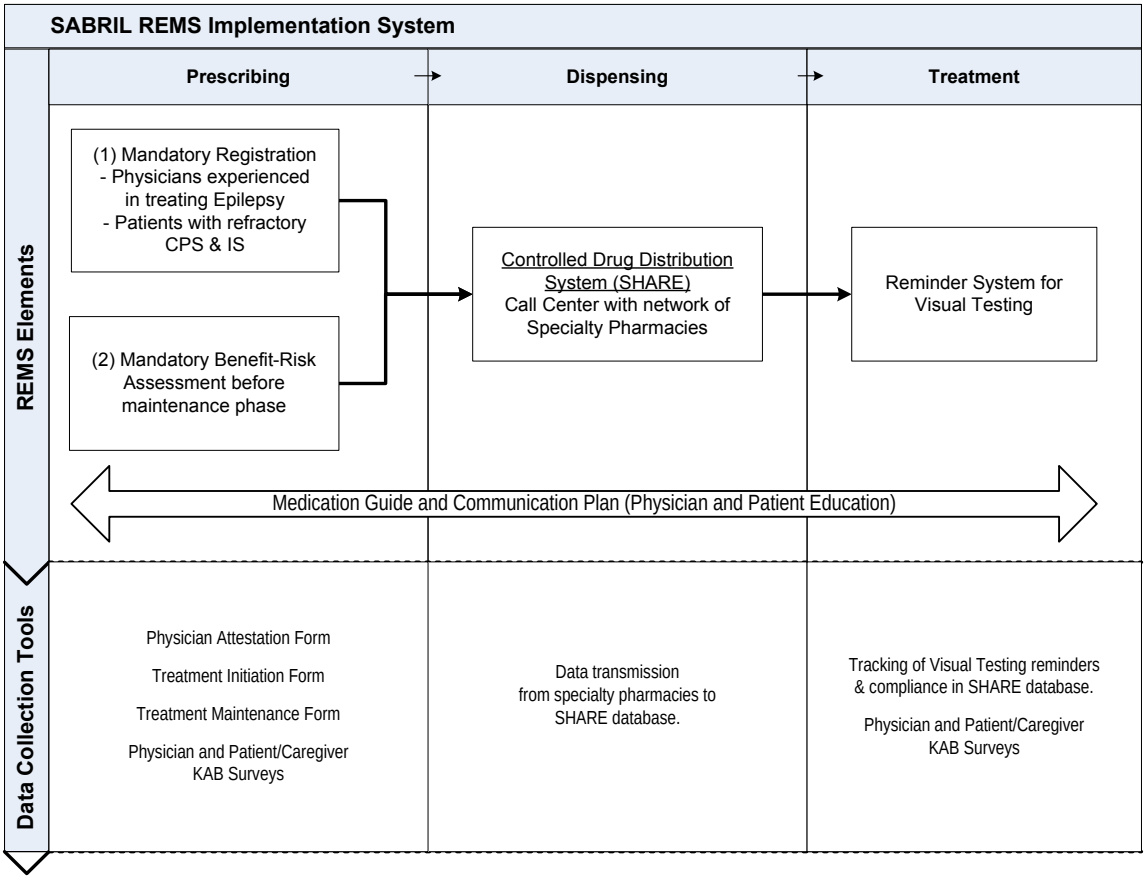
- Refractory CPS: Visual testing is recommended at baseline and every 6 months while on therapy. Depending on patient age and cognitive status, a variety of ophthalmologic testing modalities can be used; including confrontation, perimetry, and electrophysiologic testing. A pVFD detected during ophthalmologic testing should be confirmed in a timely fashion by additional testing. If confirmed and the patient and physician decide to continue therapy, ophthalmologic testing should be increased in frequency to 3 month intervals with ongoing benefit risk assessments.
- IS: Visual testing is recommended at baseline and every 3 months for the first 18 months and 6 monthly thereafter while on therapy. Confrontation or electrophysiologic testing should be used. A retinal abnormality detected during ophthalmologic testing should be confirmed in a timely fashion by additional testing. If confirmed and the parent/legal guardian and physician decide to continue therapy, ophthalmologic testing should be conducted at 3 month intervals with ongoing benefit risk assessments.

REMS IMPLEMENTATION SYSTEM

The implementation system to monitor and evaluate the effectiveness of the REMS in meeting its goals and objectives will utilize data collected in the SHARE Database and Surveys of Physicians and Patients/Guardians. REMS elements and data collection tools

utilized during prescribing, dispensing, and treatment are summarized in the implementation system map in Figure 18.

Figure 18. Sabril REMS Implementation System



6.2.4 REMS Data Collection

Data will be collected to assess each individual element of REMS.

6.2.4.1 Medication Guide

Assessment of compliance with distribution of the Medication Guide to patients will involve data collected on a variety of forms to be implemented during the prescription and dispensing stages of treatment and data transmitted directly from the specialty pharmacies to the SHARE database (Table 66). Completed forms will be stored at the SHARE Call Center. All collected data will be entered in the SHARE Database which will serve as data source for analysis.

Table 66. Assessment of Compliance: Medication Guide

Medication Guide	Data Collection Tools for Assessment of Effectiveness
Provision to Patient/Parents or Legal Guardian	• Treatment Initiation Form • Treatment Maintenance Form • Data transmission from specialty pharmacies to SHARE database

6.2.5 Communication Plan

Assessment of Physician and Patient/Parent or Legal Guardian knowledge and understanding of key Sabril safety messages as well as compliance with recommendations for patient management will utilize data collected from Knowledge, Attitude and Behavior (KAB) Surveys (Table 67). The surveys will be implemented by Ovation according to protocol and using standardized questionnaires distributed to a representative sample of physicians and patients registered in the SHARE program. Completed questionnaires will be stored with Ovation which will undertake analysis and evaluation of survey results.

Table 67. Assessment of Compliance: Communication Plan

Communication Plan	Data Collection Tools for Assessment of Effectiveness
Physician Education • Package Insert with BBW • Visual Testing Guidance • Dear HCP letter • Sabril Benefits & Risk Slide Presentation • Newsletters • Sabril Product Website	Physician KAB surveys
Patient Education • Medication Guide • Patient-Physician Agreement • Patient education brochures • Seizure Diary • SHARE Program Information • Web Based Visual Field Simulator • Sabril Product Website	Patient/Parent or Legal Guardian KAB surveys

6.2.6 ETASU

Assessment of compliance with ETASU will involve data collected on a variety of forms to be implemented during the prescription and drug use stages of treatment (Table 68). Completed forms will be stored at the SHARE Call Center. All collected data will be entered in the SHARE Database which will serve as data source for analysis.

Table 68. Assessment of Compliance: ETASU

ETASU	Data Collection Tools for Assessment of Effectiveness
▪ Mandatory registration of Physicians and Patients • Registration of physicians with experience in treating epilepsy. • Attestation of Physicians	• Physician Attestation Form • Treatment Initiation Form
• Mandatory benefit-risk assessment before treatment maintenance phase.	• Treatment Maintenance Form
• Reminder system for visual testing	• Tracking in SHARE Database of all reminder contacts made with individual patients.

6.2.7 Timetable for Submission of Assessments

Periodic assessments of the REMS effectiveness will be performed by Ovation and results will be submitted and discussed with the agency. The following assessments of the REMS will be performed:

- KAB Surveys: Knowledge, attitude and behavior of Physicians and Patients/Parents or Legal Guardians with respect to REMS requirements will be assessed through conduct of surveys. The SHARE database will also provide supportive data for assessment of compliance with REMS requirements. It is proposed that the KAB Surveys be performed at 1 year, 2 years, 3 years and 7 years post approval.

- Periodic Adverse Drug Experience Reports (PADER): Pharmacovigilance information including spontaneous reports and literature reports will be obtained from Ovation's Safety Database (AERS) and evaluated on an ongoing and periodic schedule. PADERs will be used for assessment of occurrence of pVFD and will be submitted to the FDA on a quarterly basis for the first three years and then annually post approval.

6.3. Planned Studies with Vigabatrin

6.3.1 University of Toronto Infantile Spasms Study

Ovation will continue to support the study of serial ERG measurements in children treated with VGB for IS described in detail in Section 5.4.9.1. This study has already produced valuable information concerning the retinal effects of VGB in infants. It is anticipated that forthcoming data will characterize retinal electrophysiology in infants after discontinuing VGB, as infants are now typically treated for only 6 months and Dr. Westall has succeeded in examining infants up to 6 months after stopping drug.

6.3.2 Groupe Hospitalier Necker-Enfants Maladies Study

A protocol is in development with Drs. Oliver Dulac, Catherine Chiron, and Serge Picaud in Paris to examine children treated with VGB for IS over 10 years ago with a combination of electrophysiologic and perimetric techniques to determine retinal function. Studying this group of children (among the first to receive VGB anywhere in the world) will define the long-term visual consequences of VGB exposure in childhood.

6.3.3 Basic Mechanisms of pVFD and IME and Agents That Can Arrest or Prevent Development

Ovation Pharmaceuticals has partnered with Dr. Serge Picaud and the Laboratoire de Physiopathologie Cellulaire et Moléculaire de la Rétine, INSERM Paris to study the molecular mechanism of toxicity of VGB, specifically in relation to pVFD formation and IME in rodents. The goals of this research are to enhance our understanding of pVFD formation and IME in animal models, and to test various agents which may arrest retinal injury from VGB.

6.3.4 Prospective Study of Retinal Function in Patients Taking VGB for Refractory CPS

A prospective study will be carried out to assess the specificity and sensitivity of OCT as compared with kinetic perimetry in the detecting the retinal effects of VGB. This study will also contribute to the data concerning visual function in patients during their first year of VGB exposure, and will assess the relationship between automated kinetic perimetry and Goldmann perimetry in a population of patients with refractory CPS.

Patients intending to begin VGB for refractory CPS at selected centers will be recruited prior to starting drug. They will undergo a baseline neuro-ophthalmologic examination, including Goldmann kinetic perimetry, automated kinetic perimetry (Humphries Visual Field Analyzer SSA II program using a III-4e target) and OCT to measure retinal nerve fiber layer (RNFL) thickness. Patients with pre-existing VFD or primary ophthalmic disease that could affect visual fields or acuity, including aphasic patients, will be excluded from the study. Perimetry, corrected visual acuity and color vision will be repeated every 3 months after starting VGB. Detailed dosing data will be collected. Perimetry will continue to be performed for 1 year after stopping drug for those who discontinue VGB use. OCT will be performed every 6 months over this same period.

Perimetries and OCT records will be reviewed centrally and independently. The width of the RNFL as determined by OCT will be compared to the width of the visual field, in degrees, along the horizontal meridian, as determined by kinetic perimetry. Comparisons will be by statistical correlation and by assessing positive and negative agreement of OCT measurement of RNFL thickness with visual field width determined by kinetic perimetry.

6.3.5 Prospective Study on MRI Abnormalities in Patients on VGB Therapy (OV-1034)

An open-label, multicenter, observational study will be conducted in the U.S. and Canada to prospectively determine the incidence, prevalence, and clinical accompaniments of cranial MRI signal abnormalities in infants with IS treated with VGB or other modalities. In addition, the study will evaluate the correlation of cranial MRI signal abnormalities with neurodevelopment and cognitive outcomes of IS. The study also seeks to identify risk factors associated with the MRI abnormalities.

Patients will be newly diagnosed with IS and their treatment will be determined by their treating physician. Inclusion criteria include clinically and electrophysiologically confirmed primary or secondary diagnosis of IS; male or female ≤24 months of age; and no prior exposure to drugs or therapies with proven efficacy in IS. Patients' legally authorized representative will sign and date an informed consent/HIPAA authorization form (or country-specific equivalent) prior to any study related procedures being performed.

Patients will receive a complete MRI examination under sedation including T2/FLAIR and DWI and T1 images for volumetric analysis at baseline. At 2 and 6 weeks and 3 and 6 months after starting therapy they will undergo MRI with DWI sequences only, not requiring sedation, to monitor the development of signal abnormalities. Complete MRI examinations

will be repeated at 1 and 2 years and will include volumetric analysis of key brain regions to assess long-term imaging consequences of the transient, treatment related abnormalities. In addition, cranial MRI obtained to address clinical questions will be captured for the study.

The neurological, developmental and cognitive status of the patients will be assessed with neurological examinations and the Vineland Adaptive Behavioral Scale performed at each visit and the Bayley Scales of Infant Development-II at baseline and at 1 and 2 years. The primary endpoint will be the occurrence of treatment emergent DWI abnormalities. Secondary endpoints will include findings on neurological examinations and cognitive testing. Potential risk factors for the occurrence of DWI abnormalities will be analyzed by logistic regression.

7 CONCLUSIONS

Proposed indications for VGB include adjunctive treatment of refractory CPS in adults and as monotherapy for IS, two devastating conditions that affect small patient populations, and if left uncontrolled, carry extremely poor prognoses. Refractory CPS is a severe form of epilepsy and is associated with significant morbidity and mortality. Rates of SUDEP and suicide are notably higher in patients with chronic epilepsy and higher still in refractory or uncontrolled epilepsy. In addition, recurrent episodes of impaired consciousness associated with CPS impair vocational and social function and can lead to an increased risk of falls, burns, drowning, and accidents. Patients with refractory CPS who have failed multiple other therapies would benefit from access to VGB, an AED acting through a novel mechanism and able to achieve substantial reduction in seizure frequency, even seizure freedom, in a subset of patients with CPS.

IS is one of the most severe forms of epilepsy. Children with uncontrolled spasms suffer impaired central nervous system development and may never attain critical developmental milestones. There are no approved treatments for IS in the U.S

VGB has well-documented efficacy in the treatment of epilepsy and is approved in Europe, Canada, and many other countries as adjunctive therapy in refractory CPS and for the monotherapy treatment of IS, with an estimated 1.5 million patients exposed worldwide. Numerous studies have been performed in patients with a wide age range and a variety of seizure types. The efficacy of VGB in partial epilepsy has been extensively documented. In the two pivotal studies of refractory CPS (Studies 025 and 024) VGB as add-on therapy achieved statistically significant, and clinically meaningful reductions in seizure frequency. Among responders, a reduction in seizure frequency was generally noted within 4-6 weeks of the initiation of treatment. These studies were multicenter, double-blind, randomized, placebo-controlled, dose-ranging studies conducted in the U.S.

The effectiveness of VGB as monotherapy treatment for IS was established in 3 adequate and well-controlled studies (Studies 1A, W019, and FR03) and numerous uncontrolled supportive studies. The results demonstrated statistically significant and clinically meaningful effects of VGB on spasm cessation in IS, and onset of this effect noted within 2-4 weeks of the initiation of treatment.

Despite its proven efficacy as an AED, its clinical use has been limited by the occurrence of pVFD in some patients. Recently, for infants with IS, concerns have also been raised regarding the development of MRI abnormalities. The general safety profile of VGB is well characterized via extensive clinical and postmarketing experience.

VGB has been associated with induction of a bilateral and concentric peripheral visual field defect. A considerable body of data characterizing pVFD now exists from the Ovation-sponsored Study 4020, the Investigator-initiated Toronto IS Study, and the scientific literature. For VGB-induced pVFD, the available evidence supports the following overall conclusions: the extent of the binocular pVFD, if it occurs, is typically mild (120-160 degrees binocular field remaining) or moderate (60-120 degrees remaining) and rarely severe (<60 degrees remaining), and central visual acuity is not affected. Studies designed to specifically evaluate the prevalence of this issue have estimated the prevalence of confirmed VGB-induced pVFD in 25% of adult patients, 15% of children, and 31% of infants receiving long-term VGB therapy. Prevalence estimates reported in the literature of the distinctive pVFD vary widely (17-92%). Although infrequent reports have been noted within the first 12 months of treatment, the defect does not generally appear to manifest early following initiation of therapy and the median time to onset has been estimated at 4.3-4.7 years following initiation of therapy. Following discontinuation of VGB, pVFD does not progress; however VGB- induced pVFD appears to be irreversible. Importantly, although visual assessment in patients with refractory CPS and IS can be challenging because of behavioral and cognitive limitations, patient-specific and age-appropriate methods can be employed to detect and monitor for pVFD.

VGB treatment of IS is associated with MRI abnormalities in infants. In a retrospective clinical study in pediatric patients with IS (OV-1019), VGB was associated with an increase in the occurrence of T2 signal changes in certain brain regions on MRI. The study suggested a VGB dose effect, in that patients receiving a higher dose of VGB (≥125 mg/kg/d) were at greater risk of developing an abnormal MRI. The MRI abnormalities have been noted to resolve, whether VGB was continued or discontinued. To date, no clinical correlate of the imaging abnormalities has been identified beyond transient motor abnormalities in a few patients, but longitudinal clinical observations are lacking, to determine whether the MRI abnormalities have long term clinical sequelae.

Because of the potential for development of pVFD, a comprehensive REMS will accompany the commercialization of VGB in the U.S. The proposed REMS takes into account the consequences of uncontrolled seizures as well as the potential benefits and risks of VGB. REMS objectives will be accomplished by controlled distribution and physician/legal guardian/patient education.

Due to the risk for developing pVFD, VGB should only be added to the treatment regimen of patients with refractory CPS when other appropriate therapies have proved inadequate or have not been tolerated. If substantial clinical benefit is not achieved with the first 3 months of therapy VGB should be discontinued. In those patients achieving meaningful clinical benefit from VGB and choosing to continue therapy, monitoring of visual function including patient-specific, age-appropriate visual field testing will be essential in informing ongoing discussions between the physician and patient concerning benefit-risk assessments.

For IS patients whose disease is adequately controlled with VGB, the risk of the pVFD and MRI signal changes is outweighed by the benefit of this drug for this patient population for which there is no currently approved treatment. For both populations, patients or their legal guardian must have a clear understanding of the risk of acquiring the pVFD, and of the recommended monitoring that can be crucial for early detection

In summary, given the risks of death and significant morbidity from refractory CPS and IS, VGB yields a greater potential benefit than the associated risks. Furthermore, the ability to detect efficacy with VGB early, relative to the risk of pVFD, as well as the controls afforded by the proposed REMS for VGB will serve to mitigate the risk of the pVFD and other safety concerns to ensure that VGB therapy is available to patients in the U.S. with two catastrophic illnesses who have limited or no other treatment alternatives.

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