HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
24 July 2013

FYCOMPA 2 mg, film-coated tablet
B/7 (CIP: 34009 267 760 0 8)
B/28 (CIP: 34009 268 447 4 5)

FYCOMPA 4 mg, film-coated tablet
B/28 (CIP: 34009 267 762 3 7)

FYCOMPA 6 mg, film-coated tablet
B/28 (CIP: 34009 267 765 2 7)

FYCOMPA 8 mg, film-coated tablet
B/28 (CIP: 34009 267 767 5 6)

FYCOMPA 10 mg, film-coated tablet
B/28 (CIP: 34009 267 769 8 5)

FYCOMPA 12 mg, film-coated tablet
B/28 (CIP: 34009 267 771 2 8)

Applicant: EISAI SAS

INN	Perampanel
ATC Code (2012)	N03AX22 (antiepileptic drugs)
Reason for the request	**Inclusion**
List concerned	**National Health Insurance** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indication concerned	**"FYCOMPA is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older."**

Actual Benefit (AB)	**The actual benefit is substantial in the indication in the Marketing Authorisation.**
Improvement in Actual Benefit (IAB)	**FYCOMPA does not provide an improvement in actual benefit (IAB V, non-existent) compared with other antiepileptic medication used in the treatment of refractory partial-onset seizures with or without secondarily generalised seizures in patients aged 12 years and older.**
Therapeutic use	**FYCOMPA is an adjunctive treatment for partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older in cases of failed monotherapy treatments.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (centralised procedure): 26 July 2012
Prescribing and dispensing conditions	List I

ATC Classification	2012	
	N	Nervous system
	N03	Antiepileptic drugs
	N03A	Antiepileptic drugs
	N03AX	Other antiepileptic drugs
	N03AX22	perampanel

02 BACKGROUND

The applicant is requesting that FYCOMPA be included in the list of medicines refundable by the National Health Insurance and in the list of medicines approved for hospital use.

Perampanel is the first representative of the category of selective, non-competitive antagonist of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) type glutamate ionotropic receptors, present on post-synaptic neurons. Glutamate is the main excitatory neurotransmitter of the central nervous system and is involved in several neurological conditions caused by neuron hyperexcitability. Activation of AMPA receptors by glutamate is thought to be responsible for most of the rapid synaptic excitatory neurotransmission within the brain.
The precise mechanism of action of the antiepileptic effects of perampanel in humans is yet to be fully understood.

03 THERAPEUTIC INDICATION

"FYCOMPA is indicated for the adjunctive treatment of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older."

04 DOSAGE

"Posology:
Adults and adolescents:
FYCOMPA must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability.
Perampanel should be taken orally once daily before bedtime.
Perampanel at doses of 4 mg/day to 12 mg/day has been shown to be effective therapy in partial-onset seizures.

Treatment with FYCOMPA should be initiated with a dose of 2 mg/day. The dose may be increased based on clinical response and tolerability by increments of 2 mg/day to a maintenance dose of 4 mg/day to 8 mg/day. Depending upon individual clinical response and tolerability at a dose of 8 mg/day, the dose may be increased by increments of 2 mg/day to 12 mg/day. Patients who are taking concomitant medicinal products that do not shorten the half-life of perampanel (see section 4.5 of the SmPC), should be titrated no more frequently than at 2-week intervals. Patients who are taking concomitant medicinal products that shorten the half-life of perampanel (see section 4.5 of the SmPC), should be titrated no more frequently than at 1-week intervals.

When withdrawing FYCOMPA, the dose should be gradually reduced (see section 4.4 of the SmPC).

Single missed dose: as perampanel has a long half-life, the patient should wait and take his/her next dose as scheduled.

If more than 1 dose has been missed, for a continuous period of less than 5 half-lives (3 weeks for patients not taking perampanel metabolism-inducing antiepileptic drugs (AED), 1 week for other patients (see section 4.5 of the SmPC)), consideration should be given to restart treatment from the last dose level.

If a patient has discontinued perampanel for a continuous period of more than 5 half-lives, initial dosing recommendations given above should be followed.

Elderly (65 years of age and above):
Clinical studies of FYCOMPA in epilepsy did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Analysis of safety information in 905 perampanel-treated elderly subjects (in double-blind studies conducted in non-epilepsy indications) revealed no age-related differences in the safety profile. In combination with the lack of age-related difference in perampanel exposure, the results indicate that dose adjustment in the elderly is not required. Perampanel should be used with caution in elderly taking into account the drug interaction potential in polymedicated patients (see section 4.4 of the SmPC).

Renal impairment:
Dose adjustment is not required in patients with mild renal impairment. Use in patients with moderate or severe renal impairment or patients undergoing haemodialysis is not recommended.

Hepatic impairment:
Dose increases in patients with mild and moderate hepatic impairment should be based on clinical response and tolerability. For patients with mild or moderate hepatic impairment, dosing can be initiated at 2 mg. Patients should be up-titrated using 2 mg doses no faster than every 2 weeks based on tolerability and effectiveness.
Perampanel dosing for patients with mild and moderate impairment should not exceed 8 mg.
Use in patients with severe hepatic impairment is not recommended.

Paediatric population:
The safety and efficacy of perampanel in children below 12 years of age have not been established yet. No data are available.

Method of administration
FYCOMPA should be taken as single oral dose at bedtime. It may be taken with or without food (see section 5.2 of the SmPC). The tablet should be swallowed whole with a glass of water. It should not be chewed, crushed or split. The tablets cannot be split accurately as

there is no score line. To ensure the patient receives the entire dose the tablets should be swallowed whole without chewing or crushing."

05 THERAPEUTIC NEED[1]

International classification of epileptic seizures[2] distinguishes between generalised and partial-onset seizures based on clinical and electroencephalographic criteria (Table 1).

Table 1: International classification of epileptic seizures

A Generalised seizures	**B Partial seizures**
Absence: Typical Atypical Seizures: myoclonic clonic tonic tonic-clonic atonic	Simple partial seizures, with: motor symptoms somatic, sensitive or sensory symptoms vegetative symptoms psychic symptoms Complex partial seizures: Simple partial onset, followed by impairment of consciousness and/or automatism
C Partial secondarily generalised seizures With impairment of consciousness from the start of the seizure ± automatism Any partial-onset seizure can evolve to a secondarily generalised seizure.	

When prescribing an antiepileptic, the type of epilepsy and above all the type of seizure, the co-morbidities, associated treatments, the need for contraception or the desire to become pregnant in women of child-bearing age, are all taken into account.
Treatment with a first-line monotherapy introduced incrementally is recommended to avoid adverse effects at the start of treatment (gastrointestinal problems and drowsiness). If needed, this monotherapy can be progressively increased to the maximum tolerated dosage.
In case of failure or intolerance, an alternative monotherapy treatment should be introduced under the same conditions.

The use of a triple or quadruple therapy should be restricted to the most serious cases. Treatment overlapping enables switches from one molecule to another.

It is estimated that approximately 20% to 30% of partial-onset epilepsy cases are drug-resistant.

06 CLINICALLY RELEVANT COMPARATORS

Antiepileptic drugs indicated in the treatment of partial-onset epilepsy with or without secondary generalisation may be used as monotherapy or solely as a combination, like FYCOMPA. However, the majority of antiepileptic drugs can be used as a combination or as monotherapy.
They are indicated in adults and potentially in children and adolescents (Table 2).

[1] HAS, Consensus conference "Prise en charge des épilepsies partielles pharmaco-résistantes 2004" [Management of drug-resistant partial-onset epilepsy 2004].
[2] Commission on classification and terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 1981; 22:489-501.

Table 2: Antiepileptic drugs indicated in partial-onset epilepsy, based on age

3rd generation antiepileptic drugs	Indication	Adults	Adolescent	Children	Company
Only as a combination					
GABITRIL (tiagabine)	An add-on treatment for partial seizures with or without secondary generalisation where control is not achieved with other antiepileptic drugs. **In adults and adolescents 12 years and above only**	Adults	Adolescents 12 years and above		Cephalon
LYRICA (pregabalin), adult patients	LYRICA is indicated as an adjunctive therapy in partial seizures with or without secondary generalisation.	Adults			Pfizer
TROBALT (retigabine)	As an adjunctive treatment of partial onset seizures with or without secondary generalization in **patients with epilepsy aged 18 years or older**	Adults			GlaxoSmithKline
VIMPAT (lacosamide)	As adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation **in patients with epilepsy aged 16 years and above.**		Patients with epilepsy aged 16 years and above		UCB
ZEBINIX (eslicarbazepine)	As adjunctive therapy in **adults** with partial-onset seizures with or without secondary generalisation.	Adults			Eisai
As a combination or monotherapy					
EPITOMAX (topiramate),	. **As monotherapy** in adults, adolescents and children aged 6 years and above with partial-onset seizures with or without secondary generalisation or for generalised tonic-clonic seizures. . **In combination** with other **antiepileptic drugs in children from 2 years, adolescents and adults** with partial-onset seizures with or without secondary generalisation or in generalised tonic-clonic seizures, as well as in the treatment of seizures associated with Lennox-Gastaut syndrome.	Adults Adults	Adolescent Adolescent	Children aged 6 years and above Children from 2 years of age	Janssen-Cilag
KEPPRA (levetiracetam)	. KEPPRA is indicated as **monotherapy** in the treatment of partial onset seizures with or without	Adults	From 16 years		UCB

	secondary generalisation in **patients from 16 years of age** with newly diagnosed epilepsy. . KEPPRA is indicated as **adjunctive therapy:** o in the treatment of partial onset seizures with or without secondary generalisation **in adults, children and infants from 1 month of age with epilepsy;** o in the treatment of myoclonic seizures in **adults and adolescents from 12 years of age** with juvenile myoclonic epilepsy; o in the treatment of primary generalised tonic-clonic seizures in **adults and adolescents from 12 years of age** with idiopathic generalised epilepsy.	Adults Adults Adults	 Adolescents from 12 years Adolescents from 12 years	Children and infants from 1 month	
LAMICTAL (lamotrigine)	**Adults and adolescents aged 13 years and above:** . Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures. . Seizures associated with Lennox-Gastaut syndrome. LAMICTAL® is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome. **Children and adolescents aged 2 to 12 years:** . Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome. . Monotherapy for typical absence seizures.	Adults	Adolescents aged 13 years and above *Children and* adolescents from 2 to 12 years	Children from 2 to 12 years	GlaxoSmithKline
NEURONTIN (gabapentin)	Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with or without secondary generalisation **in adults and children from 6 years of age.** Gabapentin is indicated as monotherapy in the	Adults		Children from 6 years	Pfizer

	treatment of partial seizures with and without secondary generalization in adults and adolescents from 12 years of age.				
SABRIL (vigabatrin)	. In combination with other antiepileptic drugs for patients with resistant partial epilepsy with or without secondary generalisation, where all other appropriate drug combinations have proved inadequate or have not been tolerated. .Monotherapy in the treatment of infantile spasms (West's syndrome).	Adults		Children with "infantile spasms"	Sanofi-Aventis
TRILEPTAL (oxcarbazepine)	. Treatment of partial seizures with or without secondary generalisation . As monotherapy or adjunctive antiepileptic therapy in **adults and children from 6 years of age.**	Adults		Children from 6 years	Novartis
ZONEGRAN (zonisamide)	As adjunctive therapy in **adults** with partial-onset seizures with or without secondary generalisation. As monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults with newly diagnosed epilepsy.	Adults			Eisai
. 1st and 2nd generation antiepileptic drugs:					
DEPAKINE (sodium valproate)	**Adults and children:** . Either as monotherapy, or in combination with another antiepileptic treatment: . Treatment of generalised seizures: clonic, tonic, tonic-clonic, absence, myoclonic, atonic seizures and Lennox-Gastaut syndrome seizures. . Treatment of partial-onset seizures: partial seizures with or without secondary generalisation **Children:** Prevention of relapse in seizures after one or several febrile convulsions with complicated febrile convulsion criteria, in the absence of efficacy of intermittent prophylaxis with benzodiazepines.	Adults		Children	Sanofi-Aventis
DIHYDAN (phenytoin)	**In adults:** . Either as monotherapy.	Adults		Children	Alkopharma

	. or in combination with another antiepileptic treatment . Treatment of generalised seizures: tonic-clonic seizures. . Treatment of partial-onset seizures: partial seizures, with or without secondary generalisation. **In children:** . Either as monotherapy. . or in combination with another antiepileptic treatment . Treatment of generalised seizures: tonic-clonic seizures. . Treatment of partial-onset seizures: partial seizures, with or without secondary generalisation.				
GARDENAL (phenobarbital)	**Adults, Children** Either as monotherapy, or in combination with another antiepileptic treatment: . Treatment of generalised seizures: clonic, tonic and tonic-clonic seizures. . Treatment of partial-onset seizures: partial seizures, with or without secondary generalisation	Adults		Children	Sanofi-Aventis
MYSOLINE (primidone)	**In adults:** . either as monotherapy, . or in combination with another antiepileptic treatment: - Treatment of generalised seizures: clonic, tonic and tonic-clonic seizures. - Treatment of partial-onset seizures: partial seizures, with or without secondary generalisation. **In children:** . either as monotherapy, . or in combination with another antiepileptic treatment: - Treatment of generalised seizures: clonic, tonic and tonic-clonic seizures. - Treatment of partial-onset seizures: partial seizures, with or without secondary generalisation.	Adults		Children	SERB
TEGRETOL (carbamazepine)	Epilepsy: **Adults and children:** As monotherapy, or in combination with another	Adults		Children	Novartis

	antiepileptic treatment: . Treatment of partial-onset seizures, with or without secondary generalisation. . Treatment of generalised seizures: tonic-clonic seizures.				

The antiepileptic drugs that can be used as adjunctive therapy in children with partial-onset seizures are:

DEPAKINE (sodium valproate)
DIHYDAN (phenytoin)
EPITOMAX (topiramate)
GABITRIL (tiagabine)
KEPPRA (levetiracetam)
GARDENAL (phenobarbital)
LAMICTAL (lamotrigine)
MYSOLINE (primidone)
NEURONTIN (gabapentin)
TEGRETOL (carbamazepine)
TRILEPTAL (oxcarbazepine)
VIMPAT (lacosamide), from 16 years of age.
The treatment chosen depends on the type of epilepsy and the specific characteristics of the patient.

The actual benefit of these medicinal products is substantial.
The Transparency Committee concluded that, in the treatment of partial-onset seizures, these medicinal products do not provide an improvement in the actual benefit.

◗ Conclusion

The active comparators cited are all clinically relevant.

07 ANALYSIS OF AVAILABLE DATA

The evaluation of the efficacy and safety of perampanel is based on three phase III studies (studies 304, 305 and 306).
The methods for studies 304, 305 and 306 were similar and enabled a pooled analysis of their results to be carried out.

07.1 Efficacy

Method

Studies 304, 305 and 306 were all multi-centred, randomised, double-blind placebo-controlled studies. Their aim was to compare the efficacy and safety of perampanel (at various doses) with that of the placebo in children aged 12 years and above with refractory partial-onset seizures that had already been treated with one to three antiepileptic drugs.
Perampanel or placebo was combined with the antiepileptic treatments the patients were already taking (1 to 3 antiepileptic drugs before inclusion).
These were superiority studies.

Inclusion and exclusion criteria

The main inclusion criteria were:

- patients of both genders, aged 12 years and above (in Germany, Bulgaria, France, The Netherlands, Portugal, Lithuania, India and China the age had to be ≥18 years);
- patients with uncontrolled partial-onset seizures despite treatment including at least two different antiepileptic drugs during the last two years;
- patients being treated with stable doses of one to three antiepileptic drugs. Only one single enzyme inducer (carbamazepine, phenytoin, phenobarbital or primidone) could be prescribed within these three antiepileptic drugs.

The main exclusion criteria were:

- patients with epilepsy or frequent generalised seizures, such as absence and/or monoclonic seizures;
- patients with a history of Lennox-Gastaut syndrome, a history of status epilepticus in the 12 months prior to the 1st visit;
- concomitant use of vigabatrin. Patients who had been treated with vigabatrin needed to have discontinued treatment 5 months prior to visit 1.

Treatments

These studies were organised into three stages:

- A pre-randomisation phase lasting 6 weeks:

During this phase, each patient was required to have had at least five seizures (at least two partial seizures per three week period) and no seizure-free period lasting more than 25 days.

- A double-blind phase lasting 19 weeks:

This phase started at the second visit (week 6) and included two periods: one titration period and one maintenance period.

Patients were randomised into two equal groups receiving either the placebo or perampanel at a dose of 2, 4, 8 or 12 mg/day depending on the study (see Figures 1 and 2), in addition to the antiepileptic treatment already in placeat inclusion in this double-blind phase.

  - The 6 week titration phase:

During this titration period, all patients started by receiving 6 tablets: one 2 mg perampanel tablet and 5 placebo tablets or 6 placebo tablets. In the 4, 8 and 12 mg groups, the dose was gradually increased by replacing the placebo tablets with perampanel tablets (weekly increments of 2 mg to achieve target dose). In agreement with the investigators, dosage adjustments could be made in cases of poor tolerance, with changes being made in a single step where possible.

  - The 13 week maintenance phase:

During the maintenance period, patients continued with the blind treatment, taking a single daily dose.

Dosage adjustments during this stage were not recommended, except if the investigator judged it necessary or in cases of a non-tolerable adverse event.

Patients completing the double-blind phase could then be included in an open-label follow-up study (study 307).

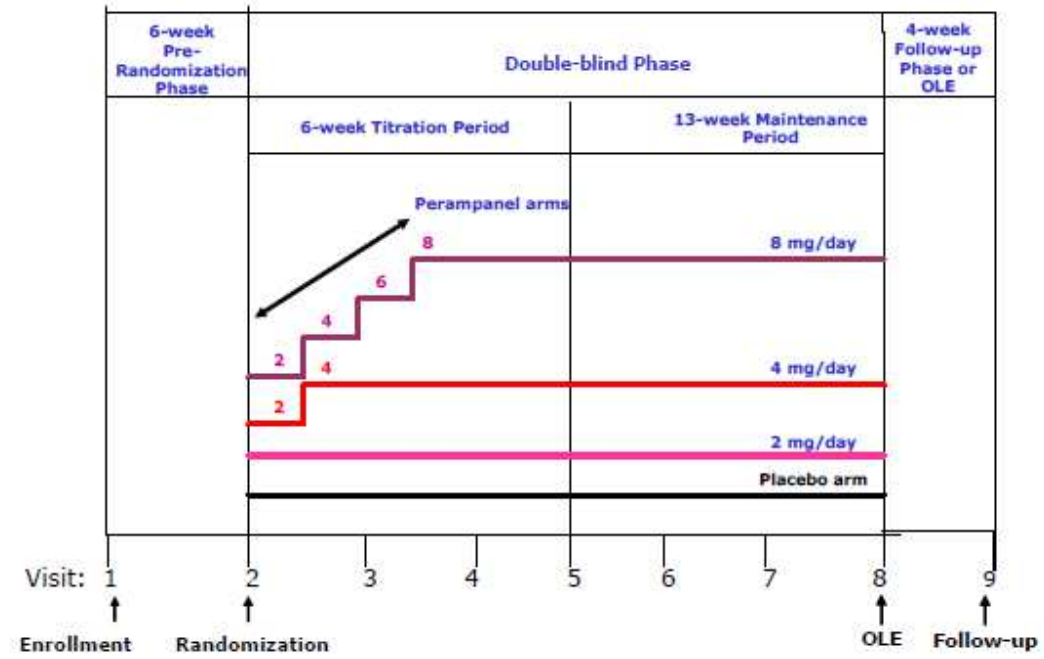
- Follow-up phase:

Patients who completed the double-blind phase and were not eligible to continue with perampanel,therefore not included in the open-label extension study, as well as those who stopped their treatment prematurely during the double-blind phase, were entered into the follow-up phase.

During this phase, which lasted 4 weeks, patients continued to be treated with their initial antiepileptic medication.

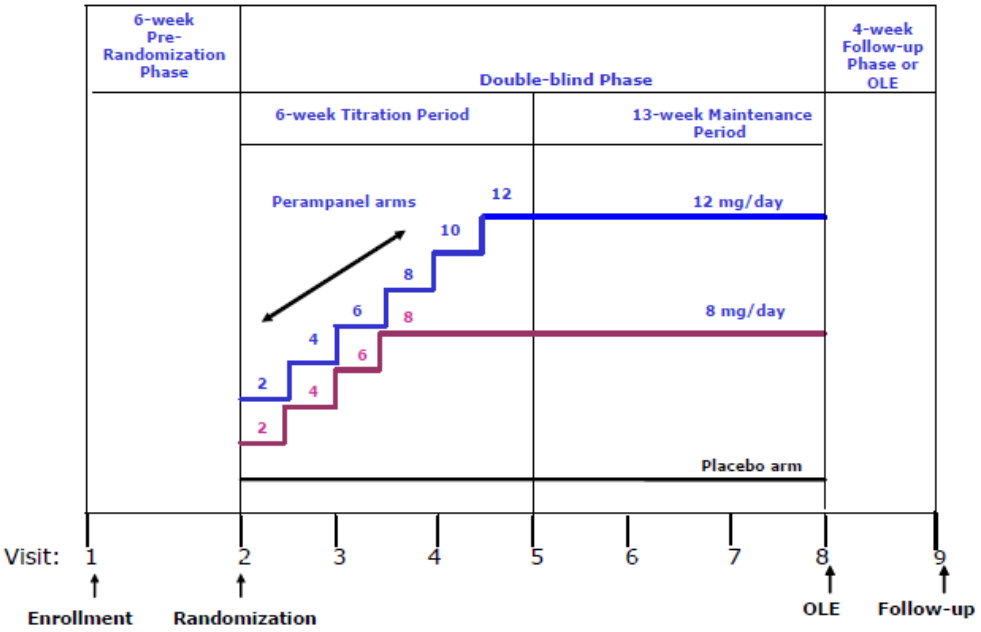
Study treatment regimens are presented in Figures 1 and 2.

Figure 1 – Study 306: treatment regimen



OLE: Open Label Extension

Figure 2 – Studies 305 and 304: treatment regimen



OLE: Open Label Extension

Endpoints

Primary endpoints:

The primary endpoint used by the EMA was defined as the responder rate, i.e. proportion of patients achieving a reduction in the frequency of seizures by at least 50% over a 28 day

period of treatment during the maintenance phase compared with the baseline seizure frequency.

The FDA used the variation in the frequency of seizures as the primary endpoint: variation evaluated over a 28 day period in comparison with the baseline frequency. The sample sizes were calculated based on this endpoint. This endpoint was used by the EMA as a secondary endpoint.

Secondary and exploratory endpoints included:
- Variation in frequency of complex partial seizures and secondarily generalised seizures: the variation was evaluated over a 28 day period in comparison with the baseline frequency.
- Proportion of patients with no seizure during the maintenance phase.

Number of patients included

Results from the phase II studies suggested that the variation in frequency of the occurrence of seizures during the maintenance phase compared with the pre-randomisation phase are 10% in the placebo group, 26% in the perampanel 4 mg/day group and 32% in the perampanel 8 mg/day group.

Study 306

A sample size of 162 patients per treatment group enabled a power of 92% likely to highlight a difference of 22% in terms of variation in the frequency of the occurrence of seizures between the perampanel 8 mg/day group and the placebo group with an α risk of 0.05.

This sample of 162 patients per treatment group was satisfactory to achieve a power of 71% to highlight a difference of 16% in terms of the variation in the frequency of the occurrence of seizures between the perampanel 4 mg/day group and the placebo group with an α risk of 0.05.
By taking into account the patients who could be randomised but not included in the ITT population, the number of patients randomised needed to be in the order of 170 per treatment group.

The sample of 162 patients per treatment group was satisfactory to achieve a power of 96% to highlight a difference of 16% in terms of response to treatment between the placebo group and the perampanel 8 mg/day group with an α risk of 0.05.
A power of 80% was achieved to highlight a difference of 12% in terms of patients responding to treatment between the placebo group and the perampanel 4 mg/day group.

Studies 305 and 304

A sample size of 120 patients per treatment group achieved a power of 83% likely to highlight a difference of 22% in terms of variation in the frequency of the occurrence of seizures between the perampanel 8 mg/day group and the placebo group with an α risk of 0.05.
By taking into account the patients who could be randomised but not included in the ITT population, the number of patients randomised needed to be of the order of 125 per treatment group.
This sample of 120 patients per treatment group was satisfactory to achieve a power of 90% to highlight a difference of 16% in terms of response to treatment between the placebo group and the perampanel 8 mg/group with an α risk of 0.05.

Conclusion regarding the determination of the sample sizes:

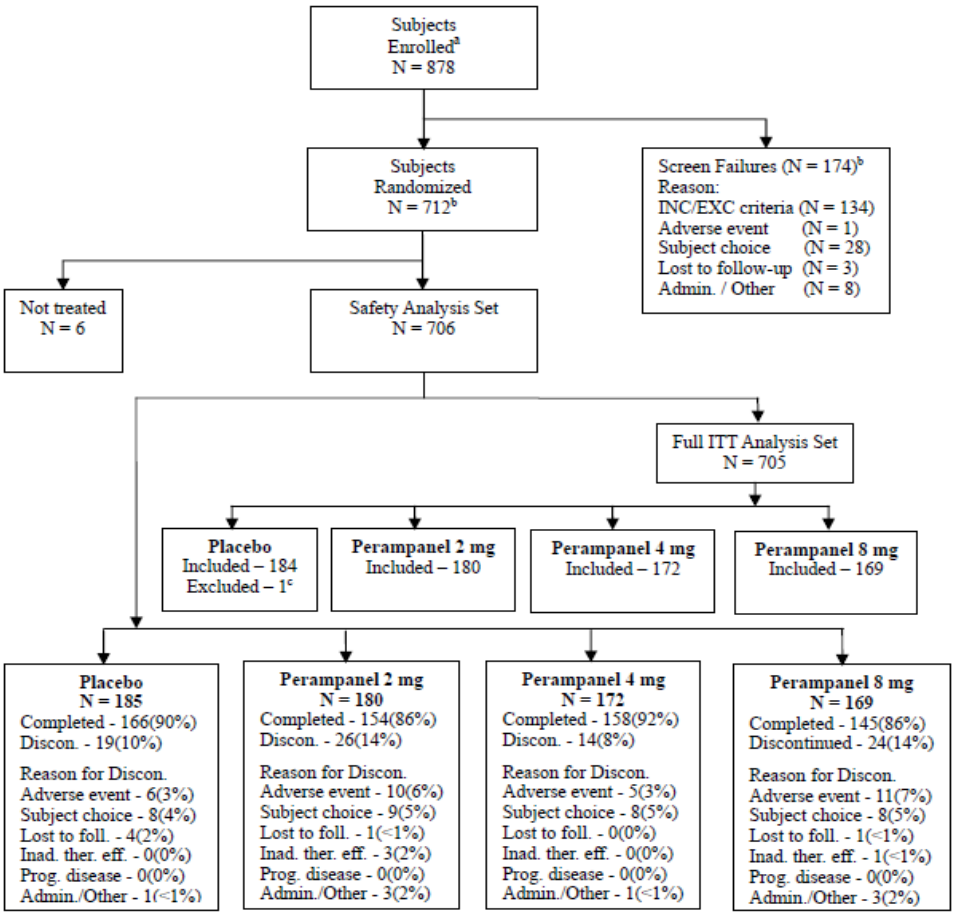
For the three studies, the sample size was based on the endpoint of the FDA, i.e. on the variation in frequency of seizures. Calculation of the number of patients to include based on the responder rate endpoint would have led to more reduced sample sizes.

7.1.1 Study 306[3]

Distribution of participants

A total of 712 patients were randomised into the four treatment groups: placebo, perampanel 2, 4 or 8 mg/day. Of the 712 randomised patients, 704 patients were eligible and 8 other patients did not meet the inclusion and exclusion criteria and were unduly randomised. Six of these eight patients were excluded; the two other patients (one in the placebo group and one in the perampanel 2 mg/day group) continued with the study.
In summary, 706 patients received at least one dose of the study treatment. The distribution of patients in the four study groups is presented in Figure 3.

Figure 3 – Study 306: Distribution of patients



a Patients who signed an informed consent.
b Including the 8 patients who failed inclusion but were unduly randomised into one of the treatment groups.
c One patient was treated for one day and did not complete the follow-up document the same day.

Patient characteristics

Demographic information and characteristics of the randomised population who received at least one dose of treatment (ITT population, n=706) were similar between the four treatment groups.

[3] Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 2012; 78(18): 1408-15.

Most patients were aged between 18 and 64 years while 60 patients (8.5%) were under 18 years of age.
The mean time since diagnosis was approximately 19 years.
At the start of the study, 14.7% of patients were treated with a monotherapy, 48.2% with two antiepileptic drugs and 37.1% with three antiepileptic drugs. The distribution of patients was similar between the four treatment groups. The most commonly prescribed antiepileptic drugs (more than 10% in at least one of the treatment groups) were valproic acid, lamotrigine, carbamazepine, levetiracetam, topiramate, oxcarbazepine and clobazam.

Results

Responder patients

A patient was considered a responder to treatment if he/she experienced a reduction by at least 50% in the frequency of the occurrence of seizures over a 28 day period compared with the frequency observed during the pre-randomisation phase.
Results for responder patients are presented in Table 3.

Table 3 – Study 306: responder patients

n (%)	**Placebo n=184**	**Perampanel 2 mg/day n=180**	**Perampanel 4 mg/day n=172**	**Perampanel 8 mg/day n=169**
Responders	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)
Non-responders	151 (82.1)	143 (79.4)	123 (71.5)	110 (65.1)
p versus placebo		NS	0.0132	0.0003

NS: not significant

The patient responder rate was significantly higher than placebo in the perampanel 4 and 8 mg/day groups, but not in the perampanel 2 mg/day group.

Analysis in the children and adolescents aged 12-17 years sub-group:
This analysis was scheduled *a priori* in the protocol (and also in studies 305 and 304).
Results for the number of responder patients for children and adolescents are presented in Table 4.

Table 4 – Study 306: responder patients in the children and adolescents sub-group

n (%)	**Placebo n=14**	**Perampanel 2 mg/day n=21**	**Perampanel 4 mg/day n=13**	**Perampanel 8 mg/day n=12**
Responders	2 (14.3)	1 (4.8)	3 (23.1)	4 (33.3)
Non-responders	12 (85.7)	20 (95.2)	10 (76.9)	8 (66.7)

p versus placebo not available

The patient responder rate was higher in the perampanel 4 and 8 mg/day groups than that in the placebo group but due to the small number of patients involved, no test was performed. These results are therefore to be interpreted with caution.

Variation in the frequency of the occurrence of seizures

Variation in the frequency of the occurrence of seizures was evaluated over a 28 day period during the double-blind phase compared with the frequency observed during the pre-randomisation phase.
Results for this variation are presented in Table 5.

Table 5 – Study 306: variation in the frequency of the occurrence of seizures

	Placebo n=184	Perampanel 2 mg/day n=180	Perampanel 4 mg/day n=172	Perampanel 8 mg/day n=169
Frequency of seizures during pre-randomisation phase - Median	9.33	10.12	10.02	10.93
Variation versus pre-randomisation phase (%) - Median	-10.69	-13.63	-23.33	-30.80
p versus placebo		NS	0.0026	<0.0001

A significant lowering in the frequency of the occurrence of seizures was observed in the perampanel 4 and 8 mg/day groups compared with that of the placebo group, with a difference compared with placebo of approximately 14% to 20% depending on the group.

Analysis in the children and adolescents (12-17 years) sub-group:
The results for this variation are presented in Table 6.

Table 6 – Study 306: variation in the frequency of the occurrence of seizures in the children and adolescent sub-group

	Placebo n=14	Perampanel 2 mg/day n=21	Perampanel 4 mg/day n=13	Perampanel 8 mg/day n=12
Frequency of seizures during pre-randomisation phase - Median	12.95	18.44	12.67	55.44
Variation versus pre-randomisation phase (%) - Median	4.57	12.77	-23.91	-34.61

p versus placebo not available

In children and adolescents, an increase in the frequency of seizures by approximately 5% in the placebo group and approximately 13% in the perampanel 2 mg/day group was observed, while this frequency was lowered by 24% to 35% in the perampanel 4 and 8 mg/day groups.

Variation in frequency of the occurrence of complex partial seizures and secondarily generalised seizures
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures was evaluated over a 28 day period during the double-blind phase compared with the frequency during the pre-randomisation phase.
Results for this variation are presented in Table 7.

Table 7 – Etude 306: variation in frequency of the occurrence of complex partial seizures and of secondarily generalised seizures

	Placebo n=184	Perampanel 2 mg/day n=180	Perampanel 4 mg/day n=172	Perampanel 8 mg/day n=169
Frequency of seizures during pre-randomisation phase - Median	6.15	6.83	7.51	7.70
Variation versus pre-randomisation phase (%) - Median	-17.63	-20.50	-31.18	-38.69
p versus placebo		NS	0.0070	0.0005

A variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures was observed in favour of the perampanel 4 and 8 mg/day groups (-31.18% and -38.69%) compared with placebo (-17.63%). There was no difference highlighted between the perampanel 2 mg/day group and the placebo for this endpoint.

Percentage of seizure-free patients
The proportions of patients who completed the maintenance phase and were seizure-free during this period were as follows in the different study groups:
- 1.2% in the placebo group,
- 1.9% in the perampanel 2 mg/day group (NS),
- 4.4% in the perampanel 4 mg/day group (NS),
- 4.8% in the perampanel 8 mg/day group (NS).

Conclusion from study 306

The aim of study 306 was to compare the efficacy and safety of perampanel (2, 4 and 8 mg/day) with that of placebo as adjunctive treatment for patients aged 12 years and above with refractory partial-onset seizures who had already been treated with one to three antiepileptic drugs.
The main results are presented in Table 8.

Table 8 – Study 306: results for responder patients, variation in frequency of the occurrence of partial seizures, complex partial seizures and secondarily generalised seizures.

	Placebo (n=184)	Perampanel 2 mg/day (n=180)	Perampanel 4 mg/day (n=172)	Perampanel 8 mg/day (n=169)
Responder patients n (%)	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)
p versus placebo		NS	0.0132	0.0003
Variation in the frequency of the occurrence of seizures -Median	-10.69	-13.63	-23.33	-30.80
p versus placebo		NS	0.0026	<0.0001
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures -Median	-17.63	-20.50	-31.18	-38.69
p versus placebo		NS	0.0070	0.0005

The proportion of patients who completed the maintenance phase and were seizure-free was not significantly different between the perampanel groups and the placebo group.

Perampanel at doses of 4 and 8 mg/day demonstrated its efficacy compared with placebo in terms of responder patients and variation in the frequency of occurrence of seizures, regardless of the type of seizure.

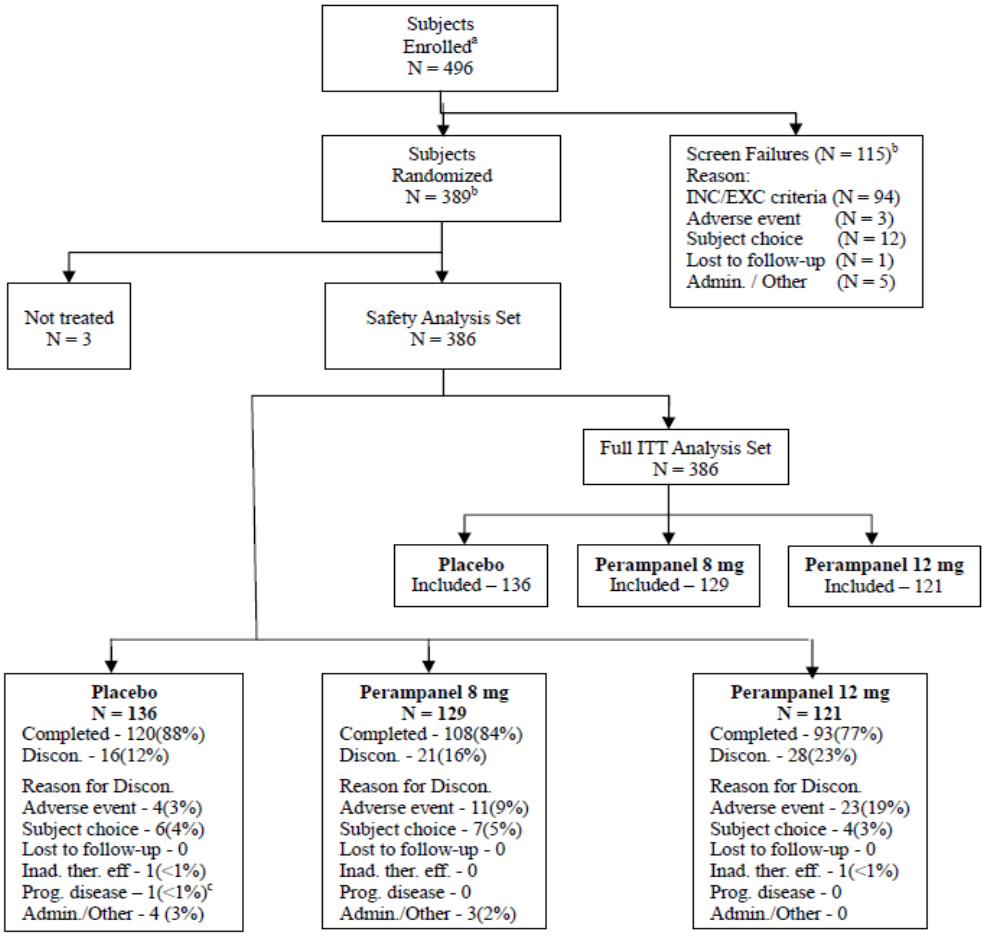
7.1.2 Study 305

Distribution of participants

A total of 389 patients were randomised into the three groups: placebo, perampanel 8 or 12 mg/day. Of the 389 patients, 381 were eligible and 8 patients did not meet the inclusion and exclusion criteria and were unduly randomised.

In summary, 386 patients received at least one dose of the study treatment. The distribution of patients in the three study groups is presented in Figure 4.

Figure 4 – Study 305: distribution of patients



a. Patients who signed an informed consent

b. Including the 8 patients who should not have been included and were inappropriately randomised into one of the treatment arms.

c. One patient was falsely considered as having disease progression instead of being classified as having progression of seizures.

Patient characteristics

Demographic information and characteristics of the randomised population who received at least one dose of treatment (ITT population, n=386) were similar between the 3 treatment groups.

Most patients were aged between 18 and 64 years (87%); 44 patients (11.4%) were under 18 years of age.

The mean time since diagnosis was approximately 22 years.

Regarding antiepileptic treatments associated with placebo or perampanel, 10.9% of patients were treated with monotherapy at the start of the study, 50.5% of patients were receiving two antiepileptic drugs and 38.6% of them were being treated with three antiepileptic drugs. The distribution of patients was similar between the three treatment groups.

The most commonly prescribed antiepileptic drugs (more than 10% in at least one of the treatment groups) were carbamazepine, phenytoin, clobazam, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproic acid and zonisamide.

Results

Responder patients

Results for the number of responder patients are presented in Table 9.

Table 9 – Study 305: responder patients

n (%)	Placebo n=136	Perampanel 8 mg/day n=129	Perampanel 12 mg/day n=121
Responders	20 (14.7)	43 (33.3)	41 (33.9)
Non-responders	116 (85.3)	86 (66.7)	80 (66.1)
p versus placebo		0.0018	0.0006

The efficacy of perampanel 8 and 12 mg/day was demonstrated versus placebo in terms of response to treatment (33-34% versus 14.7%).

Analysis in the children and adolescents (12-17 years) sub-group:
This analysis was scheduled *a priori* in the protocol.
The results for responder patients for children and adolescents are presented in Table 10.

Table 10 – Study 305: responder patients in the children and adolescents sub-group

n (%)	Placebo n=13	Perampanel 8 mg/day n=16	Perampanel 12 mg/day n=10
Responders	3 (23.1)	5 (31.3)	5 (50.0)
Non-responders	10 (76.9)	11 (68.8)	5 (50.0)

p versus placebo not available

The response to treatment is superior in the 8 and 12 mg/day groups to that of placebo. Due to the small number of patients in this sub-group, no statistical test could be carried out.

Variation in the frequency of the occurrence of seizures

Variation in the frequency of the occurrence of seizures was evaluated over a 28 day period during the double-blind phase compared with the frequency measured during the pre-randomisation phase.
Results for this variation are presented in Table 11.

Table 11 – Study 305: variation in the frequency of the occurrence of seizures

	Placebo n=136	Perampanel 8 mg/day n=129	Perampanel 12 mg/day n=121
Frequency of seizures during pre-randomisation phase - Median	11.79	13.02	13.69
Variation versus pre-randomisation phase (%) - Median	-9.72	-30.52	-17.57
p versus placebo		0.0008	0.0105

A lowering in the frequency of the occurrence of seizures was observed in favour of perampanel compared with placebo. The results were better for this endpoint in the perampanel 8 mg/day group (-30.52%) than in the perampanel 12 mg/day group (-17.57%).

Analysis in the children and adolescents (12-17 years) sub-group:
Results for this variation are presented in Table 12.

Table 12 – Study 305: variation in the frequency of the occurrence of seizures in the children and adolescents sub-group

	Placebo n=17	Perampanel 8 mg/day n=17	Perampanel 12 mg/day n=10
Frequency of seizures during pre-randomisation phase - Median	38.18	21.70	31.25
Variation versus pre-randomisation phase (%) - Median	-22.86	-32.72	-43.87

p versus placebo not available

In the small population involved a more significant lowering in the occurrence of seizures was observed in the perampanel 8 and 12 mg/day groups than in the placebo group, however the p values are not available.

Variation in frequency of the occurrence of complex partial seizures and secondarily generalised seizures
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures was evaluated in the ITT population over a 28 day period during the double-blind phase compared with the frequency measured in the pre-randomisation phase.
Results for this variation are presented in Table 13.

Table 13 – Study 305: variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures

	Placebo n=126	Perampanel 8 mg/day n=119	Perampanel 12 mg/day n=113
Frequency of seizures during pre-randomisation phase - Median	8.20	7.51	10.18
Variation versus pre-randomisation phase (%) - Median	-8.05	-32.72	-21.89
p versus placebo		0.0007	0.0045

From these results for the variation in partial seizures, the efficacy of perampanel 8 mg/day and that of perampanel 12 mg/day was demonstrated in terms of variation in the occurrence of complex partial seizures and secondarily generalised seizures. The results observed were better in the perampanel 8 mg/day group than in the perampanel 12 mg/day group.

Percentage of seizure-free patients
The proportions of patients from the ITT population who completed the maintenance phase and were seizure-free during this period were as follows in the different study groups:
- 1.7% in the placebo group,
- 2.8% in the perampanel 8 mg/day group (not significant),
- 6.5% in the perampanel 12 mg/day group (not significant).

Conclusion from study 305

The aim of study 305 was to compare the efficacy and safety of two dosages of perampanel (8 and 12 mg/day) with that of placebo as adjunctive treatment for patients aged 12 years and above with refractory partial-onset seizures who had already been treated with one to three antiepileptic drugs.

The main results are presented in Table 14.

Table 14 – Study 305: results for responder patients, variation in frequency of the occurrence of partial seizures, complex partial seizures and secondarily generalised seizures.

		Perampanel	
	Placebo (n=136)	**8 mg/day (n=129)**	**12 mg/day (n=121)**
Responder patients n (%)	20 (14.7)	43 (33.3)	41 (33.9)
p versus placebo		0.0018	0.0006
Variation in the frequency of the occurrence of seizures -Median	-9.72	-30.52	-17.57
p versus placebo		0.0008	0.0105
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures - Median	-8.05	-32.72	-21.89
p versus placebo		0.0007	0.0045

The proportion of patients who completed the maintenance phase and were seizure-free was not significantly different between the treatment groups.

Compared with placebo, the results in the perampanel 12 mg/day group were inferior to those observed in the perampanel 8 mg/day group in terms of response to treatment, variation in the frequency of the occurrence of partial seizures, complex partial seizures and secondarily generalised seizures.

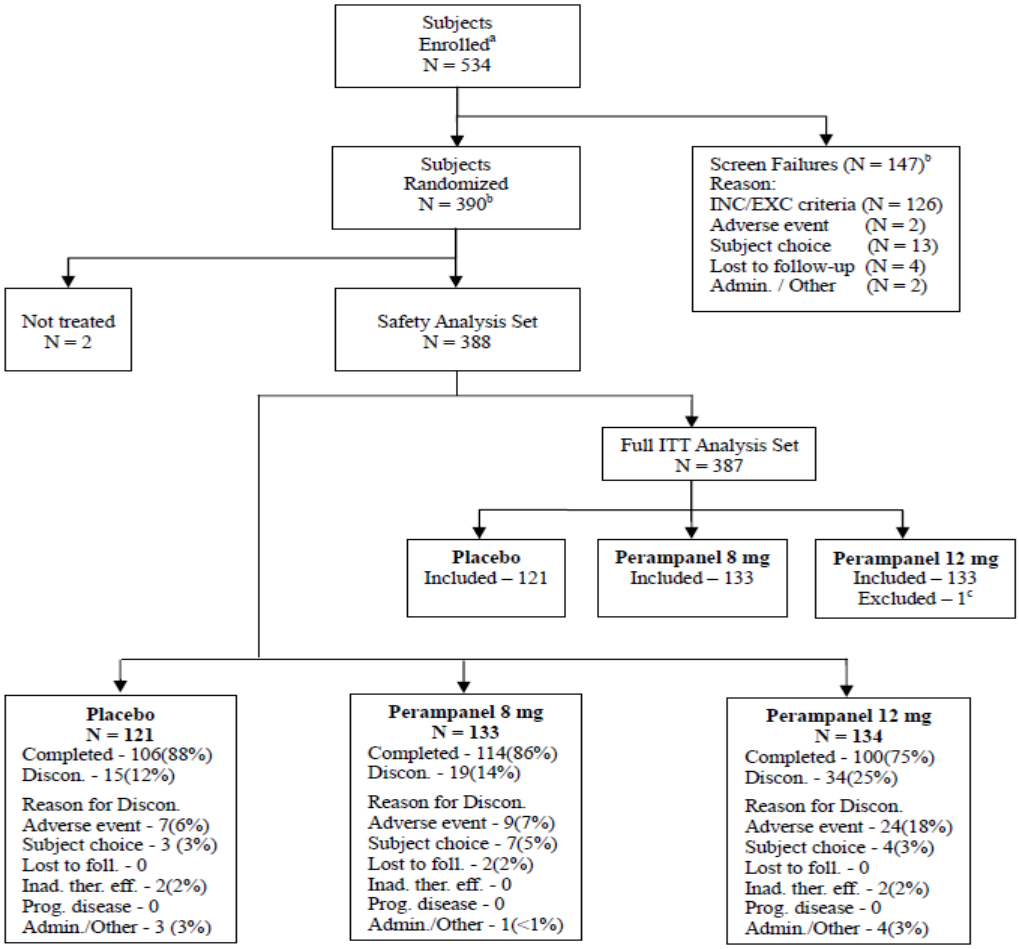
7.1.3 Study 304[4]

Distribution of participants

A total of 390 patients were randomised into the three groups: placebo, perampanel 8 or 12 mg/day. Of the 390 patients, 387 patients were eligible and three other patients did not meet the inclusion and exclusion criteria and were unduly randomised.
In summary, 388 patients received at least one dose of the study treatment. The distribution of patients in the three study groups is presented in Figure 5.

[4] French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures. Randomized phase III study 304. Neurology 2012; 79:589-96.

Figure 5 – Study 304: distribution of patients during the study



a. Patients who signed an informed consent.
b. Including the 3 patients who should not have been included and were incorrectly randomised into one of the treatment arms.
c. One patient was treated for one day and did not complete the follow-up document the same day.

Patient characteristics

Demographic information and characteristics of the randomised population and who received at least one dose of treatment (ITT population, n=388) were similar between the three treatment groups.
Most patients were aged between 18 and 64 years (86.9%); only 10.1% (n=39) of patients were under 18 years old.
The mean time since diagnosis was approximately 23.6 years.

Regarding antiepileptic treatments associated with placebo or perampanel, 15.5% of patients were treated with monotherapy at the start of the study, 55.7% of patients were taking two antiepileptic drugs and 28.9% were treated with three antiepileptic drugs. The distribution of patients was similar for the three treatment groups. The most commonly prescribed antiepileptic drugs (more than 10% in at least one of the treatment groups) were carbamazepine, lamotrigine, levetiracetam, valproic acid, oxcarbazepine, topiramate, phenytoin, clonazepam and zonisamide.

Results

Responder patients

Results for responder patients are presented in Table 15.

Table 15 – Study 304: responder patients

n (%)	Placebo n=121	Perampanel 8 mg/day n=133	Perampanel 12 mg/day n=134
Responders	32 (26.4)	50 (37.6)	48 (36.1)
Non-responders	89 (73.6)	83 (62.4)	85 (63.9)
p versus placebo		NS	NS

No significant difference was highlighted between the perampanel groups and the placebo group.

A sub-group analysis, scheduled in the protocol, was carried out in order to determine the reason why the results were discordant with those of Studies 306 and 305. This analysis showed that in North America the rate of responder patients was more significant in the 8 mg and 12 mg groups (40.5% and 40.0% respectively) compared with the placebo group (21.9%), i.e. comparable results to those observed in Europe. In contrast, in Central and South America, the response to treatment was fairly similar in each of the three groups (33.3%, 33.9% and 30.2% in the placebo, perampanel 8 mg/day and 12 mg/day respectively). The reason for this placebo effect is unknown.

Analysis in the children and adolescents (12-17 years) sub-group:

This analysis was scheduled *a priori* in the protocol.

The results regarding responder patients for children and adolescents are presented in Table 16.

Table 16 – Study 304: responder patients in the children and adolescent sub-group

n (%)	Placebo n=14	Perampanel 8 mg/day n=15	Perampanel 12 mg/day n=10
Responders	4 (28.6)	9 (60.0)	4 (40.0)
Non-responders	10 (71.4)	6 (40.0)	6 (60.0)

p versus placebo not available

The number of responder patients in the children and adolescents group was higher in the perampanel 8 mg/day group than in the placebo and perampanel 12 mg/day groups (p not available). These results are to be interpreted with caution.

Variation in the frequency of the occurrence of seizures

Variation in the frequency of the occurrence of seizures was evaluated over a 28 day period during the double-blind phase compared with the frequency measured during the pre-randomisation phase.

Results for this variation are presented in Table 17.

Table 17 – Study 304: variation in the frequency of the occurrence of seizures

	Placebo n=121	Perampanel 8 mg/day n=133	Perampanel 12 mg/day n=134
Frequency of seizures during pre-randomisation phase - Median	13.66	14.34	12.00
Variation versus pre-randomisation phase (%) - Median	-20.95	-26.34	-34.49
p versus placebo		0.0261	0.0158

A lowering in the frequency of the occurrence of seizures was observed in favour of the perampanel 8 mg/day and 12 mg/day groups compared with that in the placebo group.

Analysis in the children and adolescents (12-17 years) sub-group:
Results for this variation are presented in Table 18.

Table 18 – Study 304: variation in the frequency of the occurrence of seizures in the children and adolescent sub-group

	Placebo n=14	Perampanel 8 mg/day n=15	Perampanel 12 mg/day n=10
Frequency of seizures during pre-randomisation phase - Median	16.27	13.66	21.47
Variation versus pre-randomisation phase (%) - Median	-15.90	-56.45	-35.56

p versus placebo not available

In the children and adolescents sub-group, the lowering in the frequency of the occurrence of seizures was more significant in the perampanel 8 mg/day group than in the placebo and perampanel 12 mg/day groups, however due to small size of the population in this sub-group, no test was carried out. These results should therefore be interpreted with caution.

Variation in frequency of the occurrence of complex partial seizures and secondarily generalised seizures
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures was evaluated in the ITT population over a 28 day period during the double-blind phase compared with the frequency measured in the pre-randomisation phase.
Results for this variation are presented in Table 19.

Table 19 – Study 304: Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures

n (%)	Placebo n=121	Perampanel 8 mg/day n=133	Perampanel 12 mg/day n=134
Frequency of seizures during pre-randomisation phase - Median	9.45	8.20	9.68
Variation versus pre-randomisation phase (%) - Median	-17.88	-33.03	-33.06
p versus placebo		0.002	0.0081

A significant reduction by approximately 1/3 was observed in the frequency of the occurrence of complex partial and secondarily generalised seizures in the perampanel 8 mg/day and 12 mg/day groups compared with the placebo group, which was 18%.

Percentage of seizure-free patients
The proportions of patients in the ITT population who completed the maintenance phase and were seizure-free during this period were as follows in the different study groups:
- 0% in the placebo group,
- 2.6% in the perampanel 8 mg/day group (not significant),
- 2.0% in the perampanel 12 mg/day group (not significant).

Conclusion from Study 304

The aim of Study 304 was to compare the efficacy and safety of two dosages of perampanel (8 and 12 mg/day) with that of placebo as adjunctive treatment for patients aged 12 years and above with refractory partial-onset seizures who had already been treated with one to three antiepileptic drugs.

The main results are presented in Table 20.

Table 20 – Study 304: results for responder patients, variation in the frequency of the occurrence of partial seizures, complex partial seizures and secondarily generalised seizures.

		Perampanel	
	Placebo (n=121)	**8 mg/day (n=133)**	**12 mg/day (n=133)**
Responder patients n (%)	32 (26.4)	50 (37.6)	48 (36.1)
p versus placebo		0.0760	0.0914
Variation in the frequency of the occurrence of seizures -Median	-20.95	-26.34	-34.49
p versus placebo		0.0261	0.0158
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures -Median	-17.88	-33.03	-33.06
p versus placebo		0.0020	0.0081

The proportion of patients who completed the maintenance phase and were seizure-free was not significantly different between the treatment groups.

There was no significant difference between the perampanel groups and the placebo group for the response to treatment endpoint (similar results observed in South and Central America, see above). The lowering in the occurrence of partial seizures was greater in the perampanel groups than in that of the placebo group.
Regarding complex partial seizures with secondary generalisation, the results are similar in both perampanel groups.

7.1.4 Pooled analysis of the phase III studies

A pooled analysis of the results from the three studies was scheduled in the protocol. A total of 1,480 patients had been randomised, including 143 children and adolescents. In total, 1,478 patients were included in the ITT population.
The demographic characteristics were similar in all five groups.
The mean time since diagnosis was over 20 years in all groups.

A summary of the number of antiepileptic drugs combined with perampanel at the time of randomisation as well as the most commonly used antiepileptic agents are presented in Table 21.

Table 21 – Pooled analysis: summary of the number of antiepileptic drugs taken and the most commonly used antiepileptic drugs

		Perampanel			
	Placebo n=442	**2 mg/day n=180**	**4 mg/day n=172**	**8 mg/day n=431**	**12 mg/day n=255**
Number of antiepileptic drugs at the time of randomisation, n (%)					
1	60 (13.6)	30 (16.7)	19 (11.0)	69 (16.0)	28 (11.0)
2	218 (49.3)	80 (44.4)	88 (51.2)	220 (51.0)	145 (56.9)
3	164 (37.1)	70 (38.9)	65 (37.8)	141 (32.7)	82 (32.2)
Patients who received one of the 4 most commonly used antiepileptic drugs, n (%)					
Carbamazepine	143 (32.4)	58 (32.2)	56 (32.6)	138 (32.0)	96 (37.6)
Valproic acid	140 (31.7)	80 (44.4)	75 (43.6)	120 (27.8)	63 (24.7)
Lamotrigine	125 (28.3)	56 (31.1)	68 (39.5)	146 (33.9)	63 (24.7)
Levetiracetam	125 (28.3)	48 (26.7)	45 (26.2)	130 (30.2)	87 (34.1)

During randomisation, the majority of patients received two antiepileptic drugs or more (1: n=206 (13.9%); 2: n=751 (50.7%); 3: n=522 (35.3%)).
The most commonly used adjunctive antiepileptic drugs were carbamazepine (n=491: 33.2%), valproic acid (n=478; 32.3%), lamotrigine (n=458; 30.9%) and levetiracetam (n=435; 29.4%).

In total 143 children and adolescents aged between 12 and 17 years who were randomised in the three studies 306, 305 and 304 were included in this analysis. The demographic and disease characteristics were comparable in the five treatment groups. The mean age was 14.8 years. The mean time since diagnosis was between 6 and 10 years, depending on the treatment group. At the start of the study, 18.2% of patients were treated with a monotherapy, 46.2% were taking two antiepileptic drugs and 35.7% were treated with three antiepileptic drugs.

Results

Responder patients

The results for responder patients are presented in Table 22.

Table 22 – Pooled analysis: responder patients

n (%)	Placebo n=441	Perampanel 2 mg/day n=180	Perampanel 4 mg/day n=172	Perampanel 8 mg/day n=431	Perampanel 12 mg/day n=254
Responders	85 (19.3)	37 (20.6)	49 (28.5)	152 (35.3)	89 (35.0)
Non-responders	356 (80.7)	143 (79.4)	123 (71.5)	279 (64.7)	165 (65.0)
p versus placebo		NS	p<0.05	p<0.001	p<0.001

There was no significant difference between the percentage of responder patients in the perampanel 2 mg/day group and the placebo group.
The percentage of responder patients in the perampanel 4 mg/day, 8 mg/day and 12 mg/day groups was significantly higher than that of the placebo group. The percentage of responder patients was about the same in the perampanel 8 mg/day and 12 mg/day groups.

Analysis in the children and adolescents (12-17 years) sub-group:
The results for the percentage of responder patients for children and adolescents are presented in Table 23.

Table 23 – Pooled analysis: responder patients in the children and adolescent sub-group

n (%)	Placebo n=45	Perampanel 2 mg/day n=21	Perampanel 4 mg/day n=13	Perampanel 8 mg/day n=44	Perampanel 12 mg/day n=20
Responders	10 (22.2)	1 (4.8)	3 (23.1)	18 (40.9)	9 (45.0)
Non-responders	35 (77.8)	20 (95.2)	10 (76.9)	26 (59.1)	11 (55.0)

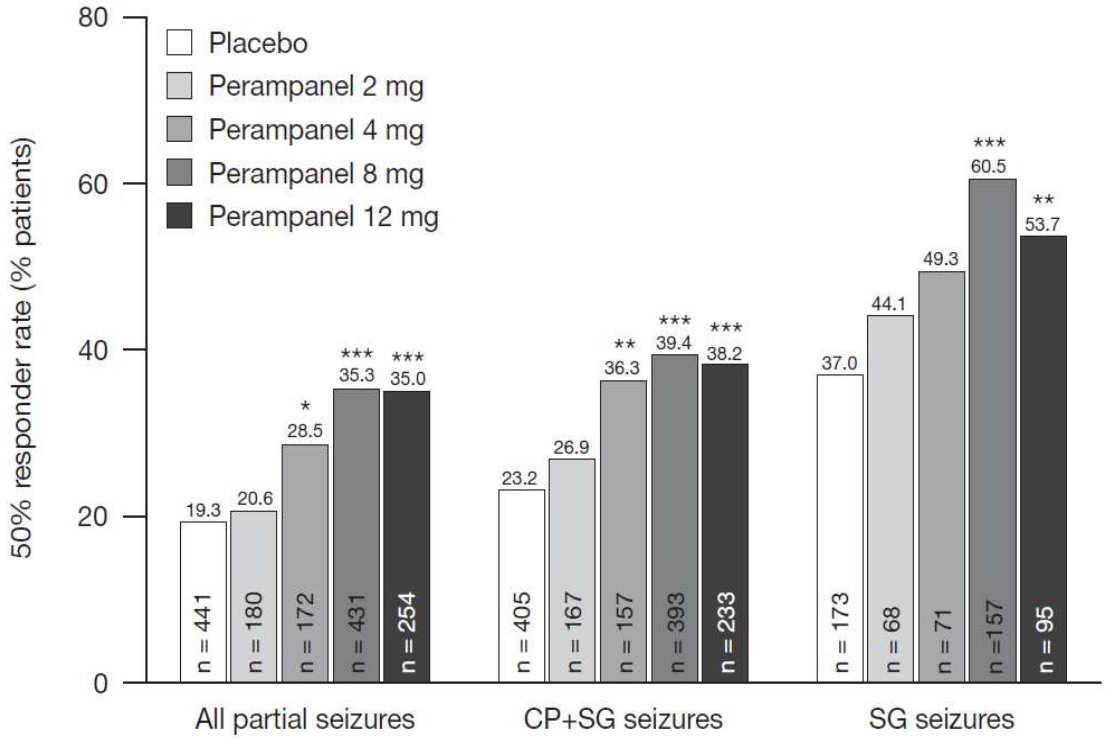
p versus placebo not available

For the pooled analysis of the results from three studies, due to the small size of thepopulation involved, no statistical test could be carried out. These results should therefore be interpreted with caution.
The percentage of responders was of the same order in the perampanel 4 mg/day and placebo groups. The percentages were also of the same order of magnitude in the perampanel 8 mg/day and 12 mg/day groups.
Due to the small size of the population involved these results should be interpreted with caution.

Variation in the frequency of occurrence as a function of the type of seizure

The pooled analysis enabled the variations in the occurrence of seizures to be evaluated by type of seizure: all partial seizures, complex partial and secondarily generalised seizures, secondarily generalised seizures. The results for this variation are presented in Figure 6.

Figure 6 – Pooled analysis: median variation in the frequency of the occurrence of seizures by type of seizure (all partial-onset types, complex partial seizures with or without secondary generalisation, secondarily generalised seizures)



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

The decrease in the frequency of seizures regardless of the type was more significant in the perampanel 8 mg/day group.
Regardless of the seizure type, no significant difference was highlighted between the perampanel 2 mg/day group and the placebo group.

Analysis in the children and adolescents (12-17 years) sub-group:
Results for this variation are presented in Table 24.
Table 24 – Pooled analysis for children and adolescents: variation in the frequency of the occurrence of partial-onset seizures

	Placebo n=45	Perampanel 2 mg/day n=21	Perampanel 4 mg/day n=13	Perampanel 8 mg/day n=44	Perampanel 12 mg/day n=20
Frequency of seizures during pre-randomisation phase - Median	18.23	18.44	12.67	17.70	23.54
Variation versus pre-randomisation phase (%) - Median	-17.97	12.77	-23.91	-34.84	-35.56

p versus placebo not available

An increase in the frequency of the occurrence of seizures was observed for patients receiving perampanel 2 mg/day. The most significant decrease in this frequency was in the perampanel 8 and 12 mg/day groups. Due to the small number of patients in this sub-group, no test was carried out.

Percentage of seizure-free patients
In the ITT population, the highest percentage of patients who were seizure-free during the maintenance phase was in the perampanel 4 mg/day group:
- 1.0% in the placebo group,
- 1.8% in the perampanel 2 mg/day group,
- 4.3% in the perampanel 4 mg/day group (p<0.05)
- 3.3% in the perampanel 8 mg/day group (p<0.05),
- 3.7% in the perampanel 12 mg/day group (p<0.05).

Conclusion from the pooled analysis

The pooled analysis is based on the evaluation of all patients randomised into the three phase III studies (306, 305 and 304).
Of the 1,480 patients included, 1,478 received at least one dose of treatment, including 143 patients who were under the age of 18 years.
At the start of the study, 13.9% of patients were treated with a monotherapy, 50.7% of patients were receiving two antiepileptic drugs and 35.3% were treated with three antiepileptic agents.

The main results are presented in Table 25.

Table 25 – Pooled analysis: results for responder patients, variation in frequency of the occurrence of partial seizures, complex partial seizures and secondarily generalised seizures.

Pooled analysis	**Placebo**	**Perampanel**			
	(n=441)	**2 mg/day (n=180)**	**4 mg/day (n=172)**	**8 mg/day (n=431)**	**12 mg/day (n=254)**
Responder patients n (%)	19.3	20.6	28.5	35.3	35.0
p versus placebo		NS	< 0.05	< 0.001	< 0.001
Median variation in frequency versus pre-randomisation phase (%)	-12.8	-13.6	-23.3	-28.8	-27.2
p versus placebo		NS	< 0.01	< 0.001	< 0.001

Pooled analysis	**Placebo**	**Perampanel**			
	(n=405)	**2 mg/day (n=167)**	**4 mg/day (n=157)**	**8 mg/day (n=393)**	**12 mg/day (n=233)**
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures - Median (%)	-13.9	-20.5	-31.2	-35.6	-28.6
p versus placebo		NS	< 0.001	< 0.001	< 0.001

This data confirmed the results from each of the phase III studies: the efficacy of perampanel 2 mg/day is not demonstrated for the endpoints presented above, however its efficacy is demonstrated at doses of 4 mg/day, 8 mg/day and 12 mg/day; the percentage of responder patients and the decrease in the frequency of seizures (regardless of the type of seizure) were slightly in favour of the 8 mg/day group compared with the perampanel 12 mg/day group.

For children and adolescents data showed better results for the perampanel 8 mg/day and 12 mg/day groups, was not be carried out. These results should therefore be interpreted with caution.

Furthermore an open-label extension study for patients who completed one of the three double-blind, placebo-controlled phase III study (studies 304, 305 and 306) is in progress. This study is scheduled to last for 5 years and started on 17 October 2008. The aim of the study is to evaluate the long-term safety of treatment with perampanel at the maximum daily dose (12 mg/day). The final results from this study are not yet available.

7.1.5 Network meta-analysis[5]

Method

This network meta-analysis was carried out in order to evaluate the relative effect of perampanel compared with three antiepileptic drugs (chosen based on the opinion of experts): lacosamide (Vimpat), retigabine (Trobalt) and eslicarbazepine (Zebinix) in terms of efficacy and safety.

The comparison criteria were as follows:

- response to treatment,
- absence of seizure,
- withdrawal from study due to an adverse effect.

These criteria were considered as dichotomous variables. The analysis was carried out based on an odds ratio.

Analysis of data from the maintenance phases was used to evaluate the percentage of responder patients and the seizure-free status. If the study did not have a maintenance phase in its design, then the results from the double-blind phase were taken into consideration.

Inclusion criteria:

The following inclusion criteria applied:

Type of study: randomised and controlled, blind, double-blind or open-label phase III studies, using either a parallel or cross-over method.

Patients:

- Patients with refractory partial-onset seizures, with or without secondary generalisation;
- Patients aged 12 years and above.

Treatments:

Patients from at least one of the treatment groups of these studies had to receive either one of the following medicinal products as an adjunctive treatment: retigabine, lacosamide, eslicarbazepine, or no adjunctive treatment or a placebo.

The three studies 306, 305 and 304 evaluating the efficacy and safety of perampanel were included.

Exclusion criteria included:

- Phase I and II studies;
- Non-comparative or non-randomised studies;
- Retrospective studies, including post hoc pooled analyses of clinical trials;
- Studies with a short follow-up period (<4 weeks);
- Studies including less than 10 patients per treatment group;
- Studies including patients treated with a monotherapy;
- Studies with surgery as a comparator;
- Patient populations aged under 12 years of age.

[5] Khan N. et al, The efficacy and tolerability of perampanel and other recently approved anti-epileptic drugs for the treatment of refractory partial onset seizure: a systematic review and Bayesian network meta-analysis, Curr Med Res Opin 2013; 29:1-13

Analysis
A network of randomised and controlled studies for each of the treatments used was created using the placebo groups from each study as a common comparator, which enabled an indirect comparison of perampanel, lacosamide, eslicarbazepine and retigabine to be made.
In summary, three studies for each of the three comparators were used.

Results:
The comparison of the treatments with each other did not show any significant difference in terms of responder patients or seizure-free patients. Results were also similar for withdrawal from the study due to an adverse event.

Comments:
The limited choice of comparators to only three comparators "of interest" (lacosamide, retigabine and eslicarbazepine) was not based on any specific scientific argument, as some products that were excluded could also be prescribed as adjunctive treatments.

The proposed methodology (meta-analysis) is retrospective in nature and it is therefore impossible to guarantee within this context that the power of the indirect comparisons is satisfactory to show a superiority of one treatment over another. The power of indirect comparisons is dependent on the number of patients included in each study, numbers which were calculated with the sole aim of guaranteeing the power of comparisons versus placebo. This limitation applies to both the evaluation of the efficacy and the relative safety. For the latter evaluation, this limit was even more problematic as studies were not designed with a power sufficient to evaluate the safety endpoints.

Thus, the conclusion of a "comparable" efficacy/safety within the aforementioned context led to an over-interpretation of the statistical results, as this conclusion is made based on the absence of a statistically significant difference.

7.1.6 Conclusion for efficacy

The efficacy of perampanel is based on three phase III studies (306, 305 and 304).
The results from these studies are presented in Table 26.
Study 306, which included 706 patients, compared the efficacy of perampanel 2, 4 and 8 mg/day with that of a placebo. The superiority of perampanel 4 and 8 mg/day compared with placebo was highlighted in terms of responder patients (28.5% and 34.9% versus 17.9%) and variation in the frequency of the occurrence of seizures (-23.33% and -30.8% versus -10.69%).
Study 305, which included 386 patients and study 304, which included 388 patients, showed the superiority of perampanel 8 and 12 mg/day compared with placebo for these same endpoints (responder patients [33.3% to 37.6% versus 14.7% to 28.4%] and variation in the frequency of the occurrence of seizures [17.57% to 34.49% versus 9.72% to 20.95%]).
Pooled analysis of data from the three studies highlighted an efficacy of the same order of magnitude for perampanel 8 and 12 mg/day compared to placebo in the general population, as well as that for children and adolescents.

Table 26 – Summary of the efficacy results for Studies 306, 305 and 304 and summary of the pooled analysis

	Study 306				Etude 305			Study 304		
		Perampanel				Perampanel			Perampanel	
	Placebo (n=184)	2 mg/day (n=180)	4 mg/day (n=172)	8 mg/day (n=169)	Placebo (n=136)	8 mg/day (n=129)	12 mg/day (n=121)	Placebo (n=121)	8 mg/day (n=133)	12 mg/day (n=133)
Responder patients n (%)	33 (17.9)	37 (20.6)	49 (28.5)	59 (34.9)	20 (14.7)	43 (33.3)	41 (33.9)	32 (26.4)	50 (37.6)	48 (36.1)
p versus placebo		NS	0.0132	0.0003		0.0018	0.0006		0.0760	0.0914
Median variation in frequency versus pre-randomisation phase (%)	-10.69	-13.63	-23.33	-30.80	-9.72	-30.52	-17.57	-20.95	-26.34	-34.49
p versus placebo		NS	0.0026	<0.0001		0.0008	0.0105		0.0261	0.0158
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures - Median (%)	-17.63	-20.50	-31.18	-38.69	-8.05	-32.72	-21.89	-17.88	-33.03	-33.06
p versus placebo		NS	0.0070	0.0005		0.0007	0.0045		0.0020	0.0081

Pooled analysis	Placebo (n=441)	Perampanel 2 mg/day (n=180)	4 mg/day (n=172)	8 mg/day (n=431)	12 mg/day (n=254)
Responder patients n (%)	19.3	20.6	28.5	35.3	35.0
p versus placebo		NS	< 0.05	< 0.001	< 0.001
Median variation in frequency versus pre-randomisation phase (%)	-12.8	-13.6	-23.3	-28.8	-27.2
p versus placebo		NS	< 0.01	< 0.001	< 0.001

Pooled analysis	Placebo (n=405)	Perampanel 2 mg/day (n=167)	4 mg/day (n=157)	8 mg/day (n=393)	12 mg/day (n=233)
Variation in the frequency of the occurrence of complex partial seizures and secondarily generalised seizures - Median (%)	-13.9	-20.5	-31.2	-35.6	-28.6
p versus placebo		NS	< 0.001	< 0.001	< 0.001

07.2 Adverse Effects

General safety profile

The safety profile was established based on the pooled analysis. The population of randomised patients who received at least one dose of perampanel and had at least one evaluation after taking their treatment included 1,478 patients: 441 in the placebo group, 180 in the perampanel 2 mg/day group, 172 in the perampanel 4 mg/day group, 431 in the perampanel 8 mg/day group and 254 in the perampanel 12 mg/day group.

Overall an adverse event was observed for 294 patients (66.5%) in the placebo group and 799 patients (77.0%) in the perampanel groups.
The most commonly observed adverse events were dizziness, somnolence and headaches. The adverse events reported for at least 5% of patients from one of the treatment groups are presented in Table 27.

Table 27: Adverse events reported for more than 5% of patients

		Perampanel			
	Placebo (n=441) n (%)	**2 mg/day** (n=180) n (%)	**4 mg/day** (n=172) n (%)	**8 mg/day** (n=431) n (%)	**12 mg/day** (n=254) n (%)
Adverse events	294 (66.5)	111 (61.7)	111 (64.5)	350 (81.2)	227 (89.0)
Dizziness	40 (9.0)	18 (10.0)	28 (16.3)	137 (31.8)	109 (42.7)
Somnolence	32 (7.2)	22 (12.2)	16 (9.3)	67 (15.5)	45 (17.6)
Headaches	50 (11.3)	16 (8.9)	19 (11.0)	49 (11.4)	4 (13.3)
Fatigue	21 (4.8)	8 (4.4)	13 (7.6)	36 (8.4)	31 (12.2)
Irritability	13 (2.9)	7 (3.9)	7 (4.1)	29 (6.7)	30 (11.8)
Nausea	20 (4.5)	4 (2.2)	5 (2.9)	25 (5.8)	20 (7.8)
Falls	15 (3.4)	2 (1.1)	(1.7)	22 (5.1)	26 (10.2)
Rhinopharyngitis	18 (4.1)	7 (3.9)	9 (5.2)	23 (5.3)	11 (4.3)
Upper respiratory tract infection	12 (2.7)	11 (6.1)	6 (3.5)	14 (3.2)	10 (3.9)
Ataxia	0 (0.0)	0 (0.0)	1 (0.6)	14 (3.2)	21 (8.2)
Balance disorder	2 (0.5)	0 (0.0)	0 (0.0)	22 (5.1)	8 (3.1)

The majority of events were mild to moderate in intensity: 24 patients (5.4%) from the placebo group and 92 patients (8.9%) treated with perampanel had a grade ≥3 event.
No death was reported during the studies.

A serious adverse event was observed for 22 patients (5.0%) from the placebo group and 57 patients (5.5%) treated with perampanel (2 mg/day: n=6 (3.3%); 4 mg/day: n=6 (3.5%); 8 mg/day: n=24 (5.6%); 8 mg/day: n=21 (8.2%)).
A serious fall event was reported for one patient treated with perampanel 12 mg/day.
Serious psychiatric events (irritability, aggression, anxiety and agitation) were reported for 4 patients (0.9%) treated with placebo and for 12 patients (1.2%) treated with perampanel.
One serious case of suicidal thoughts was observed for one patient treated with perampanel 8 mg/day.

Treatment discontinuation linked to an adverse event was observed for 99 patients (9.5%) treated with perampanel (2 mg: 6.7% [n=12]; 4 mg: 2.9% [n=5]; 8 mg: 7.7% [n=33]; 12 mg: 19.2% [n=49]) as opposed to 4.8% for placebo [n=21 patients]). The most common adverse events (≥ 1% in all perampanel groups and incidence above that observed for patients receiving the placebo) that led to treatment discontinuation were dizziness and somnolence.

Children and adolescents sub-group:
In the pooled analysis carried out on the children and adolescents sub-group, 70 of the 98 patients (71.4%) in the perampanel group and 31 of the 45 patients (68.9%) in the placebo group reported at least one adverse event.

Table 28: adverse events reported for children and adolescents

n (%)	**Placebo** (n=45) n (%)	**Perampanel** **2 mg/day** (n=21) n (%)	**4 mg/day** (n=13) n (%)	**8 mg/day** (n=44) n (%)	**12 mg/day** (n=20) n (%)	**Total** (n=98) n (%)
Adverse events	31 (68.9)	15 (71.4)	8 (61.5)	33 (75.0)	14 (70.0)	70 (71.4)
Serious adverse events	3 (6.7)	1 (4.8)	0	0	2 (10.0)	3 (3.1)
Adverse event requiring treatment discontinuation	3 (6.7)	0	0	1 (2.3)	1 (5.0)	2 (2.0)

The main adverse events reported for child and adolescent patients treated with perampanel, regardless of the dose taken, were dizziness (20.4%), somnolence (15.3%), headaches (13.3%) and rhinopharyngitis (10.2%).
The majority of these adverse events were of mild to moderate intensity.
The frequency of adverse events was similar in both the children and adolescents sub-group and the adult population. However, aggression was more commonly reported in the children and adolescents group than in the adult population: 8.2% for children and adolescents for all of the groups treated with perampanel and 1.2% for adults.

Risk Management Plan

The risk management plan (RMP) has identified the following significant risks:
- dizziness;
- somnolence;
- aggression;
- balance disorders, ataxia and falls (especially in the elderly)
- interaction with levonorgestrel-based oral contraceptives and unexpected exposure during pregnancy;
- weight gain;
- vision disorders.

The RMP scheduled a post-authorisation observational study (Study E2007-G000-402) with the aim of evaluating the long-term safety of perampanel as an adjunctive treatment for patients with partial-onset seizures.

FDA data

The FDA granted FYCOMPA a Marketing Authorisation in the U.S.A. on the condition that there was a "black box" on the risk of psychiatric effects: irritability, aggression, anger, anxiety, paranoia, euphoria, agitation and changes in mental state. According to the FDA, some of these events may be serious and potentially life-threatening.

Conclusion for safety

Approximately three quarters of patients treated with perampanel reported an adverse effect. The most commonly observed adverse events were dizziness, somnolence and headaches.
Perampanel mainly exposes the patient to neurological (vertigo, risk of falls) and psychiatric (irritability, aggression) effects, some of which can be serious.
For children and adolescents, the frequency and nature of the adverse events was similar overall to those for adults. However, aggression was more commonly reported in the children and adolescents group than in the adult population.

07.3 Summary & discussion

Different dosages of perampanel (2, 4, 8 and 12 mg/day) were evaluated in three randomised, double-blind placebo-controlled studies on patients aged 12 years and above with refractory partial-onset seizures who had already been treated with one to three antiepileptic drugs.
Perampanel or placebo was combined with patients' initial treatment (1 to 3 antiepileptic drugs before inclusion).

Perampanel at a dosage of 2 mg/day did not show any difference to the placebo.
Perampanel at the 4 mg/day, 8 mg/day and 12 mg/day dosages showed superior results to those with placebo in terms of:

- responder rate: 28.5% to 37.6% with the different dosages of perampanel versus 14.7% to 26.4% with placebo
- reduction in the frequency of seizures: 17.57% to 34.49% with the different dosages of perampanel versus 9.72 to 20.95% with placebo

A pooled analysis of the three studies highlighted a comparable efficacy for the 8 mg/day and 12 mg/day dosages of perampanel in terms of:

- responder rate: 35.3% with 8 mg/day versus 35% with 12 mg/day
- decrease in the frequency of seizures: 28.8% with 8 mg/day versus 27.2% with 12 mg/day.

Efficacy appeared to be about the same in both the general population and the children and adolescents group.

The most commonly reported adverse events were dizziness, somnolence and headaches.
The frequency of adverse effects is similar for adults and children and adolescents, apart from aggression, which is more common in children and adolescents than in adults.

No comparative study versus another antiepileptic drug is available.

08 THERAPEUTIC USE[6]

The antiepileptic treatment chosen depends on the characteristics of the epileptic syndrome and the specifics of the patient. Treatment is started with monotherapy. In current clinical practice, the monotherapy treatment chosen will depend on the epileptic syndrome and the typology of the patient: weight, gender, whether they are taking contraceptives, sleep patterns, depression, cognitive state, risk of compliance and the desire of pregnancy in women of child-bearing age.
In the treatment of partial-onset seizures, carbamazepine and sodium valproate are the standard therapies.

In the event of failure (inadequate response, adverse effects resulting in discontinuation of treatment) in spite of an adequate dosage and adequate compliance with the treatment, replacement monotherapy is gradually introduced. At least two different monotherapies must be attempted.
Addition of a second antiepileptic drug is recommended if the response to the preceding monotherapies is insufficient. It is not possible to say whether a particular drug combination should be preferred, as there are insufficient data available.
It is recommended that the epilepsy and its treatment be reassessed at a specialist centre in the event of the failure of one or more dual therapies.

In the treatment of partial-onset seizures, the therapeutic use of FYCOMPA is as an adjunctive treatment for partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and above in cases of failed monotherapy treatments.

09 TRANSPARENCY COMMITTEE CONCLUSION

In view of all of the above data and information, and following the debate and vote, the Committee's opinion is as follows:

09.1 Actual benefit

- Epileptic seizures are symptoms of a highly heterogeneous array of disorders. Over the medium- to long-term, epilepsy can markedly impair patients' quality of life.
- FYCOMPA is intended as a symptomatic treatment.
- The efficacy/adverse effects ratio is high.
- There are numerous treatment alternatives.
- FYCOMPA is a second-line treatment (after failure of at least two monotherapies) that should be used as an adjunctive therapy with another antiepileptic agent.

- Public health benefit:
  Partial-onset epilepsy is a common disease, and the repetition of the seizures in some patients can markedly impair their quality of life. Overall it is considered a moderate public health burden. The burden in respect of the population of patients with partial-onset epilepsy after failure of monotherapy is also considered moderate.
  There is a public health need insofar as drug-resistant partial-onset epilepsy is still common and is the cause of considerable disability.

[6] HAS, Consensus conference "Prise en charge des épilepsies partielles pharmaco-résistantes 2004" [Management of drug-resistant partial-onset epilepsy 2004].

According to clinical data available (placebo-controlled studies and improvement in responder rate) it is not to possible to know whether FYCOMPA will have any additional impact on morbidity and quality of life in the population treated compared with existing treatments.
In addition, it is not possible to know whether FYCOMPA, in this indication, will meet the identified public health need.
Consequently, in the current state of knowledge and in view of the fact that other therapies are already available, it is not expected that this proprietary medicinal product will benefit public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of FYCOMPA is substantial in the Marketing Authorisation indication.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indication and at the dosages in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

09.2 Improvement in actual benefit (IAB)

FYCOMPA does not provide any improvement in the actual benefit (IAB V, non-existent) compared with other antiepileptic medications used in the treatment of refractory partial-onset seizures with or without secondarily generalised seizures in patients aged 12 years and above.

09.3 Target population[7]

The target population of FYCOMPA is represented by patients aged 12 years and above with partial-onset epileptic seizures with or without secondary generalisation requiring adjunctive treatment.
The prevalence of epilepsy in France is 5 to 8/1000, that is 383,000 to 441,000 patients.
Partial-onset epilepsy represents approximately 60% of all cases of epilepsy, that is approximately 230,000 to 265,000 patients.
Monotherapy is effective for 70% to 80% of cases; therefore the number of patients receiving FYCOMPA treatment is estimated to be **46,000 to 80,000**.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ **Packaging**
They are appropriate for the prescription conditions according to the indication, the dosage and the treatment duration.

[7] Jallon P. Epidémiologie des épilepsies partielles pharmacorésistantes. Revue de neurologie. 2004;160:5S22-5S30