HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

6 July 2011

TROBALT 50 mg, film-coated tablet
B/21 (CIP code: 417 163-2)
B/84 (CIP code: 417 164-9)

TROBALT 100 mg, film-coated tablet
B/21 (CIP code: 417 165-5)
B/84 (CIP code: 417 166-1)

TROBALT 200 mg, film-coated tablet
B/84 (CIP code: 417 167-8)

TROBALT 300 mg, film-coated tablet
B/84 (CIP code: 417 168-4)

TROBALT 400 mg, film-coated tablet
B/84 (CIP code: 417 169-0)

TROBALT 50 mg/100 mg, film-coated tablet, treatment starter pack
B/21 (50 mg) + 42 (100 mg) (CIP code: 417 170-9)

Applicant: GLAXOSMITHKLINE

Retigabine

ATC code (2011): N03AX21

List I

Date of the Marketing Authorisation and its amendments: 28 March 2011

Reason for the request: Inclusion in the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Retigabine

1.2. Background

Retigabine is a first-in-class potassium channel opener for the treatment of epilepsy.

1.3. Indication

“Trobalt is indicated as adjunctive treatment of partial onset seizures with or without secondary generalisation in epileptic patients aged 18 years and over.”

1.4. Dosage

“TROBALT must be titrated, according to individual patient response, in order to optimise the balance between efficacy and tolerability.
The maximum daily starting dose is 300 mg (100 mg three times daily). Thereafter, the total daily dose is increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. An effective maintenance dose is expected to be between 600 mg/day and 1,200 mg/day.
The maximum total maintenance dose is 1,200 mg/day. The safety and efficacy of doses higher than 1,200 mg/day have not been established.
If patients miss one dose or more, it is recommended that they take a single dose as soon as they remember.
After taking a missed dose, at least 3 hours should be allowed before the next dose, and then the normal dosing schedule should be resumed.
When withdrawing TROBALT, the dose must be gradually reduced.

Renal impairment
Retigabine and its metabolites are eliminated principally by renal excretion.
No dosage adjustment is required in patients with mild renal impairment (creatinine clearance 50 to 80 ml/minute).
A 50% reduction in the initial and maintenance dose of TROBALT is recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 ml/minute).
The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose be increased by 50 mg every week, to a maximum total dose of 600 mg/day.
The effect of haemodialysis on retigabine clearance has not been adequately evaluated.

Hepatic impairment
No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6).
A 50% reduction in the initial and maintenance dose of TROBALT is recommended in patients with moderate or severe hepatic impairment (Child-Pugh score ≥ 7). The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose be increased by 50 mg every week, to a maximum total dose of 600 mg/day.

Paediatric population
The efficacy and tolerance of retigabine in children below 18 years of age have not been established yet. No data are available.

Elderly (65 years of age and above)
There are only limited data on the safety and efficacy of retigabine in patients aged 65 years and above. A reduction in the initial and maintenance dose of TROBALT is recommended in elderly patients. The total daily starting dose is 150 mg/day and during the entire maintenance period the total daily dose should be increased by a maximum of 150 mg every week, according to the individual patient response and tolerability. Doses greater than 900 mg/day are not recommended.

Method of administration
TROBALT must be taken orally in three divided doses each day. It may be taken with or without food. The tablets should be swallowed whole, and not chewed, crushed or divided."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Code (2011)

N : Nervous system
N03 : Antiepileptics
N03A : Antiepileptics
N03AX : Other antiepileptics
N03AX 21 : Retigabine

2.2. Medicines in the same therapeutic category

TROBALT (retigabine) is the only antiepileptic whose mechanism of action is potassium channel opening.

2.3. Medicines with a similar therapeutic aim

2.3.1 Medicines indicated as adjuncts in the treatment of partial onset seizures:

Oral administration

- VIMPAT (lacosamide), in patients 16 years of age and older (2009: AB substantial, IAB V, useful additional therapeutic resource).
- GABITRIL (tiagabine), in patients 12 years of age and older (AB re-evaluated in 2001: moderate)
- LYRICA (pregabalin), in adult patients (2005: AB substantial, IAB V)
- SABRIL (vigabatrin), indicated exclusively when other appropriate therapeutic adjuncts have proved inadequate or poorly tolerated. (2001: AB substantial)
- ZONEGRAN (zonisamide), in adult patients (2005: AB substantial, IAB V)
- ZEBINIX* (eslicarbazepine), in adult patients (2010: AB substantial, ASMR V)
- URBANYL (clonazepam) (1999: AB substantial)

Parenteral administration

- VIMPAT (lacosamide) (2009: AB substantial, IAB V, useful additional therapeutic resource).

2.3.2 Medicines indicated as monotherapy or in combination in the treatment of partial onset seizures

Oral administration

- EPITOMAX (topiramate) as monotherapy after failure of a previous treatment, in combination with other antiepileptics when the latter are insufficiently effective
- KEPPRA (levetiracetam)
- LAMICTAL (lamotrigine)
- NEURONTIN (gabapentin)
- TRILEPTAL (oxcarbazepine)
- DEPAKINE (sodium valproate)
- TEGRETOL (carbamazepine)
- DI-HYDAN (phenytoin)
- MYSOLINE (primidone)
- RIVOTRIL (clonazepam)

Parenteral administration

- GARDENAL (phenobarbital)
- KEPPRA (levetiracetam)

2.3.3 All other proprietary medicines indicated in the treatment of epilepsy.

3. ANALYSIS OF AVAILABLE DATA

The applicant has submitted three parallel group, randomised, double-blind, placebo-controlled clinical studies. In these three studies, retigabine or placebo was administered as an adjunct to the patient's usual treatment.

3.1. Efficacy

3.1.1 Study 205

Objective

To assess the efficacy and tolerability of three doses of retigabine as adjunctive treatment in adult partial epilepsy patients already being treated with one or two antiepileptics.

Method

Randomised study in four parallel groups (1.1.1.1)

The study comprised four phases:

- an eight-week selection and observation phase during which seizure frequency was assessed
- an eight-week retigabine titration phase
- an eight-week maintenance phase, during which patients received the dose of retigabine reached at the end of the previous phase
- an interim phase of five-weeks, during which the daily dose was adjusted to 300 mg three times a day for all patients wishing to participate in the open-label extension study, or an interim phase of three-weeks, in which the daily dose was gradually decreased for patients wishing to discontinue their treatment.

Principal inclusion criteria

- adults 16 to 70 years of age
- partial epilepsy with simple partial onset seizures having a motor component or complex partial onset seizures with or without secondary generalisation (according to the ILAE Classification)[1]
- stable treatment for at least one month with one or two antiepileptic medicines
- an average of at least four partial onset seizures in a 28-day period during the two months prior to inclusion. Patients having a seizure-free period of more than 30 consecutive days during the selection phase were not included.

Treatment

- The initial dose of retigabine was 300 mg/day, increased by 150 mg/day every week up to the target dose of the maintenance phase. If a patient did not tolerate the target dose, a weekly decrease of 100 mg/day, with a maximum decrease of 200 mg/day, was allowed; the dose reached was then maintained throughout the maintenance phase.
- During the maintenance phase, patients received 600, 900 or 1,200 mg/day of retigabine or a placebo in three divided doses in combination with their usual treatment. If a patient did not tolerate the dose reached at the start of the maintenance phase, he/she was withdrawn from the study and the daily dose was gradually decreased.
- During the interim phase, patients who did not tolerate the adjustment of the dose to 900 mg/day were withdrawn from the study and their daily dose was gradually decreased or they could participate in the open-label extension study at a lower dose.

[1] International League Against Epilepsy Classification.
http://www.ilae-epilepsy.org/Visitors/Centre/ctf/ClassificationTable2.cfm

- Adjunctive treatments: the usual admissible treatments were one or two of the following treatments: valproic acid, carbamazepine, phenytoin, topiramate, lamotrigine, gabapentin, oxcarbazepine, benzodiazepines, barbiturates and vagal stimulation. Treatments with felbamate, vigabatrin and tiagabine were not admissible.

Endpoints

- Primary endpoint: median reduction (expressed as a % of the initial value) in the monthly (28-day) frequency of partial onset seizures between the double-blind observation phase (i.e., the dose titration phase and the maintenance phase). In other words:

$$\frac{\text{Monthly frequency of partial onset seizures during the double-blind phase} - \text{baseline monthly frequency}}{\text{Baseline monthly frequency}} \times 100$$

- Main secondary endpoint: percentage of responders, defined as patients experiencing a reduction of at least 50% in seizure frequency in 28 days between the observation phase and the double-blind phase (i.e., the dose titration phase and the maintenance phase).

Statistics

The endpoint underwent a nonparametric analysis of covariance (ANCOVA) with an adjustment for the monthly frequency of seizures during the observation phase.
The secondary endpoint was analysed by logistic regression.

Results

The characteristics of the included patients are shown in *Table 1*

Table 1: Characteristics of included patients

	Placebo n = 96	Retigabine 600 mg/d n = 100	Retigabine 900 mg/d n = 95	Retigabine 1,200 mg/d n = 106
Mean age (years)	34.5 ± 10.3*	36.8 ± 10.9*	37 ± 10.1*	38.3 ± 11.9*
Baseline monthly frequency of seizures (median and [duration])	8.5 [3; 868.5]	8.5 [1; 271.4]	7.7 [3.5; 230.3]	10.4 [2.4; 220.1]
Number of epileptics, n (%) 1 2 3	 33 (34) 62 (65) 1 (1)	 26 (26) 72 (72) 2 (2)	 26 (27) 69 (73) 0	 31 (29) 74 (70) 1 (< 1)
Mean disease duration (years)	20.8 ± 11.2*	21.2 ± 12*	19.7 ± 12*	20.1 ± 11.3*

* standard deviation

The results for the primary endpoint are shown in *Table 2*

Table 2: Reduction (as a % of the baseline value) in the monthly (28-day) frequency of seizures between the observation phase and the double-blind phase – ITT population*

	Placebo n = 96	Retigabine 600 mg/day n = 99	Retigabine 900 mg/day n = 95	Retigabine 1,200 mg/day n = 106	p (overall)
Mean (%)	-3.3 ± 75†	8.6 ± 190.9†	-14,1 ± 70.3†	-23.5 ± 64.9†	-
Median (%) [range]	-13.1 [-100; 533.3]	-23.4 [-100; 1703.1]	-29.3 [-100; 297.6]	-35.2 [-100; 375]	< 0.001‡
p versus placebo ‡	-	NS	= 0.043	< 0.001	-

*: randomised patients who have taken at least one dose of the investigational product and have had a baseline evaluation of the number of seizures and at least one assessment during treatment; †: standard deviation; ‡: ANCOVA

The results for the secondary endpoint are shown in *Table 3*

Table 3: Percentage of responder patients during the double-blind period – ITT population

	Placebo n = 96	Retigabine 600 mg/day n = 99	Retigabine 900 mg/day n = 95	Retigabine 1,200 mg/ day n = 106	p (overall)
Responders (%)	15.6	23.2	31.6	33	= 0.001*
p versus placebo	-	NS	= 0.008	= 0.003	-

*: logistic regression

For the two endpoints, the overall analysis showed a significant difference between the treated groups as a whole and the placebo group. The analyses comparing each dosage group with the placebo group showed a significant difference only for the 900 and 1,200 mg/day doses.

3.1.2 Study 301

Objective

To assess the efficacy and tolerance of retigabine at a daily dose of 1,200 mg in three divided doses versus placebo as adjunctive treatment in adult patients with refractory partial epilepsy.

Method

Randomised study in two parallel groups (1.1). The study consisted of four phases:

- an eight-week selection and observation phase during which seizure frequency was assessed
- a six-week titration phase
- a twelve-week maintenance phase, during which patients received the dose reached at the end of the previous phase
- a six-week interim phase during which the patients in the active group continued to take the daily dose of 1,200 mg/day and the patients in the placebo group who wished to take part in the open-label extension study took gradually increasing doses of up to 1,200 mg/day. The patients not wishing to take part in the open-label study or not able to complete the interim phase gradually reduced the dose over a three-week period.

Principal inclusion criteria

- adults 18 to 75 years of age
- drug-resistant partial epilepsy with simple or complex partial onset seizures, with or without secondary generalisation.
  Drug-resistant epilepsy was defined partial onset seizures for at least two years despite treatment comprising at least two antiepileptics administered separately or in combination at adequate doses and for a sufficiently long time according to the investigator.
- for at least one month prior to the selection visit, stable treatment comprising one to three antiepileptic agents. In cases of vagal stimulation, the stimulation must have been in place for at least six months and the stimulation parameters must have been constant for at least one month prior to inclusion.
- an average of at least four partial onset seizures per 28-day period. Patients having a seizure-free period of more than 21 consecutive days during the selection phase were not included.

Treatment

- The initial dose was 300 mg/day, increased by 150 mg/day every week up to the target dose of 1,200 mg/day. Patients who did not tolerate the increase in dose were excluded from the study.
- During the maintenance phase, patients who did not tolerate the daily retigabine 1,200 mg dose were allowed to reduce their dose to 1050 mg/day at the week 7 consultation and were required to continue at this dose until the end of the maintenance phase.
- Admissible adjunctive treatments: one to three antiepileptics; vagal stimulation was allowed in addition to the antiepileptics.
- Admissible adjunctive treatments: felbamate or vigabatrin in the previous six months.

Primary endpoints:
The primary endpoints were chosen in such a way as to satisfy the different requirements of EMA and the FDA. The definition of the ITT population was not the same for the two agencies (see notes below the tables).

- percentage of responders, defined as patients experiencing a reduction of at least 50% in seizure frequency in 28 days between the observation phase and the maintenance phase (EMA).
- median reduction (expressed as a % of the initial value) in the monthly (28-day) frequency of partial onset seizures between the observation phase and the double-blind phase (i.e., the titration phase and the maintenance phase) (FDA). In other words:

$$\frac{\text{Monthly frequency of partial onset seizures during the double-blind phase} - \text{baseline monthly frequency}}{\text{Baseline monthly frequency}} \times 100$$

Secondary endpoint

- median reduction (expressed as a % of the baseline value) in the monthly (28-day) frequency of partial onset seizures between the observation phase and the maintenance phase (EMA).

Statistics
The response rate among the groups was compared using the Fisher's exact test.
The reduction in the monthly frequency of partial onset seizures underwent a nonparametric analysis of covariance (ANCOVA).

Results

The characteristics of the included patients are shown in *Table 4*

Table 4: Characteristics of included patients

	Placebo n = 152	Retigabine 1,200 mg/day n = 153
Mean age (years)	36.7 ± 11.6*	37.7 ± 12.5*
Number of antiepileptics, n (%) 1 2 3	 21 (13.8) 70 (46.1) 61 (40.1)	 32 (20.9) 79 (51.6) 42 (27.5)
Vagal stimulation, n (%)	17 (11.2)	12 (7.8)
Mean duration of the disease (years)	23.1 ± 12.8*	23.7 ± 13*

*: standard deviation

The results for the principal endpoints are shown in *Tables 5 and 6*

Table 5: Percentage of responder patients during the maintenance period; ITT population*

	Placebo n = 137	Retigabine 1,200 mg/day n = 119	p†
Percentage of responders	22.6	55.5	<0.001

* EMA: randomised patients who received at least one maintenance dose and have had the frequency of their seizures measured at least once; †: Fisher's exact test.

Table 6: Monthly (28-day) frequency of partial onset seizures during the observation phase and the double-blind phase and reduction under treatment* (as a % of the baseline value) – ITT population*

	Placebo n = 150	Retigabine 1,200 mg/day n = 151	p
Baseline seizure frequency ▪ mean ▪ median ▪ range	 35.3 ± 87† 11.3 [4-885]	 46.1 ± 184.8† 12.1 [4-2166]	-
Frequency during the double-blind phase ▪ mean ▪ median ▪ range	 29.9 ± 54.8† 9.5 [1-420]	 36.1 ± 151.8† 7.4 [0-1736]	-
Reduction in seizure frequency (% of the baseline value) ▪ mean ▪ median ▪ range	 1.6 ± 95.1† -17.5 [-90; 628]	 -25.1 ± 64.7† - 44.3 [-100; 302]	 < 0.001‡

*: the reduction in the absolute value of seizure frequency was not an endpoint of the study and did not undergo statistical analysis. FDA: randomised patients who have taken at least one dose of the investigational product; †: standard deviation; ‡: ANCOVA

The results for the secondary endpoints are shown in Table 7.

Table 7: 28-day frequency of partial onset seizures during the observation phase and the maintenance phase and reduction under treatment (as a % of the baseline value) – ITT population*

	Placebo n = 137	Retigabine 1,200 mg/day n = 119	p
Baseline seizure frequency ▪ mean ▪ median ▪ range	 33.6 ± 83.8† 11.3 [4-885]	 34.2 ± 69.5† 12.4 [4-632]	-
Frequency during maintenance phase ▪ mean ▪ median ▪ range	 28.7 ± 56.7† 9.2 [0-439]	 23.2 ± 60.9† 5.6 [0-583]	-
Reduction in seizure frequency (% of the baseline value) ▪ mean ▪ median ▪ range	 -3.1 ± 135.7† -18.9 [-100; 1382]	 -32 ± 91.9† -54.5 [-100; 660]	 < 0.001‡

* EMA: randomised patients who have received at least one maintenance dose and have had the frequency of their seizures measured at least once during this phase; †: standard deviation; ‡: ANCOVA

These analyses demonstrated a significant difference between the results for the group treated with retigabine at a dose of 1,200 mg/day and those of the placebo group:
- in terms of the percentage of responders during the maintenance period
- in terms of the reduction in the median frequency of monthly seizures according to the EMA and FDA criteria.

3.1.3 Study 302

Objective

To assess the efficacy and tolerability of retigabine at daily doses of 600 and 900 mg in three divided doses versus placebo as an adjunctive treatment in adult patients with refractory partial epilepsy.

Method

Randomised study in three parallel groups (1:1:1). The study consisted of four phases:
- an eight-week selection and observation phase during which seizure frequency was assessed
- a four-week titration phase
- a twelve-week maintenance phase, during which patients received the dose of retigabine reached at the end of the previous phase
- a four-week interim phase, during which the patients treated with retigabine 900 mg/day continued to take the same daily dose and the patients in the placebo group and the 600 mg group who wanted to participate in the open-label extension study took doses gradually increasing to 900 mg/day. The patients not wishing to take part in the open-label study or not able to complete the interim phase gradually reduced the dose over a three-week period.

The main inclusion criteria were the same as those in Study 301.

Treatment

- The starting dose was 300 mg/day, increasing by 150 mg/day every week up to the target dose of 600 or 900 mg/day. Patients who did not tolerate the increase in dose were excluded from the study.
- Admissible adjunctive treatments: one to three antiepileptics; vagal stimulation was allowed in addition to the antiepileptics.
- The non-admissible adjunctive treatments were: felbamate or vigabatrin in the previous six months.

Primary endpoints:

- percentage of responders, defined as patients experiencing a reduction of at least 50% in seizure frequency in 28 days between the observation phase and the maintenance phase (EMA).
- median reduction (expressed as a % of the initial value) in the monthly (28-day) frequency of partial onset seizures between the observation phase and the double-blind phase (i.e., dose titration phase and maintenance phase) (FDA). In other words:

$$\frac{\text{Monthly frequency of partial onset seizures during the double-blind phase} - \text{baseline monthly frequency}}{\text{Baseline monthly frequency}} \times 100$$

Secondary endpoint

- median reduction (expressed as % of the initial value) in the monthly (28-day) frequency of partial onset seizures between the observation phase and the maintenance phase (EMA).

Statistics

The response rate among the groups was compared between the groups using the Fisher's exact test.

The percent reduction in the monthly frequency of partial onset seizures underwent a nonparametric analysis of covariance (ANCOVA).

Results

The characteristics of the included patients are shown in *Table 8*

Table 8: Characteristics of included patients

	Placebo n = 179	Retigabine 600 mg/day n = 181	Retigabine 900 mg/day n = 178
Mean age (years)	37.7 ± 11.7*	37.5 ± 12*	37.7 ± 12.8*
BMI (kg/m^2)	25.9 ± 5.9	25.3 ± 4.9	25.5 ± .9
Number of antiepileptics, n (%) 1 2 3	 40 (22.3) 87 (48.6) 52 (29.1)	 49 (27.1) 76 (42) 56 (30.9)	 35 (19.7) 99 (55.6) 44 (24.7)
Vagal stimulation, n (%)	6 (3.4)	4 (2.2)	4 (2.2)
Mean duration of the disease (years)	22.8 ± 11.8*	22.5 ± 13*	22.5 ± 12.7*

*: standard deviation; BMI: Body Mass Index

The results for the primary endpoints are shown in *Tables 9* and *10*

Table 9: Percentage of responder patients during the maintenance period; ITT population*

	Placebo n = 164	Retigabine 600 mg/day n = 158	Retigabine 900 mg/day n = 149
Responders (%)	18.9	38.6	47
p versus placebo	-	< 0.001†	< 0.001†

* EMA: randomised patients who have received at least one maintenance dose and have had the frequency of their seizures measured at least once during this phase; †: Fisher's exact test

Table 10: 28-day frequency of partial onset seizures during the observation phase and the double-blind phase and reduction under treatment* (as a % of the baseline value) – ITT population*

	Placebo n = 176	Retigabine 600 mg/day n = 179	Retigabine 900 mg/day n = 175
Baseline seizure frequency ▪ mean ▪ median ▪ range	 30.3 ± 68.9† 9.3 [3; 485]	 25.2 ± 67.3† 9.5 [3; 858]	 24.2 ± 39.4 10.3 [3; 343]
Frequency during the double-blind phase ▪ mean ▪ median ▪ range	 29.1 ± 68.2† 8.2 [0; 450]	 19.9 ± 40† 7.4 [0; 393]	 17.7 ± 31.3 6.7 [0; 214]
Reduction in seizure frequency (% of the baseline value) ▪ mean ▪ median ▪ range	 -1.1 ± 138.4† -15.9 [-100; 1712]	 -20.4 ± 51† -27.9 [-94; 250]	 -27.8 ± 56.1 -39.9 [-100; 226]
p versus placebo‡	-	0.007	<0.001

*: the reduction in the absolute value of seizure frequency was not an endpoint of the study and did not undergo statistical analysis; FDA: randomised patients who have taken at least one dose of the investigational product; †: standard deviation; ‡: ANCOVA

The results for the secondary endpoints are shown in *Table 11*.

Table 11: 28-day frequency of partial onset seizures during the observation phase and the maintenance phase and reduction under treatment – ITT population*

	Placebo n = 164	Retigabine 600 mg/day n = 158	Retigabine 900 mg/day n = 149
Baseline seizure frequency			
▪ mean	31 ± 71.2†	25.6 ± 70.7†	23.1 ± 32.7
▪ median	9.2	9.8	10.1
▪ range	[3-485]	[3-858]	[3; 186]
Frequency during maintenance phase			
▪ mean	28.7 ± 69.4†	18.7 ± 36.5†	16.9 ± 32.2
▪ median	8	6.8	5.7
▪ range	[0-473]	[0-336]	[0-220]
Reduction in seizure frequency (% of the baseline value)			
▪ mean	-5.1 ± 133.3†	-25 ± 56†	30.9 ± 80.5
▪ median	-17.4	-35.3	-44.3
▪ range	[-100; 1589]	[-100; 253]	[-100; 714]
p‡	-	0.002	< 0.001

* EMA: randomised patients who have received at least one maintenance dose and have had the frequency of their seizures measured at least once during this phase; †: standard deviation; ‡: ANCOVA

These analyses demonstrated a significant difference between the results for each of the groups treated with retigabine (600 and 900 mg/day) and those in the placebo group:

- in terms of the percentage of responders during the maintenance period
- in terms of the reduction in the median frequency of monthly seizures according to the EMEA and FDA criteria.

3.1.4 Extension studies

Studies 205, 301 and 302 were followed by open-label studies including the patients who had completed these double-blind studies. For the interim analysis, the data from Studies 301 and 302 were stopped on 30 June 2008.

Study 212 (extension of Study 205)

Objective

To assess the long-term (18-month) efficacy and tolerance of retigabine treatment in patients who completed Study 205.

Method

Open-label, uncontrolled study.

Inclusion criteria

- patients who participated in Study 205 at least until completion of part of the interim phase
- patients who experienced improvement under treatment according to the investigator
- patients who did not significantly deviate from the protocol
- patients who did not experience any adverse events preventing their participation in the study according to the investigator. Patients who withdrew from Study 205 during the interim phase due to intolerance in the course of dose titration were eligible so long as they satisfied the other criteria.

Treatment
The patients continued to take the daily dose from the end of the interim phase of Study 205. Patients who had completed the interim phase continued the study with 900 mg/day, in three divided doses. If the patient was not receiving the maximum effective dose according to the investigator, it could be increased by 150 mg/day in weekly increments up to a maximum of 1,200 mg/day. In the case of an adverse event attributable to retigabine, the daily dose could be decreased by around 30% every week.
The treatment should have lasted 18 months (540 days), followed by a two-week step-down phase of decreasing doses.

Endpoints
- Reduction (expressed as a % of the initial value) in the monthly (28-day) frequency of partial onset seizures between the observation phase of Study 205 and the open-phase period.
- Percentage of responder patients (having a decrease of at least 50% in seizure frequency).

Results
In total, 222 patients out of the 279 who had completed Study 205 were included.
Their characteristics and methods of treatment are shown in *Table 12*.

Table 12: Characteristics of the included patients and of the treatment (n = 222)

Mean age (years)	36.1 ± 10.9*
Mean BMI (kg/m^2)	25.3 ± 4.8*
Maximum dose used – n patients (%) ▪ 900 mg/day ▪ 1,200 mg/day ▪ > 1,200 mg/day	 105 (47.3) 52 (23.4) 12 (5.4)
Treatment duration† ▪ mean ▪ median ▪ range	 325.5 ± 172.1* 358 [5; 682]

* standard deviation; †: 131 patients out of 222 withdrew before the planned end of the study; 59 of these withdrew for insufficient response; BMI: Body Mass Index

The efficacy results are shown in *Table 13*

Table 13: Efficacy results

Number of patients	n = 222
Baseline monthly frequency of seizures: ▪ mean ▪ median ▪ range	 15.4 ± 21.9* 8.2 3; 230.3
Reduction in seizure frequency (% of the baseline value) ▪ mean ▪ median ▪ range	 -32.9 ± 82.8 - 48.3 [-100; 612.5]
Responder rate – no. of patients (%)	103 (46.4)

*: standard deviation

Studies 303 (extension of Study 301) and 304 (extension of Study 302*) – interim data on 30 June 2008*

The aim, study design and inclusion criteria were the same as those of Study 212.

The treatment and the endpoints were the same in Studies 303 and 304:

Treatment
The daily dose could be modified by the investigator according to the patient's response and treatment tolerance. The daily dose could be modified in increments of 150 mg/day every week. The patients remained in the study so long as the daily dose was between 600 and 1,200 mg/day, depending on the efficacy and tolerability of the treatment.
The treatment was to last until the proprietary medicinal product was approved and launched on the market or until the programme was suspended. Monitoring visits were planned to continue for up to 48 months.

Endpoints
- Reduction (expressed as a % of the initial value) in the monthly (28-day) frequency of partial onset seizures between the observation phase of Study 301 and 302 and the open-label phase.
- Response rate

Results
In *Study 303*, 181 patients were included from among the 224 who had completed the maintenance phase of *Study 301*.
In *Study 304*, 375 patients were included from among the 409 who had completed the maintenance phase of Study 302.

Their characteristics and methods of treatment are shown in *Table 14*.

Table 14: Characteristics of the included patients and their treatment

	STUDY 303 n = 181	STUDY 304 n = 375
Mean age (years)	37 ± 11.9*	36.5 ± 11.9*
Mean BMI (kg/m^2)	27.8 ± 7.1*	25.9 ± 5.3*
Dose used (mg/day) ▪ mean ▪ median ▪ range	 1052.3 ± 274 1063.3 442-2500	 860.9 ± 239.6 875.5 190-1950
Treatment duration (days) ▪ mean ▪ median ▪ range	 342.7 ± 200.2* 357 6; 843	 321.1 ± 204.5 275 1-842

*: standard deviation; BMI: Body Mass Index

The efficacy results are shown in *Table 15*.

Table 15: Efficacy results

No. of patients	*STUDY 303* n = 181	*STUDY 304* n = 375
Baseline monthly frequency of seizures: ▪ mean ▪ median ▪ range	n = 179 34.5 ± 77.8* 13.3 4; 885	n = 373† 28.6 ± 68.1 9.3 3; 858
Reduction in seizure frequency (% of the baseline value) ▪ mean ▪ median ▪ range	 -36 ± 65.5 - 56.5 -100; 247	 -42.4 ± 54.2 -53.4 -100; 470
Responder patients n (%)	102/179† (57)	201/373† (53.9)

*: standard deviation; †: no efficacy data available for two of the patients

By the day when the data were frozen, 79 patients (43.6%) in *Study 303* had discontinued the treatment, and 30 (16.6%) of these patients had discontinued due to an inadequate

response; in addition, 164 patients (43.7%) in *Study 304* had discontinued the treatment, and 38 (10.1%) of these patients had discontinued due to an inadequate response.

3.1.5 In total

The median reduction (expressed as a % of the baseline value) in the monthly frequency of partial onset seizures under treatment with retigabine was compared with that observed under placebo in three controlled studies. The median reduction was significantly greater in the treated group:

- in two studies *(*205 and 301*)* at the 1,200 mg/day daily dose: - 35.2 [-100; 375] versus -13.1[-100; 533.3] and – 44.3 [-100; 302] versus -17.5 [-90; 628]
- in two studies (205 and 302) at the daily dose of 900 mg/day: -29.3 [-100; 297.6] versus -13.1 [-100; 533.3] and -39.9 [-100; 226] versus -15.9 [-100; 1712]
- in one study (302) at the daily dose of 600 mg: -27.9 [-94; 250] versus -15.9 [-100; 1712]. The difference was not significant in another study: - 23.4 [-100; 1703.1] versus -13.1 [-100; 533.3].

The percentage of responders (reduction by at least 50% in seizure frequency/28 days) under treatment with retigabine was compared with that observed under placebo in three controlled studies. It was significantly greater in the treated group:

- in two studies at the daily dose of 1,200 mg/day: 33% versus 15.6% and 55.5% versus 22.6%
- in two studies at the daily dose of 900 mg/day: 31.6% versus 15.6% and 47% versus 18.9%
- in one study at the daily dose of 600 mg: 38.6% versus 18.9%. The difference was not significant in another study: 23.2% versus 15.6%.

The efficacy results on the reduction in the monthly frequency of partial onset seizures were maintained during the open-label extension studies, although there was a high rate of study dropout between the double-blind and open-label extension phases and during these open-label phases.

3.1.6 EPAR[2]

In the EPAR report for TROBALT, it was stipulated that the quantity of its observed effect under retigabine is similar to that of other antiepileptics on the market, in particular at the 900 and 1,200 mg/day doses. At the 600 mg/day dose, the efficacy results were considered to be less robust and less convincing.

3.2. Adverse effects

3.2.1 Study 205

The most common adverse events, which were observed more frequently in the treated groups than in the placebo group, and whose incidence increased with the administered dose, were related to the central nervous system: drowsiness (17 to 23% in the treated groups, 6.3% in the placebo group), dizzy spells (8 to 20.8% versus 4.2%), vertigo (6 to 14.2% versus 0%), confusion (5 to 17.9% versus 5.2%), speech disorders (5 to 16% versus 0%), tremors (3 to 12.3% versus 2.1%), amnesia (0 to 11.3% versus 1%) and abnormal thoughts (8 to 10.5% versus 0%).
The other common adverse events observed were diplopia (8 to 8.5% versus 0%) and abnormal vision (7 to 8.5% versus 4.2%), asthenia (13.2 to 18.9% versus 9.4%) and headache (11 to 17% versus 10.4%).

[2] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/001245/WC500104839.pdf

Treatment discontinuation due to an adverse event occurred in 12.5% of the patients in the placebo group, 21% in the 600 mg group, 22.1% in the 900 mg group and 31.1% in the 1,200 mg group; 72/91 of these adverse events occurred during the dose titration phase.

Of patients who experienced one or more serious adverse events, 9% were in the placebo group, 10% in the 600 mg/day group, 3% in the 900 mg/day group and 10% in the 1,200 mg/day group.

A dose-dependent weight increase was observed in the treated groups: on average, 0.56 kg in the placebo group, 1.41 kg in the 600 mg/day group, 1.82 kg in the 900 mg/day group and 2.68 kg in the 1,200 mg/day group.

Transient increases in transaminase levels and a minor increase in gamma-GT levels were observed.

No ECG anomalies were observed.

3.2.2 Study 301

The most common adverse events, which were observed more often in the treated group than in the placebo group, were: dizzy spells (40.5% versus 13.8 %), drowsiness (31.4% versus 18%), fatigue (15.7% versus 7.9%), confusion (14.4% versus 2%), dysarthria (12.4% versus 2%), urinary infection (11.8% versus 8.6%), ataxia (11.8% versus 3.9%), blurred vision (11.8% versus 2.6%), tremor (11.1% versus 3.9%), nausea (10.5% versus 6.6%) and speech disturbances (8.5% versus 0%).

Adverse events resulted in treatment discontinuation in 31% of the patients treated with retigabine and 12% of the patients in the placebo group. The most common adverse events were dizzy spells (9% versus 2%) and confusional state (7% versus 1%).

In all, of patients experiencing one or more serious adverse events, 5% were in the placebo group and 12% were in the 1,200 mg/day group. The most common adverse events, which were observed more often in the treated groups than in the placebo group, were: psychotic disturbances (2% versus 0%), encephalopathy (1.3% versus 0%) and confusional state (1.3% versus 0%).

One patient in the retigabine group died from diabetic acidosis, the cause of which was considered to be possibly related to the treatment.

At the end of the maintenance phase, the mean weight variation was greater in the retigabine groups (+ 2.6 kg) than in the placebo group (+ 0.3 kg).

An increase in transaminase levels was found in nine patients, including one from the placebo group.

Renal or urinary adverse events were recorded in 6.6% of patients in the placebo group versus 22.9% of the patients in the 1,200 mg/day group.

3.2.3 Study 302

The adverse events observed in at least 5% of the patients in any group and whose frequency showed a dose-related increase were: drowsiness (10% in the placebo group, 14% in the group on 600 mg/day and 26% in the group on 900 mg/day), dizzy spells (7%, 17% and 26%); nausea (4%, 6% and 7%), asthenia (2%, 5%, 7%), memory disturbances (2%, 4% and 6%), confusional state (0%, 2% and 5%) and gait disorders (1%, 3% and 5%).

The adverse events observed in at least 5% of the patients in a treated group, and which were less frequent in the placebo group as well as being non-dose dependent, were: fatigue (3% in the placebo group, 17% in the group on 600 mg/day and 15% in the group on 900 mg/day), vertigo (3%, 8% and 7%), diplopia (1%, 7% and 6%), attentional disturbances (2%, 7% and 6%), coordination disturbances (2%, 6% and 5%) and dysarthria (0%, 5% and 2%).

Adverse events led to treatment discontinuation in 8% of the patients in the placebo group, 17% of those on 600 mg/day and 26% of those on 900 mg/day. The most common were dizzy spells (1%, 4% and 7%) and drowsiness (1%, 2% and 6%).

Serious adverse events were observed in 4% of the patients in the placebo group, 8% of patients on 600 mg/day and 8% of those on 900 mg/day. The most serious adverse event was the appearance of convulsions.

Two deaths occurred under treatment, one in the placebo group and one in the group on 600 mg/day. These were sudden, unexplained deaths, which were considered by the investigator to be possibly treatment-related.

A patient in the group on 900 mg/day showed an increase in the QT interval > 60 msec under treatment.

During the double-blind phase, six patients in the 900 mg/day group, three patients in the 600 mg/day group and five patients in the placebo group had abnormal liver function tests (all were increases in transaminase levels apart from one case of elevated alkaline phosphatase in the placebo group). During the interim phase, three patients belonging to the placebo group exhibited raised transaminase levels.

At the end of the maintenance phase the average weight variation was greater in the retigabine group (+1.1 kg in the 600 mg group, +1.4 kg in the 900 mg group) than in the placebo group (-0.1 kg).

Renal or urinary adverse events were recorded in 7.8% of the patients in the placebo group, 12.7% of the patients in the 600 mg/day group and 8.4% of the patients in the 900 mg/day group. In this group, two of these events were considered to be serious: one urinary retention and one atonic bladder with urinary incontinence.

3.2.4 Extension studies (212, 303 and 304)

The most frequent adverse events reported in the three studies were: drowsiness (16.6 to 17.2%, depending on the study), dizzy spells (17.1 to 23.8%), tremors (6.7 to 10.9%), fatigue (8.8 to 9.5%) and headache (6.4 to 11.5%).
The other most frequent adverse events in at least one study were: convulsions (8.6 to 8.8%), confusional state, urinary infection (8.3% each), coordination disturbances, dysarthria (7.2% each), flu, anxiety, abdominal pains (6.1% each), diplopia (6.4%), memory disturbances (5.6%), vomiting, amnesia, speech disorders (5.5% each) and vertigo (5%).

Adverse events led to treatment discontinuation for 13.5 to 18.9% of the patients, depending on the study, in the majority of cases affecting the central nervous system.

Serious adverse events were reported in 11.2 to 16.6% of the patients, depending on the studies. Most of these serious adverse events were related to the central nervous system.
Three deaths occurred during Study 304: two sudden deaths considered being possibly treatment-related and one asphyxia during an epileptic seizure not considered to be treatment-related.

There was an average 13 to 19 msec increase in the corrected QT interval in comparison with the baseline values established in Study 212 and a prolongation of the QT interval > 60 msec in comparison with the baseline values in two patients in Study 304. The largest average increase was recorded at the start of the extension study and was not maintained after the study.

An average 1.05 to 2 kg increase in weight compared with the baseline values was established at the start of Studies 212 and 304; this increase was not maintained after the study.

Renal and urinary adverse events, four of them serious, were observed in 12.2% and 8.3% of the patients in Studies 303 and 304 respectively.

A median increase of 10% in gamma GT was observed in Study 212 and an increase in transaminase levels was observed in eight patients in Studies 303 and 304.

3.2.5 EPAR and the risk management plan

The CHMP evaluation report identified certain adverse events that necessitate specific and detailed risk management:

- the slight, dose-dependent increase in the QT-interval, which was of uncertain clinical significance
- the risk of urinary retention/dysuria/renal lithiasis, since the causal relationship is supported by the preclinical studies and attributed to the product's mode of action (potassium channel activation)
- the dose-dependent risk of hallucinations and psychosis, reported exclusively in the groups treated with TROBALT.

The special measures include:

- a prescription guide containing the following recommendations:
  Inform patients that TROBALT can cause or aggravate symptoms of urinary retention/dysuria.
  Inform patients about the adverse events connected with the QT-interval prolongation.
  Use TROBALT with caution in patients suffering from heart disease or in patients taking a treatment known to prolong the QT-interval.
  Inform patients about the need to adhere to the proposed dose increases in order to minimise the risks of hallucinations and psychotic disturbances.
- monitoring of the ECG and study of the dose/effect relationship in trials in healthy volunteers; monitoring of ECGs in clinical studies
- prospective epidemiological study of the risk of urinary retention during TROBALT treatment, especially in patients aged 65 and older, monitoring of urinary adverse events in clinical studies
- study in progress concerning the effect of a more flexible dosage regimen on the risk of hallucinations, psychotic disturbances and accidents secondary to the neuropsychiatric effects of TROBALT.

3.3. Conclusion

Three double-blind trials have studied the efficacy and tolerance of retigabine versus placebo in the treatment of partial epilepsy. The included patients had at least four seizures per 28-day period despite stable treatment with one to three antiepileptics with or without vagal stimulation. Their mean age was 34 to 38 years of age and the mean duration of the disease was 20 to 23 years according to the studies.
One of these studies compared three doses of retigabine (600, 900 and 1,200 mg/day in three divided doses) with a placebo and an eight-week maintenance period. The second

study compared one dose of retigabine (1,200 mg/day in three divided doses) with the placebo, and the third compared two doses of retigabine (600 and 900 mg/day in three divided doses) with placebo and had a maintenance phase of 12 weeks.
The two primary efficacy endpoints of these studies were:

- the percentage of responders, defined as patients experiencing a reduction of at least 50% in the monthly seizure frequency between the observation phase and the maintenance phase
- the median reduction (expressed as a % of the baseline value) in the monthly frequency of seizures between the observation phase and the double-blind phase (i.e., the dose titration phase and the maintenance phase).

The response rate was higher with retigabine than with the placebo:

- with 1,200 mg/day in two studies: 33% versus 15.6% and 55.5% versus 22.6%
- with 900 mg/day in two studies: 31.6% versus 15.6% and 47% versus 18.9%
- with 600 mg/day in one study: 38.6% versus 18.9%, although the difference was not significant in another study (23.2% versus 15.6%).

The median reduction in the monthly frequency of seizures was greater with retigabine than with the placebo.

- with 1,200 mg/day in two studies: -35.2 versus -13.1 and -44.3 versus -17.5
- with 900 mg/day in two studies: -29.3 versus -13.1 and -39.9 versus -15.9
- with 600 mg/day in one study: -27.9 versus -15.9, although the difference was not significant in another study (-23.4 versus -13.1)

The quantity of effect, in particular for the 900 and 1,200 mg/day doses, was the same as those of other antiepileptics.

The percentage of patients who discontinued the treatment due to adverse events in the controlled studies was 8 to 12.5% with the placebo, 17 to 21% with 600 mg retigabine/day, 22.1 to 26% with 900 mg retigabine/day and 31 to 31.1 with 1,200 mg retigabine/day. These treatment withdrawal rates were higher than those observed in the clinical studies of most of the other antiepileptics that have been marketed in recent years.
The dose-dependent adverse reactions most frequently observed under treatment were: drowsiness, dizzy spells, fatigue, vertigo, confusion, speech disturbances, tremors and amnesia. A usually moderate and transient increase in the transaminase levels and moderate weight gain were also most frequently observed in the treated groups. Adverse events of particular interest were identified: dose-dependent hallucinations and psychoses observed only in the treated groups, renal or urinary disturbances (retention, renal lithiasis) and a moderate, dose-dependent QT-interval prolongation.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Seizures are symptoms associated with very mixed conditions. Epilepsy, defined as the generally spontaneous repetition of these seizures over the medium or long term, can result in a marked deterioration in patient quality of life.

TROBALT can be characterised as a symptomatic treatment.

The efficacy/adverse effects ratio is high.

Public health benefit

Partial epilepsy is a frequent disorder, and in certain patients repeated seizures are liable to bring about a marked deterioration in quality of life and may be responsible for major disability with consequences for family life, employment and social integration. All in all, partial epilepsy represents a moderate public health burden. The burden corresponding to the population of patients suffering from partial epilepsy after monotherapeutic failure is also regarded as moderate.

The prevention of the disabilities associated with epilepsy and of the consequences of these disabilities, to which TROBALT could make a contribution, is a public health objective and an established priority according to the *Groupe Technique National de Définition des Objectifs* (a French health ministry-designated group of experts that defines national public health objectives) (DGS/General Directorate for Health, 2003). This is a continuing need, insomuch as drug-resistant partial epilepsy remains frequent and is responsible for a major disability.

In the absence of data versus an active comparator and given the limited available data on continued treatment and its medium and long-term tolerance, it cannot be assumed that TROBALT as adjunctive and second-line treatment (i.e., after the failure of at least two monotherapies) will have any additional expected impact on patient morbidity in this indication.

Furthermore, the data that are available do not enable an assessment of TROBALT's impact on the quality of life of treated patients. The impact of the treatment on other criteria, such as disability, work and social inclusion has not been documented.

There is no expected impact on the organisation of care services.

It is impossible to know, therefore, whether TROBALT in this indication will be able to offer anything more by way of response to an identified public health need.

Consequently, given the present state of knowledge and the other currently available treatments, there is no expected public health benefit from the use of TROBALT proprietary medicinal products as adjunctive and second-line treatment in this indication.

TROBALT is a second-line medicinal product (i.e., used after two monotherapies have failed), which should be used in combination with another antiepileptic.

Alternative medicinal products exist.

The actual benefit provided by TROBALT is substantial.

4.2. Improvement in actual benefit (IAB)

TROBALT proprietary medicinal products do not offer any improvement in terms of actual benefit (IAB V) compared with other proprietary medicinal products indicated as adjunctive treatment for partial onset seizures with or without secondary generalisation in epileptic patients aged 18 years and over.

4.3. Therapeutic use

4.3.1 Treatment strategy

According to consensus text 2004 ANAES-FFN-LFCE[3] concerning the treatment strategy for the management of drug-resistant partial epilepsy in adults, it is recommended to use bitherapy only after at least two monotherapies have failed (Grade D recommendation)[4].
It is recommended to avoid using a combination of more than two antiepileptic agents in treating drug-resistant partial epilepsy (Grade C).
When using drug combinations, increasing the doses very gradually could help limit the onset of side effects and providing information for the patient could be beneficial in terms of compliance.
First-line drugs recommended as monotherapy are carbamazepine and valproic acid owing to the better risk/benefit ratio compared with phenytoin and phenobarbital (Grade C).
An optimum dose treatment with carbamazepine should be used at least once as part of this monotherapy (expert consensus).
There is insufficient data to endorse any one particular drug combination.
Should one or more bitherapies fail, it is recommended to reassess the epilepsy and its treatment at a specialist centre.

4.3.2 Role in treatment strategy

TROBALT is a second-line medicine (i.e., used after at least two monotherapies have failed), which should be used in combination with another antiepileptic.
Its administration in three divided daily doses may not be ideal from a compliance point of view.

4.4. Target population

The target population for TROBALT is patients aged 18 years and over with partial epilepsy, with or without secondary generalisation, requiring an adjunctive treatment.
According to P. Jallon (2004), the prevalence of epilepsy in France is 5 – 7/1000, with drug-resistant epilepsy accounting for 20% of the cases, 60% of which are partial epilepsies[5].
This would correspond to a target population of between 39,000 and 55,000 individuals.
However, according to P. Jallon, estimating the number of patients suffering from drug-resistant partial epilepsy comes up against two difficulties: the lack of a consensus definition of drug-resistance and its random assessment based indirectly on a large number of studies in mixed patient populations.

[3] Consensus Conference, *Prise en charge des épilepsies partielles pharmaco-résistantes* (Management of drug-resistant partial epilepsy). Consensus text. March 2004. ANAES, FFN and LFCE.
[4] Grade A: Recommendation based on a systematic review or meta-analysis of randomised controlled trials or at least one controlled trial; Grade B: At least 1 non-randomised controlled trial or one quasi-experimental study, such as a cohort study; Grade C: Recommendation based on good-quality non-experimental descriptive studies, case-control studies or case series; Grade D: Reports by committees of experts or the opinion of recognised experts
5 Jallon P. Epidémiologie des épilepsies partielles pharmacorésistantes. Revue de neurologie. 2004; 160: 5S22-5S30

4.5. Transparency Committee recommendations

4.5.1 Reimbursement scope

The transparency Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services for second-line treatment, i.e., after the failure of at least two monotherapies at the dosages mentioned in their Marketing Authorisation, in the treatment of partial epilepsy with or without secondary generalisation in patients aged 18 and older, in combination with another antiepileptic agent.

4.5.2 Packaging: Appropriate for the prescription conditions.

4.5.3 Reimbursement rate: 65%

4.5.4 Study request

In order to determine the proprietary medicinal product TROBALT's place in the treatment strategy for partial epilepsy, to assess treatment compliance given the three daily divided doses, and its persistence given the large number of treatment withdrawals in the studies, the Transparency Committee would like to see a study following up adult patients treated with TROBALT. This study will make it possible to describe:

- the characteristics of the treated patients (social and demographic data, type of epilepsy, disease duration, previous history including therapeutic history and associated pathologies),
- prescribing practices (indication, dosage, treatment duration and so on), and the treatment strategy (line of treatment, co-prescriptions and so on)
- treatment compliance by patients, treatment withdrawals and their reasons.

The study duration will need to be justified by an independent scientific committee.

In addition, the Transparency Committee wishes to have fresh data on medium and long-term tolerance (particularly urinary, neuropsychiatric and cardiac) as soon as they are available.