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February 4, 2014

Dear Healthcare Provider:

Thank you for your interest in **FYCOMPA™** *(perampanel)* **CIII**. Per your request to Jill Walker, your Eisai Inc. Medical Science Liaison, we are enclosing specific information regarding:

FYCOMPA™ (perampanel) – Formulary Dossier

Please note that FYCOMPA is approved for those indications and dosages that appear in the enclosed FYCOMPA Full Prescribing Information. The enclosed information and/or its appendices may summarize publications or guidelines that describe indications or treatment modalities for the use of FYCOMPA that have not been approved by the Food and Drug Administration.

The enclosed information is provided by Eisai Inc. as a service to healthcare professionals and is intended to assist you in forming your own clinical conclusions regarding the use of Eisai products. Eisai Inc. does not recommend or endorse the use of this product in any manner other than as described in the Full Prescribing Information.

INDICATION

FYCOMPA, a non-competitive AMPA glutamate receptor antagonist, is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA**
- **Closely monitor patients particularly during the titration period and at higher doses**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

Serious Psychiatric and Behavioral Reactions
Hostility- and aggression- related adverse reactions occurred in 12% and 20% of clinical trial patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects in FYCOMPA treated patients led to dose

reduction, interruption, and discontinuation more frequently than placebo-treated patients. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol. Patients their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least one month after the last dose of FYCOMPA and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases.

Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm and/or any unusual changes in mood or behavior. Should suicidal thoughts or behavior emerge during treatment consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Dizziness and Gait Disturbance
FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination. Dizziness and vertigo were reported in 35% and 47% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 10% of placebo-treated patients. Gait disturbance related events were reported in 12% and 16% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase.

Somnolence and Fatigue
FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events. Somnolence was reported in 16% and 18% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 7% of placebo patients. Fatigue-related events were reported in 12% and 15% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 5% of placebo patients. In the controlled Phase 3 epilepsy clinical trials these adverse reactions occurred mostly during the titration phase. Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known.

Falls
Falls were reported in 5% and 10% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo-treated patients.

Withdrawal of AEDs
A gradual withdrawal is generally recommended with anti-epileptic drugs to minimize the potential of increased seizure frequency.

Most Common Adverse Reactions
In clinical trials the most frequently reported dose-related adverse reactions in patients receiving FYCOMPA 8 mg or 12 mg vs placebo (=4% and at least 1% higher than the placebo group)

included dizziness (36% vs 9%), somnolence (16% vs 7%), fatigue (10% vs 5%), irritability (9% vs 3%), falls (7% vs 3%), nausea (7% vs 5%), ataxia (5%vs 0%), balance disorder (4% vs 1%), gait disturbance (4% vs 1%), vertigo (4% vs 1%), and weight gain (4% vs 1%).

Drug Interactions
FYCOMPA may decrease the efficacy of contraceptives containing levonorgestrel. Plasma levels of FYCOMPA were decreased when administered with carbamazepine, phenytoin and oxcarbazepine. Concomitant use with strong CYP3A inducers such as St. John's wort and rifampin should be avoided. Multiple dosing of FYCOMPA 12 mg/day enhanced the effects of alcohol on vigilance and alertness, and increased levels of anger, confusion, and depression. These effects may also be seen when FYCOMPA is used in combination with other CNS depressants.

Pregnancy Category C and Lactation
FYCOMPA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Physicians are advised to recommend that pregnant patients taking FYCOMPA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Caution should be exercised when FYCOMPA is administered to a nursing woman.

Hepatic and Renal Impairment
Use in patients with severe hepatic or severe renal impairment is not recommended. Dosage adjustments are recommended in patients with mild or moderate hepatic impairment. Use with caution in patients with moderate renal impairment.

Thank you for the opportunity to respond to your inquiry, and for your interest in FYCOMPA.

Sincerely,

Adelle Berezinsky, PharmD
Manager, Medical Information

SR#: 00061543

Enclosures: FYCOMPA Full Prescribing Information; Formulary Dossier

FYCOMPA™
(perampanel) Tablets

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This dossier is provided in response to your unsolicited request to Eisai Inc. for a formulary submission document for FYCOMPA™.

In addition to published data and information included in the FDA-approved product labeling, this dossier contains information not included in the product labeling as well as unpublished data. These data are provided to assist pharmacist and physician managed care decision makers in formulary and coverage evaluations.

This dossier is intended for use only by this health plan, and its distribution and/or duplication is prohibited. Please consult the enclosed package insert for complete safety and prescribing information for FYCOMPA™.

If you have any additional questions, please contact Eisai Medical Information:

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Visit us at: eisai.com/us

GLOSSARY OF TERMS

AAN	American Academy of Neurology
AE	Adverse event
AED	Antiepileptic drug
AES	American Epilepsy Society
AHFS	American Hospital Formulary Service
ALT	Alanine aminotransferase
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AST	Aspartate aminotransferase
BID	Twice daily
BIM	Budget impact model
BMI	Body mass index
BZD	Benzodiazepine
Ca^{++}	Calcium ion
CBZ	Carbamazepine
CGI-C/PGI-C	Clinical and Patient Global Impression of Change
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CNS	Central nervous system
CV	Schedule V of the Controlled Substances Act
CYP	Cytochrome P450
DEA	Drug Enforcement Administration
ECG	Electrocardiogram
ED	Emergency department
EEG	Electroencephalogram
EPSP	Excitatory postsynaptic potential
ER	Emergency room
FDA	Food and Drug Administration
FI	Fluctuation index
GABA	Gamma-aminobutyric acid
HCUP	Healthcare Cost and Utilization Project
HLA-B	Human leukocyte antigen B
HR	Hazard ratio
HRQOL	Health-related quality of life
ICU	Intensive care unit
ILAE	International League Against Epilepsy
ITT	Intent to treat
IV	Intravenous
K^{+}	Potassium ion
KCNQ	Potassium channel, voltage-gated
LGS	Lennox-Gastaut syndrome
max	Maximum
min	Minimum
MOA	Mechanism of action
MTD	Maximum tolerated dose
Na^{+}	Sodium ion
NA	Not available
NDC	National Drug Code
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NMDA	N-methyl-D-aspartic acid

NR	Not reported
NS	Not significant
OR	Odds ratio
OXC	Oxcarbazepine
PB	Phenobarbital
PD	Pharmacodynamic
PHY	Phenytoin
PI	Prescribing information
PK	Pharmacokinetic
PMIC	Practice Management Information Corporation
PMPM	Per member per month
POS	Partial-onset seizures
QD	Once daily
QHS	At bedtime
QID	Four times daily
QOD	Every other day
QOL	Quality of life
QOLIE-31-P	Quality of Life in Epilepsy questionnaire
SAE	Serious adverse event
SC	Sodium channel
SD	Standard deviation
SOC	Standard of care
SUDEP	Sudden unexpected death in epilepsy
SV2A	Synaptic vesicle glycoprotein 2A
$t_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TID	Three times daily
URI	Upper respiratory tract infection
US	United States
VPA	Valproic acid
WAC	Wholesale acquisition cost
WBC	White blood cell
WDSE	Withdrawal due to side effects
XR	Extended release

SECTION I: Executive Summary

FYCOMPA™ (perampanel) Tablets

FYCOMPA EXECUTIVE SUMMARY

This dossier describes FYCOMPA™ (perampanel), a noncompetitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons.[1] FYCOMPA is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.[1]

EPILEPSY OVERVIEW

Epilepsy, a chronic disorder characterized by recurrent unprovoked seizures, is the fourth most common neurologic disorder in the United States (US), affecting an estimated 2.2 million Americans.[2,3] Commonly reported comorbidities in patients with epilepsy include anxiety, suicidal thoughts, depression, cognitive decline, migraine, psychogenic nonepileptic disorders, injuries, and increased mortality.[4] Unfortunately, patients with epilepsy not only report poor health-related quality of life (HRQOL), they are also less likely to have full-time employment and to suffer from the stigma associated with the diagnosis.[5] Epilepsy has a substantial impact on health care utilization and cost, with the US estimated annual cost of epilepsy and seizures being $17.6 billion in direct and indirect costs.[6,7]

Epilepsy can be classified by seizure type (partial-onset [focal] seizures, generalized seizures, and unknown) and epileptic syndrome.[2,8] ***Partial-onset (focal) seizures***, occurring in 57% of newly diagnosed patients, begin in a localized area of the brain. These seizures may evolve into secondarily generalized seizures, in which the seizure activity spreads to involve both hemispheres of the brain, occurring in 60% of cases.[4,9]

Despite the availability of more than 20 marketed antiepileptic drugs (AEDs), approximately 20% to 40% of patients with epilepsy continue to have seizures and are considered refractory to therapy.[10,11] Hence, there is a need for additional safe and effective AED options.[12] The development of new AEDs with novel mechanisms of action (MOAs) may offer potential benefits to patients refractory to or unable to tolerate current therapies.[13] AEDs with new MOAs may also increase the number of possible AED combinations.[14]

There is evidence that AED combination therapy based on different MOAs may enhance effectiveness, whereas AED combination therapy with drugs that target the same MOA is likely to exacerbate adverse events (AEs).[15] In theory, combinations of AEDs with different, overlapping, or similar mechanisms may be additive or synergistic.[15] Research in this area is ongoing.

Unlike other AEDs, FYCOMPA is a noncompetitive antagonist of the AMPA receptor on postsynaptic neurons, inhibiting AMPA receptors even in the presence of high concentrations of glutamate.[1,16] Preclinical seizure models have demonstrated that FYCOMPA has broad spectrum anticonvulsant activity, and the efficacy and safety of FYCOMPA as adjunctive therapy for the treatment of partial-onset seizures has been demonstrated in clinical studies.[17]

FYCOMPA CLINICAL BENEFITS

FYCOMPA is the first FDA-approved, noncompetitive AMPA glutamate receptor antagonist.[1,18]

- Glutamate facilitates excitatory neurotransmission in the central nervous system (CNS), primarily through mediating fast excitatory signaling at the postsynaptic AMPA receptor.[19,20]
- AMPA receptor activation plays an important role in the generation and spread of seizures.[20]

FYCOMPA as adjunctive therapy has demonstrated efficacy in reducing seizures associated with partial-onset seizures, with or without secondarily generalized seizures, in patients ≥ 12 years of age.

- ***Study 304*** (French et al[21]; Study 1 in the FYCOMPA prescribing information [PI][1]) (N = 388), ***Study 305*** (French et al[22]; Study 2 in the FYCOMPA PI[1]) (N = 386), and ***Study 306*** (Krauss et al[23]; Study 3 in the FYCOMPA PI[1]) (N = 706) were similarly designed, 19-week, randomized, double-blind, placebo-controlled, multicenter studies evaluating the efficacy and tolerability of FYCOMPA as adjunctive therapy in patients ≥ 12 years of age with refractory partial-onset seizures. Whereas ***Study 306*** evaluated

the 2 mg, 4 mg, and 8 mg doses, ***Studies 304*** and ***305*** evaluated the 8 mg and 12 mg doses. These studies found:

- FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***median percent change in seizure frequency per 28 days*** (ranging from –17.6% to –34.5% vs –9.7% to –21.0%, respectively; $p < 0.05$).[21-23]
- FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a greater proportion of patients experiencing a ***≥ 50% reduction in seizure frequency (responder rate)*** (ranging from 28.5% to 37.6% vs 14.7% to 26.4%, respectively).[21-23]
- FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***reduction in the change in frequency of complex partial seizures + secondary generalized seizures*** (ranging from –21.9% to –38.7% vs –8.1% to –17.9%, respectively; $p < 0.01$).[21-23]

- A post hoc analysis of pooled study data from ***Studies 304, 305, and 306 (Steinhoff et al[24])*** found:
  - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***median percent change in seizure frequency per 28 days*** (–23.3%, –28.8%, and –27.2% vs –12.8%, respectively; $p < 0.01$ for 4 mg dose and $p < 0.001$ for 8 mg and 12 mg doses).[24]
  - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a greater proportion of patients experiencing a ***≥ 50% reduction in seizure frequency (responder rate)*** (28.5%, 35.3%, and 35.0% vs 19.3%, respectively; $p < 0.05$ for 4 mg and $p < 0.001$ for 8 mg and 12 mg).[24]
  - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***reduction in the change in frequency of complex partial seizures + secondary generalized seizures*** (–31.2%, –35.6%, and –28.6% vs –13.9%, respectively; $p < 0.001$).[24]

FYCOMPA as adjunctive therapy has demonstrated *long-term* efficacy and tolerability in reducing seizures associated with partial-onset seizures.

- **Study 307** (Krauss et al[25] [N = 1186]) is an ongoing 256-week, open-label extension of Studies 304, 305, and 306 evaluating the long-term safety, tolerability, and efficacy of FYCOMPA. Interim results (data cutoff date: December 1, 2010) are presented below:
  - At the time of the interim analysis, 840 patients (70.8%) remained on FYCOMPA, with 580 patients (48.9%) and 19 patients (1.6%) having > 1 year or 2 years of exposure, respectively. A total of 1084 patients (91%) were titrated to 10 mg or 12 mg per day. The median duration of exposure was 51.4 weeks (range: 1.1 to 128.1 weeks).[23]
  - ***Treatment-emergent AEs (TEAEs)*** were reported in 87.4% of patients, with the most frequent being dizziness, somnolence, headache, and fatigue. ***Serious AEs*** were reported in 13.2% of patients.[23]
  - The overall ***median percent change in seizure frequency*** included in each 13-week interval of FYCOMPA therapy was –39.2% for Weeks 14 to 26, –46.5% for Weeks 40 to 52, and –58.1% for Weeks 92 to 104.[23]
  - The overall ***≥ 50% reduction in seizure frequency (responder rate)*** included in each 13-week interval of FYCOMPA therapy was 41.4% for Weeks 14 to 26, 46.9% for Weeks 40 to 52, and 62.7% for Weeks 92 to 104.[23]

A pooled post hoc analysis found that FYCOMPA as adjunctive therapy has demonstrated efficacy for *secondarily generalized seizures.*

- A pooled post hoc analysis of **Studies 304, 305, and 306** (Ko and Ramsay[26] and Steinhoff et al[24]) evaluated the efficacy of FYCOMPA as adjunctive therapy for secondarily generalized seizures (N = 1480) and found:
  - At baseline, 68.4% of patients receiving FYCOMPA and 71.9% of patients receiving placebo had a history of secondarily generalized seizures.[24,26]
  - FYCOMPA 4 mg, 8 mg, and 12 mg vs placebo had a significantly greater ***median percent change in secondarily generalized seizure frequency per 28 days*** (–48.6%, –62.9%, and –53.3% vs –19.4%, respectively; $p < 0.01$ for each dose).[24,26]
  - FYCOMPA 8 mg and 12 mg vs placebo had a significantly greater proportion of patients experiencing a ***≥ 50% reduction in secondarily generalized seizure frequency (responder rate)*** (60.5% and 53.7% vs 37.0%, respectively; $p < 0.01$ for each dose).[24,26]

- FYCOMPA 8 mg and 12 mg vs placebo had a significantly greater proportion of patients experiencing a ***≥ 75% reduction in secondarily generalized seizure frequency (responder rate)*** (46.5% and 38.9% vs 24.3%, respectively; $p < 0.001$ for 8 mg, $p = 0.012$ for 12 mg).[26]
- FYCOMPA 8 mg and 12 mg vs placebo had a significantly greater proportion of patients achieving ***secondarily generalized seizure freedom*** (28.9% and 27.0% vs 14.2%, respectively; $p = 0.002$ for 8 mg, $p = 0.028$ for 12 mg).[26]

FYCOMPA is generally well tolerated in patients with partial-onset seizures.

- FYCOMPA has been administered to more than 1600 patients with epilepsy in clinical studies including open-label extension studies.[27]
- In phase III clinical studies, the most common adverse reactions in patients receiving FYCOMPA at doses of 8 mg or 12 mg (≥ 4% and ≥ 1% greater than placebo) included dizziness, somnolence, fatigue, irritability, fall, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder.[1]
- In phase III clinical studies, discontinuation rates due to AEs were 3%, 8%, and 19% in patients randomized to receive FYCOMPA 4 mg, 8 mg, or 12 mg/day, respectively, vs 5% in patients randomized to receive placebo.[1]
- There are no contraindications for FYCOMPA; please see **Section II. Product Information for FYCOMPA – Boxed WARNING and WARNINGS and PRECAUTIONS** sections.

FYCOMPA has a once daily at bedtime dosing regimen and has multiple dosages available (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets).[1]

- If patients miss a dose, patients may resume dosing the following day at their prescribed dose, given the long half-life of FYCOMPA (105 hours).[1,28]
- A simulated pharmacokinetic analysis of 19 phase I FYCOMPA studies confirmed that after a missed dose, the FYCOMPA plasma trough concentration (C_{min}) preceding the next scheduled dose would be expected to decrease mildly to moderately (18.4% and 43.9% in the absence or presence of enzyme-inducing AED, respectively) (see **Section III: Table III-13 – Gidal et al, 2012[28]**).

FYCOMPA has little impact on the pharmacokinetics of other AEDs.

- Pooled population pharmacokinetic and pharmacodynamic analyses of FYCOMPA (see **Section III: Table III-13 – Laurenza et al, 2011[29]**) have found that FYCOMPA does not have a clinically relevant effect on the pharmacokinetics of other AEDs including carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide.[29]
- Because FYCOMPA is primarily metabolized by cytochrome P450 3A4 (CYP3A4), the concomitant use of FYCOMPA with CYP3A4-inducing AEDs, such as carbamazepine, oxcarbazepine, or phenytoin, will decrease the plasma level of FYCOMPA by approximately 50% to 67% and will decrease the effectiveness of FYCOMPA.[1] Phenobarbital and primidone may also decrease the FYCOMPA concentration.

Eisai, Inc. is working to develop tools and resources related to epilepsy for both patients and health care professionals.

The FDA has recommended that FYCOMPA be classified by the Drug Enforcement Administration (DEA) as a scheduled drug. DEA scheduling for FYCOMPA is pending.[18]

CONCLUSION

In summary, FYCOMPA provides managed care organizations, clinicians, and patients with a once-daily, safe, and effective medication for adjunctive treatment of partial-onset seizures for patients 12 years of age or older when used in accordance with the full prescribing information. FYCOMPA has multiple dosages available, is administered orally, and has few drug interactions.

SECTION II:
Disease Description and Product Information for FYCOMPA™ (perampanel) Tablets

INTRODUCTION TO EPILEPSY

Epilepsy, a chronic disorder characterized by recurrent unprovoked seizures, is the fourth most common neurologic disorder in the US, affecting an estimated 2.2 million Americans.[2,3] Commonly reported comorbidities in patients with epilepsy include anxiety, suicidal thoughts, depression, cognitive decline, migraine, psychogenic nonepileptic disorders, injuries, and increased mortality.[4] Unfortunately, patients with epilepsy not only report poor HRQOL, they are also less likely to have full-time employment and to suffer from the stigma associated with the diagnosis.[5] Epilepsy has a substantial impact on health care utilization and cost, with the US estimated annual cost of epilepsy and seizures being $17.6 billion in direct and indirect costs.[6,7]

Classification of Epilepsy

Due to the complex nature of where in the brain and to what degree the brain is affected by seizures, epilepsy can be classified into three seizure types (partial-onset [focal] seizures, generalized seizures, and unknown), as well as epileptic syndromes.[2,8] ***Partial-onset (focal) seizures*** begin in a localized area of the brain and may evolve into secondarily generalized seizures in which the seizure spreads to involve both hemispheres of the brain.[4] Partial-onset seizures are further subdivided into two categories based on whether consciousness is or is not impaired (complex partial and simple partial, respectively). ***Generalized seizures*** begin with abnormal neuronal activity in both hemispheres of the brain and can result in the impairment or loss of consciousness.[4]

In 2010, the International League Against Epilepsy (ILAE) revised concepts and terminology for the classification of seizures (last updated in 1981) and epilepsies (last updated in 1989).[8] Because the FYCOMPA clinical studies in patients with partial-onset seizures were initiated before the 2010 ILAE update, the 1981 ILAE definition of partial-onset (focal) seizures was utilized.[21-23] The main difference between the 1981 and 2010 ILAE terminologies for partial-onset (focal) seizures is that the terms simple partial, complex partial, and partial seizures evolving to secondarily generalized were eliminated in 2010 because the terms were deemed imprecise and often misused or misunderstood (**Table II-1**).[8] The ILAE now recommends that focal seizures be described based on features that are most useful for a given purpose.

For this dossier, the focus of the discussion will be on partial-onset (focal) seizures.

Table II-1. Comparison Between the 1981 and 2010 ILAE Terminologies for Partial-Onset (Focal) Seizures[8]

1981 ILAE Terminology	2010 ILAE Terminology
Partial-Onset (Focal, Local) Seizures: The first clinical and EEG changes indicate initial activation of a system of neurons limited to part of one hemisphere of the brain. o **Simple partial seizures:** consciousness not impaired o **Complex partial seizures:** consciousness impaired o **Partial seizures evolving to secondarily generalized seizures**	**Focal Seizures:** Originate in a network of neurons limited to one hemisphere of the brain o **Without impairment of consciousness or awareness:** corresponds roughly to the previous term of ***simple partial seizure*** o **With impairment of consciousness or awareness:** corresponds roughly to the previous term of ***complex partial seizure*** o **Evolving to a bilateral, convulsive seizure:** replaces the term ***secondarily generalized seizure***

EEG = electroencephalogram; ILAE = International League Against Epilepsy

Epidemiology

Each year, 150,000 to 200,000 new cases of epilepsy are diagnosed in the US.[2,7] The highest incidence of epilepsy occurs among young children < 2 years of age and individuals > 65 years of age.[3,7,33] Males tend to have a slightly higher incidence of epilepsy than females.[34]

Partial-onset seizures are the most common seizure type in both children and adults.[34] Hauser et al[9] found that in newly diagnosed patients, 57% were classified with partial-onset seizures, with secondary generalization occurring in 60% of partial-onset cases.

Pathophysiology

Epilepsy can result from insult to the brain (eg, trauma, infection, stroke, tumor) or from genetic mutation of one or more of the ion channel or neurotransmitter genes or proteins mediating brain excitability.[12] However, the underlying pathophysiology leading to the development of epilepsy and the generation of seizures is complex. At a basic level, an epileptic seizure reflects abnormal, excessively synchronous electrical activity of neuronal networks, resulting from an imbalance between synaptic excitation and inhibition in the brain.[4,35] Current theories suggest that the abnormal discharge of cerebral neurons is caused by a number of factors affecting the regulation of neuronal excitability and communication such as enhanced excitatory transmission, malfunctioning of inhibitory mechanisms, and changes in intrinsic neuronal properties.[4,36]

Mechanism of Action of AEDs

Whereas further research is required to determine the pathophysiologic reason for the disorder, the mechanism of action (MOA) of antiepileptic drugs (AEDs) has provided some insight into the factors contributing to the initiation and propagation of seizures.[12] In general, the majority of available AEDs are thought to have one or more of the following MOAs (**Table II-2**) (**Figure II-1** and **Figure II-2**)[4,37-39]:

1. Altering the activity of voltage-gated ion channels (sodium and calcium channels)
2. Reducing synaptic excitation (by decreasing glutamate function)
3. Enhancing synaptic inhibition (by increasing gamma-aminobutyric acid [GABA] function)

Voltage-gated ion channels are important for the generation of seizures because these channels shape the electrical behavior of neurons, enable them to fire action potentials, regulate their responsiveness to synaptic signals, contribute to the depolarization shift, and aid in neurotransmitter release.[4]

Synaptic inhibition and excitation are mediated by neurotransmitter-regulated (ligand-gated) ion channels, with the primary excitatory and inhibitory neurotransmitters in the brain being glutamate and GABA, respectively.[4] These channels allow for the synchronization of neurons and propagation of the abnormal discharge (occurring during a seizure) to local and distant sites. Hence, AEDs that alter excitatory and inhibitory neurotransmission can suppress aberrant burst firing of neurons.[4]

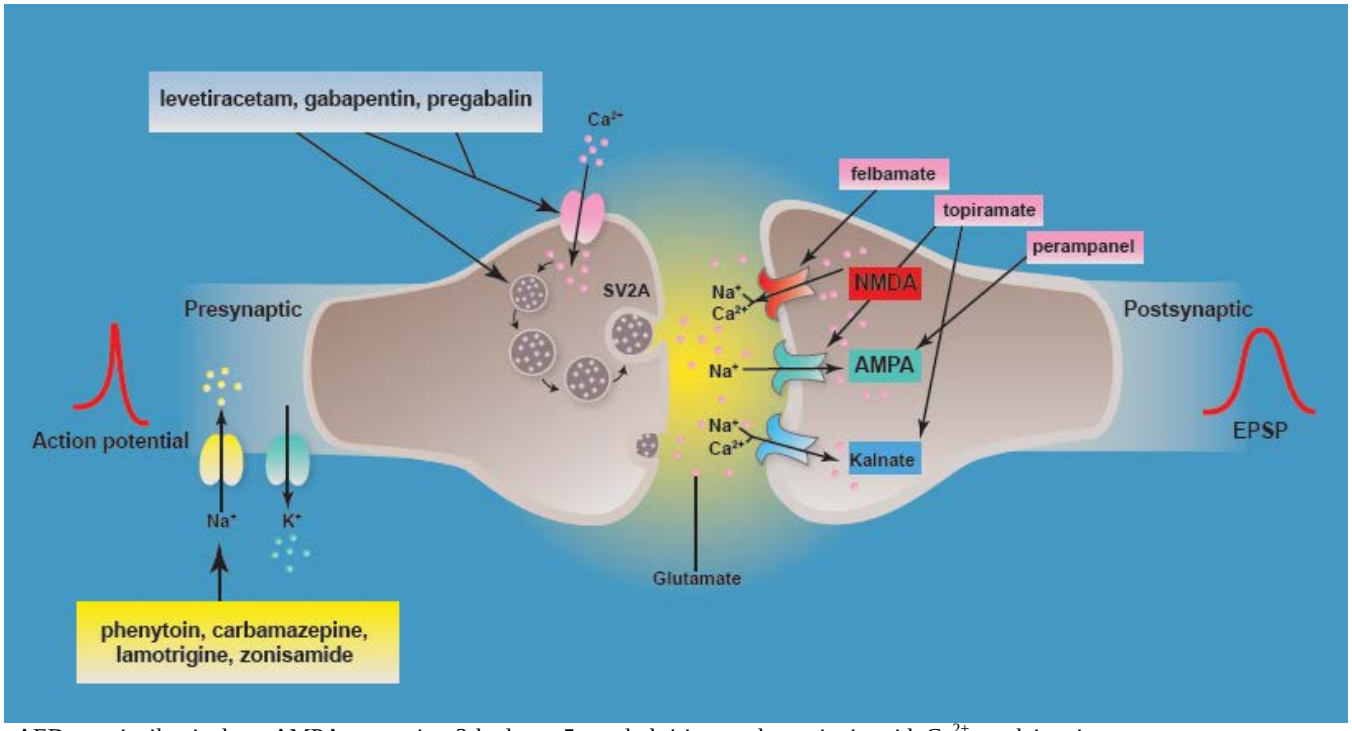
Table II-2. Proposed Mechanisms of Action of AEDs[16,40,41]

AED	Voltage-Gated Ion Channels			GABA System	Glutamate Receptors			Other
	Sodium Channels	Calcium Channels	Potassium Channels		AMPA	NMDA	Kainate	
Ezogabine			√					
Phenytoin	√							
Carbamazepine	√							
Oxcarbazepine	√							
Lacosamide	√							
Lamotrigine	√	√						
Zonisamide	√	√						
Felbamate	√	√		√		√		
Topiramate	√	√		√	√		√	
Ethosuximide		√						
Gabapentin		√						
Levetiracetam*								√
Benzodiazepines				√				
Vigabatrin				√				
Tiagabine				√				
Perampanel					√			

AED = antiepileptic drug; AMPA = α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid; GABA = gamma-aminobutyric acid; NMDA = N-methyl-D-aspartic acid

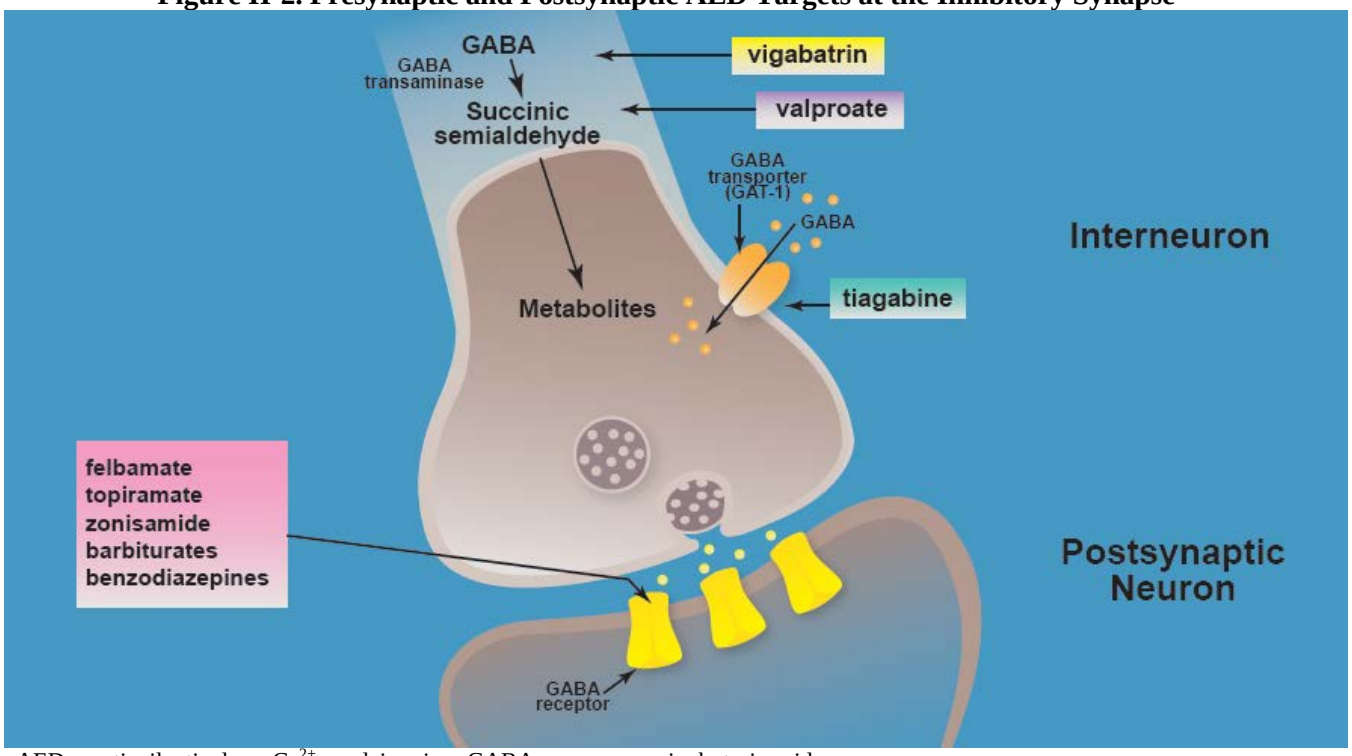
*Levetiracetam binds to synaptic vesicle glycoprotein 2A (SV2A), which may play a role in neurotransmitter release.

Figure II-1. Presynaptic and Postsynaptic AED Targets at the Excitatory Synapse[16]



AED = antiepileptic drug; AMPA = α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid; Ca^{2+} = calcium ion; EPSP = excitatory postsynaptic potential; K^+ = potassium ion; Na^+ = sodium ion; NMDA = N-methyl-D-aspartic acid; SV2A = synaptic vesicle glycoprotein 2A

Figure II-2. Presynaptic and Postsynaptic AED Targets at the Inhibitory Synapse[16]



AED = antiepileptic drug; Ca^{2+} = calcium ion; GABA = gamma-aminobutyric acid

Excitatory Neurotransmission

As mentioned above, the amino acid glutamate functions as the major excitatory neurotransmitter in the CNS.[17,20] Glutamate exerts its effects via interaction with three types of ionotropic postsynaptic receptors (**Figure II-1**): α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartic acid (NMDA), and kainate (listed in order of prevalence in the brain).[20,42]

Under normal conditions, glutamate binds to these receptors, generating the excitatory postsynaptic potential (EPSP) and therefore facilitating excitatory neurotransmission.[20] In epilepsy, however, excessive amounts of glutamate are released from neurons and astrocytes, resulting in overstimulation of postsynaptic AMPA and NMDA receptors.[16] In fact, sustained extracellular increases in glutamate have been observed in the hippocampus of patients before and during seizures.[43]

This overstimulation of these receptors results in the generation of the paroxysmal depolarization shift, the elemental electrophysiologic event in focal epilepsy. Whereas NMDA receptors maintain the paroxysmal depolarization shift, AMPA receptors trigger it.[16] Preclinical models have shown that systemic or intracerebroventricular administration of AMPA receptor agonists elicits robust seizure activity.[42] AMPA receptors, therefore, play a key role in mediating fast excitatory postsynaptic neurotransmission and in the generation and spread of seizures.[20,43]

Unlike other AEDs, FYCOMPA is a noncompetitive antagonist of the AMPA receptor on postsynaptic neurons, inhibiting AMPA receptors even in the presence of a high concentration of glutamate.[1,16] Preclinical seizure models have demonstrated that FYCOMPA has broad spectrum anticonvulsant activity, and the efficacy and safety of FYCOMPA as adjunctive therapy for the treatment of partial-onset seizures has been demonstrated in clinical studies (see **Section III**).[17]

Clinical Presentation and Diagnosis

The presentation of an epileptic seizure varies depending on the seizure's point of origin in the brain and on how much of the brain is affected.[4] Epileptic seizures can cause loss of consciousness and convulsions or confusion, or not alter consciousness at all.[44]

Depending on the point of origin and the affected brain region, a partial-onset seizure may cause any of the symptoms shown in **Table II-3**. In some cases, a patient experiencing a partial-onset seizure might appear to be awake but disengaged and may perform repetitive movements (partial-complex seizure).[44,45]

Table II-3. Examples of Symptoms of Partial-Onset Seizures[4]

• **Chewing movements or smacking of lips** • **Complex automatic behaviors** • **Visual hallucinations** • **Bilateral tonic posture**	• **Localized muscle twitching without impaired consciousness** • **Localized numbness or tingling**

A patient receives a diagnosis of epilepsy after experiencing at least two unprovoked seizures.[4] Because most first seizures are not observed directly by a physician, the diagnosis requires a complete physical examination, a neurologic examination, and the collection of a detailed medical history from the patient.[2,46] The physician may also gather details about the seizure from a caregiver who witnessed the event(s). After identifying the seizure type and precipitating factors, the physician correlates the seizure type with the patient's electroencephalogram (EEG) findings. Magnetic resonance imaging is used to detect any structural lesions that might be causing the seizures.[46]

Many other medical problems can precipitate seizures or mimic epileptic seizures, including fever, hypoglycemia, metabolic encephalopathy, and trauma.[2,47]

Consequences of Epilepsy

Comorbidities

Anxiety, suicidal thoughts, depression, cognitive decline, migraine, and psychogenic nonepileptic disorders are common comorbidities in patients with epilepsy.[4] It has been estimated that 50% of patients with refractory partial epilepsy have depression, which often remains undiagnosed and untreated.[48] According to a large national survey, patients with epilepsy are more likely than the general population to suffer from major depressive disorder, mood disorder, anxiety disorder, panic disorder, suicidal ideation, or any mental health disorder (lifetime prevalence was compared).[48]

Migraine is also more common among patients with epilepsy, especially in patients with a history of head trauma, partial-onset seizures, or a family history of migraine.[4] In addition, endocrine reproductive disorders and sexual

dysfunction have been reported in patients with epilepsy.[4] These comorbidities can be caused by more than one factor including the epilepsy itself, overuse of AEDs, AEs, surgical treatment, and psychosocial factors.[4]

Injury and Mortality

Individuals with refractory epilepsy have an increased risk of injury and a shorter life expectancy than the general population.[4] Injuries occur mostly at home and can include contusions, wounds, fractures, abrasions, and brain concussions.[4] Mortality rates in individuals with epilepsy are two to three times greater than those in the general population.[4,5]

People with epilepsy have an overall risk of sudden death that is 20 times greater than that of the general population.[49] When an otherwise healthy individual with epilepsy dies unexpectedly and the death cannot be attributed to trauma, drowning, status epilepticus, or other known causes, sudden unexpected death in epilepsy (SUDEP) is suspected. SUDEP occurs mostly in patients with chronic, therapy-resistant epilepsy and is often associated with tonic-clonic seizures.[49,50]

Finally, the comorbid mood disorders of epilepsy, particularly major depression, can contribute to suicidal ideation. One study suggests that individuals with epilepsy are more likely to commit suicide than the general population (12% vs 1% lifetime prevalence).[51]

Societal, Humanistic, and Economic Impact

Health Related Quality of Life (HRQOL)

In addition to experiencing seizures, individuals with epilepsy tend to have poor HRQOL compared to the general population.[2] In a telephone survey, a far greater percentage of patients with epilepsy than participants without epilepsy reported poor HRQOL (45.9% vs 18.5%).[52] When asked to summarize their HRQOL during the 30 days before the survey, patients with epilepsy reported more physically unhealthy days (4.4), more mentally unhealthy days (5.2), more days of activity limitation (4.0), more painful days (6.8), more days of anxiety (5.2), more days of insufficient sleep or rest (3.5), and fewer days of vitality (3.3) than participants without epilepsy. Seizure severity, injuries, and AED toxicity can all contribute to unhealthy days in individuals with epilepsy. In another telephone survey, patients with active seizures had more problems and limitations than patients whose seizures were controlled or inactive.[53]

Chung et al[54] revealed that individuals with epilepsy report poor QOL, encounter stigma and discrimination, and have considerable problems finding and maintaining employment. Patients also reported difficulty obtaining health care, health insurance, and social security income. Furthermore, individuals with epilepsy have reported that the worst aspect of epilepsy is the uncertainty, the fear of having a seizure.[55]

People with epilepsy also face stigma. A survey found that members of the general population tend to overestimate the severity of disease. Participants reported the belief that individuals with epilepsy need to limit lifestyle activities including driving, sports/fitness, and social drinking.[5] Among adolescents with epilepsy, 53% to 70% indicated that talking about their disorder was a problem, and greater rates of stigma were noted among younger adolescents with lower self-esteem. In another study, adolescents of lower socioeconomic status and those needing special education reported greater stigma scores.[56]

Economic Burden of Epilepsy

Epilepsy is a chronic and debilitating disease that is associated with considerable direct and indirect costs. Begley et al[6] estimated that in the US, the **annual total cost** of epilepsy is $12.5 billion (1995 dollars). Of the $12.5 billion, *direct costs* accounted for $1.7 billion (14%) and *indirect costs* accounted for $10.8 billion (86%).[6] Physician and hospital services accounted for the largest proportion of the direct costs (39.1%), with drug treatment accounting for 31.0% of the direct costs (**Table II-4**). Of the $10.8 billion in indirect costs, mortality associated with lost productivity due to premature death amounted to $1.4 billion (13%), whereas morbidity-related lost productivity amounted to $9.4 billion (87%).[6]

Table II-4. Annual Direct Costs for Patients With Epilepsy (1995 Dollars)[6]

Cost Item	Annual cost (Thousands of Dollars) (%)

Direct Costs	
Physician and hospital services	658,988 (39.1)
Diagnostic procedures	185,859 (13.1)
Laboratory tests	126,603 (7.6)
Other services and procedures	86,180 (5.1)
Surgery	106,388 (6.3)
Drug treatment	522,586 (31.0)
TOTAL	1,686,605 (100)

Economic Burden of Epilepsy to the Employer

Ivanova et al[30] conducted a retrospective analysis of a privately insured claims database (including employee disability claims) of 17 US companies during the period 1999 to 2005. The analysis examined the economic burden of epilepsy to the employer and found that employees with epilepsy had greater rates of direct and indirect health care costs than other employees (**Table II-5**).[30] More employees with epilepsy than without epilepsy had ≥ one claim for an inpatient visit (16.4% vs 6.6%), an emergency department (ED) visit (29.5% vs 19.3%), or an outpatient visit (94.4% vs 87.0%) ($p < 0.001$ for all comparisons).[30] More employees with epilepsy than without made ≥ one disability claim (16.5% vs 5.6%) and missed more days of work for medical reasons (mean number of days: 10.4 vs 6.3) ($p < 0.001$ for all comparisons).

Table II-5. Direct and Indirect Costs (2005 Dollars)[30]

	Employees With Epilepsy (n = 1886)	Employees Without Epilepsy (n = 1886)
Direct Costs, $ (SD)		
Drug costs	2747 (4289)*	933 (2173)
Medical costs	7656 (41,319)*	3162 (13,001)
TOTAL	10,404 (41,818)*	4096 (13,387)
Indirect Costs, $ (SD)		
Disability	1836 (7959)*	338 (2499)
Medically related absenteeism	1356 (2387)*	904 (2272)
TOTAL	3192 (8097)*	1242 (3377)
TOTAL Direct and Indirect Costs, $ (SD)		
TOTAL	**13,595 (44,093)***	**5338 (14,887)**

SD = standard deviation
*$p < 0.0001$ vs control.

Economic Burden of Epilepsy in Medicaid Patients

A study[31,32] examined health care utilization and costs among Medicaid patients with epilepsy in a multistate database. The investigators found that patients with epilepsy used substantial health care resources for comorbid conditions. In fact, epilepsy-related health care only accounted for 17.9% of total annual health care costs among patients with epilepsy (**Table II-6**).[31,32]

Table II-6. Annual Overall and Epilepsy-Related Health Care Costs in a Medicaid Population[32]

Cost Item	Pediatric Patients (n = 31,484)	Adult Patients (n = 43,627)
Overall Health Care Costs, Mean $ (SD)		
Inpatient	1717 (14,620)	7834 (36,869)
ER visits	259 (548)	838 (2161)
Physician office visits	392 (475)	514 (984)
Outpatient hospital visits	799 (3016)	1860 (5620)
Other outpatient costs	5632 (20,110)	14,398 (80,315)
Drug costs	2140 (8899)	4442 (6313)
TOTAL	10,669 (29,745)	29,886 (91,941)
Epilepsy-Related Health Care Costs, Mean $ (SD)		
Inpatient	787 (9255)	3738 (21,940)
ER visits	83 (307)	168 (557)

Physician office visits	96 (136)	86 (164)
Outpatient hospital visits	208 (702)	244 (1549)
Other outpatient costs	287 (2960)	300 (3554)
Drug costs	501 (1304)	765 (1637)
TOTAL	1962 (10,180)	5301 (22,627)

ED = emergency department; SD = standard deviation

Health Care Costs Associated With Uncontrolled Epilepsy

Patients with uncontrolled epilepsy may utilize more medical services and consequently have greater health care costs compared to patients with stable epilepsy. Cramer et al[57,58] compared health care utilization of adult patients with stable epilepsy (defined as having the same AED regimen for ≥ 12 months) to that in those with uncontrolled epilepsy (defined as addition of AED treatment[s] to the original regimen during the identification period).[57,58] The study included > 10,000 patients in a large administrative claims database who were undergoing treatment with ≥ one AED. In that population, 85% had stable epilepsy and 15% had uncontrolled epilepsy. Patients with uncontrolled epilepsy had significantly more chronic conditions compared to patients with stable epilepsy ($p < 0.001$).[57,58] Specifically, a significantly larger proportion of patients with uncontrolled epilepsy had a head injury, brain tumor, cerebrovascular disease/stroke, or depression or other mood disorder compared to patients with stable epilepsy ($p < 0.02$).[57,58]

Patients with uncontrolled epilepsy utilize more medical services than patients with stable epilepsy ($p < 0.034$).[57,58] **Table II-7** shows the adjusted odds ratios for different medical services for patients with uncontrolled epilepsy compared to those with stable epilepsy.[57,58] Although health care costs were considerable in both patient populations, patients with uncontrolled epilepsy incurred significantly greater costs compared to patients with stable epilepsy (**Table II-8**). After the data were adjusted for age, sex, region, physician specialty, and number of chronic conditions, patients with uncontrolled epilepsy spent $7187 more on overall health care costs and $6023 more on epilepsy-related health care costs ($p < 0.001$ for both comparisons).[57,58]

Table II-7. Adjusted Estimates for Health Care Utilization for Adult Patients With Uncontrolled vs Stable Epilepsy[58]

Outcome Variable	Odds Ratio	95% CI	P Value
Inpatient hospitalization	1.82	1.56–2.13	< 0.001
ED visit	1.64	1.46–1.84	< 0.001
Epilepsy-related inpatient hospitalization	2.20	1.87–2.60	< 0.001
Epilepsy-related ED visit	1.91	1.66–2.20	< 0.001

CI = confidence interval; ED = emergency department

Table II-8. Annual Overall and Epilepsy-Related Health Care Costs for Adult Patients With Uncontrolled vs Stable Epilepsy[57]

	Stable (n = 8571)	Uncontrolled (n = 1536)	All (n = 10,107)	P Value
Overall health care cost, mean $ (SD) [median]	13,839 (31,355.1) [6789]	23,238 (42,893.8) [11,380]	15,414 (33,745.5) [7481]	< 0.001
Epilepsy-related overall health care cost, mean $ (SD) [median]	5511 (11,729.6) [2647]	12,399 (25,772.9) [6256]	6558 (14,955.9) [3128]	< 0.001

SD = standard deviation

PRODUCT INFORMATION FOR FYCOMPA™

Production Information Summary

- FYCOMPA (perampanel) is an AED that is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.[1]

- FYCOMPA is the first FDA-approved, noncompetitive AMPA glutamate receptor antagonist.[1,18]
  - Glutamate facilitates excitatory neurotransmission in the CNS, primarily through mediating fast excitatory signaling at the postsynaptic AMPA receptor.[19,20]
  - AMPA receptor activation plays an important role in the generation and spread of seizures.[20]

- FYCOMPA is well tolerated in patients with partial-onset seizures.
  - FYCOMPA has been administered to more than 1600 patients with epilepsy in clinical studies including open-label extension studies.
  - In phase III clinical studies, the most common adverse reactions in patients receiving FYCOMPA at doses of 8 mg or 12 mg (≥ 4% and ≥ 1% higher than placebo) included dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder.[1]
  - In phase III clinical studies, discontinuation rates due to AEs were 3%, 8%, and 19% in patients randomized to receive FYCOMPA 4 mg, 8 mg, and 12 mg/day, respectively, vs 5% in patients randomized to receive placebo.[1]
  - There are no contraindications for FYCOMPA; please see **Boxed WARNING and WARNINGS and PRECAUTIONS** sections below.

- FYCOMPA has a once daily at bedtime dosing regimen and has multiple dosages available (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets).[1]
  - If patients miss a dose, patients may resume dosing the following day at their prescribed dose, given the long half-life of FYCOMPA (105 hours).[1,28]
  - A simulated pharmacokinetic analysis of 19 phase I FYCOMPA studies confirmed that after a missed dose, the FYCOMPA plasma trough concentration (C_{min}) preceding the next scheduled dose would be expected to decrease mildly to moderately (18.4% and 43.9% in the absence and presence of an enzyme-inducing AED, respectively) (see **Section III: Table III-13 – Gidal et al, 2012**[28]).

- FYCOMPA has little impact on the pharmacokinetics of other AEDs.
  - Pooled population pharmacokinetic and pharmacodynamic analyses of FYCOMPA (see **Section III: Table III-13 – Laurenza et al, 2011**[29]) have found that FYCOMPA does not have a clinically relevant effect on the pharmacokinetics of other AEDs including carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, or zonisamide.[29]
  - Because FYCOMPA is metabolized primarily by CYP3A4, the concomitant use of FYCOMPA with CYP3A4-inducing AEDs, such as carbamazepine, oxcarbazepine, and phenytoin, will decrease the plasma level of FYCOMPA by approximately 50% to 67% and will decrease the effectiveness of FYCOMPA.[1] Phenobarbital and primidone may also decrease the FYCOMPA concentration.

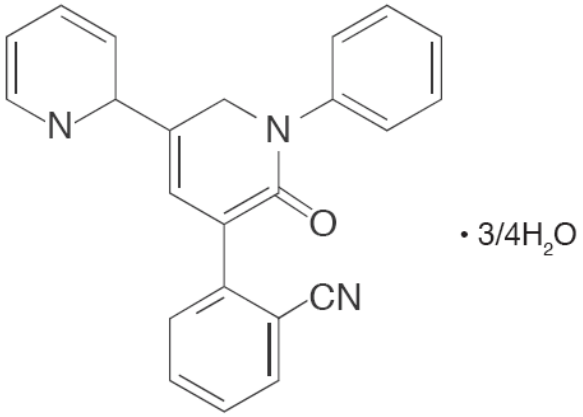
- The FDA has recommended that FYCOMPA be classified by the DEA as a scheduled drug. DEA scheduling for FYCOMPA is pending.[18]

The following discussion includes highlights from the product label and additional information on FYCOMPA. Please consult the prescribing information for FYCOMPA for complete information on pharmacology, warnings and precautions, adverse reactions, dosing and administration, and other topics. A copy of the full prescribing information for FYCOMPA is included in Section VI.

Generic, Brand, and Therapeutic Class

FYCOMPA is an AED and is the first FDA-approved noncompetitive antagonist of the ionotropic AMPA glutamate receptor on postsynaptic neurons.[1,18]

Figure II-3. Chemical Structure of FYCOMPA[1]



National Drug Code, Dose, Dosage Form, Package Size, and Cost

FYCOMPA tablets are available as 2 mg (orange), 4 mg (red), 6 mg (pink), 8 mg (purple), 10 mg (green), and 12 mg (blue) round, biconvex, film-coated tablets.[1]

Table II-9. Dosage Forms, Strengths, Package Sizes, NDC and Costs[1]

Dose	NDC	Dosage Form	Package Size	WAC
2 mg of perampanel	62856-272-30	Tablet	Bottle of 30 tablets	$284.40
4 mg of perampanel	62856-274-30	Tablet	Bottle of 30 tablets	$568.80
6 mg of perampanel	62856-276-30	Tablet	Bottle of 30 tablets	$568.80
8 mg of perampanel	62856-278-30	Tablet	Bottle of 30 tablets	$568.80
10 mg of perampanel	62856-280-30	Tablet	Bottle of 30 tablets	$568.80
12 mg of perampanel	62856-282-30	Tablet	Bottle of 30 tablets	$568.80

NDC = national drug code; WAC = wholesale acquisition cost

Classification

American Hospital Formulary Service

The American Hospital Formulary Service (AHFS) classification for FYCOMPA is pending.

Drug Enforcement Administration

The FDA has recommended that FYCOMPA be classified by the DEA as a scheduled drug. DEA scheduling for FYCOMPA is pending.

Indications

FYCOMPA is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.[1]

Clinical Pharmacology

Please refer to the **FYCOMPA Prescribing Information — Clinical Pharmacology** section for complete information.

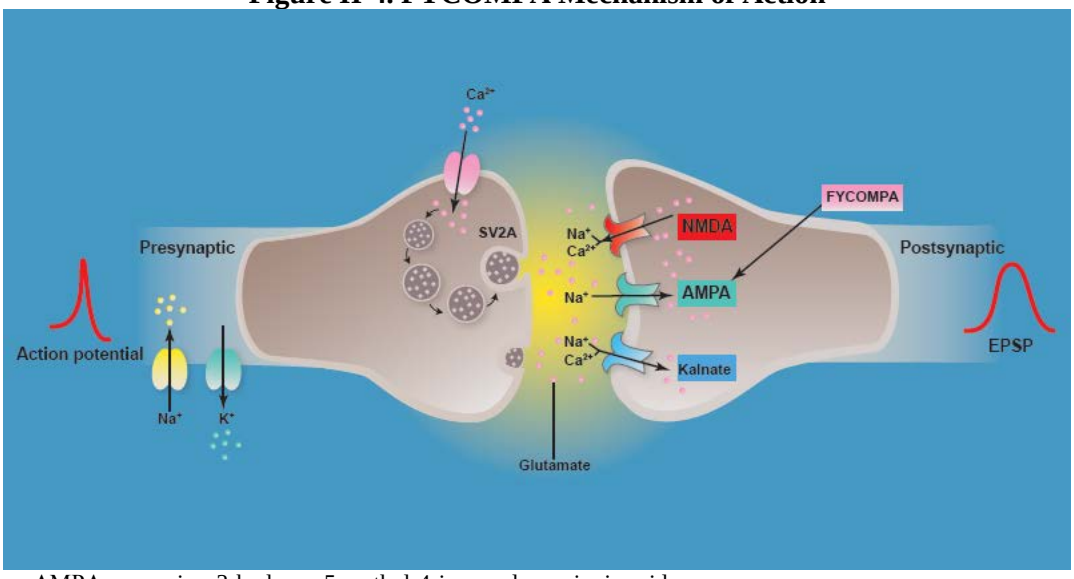
Mechanism of Action

Whereas the precise mechanism by which FYCOMPA exerts its antiepileptic effects in humans has not been fully elucidated, it is believed that FYCOMPA reduces neuronal hyperexcitation associated with seizures by targeting glutamate activity at postsynaptic AMPA receptors (**Figure II-4**).[1,20]

FYCOMPA is a ***noncompetitive (allosteric) antagonist*** of the AMPA receptor on postsynaptic neurons, inhibiting AMPA receptors even in the presence of a high concentration of glutamate (**Figure II-4**).[1,16] Whereas the antiseizure activity benefits of noncompetitive vs competitive antagonists are unclear, it is theorized that noncompetitive antagonists would retain their antagonist effects even in the presence of high agonist concentrations and may even be more effective under hyperexcitatory conditions.[17]

FYCOMPA is also a ***selective antagonist*** of the AMPA glutamate receptor. In rat cortical neurons, FYCOMPA potently inhibits AMPA-induced increases in intracellular calcium concentration ($[Ca^{2+}]_i$) but only weakly inhibits NMDA-induced increases in $[Ca^{2+}]_i$.[17] In addition, in rat hippocampal slices, FYCOMPA decreases AMPA receptor–mediated excitatory postsynaptic field potentials (f-EPSPs) while having no effect on NMDA or kainate receptor–mediated f-EPSPs at doses approximately 100-fold greater than those needed to block AMPA receptor–mediated responses.[59]

Figure II-4. FYCOMPA Mechanism of Action



AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Contraindications

There are no contraindications for FYCOMPA.[1]

Boxed Warning

BOXED WARNING: SERIOUS PSYCHIATRIC AND BEHAVIORAL REACTIONS[1]

- **Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported in patients taking FYCOMPA**
- **These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression**
- **Advise patients and caregivers to contact a healthcare provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA**
- **Closely monitor particularly during the titration period and at higher doses**
- **FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening**

Warnings and Precautions

Please refer to the **FYCOMPA Prescribing Information — Warnings and Precautions** section for complete information.

- **Serious Psychiatric and Behavioral Reactions:** Hostility- and aggression-related adverse reactions occurred in 12% and 20% of clinical study patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 6% of patients in the placebo group. These effects were dose-related and generally appeared within the first 6 weeks of treatment, although new events continued to be observed through more than 37 weeks. These effects in FYCOMPA treated patients led to dose reduction, interruption, and discontinuation more frequently than placebo-treated patients. The combination of alcohol and FYCOMPA significantly worsened mood and increased anger. Patients taking FYCOMPA should avoid the use of alcohol. Patients, their caregivers, and families should be informed that FYCOMPA may increase the risk of psychiatric events. Patients should be monitored during treatment and for at least 1 month after the last dose of FYCOMPA and especially when taking higher doses and during the initial few weeks of drug therapy (titration period) or at other times of dose increases.
- **Suicidal Behavior and Ideation:** AEDs, including FYCOMPA, increase the risk of suicidal thoughts or behavior in patients. Anyone considering prescribing FYCOMPA or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients, their caregivers, and families should be informed of the risk and advised to monitor and immediately report the emergence or worsening of depression, suicidal thoughts or behavior, thoughts about self-harm and/or any unusual changes in mood or behavior. Should suicidal thoughts or behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
- **Dizziness and Gait Disturbance:** FYCOMPA caused dose-related increases in events related to dizziness and disturbance in gait or coordination. Dizziness and vertigo were reported in 35% and 47% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 10% of placebo-treated patients. Gait disturbance related events were reported in 12% and 16% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 2% of placebo-treated patients. These adverse reactions occurred mostly during the titration phase.
- **Somnolence and Fatigue:** FYCOMPA caused dose-dependent increases in somnolence and fatigue-related events. Somnolence was reported in 16% and 18% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 7% of placebo patients. Fatigue-related events were reported in 12% and 15% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 5% of placebo patients. In the controlled Phase 3 epilepsy clinical studies, these adverse reactions occurred mostly during the titration phase. Patients should be advised against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of FYCOMPA is known.
- **Falls:** Falls were reported in 5% and 10% of patients randomized to receive FYCOMPA at doses of 8 mg and 12 mg/day, respectively, compared to 3% of placebo-treated patients.
- **Withdrawal of AEDs:** A gradual withdrawal is generally recommended with AEDs to minimize the potential of increased seizure frequency.

Adverse Reactions

Please refer to the **FYCOMPA Prescribing Information — Adverse Reactions** section for complete information.

In phase III clinical studies, the most common adverse reactions in patients receiving FYCOMPA at doses of 8 mg or 12 mg (≥ 4% and ≥ 1% higher than placebo) included dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder.[1]

In phase III clinical studies, discontinuation rates due to AEs were 3%, 8%, and 19% in patients randomized to receive FYCOMPA 4 mg, 8 mg, and 12 mg/day, respectively, vs 5% in patients randomized to receive placebo.[1] The AEs most commonly leading to discontinuation (≥ 1% in the 8 mg or 12 mg FYCOMPA group and greater

than placebo) were dizziness, somnolence, vertigo, aggression, anger, ataxia, blurred vision, irritability, and dysarthria.

No significant sex differences were noted in the incidence of adverse reactions.[1] In addition, although there were few non-Caucasian patients, no differences in the incidences of adverse reactions compared to Caucasian patients were observed.

Interactions

Please refer to the **FYCOMPA Prescribing Information — Drug Interactions** and **Pharmacokinetics** sections for complete information.

FYCOMPA is highly protein bound (95% to 96%) and is extensively metabolized via primary oxidation and sequential glucuronidation.[1] Whereas other CYP enzymes may be involved, oxidative metabolism is mediated primarily by CYP3A4.

AEDs

Because FYCOMPA is metabolized primarily by CYP3A4, the concomitant use of FYCOMPA with CYP3A4-inducing AEDs, such as carbamazepine, oxcarbazepine, or phenytoin, will decrease the plasma level of FYCOMPA by approximately 50% to 67% and will decrease the effectiveness of FYCOMPA.[1] Phenobarbital and primidone may also decrease the FYCOMPA concentration. Therefore, the starting dose for FYCOMPA should be increased in the presence of enzyme-inducing AEDs. When these enzyme-inducing AEDs are introduced or withdrawn from a patient's treatment regimen, the patient should be monitored closely for clinical response and tolerability. Dose adjustment of FYCOMPA may be necessary. However, the decrease in the therapeutic effect seen in patients on concomitant treatment was not affected by use of larger FYCOMPA doses (8 mg to 12 mg).

Pooled population pharmacokinetic and pharmacodynamic analyses of FYCOMPA (see **Section III: Table III-13 – Laurenza et al, 2011**[29]) have found that FYCOMPA does not have a clinically relevant effect on the pharmacokinetics of other AEDs including carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide.[29]

Non-AED Strong CYP3A Inducers

Concomitant use of FYCOMPA with other strong CYP3A inducers (eg, rifampin, St. John's wort) should be avoided.[1]

Oral Contraceptives

With concomitant use, FYCOMPA at a dose of 12 mg/day reduced levonorgestrel exposure by approximately 40%.[1] Use of FYCOMPA with oral or implant contraceptives containing levonorgestrel may render them less effective. Additional nonhormonal forms of contraception are recommended.

Alcohol and Other CNS Depressants

The concomitant use of FYCOMPA and CNS depressants, including alcohol, may increase CNS depression.[1] Care should be taken when administering FYCOMPA with these agents.

Dosing and Administration

Please refer to the **FYCOMPA Prescribing Information — Dosing and Administration** section for complete information.

The half-life of FYCOMPA is approximately 105 hours, allowing for once-daily dosing of FYCOMPA.[1,60] The recommended starting dosage of FYCOMPA is 2 mg once daily taken orally at bedtime for patients not on enzyme-inducing AEDs and 4 mg for patients on enzyme-inducing AEDs.[1] Based on clinical response and tolerability, the dose of FYCOMPA may be increased by a maximum of 2 mg once daily at bedtime in weekly increments to a dose of 4 mg to a maximum of 12 mg once daily at bedtime. Please refer to the FYCOMPA prescribing information for dosing recommendations for specific populations.

If patients miss a dose, they may resume dosing the following day at their prescribed dose, given the long half-life of FYCOMPA.[1,28] A simulated pharmacokinetic analysis of 19 phase I FYCOMPA studies confirmed that

following a missed dose, the FYCOMPA plasma trough concentration (C_{min}) preceding the next scheduled dose would be expected to decrease mildly to moderately (18.4% and 43.9% in the absence or presence of an enzyme-inducing AED, respectively) (see **Section III: Table III-13 – Gidal et al, 2012**[28]).

Access

There are currently no supply limitations or anticipated shortages of FYCOMPA.

Coprescribed/Concomitant Therapies

The treatment regimen for a patient with epilepsy is individualized, and drug therapy may include monotherapy AED or combination AED therapy.[2,4] Adjunctive FYCOMPA has been studied in controlled trials in patients on one to three AEDs including carbamazepine, lamotrigine, levetiracetam, valproic acid, oxcarbazepine, topiramate, phenytoin, clobazam, clonazepam, and zonisamide.[21-23]

Comparison of Agents Used for Partial-Onset Seizures

A comparison of AEDs commonly used in the treatment of partial-onset seizures is shown in **Table II-10**.

Table II-10. Comparison of AEDs Used for the Treatment of Partial-Onset Seizures

Third-Generation AEDs			
	FYCOMPA™ (perampanel)[1]	**Vimpat® (lacosamide) CV[41]**	**Potiga™ (ezogabine) CV[40]**
Available Formulations	• Tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg	• Tablets: 50 mg, 100 mg, 150 mg, and 200 mg • Oral solution: 10 mg/mL • IV injection: 200 mg/20 mL single-use vial	• Tablets: 50 mg, 200 mg, 300 mg, and 400 mg
Proposed Mechanism of Action	Precise MOA in humans has not been fully elucidated; noncompetitive antagonist of the ionotropic AMPA glutamate receptor on postsynaptic neurons	Precise MOA in humans has not been fully elucidated; in vitro studies have shown selective enhancement of slow inactivation of voltage-gated sodium channels, thereby stabilizing hyperexcitable neuronal membranes and inhibiting repetitive neuronal firing.	Precise MOA in humans has not been fully elucidated; in vitro studies indicate that ezogabine enhances transmembrane potassium currents mediated by KCNQ ion channels. By activating KCNQ channels, ezogabine is thought to stabilize the resting potential and reduce brain excitability.
Indication(s) for Epilepsy	• Adjunctive therapy for the treatment of POS with or without secondarily generalized seizures in patients ≥ 12 years of age	• Adjunctive therapy in the treatment of POS (adjunctive therapy) in patients ≥ 17 years of age • IV formulation used when oral administration is temporarily not feasible	• Adjunctive treatment of POS in patients ≥ 18 years of age
Recommended Dosing	Initiate at 2 mg once daily at bedtime in patients not on enzyme-inducing AEDs or 4 mg in patients on enzyme-inducing AEDs. May be increased no more frequently than every week by 2 mg/day to 4 mg to 12 mg once daily at bedtime. In elderly patients, dosage increases during titration are recommended no more frequently than every 2 weeks (maximum 6 mg/day for mild and 4 mg/day for moderate hepatic impairment titrated at 2-week intervals). Slower titration may be considered based on clinical response and tolerability in patients with moderate renal impairment (not recommended for patients with severe renal impairment or patients undergoing hemodialysis).	Initiate at 50 mg BID, increased at weekly intervals by 100 mg/day, divided BID, to recommended maintenance dose of 200 to 400 mg/day	Initiate at 100 mg/day TID, increased at weekly intervals by 50 mg TID, to a maximum of 200 to 400 mg TID
Contraindications	None	None	None

Third-Generation AEDs			
	FYCOMPA™ (perampanel)[1]	**Vimpat® (lacosamide) CV[41]**	**Potiga™ (ezogabine) CV[40]**
Warnings and Precautions	• BOXED WARNING: o Serious or life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats reported in patients taking FYCOMPA. o These reactions occurred in patients with and without prior psychiatric history, prior aggressive behavior, or concomitant use of medications associated with hostility and aggression. o Advise patients and caregivers to contact a health care provider immediately if any of these reactions or changes in mood, behavior, or personality that are not typical for the patient are observed while taking FYCOMPA or after discontinuing FYCOMPA. o Closely monitor particularly during the titration period and at higher doses. o FYCOMPA should be reduced if these symptoms occur and should be discontinued immediately if symptoms are severe or are worsening. • Suicidal behavior and ideation • Neurological effects, including dizziness, gait disturbance, somnolence, and fatigue • Increased risk of falls • Withdrawal of AEDs	• Suicidal behavior and ideation • Dizziness and ataxia • PR interval prolongation • Atrial fibrillation and atrial flutter • Syncope in patients with diabetic neuropathy • Withdrawal of AEDs • Multiorgan hypersensitivity • Phenylketonuria	• Urinary retention • Confusion, psychotic symptoms and hallucinations • Dizziness and somnolence • Prolonged QT interval • Suicidal behavior and ideation • Withdrawal seizures
Pregnancy Category	C	C	C
Most Common AEs	**≥ 4% incidence and ≥ 1% greater than placebo:** dizziness, somnolence, fatigue, irritability, falls, nausea, ataxia, balance disorder, gait disturbance, vertigo, and weight gain	**≥ 2% incidence in the total lacosamide group and greater than placebo:** vertigo, diplopia, blurred vision, nausea, vomiting, diarrhea, fatigue, gait disturbance, asthenia, contusion, skin laceration, dizziness, headache, ataxia, somnolence, tremor, nystagmus, balance disorder, memory impairment, depression, pruritus	**≥ 4% incidence and twice the placebo rate:** dizziness, somnolence, fatigue, confusional state, vertigo, tremor, abnormal coordination, diplopia, disturbance in attention, memory impairment, asthenia, blurred vision, gait disturbance, aphasia, dysarthria, balance disorder
Interactions	FYCOMPA may decrease efficacy of contraceptives containing levonorgestrel; based on a population PK analysis, FYCOMPA clearance was increased by CYP3A4 inducers (CBZ, PHY, or oxcarbazepine); concomitant alcohol use may increase CNS depression; alcohol impairment effects are additive with FYCOMPA, and may increase anger, confusion, and depression.	None	CBZ and PHY decrease systemic exposure of ezogabine and may require dose increase; ezogabine may increase digoxin serum concentration; alcohol increases ezogabine systemic exposure; ezogabine may interfere with clinical laboratory tests of serum and urine bilirubin, which may lead to falsely elevated readings.

Second-Generation AEDs			
	Keppra® (levetiracetam)[61]	**Lamictal® (lamotrigine)[62]**	**Topamax® (topiramate)[63]**
Available Formulations	• Tablets*: 250 mg, 500 mg, 750 mg, 1000 mg • Oral solution*: 100 mg/mL • IV injection*: 500 mg/5 mL single-use vial • Extended-release tablets*: 500 mg, 750 mg	• Tablets*: 25 mg, 50 mg, 100 mg, 200 mg • Chewable dispersible tablets*: 2 mg, 5 mg, 25 mg • Orally disintegrating tablets: 25 mg, 50 mg, 100 mg, 200 mg • Extended-release tablets: 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg	• Tablets*: 25 mg, 50 mg, 100 mg, 200 mg • Sprinkle capsules*: 15 mg, 25 mg
Proposed Mechanism of Action	Precise MOA in humans has not been fully elucidated; thought to selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity; in vitro studies have demonstrated that levetiracetam opposes the activity of negative modulators of GABA and glycine-gated currents and partially inhibits N-type calcium currents in neuronal cells. It is suggested that the interaction of levetiracetam with the SV2A protein may contribute to the antiepileptic MOA of the drug.	Precise MOA in humans has not been fully elucidated; in vitro studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids.	Precise MOA in humans has not been fully elucidated; preclinical studies revealed that topiramate blocks voltage-dependent sodium channels, augments $GABA_A$ receptor activity, antagonizes the AMPA/kainate subtype of the glutamate receptor, and inhibits carbonic anhydrase isozymes II and IV.
Indication(s) for Epilepsy	***Tablet/oral solution indications:*** • Adjunctive therapy in the treatment of: o POS in patients ≥ 1 month of age with epilepsy o Myoclonic seizures in patients ≥ 12 years of age with juvenile myoclonic epilepsy o Primary generalized tonic-clonic seizures in patients ≥ 6 years of age with idiopathic generalized epilepsy ***XR indication:*** • Adjunctive therapy in the treatment of POS in patients ≥ 16 years of age with epilepsy ***IV indications:*** • **POS:** Adjunctive therapy in patients ≥ 16 years of age when oral administration of levetiracetam is temporarily not feasible • **Myoclonic seizures in patients with juvenile myoclonic epilepsy:** Adjunctive therapy in patients ≥ 16 years of age with juvenile myoclonic epilepsy when oral administration of levetiracetam is temporarily not feasible	***Tablet indications:*** • **Epilepsy—adjunctive therapy in patients ≥ 2 years of age:** o POS o Primary generalized tonic-clonic seizures o Generalized seizures of Lennox-Gastaut syndrome • **Epilepsy—monotherapy in patients ≥ 16 years of age:** conversion to monotherapy in patients with POS who are receiving treatment with CBZ, PB, PHY, primidone, or VPA as the single AED ***XR indications:*** • Adjunctive therapy for primary generalized tonic-clonic seizures and POS with or without secondary generalization in patients ≥ 13 years of age • Conversion to monotherapy in patients ≥ 13 years of age with POS who are receiving treatment with a single AED • Limitation of use: Safety and effectiveness in patients < 13 years of age have not been established.	• Monotherapy in patients ≥ 2 years of age with POS or primary generalized tonic-clonic seizures • Adjunctive therapy for adults and pediatric patients 2 to16 years of age with POS or primary generalized tonic-clonic seizures • Adjunctive treatment of Lennox-Gastaut syndrome in patients ≥ 2 years of age

Second-Generation AEDs			
	Keppra® (levetiracetam)[61]	**Lamictal® (lamotrigine)[62]**	**Topamax® (topiramate)[63]**
Recommended Dosing	***POS:*** *Patients ≥ 16 years of age (Keppra XR and Keppra IV)* • Initiate at 1000 mg/day, divided BID (*Keppra IV*), increased at 2-week intervals by 1000 mg/day to maximum of 3000 mg/day (*Keppra tablets and oral solution*) • Initiate at 500 mg BID, increase as needed and tolerated at 2-week intervals in increments of 500 mg BID to maximum of 1500 mg BID *Children 1 month to < 6 months of age (Keppra tablet and oral solution)* • Initiate at 14 mg/kg/day, divided BID, increased at 2-week intervals by 14 mg/kg/day to maximum of 42 mg/kg/day *Children 6 months to < 4 years of age (Keppra tablet and oral solution)* • Initiate at 20 mg/kg/day, divided BID, increased at 2-week intervals by 20 mg/kg/day to maximum of 50 mg/kg/day *Children 4 years to < 16 years of age (Keppra tablet and oral solution)* • Initiate at 20 mg/kg/day, divided BID, increased at 2-week intervals by 20 mg/kg/day to maximum of 60 mg/kg/day ***Myoclonic seizures:*** *Patients ≥ 12 years of age (Keppra)* • Initiate at 500 mg BID, increase as needed and tolerated at 2-week intervals in increments of 500 mg BID to maximum of 1500 mg BID *Patients ≥ 16 years of age (Keppra IV)* • Initiate at 1000 mg/day, divided BID, increased at 2-week intervals by 1000 mg/day to maximum of 3000 mg/day ***Primary generalized tonic-clonic seizures:*** *Patients ≥ 16 years of age (Keppra tablets and oral solution)* • Initiate at 500 mg BID, increase as needed and tolerated at 2-week intervals in increments of 500 mg BID to maximum of 1500 mg BID *Children 6 to < 16 years of age (Keppra tablets and oral solution)* • Initiate at 10 mg/kg BID, increased at 2-week intervals by 10 mg/kg BID to maximum of 30 mg/kg BID	(Dose depends on patient's concomitant AED therapy, and only whole tablets should be used.) *Children 2 to 12 years of age* • Weeks 1 and 2: 0.15 to 0.6 mg/kg/d as QD or BID • Weeks 3 and 4: 0.3 to 1.2 mg/kg/d as QD or BID • Week 5 onward to maintenance: dose should be increased by 0.3 to 1.2 mg/kg/d every 1 to 2 weeks • Usual maintenance dose: 1 to 15 mg/kg/d as QD or BID (max 200 to 400 mg/d). In patients < 30 kg, dose may need to be increased by 50% based on clinical response *Patients > 12 years of age* • Weeks 1 and 2: 25 mg QOD to 50 mg QD • Weeks 3 and 4: 25 mg QD to 50 mg BID • Week 5 onward to maintenance: dose should be increased by 25 to 100 mg/d every 1 to 2 weeks • Usual maintenance dose: 100 to 500 mg/d as QD or BID	***Monotherapy:*** *Children 2 to < 10 years of age* • Initial dose: 25 mg/d nightly for the first week • Titration: increase dose at weekly intervals by 25 to 50 mg/d, divided BID, as tolerated. • Recommended maximum dose based on body weight *Patients ≥ 10 years of age* • Initial dose: 50 mg/d, divided BID • Titration: increase dose weekly to an effective dose by increments of 25 to 50 mg. • Recommended dose: 400 mg/d, divided BID ***Adjunctive therapy:*** *Children 2 to 16 years of age* • Initial dose: 25 mg/d (or less, based on a range of 1 to 3 mg/kg/d) QHS for the first week • Titration: increase dose at 1- or 2-week intervals by 1 to 3 mg/kg/d, divided BID. Dose titration should be guided by clinical outcome. • Recommended dose: 5 to 9 mg/kg/d, divided BID *Patients ≥ 17 years of age* • Initial dose: 25 to 50 mg/d • Titration: increase dose weekly to an effective dose by increments of 25 to 50 mg. • Recommended dose: 200 to 400 mg/d, divided BID

Second-Generation AEDs			
	Keppra® (levetiracetam)[61]	**Lamictal® (lamotrigine)[62]**	**Topamax® (topiramate)[63]**
Contraindications	None	Hypersensitivity to the drug or its ingredients	None
Warnings and Precautions	• Psychiatric symptoms including behavioral abnormalities • Suicidal behavior and ideation • Somnolence and fatigue • Serious dermatological reactions, including Stevens-Johnson syndrome and toxic epidermal necrosis have been reported. • Coordination difficulties have been observed in adult POS studies. • Withdrawal seizures • Hematologic abnormalities have been reported. • Blood pressure increases have been reported in children < 4 years of age.	• BOXED WARNING: o Serious skin rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and/or rash-related death. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include: coadministration with VPA and exceeding recommended initial dose or dose escalation of lamotrigine. • Fatal or life-threatening hypersensitivity reaction • Blood dyscrasias • Suicidal behavior and ideation • Aseptic meningitis • Medication errors • Withdrawal seizures • Rare treatment-emergent status epilepticus • Sudden unexplained death in epilepsy • Risk of accumulation in the eye and other melanin-containing tissues	• Acute myopia and secondary angle closure glaucoma • Oligohidrosis and hyperthermia • Metabolic acidosis • Suicidal behavior and ideation • Cognitive/neuropsychiatric: cognitive dysfunction, depression, mood problems, somnolence, fatigue • Fetal toxicity • Withdrawal of AEDs • Sudden unexplained death in epilepsy • Hyperammonemia and encephalopathy associated with or without concomitant VPA use • Kidney stones • Hypothermia has been reported with or without hyperammonemia during topiramate treatment with concomitant VPA use. • Paresthesia
Pregnancy Category	C	C	D

Second-Generation AEDs			
	Keppra® (levetiracetam)[61]	**Lamictal® (lamotrigine)[62]**	**Topamax® (topiramate)[63]**
Most Common AEs	***Keppra:*** *Adult POS patients ≥ 16 years of age* (≥ 5 % of levetiracetam-treated patients and > placebo): asthenia, somnolence, headache, infection, pain, dizziness, pharyngitis *Pediatric POS patients 4 to < 16 years of age (*≥ 5% of levetiracetam-treated patients and > placebo): headache, nasopharyngitis, somnolence, fatigue, aggression, vomiting, irritability, abdominal pain upper, diarrhea, decreased appetite, dizziness, lethargy, abnormal behavior, insomnia, cough, nasal congestion, pharyngolaryngeal pain ***Keppra XR:*** Patients with POS add-on therapy: nausea, influenza, nasopharyngitis, somnolence, dizziness, irritability	***Adjunctive Lamictal therapy:*** *Adult patients* (≥ 5% of lamotrigine-treated patients and > placebo): dizziness, ataxia, somnolence, incoordination, insomnia, headache, flu syndrome, fever, abdominal pain, diplopia, blurred vision, nausea, vomiting, diarrhea, dyspepsia, rash, rhinitis, pharyngitis, cough increased, dysmenorrhea *Pediatric patients* (≥ 5% of lamotrigine-treated patients and > placebo): infection, asthenia, flu syndrome, pain, vomiting, somnolence, fever, dizziness, pharyngitis, rash, accidental injury, diarrhea, abdominal pain, ataxia, tremor, nausea, bronchitis, increased cough, diplopia ***Adjunctive Lamictal XR***: *Epilepsy patients* (≥ 5% of lamotrigine-treated patients and > placebo): diplopia, nausea, vomiting, diarrhea, asthenia and fatigue, dizziness, tremor and intention tremor, somnolence	***Monotherapy:*** *Patients ≥ 16 years* of age (≥ 5% more frequent than low-dose topiramate): paresthesia, weight decrease, anorexia, somnolence, memory difficulty *Pediatric patients 2 to < 16 years of age* (≥ 5% more frequent than low-dose topiramate): paresthesia, weight decrease, cognitive problems, mood problems, infection, flushing ***Adjunctive therapy:*** *Patients ≥ 16 years* of age (≥ 5% more frequent than placebo or low-dose topiramate): dizziness, fatigue, somnolence, nervousness, paresthesia, psychomotor slowing, difficulty with memory, anorexia, weight decrease, confusion, depression, difficulty with concentration/attention, nausea, nystagmus, language problems, abnormal vision, diplopia, ataxia, speech disorders/related speech problems, asthenia, back pain, tremor, dyspepsia, abdominal pain, mood problems, pharyngitis, rhinitis, sinusitis *Pediatric patients 2 to < 16 years of age* (≥ 5% of topiramate-treated patients and > placebo): somnolence, anorexia, fatigue, injury, nervousness, personality disorder, difficulty with concentration/attention, abnormal gait, ataxia, hyperkinesia, nausea, increased saliva, constipation, weight decrease, purpura, aggressive reaction, insomnia, difficulty with memory, viral infection, pneumonia

Second-Generation AEDs			
	Keppra® (levetiracetam)[61]	**Lamictal® (lamotrigine)[62]**	**Topamax® (topiramate)[63]**
Interactions	None	VPA increases lamotrigine concentration more than two-fold; CBZ, PHY, PB, and primidone decrease lamotrigine concentration by approximately 40%; oral estrogen-containing contraceptives and rifampin also decrease lamotrigine concentration by approximately 50%.	Topiramate concentration decreased by 48% with PHY, 40% with CBZ, 14% with VPA, and 13% with lamotrigine. When coadministered with topiramate, PHY concentration increased by 25% or had less than 10% change, VPA concentration decreased by 11%, and CBZ, CBZ epoxide, PB, primidone, and lamotrigine concentrations (at topiramate doses up to 400 mg/d) had less than 10% change; decreased contraceptive efficacy and increased breakthrough bleeding should be considered with oral contraceptives, especially at topiramate doses > 200 mg/d; metformin is contraindicated with metabolic acidosis, an effect of topiramate; lithium levels should be monitored when coadministered with high-dose topiramate; monitor the patient for the appearance or worsening of metabolic acidosis with other carbonic anhydrase inhibitors.

First-Generation AEDs		
	Tegretol® (carbamazepine)[64]	**Depakote® (divalproex sodium)[65]**
Available Formulations	• Chewable tablets*: 100 mg • Tablets*: 200 mg • XR tablets*: 100 mg, 200 mg, 400 mg • Oral suspension*: 100 mg/5 mL	• Delayed-release tablets*: 125 mg, 250 mg, 500 mg • Sprinkle capsules*: 125 mg • Extended-release tablets*: 250 mg, 500 mg
Proposed Mechanism of Action	Precise MOA in humans has not been fully elucidated; thought to act by reducing polysynaptic responses and blocking the posttetanic potentiation	Precise MOA in humans has not been fully elucidated; thought to increase brain concentrations of GABA
Indication(s) for Epilepsy	• POS with complex symptomatology (psychomotor, temporal lobe); generalized tonic-clonic seizures (grand mal) • Mixed seizure patterns which include the above or other partial or generalized seizures • Absence seizures (petit mal) do not appear to be controlled by carbamazepine.	Monotherapy or adjunctive therapy for the treatment of patients with complex POS that occur either in isolation or in association with other types of seizures. Use as sole and adjunctive therapy in the treatment of simple and complex absence seizures and adjunctively in patients with multiple seizure types that include absence seizures.

First-Generation AEDs		
	Tegretol® (carbamazepine)[64]	**Depakote® (divalproex sodium)[65]**
Recommended Dosing	***Adults and children > 12 years of age:*** ***Initial:*** Either 200 mg BID for tablets and XR tablets, or 1 teaspoon QID for suspension (400 mg/day). Increase at weekly intervals by adding up to 200 mg/day using a BID regimen of carbamazepine-XR or a TID or QID regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily for children 12 to 15 years of age and 1200 mg daily in patients > 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800 to 1200 mg daily. ***Children 6 to 12 years of age:*** ***Initial:*** Either 100 mg BID for tablets or XR tablets, or one-half teaspoon QID for suspension (200 mg/day). Increase at weekly intervals by adding up to 100 mg/day using a BID regimen of carbamazepine-XR or a TID or QID regimen of the other formulations until the optimal response is obtained. Dosage generally should not exceed 1000 mg daily. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400 to 800 mg daily. ***Children < 6 years of age:*** ***Initial:*** 10 to 20 mg/kg/day BID or TID as tablets, or QID as suspension. Increase weekly to achieve optimal clinical response administered TID or QID. ***Maintenance:*** Ordinarily, optimal clinical response is achieved at daily doses < 35 mg/kg. If satisfactory clinical response has not been achieved, plasma level should be measured to determine whether or not it is in the therapeutic range. No recommendation regarding the safety of carbamazepine for use at doses > 35 mg/kg/24 hours can be made. ***Combination Therapy:*** Carbamazepine may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, with the exception of phenytoin, which may have to be increased.	***Complex partial seizures:*** **Adults and children ≥ 10 years of age:** *Monotherapy:* Initiated at 10 to 15 mg/kg/d, increased at weekly intervals by 10 to 15 mg/kg to achieve optimal clinical response, typically < 60 mg/kg/day. *Adjunctive therapy:* Divalproex sodium may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. Ordinarily, optimal clinical response is achieved at daily doses < 60 mg/kg/day. If satisfactory clinical response has not been achieved, plasma level should be measured to determine whether or not it is in the usually accepted therapeutic range (50 to 100 µg/mL). No recommendation regarding the safety of valproic acid for use at doses > 60 mg/kg/day can be made. If the total daily dose exceeds 250 mg, it should be given in divided doses. ***Simple and complex absence seizures:*** The recommended initial dose is 15 mg/kg/day, increasing at 1-week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dosage is 60 mg/kg/day. If the total daily dose exceeds 250 mg, it should be given in divided doses.
Contraindications	• History of previous bone marrow depression • Hypersensitivity to the drug • Known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc • Use with monoamine oxidase inhibitors within 14 days is not recommended. • Coadministration of carbamazepine with nefazodone is contraindicated.	• Hepatic disease or significant hepatic dysfunction • Hypersensitivity to the drug • Urea cycle disorder

First-Generation AEDs		
	Tegretol® (carbamazepine)[64]	**Depakote® (divalproex sodium)[65]**
Warnings and Precautions	• BOXED WARNING: o Serious dermatologic reactions and HLA-B*1502 allele, including serious and sometimes fatal dermatologic reactions, such as toxic epidermal necrolysis and Stevens-Johnson syndrome o Aplastic anemia and agranulocytosis • Multiorgan hypersensitivity • Suicidal behavior and ideation • Usage in pregnancy • Anticholinergic activity; patients with increased intraocular pressure should be observed closely during therapy. • Other tricyclic compounds; possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered. • Avoid in patients with a history of hepatic porphyria (eg, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). • Withdraw carbamazepine gradually to minimize the potential of increased seizure frequency.	• BOXED WARNING: o Hepatotoxicity, including fatalities o Pancreatitis, including life-threatening cases o Teratogenicity, including neural tube defects • Suicidal behavior and ideation • Thrombocytopenia • Hyperammonemia and hyperammonemic encephalopathy • Hypothermia • Multiorgan hypersensitivity reaction • Somnolence in the elderly
Pregnancy Category	D	D
Most Common AEs	The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting.	Adverse events reported by ≥ 10 % of patients in the controlled studies of divalproex sodium monotherapy or adjunctive therapy for complex partial seizures: headache, asthenia, nausea, vomiting, abdominal pain, diarrhea, anorexia, somnolence, tremor, dizziness, diplopia, amblyopia/blurred vision, flu syndrome, infection, alopecia, nervousness, insomnia, thrombocytopenia, dyspepsia
Interactions	Carbamazepine suspension should not be administered simultaneously with other liquid medicinal agents or diluents. **Agents that may affect carbamazepine plasma level** • CYP3A4 inhibitors may increase plasma carbamazepine level; close monitoring of carbamazepine level is indicated and dosage adjustment may be required. **Effect of carbamazepine on plasma levels of concomitant agents** • Increased levels: clomipramine HCl, phenytoin, primidone • Carbamazepine is a potent inducer of hepatic CYP3A4 and may therefore reduce plasma concentrations of concomitant CYP3A4 substrates. • Coadministration of carbamazepine with nefazodone results in insufficient plasma concentration of nefazodone and inadequate therapeutic effect. • Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. • Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity. • Concomitant medication with carbamazepine and some diuretics (eg, hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia. • Carbamazepine may antagonize the effects of nondepolarizing muscle relaxants (eg, pancuronium). • Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.	Hepatic enzyme-inducing drugs (eg, PHY, CBZ, PB, primidone, rifampin) can increase VPA clearance, whereas enzyme inhibitors (eg, felbamate) can decrease VPA clearance; coadministration of aspirin with VPA may decrease protein binding and result in an inhibition of metabolism of VPA; a clinically significant reduction in VPA concentration has been reported in patients receiving carbapenem antibiotics; serum levels of CBZ and CBZ epoxide are altered on coadministration of VPA and CBZ to epileptic patients; the concomitant use of VPA and clonazepam may induce absence status in patients with a history of absence-type seizures; coadministration of VPA can affect the PKs of other drugs (eg, diazepam, ethosuximide, lamotrigine, phenobarbital, primidone, PHY) by inhibiting their metabolism or protein binding displacement; dosage adjustment of amitriptyline/nortriptyline, warfarin, or zidovudine may be necessary if used concomitantly with VPA; hyperammonemia, with or without encephalopathy, is associated with concomitant topiramate use.

First-Generation AEDs		
	Tegretol® (carbamazepine)[64]	**Depakote® (divalproex sodium)[65]**
	• Concomitant use of carbamazepine with hormonal contraceptive products may render the contraceptives less effective. Breakthrough bleeding and unintended pregnancies have been reported.	

AE = adverse event; AED = antiepileptic drug; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BID = twice daily; CBZ = carbamazepine; CNS = central nervous system; CV = Schedule V of the Controlled Substances Act; CYP = cytochrome P450; d = day; GABA = gamma-aminobutyric acid; HLA-B = human leukocyte antigen B; IV = intravenous; KCNQ = potassium channel, voltage-gated; MOA = mechanism of action; PB = phenobarbital; PHY = phenytoin; PK = pharmacokinetic; POS = partial-onset seizure; QD = once daily; QHS = every evening; QID = four times daily; QOD = every other day; SV2A = synaptic vesicle glycoprotein 2A; TID = three times daily; VPA = valproic acid; XR = extended release
*Generic available.

PLACE OF FYCOMPA™ IN THERAPY

Approach to Treatment of Epilepsy

Epilepsy is a disorder that may include physical, psychologic, cognitive, and social manifestations.[2] Therefore, a broad range of health and community service professionals generally work cooperatively with patients and their caregivers/family members to effectively manage the condition and its associated comorbidities.[2]

Ultimately, the goal of epilepsy management is to achieve seizure control with minimal AEs.[2] There are many treatment options available to health care professionals and patients including AEDs, surgery, special diets, and vagus nerve stimulation.[4]

However, AEDs are the mainstay of epilepsy treatment, and monotherapy is considered the most appropriate approach when initiating AED therapy.[66,67] Approximately 50% of newly diagnosed patients will become seizure-free while receiving their first AED.[68] If the initial AED is not effective or tolerated, monotherapy with a different AED may be tried. Adjunctive therapy (combination therapy) should be considered if a second well-tolerated AED does not provide adequate seizure control.[67] Approximately two-thirds of patients will become seizure-free after receiving a second or third AED.[68]

Epilepsy treatment has evolved continuously over the past 20 years, with more than 20 marketed AEDs available in the US.[11] Before the 1990s, pharmacologic therapy for epilepsy consisted of a handful of drugs including carbamazepine, phenytoin, valproic acid, ethosuximide, benzodiazepines, and phenobarbital. Since then, several new AEDs have been introduced, including FYCOMPA, which have benefits over some of the older AEDs.[11] Some of these newer AEDs have improved safety, tolerability, and pharmacokinetics (eg, lack clinically significant adverse drug interactions or hypersensitivity reactions).[4,11,12] Hence, the selection of an AED should be tailored to the patient, taking into account both AED- and patient-specific factors (**Table II-11**).

Table II-11. Patient- and AED-Specific Factors in AED Selection[69]

AED-Specific Factors	Patient-Specific Factors
• Efficacy for seizure type or epilepsy syndrome • Tolerability and safety • Hypersensitivity reactions • Chronic toxicities • Teratogenicity • Drug interactions • Dosing frequency • Formulations available	• Age • Gender • Comorbidities • Concurrent medications • Ability to swallow tablets or capsules

AED = antiepileptic drug

Despite the advent of new AEDs over the past 2 decades, approximately 20% to 40% of patients with epilepsy continue to have seizures and are considered refractory to therapy.[10] Drug-resistant epilepsy is defined as failure of adequate studies of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination.[70] Uncontrolled seizures can have devastating consequences to patients such as increased risk of comorbidity and injury, shorter life expectancy, decreased HRQOL, and significant neuropsychologic, psychiatric, and social impairment.[4,10]

Considering the large proportion of patients with uncontrolled seizures, there is a need for additional safe and effective AED options.[12] The development of new AEDs with novel MOAs may offer potential benefits to patients refractory to or unable to tolerate current therapies.[13] AEDs with new MOAs may also increase the number of possible AED combinations (see **Mechanism of Action-Based Combination Therapy** section below),[14] although data on specific combinations of AEDs are not widely available.[71]

Guidelines for the Treatment of Epilepsy – Focus on Partial-Onset (Focal) Seizures

Guidelines for the treatment of epilepsy have been issued by the United Kingdom–based National Institute for Health and Care Excellence (NICE),[67] the International League Against Epilepsy (ILAE),[69] and the American Academy of Neurology (AAN) and the American Epilepsy Society (AES).[72,73] Because the NICE, ILAE, and

AAN/AES guidelines were issued before the FDA approval of FYCOMPA, FYCOMPA was not evaluated in these guidelines.

UK-Based National Institute for Health and Care Excellence (2012)[67]

First-line therapy for patients (children, young people, and adults) with newly diagnosed partial-onset (focal) seizures includes carbamazepine or lamotrigine. If these AEDs are unsuccessful or not tolerated, levetiracetam, oxcarbazepine, or sodium valproate may be tried. If the first AED tried is not effective, an alternative to these five AEDs may be offered. Adjunctive therapy should be considered if a second well-tolerated AED is not effective.

In patients with refractory partial-onset (focal) seizures, carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate, or topiramate may be offered as adjunctive therapy if first-line treatments are not effective or tolerated. If adjunctive therapy is not effective or tolerated, other AEDs, including eslicarbazepine acetate, lacosamide, phenobarbital, phenytoin, pregabalin, tiagabine, vigabatrin, or zonisamide, may be considered by a tertiary epilepsy specialist.

International League Against Epilepsy (2006)[69]

In adults with partial-onset (focal) seizures, the ILAE recommends initial monotherapy with carbamazepine, phenytoin, or valproic acid. AEDs that have been deemed "possibly" efficacious as initial monotherapy include gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin.

In pediatric patients with partial-onset (focal) seizures, oxcarbazepine is recommended as initial monotherapy, with the following AEDs being "possibly" efficacious: carbamazepine, phenobarbital, phenytoin, topiramate, and valproic acid. In elderly patients with partial-onset (focal) seizures, gabapentin and lamotrigine are recommended as initial monotherapy, with carbamazepine being "possibly" efficacious.

American Academy of Neurology and American Epilepsy Society (2004)[72,73]

The AAN/AES guidelines assessed the efficacy, safety, and tolerability of the following "new" AEDs: gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide. In patients with newly diagnosed epilepsy, the AAN/AES recommends monotherapy with carbamazepine, phenytoin, valproic acid, phenobarbital, lamotrigine, gabapentin, oxcarbazepine, or topiramate.

In patients with refractory partial-onset (focal) seizures, the AAN/AES found that it is appropriate to use any of the seven "new" AEDs mentioned above as adjunctive therapy and oxcarbazepine, topiramate, or lamotrigine as monotherapy.

Mechanism of Action-Based Combination Therapy

There is evidence that AED combination therapy based on different MOAs may enhance effectiveness, whereas AED combination therapy with drugs that target the same MOA is likely to exacerbate AEs.[15] (For additional information regarding the MOA of AEDs, please see the previous section: **Introduction to Epilepsy**.) In theory, combinations of AED drugs with different, overlapping, or similar mechanisms may be additive or synergistic.[15] Research in this area is ongoing.

A recent claims database (Truven MarketScan) study evaluated treatment duration and health care utilization for patients with partial-onset (focal) seizures on combination AED therapy based on their MOAs (N = 8615).[74] Combination AED use was defined as continuous therapy (≥ 90 days) with two AEDs after initiation of the second AED (index date). Because several AEDs are associated with more than one MOA, the AEDs included in this study were categorized based on their primary MOA: sodium channel blocker (SC), GABA analog (G), synaptic vesicle protein 2A binding (SV2A), and multiple mechanisms (M) (**Table II-12**).

Patients were categorized into one of seven MOA combinations: SC + SC, SC + SV2, SC + M, SC + G, G + G, G + SV2, and G + M.[74] AED combinations with the same MOA, including SC + SC and G + G, were compared with AED combinations with different MOAs.

Table II-12. MOA Categories for AEDs[74]

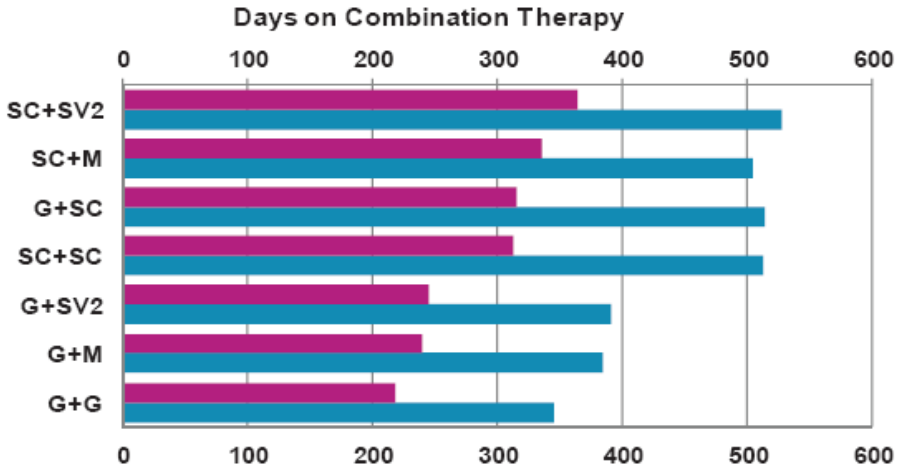
MOA Category	AEDs
Sodium channel blocker	Carbamazepine, ethotoin, fosphenytoin, lacosamide,

(SC)	lamotrigine, oxcarbazepine, phenytoin
GABA analog (G)	Clonazepam, diazepam, gabapentin, phenobarbital, pregabalin, primidone, tiagabine, vigabatrin
Synaptic vesicle protein 2A binding (SV2A)	Levetiracetam
Multiple mechanisms (M)	Divalproex sodium, felbamate, topiramate, sodium valproate, valproic acid, zonisamide

AED = antiepileptic drug; GABA = gamma-aminobutyric acid; MOA = mechanism of action

The longest duration of therapy was reported in patients taking SC + SV2, with a mean duration of 527 ± 506 days and a median of 364 days on therapy.[74] The shortest duration of therapy was reported in patients taking G + G, with a mean duration of 344 ± 345 days and a median of 218 days on therapy (**Figure II-5**). Utilizing SC + SC as the reference group, patients taking SC + SV2 were significantly less likely to discontinue therapy (hazard ratio: [HR] 0.817; $p < 0.001$), whereas patients taking G + G and G + M combinations had a greater risk of discontinuation (HR: 1.252 and 1.172, respectively; both $p = 0.002$).

Figure II-5. Persistence on Combination Therapy by MOA Combination Category[74]



	G+G	G+M	G+SV2	SC+SC	G+SC	SC+M	SC+SV2
Median Days	218	240	245	313	315	335	364
Mean Days	344	384	391	513	514	505	527
SD	345	395	406	530	526	511	506

G = GABA analog; GABA = gamma-aminobutyric acid; M = multiple mechanisms; MOA = mechanism of action; SC = sodium channel blocker; SD = standard deviation; SV2 = SV2A binding

Health care utilization (risk of hospitalization or emergency room [ER] visit) was evaluated with the use of logistic regression models to adjust the difference in baseline demographic and clinical characteristics.[74] Compared to patients receiving a G + G combination, patients receiving G + a different MOA AED had a significantly lesser risk of inpatient admission (adjusted odds ratio [OR]: 0.716; $p = 0.021$). Similarly, patients with SC combinations had significantly decreased risks of ER visits for different MOA combinations (adjusted OR: 0.853; $p = 0.025$). There was no statistical difference in the risk of hospitalization among different G combinations or in the risk of an ER visit among patients receiving SC combinations. However, point estimates were suggestive of a lower risk of hospitalization or ER visits for combinations based on different MOAs.

The analyses suggest a strategy for achieving optimal AED combination therapy outcomes based on different MOAs. However, further research is needed to more fully understand the role of MOA in achieving optimal outcomes in AED combination therapy and to identify additional factors that may influence outcomes when implementing a "rational polytherapy" approach to partial-onset seizure management.

FYCOMPA for the Treatment of Partial-Onset Seizures

FYCOMPA, a noncompetitive antagonist of the AMPA glutamate receptor on postsynaptic neurons, is indicated as adjunctive therapy for the treatment of partial-onset seizures, with or without secondarily generalized seizures

in patients with epilepsy aged 12 years and older.[1] In summary, features that make FYCOMPA a safe and effective option for this indication include:

FYCOMPA is the first FDA-approved, noncompetitive AMPA glutamate receptor antagonist.[1,18]

- Glutamate facilitates excitatory neurotransmission in the CNS, primarily through mediating fast excitatory signaling at the postsynaptic AMPA receptor.[19,20]
- AMPA receptor activation plays an important role in the generation and spread of seizures.[20]

FYCOMPA as adjunctive therapy has demonstrated efficacy in reducing seizures associated with partial-onset seizures, with or without secondarily generalized seizures, in patients ≥ 12 years of age.

- ***Study 304*** (French et al[21]; Study 1 in the FYCOMPA prescribing information [PI][1]) (N = 388), ***Study 305*** (French et al[22]; Study 2 in the FYCOMPA PI[1]) (N = 386), and ***Study 306*** (Krauss et al[23]; Study 3 in the FYCOMPA PI[1]) (N = 706) were similarly designed 19-week, randomized, double-blind, placebo-controlled, multicenter studies evaluating the efficacy and tolerability of FYCOMPA as adjunctive therapy in patients ≥ 12 years of age with refractory partial-onset seizures. Whereas ***Study 306*** evaluated the 2 mg, 4 mg, and 8 mg doses, ***Studies 304*** and ***305*** evaluated the 8 mg and 12 mg doses. These studies found:
    - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***median percent change in seizure frequency per 28 days*** (ranging from –17.6% to –34.5% vs –9.7% to –21.0%, respectively; $p < 0.05$).[21-23]
    - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a greater proportion of patients experiencing a ***≥ 50% reduction in seizure frequency (responder rate)*** (ranging from 28.5% to 37.6% vs 14.7% to 26.4%, respectively).[21-23]
    - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***reduction in the change in frequency of complex partial seizures + secondary generalized seizures*** (ranging from –21.9% to –38.7% vs –8.1% to –17.9%, respectively; $p < 0.01$).[21-23]
- A post hoc analysis of pooled study data from ***Studies 304, 305, and 306 (Steinhoff et al[24])*** found:
    - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***median percent change in seizure frequency per 28 days*** (–23.3%, –28.8%, and –27.2% vs –12.8%, respectively; $p < 0.01$ for 4 mg dose and $p < 0.001$ for 8 mg and 12 mg doses).[24]
    - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a greater proportion of patients experiencing a ***≥ 50% reduction in seizure frequency (responder rate)*** (28.5%, 35.3%, and 35.0% vs 19.3%, respectively; $p < 0.05$ for 4 mg and $p < 0.001$ for 8 mg and 12 mg).[24]
    - FYCOMPA (4 mg, 8 mg, and 12 mg) vs placebo had a significantly greater ***reduction in the change in frequency of complex partial seizures + secondary generalized seizures*** (–31.2%, –35.6%, and –28.6% vs –13.9%, respectively; $p < 0.001$).[24]

FYCOMPA as adjunctive therapy has demonstrated *long-term* efficacy and tolerability in reducing seizures associated with partial-onset seizures.

- **Study 307** (Krauss et al[25] (N = 1186) is an ongoing 256-week, open-label extension of Studies 304, 305, and 306 evaluating the long-term safety, tolerability, and efficacy of FYCOMPA. Interim results (data cutoff date: December 1, 2010) are presented below:
    - At the time of the interim analysis, 840 patients (70.8%) remained on FYCOMPA, with 580 patients (48.9%) and 19 patients (1.6%) having > 1 year or 2 years of exposure, respectively. A total of 1084 patients (91%) were titrated to 10 mg or 12 mg per day. The median duration of exposure was 51.4 weeks (range: 1.1 to 128.1 weeks).[23]
    - ***Treatment-emergent AEs (TEAEs)*** were reported in 87.4% of patients, with the most frequent AEs being dizziness, somnolence, headache, and fatigue. ***Serious AEs*** were reported in 13.2% of patients.[23]
    - The overall ***median percent change in seizure frequency*** included in each 13-week interval of FYCOMPA therapy was –39.2% for Weeks 14 to 26, –46.5% for Weeks 40 to 52, and –58.1% for Weeks 92 to 104.[23]
    - The overall ***≥ 50% reduction in seizure frequency (responder rate)*** included in each 13-week interval of FYCOMPA therapy was 41.4% for Weeks 14 to 26, 46.9% for Weeks 40 to 52, and 62.7% for Weeks 92 to 104.[23]

A pooled post hoc analysis found that FYCOMPA as adjunctive therapy has demonstrated efficacy for secondarily generalized seizures.

- A pooled post hoc analysis of **Studies 304, 305, and 306** (Ko and Ramsay[26] and Steinhoff et al[24]) evaluated the efficacy of FYCOMPA as adjunctive therapy for secondarily generalized seizures (N = 1480) and found:
  - At baseline, 68.4% of patients receiving FYCOMPA and 71.9% of patients receiving placebo had a history of secondarily generalized seizures.[24,26]
  - FYCOMPA 4 mg, 8 mg, and 12 mg vs placebo had a significantly greater ***median percent change in secondarily generalized seizure frequency per 28 days*** (–48.6%, –62.9%, and –53.3% vs –19.4%, respectively; $p < 0.01$ for each dose).[24,26]
  - FYCOMPA 8 mg and 12 mg vs placebo had a significantly greater proportion of patients experiencing a ***≥ 50% reduction in secondarily generalized seizure frequency (responder rate)*** (60.5% and 53.7% vs 37.0%, respectively; $p < 0.01$ for each dose).[24,26]
  - FYCOMPA 8 mg and 12 mg vs placebo had a significantly greater proportion of patients experiencing a ***≥ 75% reduction in secondarily generalized seizure frequency (responder rate)*** (46.5% and 38.9% vs 24.3%, respectively; $p < 0.001$ for 8 mg, $p = 0.012$ for 12 mg).[26]
  - FYCOMPA 8 mg and 12 mg vs placebo had a significantly greater proportion of patients achieving ***secondarily generalized seizure freedom*** (28.9% and 27.0% vs 14.2%, respectively; $p = 0.002$ for 8 mg, $p = 0.028$ for 12 mg).[26]

FYCOMPA is generally well tolerated in patients with partial-onset seizures.

- FYCOMPA has been administered to more than 1600 patients with epilepsy in clinical studies including open-label extension studies.[27]
- In phase III clinical studies, the most common adverse reactions in patients receiving FYCOMPA at doses of 8 mg or 12 mg (≥ 4% and ≥ 1% higher than placebo) included dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder.[1]
- In phase III clinical studies, discontinuation rates due to AEs were 3%, 8%, and 19% in patients randomized to receive FYCOMPA 4 mg, 8 mg, and 12 mg/day, respectively, vs 5% in patients randomized to receive placebo.[1]
- There are no contraindications for FYCOMPA; please see **Section II. Product Information for FYCOMPA – Boxed WARNING and WARNINGS and PRECAUTIONS** sections.

FYCOMPA has a once daily at bedtime dosing regimen and has multiple dosages available (2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets).[1]

- If patients miss a dose, they may resume dosing the following day at their prescribed dose, given the long half-life of FYCOMPA (105 hours).[1,28]
- A simulated pharmacokinetic analysis of 19 phase I FYCOMPA studies confirmed that after a missed dose, the FYCOMPA plasma trough concentration (C_{min}) preceding the next scheduled dose would be expected to decrease mildly to moderately (18.4% and 43.9% in the absence and presence of an enzyme-inducing AED, respectively) (see **Section III: Table III-13 – Gidal et al, 2012[28]**).

FYCOMPA has little impact on the pharmacokinetics of other AEDs.

- Pooled population pharmacokinetic and pharmacodynamic analyses of FYCOMPA (see **Section III: Table III-13 – Laurenza et al, 2011[29]**) have found that FYCOMPA does not have a clinically relevant effect on the pharmacokinetics of other AEDs including carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide.[29]
- Because FYCOMPA is metabolized primarily by CYP3A4, the concomitant use of FYCOMPA with CYP3A4-inducing AEDs, such as carbamazepine, oxcarbazepine, and phenytoin, will decrease the plasma level of FYCOMPA by approximately 50% to 67% and will decrease the effectiveness of FYCOMPA.[1] Phenobarbital and primidone may also decrease the FYCOMPA concentration.

Eisai, Inc. is working to develop tools and resources related to epilepsy for both patients and health care professionals.

The FDA has recommended that FYCOMPA be classified by the DEA as a scheduled drug. DEA scheduling for FYCOMPA is pending.[18]

SECTION III:
Supporting Clinical Information for FYCOMPA™ (perampanel) Tablets

SUPPORTING CLINICAL INFORMATION FOR FYCOMPA™

This section of the dossier will provide detailed and abbreviated summaries of three pivotal phase III studies, two phase II studies, and two open-label extension studies for FYCOMPA. Abbreviated summaries of post hoc and pooled analyses of the pivotal phase III studies and additional FYCOMPA clinical studies are summarized in the **FYCOMPA Supporting Clinical Evidence Table (Table III-13).**

Following **Table III-13**, the **Summary of Evidence from Secondary Sources** for FYCOMPA is presented. FYCOMPA has been studied in other neurologic diseases including Parkinson's disease, neuropathic pain, multiple sclerosis, and migraine.[27] Information on clinical studies of FYCOMPA can be found in the clinical studies registry, www.clinicaltrials.gov.

Summary of the Pivotal Phase III Partial-Onset Seizure Studies for FYCOMPA

The evidence for the efficacy and safety of FYCOMPA for partial-onset seizures is provided in three pivotal phase III studies: Studies 304,[21] 305,[22], and 306[23] (**Table III-1**). These studies were randomized, double-blind, multicenter, placebo-controlled investigations of FYCOMPA administered once daily (QD) (Study 306: 2 mg, 4 mg, or 8 mg; Studies 304 and 305: 8 mg or 12 mg). **Table III-1** provides the key inclusion and exclusion criteria for the three pivotal phase III FYCOMPA studies.

Table III-1. Key Study Inclusion and Exclusion Criteria
Studies 304, 305, and 306[21-23]

Inclusion Criteria	Exclusion Criteria

• ≥ 12 years of age, except in six countries,* where patients were ≥ 18 years of age
• Diagnosis of epilepsy with partial seizures with or without secondary generalization by clinical history and EEG results consistent with localization-related epilepsy
• ≥ five partial seizures (with ≥ two partial seizures/ 3-week period) and no 25-day seizure-free periods during the 6-week baseline
• Failure with ≥ 2 different AEDs within approximately the past 2 years
• On a stable dose (> 21days) of one to three AEDs
	• Clinically significant medical or psychiatric condition
	  • Active hepatic disease; AST or ALT elevations > three times the upper limit
	  • Active hematologic disease; WBC ≤ 2500/µL (2.50 1E + 09/L), ANC ≤ 1000/µL (1.00 1E + 09/L)
	  • Psychiatric disorder or unstable recurrent affective disorder; use of antipsychotics or suicide attempt(s) ≤ 2 years
	• ECG abnormality; prolonged QTc > 450 ms
	• Progressive degenerative CNS disease or CNS tumor
	• Drug or alcohol dependence ≤ 2 years
	• Multiple drug allergies or severe reactions to AEDs
	• Pregnant, lactating, or not using contraception
	• History of: nonepileptic or psychogenic seizures, seizure clusters (where individual seizures could not be identified), LGS, nonmotor simple partial seizures only, primary generalized seizures; status epilepticus within the past 12 months
	• Vagus nerve stimulator; use was allowed if the device was implanted ≥ 5 months before the study
	• Scheduled epilepsy surgery within 6 months
	• Use of:
	  • Felbamate; use for ≥ 2 years with a stable dose for 49 days to > 2 months
	  • Vigabatrin within the past 5 months and evidence of a vigabatrin-associated abnormality in a visual perimetry test
	  • Rescue BZDs ≥ two uses in the past month

AED = antiepileptic drug; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BZD = benzodiazepine; CNS = central nervous system; ECG = electrocardiogram; EEG = electroencephalogram; LGS = Lennox-Gastaut syndrome; WBC = white blood cell

*Germany, Bulgaria, Portugal, Lithuania, India, and China

In all three phase III studies,[21-23] after a 6-week baseline (eligibility) phase, patients were randomized to the 19-week study consisting of a 6-week titration phase and a 13-week maintenance phase. Patients were given the option to enter the open-label extension study (Study 307) at the end of the maintenance phase. The baseline period consisted of an assessment of pretreatment seizure frequency and eligibility for the double-blind phase. During the titration phase, patients in the FYCOMPA group received FYCOMPA in 2 mg/week increments up to the randomized dose. Dose reduction or postponement of up-titration was allowed for patients experiencing intolerability. Patients were removed from the study if they did not tolerate at least 2 mg of FYCOMPA or placebo by end of titration. The FYCOMPA dose that was achieved at the end of the titration phase was utilized during the maintenance phase. Dose reduction was discouraged during the maintenance period but allowed if the patient experienced intolerability. At the end of the maintenance phase, there was a 4-week follow-up phase to collect safety and efficacy data for patients discontinuing treatment during the maintenance phase or not entering the extension study.

Patients in these three phase III studies[1] had a mean duration of epilepsy of approximately 21 years and a median baseline seizure frequency ranging from 9.3 to 14.3 seizures per 28 days. During the studies, more than 85% of patients were taking two to three concomitant AEDs with or without concurrent vagal nerve stimulation, and approximately 50% were on at least one AED known to induce CYP3A4, an enzyme critical to the metabolism of FYCOMPA (ie, carbamazepine, oxcarbazepine, or phenytoin), resulting in a significant reduction in the serum FYCOMPA concentration.

The efficacy endpoints and safety assessments evaluated in these phase III studies are summarized in **Table III-2**.

Primary efficacy endpoint	• % change in seizure frequency per 28 days for the ITT population (all patients receiving ≥ one dose of study medication in the double-blind phase and providing any seizure outcome data)
Secondary efficacy endpoints	• Responder rate: % of patients achieving ≥ 50% reduction in seizure frequency in the maintenance phase • % change in the frequency of complex partial seizures plus secondary generalized seizures in the treatment phase
Exploratory endpoints	• % of patients achieving seizure reduction of 75% to 100% • CGI-C/PGI-C* and QOLIE-31-P*
Safety assessments	• AEs • Vital sign measurements • Laboratory tests • Physical and neurologic examinations • ECG • Prior, concomitant, and discontinuation of medications • Photosensitivity and withdrawal questionnaire

AE = adverse event; CGI-C/PGI-C = Clinical and Patient Global Impression of Change; ECG = electrocardiogram; ITT = intent to treat; QOLIE-31-P = Quality of Life in Epilepsy questionnaire

*The purpose of the Clinical Global Impression of Change questionnaire was to assess the subject's clinical status over the previous 4 weeks from the patient's and clinician's perspectives. This assessment evaluated seizure frequency and severity/intensity, the occurrence of AEs, and overall functional status. Each evaluation was scored using a 7-point scale where 1 = very much improved and 7 = very much worse. The QOLIE-31-P contains 30 items covering 7 subscales (seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognition, medication effects, and social function) and 1 item covering health status. It also includes seven items addressing the overall distress related to each subscale, an item addressing the relative importance of each subscale topic, and an item at the end of the study addressing perception of change in overall quality of life since the start of treatment. This questionnaire was only implemented in the countries where it was available and validated for the spoken language(s), and only in the age groups for which it has been validated.[27]

Table III-3 lists the results of the primary endpoint and secondary efficacy endpoints for the three phase III FYCOMPA studies.

Table III-3. Phase III FYCOMPA Clinical Studies Summary

Phase III FYCOMPA Clinical Studies										
Reference	French et al, 2012[21]			French et al, 2012[22]			Krauss et al, 2012[23]			
Study name	Study 304 (Study 1 in FYCOMPA PI)			Study 305 (Study 2 in FYCOMPA PI)			Study 306 (Study 3 in FYCOMPA PI)			
Population studied	Patients ≥ 12 years of age with refractory POS (failed ≥ two AEDs in last 2 years) and on one to three concomitant AEDs			Patients ≥ 12 years of age with refractory POS (failed ≥ two AEDs in last 2 years) and on one to three concomitant AEDs			Patients ≥ 12 years of age with refractory POS (failed ≥ two AEDs in last 2 years) and on one to three concomitant AEDs (six countries required patients to be ≥ 18 years of age to be included in the study)			
Study design	Double-blind, randomized, placebo-controlled, multicenter									
Duration	19 weeks (6-week titration and 13-week maintenance)			19 weeks (6-week titration and 13-week maintenance)			19 weeks (6-week titration and 13-week maintenance)			
Treatment	FYCOMPA 8 mg QD	FYCOMPA 12 mg QD	Placebo	FYCOMPA 8 mg QD	FYCOMPA 12 mg QD	Placebo	FYCOMPA 2 mg QD	FYCOMPA 4 mg QD	FYCOMPA 8 mg QD	Placebo
N	133	133	121	129	121	136	180	172	169	184
Median change in seizure frequency/28 days (%)	–26.3	–34.5	–21.0	–30.5	–17.6	–9.7	–13.6	–23.3	–30.8	–10.7
p Value*	0.026	0.016		0.0008	0.0105		NS	0.003	< 0.001	
Responder rate, ≥ 50% reduction in seizure frequency (%)	37.6	36.1	26.4	33.3	33.9	14.7	20.6	28.5	34.9	17.9
p Value*	NS			0.0018	0.0006		NS	0.013	< 0.001	
N	120	120	110	119	113	126	167	157	154	169
Change in frequency of complex partial seizures + secondary generalized seizures (%)	–33.0	–33.1	–17.9	–32.7	–21.9	–8.1	–20.5	–31.2	–38.7	–17.6
p Value*	0.0020	0.0081		< 0.001	0.005		0.0651	0.007	< 0.001	

AED = antiepileptic drug; NS = not significant; PI = prescribing information; POS = partial-onset seizure; QD = once daily

*p Values represent analysis of intent-to-treat population analysis of FYCOMPA treatment groups vs placebo.

Adjunctive FYCOMPA for Refractory Partial-Onset Seizures: A Global Randomized, Phase III Study (Study 304) French et al, 2012[21] and Study 1 in the Prescribing Information for FYCOMPA[1]

Key Findings

Objective

This was a multicenter, multinational, randomized, double-blind, placebo-controlled study consisting of a 19-week treatment phase (6-week titration and 13-week maintenance) and a 4-week follow-up phase evaluating the efficacy and safety of adjunctive FYCOMPA for the treatment of refractory partial-onset seizures (N = 388).

Primary Endpoint

- During the treatment phase, the median percent change in seizure frequency per 28 days in the intent-to-treat (ITT) population was significantly greater for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (–26.3% [p = 0.0261], –34.5% [p = 0.0158], and –21.0%, respectively) (**Figure III-2**).

Secondary Endpoints

- During the maintenance period, the ≥ 50% responder rate in the ITT population was not statistically significant for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (37.6% [p = 0.0760] and 36.1% [p = 0.0914] vs 26.4%, respectively) (**Figure III-3**).
- Patients treated with FYCOMPA had a significant decrease in the amount of complex partial + secondary generalized seizures, –33.0% (p = 0.0020) and –33.0% (p = 0.0081) for FYCOMPA 8 mg and 12 mg, respectively, compared to –17.9% for placebo.

Safety

- The majority of TEAEs were mild to moderate (FYCOMPA: 83.9%; placebo: 95.0%).
- The most common TEAEs occurred in the CNS: dizziness (8 mg: 37.6%; 12 mg: 38.1%; placebo: 9.9%), somnolence (8 mg: 18.0%; 12 mg: 17.2%; placebo: 13.2%), headache (8 mg: 15.0%; 12 mg: 13.4%; placebo: 13.2%), falls (8 mg: 9.8%; 12 mg: 12.7%; placebo: 6.6%), irritability (8 mg: 7.5%; 12 mg: 14.2%; placebo: 5%), and ataxia (8 mg: 6.0%; 12 mg: 11.9%; placebo: 0%) (**Table III-5**).
- The most common TEAEs that resulted in discontinuation (occurring in ≥ 1% of patients) included dizziness (3.0%), ataxia (2.6%), aggression (1.9%), vertigo (1.9%), dysarthria (1.1%), somnolence (1.1%), and blurred vision (1.1%).
- Worsening seizures (> 50% increase in seizures compared to baseline) occurred in 9% each of the FYCOMPA 8 mg and 12 mg groups vs 14% of the placebo group.
- Relevant serious AEs (SAEs) (occurring in ≥ one patient in any group) were those related to epilepsy (ie, convulsion, grand mal convulsion, or status epilepticus) and occurred in two patients receiving FYCOMPA 8 mg (1.5%), four patients receiving FYCOMPA 12 mg (3.0%), and one patient receiving placebo (< 1%).

Objective: To evaluate efficacy and safety of FYCOMPA administered with concomitant AEDs in patients with refractory partial-onset seizures.

Patients and Methods: This was a multicenter, multinational, randomized, double-blind, placebo-controlled study conducted in 68 centers in Argentina, Canada, Mexico, Chile, and the US from April 2008 to November 2010. Patients were randomized in a 1:1:1 ratio to receive FYCOMPA 8 mg QD, FYCOMPA 12 mg QD, or placebo QD.

Inclusion and Exclusion Criteria: The inclusion and exclusion criteria are summarized in **Table III-1**.

Primary Efficacy Endpoint: The primary endpoint was the percent change in seizure frequency per 28 days for the ITT population (all patients receiving ≥ one dose of treatment medication in the double-blind phase and providing any seizure outcome) in patients receiving FYCOMPA 8 mg and 12 mg vs placebo during the 19-week treatment phase.

Secondary Efficacy Endpoints: The secondary endpoints included responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency in the maintenance phase), change in the frequency of complex partial seizures + secondary generalized seizures in the treatment phase, and safety.

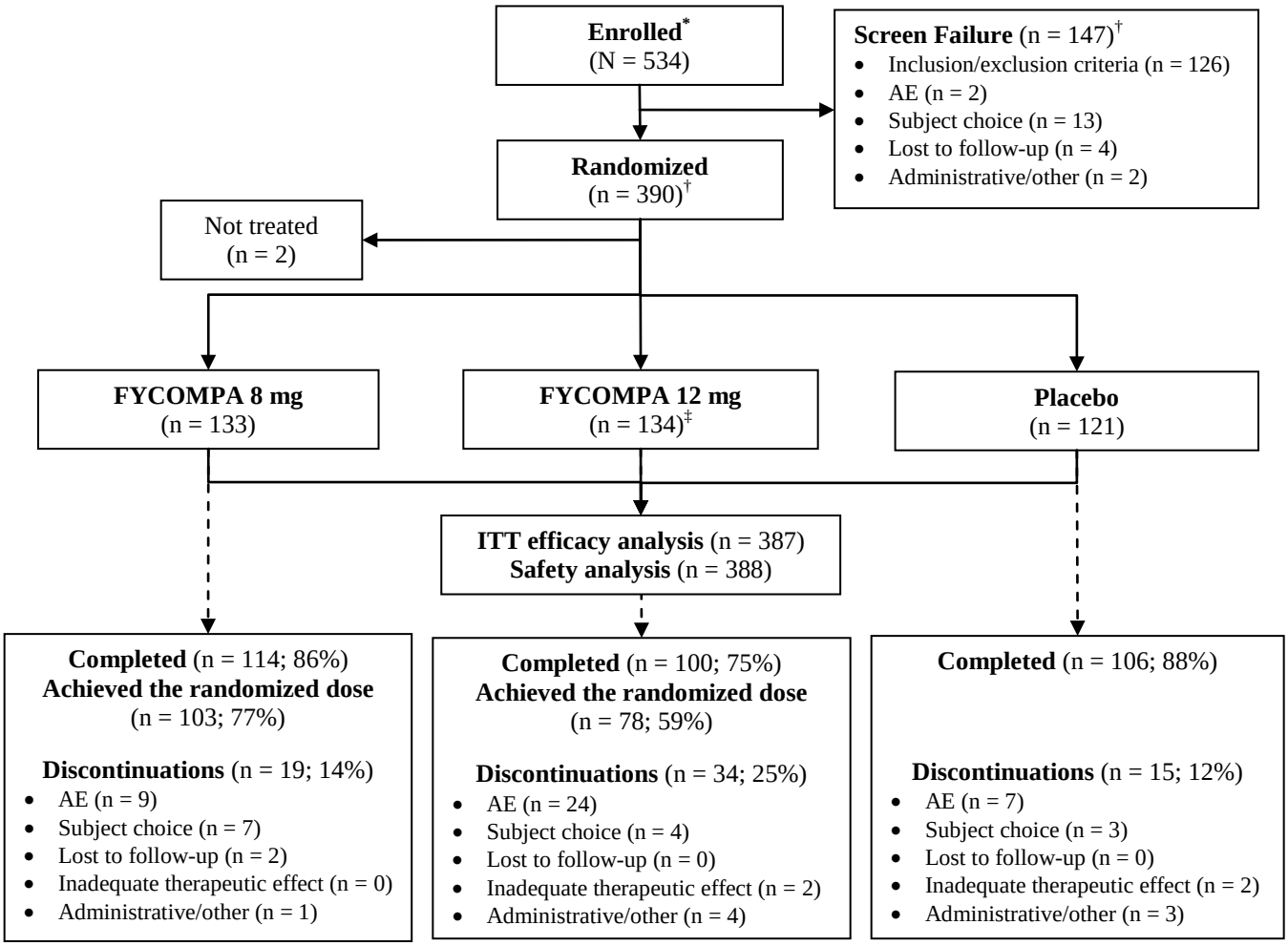
Exploratory Efficacy Endpoints: Exploratory endpoints included the percentage of patients achieving seizure reduction of 75% to 100%, the Clinical and Patient Global Impression of Change (CGI-C and PGI-C) and quality of life questionnaire (QOLIE-31-P).

Results:

Patient Disposition and Demographics: The study patient disposition is shown in **Figure III-1**. A total of 534 patients were screened, of which 388 were randomized to receive treatment medication and were included in the safety analysis. The ITT population included 387 patients. Of the randomized patients, 320 (82.5%) patients completed the study. Of the 68 (17.5%) patients that discontinued early, 40 (10.3%) were due to AEs. In the FYCOMPA 8 mg and 12 mg treatment groups, 103 (77.4%) and 78 (58.7%) patients in those treatment groups achieved their randomized dose, respectively.

Patient baseline characteristics and epilepsy characteristics were similar between the treatment groups (**Table III-4**). A total of 15.5%, 55.7%, and 28.9% of the patients were taking one, two, or three AEDs, respectively. A total of 63.4% of the patients in the study were taking a FYCOMPA-inducing AED as a concomitant medication. The most common concomitant AEDs were carbamazepine, lamotrigine, levetiracetam, valproic acid, oxcarbazepine, topiramate, phenytoin, clonazepam, and zonisamide. At baseline, the mean number ± SD of prior (past 5 years) and concomitant AEDs across all groups was 2.8 ± 1.2.

Figure III-1. Study Patient Disposition – Study 304
(Adapted from French et al, 2012[21])



AE = adverse event; ITT = intent to treat
*Patients who signed informed consent forms.
†Includes three patients who were screen failures and were inappropriately randomized to a treatment group.
‡One patient was treated for 1 day and did not complete the seizure diary that day.

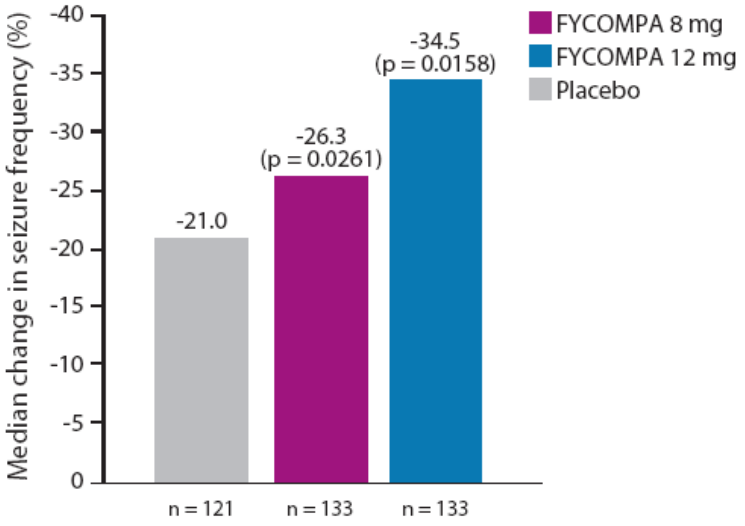
Table III-4. Partial List of Baseline Demographics – Study 304[21]

Characteristic	FYCOMPA 8 mg (n = 133)	FYCOMPA 12 mg (n = 134)	Placebo (n = 121)
Age, y; mean (SD) Min, max	35.8 (14.2) 12, 68	36.7 (14.6) 14, 77	35.6 (14.7) 12, 73
Female, n (%)	68 (51.1)	65 (48.5)	67 (55.4)
Mean time since epilepsy diagnosis, y	23.56	23.79	24.13
Seizure frequency/28 days during the prerandomization phase, mean n (min, max)*	14.3 (2.4, 1030.8)	12.0 (2.9, 1083.1)	13.7 (3.3, 227.4)
Seizure type, n (%) Simple partial without motor signs Simple partial with motor signs Complex partial Partial with secondary generalization	 50 (37.6) 47 (35.3) 116 (87.2) 91 (68.4)	 45 (33.6) 40 (29.9) 122 (91.0) 101 (75.4)	 48 (39.7) 41 (33.9) 107 (88.4) 87 (71.9)
Concomitant AEDs at baseline, n (%) One Two Three	 26 (19.5) 70 (52.6) 37 (27.8)	 19 (14.2) 82 (61.2) 33 (24.6)	 15 (12.4) 64 (52.9) 42 (34.7)

AED = antiepileptic drug; ITT = intent to treat; max = maximum; min = minimum; SD = standard deviation; y = year
*ITT population

Primary Efficacy Endpoint: During the treatment phase, the median percent change in seizure frequency per 28 days in the ITT population was significantly greater for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (–26.3% [p = 0.0261], –34.5% [p = 0.0158], and –21.0%, respectively). Overall, 77.4% of patients in the FYCOMPA 8 mg group and 58.7% in the 12 mg group achieved their randomized dose (**Figure III-2**).

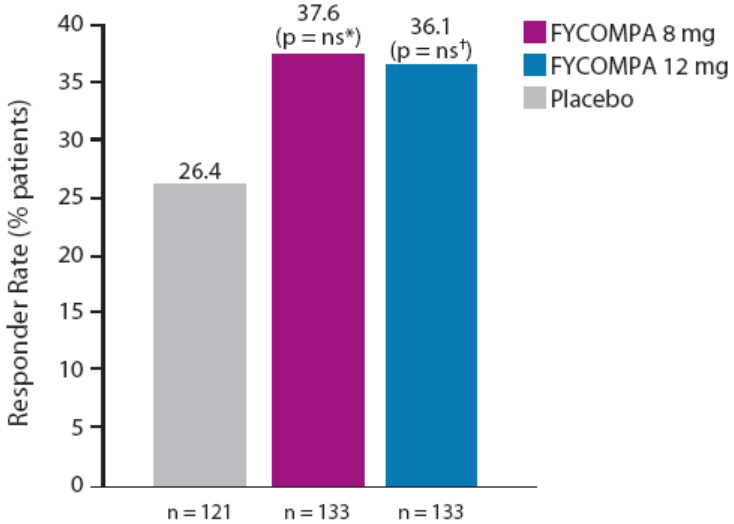
Figure III-2. Median Percent Change in Seizure Frequency per 28 Days
ITT Population – Study 304
(Adapted from French et al, 2012[21])



ITT = intent to treat

Secondary Efficacy Endpoints: During the maintenance period, the ≥ 50% responder rate in the ITT population was not statistically significant for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (37.6% [p = 0.0760], 36.1% [p = 0.0914], and 26.4%, respectively) (**Figure III-3**).

Figure III-3. Responder Rate
ITT Population – Study 304
(Adapted from French et al, 2012[21])



ITT = intent to treat
*p = 0.0760
†p = 0.0914

Patients treated with FYCOMPA had a significant decrease in the amount of complex partial + secondary generalized seizures, –33.0% (p = 0.0020) and –33.1% (p = 0.0081) for FYCOMPA 8 mg and 12 mg, respectively, compared to –17.9% for placebo.

Exploratory Efficacy Endpoints: Although the exploratory endpoints CGI-C/PGI-C showed "much" or "very much" improvement with FYCOMPA treatment, the difference vs placebo was only statistically significant for CGI-C at the FYCOMPA 8 mg dose. The QOLIE-31-P assessment was similar between groups for changes in quality of life. The difference vs placebo in percentage of patients achieving seizure reduction of 75% to 100% for the FYCOMPA 8 mg and 12 mg groups was 18.8% and 17.3% (p = 0.001), respectively, compared to 5.0% for the placebo group. The percentage of patients with 100% seizure reduction (seizure free) during the maintenance period for FYCOMPA 8 mg and 12 mg groups was 2.2% and 1.5%, respectively, vs 0% for the placebo group.

Study Limitation: The study authors observed a regional difference in data (the 50% responder rate was significantly different for FYCOMPA vs placebo among North American patients but not for Central and South American patients), and the authors considered it possible that patient selection or study conduct may have been an issue in the Central and South American centers of the study.

Safety: The majority of TEAEs were mild to moderate (FYCOMPA: 83.9%; placebo: 95.0%) and occurred most commonly in the CNS (**Table III-5**). Worsening seizures (> 50% increase in seizures compared to baseline) occurred in 9% of each of the FYCOMPA 8 mg and 12 mg groups vs 14% of the placebo group. SAEs occurred in eight patients receiving FYCOMPA 8 mg (nine SAEs), nine patients receiving FYCOMPA 12 mg (15 SAEs), and six patients receiving placebo (eight SAEs). Relevant SAEs (occurring in ≥ one patient in any group) were those related to epilepsy (ie, convulsion, grand mal convulsion, status epilepticus) and occurred in two patients receiving FYCOMPA 8 mg (1.5%), four patients receiving FYCOMPA 12 mg (3.0%), and one patient receiving placebo (< 1%). The most common TEAEs that resulted in discontinuation (occurring in ≥ 1% of patients) included dizziness (3.0%), ataxia (2.6%), aggression (1.9%), vertigo (1.9%), dysarthria (1.1%), somnolence (1.1%), and blurred vision (1.1%).

Table III-5. Treatment-Emergent Adverse Events (≥ 10% in any Treatment Group)

Safety Population – Study 304[21]

Adverse Event	FYCOMPA 8 mg (n = 133) n (%)	FYCOMPA 12 mg (n = 134) n (%)	Placebo (n = 121) n (%)
Dizziness	50 (37.6)	51 (38.1)	12 (9.9)
Somnolence	24 (18.0)	23 (17.2)	16 (13.2)
Headache	20 (15.0)	18 (13.4)	16 (13.2)
Fall	13 (9.8)	17 (12.7)	8 (6.6)
Irritability	10 (7.5)	19 (14.2)	6 (5.0)
Ataxia	8 (6.0)	16 (11.9)	0 (0)

Adjunctive FYCOMPA in Patients With Refractory Partial-Onset Seizures: A Randomized, Global, Phase III Study (Study 305) French et al, 2012[22] and Study 2 in the Prescribing Information for FYCOMPA[1]

Key Findings

Objective

This was a multicenter, multinational, randomized, double-blind, placebo-controlled study consisting of a 19-week treatment phase (6-week titration and 13-week maintenance) and a 4-week follow-up phase evaluating the efficacy and safety of adjunctive FYCOMPA for the treatment of refractory partial-onset seizures (N = 386).

Primary Endpoint

- During the treatment phase, the median percent change in seizure frequency per 28 days in the ITT population was significantly greater for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (–30.5% [p = 0.0008], –17.6% [p = 0.0105], and –9.7%, respectively) (**Figure III-5**).

Secondary Endpoints

- During the maintenance period, the ≥ 50% responder rate in the ITT population was significantly greater for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (33.3% [p = 0.0018], 33.9% [p = 0.0006], and 14.7%, respectively) (**Figure III-6**).
- Patients treated with FYCOMPA had a significant decrease in the amount of complex partial + secondary generalized seizures, –32.7% (p < 0.001) and –21.9% (p = 0.005) for FYCOMPA 8 mg and 12 mg, respectively, compared to –8.1% for placebo.

Safety

- The majority of patients experienced TEAEs that were mild to moderate (FYCOMPA: 76.4%; placebo: 61.7%), and the most common TEAEs occurred in the CNS: dizziness (8 mg: 32.6%; 12 mg: 47.9%; placebo: 7.4%), somnolence (8 mg: 12.4%; 12 mg: 18.2%; placebo: 2.9%), fatigue (8 mg: 13.2%; 12 mg: 16.5%; placebo: 8.1%), and headache (8 mg: 8.5%; 12 mg: 13.2%; placebo: 13.2%) (**Table III-7**).
- The most common TEAEs that resulted in discontinuation (occurring in ≥ 1% of patients) included dizziness (3.0%), somnolence (2.0%), rash (1.6%), convulsions (1.2%), and fatigue (1.2%).
- Worsening seizures (> 50% increase in seizures compared to baseline), occurred in 8% of the FYCOMPA 8 mg group and 9% of FYCOMPA 12 mg group vs 10% of the placebo group.
- The only SAEs (occurring in > one patient in any group) were related to epilepsy (ie, convulsions, epilepsy, partial seizures with secondary generalized seizures, status epilepticus) and affected three patients receiving FYCOMPA 8 mg (2.3%), one patient receiving FYCOMPA 12 mg (< 1%), and two patients receiving placebo (1.5%).

Objective: To evaluate the efficacy and safety of FYCOMPA administered with concomitant AEDs in patients with refractory partial-onset seizures.

Patients and Methods: This was a multicenter, multinational, randomized, double-blind, placebo-controlled study conducted in 78 centers in Australia, Austria, Belgium, Germany, Finland, France, Greece, India, Israel, Italy, Russia, Sweden, South Africa, the United Kingdom, the Netherlands, and the US from May 2008 to January 2011. Patients were randomized in a 1:1:1 ratio to receive FYCOMPA 8 mg QD, FYCOMPA 12 mg QD, or placebo QD.

Inclusion and Exclusion Criteria: The inclusion and exclusion criteria are summarized in **Table III-1**.

Primary Efficacy Endpoint: The primary endpoint was the percent change in seizure frequency per 28 days in patients receiving FYCOMPA 8 mg or 12 mg vs placebo during the 19-week treatment phase. The 50% responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency during the maintenance phase) was also a primary endpoint for registration in the European Union.

Secondary Efficacy Endpoints: The secondary endpoints included the 50% responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency during the maintenance phase), percent change in the frequency of complex partial seizures + secondary generalized seizures frequency per 28 days, and safety.

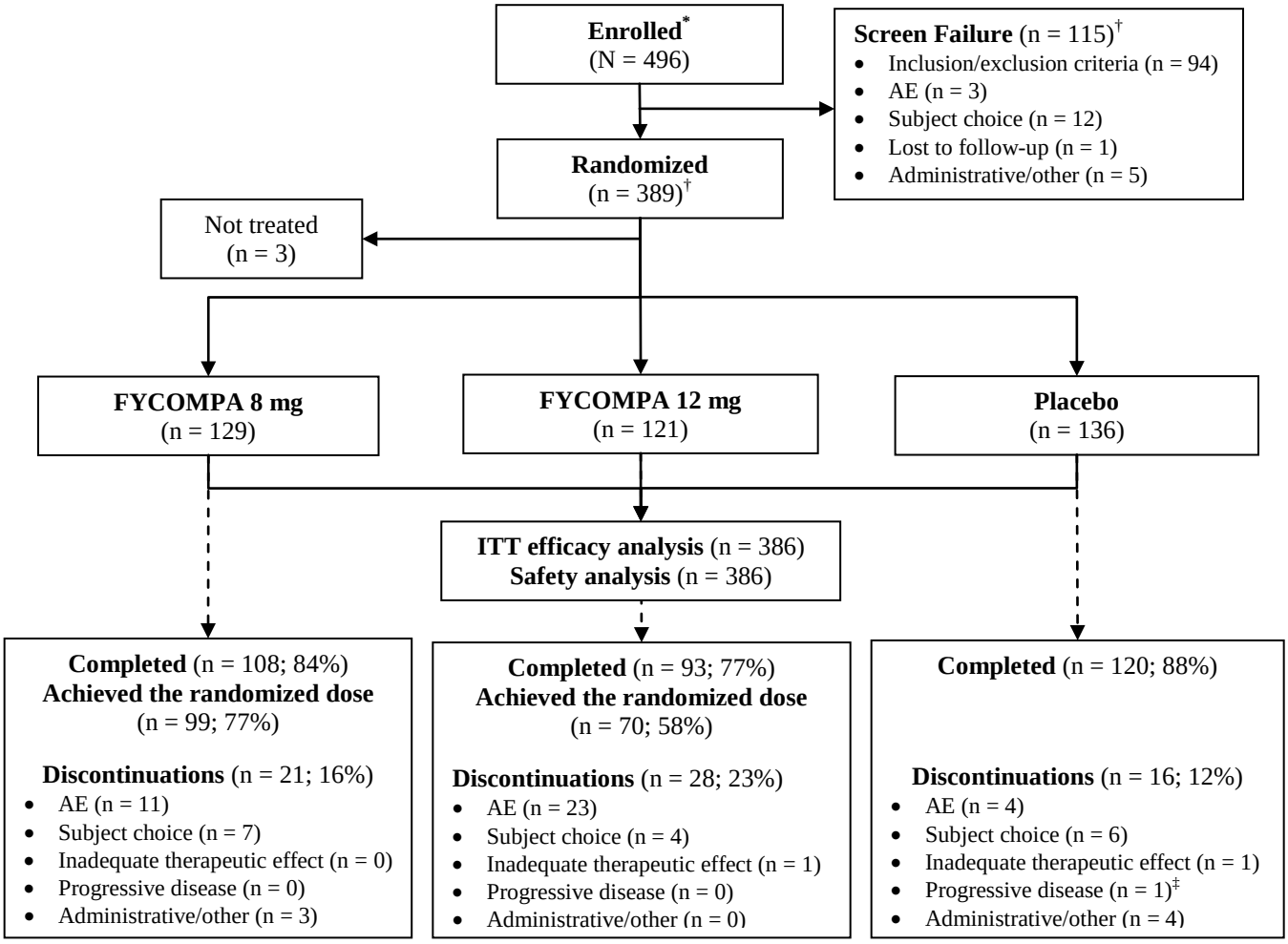
Exploratory Efficacy Endpoints: Exploratory endpoints included the percentage of patients achieving seizure reduction of 75% to 100%, CGI-C and PGI-C, and QOLIE-31-P.

Results:

Patient Disposition and Demographics: The study patient disposition is shown in **Figure III-4**. A total of 496 patients were screened, of which 386 were randomized to receive treatment medication and were included in the safety analysis. The ITT population included 386 patients. Of the randomized patients, 321 (83.2%) patients completed the study. Of the 65 (16.8%) patients who discontinued early, 38 (9.8%) did so due to AEs. In the FYCOMPA 8 mg and 12 mg treatment groups, 99 (76.7%) and 70 (57.8%) of the patients in those treatment groups achieved their randomized dose, respectively.

Patient baseline characteristics and epilepsy characteristics were similar between the treatment groups (**Table III-6**). There were 10.9%, 50.5%, and 38.6% of the patients taking one, two, and three AEDs, respectively. Approximately 60.6% of the patients in the study were taking a FYCOMPA-inducing AED as a concomitant medication. The most common concomitant AEDs were levetiracetam, carbamazepine, lamotrigine, valproic acid, oxcarbazepine, topiramate, clobazam, and zonisamide. At baseline, the mean number of AEDs across all groups was 2.3.

Figure III-4. Study Patient Disposition – Study 305
(Adapted from French et al, 2012[22])



AE = adverse event; ITT = intent to treat
*Patients who signed informed consent forms.
†Includes eight patients who were screen failures and were inappropriately randomized to a treatment group.
‡One patient was mistakenly described as having progression of disease instead of progression of seizures.

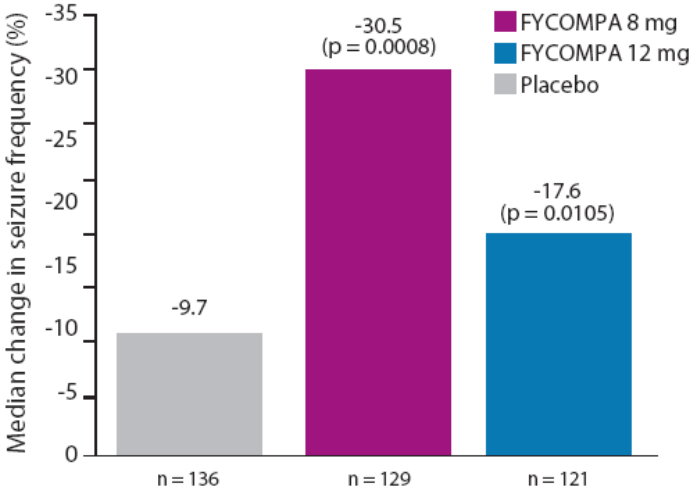
Table III-6. Partial List of Baseline Demographics – Study 305[22]

Characteristic	FYCOMPA 8 mg (n = 129)	FYCOMPA 12 mg (n =121)	Placebo (n = 136)
Mean age, y (SD)	36.7 (14.4)	35.5 (14.1)	34.4 (13.6)
Female, n (%)	64 (49.6)	71 (58.7)	65 (47.8)
Mean time since epilepsy diagnosis, y	22.5	21.3	22.0
Seizure frequency/28 days during the prerandomization phase, mean n (min, max)*	13.0 (3.3, 652.2)	13.7 (1.4, 598.4)	11.8 (3.4, 358.4)
Seizure type, n (%)			
Simple partial without motor signs	49 (38.0)	36 (29.8)	48 (35.3)
Simple partial with motor signs	39 (30.2)	38 (31.4)	30 (22.1)
Complex partial	114 (88.4)	100 (82.6)	114 (83.8)
Partial with secondary generalization	90 (69.8)	77 (63.6)	95 (69.9)
Concomitant AEDs at baseline, n (%)			
One	16 (12.4)	9 (7.4)	17 (12.5)
Two	68 (52.7)	63 (52.1)	64 (47.1)
Three	45 (34.9)	49 (40.5)	55 (40.4)

AED = antiepileptic drug; ITT = intent to treat; max = maximum; min = minimum; SD = standard deviation; y = year
*ITT population

Primary Efficacy Endpoint: During the treatment phase, the median percent change in seizure frequency per 28 days in the ITT population was significantly greater for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (30.5% [p = 0.0008], –17.6% [p = 0.0105], and –9.7%, respectively) (**Figure III-5**). Overall, 76.7% of patients in the FYCOMPA 8 mg group and 57.8% in the 12 mg group achieved their randomized dose.

Figure III-5. Median Percent Change in Seizure Frequency per 28 Days ITT Population – Study 305 (Adapted from French et al, 2012[22])

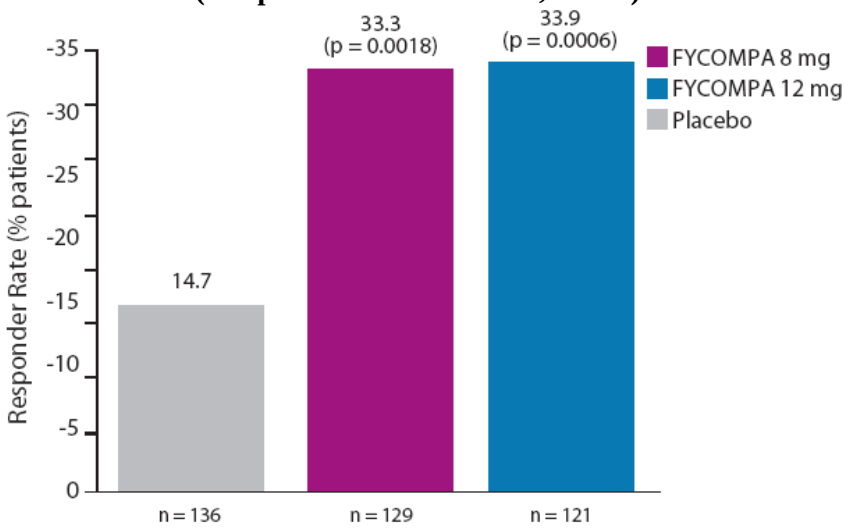


ITT = intent to treat

Secondary Efficacy Endpoints: During the maintenance period, the ≥ 50% responder rate in the ITT population was significantly greater for the FYCOMPA 8 mg and 12 mg groups vs the placebo group (33.3% [p = 0.0018], 33.9% [p = 0.0006], and 14.7%, respectively) (**Figure III-6**).

Figure III-6. Responder Rate

ITT Population – Study 305
(Adapted from French et al, 2012[22])



ITT = intent to treat

Patients treated with FYCOMPA had a significant decrease in complex partial + secondary generalized seizure frequency, –32.7% ($p < 0.001$) and –21.9% ($p = 0.005$) for FYCOMPA 8 mg and 12 mg, respectively, compared to –8.1% for placebo.

Exploratory Efficacy Endpoints: The exploratory endpoints CGI-C and PGI-C showed "much" or "very much" improvement with FYCOMPA treatment, and the difference vs placebo was statistically significant for CGI-C at both FYCOMPA doses but for PGI-C at the 8 mg dose alone. The QOLIE-31-P assessment was similar between groups for changes in QOL. The difference vs placebo in percentage of patients achieving seizure reduction of 75% to 100% was not statistically significant.

Study Limitations: None specifically mentioned by the authors.

Safety: The majority of patients experienced TEAEs that were mild to moderate (FYCOMPA: 76.4%; placebo: 61.7%), and the most common TEAEs occurred in the CNS (**Table III-7**). The most common TEAEs that resulted in discontinuation (occurring in ≥ 1% of patients) included dizziness (3.0%), somnolence (2.0%), rash (1.6%), convulsions (1.2%), and fatigue (1.2%). Worsening seizures (> 50% increase in seizures compared to baseline) occurred in 8% of the patients receiving FYCOMPA 8 mg and 9% of the patients receiving FYCOMPA 12 mg vs 10% of the patients receiving placebo. SAEs occurred in 10 patients receiving FYCOMPA 8 mg, 12 patients receiving FYCOMPA 12 mg, and 7 patients receiving placebo. Relevant SAEs (occurring in ≥ one patient in any group) were related to epilepsy (ie, convulsions, epilepsy, partial seizures with secondary generalization, status epilepticus) and affected three patients receiving FYCOMPA 8 mg (2.3%), one patient receiving FYCOMPA 12 mg (< 1%), and two patients receiving placebo (1.5%).

Table III-7. Treatment-Emergent Adverse Events (≥ 10% in Any Treatment Group)
Safety Population – Study 305[22]

Adverse Event	FYCOMPA 8 mg (n = 129) n (%)	FYCOMPA 12 mg (n = 121) n (%)	Placebo (n = 136) n (%)
Dizziness	42 (32.6)	58 (47.9)	10 (7.4)
Somnolence	16 (12.4)	22 (18.2)	4 (2.9)
Fatigue	17 (13.2)	20 (16.5)	11 (8.1)
Headache	11 (8.5)	16 (13.2)	18 (13.2)

Adjunctive FYCOMPA for Refractory Partial-Onset Seizures: A Randomized Phase III Study (Study 306) Krauss et al, 2012[23] and Study 3 in the Prescribing Information for FYCOMPA[1]

Key Findings

Objective

This was a multicenter, multinational, randomized, double-blind, placebo-controlled study consisting of a 19-week treatment phase (6-week titration and 13-week maintenance) and a 4-week follow-up phase evaluating the efficacy and safety of adjunctive FYCOMPA for the treatment of refractory partial-onset seizures (N = 706).

Primary Endpoint

- During the treatment phase, the median percent change in seizure frequency per 28 days in the ITT population was significantly greater for the FYCOMPA 4 mg and 8 mg groups vs the placebo group (–23.3% [p = 0.003], –30.8% [p < 0.001], and –10.7%, respectively) (**Figure III-8**). The difference between FYCOMPA 2 mg and placebo was not statistically significant.

Secondary Endpoints

- During treatment, the ≥ 50% responder rate in the ITT population was significantly greater for the FYCOMPA 4 mg and 8 mg groups vs the placebo group (28.5% [p = 0.013], 34.9% [p < 0.001], and 17.9%, respectively) (**Figure III-9**).
- Patients treated with FYCOMPA had a significant decrease in the amount of complex partial + secondary generalized seizures, –31.2% (p = 0.007) and –38.7% (p < 0.001) for FYCOMPA 4 mg and 8 mg respectively, compared to –17.6% for placebo.

Safety

- The majority of patients experienced TEAEs that were mild to moderate, and the most common TEAEs occurred in the CNS: dizziness (2 mg: 10.0%; 4 mg: 16.3%; 8 mg: 26.6%; placebo: 9.7%), somnolence (2 mg: 12.2%; 4 mg: 9.3%; 8 mg: 16.0%; placebo: 6.5%), headache (2 mg: 8.9%; 4 mg: 11.0%; 8 mg: 10.7%; placebo: 8.6%), fatigue (2 mg: 4.4%; 4 mg: 7.6%; 8 mg: 5.3%; placebo: 2.7%) (**Table III-9**).
- The most common TEAEs that resulted in discontinuation (occurring in ≥ 1% of any treatment group) included dizziness, convulsions, fatigue, and vertigo (< 1% each).
- Worsening seizures (> 50% increase in seizures compared to baseline) affected more patients receiving placebo than patients receiving FYCOMPA.
- SAEs occurred in six patients in each of the FYCOMPA groups and nine patients in the placebo group. The only SAE occurring in more than one patient in any group was seizures, which affected three patients receiving FYCOMPA 4 mg (1.7%), none in the other FYCOMPA groups, and five patients receiving placebo (2.7%).

Objective: To evaluate the efficacy and safety of FYCOMPA administered with concomitant AEDs in patients with refractory partial-onset seizures.

Patients and Methods: This was a multicenter, multinational, randomized, double-blind, placebo-controlled study conducted in 116 centers in 24 countries in Europe, Asia, and Australia including Bulgaria, China, Germany, India, Portugal, and Lithuania from August 2008 to May 2010. Patients were randomized in a 1:1:1:1 ratio to receive FYCOMPA 2 mg QD, FYCOMPA 4 mg QD, FYCOMPA 8 mg QD, or placebo QD.

Inclusion and Exclusion Criteria: The inclusion and exclusion criteria are summarized in **Table III-1**.

Primary Efficacy Endpoints: The primary endpoint was the percent change in seizure frequency per 28 days in patients receiving FYCOMPA 2 mg, 4 mg, or 8 mg vs placebo during the 19-week treatment phase. The responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency during the maintenance phase) was also a primary endpoint for the registration in the European Union.

Secondary Efficacy Endpoints: The secondary endpoints included the responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency during the maintenance phase), percent change in the frequency of complex partial seizures + secondary generalized seizures per 28 days, and safety.

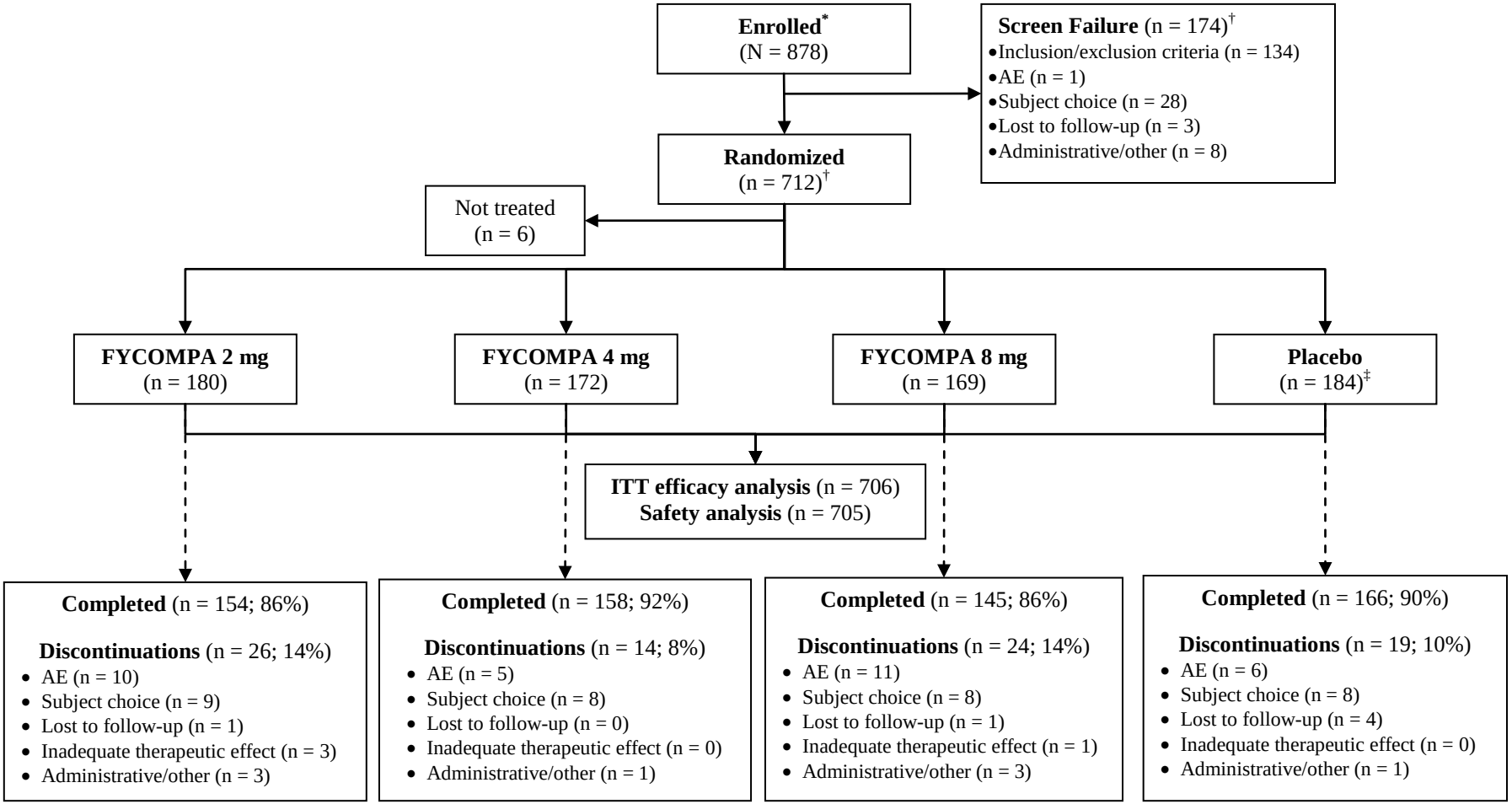
Exploratory Efficacy Endpoints: Exploratory endpoints included the percentage of patients achieving seizure reduction of 75% to 100%, CGI-C and PGI-C, and QOLIE-31-P.

Results:

Patient Disposition and Demographics: The study patient disposition is shown in **Figure III-7**. A total of 878 patients were screened, of which 712 were randomized to receive treatment. Of those, 706 were included in the safety analysis. The ITT population included 705 patients. Of the patients randomized, 623 (88.2%) completed the study. Of the 83 (11.8%) patients who discontinued early, 32 (4.5%) did so due to AEs.

Patient baseline characteristics and epilepsy characteristics were similar between the treatment groups (**Table III-8**). There were 14.7%, 48.2%, and 37.2% of patients taking one, two, or three AEDs, respectively. Approximately 56.3% of patients in the study were taking a FYCOMPA-inducing AED as a concomitant medication. The most common concomitant AEDs were valproic acid, lamotrigine, carbamazepine, levetiracetam, topiramate, oxcarbazepine, and clobazam. At baseline, the mean number of AEDs across all groups was 2.2.

Figure III-7. Study Patient Disposition – Study 306
(Adapted from Krauss et al, 2012)[23]



AE = adverse event; ITT = intent to treat
*Patients who signed informed consent forms.
†Includes eight screen failures who were incorrectly randomized.
‡One patient was excluded because they were treated for 1 day and did not complete the seizure diary.

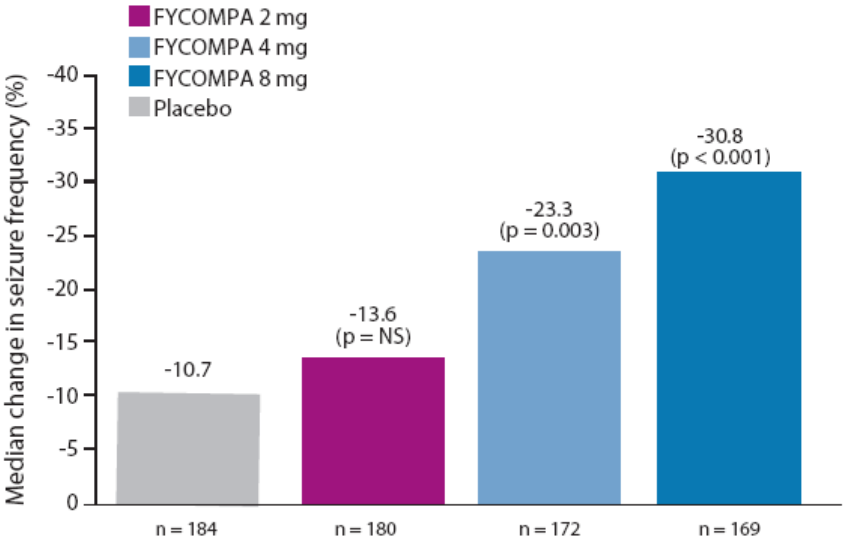
Table III-8. Partial List of Baseline Demographics – Study 306[23]

Characteristic	FYCOMPA 2 mg (n = 180)	FYCOMPA 4 mg (n = 172)	FYCOMPA 8 mg (n = 169)	Placebo (n = 185)
Mean age, y (SD)	33.8 (13.6)	33.6 (12.2)	34.6 (12.8)	33.4 (12.6)
Female, n (%)	95 (52.8)	84 (48.8)	92 (54.4)	90 (48.6)
Mean time since epilepsy diagnosis, y	19.4	19.7	19.9	17.5
Seizure frequency/28 days during the prerandomization phase, mean n (min, max)*	10.1 (3.2, 429.6)	10.0 (2.9, 4503.9)	10.9 (3.4, 723.2)	9.3 (3.3, 569.1)
Seizure type, n (%)				
Simple partial without motor signs	53 (29.4)	48 (27.9)	57 (33.7)	52 (28.1)
Simple partial with motor signs	53 (29.4)	54 (31.4)	51 (30.2)	55 (29.7)
Complex partial	153 (85.0)	147 (85.5)	138 (81.7)	155 (83.8)
Partial with secondary generalization	115 (63.9)	119 (69.2)	117 (69.2)	136 (73.5)
Concomitant AEDs at baseline, n (%)				
One	30 (16.7)	19 (11.0)	27 (16.0)	28 (15.1)
Two	80 (44.4)	88 (51.2)	82 (48.5)	90 (48.6)
Three	70 (38.9)	65 (37.8)	60 (35.5)	67 (36.2)

AED = antiepileptic drug; ITT = intent to treat; max = maximum; min = minimum; SD = standard deviation; y = year
*ITT population

Primary Efficacy Endpoint: During the treatment phase, the median percent change in seizure frequency per 28 days in the ITT population was significantly greater for the FYCOMPA 4 mg and 8 mg groups vs the placebo group (–23.3% [p = 0.003], –30.8% [p < 0.001], and –10.7%, respectively) (**Figure III-8**). The difference between placebo and the FYCOMPA 2 mg dose was not statistically significant (p = 0.420).[27]

Figure III-8. Median Percent Change in Seizure Frequency ITT Population – Study 306 (Adapted from Krauss et al, 2012[23])

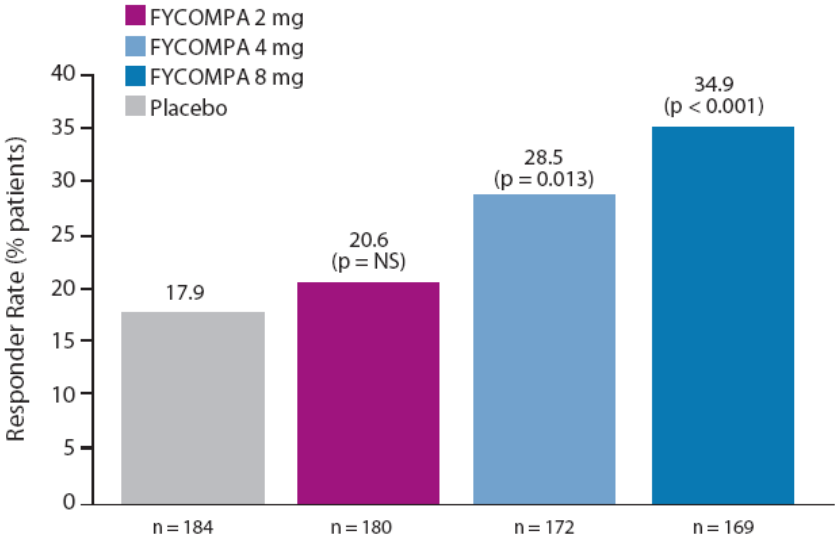


ITT = intent to treat; NS = not significant

Secondary Efficacy Endpoints: During treatment, the responder rate in the ITT population was significantly greater for the FYCOMPA 4 mg and 8 mg groups vs the placebo group (28.5% [p = 0.013]), 34.9% [p < 0.001], and 17.9%, respectively) (**Figure III-9**). The difference between placebo and the FYCOMPA 2 mg dose was not statistically significant.

Figure III-9. Responder Rate

ITT Population – Study 306
(Adapted from Krauss et al, 2012[23])



ITT = intent to treat; NS = not significant

Patients treated with FYCOMPA had a significant decrease in the amount of complex partial + secondary generalized seizure frequency per 28 days, –31.2% (p = 0.007) and –38.7% (p < 0.001) for FYCOMPA 4 mg and 8 mg respectively, compared to –17.6% for placebo. The authors did not specify whether the difference between placebo and the FYCOMPA 2 mg dose (–20.5%) was statistically significant.

Exploratory Efficacy Endpoints: The exploratory endpoints CGI-C and PGI-C showed "much" or "very much" improvement with FYCOMPA treatment but the difference vs placebo was not significant for PGI-C and was statistically significant for CGI-C at the FYCOMPA 4 mg and 8 mg doses alone. The QOLIE-31-P assessment was similar between groups for changes in quality of life.

Study Limitations: None specifically mentioned by the authors.

Safety: The majority of patients experienced TEAEs that were mild to moderate, and the most common TEAEs occurred in the CNS (**Table III-9**). Worsening seizures (> 50% increase in seizures compared to baseline) occurred in 11% of the patients receiving FYCOMPA 2 mg and 8% of patients receiving FYCOMPA 4 mg or 8 mg vs 15% of patients receiving placebo. SAEs occurred in six patients in each of the FYCOMPA groups and nine patients in the placebo group. The only SAE occurring in more than one patient in any group was seizures, which affected three patients receiving FYCOMPA 4 mg (1.7%), none in the other FYCOMPA groups, and five patients receiving placebo (2.7%). The most common TEAEs that resulted in discontinuation (occurring in ≥ 1% of any treatment group) included dizziness, convulsions, fatigue, and vertigo (< 1% each).

Table III-9. Treatment-Emergent Adverse Events (≥ 5% in Any Treatment Group)
Safety Population – Study 306[23]

Adverse Event	FYCOMPA 2 mg (n = 180) n (%)	FYCOMPA 4 mg (n = 172) n (%)	FYCOMPA 8 mg (n =169) n (%)	Placebo (n = 185) n (%)
Dizziness	18 (10.0)	28 (16.3)	45 (26.6)	18 (9.7)
Somnolence	22 (12.2)	16 (9.3)	27 (16.0)	12 (6.5)
Headache	16 (8.9)	19 (11.0)	18 (10.7)	16 (8.6)
Fatigue	8 (4.4)	13 (7.6)	9 (5.3)	5 (2.7)
URI	11 (6.1)	6 (3.5)	3 (1.8)	5 (2.7)
Nasopharyngitis	7 (3.9)	9 (5.2)	3 (1.8)	3 (1.6)
Gait disturbance	1 (< 1)	2 (1.2)	9 (5.3)	2 (1.1)

URI = upper respiratory tract infection

FYCOMPA as Adjunctive Therapy for Refractory Partial-Onset Seizures: Interim Results From a Phase III Open-Label Extension Study (Study 307) Krauss et al, 2012[25]

Key Findings

Objective

This was a multicenter, multinational, open-label extension study consisting of a 272-week treatment phase (16-week blinded conversion and 256-week maintenance) and a 4-week follow-up phase evaluating the safety, tolerability, and efficacy of adjunctive FYCOMPA for the treatment of refractory partial-onset seizures (N = 1207). This publication is an interim analysis of that study.

Primary Endpoint

- During the period spanning studies 304, 305, 306, and this open-label extension study, out of 87.4% of the patients who experienced any TEAEs, 78.2% experienced treatment-related AEs, and 73.0% reported the TEAEs as mild to moderate in severity.
- The most common TEAEs were dizziness, somnolence, headache, fatigue, irritability, nasopharyngitis, fall, nausea, weight increase, ataxia, gait disturbance, convulsion, vertigo, balance disorder, vomiting, and upper respiratory tract infection (**Table III-10**).
- SAEs occurred in 157 (13.2%) patients, and SAEs occurring in > 1% of patients were related to epilepsy.
- TEAEs led to withdrawal in 157 cases (13.2%), dose reduction in 428 cases (36.1%), and dose interruptions in 39 cases (3.3%).
- Abnormal laboratory values were not common during the study and occurred mostly in patients taking concomitant carbamazepine, oxcarbazepine, or valproic acid.

Secondary Endpoints

- Patients taking FYCOMPA experienced a decrease in seizure frequency that was sustained over time. Median percent changes in seizure frequency are shown in **Figure III-11**.
- During FYCOMPA treatment, the responder rate initially increased and then remained stable (**Figure III-12**).

Objective: To evaluate the long-term safety, tolerability, and efficacy of FYCOMPA administered with concomitant AEDs in patients with refractory partial-onset seizures.

Patients and Methods: This open-label extension study was conducted in 249 centers in 39 countries starting in October 2008 and was planned to last for 256 weeks; the data analyzed in this publication cutoff at December 1, 2010. Patients were titrated up from their previous FYCOMPA dose or placebo to receive their maximum tolerated dose (≤ FYCOMPA 12 mg daily). This was an open-label extension of studies 304, 305, and 306, which were multicenter, multinational, randomized, double-blind, placebo-controlled studies.

The 272-week study consisted of a 16-week blinded conversion phase and a 256-week open-label maintenance phase. At the end of the maintenance phase, there was a 4-week follow-up phase during which safety and efficacy data for patients without treatment were collected. During the blinded conversion phase, patients treated with FYCOMPA received FYCOMPA titrated in 2 mg/2-week increments up to the individualized maximum tolerated dose (MTD; ≤ 12 mg daily). Dose adjustment, discontinuation, or change in other AEDs was allowed by the investigators, if necessary. Patients were removed from the study if they did not tolerate at least 2 mg of FYCOMPA daily. The FYCOMPA dose that was achieved at the end of the blinded conversion phase was utilized during the maintenance phase.

Inclusion and Exclusion Criteria: To be included in this study, patients were required to complete the double-blind phase of study 304, 305, or 306. Inclusion/exclusion criteria for those studies are listed in **Table III-1**.

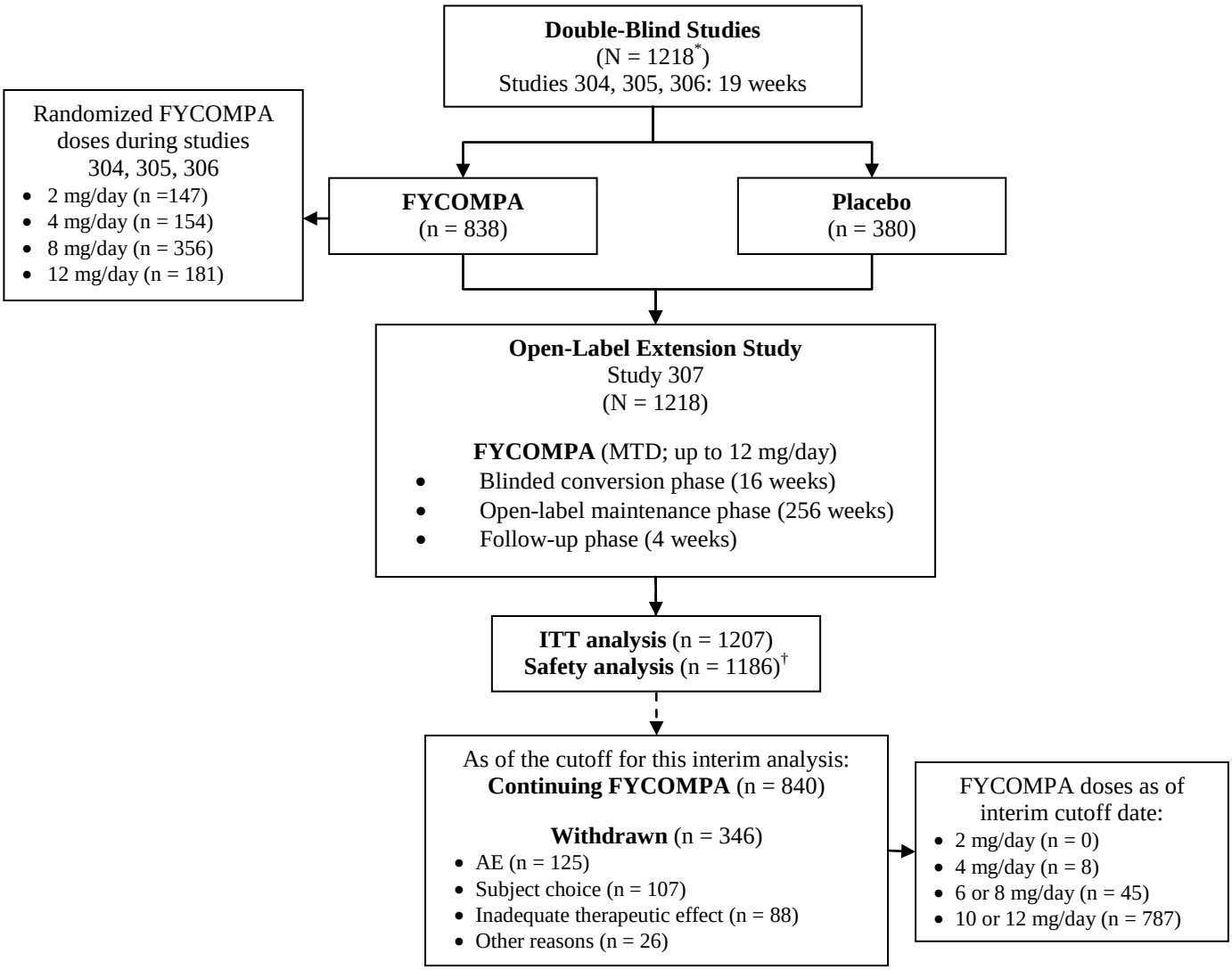
Endpoints: Endpoints included the safety and tolerability of the MTD of FYCOMPA (≤ 12 mg/day) as measured by TEAEs, laboratory parameters, vital signs, weight changes, and ECG changes. In addition, the percent change in seizure frequency per 28 days in patients receiving the MTD of FYCOMPA during the maintenance phase vs pre-FYCOMPA baseline frequency was assessed. The responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency per 28 days during maintenance vs pre-FYCOMPA baseline) was also an endpoint.

Results:

Patient Disposition and Demographics: The study patient disposition is shown in **Figure III-10**. A total of 1218 patients from the double-blind phases of the study entered the open-label extension, and of those, 1186 were included in the safety analysis. Patients included in the safety analysis received ≥ one dose of study drug and had ≥ one safety evaluation after that dose during the open-label extension; at the time of the cutoff for this analysis, 32 were excluded due to lack of safety data. The ITT efficacy analysis included 1207 patients who had seizure data at any time during FYCOMPA treatment. Of the patients in the safety analysis, 840 continued FYCOMPA at the cutoff for the interim analysis. Of the 346 (29.2%) who discontinued early, 125 (10.5%) did so due to AEs. As of the cutoff, the proportion discontinuing FYCOMPA treatment (29.2%) during the open-label extension was similar to the proportion in studies 304, 305, and 306 who discontinued placebo (27.6%) or FYCOMPA (27.9%).

The population was 50.4% male, and the mean age was 34.3 years. A total of 13.4%, 50.3%, and 36.3% of the patients were taking one, two, or three concomitant AEDs, respectively. The most common concomitant AEDs were carbamazepine, valproic acid, lamotrigine, levetiracetam, topiramate, and oxcarbazepine. At baseline, the mean number of AEDs was 2.2. Patients were treated with FYCOMPA for a median of 51.4 weeks (range, 1.1 to 128.1 weeks), and the mean dose of FYCOMPA was 10.1 mg/day (± 2.3 mg SD). Before the cutoff for interim analysis, almost all patients (94.9%) remained on the same number of AEDs, and very few had changed the doses of those drugs.

Figure III-10. Study Patient Disposition – Study 307[25]



AE = adverse event; ITT = intent to treat; MTD = maximum tolerated dose
*Of the 1265 patients who completed the previous studies, 1218 continued to the open-label extension study.
†As of the cutoff date, 32 patients had no safety data during the open-label extension and were excluded from the safety analysis.

Endpoints: During the period spanning studies 304, 305, 306 and this open-label extension study, the majority of patients (78.2%) experienced TEAEs, and 73.0% reported the TEAEs as mild to moderate in severity. The most common TEAEs occurred in the CNS (**Table III-10**). After 1 year of this open-label extension, worsening seizures (> 50% increase in seizures compared to baseline) occurred in 4.7% of patients previously randomized to placebo and at a range of rates among patients previously randomized to FYCOMPA (2 mg dose: 0%; 4 mg: 2.5%; 8 mg: 8.3%; 12 mg: 10.7%). TEAEs led to withdrawal in 157 cases (13.2%), dose reduction in 428 cases (36.1%), and dose interruptions in 39 cases (3.3%). The most common TEAEs that led to withdrawal were dizziness and irritability (3.0% and 1.2%, respectively), and the TEAEs that led to dose reductions and interruptions in ≥ 2% of the sample were dizziness, somnolence, ataxia, fatigue, headache, and gait disturbance. SAEs occurred in 157 patients, and SAEs occurring in ≥ 1% of patients were related to epilepsy. There were three deaths, but none were considered related to study treatment. Abnormal laboratory values were not common during the study, and occurred mostly in patients taking concomitant carbamazepine, oxcarbazepine, or valproic acid.

Table III-10. Treatment-Emergent Adverse Events (≥ 5% in Any Treatment Group)
Safety Population – As Reported in Studies 304, 305, 306, and 307[25]

Adverse Event	FYCOMPA 4 mg (n = 15)	FYCOMPA 6 to 8 mg (n = 86)	FYCOMPA 10 to 12 mg (n = 1084)	All FYCOMPA (n = 1186)

	n (%)	n (%)	n (%)	n (%)
Dizziness	9 (60.0)	51 (59.3)	461 (42.5)	521 (43.9)
Somnolence	3 (20.0)	23 (26.7)	214 (19.7)	240 (20.2)
Headache	2 (13.3)	24 (27.9)	172 (15.9)	198 (16.7)
Fatigue	2 (13.3)	13 (15.1)	128 (11.8)	143 (12.1)
Irritability	1 (6.7)	8 (9.3)	107 (9.9)	116 (9.8)
Nasopharyngitis	0	2 (2.3)	85 (7.8)	87 (7.3)
Fall	1 (6.7)	5 (5.8)	75 (6.9)	81 (6.8)
Nausea	2 (13.3)	7 (8.1)	72 (6.6)	81 (6.8)
Weight increase	0	3 (3.5)	78 (7.2)	81 (6.8)
Ataxia	0	10 (11.6)	63 (5.8)	73 (6.2)
Gait disturbance	0	7 (8.1)	62 (5.7)	69 (5.8)
Convulsion	0	3 (3.5)	62 (5.7)	65 (5.5)
Vertigo	1 (6.7)	7 (8.1)	57 (5.3)	65 (5.5)
Balance disorder	0	5 (5.8)	59 (5.4)	64 (5.4)
Vomiting	2 (13.3)	0	61 (5.6)	63 (5.3)
URI	1 (6.7)	5 (5.8)	56 (5.2)	62 (5.2)

URI = upper respiratory tract infection

Patients taking FYCOMPA experienced a decrease in seizure frequency that was sustained over time. During this open-label extension, the median percent change in seizure frequency (shown in **Figure III-11**) was similar for patients previously randomized to placebo and those previously randomized to FYCOMPA, and there was no difference between those groups at the end of the conversion period.

Figure III-11. Median Percent Change in Seizure Frequency – Study 307 (Adapted from Krauss et al, 2012[25])

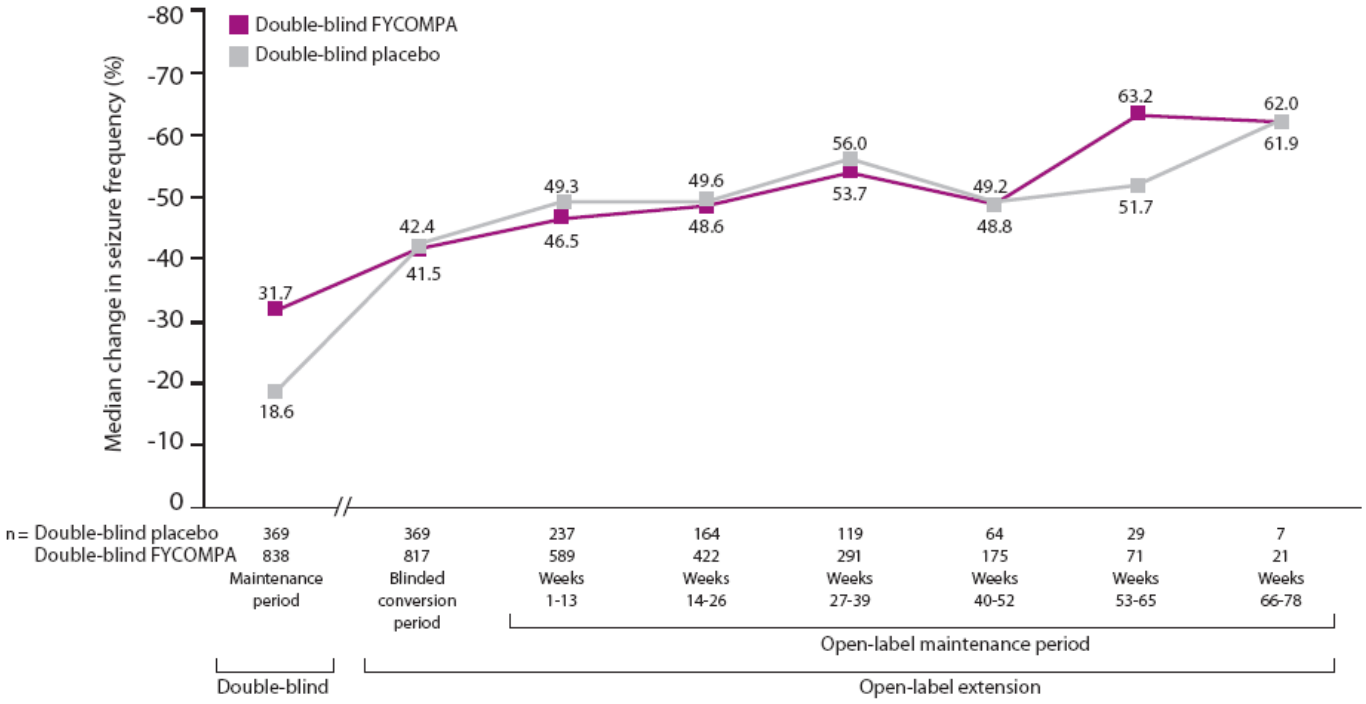
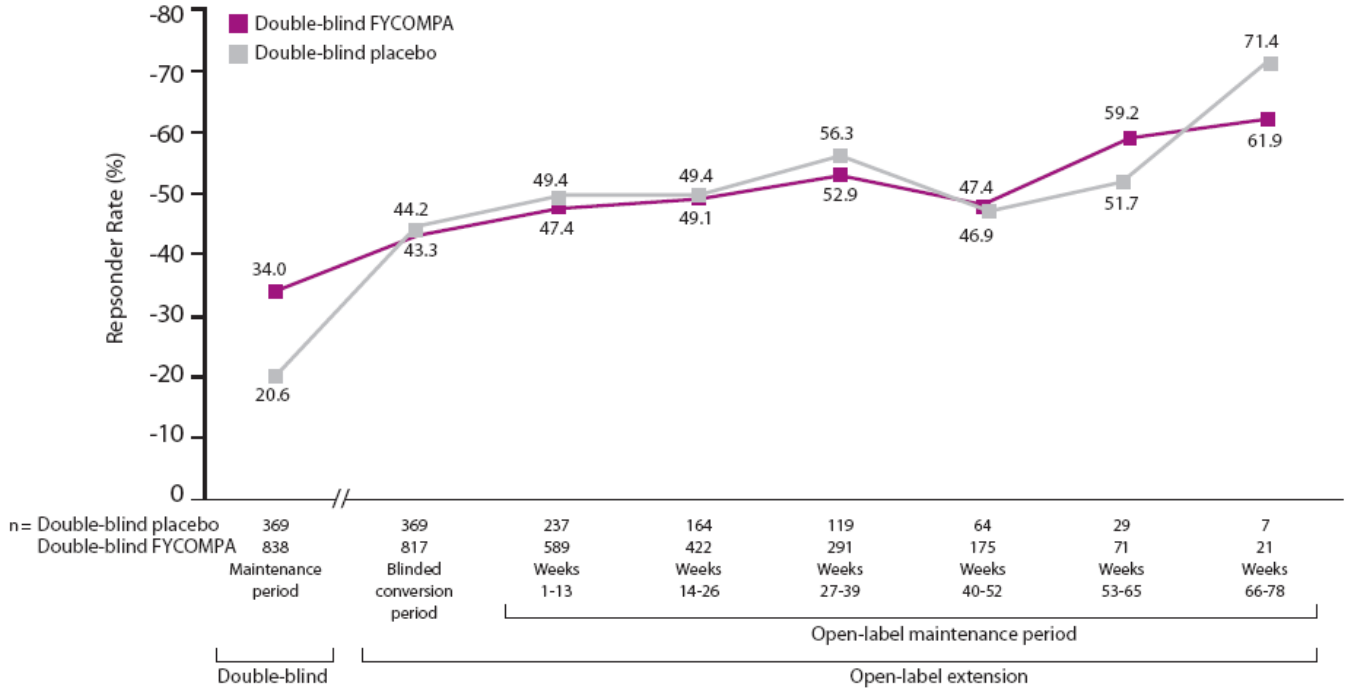


Figure III-12. Responder Rate - Study 307 (Adapted from Krauss et al, 2012[25])



Study Limitations: None specifically mentioned by the authors.

FYCOMPA as Adjunctive Therapy for Refractory Partial-Onset Seizures: Interim Results from a Phase II Open-Label Extension Study (Study 207) Rektor et al, 2012[75]

Key Findings

Objective

This was a multicenter, multinational, open-label extension study consisting of a 436-week treatment phase (12-week titration and 424-week maintenance) and a 4-week follow up phase evaluating the safety, tolerability, and efficacy of adjunctive FYCOMPA for the treatment of refractory partial-onset seizures (N = 138). This publication is an interim analysis of that study at its midpoint.

Primary Endpoints

- The majority of patients (93.5%) experienced TEAEs, most TEAEs were mild to moderate in severity, and the most common TEAEs occurred in the CNS (**Table III-11**).
- The frequencies of the most common TEAEs were greatest in the first year and decreased each year thereafter (**Table III-12**).
- SAEs occurred in 21 patients, 13 of which were related to epilepsy; 4 were possibly related to treatment.
- The frequency of dizziness and somnolence increased with dose.
- There were no new safety signals during long-term treatment.
- TEAEs led to withdrawal in 17 cases (12.3%), dose reduction in 45 cases (32.6%), and dose interruption in 6 cases (4.3%).
- TEAEs that most commonly led to discontinuation (> 1% of patients) included dizziness (2.2%), vertigo, upper abdominal pain, fatigue, headache, and status epilepticus (1.4% each).
- Abnormal laboratory values were not common, and other safety parameter findings were not remarkable.

Secondary Endpoints

- Patients taking FYCOMPA experienced a –31.5% median change in seizure frequency, and seizure frequency reductions were sustained over time.
- The responder rate was 37.0% during FYCOMPA treatment and remained stable.

Objective: To evaluate the long-term tolerability, safety, and efficacy of FYCOMPA administered with concomitant AEDs in patients with refractory partial-onset seizures.

Patients and Methods: This open-label extension study was conducted in 48 centers in Australia, Europe, and the US starting in October 2006; the data analyzed in this publication cutoff at December 1, 2010. Patients were titrated up from their previous FYCOMPA dose or placebo to receive their MTD (≤ FYCOMPA 12 mg daily). This was an open-label extension of Studies 206 and 208, which were multicenter, multinational, randomized, double-blind, placebo-controlled, phase II dose-escalation studies (**Table III-13. FYCOMPA Clinical Evidence Table**).

The 436-week open-label study consisted of a 12-week titration phase and up to a 424-week maintenance phase. At the end of the maintenance phase, there was a 4-week follow-up phase. During the titration phase, all patients received FYCOMPA titrated in 2 mg/2-week increments up to the MTD (≤ 12 mg daily). FYCOMPA dose adjustment and changes in other AEDs were allowed by the investigators if necessary. Patients were removed from the study if they did not tolerate at least 2 mg of FYCOMPA daily.

Inclusion and Exclusion Criteria: To be included in this study, patients were required to complete Study 206 or 208. Inclusion/exclusion criteria for those studies are listed in **Table III-13**.

Endpoints: The primary endpoint was the tolerability and safety of the individualized MTD of daily FYCOMPA (≤ 12 mg/day) as measured by TEAEs. Other safety parameters included laboratory values, vital signs, weight

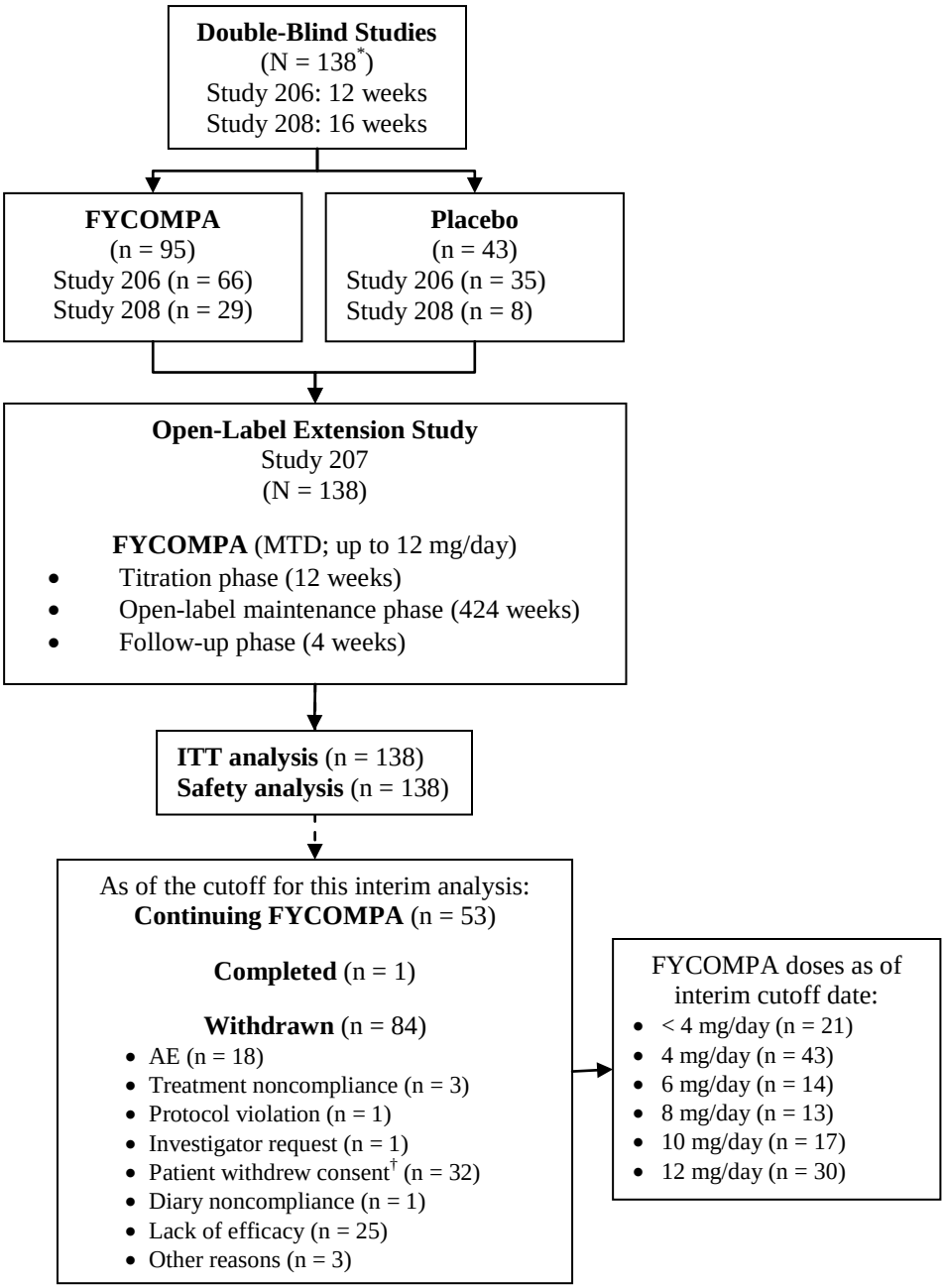
changes, and ECG changes. In addition, the percent change in seizure frequency per 28 days in patients receiving the MTD of FYCOMPA during the maintenance phase vs pre-FYCOMPA baseline frequency was assessed. The responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency per 28 days during maintenance vs pre-FYCOMPA baseline) was another endpoint.

Results:

Patient Disposition and Demographics: The study patient disposition is shown in **Figure III-13**. A total of 138 patients from the double-blind phases of the study entered the open-label extension, and all of them were included in the safety and the ITT efficacy analyses. Patients included in the safety analysis received ≥ one dose of study drug and had at least one safety evaluation during the open-label extension. The ITT efficacy analysis included patients who had seizure data during open-label FYCOMPA treatment. Of the patients in the safety analysis, 53 continued FYCOMPA at the cutoff for the interim analysis. Of the 84 (60.9%) who discontinued early, 17 (12.3%) did so due to TEAEs.

The population was 42.0% male, and the mean age was 40.7 years. A total of 22.5%, 68.1%, and 9.4% of the patients were taking one, two, or three concomitant AEDs, respectively. The most common concomitant AEDs were carbamazepine, lamotrigine, levetiracetam, valproic acid, topiramate, and oxcarbazepine. At the baseline of the double-blind studies, the mean number of AEDs was 1.9. Patients were treated with FYCOMPA for a mean of 116.4 weeks (± 74.9 weeks SD), and the mean dose of FYCOMPA was 7.3 mg/day (± 3.3 mg SD).

Figure III-13. Study Patient Disposition – Study 207[75]



AE = adverse event; ITT = intent to treat
*Of the 180 patients who completed the previous studies, 138 continued to the open-label extension.
†Includes some patients who discontinued because of lack of efficacy.

Primary Endpoints: The majority of patients (93.5%) experienced TEAEs, most TEAEs were mild to moderate in severity, and the most common TEAEs occurred in the CNS (**Table III-11**). The frequencies of the most common TEAEs (dizziness, headache, somnolence, and fatigue) were greatest in the first year and decreased each year thereafter (**Table III-12**). The frequency of dizziness and somnolence increased with dose. TEAEs led to withdrawal in 17 cases (12.3%), dose reduction in 45 cases (32.6%), and dose interruption in 6 cases (4.3%). The most common TEAEs that led to withdrawal were dizziness (2.2%), vertigo, upper abdominal pain, fatigue, headache, and status epilepticus (1.4% each), and the majority of the withdrawals (10) occurred in the first year. SAEs occurred in 21 patients, 13 of which were related to epilepsy; 4 were possibly related to treatment. There were no new safety signals during long-term treatment. There was one death, but it was not considered related to study treatment. Abnormal laboratory values were not common during the study. Mean changes in vital signs and

body weight were not clinically important, and ECG results and physical and neurologic examination findings were not remarkable.

Table III-11. Treatment-Emergent Adverse Events (≥ 10% in Any Treatment Group) Safety Population – As Reported in Studies 206, 208, and 207[75]

Adverse Event	All FYCOMPA (n = 138) n (%)
Dizziness	57 (41.3)
Headache	29 (21.0)
Somnolence	27 (19.6)
Fatigue	19 (13.8)
Contusion	16 (11.6)
Back pain	14 (10.1)
Nasopharyngitis	14 (10.1)
URI	14 (10.1)

URI = upper respiratory tract infection

Table III-12. Frequency of Treatment-Emergent Events Declined Over Time Safety Population – Study 207[75]

Adverse Event	Year 1, %	Year 2, %	Year 3, %	Year 4, %
Dizziness	30.4	14.7	3.7	6.7
Headache	16.7	4.6	2.4	5.0
Somnolence	17.4	5.5	1.2	1.7

During FYCOMPA treatment, patients experienced a –31.5% median change in seizure frequency compared to baseline (range –99.2% to 512.2%), and reductions in seizure frequency were sustained over time (**Figure III-14**). The responder rate was 37.0% and remained stable (**Figure III-15**). At the cutoff for the interim analysis, four patients experienced a 100% reduction in seizure frequency.

Figure III-14. Responder Rate - Study 207 (Adapted from Rektor et al, 2012[75])

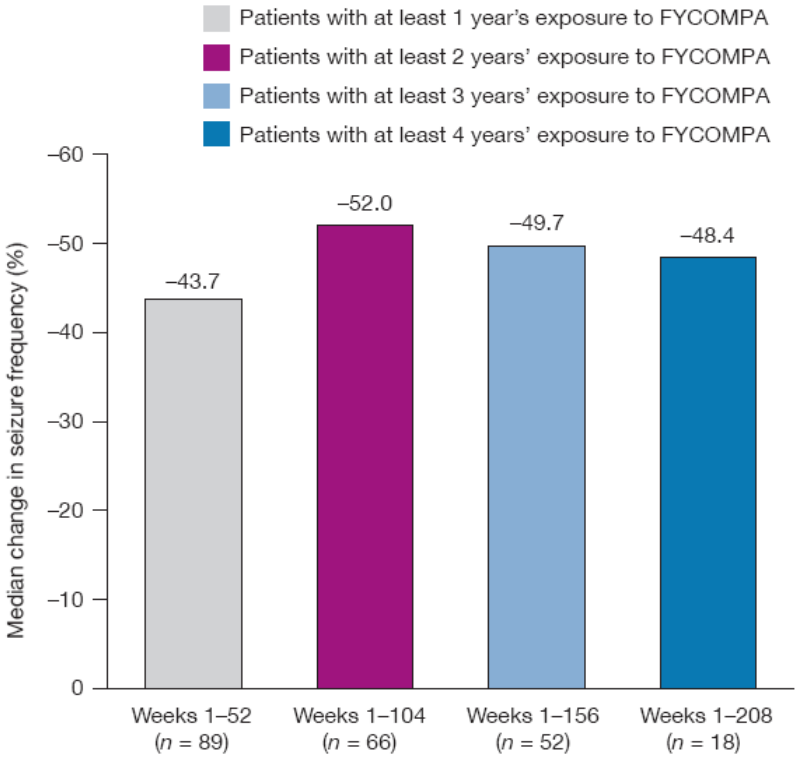
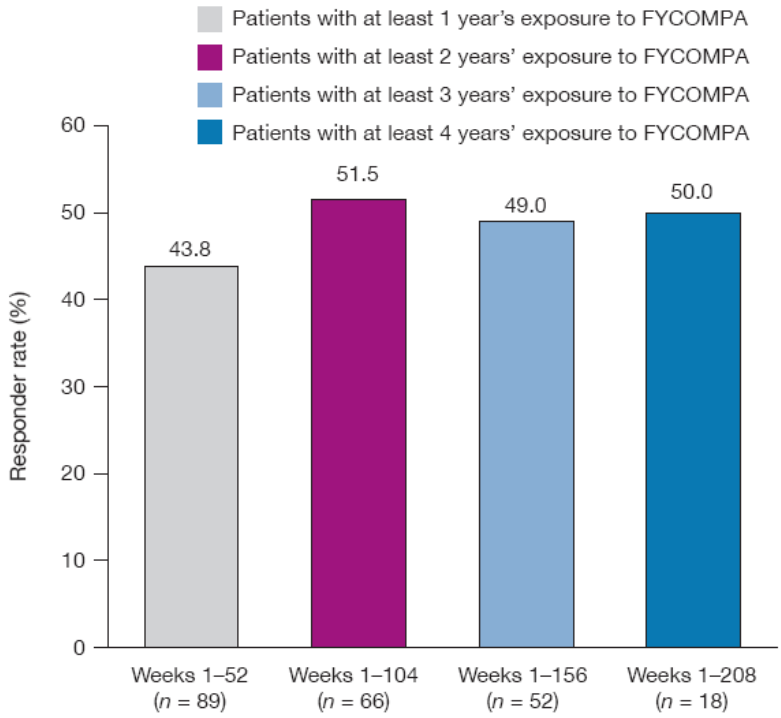


Figure III-15. Responder Rate - Study 207
(Adapted from Rektor et al, 2012[75])



Study Limitations: None specifically mentioned by the authors.

Table III-13. FYCOMPA Clinical Evidence Table

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
PHASE III STUDIES					
PIVOTAL DRUG STUDIES					
Evaluate efficacy and safety of FYCOMPA for adjunctive treatment in POS ***Study 304*** ***Study 1 in FYCOMPA prescribing information***[1] ***French et al, 2012***[21] *Full write-up in Section III*	Randomized, double-blind, placebo-controlled, multinational, multicenter, phase III study N = 388 patients with refractory POS ITT efficacy analysis (n = 387) Safety analysis (n = 388) 19-week study (6-week titration phase and 13-week maintenance phase)	Inclusion: ≥ 12 years of age; diagnosis of POS with or without secondary generalization; minimum of five partial seizures and no 25-day seizure-free periods during the 6-week baseline period; uncontrolled partial seizures with treatment of at least two different AEDs within the past 2 years; on a stable dose of one to three AEDs Exclusion: Clinically significant medical or psychiatric condition; suicide attempt ≤ 2 years; ECG abnormality; progressive degenerative CNS disease or CNS tumor; drug or alcohol dependence ≤ 2 years; multiple drug allergies or severe drug reaction to AEDs; pregnant, lactating, or not using contraception; felbamate use as a concomitant AED, if patient had been on it for ≥ 2 years, and on a stable dose for ≥ 49 days; vigabatrin ≤ 5 months and evidence of abnormal associated visual perimetry test; BZD use, unless patient was on a stable dose; history of nonepileptic or psychogenic seizures,	***FYCOMPA titrated in weekly 2 mg increments to 8 mg/day (n = 133) or 12 mg/day (n = 133)*** ***Placebo (n = 121)***	Primary: Median percent change in seizure frequency per 28 days Secondary: Responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency); percent change in frequency of complex partial seizures + secondary generalized seizures Exploratory: Percent of patients achieving 75% to 100% seizure reduction Safety assessments: AEs; vital signs; laboratory tests; physical/ neurologic examination; ECG; prior and concomitant/ discontinuation of medications; photosensitivity; withdrawal questionnaire	***Baseline Characteristics*** **Baseline Characteristics of Patients per Treatment Group** **Characteristic** / **FYCOMPA 8 mg (n = 133)** / **FYCOMPA 12 mg (n = 134)** / **Placebo (n = 121)** **Age, y; mean (SD) min–max**: 35.8 (14.2) 12 to 68 / 36.7 (14.6) 14 to 77 / 35.6 (14.7) 12 to 73 **Female, n (%)**: 68 (51.1) / 65 (48.5) / 67 (55.4) **Mean time since epilepsy diagnosis, y**: 23.56 / 23.79 / 24.13 **Seizure frequency/28 days during the prerandomization phase, mean n (min, max)**: 14.3 (2.4, 1030.8) / 12.0 (2.9, 1083.1) / 13.7 (3.3, 227.4) **Seizure type, n (%)** **Simple partial without motor signs**: 50 (37.6) / 45 (33.6) / 48 (39.7) **Simple partial with motor signs**: 47 (35.3) / 40 (29.9) / 41 (33.9) **Complex partial**: 116 (87.2) / 122 (91.0) / 107 (88.4) **Partial with secondary generalization**: 91 (68.4) / 101 (75.4) / 87 (71.9) **Concomitant AEDs at baseline, n (%)** **One**: 26 (19.5) / 19 (14.2) / 15 (12.4) **Two**: 70 (52.6) / 82 (61.2) / 64 (52.9) **Three**: 37 (27.8) / 33 (24.6) / 42 (34.7) AED = antiepileptic drug; max = maximum; min = minimum • The most common concomitant AEDs (≥ 10%) were carbamazepine, lamotrigine, levetiracetam, valproic acid, oxcarbazepine, topiramate, phenytoin, clonazepam, and zonisamide. • Use of a concomitant FYCOMPA-inducing AEDs was reported in 59.4% of the FYCOMPA 8 mg group, 63.4% of the FYCOMPA 12 mg group, and 67.8% of the placebo group. • Overall, 82.5% of patients completed the study. ***Results*** **Efficacy Endpoints for FYCOMPA vs Placebo** **FYCOMPA 8 mg** / **FYCOMPA 12 mg** / **Placebo** **Primary Endpoint** **n**: 133 / 133 / 121 **Median change in seizure frequency/28 days (%)**: –26.3 (p = 0.0261) / –34.5 (p = 0.0158) / –21.0 **Secondary Endpoints** **n**: 133 / 133 / 121 **Responder rate: % of patients**: 37.6 / 36.1 / 26.4

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr>
<td></td>
<td></td>
<td>seizure clusters (where individual seizures could not be identified), LGS, nonmotor simple partial seizures only, primary generalized seizures; history of status epilepticus ≤ 12 months prior; scheduled epilepsy surgery</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>achieving ≥ 50% reduction in seizure frequency</td><td>(p = 0.0760)</td><td>(p = 0.0914)</td><td></td></tr>
<tr><td>n</td><td>120</td><td>120</td><td>110</td></tr>
<tr><td>Median change in complex partial + secondary generalized seizures (%)</td><td>–33.0
(p = 0.0020)</td><td>–33.1
(p = 0.0081)</td><td>–17.9</td></tr>
<tr><td colspan="4">Exploratory Endpoint</td></tr>
<tr><td>n</td><td>133</td><td>133</td><td>121</td></tr>
<tr><td>Categorical seizure reduction at 75% to 100% (%)</td><td>18.8
(p = 0.001)</td><td>17.3
(p = 0.001)</td><td>5.0</td></tr>
</table>

Safety and Discontinuations
<table>
<tr><th colspan="4">TEAEs Occurring in ≥ 10% of Patients in Any Group</th></tr>
<tr><th rowspan="2">AE</th><th colspan="2">FYCOMPA</th><th rowspan="2">Placebo
(n = 121)
n (%)</th></tr>
<tr><th>8 mg
(n = 133)
n (%)</th><th>12 mg
(n = 134)
n (%)</th></tr>
<tr><td>Dizziness</td><td>50 (37.6)</td><td>51 (38.1)</td><td>12 (9.9)</td></tr>
<tr><td>Somnolence</td><td>24 (18.0)</td><td>23 (17.2)</td><td>16 (13.2)</td></tr>
<tr><td>Headache</td><td>20 (15.0)</td><td>18 (13.4)</td><td>16 (13.2)</td></tr>
<tr><td>Fall</td><td>13 (9.8)</td><td>17 (12.7)</td><td>8 (6.6)</td></tr>
<tr><td>Irritability</td><td>10 (7.5)</td><td>19 (14.2)</td><td>6 (5.0)</td></tr>
<tr><td>Ataxia</td><td>8 (6.0)</td><td>16 (11.9)</td><td>0 (0)</td></tr>
</table>
AE = adverse event; TEAE = treatment-emergent adverse event

FYCOMPA AEs that were more frequent (≥ 1%) vs placebo and led to treatment discontinuation were dizziness (3.0%), ataxia (2.6%), aggression (1.9%), vertigo (1.9%), dysarthria (1.1%), somnolence (1.1%), and blurred vision (1.1%).
Overall, AEs led to treatment discontinuation in 40 patients (10.3%).
Most TEAEs were mild to moderate (83.9% for FYCOMPA vs 95.0% for placebo).
Worsening seizures (> 50% increase vs baseline) occurred in 9% receiving FYCOMPA 8 mg, 9% receiving FYCOMPA 12 mg, and 14% receiving placebo.
SAEs occurred in eight patients receiving FYCOMPA 8 mg, nine patients receiving FYCOMPA 12 mg, and six patients receiving placebo.
Epilepsy-related SAEs (convulsion, grand mal convulsion, status epilepticus, etc) occurred in one patient receiving placebo (<1%), two patients receiving FYCOMPA 8 mg (1.5%), and four patients receiving FYCOMPA 12 mg (3.0%).

</td>
</tr>
<tr>
<td>Evaluate efficacy and safety of FYCOMPA for adjunctive treatment in POS</td>
<td>Randomized, double-blind, placebo-controlled, multinational, multicenter, phase III study</td>
<td><u>Inclusion:</u> ≥ 12 years of age; diagnosis of POS with or without secondary generalization; minimum of five partial seizures and no 25-day seizure-free period during the 6-week baseline period;</td>
<td>FYCOMPA titrated in weekly 2 mg increments to 8 mg/day (n = 129) or 12 mg/day (n = 121)</td>
<td><u>Primary:</u> Median percent change in seizure frequency per 28 days

<u>Secondary:</u> Responder rate (percent of patients</td>
<td>
Baseline Characteristics
<table>
<tr><th colspan="4">Baseline Characteristics of Patients per Treatment Group</th></tr>
<tr><th rowspan="2">Characteristic</th><th colspan="2">FYCOMPA</th><th rowspan="2">Placebo
(n = 136)</th></tr>
<tr><th>8 mg
(n = 129)</th><th>12 mg
(n = 121)</th></tr>
<tr><td>Mean age, y (SD)</td><td>36.7 (14.4)</td><td>35.5 (14.1)</td><td>34.4 (13.6)</td></tr>
<tr><td>Female, n (%)</td><td>64 (49.6)</td><td>71 (58.7)</td><td>65 (47.8)</td></tr>
</table>
</td>
</tr>
</table>

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
Study 305 ***Study 2 in FYCOMPA prescribing information***[1] ***French et al, 2012***[22] *Full write-up in Section III*	N = 386 patients with refractory POS ITT efficacy analysis (n = 386) Safety analysis (n = 386) 19-week study (6-week titration phase and 13-week maintenance phase)	uncontrolled partial seizures with treatment of at least two different AEDs within the past 2 years; on a stable dose of one to three AEDs Exclusion: Clinically significant medical or psychiatric condition; suicide attempt ≤ 2 years; ECG abnormality; progressive degenerative CNS disease or CNS tumor; drug or alcohol dependence ≤ 2 years; pregnant, lactating, or not using contraception; use of > one inducer AED; felbamate use as a concomitant AED, if patient had been on it for ≥ 2 years, and on a stable dose for ≥ 49 days; use of vagus nerve stimulator if implanted < 5 months prior; BZD use, unless patient was on a stable dose; history of nonepileptic or psychogenic seizures, seizure clusters (where individual seizures could not be identified), LGS, nonmotor simple partial seizures only, primary generalized seizures; history of status epilepticus ≤ 12 months prior; scheduled epilepsy surgery	***Placebo (n = 136)***	achieving ≥ 50% reduction in seizure frequency); percent change in frequency of complex partial seizures + secondary generalized seizures Exploratory: % of patients achieving 75% to 100% seizure reduction Safety assessments: AEs; vital signs; laboratory tests; physical/ neurologic examination; ECG; prior and concomitant/ discontinuation of medications; photosensitivity; withdrawal questionnaire	

Mean time since epilepsy diagnosis, y	22.5	21.3	22.0
Seizure frequency/28 days during the prerandomization phase, mean n (min, max)	13.0 (3.3, 652.2)	13.7 (1.4, 598.4)	11.8 (3.4, 358.4)
Seizure type, n (%)			
Simple partial without motor signs	49 (38.0)	36 (29.8)	48 (35.3)
Simple partial with motor signs	39 (30.2)	38 (31.4)	30 (22.1)
Complex partial	114 (88.4)	100 (82.6)	114 (83.8)
Partial with secondary generalization	90 (69.8)	77 (63.6)	95 (69.9)
Concomitant AEDs at baseline, n (%)			
One	16 (12.4)	9 (7.4)	17 (12.5)
Two	68 (52.7)	63 (52.1)	64 (47.1)
Three	45 (34.9)	49 (40.5)	55 (40.4)

AED = antiepileptic drug; max = maximum; min = minimum

- The most common concomitant AEDs (≥ 10%) were levetiracetam, carbamazepine, lamotrigine, valproic acid, oxcarbazepine, topiramate, and clobazam.
- A total of 60.6% of the patients in the study were taking a FYCOMPA-inducing AED as a concomitant medication.
- Overall, 83.2% of patients completed the study.

Efficacy

Efficacy Endpoints for FYCOMPA vs Placebo			
	FYCOMPA		**Placebo**
	8 mg	**12 mg**	
Primary Endpoint			
n	129	121	136
Median change in seizure frequency/28 days (%)	–30.5 (p = 0.0008)	–17.6 (p = 0.0105)	–9.7
Secondary Endpoints			
n	129	121	136
Responder rate: % of patients achieving ≥ 50% reduction in seizure frequency	33.3 (p = 0.0018)	33.9 (p = 0.0006)	14.7
n	119	113	126
Median change in complex partial + secondary generalized seizures (%)	–32.7 (p < 0.001)	–21.9 (p = 0.005)	–8.1
Exploratory Endpoints			
n	129	121	136
Categorical seizure reduction at 75% to 100% (%)	15.5 (p = 0.0112)	16.5 (p = 0.0058)	4.4

Safety and Discontinuations

TEAEs Occurring in ≥ 10% of Patients in Any Group			
AE	**FYCOMPA**		**Placebo (n = 136)**
	8 mg	**12 mg**	

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><th></th><th>(n = 129)
n (%)</th><th>(n = 121)
n (%)</th><th>n (%)</th></tr>
<tr><td>Dizziness</td><td>42 (32.6)</td><td>58 (47.9)</td><td>10 (7.4)</td></tr>
<tr><td>Somnolence</td><td>16 (12.4)</td><td>22 (18.2)</td><td>4 (2.9)</td></tr>
<tr><td>Fatigue</td><td>17 (13.2)</td><td>20 (16.5)</td><td>11 (8.1)</td></tr>
<tr><td>Headache</td><td>11 (8.5)</td><td>16 (13.2)</td><td>18 (13.2)</td></tr>
</table>
AE = adverse event; TEAE = treatment-emergent adverse event

• The majority of patients experienced TEAEs that were mild to moderate (76.4% for FYCOMPA groups vs 61.7% for placebo).
• Worsening seizures (> 50% increase in seizures compared to baseline) occurred in 8% of patients receiving FYCOMPA 8 mg and 9% of patients receiving FYCOMPA 12 mg vs 10% of the placebo group.
• SAEs occurred in 10 patients in the FYCOMPA 8 mg group, 12 patients in the 12 mg FYCOMPA group, and 7 patients in the placebo group.
• Overall, AEs led to treatment discontinuation in 38 patients (9.8%).
• The most common AEs leading to discontinuation were dizziness (3.6%), somnolence (2.0%), and convulsion (1.2%).
</td></tr>
<tr><td>Evaluate efficacy and safety of FYCOMPA for adjunctive treatment in POS

Study 306

Study 3 in FYCOMPA prescribing information[1]

Krauss et al, 2012[23]

Full write-up in Section III</td><td>Randomized, double-blind, placebo-controlled, multinational, multicenter, phase III study

N = 706 patients with refractory POS

ITT efficacy analysis (n = 705)

Safety analysis (n = 706)

19-week study (6-week titration phase and 13-week maintenance phase)</td><td><u>Inclusion:</u> ≥ 12 years of age (except for a subset in six countries who were all ≥ 18 years of age); diagnosis of partial seizures with or without secondary generalization; minimum of five partial seizures and no 25-day seizure-free period during the 6-week baseline period; uncontrolled partial seizures with treatment of at least two different AEDs within the past 2 years; on a stable dose of one to three AEDs

<u>Exclusion:</u> Clinically significant medical or psychiatric condition; suicide attempt ≤ 2 years; ECG abnormality; progressive degenerative CNS disease or CNS tumor; drug or alcohol</td><td>FYCOMPA titrated weekly by 2 mg/day to 2 mg/day (n = 180), 4 mg/day (n = 172), or 8 mg/day (n = 169)

Placebo (n = 184)</td><td><u>Primary:</u> Median percent change in seizure frequency per 28 days

<u>Secondary:</u> Responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency); percent change in frequency of complex partial seizures + secondary generalized seizures

<u>Exploratory</u>: Percent of patients achieving 75% to 100% seizure reduction

<u>Safety</u></td><td>Baseline Characteristics
<table>
<tr><th colspan="5">Baseline Characteristics of Patients per Treatment Group</th></tr>
<tr><th rowspan="2">Characteristic</th><th colspan="3">FYCOMPA</th><th rowspan="2">Placebo (n = 185)</th></tr>
<tr><th>2 mg (n = 180)</th><th>4 mg (n = 172)</th><th>8 mg (n = 169)</th></tr>
<tr><td>Mean age, y (SD)</td><td>33.8 (13.6)</td><td>33.6 (12.2)</td><td>34.6 (12.8)</td><td>33.4 (12.6)</td></tr>
<tr><td>Female, n (%)</td><td>95 (52.8)</td><td>84 (48.8)</td><td>92 (54.4)</td><td>90 (48.6)</td></tr>
<tr><td>Mean time since epilepsy diagnosis, y</td><td>19.4</td><td>19.7</td><td>19.9</td><td>17.5</td></tr>
<tr><td>Seizure frequency/28 days during the prerandomization phase, mean n (min, max)</td><td>10.1
(3.2, 429.6)</td><td>10.0
(2.9, 4503.9)</td><td>10.9
(3.4, 723.2)</td><td>9.3
(3.3, 569.1)</td></tr>
<tr><td>Seizure type, n (%)
Simple partial without motor signs
Simple partial with motor signs
Complex partial
Partial with secondary generalization</td><td>
53 (29.4)
53 (29.4)
153 (85.0)
115 (63.9)</td><td>
48 (27.9)
54 (31.4)
147 (85.5)
119 (69.2)</td><td>
57 (33.7)
51 (30.2)
138 (81.7)
117 (69.2)</td><td>
52 (28.1)
55 (29.7)
155 (83.8)
136 (73.5)</td></tr>
<tr><td>Concomitant AEDs at baseline, n (%)
One
Two
Three</td><td>
30 (16.7)
80 (44.4)
70 (38.9)</td><td>
19 (11.0)
88 (51.2)
65 (37.8)</td><td>
27 (16.0)
82 (48.5)
60 (35.5)</td><td>
28 (15.1)
90 (48.6)
67 (36.2)</td></tr>
</table>
AED = antiepileptic drug; max = maximum; min = minimum

• The most common concomitant AEDs (≥ 10%) were valproic acid, lamotrigine, carbamazepine, levetiracetam, topiramate, oxcarbazepine, and clobazam.</td></tr>
</table>

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
		dependence ≤ 2 years; pregnant, lactating, or not using contraception; use of other investigational drugs ≤ 3 weeks; use of FYCOMPA in another study; felbamate use as a concomitant AED, if patient had been on it for ≥ 2 years, and on a stable dose for ≥ 49 days; use of vigabatrin ≤ 5 months and evidence of abnormal associated visual perimetry test; use of rescue BZDs ≥ 2 times in past month; history of nonepileptic or psychogenic seizures, seizure clusters (where individual seizures could not be identified), LGS, nonmotor simple partial seizures only, primary generalized seizures; history of status epilepticus ≤ 12 months prior; scheduled epilepsy surgery		assessments: AEs; vital signs; laboratory tests; physical/ neurologic examination; ECG; prior and concomitant/ discontinuation of medications; photosensitivity; withdrawal questionnaire	• A total of 56.3% of the patients in the study were taking a FYCOMPA-inducing AED as a concomitant medication. • Overall, 88.2% of patients completed the study. ***Efficacy*** **Efficacy Endpoints for FYCOMPA vs Placebo** **Primary Endpoint** **n**: 180, 172, 169, 184 **Median change in seizure frequency/28 days (%)**: –13.6 (p = NS), –23.3 (p = 0.003), –30.8 (p < 0.001), –10.7 **Secondary Endpoints** **n**: 180, 172, 169, 184 **Responder rate: % of patients achieving ≥ 50% reduction in seizure frequency**: 20.6 (p = NS), 28.5 (p = 0.013), 34.9 (p < 0.001), 17.9 **n**: 167, 157, 154, 169 **Median change in complex partial + secondary generalized seizures (%)**: –20.5 (p = 0.6506), –31.2 (p = 0.007), –38.7 (p < 0.001), –17.6 **Exploratory Endpoints** **n**: 180, 172, 169, 184 **Categorical seizure reduction at 75% to 100% (%)**: 10.0 (p = 0.6714), 12.2 (p = 0.0744), 17.8 (p = 0.0530), 8.2 ***Safety and Discontinuations*** **TEAEs Occurring in ≥ 5% of Patients in Any Group** **AE** / **FYCOMPA 2 mg (n = 180) n (%)** / **FYCOMPA 4 mg (n = 172) n (%)** / **FYCOMPA 8 mg (n =169) n (%)** / **Placebo (n = 185) n (%)** **Dizziness**: 18 (10.0), 28 (16.3), 45 (26.6), 18 (9.7) **Somnolence**: 22 (12.2), 16 (9.3), 27 (16.0), 12 (6.5) **Headache**: 16 (8.9), 19 (11.0), 18 (10.7), 16 (8.6) **Fatigue**: 8 (4.4), 13 (7.6), 9 (5.3), 5 (2.7) **URI**: 11 (6.1), 6 (3.5), 3 (1.8), 5 (2.7) **Nasopharyngitis**: 7 (3.9), 9 (5.2), 3 (1.8), 3 (1.6) **Gait disturbance**: 1 (< 1), 2 (1.2), 9 (5.3), 2 (1.1) AE = adverse event; TEAE = treatment-emergent adverse event; URI = upper respiratory tract infection • TEAEs were reported in 61.7% of patients on FYCOMPA 2 mg/day, 64.5% on FYCOMPA 4 mg/day, 71.6% on FYCOMPA 8 mg/day, and 54.6% on placebo, with most reported as mild to moderate.

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>• Worsening seizures, defined as a > 50% increase compared to baseline, occurred in 11% of patients on FYCOMPA 2 mg/day, 8% on FYCOMPA 4 mg/day, 8% on FYCOMPA 8 mg/day, and 15% on placebo.
• SAEs occurred in six patients in each of the FYCOMPA groups and nine patients in the placebo group.
• Overall, AEs led to discontinuation in 36 patients (5.1%), with the most common being dizziness, convulsion, fatigue, and vertigo.</td></tr>
<tr><td colspan="6">PHASE III OPEN-LABEL EXTENSION</td></tr>
<tr><td>Evaluate long-term safety and efficacy of FYCOMPA for adjunctive treatment in POS

Study 307

Krauss et al, 2012[25]

Full write-up in Section III</td><td>Open-label extension study

N = 1218 patients with refractory POS

Prior placebo (n = 380)

Prior FYCOMPA (n = 838)
(2 mg [n = 147];
4 mg [n = 154];
8 mg [n = 356];
12 mg [n = 181])

Interim data cutoff date: December 1, 2010

ITT efficacy analysis (n = 1207)

Safety analysis (n = 1186)

276-week study (16-week blinded conversion phase, 256-week maintenance phase, and 4-week follow-up</td><td><u>Inclusion:</u> ≥ 12 years of age with refractory partial seizures that completed the double-blind phase of studies 304, 305, 306

<u>Exclusion:</u> See Studies 304, 305, 306</td><td>FYCOMPA QHS with food and titrated in 2 mg increments every 2 weeks to MTD for patients on ≤ 12 mg/day or placebo during double-blind phase

Patients taking 12 mg/day in double-blind phase continued on their treatment in the open-label phase

Dose adjustment to individual's MTD was permitted based on tolerability.

Change in dose, discontinuation, or change of concomitant AEDs was allowed per investigator.

MTD: ≤ 12 mg/day</td><td>Safety and tolerability; median percent change in seizure frequency per 28 days during treatment relative to pre-FYCOMPA baseline; responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency) during treatment per 28 days relative to pre-FYCOMPA baseline</td><td>Baseline Characteristics
• Approximately half of the patients (49.6%) were female, and the mean age was 34.3 years.
• Patients intolerant of FYCOMPA 2 mg were discontinued from the study.
• The mean number of AEDs at baseline was 2.2, and 94.9% remained on the same number of concomitant AEDs at interim analysis or study discontinuation.
• The most common concomitant AEDs (≥ 10%) were carbamazepine, valproic acid, lamotrigine, levetiracetam, topiramate, and oxcarbazepine.
• Most patients (91.8%) received > 16 weeks of FYCOMPA treatment, 48.9% received > 52 weeks, and 21.1% received > 76 weeks.
• At the interim data cutoff, 840 patients (70.8%) in the safety analysis remained on FYCOMPA treatment, and 346 (29.2%) discontinued treatment.

Safety and Discontinuations
<table>
<tr><th colspan="5">Incidence of Treatment-Related AEs (As Reported in Studies 304, 305, 306, and 307)</th></tr>
<tr><th></th><th>4 mg/day (n = 15) (%)</th><th>6–8 mg/day (n = 86) (%)</th><th>10–12 mg/day (n = 1084) (%)</th><th>Total (n = 1186) (%)</th></tr>
<tr><td>Any AEs</td><td>86.7</td><td>96.5</td><td>86.7</td><td>87.4</td></tr>
<tr><td>Severe AEs</td><td>13.3</td><td>18.6</td><td>14.1</td><td>14.4</td></tr>
<tr><td>Discontinuation due to AEs</td><td>40.0</td><td>26.7</td><td>11.7</td><td>13.2</td></tr>
<tr><td>Any serious AEs</td><td>13.3</td><td>12.8</td><td>13.3</td><td>13.2</td></tr>
<tr><td colspan="5">Most Common AEs (≥ 5%)</td></tr>
<tr><td>Dizziness</td><td>60.0</td><td>59.3</td><td>42.5</td><td>43.9</td></tr>
<tr><td>Somnolence</td><td>20.0</td><td>26.7</td><td>19.7</td><td>20.2</td></tr>
<tr><td>Headache</td><td>13.3</td><td>27.9</td><td>15.9</td><td>16.7</td></tr>
<tr><td>Fatigue</td><td>13.3</td><td>15.1</td><td>11.8</td><td>12.1</td></tr>
<tr><td>Irritability</td><td>6.7</td><td>9.3</td><td>9.9</td><td>9.8</td></tr>
<tr><td>Nasopharyngitis</td><td>0</td><td>2.3</td><td>7.8</td><td>7.3</td></tr>
<tr><td>Fall</td><td>6.7</td><td>5.8</td><td>6.9</td><td>6.8</td></tr>
<tr><td>Nausea</td><td>13.3</td><td>8.1</td><td>6.6</td><td>6.8</td></tr>
<tr><td>Weight increase</td><td>0</td><td>3.5</td><td>7.2</td><td>6.8</td></tr>
<tr><td>Ataxia</td><td>0</td><td>11.6</td><td>5.8</td><td>6.2</td></tr>
<tr><td>Gait disturbance</td><td>0</td><td>8.1</td><td>5.7</td><td>5.8</td></tr>
<tr><td>Convulsion</td><td>0</td><td>3.5</td><td>5.7</td><td>5.5</td></tr>
<tr><td>Vertigo</td><td>6.7</td><td>8.1</td><td>5.3</td><td>5.5</td></tr>
<tr><td>Balance disorder</td><td>0</td><td>5.8</td><td>5.4</td><td>5.4</td></tr>
</table></td></tr>
</table>

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	phase)				

Vomiting	13.3	0	5.6	5.3
URI	6.7	5.8	5.2	5.2

AE = adverse event; URI = upper respiratory tract infection

- The primary reasons for discontinuation were AEs (10.5%), subject choice (9.0%), and inadequate efficacy (7.4%).
- AEs leading to dose adjustment or interruption in ≥ 2% of patients were dizziness (20.7%), somnolence (7.3%), ataxia (3.3%), fatigue (2.9%), headache (2.3%), and gait disturbance (2.0%).
- The number of concomitant AEDs decreased in 1.5% of patients and increased in 3.6%.
- AEs were reported in 87.4% of patients, with 73.0% rated as mild or moderate.
- AEs leading to discontinuation in ≥ 1% of patients included dizziness (3.0%), irritability (1.2%), and aggression (1.1%).
- SAEs occurred in 13.2% (157) patients, with SAEs related to seizures occurring in > 1% of the patients and reported by 2% (24) patients including increased seizure frequency (n = 7/24), breakthrough seizures (n = 3/24), exacerbation of seizures (n = 4/24), seizure cluster (n = 2/24), recurrent seizures (n = 4/24), convulsion (n = 3/24), and uncontrolled or intractable seizures (n = 2/24).
- Nine (< 1%) patients reported status epilepticus as an SAE.
- Other SAEs reported included aggression (n = 10, < 1%), psychotic disorder (n = 6, < 1%), and suicidal ideation (n = 6, < 1%).
- No deaths related to study treatment occurred during this study.

Efficacy

- Seizure frequency per 28 days decreased over the first 26 weeks and was maintained for the study duration.
- At the end of the blinded 16-week conversion period, there was no difference in the median percent change in seizure frequency between patients previously randomized to placebo (–42.4%) or FYCOMPA (–41.5%).
- At the end of the blinded 16-week conversion period, there was no difference in the responder rate between patients previously randomized to placebo (44.2%) or FYCOMPA (43.3%).

Efficacy Endpoints per Follow-Up Time Period		
	Median Change in Seizure Frequency (%)	**Overall Responder Rate (%)**
Weeks 1–13 (n = 1207)	–29.1	31.1
Weeks 14–26 (n = 1114)	–39.2	41.4
Weeks 27–39 (n = 979)	–44.0	45.3
Weeks 40–52 (n = 731)	–46.5	46.9
Weeks 53–65 (n = 495)	–51.2	50.7
Weeks 66–78 (n = 323)	–52.3	51.1
Weeks 79–91 (n = 176)	–51.2	51.7
Weeks 92–104 (n = 59)	–58.1	62.7

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>A total of 16.4% of patients were seizure free for the past 3 months, 8.9% for 6 months, 7.6% for 9 months, and 7.1% for 12 months.</td></tr>
<tr><td>Interim analysis of efficacy and safety of adjunctive FYCOMPA in the adolescent population with refractory POS in the open-label extension

Study 307

Conry et al, 2012[76]</td><td>Open-label extension study

N = 124 adolescents with refractory POS

ITT efficacy analysis (n = 122)

Safety analysis (n = 121)

Interim data cutoff date: December 1, 2010

276-week study (16-week blinded conversion phase, 256-week maintenance phase, and 4-week follow-up phase)</td><td><u>Inclusion:</u> Adolescents ages 12 to 17 years with refractory POS that completed studies 304, 305, or 306

<u>Exclusion:</u> See Studies 304, 305, and 306</td><td>FYCOMPA titrated to individualized MTD (≤ 12 mg/day)</td><td>Safety and tolerability; median percent change in seizure frequency per 28 days; responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency)</td><td>Baseline Characteristics
<table>
<tr><th colspan="2">Baseline Characteristics of Patients in the Open-Label Extension Study</th></tr>
<tr><th>Parameter</th><th>Total Adolescent Population (N = 121)</th></tr>
<tr><td>Median age, y (range)</td><td>15.0 (12–17)</td></tr>
<tr><td>Age group, n (%)</td><td></td></tr>
<tr><td>12–13 years</td><td>32 (26.4)</td></tr>
<tr><td>14–15 years</td><td>38 (31.4)</td></tr>
<tr><td>16–17 years</td><td>51 (42.1)</td></tr>
<tr><td>Male, n (%)</td><td>71 (58.7)</td></tr>
<tr><td>Seizure type, n (%)</td><td></td></tr>
<tr><td>Simple partial without motor signs</td><td>27 (22.3)</td></tr>
<tr><td>Simple partial with motor signs</td><td>55 (45.5)</td></tr>
<tr><td>Complex partial</td><td>108 (89.3)</td></tr>
<tr><td>Partial with secondary generalization</td><td>78 (64.5)</td></tr>
<tr><td>Number of concomitant AEDs, n (%)</td><td></td></tr>
<tr><td>One</td><td>22 (18.2)</td></tr>
<tr><td>Two</td><td>54 (44.6)</td></tr>
<tr><td>Three</td><td>45 (37.2)</td></tr>
</table>
AED = antiepileptic drug

A total of 92.6% of the patients took > 8 to 12 mg/day of FYCOMPA.
Safety and Discontinuations
<table>
<tr><th colspan="2">Overall Incidence of TEAEs During FYCOMPA Exposure</th></tr>
<tr><th>Category, n (%)</th><th>Total Adolescent Population (N = 121)</th></tr>
<tr><td>TEAEs</td><td>107 (88.4)</td></tr>
<tr><td>Treatment-related TEAEs</td><td>94 (77.7)</td></tr>
<tr><td>Severe TEAEs</td><td>19 (15.7)</td></tr>
<tr><td>Serious TEAEs</td><td>17 (14.0)</td></tr>
<tr><td>Deaths</td><td>0</td></tr>
<tr><td>Required or prolonged hospitalization</td><td>17 (14.0)</td></tr>
</table>
TEAE = treatment-emergent adverse event

Overall, 67.8% of adolescents remained in the study as of the cutoff date
The most common concomitant AEDs were valproic acid (38%), topiramate (30%), carbamazepine (27%), levetiracetam (27%), lamotrigine (22%), and oxcarbazepine (22%).
The most common treatment related AEs (incidence ≥ 10%) were dizziness, somnolence, nasopharyngitis, aggression, headache, convulsion, and pyrexia.
Nasopharyngitis, aggression, convulsion, and pyrexia occurred more often in adolescents than in the overall population.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>

Overall, 14.9% of patients discontinued the study or study drug due to TEAEs.
AEs leading to discontinuation in > 1% of patients included dizziness, somnolence, and aggression (all n = 3) and convulsion and anger (each n = 2).
A weight increase > 7% occurred in 48.8% of adolescents, with the median change in weight being 3.0 kg at the end of treatment.
Weight gain was considered a TEAE in 1.7% of adolescents vs 6.8% of the overall population.

Efficacy

Data showed improvements in seizure control after initiation of FYCOMPA (for patients taking placebo in the core studies) and sustained improvement for patients who received FYCOMPA in the double-blind study.
In this interim analysis of an ongoing study, the decrease in seizure frequency was maintained up to 52 weeks.

<table>
<tr><th colspan="6">Efficacy Endpoints per Follow-Up Time Period</th></tr>
<tr><th></th><th>Blinded Conversion (n = 121)</th><th>1–13 weeks (n = 83)</th><th>14–26 weeks (n = 64)</th><th>27–39 weeks (n = 52)</th><th>40–52 weeks (n = 33)</th></tr>
<tr><td>Median change in seizure frequency/ 28 days (%)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Prior Placebo</td><td>–35.8</td><td>–45.9</td><td>–30.7</td><td>–56.9</td><td>–35.1</td></tr>
<tr><td>Prior FYCOMPA</td><td>–40.9</td><td>–43.9</td><td>–52.0</td><td>–61.1</td><td>–51.3</td></tr>
<tr><td>% of patients achieving ≥ 50% reduction in seizures</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Prior Placebo</td><td>35.3</td><td>47.1</td><td>27.3</td><td>60.0</td><td>40.0</td></tr>
<tr><td>Prior FYCOMPA</td><td>41.4</td><td>40.9</td><td>50.9</td><td>54.8</td><td>50.0</td></tr>
</table>

Through 52 weeks of open-label maintenance, 27%–60% of adolescents were responders.

</td></tr>
<tr><td colspan="6">PHASE III POOLED ANALYSIS – Efficacy and Safety</td></tr>
<tr><td>Post hoc analysis of pooled efficacy and safety data

Steinhoff et al, 2013[24]</td><td>Post hoc analysis of pooled data of three randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306)

N = 1480 patients with refractory POS</td><td>See Studies 304, 305, and 306 for detailed inclusion and exclusion criteria.</td><td>FYCOMPA 2 mg (n = 180)

FYCOMPA 4 mg (n = 172)

FYCOMPA 8 mg (n = 431)

FYCOMPA 12 mg (n = 255; 254 for</td><td>Median percent change in seizure frequency per 28 days; 50% and 75% responder rates; seizure-free rate; safety</td><td>
Baseline Characteristics

No significant differences in demographics were noted between treatment groups.
The most common concomitant AEDs at baseline were carbamazepine (33.2%), valproic acid (32.3%), lamotrigine (30.9%), and levetiracetam (29.4%).
The median prerandomization frequency of all partial seizures per 28 days was similar in the FYCOMPA groups (10.0–13.0) and the placebo group (11.1).

<table>
<tr><th colspan="6">Baseline Characteristics of Patients per Treatment Group</th></tr>
<tr><th></th><th colspan="4">FYCOMPA</th><th rowspan="2">Placebo (n = 442)</th></tr>
<tr><th></th><th>2 mg (n = 180)</th><th>4 mg (n = 172)</th><th>8 mg (n = 431)</th><th>12 mg (n = 255)</th></tr>
<tr><td>Completers, n (%)</td><td>154 (85.6)</td><td>158 (91.9)</td><td>367 (85.2)</td><td>193 (75.7)</td><td>392 (88.7)</td></tr>
</table>
</td></tr>
</table>

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	ITT efficacy analysis (n = 1478) Safety analysis (n = 1480)		***ITT analysis)*** ***Placebo (n = 442; 441 for ITT analysis)***		

Seizure type, n (%)					
Simple partial seizures with/without motor signs	85 (47.2)	80 (46.5)	228 (52.9)	126 (49.4)	210 (47.5)
Complex partial	153 (85.0)	147 (85.5)	368 (85.4)	222 (87.1)	376 (85.1)
Secondarily generalized	115 (63.9)	119 (69.2)	298 (69.1)	178 (69.8)	318 (71.9)
Number of concomitant AEDs, n (%)					
One	30 (16.7)	19 (11.0)	69 (16.0)	28 (11.0)	60 (13.6)
Two	80 (44.4)	88 (51.2)	220 (51.0)	145 (56.9)	218 (49.3)
Three	70 (38.9)	65 (37.8)	141 (32.7)	82 (32.2)	164 (37.1)

AED = antiepileptic drug

Results

- For all partial seizures, the median percent change in frequency of seizures and the 50% and 75% responder rates were greater with all FYCOMPA doses vs placebo.
- More patients treated with FYCOMPA achieved a 100% reduction in seizure frequency vs patients receiving placebo.
- For complex partial + secondary generalized seizures, the median percent change in frequency of seizures and the 50% responder rate were greater with all FYCOMPA doses vs placebo.
- For secondary generalized seizures, the median percent change in frequency of seizures and the 50% responder rate were greater with all FYCOMPA doses vs placebo.

Efficacy Endpoints – FYCOMPA vs Placebo

Endpoint	FYCOMPA				Placebo
	2 mg	4 mg	8 mg	12 mg	
Median change in seizure frequency/28 days (double-blind vs baseline) (%)					
All partial seizures	–13.6	–23.3*	–28.8**	–27.2**	–12.8
Complex partial + secondary generalization	–20.5	–31.2**	–35.6**	–28.6**	–13.9
Secondary generalized	–28.0	–48.6*	–62.9**	–53.3**	–19.4
50% responder rate (%)					
All partial seizures	20.6	28.5†	35.3**	35.0**	19.3
Complex partial + secondary generalization	26.9	36.3*	39.4**	38.2**	23.2
Secondarily generalized	44.1	49.3	60.5**	53.7*	37.0
75% responder rate (%)					
All partial seizures	10.0	12.2†	17.4**	16.9**	6.1
Seizure free (%)	1.9	4.4†	3.5†	4.1†	1.0

*p < 0.01 vs placebo; **p < 0.001 vs placebo; †p < 0.05 vs placebo

- A subanalysis examined the impact of patients receiving one or more of the four most commonly administered AEDs (carbamazepine, lamotrigine, valproic acid, levetiracetam) along with FYCOMPA. FYCOMPA vs placebo consistently demonstrated greater reductions in seizure frequency and 50% responder rates for all partial seizures,

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments

complex partial + secondary generalized seizures, and secondarily generalized seizures.

Efficacy of FYCOMPA Relative to Concomitant AEDs vs Placebo					
	FYCOMPA				Placebo (%)
	2 mg (%)	4 mg (%)	8 mg (%)	12 mg (%)	
Median Change in Seizure Frequency per 28 Days					
All Partial Seizures					
Carbamazepine	–5.9	–19.7	–25.4	–20.3	–12.7
Lamotrigine	–21.3	–20.6	–29.6	–31.2	–11.4
Valproic acid	–16.0	–26.2	–27.7	–37.2	–17.2
Levetiracetam	–10.2	–19.0	–25.7	–34.7	–18.2
Complex Partial + Secondary Generalized Seizures					
Carbamazepine	–7.6	–28.7	–25.5	–20.3	–13.9
Lamotrigine	–20.5	–40.3	–38.8	–31.8	–11.5
Valproic acid	–21.5	–37.5	–36.3	–38.3	–17.2
Levetiracetam	–11.1	–23.4	–36.8	–39.2	–19.5
Secondarily Generalized Seizures					
Carbamazepine	–30.1	–33.2	–53.8	–52.8	–12.7
Lamotrigine	–65.4	–60.5	–61.1	–75.5	–22.9
Valproic acid	–19.7	–48.3	–65.4	–75.4	–34.4
Levetiracetam	–26.9	–63.6	–61.1	–70.7	–19.1
50% Responder Rate					
All Partial Seizures					
Carbamazepine	13.8	19.6	29.7	31.3	23.1
Lamotrigine	21.4	32.4	35.6	30.6	13.6
Valproic acid	18.8	34.7	38.3	36.5	20.0
Levetiracetam	14.6	20.0	35.9	43.0	20.0
Complex Partial + Secondary Generalized Seizures					
Carbamazepine	17.9	25.5	31.4	33.7	26.7
Lamotrigine	28.3	42.6	42.1	32.7	16.1
Valproic acid	28.2	43.5	40.5	48.3	24.4
Levetiracetam	25.0	28.6	39.2	45.6	26.7
Secondarily Generalized Seizures					
Carbamazepine	38.1	35.0	51.2	51.5	37.3
Lamotrigine	54.5	63.0	55.6	68.2	35.6
Valproic acid	27.6	43.3	67.4	62.5	42.2
Levetiracetam	45.0	66.7	61.0	66.7	39.5

AED = antiepileptic drug

Safety and Discontinuations

- TEAEs were reported by 77.0% of patients receiving FYCOMPA and 66.5% of patients receiving placebo, with the majority being mild to moderate in severity.
- Whereas no deaths were reported, severe TEAEs were reported by 8.9% of patients receiving FYCOMPA and 5.4% of patients receiving placebo.
- Serious psychiatric TEAEs occurred in 1.2% of patients receiving FYCOMPA and 0.9% of patients receiving placebo.

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>

TEAEs led to discontinuation in 9.5% of patients receiving FYCOMPA and 4.8% of patients receiving placebo, with the most common TEAEs leading to discontinuation being dizziness, convulsion, and somnolence.
No clinically relevant changes in laboratory values, ECG results, or vital signs were noted. Weight increase > 7% was reported in 14.6% of patients receiving FYCOMPA and 7.1% of patients receiving placebo.

<table>
<tr><th colspan="6">TEAEs Occurring in ≥ 10% of Patients in Any Treatment Group</th></tr>
<tr><th rowspan="2">AE</th><th colspan="4">FYCOMPA</th><th rowspan="2">Placebo (n = 442) n (%)</th></tr>
<tr><th>2 mg (n = 180) n (%)</th><th>4 mg (n = 172) n (%)</th><th>8 mg (n = 431) n (%)</th><th>12 mg (n = 255) n (%)</th></tr>
<tr><td>Dizziness</td><td>18 (10.0)</td><td>28 (16.3)</td><td>137 (31.8)</td><td>109 (42.7)</td><td>40 (9.0)</td></tr>
<tr><td>Somnolence</td><td>22 (12.2)</td><td>16 (9.3)</td><td>67 (15.5)</td><td>45 (17.6)</td><td>32 (7.2)</td></tr>
<tr><td>Headache</td><td>16 (8.9)</td><td>19 (11.0)</td><td>49 (11.4)</td><td>34 (13.3)</td><td>50 (11.3)</td></tr>
<tr><td>Fatigue</td><td>8 (4.4)</td><td>13 (7.6)</td><td>36 (8.4)</td><td>31 (12.2)</td><td>21 (4.8)</td></tr>
<tr><td>Irritability</td><td>7 (3.9)</td><td>7 (4.1)</td><td>29 (6.7)</td><td>30 (11.8)</td><td>13 (2.9)</td></tr>
<tr><td>Fall</td><td>2 (1.1)</td><td>3 (1.7)</td><td>22 (5.1)</td><td>26 (10.2)</td><td>15 (3.4)</td></tr>
</table>
AE = adverse event; TEAE = treatment-emergent adverse event
</td></tr>
<tr><td>Efficacy of FYCOMPA in secondarily generalized seizures in patients with refractory POS

Ko and Ramsay, 2013[26]</td><td>Pooled analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306) and one open-label extension study (307)

N = 1480 patients with refractory POS

ITT efficacy analysis (n = 1478)

Safety analysis (n = 1480)

Study 304, 305, 306:
6-week baseline phase, 19-week study (6-week</td><td><u>Inclusion:</u> ≥ 12 years of age; treatment-resistant partial seizures despite treatment with one to three AEDs

<u>See Studies 304, 305, 306, and 307 above for detailed inclusion and exclusion criteria.</u></td><td>Study 304, 305: FYCOMPA titrated in weekly 2 mg increments to 8 mg/day or 12 mg/day

Placebo

Study 306: FYCOMPA titrated in weekly 2 mg increments to 2 mg/day, 4 mg/day, or 8 mg/day

Placebo

Study 307: FYCOMPA QHS with food and titrated in 2 mg increments every 2 weeks to MTD for patients on ≤ 12 mg/day</td><td><u>Exploratory Efficacy Endpoints:</u>
Median percent change in seizure frequency per 28 days; responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency)

<u>Post hoc Analysis:</u>
75% and 100% response rates</td><td>
Baseline Characteristics

Please see Studies 304, 305, 306, and Steinhoff et al[24] for additional information regarding baseline characteristics.
Secondarily generalized seizures were reported during baseline in 37.8% of patients receiving FYCOMPA 2 mg, 41.3% receiving FYCOMPA 4 mg, 36.4% receiving FYCOMPA 8 mg, and 37.3% receiving FYCOMPA 12 mg.
Patients were on a mean 2.2 AEDs at baseline.

Efficacy
<table>
<tr><th colspan="6">Efficacy Endpoints for Secondary Generalized Seizures by Randomized FYCOMPA Dose in the Pooled Phase III Analysis Set</th></tr>
<tr><th rowspan="2"></th><th colspan="4">FYCOMPA</th><th rowspan="2">Placebo (n = 173)</th></tr>
<tr><th>2 mg (n = 68)</th><th>4 mg (n = 71)</th><th>8 mg (n = 157)</th><th>12 mg (n = 95)</th></tr>
<tr><td>75% responder rate (maintenance vs baseline) (%)</td><td>32.4</td><td>31.0</td><td>46.5*</td><td>38.9**</td><td>24.3</td></tr>
<tr><td>Seizure-free rate (%)</td><td>15.3</td><td>22.7</td><td>28.9†</td><td>27.0**</td><td>14.2</td></tr>
</table>
*p < 0.001 vs placebo; **p < 0.05 vs placebo; †p < 0.01 vs placebo

Of 1264 patients who completed the double-blind phase of studies 304, 305, or 306, 96.4% continued into study 307.
Approximately 70% of patients had a history of secondary generalized seizures.

<table>
<tr><th colspan="3">Efficacy Endpoints per Follow-Up Time Period</th></tr>
<tr><th></th><th>Median Change in Seizure Frequency (%)</th><th>Overall Responder Rate (%)</th></tr>
<tr><td>Open-label extension conversion period</td><td>–65.3</td><td>59.1</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr><td></td><td>titration phase and 13-week maintenance phase), and 4-week follow-up

Study 307:
276-week study (16-week blinded conversion phase, a planned 256-week maintenance phase, and 4-week follow-up phase); interim data cutoff date: December 1, 2010</td><td></td><td>or placebo during double-blind phase

Patients taking 12 mg/day in double-blind phase continued on their treatment in the open-label phase

Dose adjustment to individual’s MTD was permitted based on tolerability.</td><td></td><td>
<table>
<tr><td>(n = 465)</td><td></td><td></td></tr>
<tr><td>Weeks 1–13 open-label extension (n = 333)</td><td>–77.5</td><td>68.2</td></tr>
<tr><td>Weeks 14–26 open-label extension (n = 233)</td><td>–88.2</td><td>69.1</td></tr>
<tr><td>Weeks 27–39 open-label extension (n = 168)</td><td>–86.1</td><td>67.3</td></tr>
<tr><td>Weeks 40–52 open-label extension (n = 104)</td><td>–87.1</td><td>68.3</td></tr>
</table>

During the 16-week conversion period, there was a small difference in the percent change in secondary generalized seizures during the double-blind period between patients previously on placebo (–59.9%, n = 148) and those previously on FYCOMPA (–69.9%, n = 317), which was maintained in both groups in the open-label extension period.
During the 16-week conversion period, there was a small difference in responder rate during the double-blind period between patients previously on placebo (55.4%, n = 148) and those previously on FYCOMPA (60.9%, n = 317), which was maintained in both groups in the open-label extension period.

</td></tr>
<tr><td>FYCOMPA as adjunctive therapy in patients with refractory POS: a dose-response analysis

Kramer et al, 2012[77]</td><td>Pooled actual dose analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306) and the blinded conversion period of an open-label extension study (307)

N = 209 patients with refractory POS who received FYCOMPA 8 mg in double-blind studies and increased to 12 mg during the blinded conversion period of the open-label</td><td>Inclusion: ≥ 12 years of age; treatment resistant partial seizures despite treatment with 1-3 AEDs</td><td>FYCOMPA 12 mg (n = 209)</td><td>Median percent change in seizure frequency; responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency); median percent change in seizure frequency, responder rate, and seizure-freedom rates for patients completing studies 304 and 305 based on the last dose of FYCOMPA received</td><td>
Baseline Characteristics

Central/South American patients were excluded due to a significant treatment-by-region interaction (high placebo response).

Efficacy

Patients who completed studies 304, 305, or 306 on FYCOMPA 8 mg and completed the blinded conversion period of the extension study (307):

<table>
<tr><th colspan="3">Seizure Frequency in Patients Increasing FYCOMPA Dose to 12 mg</th></tr>
<tr><th rowspan="2"></th><th colspan="2">FYCOMPA</th></tr>
<tr><th>8 mg (n = 209)</th><th>12 mg (n = 209)</th></tr>
<tr><td>Median change in seizure frequency (%)</td><td>–32.4</td><td>–43.3</td></tr>
<tr><td>Patients achieving ≥ 50% reduction in seizures (%)</td><td>37.8</td><td>43.5</td></tr>
<tr><td>Seizure freedom during entire maintenance period</td><td>5.4</td><td>15.5</td></tr>
<tr><td>Seizure freedom during last 28 days of maintenance period</td><td>13.2</td><td>20.9</td></tr>
</table>

Patients who completed studies 304 or 305, at the end of the maintenance period based on the actual dose received.

<table>
<tr><th colspan="4">Seizure Frequency for Actual Dose Analysis (Completion of Study 304, 305)</th></tr>
<tr><th rowspan="2"></th><th colspan="2">FYCOMPA</th><th rowspan="2">Placebo</th></tr>
<tr><th>8 mg</th><th>12 mg</th></tr>
<tr><th colspan="4">All Partial Seizures</th></tr>
<tr><td>n</td><td>158</td><td>114</td><td>182</td></tr>
<tr><td>Median change in seizure frequency (%)</td><td>–32.4</td><td>–34.0</td><td>–14.1</td></tr>
</table>
</td></tr>
</table>

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	extension 6-week baseline phase, 19-week study (6-week titration phase and 13-week maintenance phase), and 4-week follow-up				
Efficacy and safety of adjunctive FYCOMPA in adolescent patients with refractory POS ***Rosenfeld et al, 2012***[78]	Pooled analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306) N = 145 adolescent patients with refractory POS N = 143 patients receiving ≥ one dose of study drug	Inclusion: Ages 12 to 17 years old; treatment-resistant partial seizures despite treatment with one to three AEDs See Studies 304, 305, and 306 above for detailed inclusion and exclusion criteria.	***FYCOMPA 2 mg (n = 21, Study 306)*** ***FYCOMPA 4 mg (n = 13, Study 306)*** ***FYCOMPA 8 mg (n = 44, all studies)*** ***FYCOMPA 12 mg (n = 20, all studies)*** ***Placebo (n = 45, all studies)***	Median change from baseline in seizure frequency per 28 days; 50% responder rate; percent change in frequency of complex partial + secondary generalized seizures per 28 days during double-blind phase vs baseline; population pharmacokinetics/ pharmaco-dynamics; safety	

Patients achieving ≥ 50% reduction in seizures (%)	38.6	39.5	18.1
100% response (seizure freedom) (%)	2.5	4.4	1.1
Secondarily Generalized Seizures			
n	622	43	70
Median change in seizure frequency (%)	–46.0	–54.0	–15.9
Patients achieving ≥ 50% reduction in seizures (%)	46.8	53.5	30.0

Baseline Characteristics

Baseline Characteristics of Adolescents per Treatment Group						
Category	**FYCOMPA**					**Placebo (n = 45)**
	2 mg (n = 21)	**4 mg (n = 13)**	**8 mg (n = 44)**	**12 mg (n = 20)**	**Total (n = 98)**	
Median age, y	15	16	16	15	15	15
12–13 y (%)	28.6	38.5	25.0	20.0	26.5	31.1
14–15 y (%)	23.8	7.7	20.5	50.0	25.5	42.2
16–17 y (%)	47.6	53.8	54.5	30.0	48.0	26.7
Male, n (%)	9 (42.9)	9 (69.2)	26 (59.1)	11 (55.0)	55 (56.1)	10 (22.2)
Median weight, kg (range)	49 (35–105)	50 (23–76)	52 (34–99)	63 (35–105)	53 (23–105)	55 (31–92)

Results

Efficacy Endpoints in Adolescents per Treatment Group					
	FYCOMPA				**Placebo n (%)**
	2 mg n (%)	**4 mg n (%)**	**8 mg n (%)**	**12 mg n (%)**	
Median Change in Seizure Frequency/28 Days vs Baseline					
Study 306	21 (12.8)	13 (–23.9)	12 (–34.6)	NR	14 (4.6)
Studies 304 and 305	NR	NR	44 (–34.8)	20 (–35.6)	45 (–18.0)
50% Responder Rate					
Study 306	1 (4.8)	2 (15.4)	4 (33.3)	NR	1 (7.1)
Studies 304 and 305	NR	NR	18 (40.9)	9 (45.0)	10 (22.2)
Median Change in Complex Partial Seizures ± Secondary Generalization					
All studies	18 (17.0)	12 (–42.9)	42 (–40.3)	15 (–39.2)	39 (–4.4)

NR = not reported

- 4 mg was identified as the minimal effective dose of FYCOMPA.

<table>
<tr><th>Study</th><th>Design</th><th>Inclusion/Exclusion Criteria</th><th>Treatment Regimen</th><th>Endpoints</th><th>Results/Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Safety and Discontinuations
• TEAEs were reported in 71.4% of patients receiving FYCOMPA 2 mg, 61.5% receiving FYCOMPA 4 mg, 75.0% receiving FYCOMPA 8 mg, 70.0% receiving FYCOMPA 12 mg, and 68.9% receiving placebo.
• TEAEs were considered treatment related in 52.4% of patients receiving FYCOMPA 2 mg, 46.2% receiving FYCOMPA 4 mg, 65.9% receiving FYCOMPA 8 mg, 65.0% receiving FYCOMPA 12 mg, and 40.0% receiving placebo.
• The most common AEs (incidence > 5% and twice the placebo group) were dizziness (20.4% vs 8.9%), somnolence (15.3% vs 6.7%), aggression (8.2% vs 0%), decreased appetite (6.1% vs 2.2%), and rhinitis (5.1% vs 2.2%).
• No deaths occurred.
• AE-induced discontinuation occurred more frequently with placebo (6.7%) vs FYCOMPA (2.0%).
• The most common AEs (> 5%) causing dose interruption/reduction were dizziness and somnolence.</td></tr>
<tr><td>Efficacy and safety of FYCOMPA in the presence of concomitant CYP3A4-inducing AEDs

Laurenza et al, 2012[82]</td><td>Pooled PK analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306)

N = 1109 patients with refractory POS

PK population (n = 770)

Actual dose analysis (n = 745)

6-week baseline phase, 19-week double-blind phase (6-week titration phase and 13-week maintenance phase), 4-week</td><td>Inclusion: ≥ 12 years of age; treatment-resistant partial seizures despite treatment with one to three AEDs; only one inducer AED was permitted: carbamazepine (CBZ), oxcarbazepine (OXC), and phenytoin (PHY) were considered enzyme-inducing AEDs for this analysis.

Exclusion: Not reported</td><td>FYCOMPA 2 mg (n = 162)

FYCOMPA 4 mg (n = 161)

FYCOMPA 6 mg (n = 56)

FYCOMPA 8 mg (n = 329)

FYCOMPA 10 mg (n = 24)

FYCOMPA 12 mg (n = 140)

Placebo (n = 392)</td><td>Effect of concomitant CYP3A4-inducing AEDs on efficacy and safety

Population PK and PK/PD models were estimated by nonlinear mixed-effect modeling.

Probability of response and occurrence of most frequent AEs were analyzed by logistic regression.</td><td>Baseline Characteristics
• Baseline characteristics of patients taking CBZ, OXC, or PHY by last (actual) dose of FYCOMPA were similar between groups and similar to those of patients not taking concomitant AEDs.

Results
• Average steady-state FYCOMPA plasma concentration was reduced in the presence of enzyme-inducing AEDs but still increased linearly in a dose-dependent manner.
• Median percent change in seizure frequency as well as responder rate were more robust when FYCOMPA was given concomitant with noninducing AEDs but reduced in the presence of enzyme-inducing AEDs.
<table>
<tr><th colspan="8">Efficacy Endpoints With FYCOMPA ± an Inducing AED</th></tr>
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<tr><th colspan="8">Responder rate (%)</th></tr>
<tr><td>n</td><td>162</td><td>161</td><td>56</td><td>329</td><td>24</td><td>140</td><td>392</td></tr>
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Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	follow-up phase				

With inducing AED	20.7	27.1	13.8	33.5	35.3	30.7	21.8
Without inducing AED	25.7	35.5	51.9	44.7	28.6	51.3	17.2

AED = antiepileptic drug

- The median % reduction in seizure frequency/28 days and responder rate were more robust when FYCOMPA was given in the presence of noninducing AEDs but was reduced when given in the presence of inducing AEDs, as shown in the completers by last (actual dose) excluding the patients from Central/South America (table below).

Efficacy Endpoints Excluding Patients From Central/South America				
	Median Reduction From Placebo, %		Responder Rate (Drug–Placebo), %	
	With Inducing AED	Without Inducing AED	With Inducing AED	Without Inducing AED
2 mg/day	0.5	8.2	1.9	6.3
4 mg/day	11.9	15.3	8.1	15.4
8 mg/day	14.4	25.7	13.0	28.2
12 mg/day	19.2	33.2	12.3	39.3

AED = antiepileptic drug

Safety and Discontinuations

- Completion rates were similar for patient groups receiving and not receiving inducing AEDs; the primary reason for discontinuation in both groups was TEAEs.

Completion and Discontinuation Rates ± Inducing AEDs by Treatment Group					
	FYCOMPA				Placebo n (%)
	< 4 mg n (%)	4 mg n (%)	> 4 mg–8 mg n (%)	> 8–12 mg n (%)	
With Concomitant Inducing AEDs					
n	115	100	264	131	255
Completed	92 (80.0)	85 (85.0)	226 (85.6)	118 (90.1)	229 (89.8)
Discontinued due to TEAE	6 (5.2)	8 (8.0)	17 (6.4)	10 (7.6)	8 (3.1)
No Concomitant Inducing AEDs					
n	86	87	192	62	187
Completed	70 (81.4)	76 (87.4)	158 (82.3)	46 (74.2)	163 (87.2)
Discontinued due to TEAE	9 (10.5)	5 (5.7)	23 (12.0)	15 (24.2)	9 (4.8)

AED = antiepileptic drug; TEAE = treatment-emergent adverse event

TEAEs Reported by ≥5% of Patients in Any Group According to Last Actual FYCOMPA Dose With Inducing AED					
	FYCOMPA				Placebo (n = 255) n (%)
	< 4 mg (n = 115) n (%)	4 mg (n = 100) n (%)	> 4 mg–8 mg (n = 264) n (%)	> 8–12 mg (n = 131) n (%)	
Dizziness	13 (11.3)	19 (19.0)	96 (36.4)	47 (35.9)	23 (9.0)
Somnolence	19 (16.5)	11 (11.0)	38 (14.4)	15 (11.5)	21 (8.2)

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments

Headache	15 (13.0)	14 (14.0)	28 (10.6)	17 (13.0)	28 (11.0)
Fatigue	7 (6.1)	7 (7.0)	18 (6.8)	9 (6.9)	13 (5.1)
Irritability	4 (3.5)	7 (7.0)	14 (5.3)	12 (9.2)	4 (1.6)
Nausea	3 (2.6)	1 (1.0)	13 (4.9)	9 (6.9)	13 (5.1)
Fall	2 (1.7)	3 (3.0)	14 (5.3)	10 (7.6)	8 (3.1)

AED = antiepileptic drug; TEAE = treatment-emergent adverse event

PHASE III POOLED QOL ANALYSIS

Relationship between QOL and frequency of refractory partial seizures

Krauss et al, 2012[79]

Pooled analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306)

N = 959 patients with refractory POS included in the ITT population and had evaluable QOLIE-31-P* data

Inclusion: ≥ 12 years of age; treatment-resistant partial seizures despite treatment with one to three AEDs

Exclusion: Not reported

FYCOMPA 2 mg (n = 121)

FYCOMPA 4 mg (n = 127)

FYCOMPA 8 mg (n = 261)

FYCOMPA 12 mg (n = 132)

Placebo (n = 262)

QOLIE-31-P; marginal effects (noise from confounders removed) of being a responder (proportion of patients achieving ≥ 50% reduction in seizure frequency) vs nonresponders; change in QOLIE-31-P with FYCOMPA vs placebo; minimally important difference (MID) for QOLIE-31-P of an 11.8% change in overall score

Baseline Characteristics

- Of the 959 patients in the ITT population and who had evaluable QOLIE-31-P data, 903 had baseline and postbaseline overall QOLIE-31-P scores.
- Overall, 62.4% of patients had a baseline QOLIE-31-P score < 50.

Baseline Characteristics of Patients per Treatment Group

	FYCOMPA				Placebo (n = 262)
	2 mg (n = 121)	4 mg (n = 127)	8 mg (n = 261)	12 mg (n = 132)	
Mean QOLIE-31-P score at baseline	53.8	55.5	55.0	56.7	57.0

QOLIE-31-P = Quality of Life in Epilepsy questionnaire

Results

- The average improvement in QOLIE-31-P score for patients treated with FYCOMPA was 12.5% (p = 0.01 vs placebo), and 33.8% were responders.
- Marginal changes in overall QOLIE-31-P score and the domains of emotional well-being, seizure worry, energy/fatigue, distress, medication effects, and health status for 50% responders taking FYCOMPA were significantly improved vs nonresponders (p < 0.01 vs placebo for all except emotional well-being and energy/fatigue, which were p < 0.05). Similar significant improvements were seen in 50% responders taking placebo, with the exception of the distress domain (p = 0.76).
- There was a greater increase in marginal change in overall QOLIE-31-P score in the domains of emotional well-being and social functioning and in the epilepsy-specific domains of seizure worry and health status as response rates increased from 25% to 100%.
- Responders vs nonresponders had greater mean improvements in overall QOLIE-31-P score (an additional 21.1% that achieved by nonresponders) and for the subscales for seizure worry (55.3%), cognition (35.1%), and emotional well-being (38.1%) (p < 0.01 for all).
- The largest marginal change in both 50% and 75% responders was demonstrated in the seizure worry domain.
- A 48% reduction in seizure frequency was needed to produce QOLIE-31-P MID. A 1% reduction in seizure frequency was associated with a change of 0.01 in overall QOLIE-31-P score (p = 0.03).

Comparative Marginal QOLIE-31-P Effect for FYCOMPA vs Placebo

	50% Response	75% Response	100% Response
Responder	33.8%	16.2%	3.9

<table>
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<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>rate</td><td colspan="2">(p < 0.01*)</td><td colspan="2">(p < 0.01*)</td><td colspan="2">(p < 0.01*)</td></tr>
<tr><th>QOLIE-31-P domain</th><th>Change in QOLIE**</th><th>% Change*</th><th>Change in QOLIE**</th><th>% Change*</th><th>Change in QOLIE**</th><th>% Change*</th></tr>
<tr><td>Overall score</td><td>8.6</td><td>2.9</td><td>12.6</td><td>2.0</td><td>21.9</td><td>11.1</td></tr>
<tr><td>Seizure worry</td><td>47.9</td><td>16.1</td><td>45.2</td><td>7.3</td><td>103.7</td><td>52.4</td></tr>
<tr><td>Cognitive functioning</td><td>5.5</td><td>1.9</td><td>3.5</td><td>0.6</td><td>–3.3</td><td>–1.7</td></tr>
<tr><td>Emotional well-being</td><td>7.4</td><td>2.5</td><td>12.9</td><td>2.1</td><td>24.1</td><td>12.2</td></tr>
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<tr><td>Energy/ fatigue</td><td>15.2</td><td>5.1</td><td>17.6</td><td>2.9</td><td>7.4</td><td>3.7</td></tr>
<tr><td>Distress</td><td>–10.8</td><td>–3.7</td><td>–10.2</td><td>–1.7</td><td>–13.6</td><td>–6.9</td></tr>
<tr><td>Medication effects</td><td>32.1</td><td>10.8</td><td>15.4</td><td>2.5</td><td>–10.6</td><td>–5.4</td></tr>
<tr><td>Health status</td><td>20.0</td><td>6.7</td><td>34.5</td><td>5.6</td><td>84.2</td><td>42.5</td></tr>
</table>
QOLIE-31-P = Quality of Life in Epilepsy questionnaire
*for responders; ** for FYCOMPA vs placebo
</td></tr>
<tr><td>Effects of treatment response and side effects on overall QOL and distress

Simons et al, 2013[80]</td><td>Pooled analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306)

N = 959 patients with refractory POS included in the ITT population and had evaluable QOLIE-31-P data</td><td><u>Inclusion:</u> Not reported

<u>Exclusion:</u> Not reported</td><td>Not mentioned</td><td>Marginal effects of 50%, 75%, and 100% responder rates and time spent with mild, moderate, and severe AEs on overall QOL (QOL measured via QOLIE-31-P)</td><td>Baseline Characteristics
• Not mentioned

Results
• The average improvement in overall QOL was 20 (p < 0.01).
• The 50% responders improved an additional 8.9% (p < 0.01), for a total of 28.9% (p < 0.01), with moderate to severe AEs decreasing QOL for patients by 0.178 (p = 0.02) and 0.752 (p = 0.04) per day spent with the AE, respectively.
• QOL improvement in 75% responders (13.9%; p < 0.01) and 100% responders (22.4%; p < 0.01) were incremental and monotonic, with moderate to severe AEs having similar effects on QOL.
• Distress decreased for 50% responders (–11.08; p < 0.01), 75% responders (–11.66; p < 0.01), and 100% responders (–14.11; p < 0.01), with moderate to severe AEs increasing distress (all p < 0.05).</td></tr>
<tr><td colspan="6">POOLED PHARMACOKINETIC (PK)/PHARMACODYNAMIC (PD) AND DRUG INTERACTIONS</td></tr>
<tr><td>Population PK and PD of FYCOMPA

Laurenza et al, 2011[29]</td><td>Pooled population PK analysis of randomized, double-blind, placebo-controlled, phase III studies (304,</td><td><u>Inclusion:</u> ≥ 12 years of age; treatment-resistant partial seizures despite treatment with one to three AEDs; use of only one CYP-inducer AED (carbamazepine, phenytoin, phenobarbital,</td><td>FYCOMPA 2 mg (n = 134)

FYCOMPA 4 mg (n = 136)

FYCOMPA 8 mg (n = 324)</td><td>Population PK/PD</td><td>Baseline Characteristics
• Approximately half of the patients were female (56.7% of the FYCOMPA 2 mg group, 50.0% of the 4 mg group, 49.7% of the 8 mg group, 53.4% of the 12 mg group, and 49.9% of the placebo group).
• The mean age was 33.2 years in the FYCOMPA 2 mg group, 33.4 years in the 4 mg group, 35.6 years in the 8 mg group, 35.0 years in the 12 mg group, and 34.3 years in the placebo group.</td></tr>
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Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	305, 306) N = 1491 patients with refractory POS Pooled PK/PD analysis (n = 1109) PK population (n = 770) 6-week baseline, 19-week study (6-week titration phase and 13-week maintenance phase), 4-week follow-up	or primidone) Exclusion: Not reported	***FYCOMPA 12 mg (n = 176)*** ***Placebo (n = 339)***		***Results*** • The plasma concentration of FYCOMPA increased in a dose-proportional manner, except that exposure was lower in the presence of FYCOMPA-inducing AEDs (carbamazepine, oxcarbazepine, or phenytoin). • FYCOMPA PK was adequately described by a one-compartment model. • Sex, fat body mass, carbamazepine, oxcarbazepine, phenytoin, topiramate, time, and dose were significant covariates for apparent clearance (CL/F). • CL/F was slightly lower in females (0.605 L/h) vs males (0.730 L/h). • CL/F increased three-fold with concomitant carbamazepine, two-fold with oxcarbazepine, two-fold with phenytoin, and slightly with topiramate, and resulted in decreased exposure. • CL/F increased slightly with dose (10% with FYCOMPA 12 mg vs 8 mg) and decreased slightly with each visit (5% at visit 8 vs visit 6). • There was no effect of race, age, creatinine clearance, liver enzymes, or other AEDs on FYCOMPA CL/F. • Effects of dose, visit, topiramate, and sex on FYCOMPA CL/F were not considered to be clinically relevant. • FYCOMPA had no clinically relevant effect on the PK of carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, or zonisamide. • Seizure frequency decreased linearly as average steady-state exposure of FYCOMPA increased. • The proportion of patients achieving ≥ 50% reduction in seizure frequency increased as the average steady-state concentration increased. • The probability of being a responder increased without concomitant clobazam but was not considered to be clinically significant. ***Safety and Discontinuations*** • There was a statistical correlation between increased plasma concentration of FYCOMPA and experiencing fatigue, somnolence, gait disturbance, dizziness, weight increase, irritability, dysarthria, or euphoric mood. • Changes in appetite or headache frequency were not associated with plasma FYCOMPA concentration.
Demographic factors and concomitant AEDs have no effect on the PD of FYCOMPA ***Hussein et al, 2012[81]***	Pooled population PK analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306)	Inclusion: ≥ 12 years of age; treatment-resistant partial seizures despite treatment with 1 to 3 AEDs; use of only one CYP-inducer AED (carbamazepine, phenytoin, phenobarbital, or primidone)	***FYCOMPA 2 mg (n = 134)*** ***FYCOMPA 4 mg (n = 136)*** ***FYCOMPA 8 mg (n = 324)*** ***FYCOMPA***	Effect of demographic factors and concomitant AEDs on population PK/PD	***Baseline Characteristics*** • Approximately half of the patients were female (56.7% of the FYCOMPA 2 mg group, 50.0% of the 4 mg group, 49.7% of the 8 mg group, 53.4% of the 12 mg group, and 49.9% of the placebo group). • The mean age was 33.2 years in the FYCOMPA 2 mg group, 33.4 years in the 4 mg group, 35.6 years in the 8 mg group, 35.0 years in the 12 mg group, and 34.5 years in the placebo group. • Twelve concomitant AEDs were used by > 50 patients in the PK/PD population: carbamazepine, lamotrigine, valproic acid, levetiracetam, topiramate, oxcarbazepine, clobazam, zonisamide, phenytoin, clonazepam, pregabalin, and phenobarbital.

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<td>N = 1480 patients with refractory POS

Pooled PK/PD analysis
(n = 1109)

PK population
(n = 770)

6-week baseline, 19-week study (6-week titration phase and 13-week maintenance phase), 4-week follow-up</td>
<td><u>Exclusion:</u> Not reported</td>
<td>12 mg
(n = 176)

Placebo
(n = 339)</td>
<td></td>
<td>Results
• FYCOMPA PK was linear over the dose range, regardless of concomitant AEDs, except that exposure was lower with FYCOMPA-inducing AEDs.
• Seizure frequency decreased linearly with increasing average FYCOMPA exposure at steady state.
• The proportion of patients achieving ≥ 50% reduction in seizure frequency increased as average steady-state exposure increased.
• The probability of being a responder increased significantly with increased average FYCOMPA steady-state exposure.
• No demographic factor (age, sex, body mass, race) or concomitant AED affected the exposure/efficacy relation, probability of response, or occurrence of AEs.
• The probability of being a responder increased without concomitant clobazam but was not considered to be clinically significant.

Safety and Discontinuations
• The probability of fatigue, somnolence, gait disturbance, dizziness, weight increase, irritability, dysarthria, or euphoric mood increased with increased FYCOMPA exposure.
• Change in appetite or headache frequency was not associated with plasma FYCOMPA concentration.</td>
</tr>
<tr>
<td>Efficacy and safety of FYCOMPA in the presence of concomitant CYP3A4-inducing AEDs

Laurenza et al, 2012⁸²</td>
<td>Pooled PK analysis of randomized, double-blind, placebo-controlled, phase III studies (304, 305, 306)

N = 1109 patients with refractory POS

PK population
(n = 770)

Actual dose analysis
(n = 745)

6-week baseline phase, 19-week double-blind phase (6-week</td>
<td><u>Inclusion:</u> ≥ 12 years of age; treatment-resistant partial seizures despite treatment with one to three AEDs; only one inducer AED was permitted: carbamazepine (CBZ), oxcarbazepine (OXC), and phenytoin (PHY) were considered enzyme-inducing AEDs for this analysis.

<u>Exclusion:</u> Not reported</td>
<td>FYCOMPA 2 mg
(n = 162)

FYCOMPA 4 mg
(n = 161)

FYCOMPA 6 mg
(n = 56)

FYCOMPA 8 mg
(n = 329)

FYCOMPA 10 mg
(n = 24)

FYCOMPA 12 mg
(n = 140)

Placebo
(n = 392)</td>
<td>Effect of concomitant CYP3A4-inducing AEDs on efficacy and safety

Population PK and PK/PD models were estimated by nonlinear mixed-effect modeling.

Probability of response and occurrence of most frequent AEs were analyzed by logistic regression.</td>
<td>Baseline Characteristics
• Baseline characteristics of patients taking CBZ, OXC, or PHY by last (actual) dose of FYCOMPA were similar between groups and similar to those of patients not taking concomitant AEDs.

Results
• Average steady-state FYCOMPA plasma concentration was reduced in the presence of enzyme-inducing AEDs but still increased linearly in a dose-dependent manner.
• Median percent change in seizure frequency as well as responder rate were more robust when FYCOMPA was given concomitant with noninducing AEDs but reduced in the presence of enzyme-inducing AEDs.
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Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	titration phase and 13-week maintenance phase), 4-week follow-up phase				

Without inducing AED	–23.01	–20.12	–49.91	–35.87	–38.95	–43.5	–16.42
Responder rate (%)							
n	162	161	56	329	24	140	392
With inducing AED	20.7	27.1	13.8	33.5	35.3	30.7	21.8
Without inducing AED	25.7	35.5	51.9	44.7	28.6	51.3	17.2

AED = antiepileptic drug

- The median % reduction in seizure frequency/28 days and responder rate were more robust when FYCOMPA was given in the presence of noninducing AEDs but was reduced when given in the presence of inducing AEDs, as shown in the completers by last (actual dose) excluding the patients from Central/South America (table below).

Efficacy Endpoints Excluding Patients From Central/South America				
	Median Reduction From Placebo, %		Responder Rate (Drug–Placebo), %	
	With Inducing AED	Without Inducing AED	With Inducing AED	Without Inducing AED
2 mg/day	0.5	8.2	1.9	6.3
4 mg/day	11.9	15.3	8.1	15.4
8 mg/day	14.4	25.7	13.0	28.2
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Safety and Discontinuations

- Completion rates were similar for patient groups receiving and not receiving inducing AEDs; the primary reason for discontinuation in both groups was TEAEs.

Completion and Discontinuation Rates ± Inducing AEDs by Treatment Group					
	FYCOMPA				Placebo n (%)
	< 4 mg n (%)	4 mg n (%)	> 4 mg–8 mg n (%)	> 8–12 mg n (%)	
With Concomitant Inducing AEDs					
n	115	100	264	131	255
Completed	92 (80.0)	85 (85.0)	226 (85.6)	118 (90.1)	229 (89.8)
Discontinued due to TEAE	6 (5.2)	8 (8.0)	17 (6.4)	10 (7.6)	8 (3.1)
No Concomitant Inducing AEDs					
n	86	87	192	62	187
Completed	70 (81.4)	76 (87.4)	158 (82.3)	46 (74.2)	163 (87.2)
Discontinued due to TEAE	9 (10.5)	5 (5.7)	23 (12.0)	15 (24.2)	9 (4.8)

AED = antiepileptic drug; TEAE = treatment-emergent adverse event

TEAEs Reported by ≥5% of Patients in Any Group According to Last Actual FYCOMPA Dose With Inducing AED					
	FYCOMPA				Placebo (n = 255)
	< 4 mg	4 mg	> 4 mg–8 mg	> 8–12 mg	

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments

	(n = 115) n (%)	(n = 100) n (%)	(n = 264) n (%)	(n = 131) n (%)	n (%)
Dizziness	13 (11.3)	19 (19.0)	96 (36.4)	47 (35.9)	23 (9.0)
Somnolence	19 (16.5)	11 (11.0)	38 (14.4)	15 (11.5)	21 (8.2)
Headache	15 (13.0)	14 (14.0)	28 (10.6)	17 (13.0)	28 (11.0)
Fatigue	7 (6.1)	7 (7.0)	18 (6.8)	9 (6.9)	13 (5.1)
Irritability	4 (3.5)	7 (7.0)	14 (5.3)	12 (9.2)	4 (1.6)
Nausea	3 (2.6)	1 (1.0)	13 (4.9)	9 (6.9)	13 (5.1)
Fall	2 (1.7)	3 (3.0)	14 (5.3)	10 (7.6)	8 (3.1)

AED = antiepileptic drug; TEAE = treatment-emergent adverse event

PHASE II STUDIES					
Evaluate tolerability and safety of FYCOMPA: two randomized dose-escalation studies ***Studies 206 and 208*** ***Krauss et al, 2012***[83]	Randomized, double-blind, placebo-controlled, multinational, multicenter, dose-escalation, parallel-group, phase II study Study 206: N = 153 ITT population (n = 152) Safety population (n = 153) 18-week study (4-week baseline phase, 8-week titration phase, 4-week maintenance phase, 2-week transition phase) Study 208: N = 48 ITT population (n = 47) Safety population (n = 48)	Inclusion: 18–70 years of age with uncontrolled POS with or without secondary generalization; body weight ≥ 40 kg; failed treatment with ≥ three different AEDs for any duration over the past 2 years; on stable dose of one to three AEDs; monthly average ≥ 4 (Study 206) or ≥ 3 (Study 208) partial seizures with no 21-day seizure-free period during the 2 months before randomization; ≥ three documented seizures during 28-day baseline period (Study 206) Exclusion: Any clinically significant medical or psychiatric condition; evidence of impaired renal function, significant hepatic disease, significant hematologic disease, major psychiatric disease; clinically significant ECG abnormality; a progressive CNS disease; history of drug or alcohol	Study 206: ***FYCOMPA 1 mg QD titrated in 1 mg/day increments every week to maximum 4 mg QD (n = 51)*** ***FYCOMPA 0.5 mg BID titrated in 1 mg/day increments every week to maximum 2 mg BID (n = 51)*** ***Placebo (n = 51)*** Study 208: ***FYCOMPA 2 mg QD titrated in 2 mg/day increments every 2 weeks to maximum 12 mg QD (n = 38)*** ***Placebo***	Primary: Tolerability of FYCOMPA up to 4 mg daily (study 206) or up to 12 mg daily (study 208); MTD Secondary: Responder rate (proportion of patients experiencing ≥ 50% reduction in seizure frequency), median percent change in seizure frequency	***Baseline Characteristics*** • Approximately half of all patients were female with 59.6% receiving FYCOMPA QD, 59.6% receiving FYCOMPA BID, and 54.9% receiving placebo in Study 206, and 52.6% receiving FYCOMPA QD and 50.0% receiving placebo in Study 208. • Mean age was 42.5 years for FYCOMPA QD, 40.0 years for FYCOMPA BID, and 38.1 years for placebo in Study 206, and 40.7 years for FYCOMPA QD and 45.5 years for placebo in Study 208. • The mean time since epilepsy onset was 18.0 to 25.1 years, and most patients were on two or three AEDs. • In Study 206, 44.6% of patients receiving FYCOMPA and 47.1% of patients receiving placebo were taking a concomitant CYP-inducer AED. • In Study 208, 50.0% of patients receiving FYCOMPA and 30.0% of patients receiving placebo were taking a concomitant CYP-inducer AED. ***Safety*** Study 206 • Overall, 138 (90.2%) patients completed Study 206, including 46 (90.2%) in the placebo group, 47 (92.2%) in the FYCOMPA BID group, and 45 (88.2%) in the FYCOMPA QD group. • Nine of the 15 patients that discontinued the study did so due to an AE; other reasons for study discontinuation included protocol deviation (n = 3), investigator request (n = 1), subject withdrawn consent (n = 1), and other (n = 1). • A total of 82.4% of patients tolerated FYCOMPA 4 mg/day. • AEs were reported by 62.7% of patients receiving placebo and 66.7% of patients receiving FYCOMPA. • Most AEs were mild or moderate, with serious AEs reported by 3.9% of patients receiving placebo (n = 2) and 2.0% of patients receiving FYCOMPA (n = 2). • The most common AEs (≥ 5%) were dizziness, headache, somnolence, contusion, fatigue, nausea, and nasopharyngitis. • No deaths occurred during the study. • There were no clinically significant differences between groups in regard to laboratory values, ECG results, or any other safety variable. • Based on the tolerability, dose-titration, and safety data, the majority of patients tolerated

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	20-week study (4-week baseline phase, 12-week titration phase, 4-week maintenance phase)	dependence ≤ 2 years; history of multiple drug allergies; pregnant, lactating, or of child-bearing potential and not using approved methods of contraception	***(n = 10)***		the highest dose tested in the study (4 mg/day), and the MTD of FYCOMPA was not reached. Study 208 • Overall, 42 (87.5%) patients completed Study 208, including 8 (80.0%) in the placebo group and 34 (89.5%) in the FYCOMPA QD group. • Discontinuation was due to AEs (n = 3), protocol deviation (n = 2), and other (n = 1). • Twelve (32%) patients receiving FYCOMPA reached the highest tested dose (12 mg), and 11 remained on this dose, compared to 6 (60%) in the placebo group reaching the highest tested dose, with all remaining on this dose. • FYCOMPA 8 mg, 10 mg, and 12 mg doses were well tolerated, with Kaplan-Meier probabilities of 0.55, 0.48, and 0.44, respectively. • One or more AE was reported in 80.0% of patients receiving placebo and 84.2% of patients receiving FYCOMPA. • Most AEs were mild or moderate, with three patients receiving FYCOMPA reporting severe drug-related dizziness. • The most common AEs (≥ 10% in FYCOMPA-treated patients) were dizziness, somnolence, headache, fatigue, diarrhea, and rhinitis. • Serious AEs occurred in one (10%) patient receiving placebo and one (2.6%) patient receiving FYCOMPA. • There were no differences between groups in regard other safety parameters. ***Efficacy*** Study 206 • The responder rate was 30.7% for FYCOMPA (28.0% BID, and 33% QD) and 21.6% for placebo (p = 0.19). • The median reduction in seizure frequency was 25.7% for FYCOMPA and 19.5% for placebo (p = 0.43). Study 208 • The responder rate was 39.5% for FYCOMPA and 22.2% for placebo. • The median reduction in seizure frequency was 39.6% for FYCOMPA, and a median increase of 2.1% was observed for placebo.
PHASE II OPEN-LABEL EXTENSION					
Long-term open-label evaluation of FYCOMPA in patients with epilepsy ***Study 207*** ***Rektor et al, 2012***[75]	Open-label extension, phase II study N = 138 (73.2% from Study 206, 26.8% from Study 208) 440-week study (12-week titration	Inclusion: Patients who completed Study 206 or 208; See inclusion criteria above Exclusion: See Studies 206 and 208	***FYCOMPA titrated by 2 mg increments every 2 weeks to maximum 12 mg QD***	Primary: Long-term tolerability and safety Secondary: Whether efficacy demonstrated in phase II studies was maintained with long-term use	***Baseline Characteristics*** • Approximately half of all patients (58%) were female, and the mean age was 40.7 years. • In the double-blind studies, 31.2% of the participants had been randomized to placebo and 68.8% to FYCOMPA, with approximately 80.0% entering the open-label extension study with either no prior FYCOMPA exposure or a maximum of 4 mg/day. • A total of 38.4% of the patients remained on the study at approximately 4 years after the study start. • Most patients were on two or three AEDs, with an average of 1.9 per patient. • The four most common AEDs were carbamazepine, lamotrigine, levetiracetam, and valproic acid.

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
	phase, 424-week maintenance phase, 4-week follow-up phase)				***Safety and Discontinuations*** • Overall, 86.2% of patients received treatment for > 6 months, 69.6% for > 1 year, 50.7% for > 2 years, 41.3% for > 3 years, and 13.0% for > 4 years. • A MTD of 8 mg to 12 mg/day was reached by 46% of patients. • Discontinuation was due to AEs (13%), treatment noncompliance (2.2%), protocol deviation (0.7%), investigator request (0.7%), withdrawn consent (23.2%), and other (20.3%). • A total of 93.5% of patients reported ≥ one AE, with most rated mild to moderate in severity. • SAEs were reported by 15.2% of patients. SAEs were considered possibly treatment related in four patients (convulsion, schizophrenia, status epilepticus, grand mal convulsion) and probably treatment related in one patient (epilepsy). • Over the 4 years, the most common AEs (≥ 15%) were dizziness, headache, and somnolence, with frequencies greatest in the first year. • AEs occurring in > 10% of patients were dizziness, headache, somnolence, fatigue, contusion, back pain, nasopharyngitis, and upper respiratory tract infection. • AEs led to discontinuation in 12.3%, dose interruption in 4.3%, dose reduction in 32.6%, and dose increase in 3.6% of patients. • One death of a morbidly obese patient occurred during the study, due to cardiac arrest and considered unrelated to treatment, but sudden unexpected death from epilepsy could not be ruled out. • There were no clinically significant differences in laboratory values. • The mean change in body weight was 0.2 kg (range –18.0 to 17.0 kg). ***Preliminary Efficacy*** • The median change in seizure frequency per 28 days during open-label treatment was –31.5%, and –39.4% during the open-label extension maintenance period alone. • The responder rate (percent of patients achieving ≥ 50% reduction in seizure frequency) during open-label treatment was 37.0%, and 45.8% during the open-label extension maintenance period alone. • The reduction in seizure frequency observed during the core phase II studies was maintained during long-term treatment. • The median change in seizure frequency per 28 days was –43.7% in patients receiving at least 1 year of treatment, –52.0% for 2 years, –49.7% for 3 years, and –48.4% for 4 years. • The responder rate for these patients at the end of 1, 2, 3, or 4 years was 43.8%, 51.5%, 49.0%, and 50.0%, respectively. • By the interim cutoff date, 4 patients (2.9%) were seizure free, and 15 patients (10.9%) had a ≥75% reduction in seizures.
PHASE I STUDY					

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
Impact of delayed or missed dose on FYCOMPA plasma concentration ***Gidal et al, 2012***[28]	Simulated PK analysis of 19 phase I studies N = 606 subjects	Inclusion: Healthy males and females age ≥18 years, with hepatic impairment, and polydrug users Exclusion: Not reported	***Single FYCOMPA doses of 0.2 mg to 36 mg*** ***or*** ***FYCOMPA repeated QD in doses of 1 mg to 12 mg*** ***Based on FYCOMPA population PK parameters, simulated FYCOMPA concentration time profiles were created for a typical patient receiving FYCOMPA 8 mg QD.***	Effect of simulated delayed or missed dose on FYCOMPA PK for missed dose followed by delayed replacement of missed dose in the presence/absence of carbamazepine (CBZ) and missed dose followed by resumption of scheduled therapy in the presence/absence of carbamazepine (CBZ)	***Baseline Characteristics***

Baseline Characteristics of All Study Patients	
Parameter	**Value**
Gender, n (%)	
Male	436 (71.9)
Female	170 (28.1)
Subject type, n (%)	
Healthy volunteer	506 (83.5)
Mild hepatic impairment (Child-Pugh A)	6 (1.0)
Moderate hepatic impairment (Child-Pugh B)	6 (1.0)
Recreational polydrug user	88 (14.5)
Concomitant medication, n (%)	
Carbamazepine	16 (2.6)
Ketoconazole	26 (4.3)
Alcohol	53 (8.7)
Continuous variables, mean (SD)	
Age, yr [range]	32 (11.8) [18 to 76]
BMI, kg/m^2 [range]	24.5 (3.4) [18 to 46]

BMI = body mass index

Results

Missed dose

- Peak-trough fluctuation after QD dosing was relatively flat, as expected with a long $t_{1/2}$.
- The fluctuation index (FI) was greater when FYCOMPA was taken with inducing AEDs.
- After a missed dose without inducing AEDs, the FYCOMPA trough concentration was expected to decrease mildly (18.4%) preceding the next scheduled dose, whereas in the presence of inducing AEDs, the reduction was moderate (43.9%).

Delayed Replacement with or without CBZ

- Replacing a missed dose after 6 hours resulted in a mild decrease in FYCOMPA trough concentration both with and without CBZ (5.0% and 13.9%, respectively).
- Replacing a missed dose after 12 hours resulted in a mild decrease in FYCOMPA trough concentration both with and without CBZ (9.7% and 25.2%, respectively).
- Changes in FYCOMPA peak concentration were only minor after dose replacement at 6 hours (without CBZ: 1.7%; with CBZ: 2.5%) and at 12 hours (without CBZ: 2.5%; with CBZ: 5.3%).

PK of FYCOMPA With Delayed Administration Times ± an Inducing AED						
	Without inducer			**With inducer**		
	Change in C_{min} (%)	**Change in C_{max} (%)**	**FI (%)**	**Change in C_{min} (%)**	**Change in C_{max} (%)**	**FI (%)**
Adherent	NR	NR	41.3	NR	NR	122
Missed dose	–18.4	–11.8	51.2	–43.9	–15.2	159
6-hour delayed dose	–5.0	–3.0	NR	–13.9	–4.6	NR
12-hour	–9.7	–6.2	NR	–25.2	–8.7	NR

Study	Design	Inclusion/Exclusion Criteria	Treatment Regimen	Endpoints	Results/Comments
					delayed dose | | | | | | | AED = antiepileptic drug; C_{max} = maximum concentration; C_{min} = minimum concentration; FI = fluctuation index; NR = not reported

AE = adverse event; AED = antiepileptic drug; BID = twice daily; BMI = body mass index; BZD = benzodiazepine; CBZ = carbamazepine; CL/F = apparent clearance; C_{max} = maximum concentration; C_{min} = minimum concentration; CNS = central nervous system; CYP = cytochrome P450; ECG = electrocardiogram; FI = fluctuation index; ITT = intent to treat; LGS = Lennox-Gastaut syndrome; max = maximum; MID = minimally important difference; min = minimum; MTD = maximum tolerated dose; NR = not reported; NS = not significant; OXC = oxcarbazepine; PD = pharmacodynamics; PHY = phenytoin; PK = pharmacokinetics; POS = partial-onset seizures; QD = once daily; QHS = at bedtime; QOL = quality of life; QOLIE-31-P = Quality of Life in Epilepsy questionnaire; SAE = serious adverse event; SD = standard deviation; $t_{1/2}$ = half-life; TEAE = treatment-emergent adverse event.

*The QOLIE-31-P contains 30 items covering seven subscales (seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognition, medication effects, and social function) and one item covering health status. It also includes seven items addressing the overall distress related to each subscale, an item addressing the relative importance of each subscale topic, and an item, at the end of the study, addressing perception of change in overall quality of life since the start of treatment.

Summary of Evidence From Secondary Sources for FYCOMPA

Technology Assessments for FYCOMPA

Currently there have not been any technology assessments completed for FYCOMPA.

SECTION V:
Other Supporting Evidence for FYCOMPA™ (perampanel) Tablets

OTHER SUPPORTING EVIDENCE FOR FYCOMPA™

There is currently no additional relevant supporting evidence for FYCOMPA.

SECTION VI:
Supporting Information for FYCOMPA™ (perampanel) Tablets

SUPPORTING INFORMATION FOR FYCOMPA™

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