EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/407212/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trobalt

International Nonproprietary Name: retigabine

Procedure No. EMEA/H/C/001245

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AED	Antiepileptic drug
AUA	American Urological Association
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUA SI	American Urological Association Symptom Index
AUC	Area under the plasma concentration-time curve
AUC(0-τ)	Area under the plasma concentration-time curve over the dosing interval
AUC(0-∞)	Area under the plasma concentration-time curve from zero up to infinity
BID	Two times daily
BSA	Body surface area
CBZ	Carbamazepine
CHMP	Committee for Medicinal Products for Human Use
CL	Systemic clearance
CL/F	Apparent oral clearance
Cmax	Maximum concentration
CNS	Central nervous system
CrCL	Creatinine clearance
CSR	Clinical Study Report
ECF	Ethyl Chloroformate
ECG	Electrocardiogram
EMA	European Medicines Agency
FD	Fluorescence Direct
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
IA	Intraarterial
ICH	International Conference of Harmonization
ID	Intradermal
ILAE	International League Against Epilepsy
IP	Intraperitoneal
IR	Immediate release
ITT	Intent-to-treat
LEV	Levetiracetam
LTG	Lamotrigine
MES	Maximal Electroshock
MR	Modified release
MS	Mass Spectroscopy
MTD	Maximum Tolerated Dose
n/a	not applicable
NAMR	N-acetyl metabolite
NAT	N-Acetyl Transferase
NDA	New Drug Application
NOAEL	No observed adverse effect level
NTEL	No-Toxic-Effect Level
PB	Phenobarbital
PCC	Potential Clinical Concern
PCT	Pivotal Controlled Trials
PD	Pharmacodynamic
PDCO	Paediatric Committee
PEC	Predicted Environmental Concentration

PHN	Post-herpetic neuralgia
PHT	Phenytoin
PhVWP	Pharmacovigilance Working Party
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PND	Post Natal Day
PO	Per Os
popPK	Population pharmacokinetic
PPSR	Proposed Paediatric Study Request
PREA	Paediatric Research Equity Act
PTZ	Pentylenetetrazol
PVT	Pivotal Trial
QTc	QT interval corrected
QTcB	QT interval corrected with Bazett's formula
QTcF	QT interval corrected with Fridericia's formula
RTG	Retigabine
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SPA	Special Protocol Assessment
SUDEP	Sudden unexplained death in epilepsy
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TID	Three times daily
TK	Toxicokinetic
Tmax	Time to maximum concentration / reach Cmax
TPM	Topiramate
US	United States
UV	Ultraviolet
VNS	Vagus nerve stimulation
VPA	Valproic acid
Vss	Steady State Volume of Distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxo Group Ltd. submitted on 30 October 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Trobalt, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2007.

The applicant applied for the following indication:

As adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006 the application included an Agency Decision P/153/2009 for the following conditions:

- Epilepsy with partial onset seizures
- Lennox-Gastaut Syndrome

On the agreement of a paediatric investigation plan (PIP).

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice

The Applicant has received a CHMP Scientific Advice in 2005. The main issues pertaining to efficacy and safety concerned the duration of the treatment maintenance phase. Moreover, it was recommended that the induction potential should be investigated. The sufficient number of subjects and patients with epilepsy was also an issue, and finally, assessment of the cardiovascular safety was an important topic.
The preclinical advice related to the preclinical program in general and the investigation of the toxicity (including cardiovascular toxicity) of the N-acetyl metabolite of RTG (NAMR) in dogs in particular.

Licensing status

A new application was filed in the following countries: USA

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP was:

Rapporteur: **Jens Heisterberg** Co-Rapporteur: **Luca Pani**

- The application was received by the EMA on 30 October 2009.
- The procedure started on 18 November 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 February 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2010.
- During the meeting on 15 - 18 March 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 March 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2010.
- The summary report of the GCP inspection carried out at the following sites: Prof Elger (Bonn, Germany), Dr. Abou-Khalil (South Nashville, USA) and at Sponsor site Valeant (Durham , USA), respectively, on 16-19 March 2010, on 27-30 April 2010 and on 24-28 May 2010, was issued on 11 August 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 September 2010.
- During the CHMP meeting on 20 – 23 September 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 October 2010.
- During the CHMP meeting on 15 – 18 November 2010, the CHMP agreed on a second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP second list of outstanding issues on 24 November 2010.
- During the meeting on 17 - 20 January 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Trobalt on 20 January 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 January 2011.

2. Scientific discussion

2.1. Introduction

Epilepsy is a common neurological disorder, with a worldwide estimated prevalence of 0.7% of the population (50 million people). It is characterized by excessive electrical discharges in the brain leading to seizures. For epidemiological purposes, the definition requires more than one unprovoked seizure of any type.

Patients with epilepsy have an increased mortality risk compared to the general population. Overall, this risk is due primarily to the aetiology of epilepsy. However, in patients with uncontrolled epilepsy, the greatest seizure related risk of mortality is due to sudden unexpected death in epilepsy (SUDEP). Patients who participate in clinical trials of investigational antiepileptic drugs (AEDs) generally have had epilepsy for more than 10 years, have failed multiple AED therapies, and are considered unlikely to become seizure free with currently available AED therapy.

According to the current International Classification of Epileptic Seizures [ILAE on Classification, 1981], the classification of epileptic seizures depends upon the age of onset and clinical symptoms and signs. Both aetiology (idiopathic, symptomatic and cryptogenic) and localization (partial vs. generalized) are considered crucial prerequisites for an adequate evaluation and treatment of epileptic disorders. For partial seizures, there is a focal epileptic zone (site of seizure onset), and seizure activity is initially limited to one hemisphere. Partial seizures can be further sub-divided into simple partial (without impairment of consciousness), complex partial (with impairment of consciousness with or following a simple partial onset) and secondarily generalized (i.e. partial seizures, either simple or complex, which evolve to generalized tonic-clonic seizures). Simple partial seizures, depending on the anatomical site of origin of the seizure, may have motor, somatosensory, or special sensory, autonomic or psychic signs or symptoms. Generalized seizure disorders do not have a focus and are classified as absence, myoclonic, tonic, clonic, tonic clonic or atonic seizures. Partial seizures (simple, complex and secondarily generalized tonic-clonic) account for the majority (60 to 70%) of seizures in adults with epilepsy.

The treatment of an individual patient with partial seizures is focused on reduction of seizure frequency, with seizure freedom as the ultimate goal. Usually, treatment consists of daily anticonvulsant medication. Antiepileptic drugs exert their therapeutic effect in the central nervous system (CNS), and generally have similar CNS side effects, i.e. sedation, somnolence, lethargy and ataxia. Variable efficacy and individual differences in tolerability require a treatment regimen that is adjusted to the individual patient. Over the past decade, several new antiepileptic drugs were developed and marketed to expand the therapeutic spectrum and to improve the risk/benefit profile. Despite this, up to 30% of patients remain refractory to conventional treatment and continue to have uncontrolled seizures. Uncontrolled epilepsy is associated with an increased risk of mortality due to SUDEP. In addition, the quality of life in medically refractory patients is poor, as they cannot drive a car, and they have difficulties working or living independently. Additionally, many patients have behavioural, neurological and/or intellectual disturbances, as sequelae of their seizure disorder.

The therapeutic strategy in treating epilepsy involves reducing neuronal excitability through various mechanisms. Most current therapies work via blocking sodium gated neuronal channels or via potentiating gamma-aminobutyric acid (GABA) mediated transmission. Medicines with novel mechanisms of action are needed to try to address the unmet clinical need for seizure control in patients with treatment-resistant epilepsy. Current agents have minimal to no effects on neuronal potassium gated channels, in spite of the fact that these channels have a major role in the control of neuronal excitability. Retigabine facilitates the opening of neuronal potassium channels and hence is a novel agent which offers an additional treatment option for seizure control.

Retigabine has been developed and studied to demonstrate efficacy and safety in the treatment of partial onset seizures with or without secondarily generalized seizures in a population of patients who have failed to adequately respond to currently available AEDs.

The claimed and approved indication is “adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy”. The dosing starts on 300 mg daily with increasing doses optimized to an effective dose between 600 to 1200 mg/day.

This is a centralised application, submitted to the EMA, according to Article 3(2)(a) of Regulation (EC) No. 726/2004.

An application for an initial Paediatric Investigation Plan (PIP) for retigabine was submitted to EMA in December 2007. The Paediatric Committee's (PDCO) positive opinion for the initial PIP, issued in July 2008, and the EMA decision on the modification of an agreed PIP, issued on 9 October 2009, confirmed a deferral and partial waiver for paediatric studies.

The Applicant has received a CHMP Scientific Advice in 2005. The main issues pertaining to efficacy and safety concerned the duration of the treatment maintenance phase. Moreover, it was recommended that the induction potential should be investigated. The sufficient number of subjects and patients with epilepsy was also an issue, and finally, assessment of the cardiovascular safety was an important topic.

The preclinical advice related to the preclinical program in general and the investigation of the toxicity (including cardiovascular toxicity) of the N-acetyl metabolite of RTG (NAMR) in dogs in particular.

2.2. Quality aspects

2.2.1. Introduction

Trobalt contains the active substance retigabine. For other ingredients see the SmPC. The product is formulated as immediate-release film-coated tablets in the strengths 50 mg, 100 mg, 200 mg, 300 mg and 400 mg.

The product is packaged in PVDC/PE/PVC/Alu blisters.

2.2.2. Active Substance

Retigabine (RTG) is a well-characterized white to slightly coloured solid. It is neither optically active nor hygroscopic. The active substance is poorly soluble in water at pH ≥2.8. There are no chiral centres in the molecule. The substance exhibits polymorphism; there are several polymorphic forms one of which was selected for development. All significant non-clinical, clinical and formulation studies with RTG were performed using this solid-state. Each of the known solid-state forms can be differentiated using X-ray powder diffraction and IR spectroscopy. The particle size is controlled by the recrystallisation and milling process.

Manufacture

The synthesis involves a multi step synthesis with a recrystallisation and milling step. The route of synthesis has not changed since the initiation of clinical studies, although changes to solvents and process parameters have been introduced during development. Starting materials are well characterised, specifications and testing procedures being acceptable. The impurity limits for the starting materials and isolated intermediates have been set and justified by spiking experiments demonstrating satisfactory purification in the down stream synthesis.

The description of the manufacturing process, characterisation of the active substance and impurities are in general in accordance with the EU guideline on *Chemistry of new active substances*.

Specification

The active substance is tested for description, identity by HPLC, polymorphic form by X-ray diffraction, assay and related substances by HPLC, residual solvents by GC, particle size by laser light diffraction, nickel content by ICP, residue on ignition and heavy metals.

The requirements in the active substance specification are in accordance with the relevant European guidelines and Ph. Eur. The analytical methods are validated in accordance with relevant European guidelines and found to be acceptable.

A detailed discussion of potential impurities is present and their control is described. Impurity limits in the specification are justified by toxicology studies and found safe.

The reference materials have been described and characterised and information on the source of all impurity standards is available.

Stability

Stability studies have been carried out on four pilot-scale batches manufactured at the commercial facility and data covering 24 months are provided. Improvements to the process were implemented after the manufacture of the primary stability batches. The stability data presented indicate that the active substance is stable, although out of specification results for a subsequently identified process related impurity are seen. The content of this impurity has been reduced by the changes to the process implemented for the commercial process.

Additional stability data covering 9 months for active substance batches manufactured using the commercial process are available. The stability data support a re-test period. There is no strict need for the additional proposed precautions for storage: “Protect from light” and “Store up to 30°C”, based on the presented stability and photostability results. Based on experience with past batches, darkening of the active substance may occur, if exposed to light.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Retigabine is provided as an immediate-release, film-coated tablet in five different strengths (50, 100, 200, 300, and 400 mg). The five different strengths of the Retigabine Tablets are coated in three different colours and are differentiated by a combination of size, colour and shape. The tablet cores are in addition to the active substance composed of microcrystalline cellulose, hypromellose croscarmellose sodium and magnesium stearate. The manufacturer uses commercially available film coat mixtures.

Pharmaceutical Development

The development work is satisfactorily described in accordance with the relevant European guideline on pharmaceutical development. The composition of the five strengths is directly dose-proportional as they are made from a common granulation blend. Compatibility between the active substance and excipients has been demonstrated.

It has been recognised that the active substance particle size is likely to affect bioavailability. The applicant provided some comparative particle size data from several stages of the product development. However, since a different method has been used for determination of the particle size of the active substance used in the initial IR tablet, this particle size cannot be compared with the particle size of the active substance used in clinical trial IR batches and market image IR batches. The applicant was asked to perform a new comparison between Initial IR tablets and Clinical IR tablets in terms of particle size of the active substance, using the method submitted in Module 3 of the marketing authorisation application. Satisfactory results of particle size studies between Initial IR Tablets and Clinical IR tablets were provided.

During development of the finished product several different formulations have been used and also differences in active substance particle size have been introduced as mentioned above. Bioequivalence between clinical phase III IR and market image IR batches has been extensively discussed. As a result of this discussion, limits for particle size have been tightened accordingly.

Dissolution of the tablets is fast in the chosen medium. The acceptance criteria after tightening of the dissolution limit during the procedure reflect the obtained results and are set to control a consistent manufacture and quality.

Adventitious agents

Only one material of animal origin is used in the manufacture of the finished product. Carmine is used as a colouring agent in one of the film coating mixtures and is extracted from insects. As insects are not subject to BSE/TSE infection, there is no risk of BSE/TSE transmission.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

Manufacture of the product

The description of the manufacturing process, in-process controls including testing frequency and validation studies are acceptable and in accordance with relevant European guidelines. Evidence has been provided that no solid-state transformation of the active substance occurs during product manufacturing and storage. Stability data supporting the proposed holding times for manufacture intermediates have been provided. Primary packaging may be conducted at a different site than the bulk manufacturing site, and information on the stability of bulk film-coated tablets has therefore been provided supporting a bulk holding time.

Process validation has been conducted on full-scale for the granulation and blending steps. A commitment has been made to conduct process validation on commercial scale batches prior to placing the product on the market. A satisfactory process validation scheme has been provided.

Product specification

The specification of the finished product covers appropriate parameters for the dosage form. The product is tested for description, identification by UV and HPLC, assay and related impurities by HPLC, dose uniformity by mass variation, dissolution and microbial purity. The acceptance criteria for dissolution have been tightened to reflect the actual dissolution profiles obtained. Test for related substances has been included in the finished product release specification. Non-routine testing of microbial quality is acceptable. The shelf-life specification includes tests for related substances and the limits for specified impurities; these are acceptable based on qualification, batch analysis and stability results.

The analytical methods have been satisfactorily described and validated in accordance with the European validation guidelines, and the stability-indicating nature and specificity of impurity methods have been demonstrated.

Stability of the product

Stability studies on pilot scale batches of the finished product have been conducted in accordance with general European requirements, applying a bracketing approach (three batches for each of the lowest and highest strength, one batch for each of intermittent strengths). The stability batches were packed in blisters of clear PVDC/PE/PVC film with aluminium foil backing. The finished product is stable at 25°C/60% RH up to 18 months. Significant changes to description, related substances and assay are seen at accelerated conditions together with a drop in dissolution. Significant changes in impurities are also seen at intermediate conditions.

For commercial presentation an opaque PVDC/PE/PVC film will be used, to avoid changes in appearance of the tablets seen with the clear film, due to darkening of the active substance, when exposed to light. The adequacy of the light-protective properties of the commercial blister configuration has been confirmed by photostability studies conducted under ICH conditions.

In general, the results of stability studies support the shelf-life and storage conditions as defined in the SmPC.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Initially three major objections related to active substance particle size, discriminatory properties of the dissolution method and bridging between Initial IR tablets and Clinical trial IR tablets were raised. All of these are now considered resolved (see above in the Pharmaceutical Development section).

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal toxicology/toxicokinetic studies have been performed in accordance with GLP or performed to high scientific standards comparable to GLP. However, several of the safety pharmacology studies were not conducted in compliance with GLP. Nevertheless, this was deemed acceptable as the studies are conducted before the guideline came into effect.

Initial development activities were conducted with the dihydrochloride salt of retigabine (RHCl). However, due to weak positive responses in the Ames' test probably caused by low levels of genotoxic impurities owing to the synthesis of RHCl, the subsequent development was based on the free base (RTG).

2.3.2. Pharmacology

Primary pharmacodynamic studies

The mechanism of action of RTG is thought to involve activation of specific KCNQ2-5 voltage-gated potassium channels. KCNQ2, KCNQ3 and KCNQ5 are expressed in neural tissues in addition to urinary bladder (all but predominantly KCNQ3), intestine (KCNQ3 in combination with KCNQ1) and skeletal muscles (KCNQ5). KCNQ4 is mainly expressed in the cardiovascular and auditory systems.

RTG concentration dependently and reversibly enhanced the outward current mediated by these receptors. In addition, RTG caused a hyperpolarising shift, which is likely to increase the activity of these channels at sub-threshold potentials.

The EC50 values were all with the range a few micromolar for KCNQ2-4 and KCNQ2/3. Thus, RTG is only likely to cause a slight positive modulation of the KCNQ-mediated currents at clinical relevant concentrations considering a human plasma protein binding of 80% and a Cmax of 5 μM following administration of MRHD.

Electrophysiological recordings conducted in cultured native neurons confirmed the anti-epileptic potential of RTG due to its potentiation of the inhibitory postsynaptic potential leading to a decrease in neural firing. More importantly, RTG was effective against epileptiform discharges in brain slice preparations obtained from rats and from epileptic patients who underwent neurosurgery.

RTG was effective in several genetically-, electrically- and chemically-induced seizure models following intraperitoneal (IP) and per os (PO) administration. Interestingly, RTG was ineffective against seizures induced chemically by some compounds inhibiting the GABAA receptor complex (picrotoxin and bicuculline) and the glycine receptor (strychnine). RTG showed significant anticonvulsant effect against seizures induced by two GABAergic antagonists (e.g., pentylenetetrazol (PTZ) and penicillin).

RTG was evaluated following IP and PO administration in several models that are considered to be predictive of complex partial seizures in humans, e.g., amygdala and hippocampal kindling model. Overall, RTG inhibited the establishment of partial seizures in the two kindling models as the progression of seizures in terms of frequency and initiation was inhibited and in some instances RTG also reduced the severity of the established seizures. RTG showed greater potency than other anti-epileptic drugs currently on the market. However, the effect on inhibition of kindling epileptogenesis was less obvious.

RTG was shown to be effective in a rat model of status epilepticus following IP and PO administration.

Although some variation was observed, RHCl and RTG generally appeared equipotent when tested in the same type of animal seizure models (i.e., MES, PTZ, amygdale kindling, and audiogenic models).

In addition to the effect on the KCNQ channels, in vivo and in vitro data indicated that RTG may influence the neurochemical regulation of the excitatory and inhibitory amino acids, e.g., RTG seemed to inhibit GABA metabolism and to lower brain concentrations of the excitatory neurotransmitter glutamate and its precursor glutamine. The pharmacological effects of RTG main metabolite NAMR were tested in several in vivo models and it was concluded that NAMR did not contribute significantly to the overall activity profile of RTG.

Secondary pharmacodynamic studies

Like several other antiepileptic drugs, RTG showed some potential for neuroprotective actions in several in vitro and in vivo models. Although the mechanism of action has not been fully elucidated, it was considered likely that the inhibitory effect on the potassium channels in itself would provide some neuroprotection due to reduced release of excitatory amino acids such as glutamate.

Safety pharmacology programme

RTG showed CNS-related effects following IP and PO administration. Generally, effects were observed at dose levels below those used in the clinical program. The effects of RTG on the cardiovascular system were investigated in several in vitro and in vivo non-clinical studies using mice, rats, guinea pigs, pigs and dogs. RTG had no significant effect on the recombinant rat potassium channels belonging to the same receptor family as the hERG at 10 µM. However, a partially reversible concentration-dependent inhibition was observed for recombinant hERG channels at concentrations ≥1 µM. Furthermore, a concentration-dependent irreversible inhibition of the cardiac KCNQ1/KCNE1 channels was observed at ≥1 µM with an IC50 value around 100 µM. The exposure margin at this concentration was approximately 1000-fold assuming a human plasma protein binding of 80% and a Cmax of 5 µM. Other in vitro studies using murine arteries, feline ventricular myocytes, canine purkinje fibres and hearts from guinea pigs also indicated a safety margin of at least 100-fold.

RTG and NAMR administration were not associated with ECG effects in dogs when investigated in the safety pharmacology cardiovascular (CVS) studies and long-term toxicity studies up to 52 weeks duration. RTG reached an AUC of approximately 8,300-25,300 ng•hr/mL (52 week dog study). Following NAMR administration (13- week dog study), the AUC for NAMR reached 36,400-55,900 ng•hr/mL at the top dose of 100 mg/kg/day. These values provide a safety margin of <0.8 and <2.4, respectively.

Evaluation in conscious telemetered dogs showed dose-dependent decreases in blood pressure (up to -21%), cardiac output (up to -11%), heart rate (up to -42%) and left ventricular contractivity (up to -36%) following intravenous (IV), intradermal (ID) and PO administration.

RTG caused a 20% fall in dynamic compliance in anaesthetised guinea pigs (10 mg/kg IV) and a slight increase in airway resistance, leading to an increase in respiratory rate and respiratory minute volume in anaesthetised intubated, spontaneously breathing dogs (100 mg/kg ID). The changes observed were not considered statistically or biologically significant.

RTG had no significant effect on gastrointestinal transit in mice. Several effects were observed on the renal system (urinary bladder function) in rodents (see Section 3.3.4 Toxicology).

Pharmacodynamic drug interactions

Several pharmacodynamic drug-drug interaction studies were performed on mice and rats.

The interaction of RTG with conventional AEDs (Carbamazepine, Valproate and Lamotrigine) was investigated in several studies to assess any additive or synergistic effects after maximal electroshock (MES)-induced convulsions. A low potential for interaction was shown.

The effect of retigabine in combination with four anaesthetics (halothane, methohexital, thiopental, propofol) was evaluated in a rat study to determine effects on sleep time and righting reflex. This study demonstrated that halothane- and methohexital-induced sleep times were not significantly influenced by retigabine, but an increase in respiratory depression was observed. Retigabine weakly affected (~1.4 times) propofol-induced sleep time but strongly prolonged (~14 times) thiopental-induced sleep time. Respiratory depression was not increased by retigabine in thiopental or propofol-induced anaesthesia. These results suggest a potential interaction between retigabine and thiopental, but no or weak interactions with the other tested anesthetic agents. Those results are reflected in section 5.1 of the SmPC even though there are no clinical data confirming these findings.

The Applicant has agreed to monitor the interactions between retigabine and anaesthetic drugs as part of routine pharmacovigilance and to consider the need to update the SmPC as further information becomes available.

2.3.3. Pharmacokinetics

The pharmacokinetics (PK) parameters of RTG were examined in more than 50 ADME studies in a range of species including mouse, rat, rabbit, dog, monkey and minipig. The mouse, rat and dog were the predominant species employed in the toxicity studies; while the rabbit was used for developmental toxicity investigations. The PK studies focused on the oral route of administration, since this is the intended clinical route. IV studies were also undertaken to further characterize the systemic PK of RTG. Samples from a majority of the PK studies were assayed using validated bioanalytical methods. However, data from some exploratory studies were generated with non-validated methods.

The PK data for RTG and NAMR were obtained from single-dose studies in mice, rats, rabbits, dogs, monkeys and minipigs. Repeat-dose toxicokinetic (TK) data were obtained from toxicity studies in mice, rats, rabbits (developmental toxicity), dogs, monkeys and minipigs.

Methods of analysis

A series of bioanalytical methods, all employing high-pressure performance liquid chromatography (HPLC), were developed for the quantification of RTG and metabolites in plasma and other biological matrices from non-clinical species. The methods varied based on the specifics of the HPLC conditions. The extraction methods were primarily protein precipitation or on-line or off-line solid-phase extraction, and quantification methods were primarily ultraviolet (UV), fluorescence detector (FD) or mass spectroscopy (MS) for non-labelled compound. As additional information on the metabolic profile became available, additional/alternate analytes (metabolites) were included in the validations and the methods were optimized to minimize potential breakdown of metabolites during analysis. Those methods of analysis were considered of adequate quality and consistent with those applied in the clinical studies.

Absorption

In all tested species, RTG was rapidly absorbed from the gastro-intestinal tract following single PO administration (< 2 hr). Dietary dosing in rodents expectedly resulted in substantially lower Cmax values obtained several hours after treatment.

A high variability was generally observed in the elimination half-life values (T½) of RTG. The T½ was in the range of 1.4-9 hr in rats, 4-22 hr in rabbits, 0.9-20 hr in dogs, compared to 6-10 hr in humans. Thus, rats were generally having lower values for T½ than rabbits, dogs and humans. The bioavailability of RTG following PO administration was in the high end (>60%) in rats, dogs and humans. A dose-dependent increase in exposure was recorded with no indication of drug accumulation. Gender-related differences were only observed in mice regardless of the strain used as the exposure of RTG in male mice exposure was recorded as being twice the exposure in females. The volume of distribution was approximate 3-6-fold larger than the total body water of the respective species indicating that RTG is widely distributed throughout the body.

The bioavailability of the metabolite NAMR was also high in rats and dogs indicating that sufficient systemic exposure will be achieved in these species following PO administration. Contrary to RTG, the T½ of NAMR did not vary significant between species (rats, rabbits and dogs; 1.7-10 hr).

Distribution

The tissue distribution of [14C]-RTG was investigated in rats following a single PO administration. Most of the RTG-related radioactivity was recovered in the gastrointestinal (GI) tract and liver, but also in most other tissues, e.g., adrenal, kidney, heart and spleen. Tissue Cmax was obtained within first 4 hours after dosing. The tissue elimination half-life was longer compared to plasma and 72-hour post-dosing RTG-related radioactivity was still present with highest concentrations observed in the liver, adrenal gland and kidneys.

In pregnant rats, the tissue distribution pattern was similar in dams and foetuses but the tissue exposure in foetal tissue was lower and more uniform with no high concentration organs as seen in the

dams. The tissue elimination half lives in dams were between 4-18 hours and in foetuses between 6-12 hours.

In lactating rats, less than 2 % of administrated dose was recovered in milk and tissues of the pups at >24 hours post-dosing. The majority of radioactivity (up to 85 %) in rat milk was related to a rat specific metabolite with a milk/plasma ratio of 35:1. Nevertheless, the combined data indicated that minor paediatric exposure through milk ingestion in clinical use could not be excluded. Those findings are reflected in sections 4.6 and 5.3 of the SmPC.

RTG showed a relatively low and reversible binding (around 77-87%) to plasma proteins in all the tested species including humans. The degree of binding to plasma proteins was similar in both genders. NAMR protein binding was lower (39-49%) in all the tested species including humans.

Metabolism

The primary routes of RTG metabolism were dominated by phase II processes involving hydrolysis/N-acetylation to form NAMR and N-glucuronidation of RTG and NAMR. There was no evidence of direct oxidative metabolism of RTG in any species. There was no evidence of NAMR formation in the dog and little NAMR formation in the Cynomolgus monkey. All evaluated species formed N-glucuronides of RTG. N-glucoside metabolites of RTG were also observed in dog and humans.

Excretion

In rat and dogs studies evaluating the excretion of RTG and NAMR showed that RTG and metabolites were excreted in both faeces and urine, with an approximate 2:1 faeces:urine split of the eliminated dose. Studies with bile duct cannulated rats showed that a major part of the RTG-related radioactivity in faeces originated from the bile. NAMR was excreted to a greater extent in the urine, i.e., approximately one-half to two-third of the dose. Elimination patterns were similar following both PO and IV dosing, and the elimination of drug via the faeces following IV dosing was in accordance with significant biliary excretion.

Pharmacokinetic drug interactions

The enzyme-inducing capacity of RTG was evaluated in vitro in hepatic microsomes obtained from rats treated orally with RTG (8.25, 26.1 or 82.5 mg/kg/day for 7 days). RTG did not induce the CYP P450 isozymes or N-acetyltransferases (NATs). Therefore, it was concluded that RTG had no capacity to induce CYP1A, CYP2B, CYP2E1, CYP3A, NAT1 or NAT2 in rats. Metabolism data from human in vitro studies (D-23129/9321030009) also indicated that RTG is not a significant substrate for CYP P450 enzymes. RTG inhibition of human CYP-450 isoenzymes has been investigated in vitro. Similar to the observations in the rodent, there was no evidence of inhibition of human P450 isozymes observed at clinically-relevant concentrations.

However, a dose-dependent induction by RTG of hepatic UDP-glucuronosyltransferases (measured using p-nitrophenol as substrate) was observed in rats (D-23129/FB20299). This induction was more pronounced in female rats than male rats as the increases in enzyme activity were 1.6 and 3.8-fold in males and females respectively, at the top dose. The increase in females was comparable to that observed for phenobarbital. RTG also showed the potential for induction of its own metabolism. The induction was dose-dependent and a statistically significant increase of RTG glucuronidation was observed being approximately 3-fold in females. Based on this information, it was considered that auto-induced glucuronidation of RTG and other substrates, was possible with repeated RTG administration in rats.

Studies of P-gp mediated transport indicated that RTG was not a substrate of P-gp, although the metabolite NAMR had inhibitory activity.

Due to the low plasma protein binding of RTG and its principal metabolite NAMR, the potential for pharmacokinetic drug-drug interactions with highly protein bound drugs was considered low for RTG.

2.3.4. Toxicology

Single dose toxicity

Single-dose toxicity studies with RTG and RHCl were conducted in mice (3 studies) and rats (4 studies) using both oral and IV routes of administration.

Additional single dose toxicity data were available from a feasibility study in minipigs and from 2 single-dose TK studies in mice and rats. Apart from two studies (one in CD rats and one in minipigs), all single-dose studies were GLP-compliant.

The majority of the toxicities observed with RTG were directly or indirectly attributable to its effects on KCNQ channels. The primary signs of toxicity in single dose toxicity studies were CNS-related and were considered as extended pharmacological activity of RTG on the KCNQ receptors and associated with lethality at high doses. The minimal lethal dose was around 100 mg/kg in rats and 1000 mg/kg in mice following PO administration. Intravenous lethal dose levels were lower than seen with PO dosing. Based on extrapolation via allometric scaling, RTG was lethal in mice and rats at exposures 0.8 to 4-fold the MRHD (60 kg human).

Repeat dose toxicity

The pivotal repeat-dose toxicity studies included studies of up to 13-weeks, 26-weeks and 52-weeks duration in mice, rats and dogs, respectively. All those pivotal studies were performed in accordance with GLP regulations.

The designs and the major findings of those studies and are described in the table below.

Study ID **Duration**	**Species/** **Number/ Sex/** **Group**	**Dose (mg/kg)/** **Route**	**NTEL** **(mg/kg/** **day)**	**NOAEL**
MICE				
D23129-9321020042 13 weeks	CD-1 mice/ 15/sex/group	0, 50, 120, 225 RTG/ PO (diet)	<50	50 mg/kg in males (AUC 5,441 ng·h/mL, Cmax 358 ng/kg) and females (AUC BLQ, Cmax BLQ)
D23129-3000922904 13-weeks	B6C3F1 mice/15/sex/ group	0, 120, 225, 500 RTG /PO (diet)	<120	120 mg/kg (AUC 16,929 ng·h/mL, Cmax 1,281 ng/mL) in males and females (AUC 5,654 ng·h/mL, Cmax 535 ng/mL).
RATS				
D20443-3000904746 13 weeks	SD rats/15/sex/ group	0, 5, 20, 75 RHCl/ PO (gavage)	5	20 mg/kg/day As no apparent treatment-related findings at the 20 mg/kg/day dose level
D23129-9321020143 13 weeks	SD rat/15/sex /group	0, 10, 30, 75, 100, 150 RTG/ PO (diet)	30	75 mg/kg/day (AUC: 29,805 and 30,148 ng·h/mL; Cmax 1,417 and 1,606 ng/mL in males and females, respectively)
D23129-832094 13-weeks	Wistar rats/10/sex/ group	0, 0, 5.11, 12.1, 28.7, 68.1 RTG/ PO (gavage)	12.1	28.7 mg/kg body weight/day (AUC 23,217.15 and 27,800.26 ng·h/mL in males and females; Cmax 1,740.37 and 2,353.25 ng/mL in males and females)
D23129-3000899032	Wistar rats/25/sex/ group	0 (water), 0 (propylene	5.11	17.8 mg/kg body weight per day (AUC 7,060 and 10,044

Study ID Duration	Species/ Number/ Sex/ Group	Dose (mg/kg)/ Route	NTEL (mg/kg/ day)	NOAEL
26 weeks + 6 weeks recovery		glycol), 5.11, 17.8, 61.9 RTG/ PO (gavage)		ng·h/mL for males and females; Cmax 649 and 1,640 ng/mL for males and females)
D23129-3000913454 26-weeks	Wistar rat/10/sex/ group	0, 31.6, 68.1, 82.5, 100, 147 RTG/ PO (diet)	31.6	68.1 mg/kg (AUC 47,194.1 and 36,139.4 ng·h/mL; Cmax 2,253.7 and 1,920.3 ng/mL for males and females, respectively).
DOGS				
D23129-3000896861 13 weeks + 6 weeks recovery	Beagle dog/6/sex/ group Recovery: 2/sex/group from control and high-dose	0, 8.25, 17.8, 38.3 RTG/ PO (capsule)	< 8.25	≥38.3 mg/kg/day (Week 12: AUC 37,901 and 15,538 ng·h/mL in males and females, Cmax 2615 and 1,170 ng/mL in males and females, respectively)
D23129-3000912148 52-weeks + 6 weeks recovery	Beagle dog/6/sex/ group Recovery: 2/sex/group from control and high-dose	0, 4.64, 12.1, 31.6 RTG/ PO (capsule)	< 4.64	< 4.64 mg/kg/day (Week 51: AUC <2,674 and <4,313 ng·h/mL in males and females, Cmax <302 and <410 ng/mL in males and females)

The findings consisted primarily of toxic effects on the CNS, the urinary and renal system, the liver and the thyroid.

Effects on the CNS
CNS toxicity was observed in rats in the form of hypoactivity, hyperactivity, coordination disturbances and clonic convulsions. In dogs, clinical signs of CNS toxicity consisted of salivation, hypoactivity, coordination disturbances, decreased muscle tone, loss of righting reflex, hypothermia and clonic convulsions. The reversibility of these effects and the lack of histopathological findings in the CNS suggested that these findings might result from extended pharmacology. A toxicity study for a CNS active drug would include an extended histopathological evaluation of the brain.

Effects on the urinary system
Expression of KCNQ1, 3 and 5 has been demonstrated in rat urinary bladder and expression of KCNQ3 and 5 has been demonstrated in human urinary bladder smooth cells. The effects of RTG on the urinary bladder were probably primarily mediated via an activation of KCNQ3 since mRNA for KCNQ2 and 4 was not detected in the urinary bladder and the effect of RTG on KCNQ1 and KCNQ5 was insignificant as compared to the effect on KCNQ3. RTG causes KCNQ channel mediated urinary bladder relaxation. The smooth muscle relaxation induced by RTG resulted in an inhibition of micturation and bladder distension, with secondary effects on the kidney produced by increasing urinary tract pressure. Based on the conducted repeat-dose toxicity studies, the sensitivity to retigabine-induced urinary and renal system toxicity was mice>rats>dogs. It was considered that the higher sensitivity of the rodent species to the bladder and renal effects might be due to the normal inability of rodents to exert central control over bladder musculature.

In mice, rats and dogs, histopathological findings in the urinary bladder included distension, thickened urinary bladder wall, inflammation in the urinary bladder and in rodents also bladder calculi and urothelial hyperplasia. Secondary effects in the kidneys were observed in rodents such as dilated pelvis, papillary necrosis and tubular degeneration/regeneration/dilation including focal haemorrhage in the urinary bladder and proliferation of the smooth muscle. Reversibility of the effects was observed following a 6-week recovery period.

Urinary bladder epithelial hyperplasia was reported in two pivotal repeat-dose toxicity studies: following 13/26-weeks treatment of male mice/rats at doses ≥ 100 mg/kg. Based on plasma AUC values, the hyperplasia was observed in mice and rats, respectively, at doses 0.7 and 1.8-fold the

clinical plasma exposure at the Maximum Recommended Human Dose (MRHD). Histological analysis indicated that the proliferative activity in the urinary bladder epithelia in RTG-treated mice appeared to be compensatory to epithelial inflammation. This conclusion was supported by the lack of carcinogenic potential of retigabine following 2-years dosing of rats although the plasma exposure levels obtained were only 0.7 to 0.8-fold the clinical AUC at the MRHD in males and females, respectively.

Gall Bladder and Resulting Localized Dog Liver Toxicity
RTG caused relaxation of isolated guinea pig gall bladder via an effect on KCNQ channels; similarly RTG-treatment in dogs caused gall bladder dilation. in the 52-week study in dogs, the liver tissue directly overlying the distended gall bladder was affected by focal chronic degeneration/inflammation, accompanied by significant increases in ALT levels in some dogs. A mechanistic study demonstrated that gall bladder volume both at fasting and postprandial states were increased in RTG treated animals compared to controls. There was no evidence of any treatment-related gall bladder histopathology. The local liver toxicity associated with mechanical pressure from a dilated gall bladder occurred in dog at plasma exposure levels 10-fold lower than the clinical AUC at the MRHD.

Rodent hepatic Effects
Dose-dependent increases in liver weight and centrilobular hepatocellular hypertrophy were observed in multiple mouse and rat studies. Those findings were considered to be representative of an adaptive effect of induction of metabolizing enzymes, rather than being toxic effects. Indeed, a dose-dependent induction by RTG of hepatic UDP-glucuronosyltransferases was observed in rats. The findings were associated with typically mild-moderate dose-dependent changes in liver enzyme activities. It was concluded that there were no degenerative histopathological correlates for the hepato-biliary marker enzymes elevations in the mouse and rat. There were a range of similar examples of test substances that have produced increases in hepato-biliary marker enzymes in rodents with only adaptive changes such as hypertrophy or minimal toxicological findings (Amacher, 1998). It was therefore concluded that the hepatic changes for RTG in rodent species were indicative of reversible effects associated with the induction of drug metabolizing enzymes and further non-clinical testing was not considered necessary.

Rodent thyroid Effects
Slight thyroid follicular hypertrophy and an increase to T3, T4 and TSH were observed in mice and rats. These effects were considered to be an adaptive response to increased metabolic activity of the liver resulting in increased glucuronidation of thyroid hormone, and a compensatory response to restore thyroid hormone homeostasis.

Perturbations of the pituitary-thyroid axis by various xenobiotics were considered more likely to predispose the rat to higher incidences of thyroid proliferative lesions in response to chronic TSH stimulation than is the case for the human thyroid. The sensitivity of the rodent thyroid is to a great extent related to the shorter plasma half-life of T4 compared to that of humans, due to major differences in the transport proteins for the thyroid hormones, including the lack of thyroxine-binding globulin (TBG). TBG is found in humans and dogs (Casarett & Doull's, 2001; Greaves, 2007). There is no evidence from the clinical studies performed that RTG induces any thyroid changes in patients, which confirms the well established rodent specificity for effects on this endocrine organ.

Genotoxicity

Various genotoxicity studies demonstrated that the initial synthetic process of RTG was associated to a mutagenic response of RTG. The results of the Ames' test were in several cases considered negative even though a statistically significant dose-response relationship was identified. The marginal nature of the increase in the mutagenic index (<2- or <3-fold increase depending on the strain) indicated that the statistical responses were not biologically relevant but it was considered that the dose-dependent increase might indicate the presence of a genotoxic impurity for which there was insufficient assay sensitivity due to the presence of the active substance. In order to eliminate the mutagenicity effects, RTG was synthesized by the commercial route and was tested in a battery of in vitro and in vivo mutagenicity assays to detect potential gene mutation, chromosome aberration and DNA damage.

RTG tested negative for mutagenicity in the Ames test and an extensive number of later batches were shown to be non-mutagenic.

RTG also tested negative in two independent mammalian cell forward gene mutation assays in the presence and absence of S-9, and did not induce chromosome aberrations in cultured human lymphocytes following pulse treatment for 3 or 4 hours in the absence and presence of S-9. Following

continued treatment for 20 or 22 hours in this test system, RTG induced chromosome aberrations, but only in the absence of S-9 and at relatively high cytotoxic doses.

Finally, RTG tested negative in two in vivo assays, micronucleus test in bone marrow of mice and in the in vivo / in vitro UDS assay in hepatocytes in rats. Based on those findings, it was concluded that RTG was not genotoxic.

The principal human and rat plasma metabolite NAMR tested negative in the Ames' test but showed a significant increase in structural chromosomal aberrations in the in vitro chromosomal aberration assay. However, the increase was observed under conditions of high cytotoxicity and at an exposure approximately 1000-fold higher than that observed in humans following administration of the MRHD (based on human Cmax for NAMR). No significant neoplastic findings were observed in the neonatal mouse carcinogenicity study using a species in which NAMR has also been identified as a plasma metabolite. , The increase in structural chromosomal aberrations is therefore not considered relevant for humans.

The active substance itself was considered non-genotoxic in vitro and in vivo but a thorough evaluation of the impurities/potential impurities for genotoxicity was necessary to conclude on the genotoxic profile of RTG (see section "Impurities" in this section).

Carcinogenicity

RTG was shown to be non-carcinogenic in a 2-year rat study using PO administration of 5, 20 and 50 mg/kg/day (gavage). The exposure margins for RTG and its principal rat/human metabolite were 0.73 and 0.43 as compared to the level following administration of MRHD (based on AUC). Furthermore the potential for in particular genotoxic carcinogenicity of RTG was investigated in a neonatal mouse carcinogenicity study, where mice were fed by gavage once on postnatal day (PND) 8 and once on PND 15 with RTG (32, 64 or 96 mg/kg PO). There was no significant increase in the incidence of neoplasms in the lungs and livers, i.e., the most sensitive target organs of this model (Flammang et al., 1997; McClain et al., 2001). Based on the absence of hyperplastic histopathology changes in repeat dose toxicology studies and the negative findings in the rat- and neonatal mouse carcinogenicity study, that the CHMP concluded that RTG was unlikely to be carcinogenic.

Reproduction Toxicity

The reproductive and developmental toxicity program for RTG was comprehensive and encompassed fertility, early embryonic, embryo-foetal, pre- and postnatal development. These studies were complemented by juvenile animal toxicity studies. The pivotal studies were conducted in accordance with applicable GLP regulations and standards.

The influence of RTG on fertility and general reproductive performance was evaluated in rats at exposures 0.6 times the MRHD, based on AUC. No significant effects on male or female fertility or reproductive performance and early embryonic development were observed at any of the tested dose levels.

Maternal findings related to the extended CNS pharmacological effects of RTG were observed at oral doses above 20 mg/kg in rats. RTG was not tolerated in pregnant animals at doses above 30mg/kg/day in rabbits and 70mg/kg/day in rats. No treatment-related influence of RTG on reproductive parameters was noted in the two pivotal rat studies; however, increased incidence of soft tissue variations were recorded at 46.4 mg/kg in a dose-range finding study.

The pivotal studies in rabbits were performed with two different strains (Himalayan rabbits and New Zealand White). The maternal NOAEL was comparable between strains, i.e., 12-10 mg/kg but not the foetal toxicity. In Himalayan rabbits, embryo-foetal toxicity was observed at 26.1 mg/kg in form of a reduced foetal weight and a decreased survival rate of foetuses while in New Zealand White rabbits no foetal toxicity was recorded at 40 and 60 mg/kg/day.

Overall, RTG caused several effects on the reproductive system, foetal toxicity and malformations (i.e., soft tissue variations). The RTG AUC0-24 values in both rats and rabbits were estimated to be approximately 0.6-fold of the daily human exposure at the highest intended RTG clinical dose. The NOAEL regarding embryo-foetal toxicity and developmental effect was 46.4 mg/kg in rat and 12.1 mg/kg in the most sensitive rabbit strain corresponding to an estimated RTG plasma AUC 0.02-fold the MRHD.

Maternal toxicity was recorded at 61.9 mg/kg in the rat prenatal and postnatal development study in the form of clinical signs of CNS toxicity and reduced body weight gains. Signs of reproductive toxicity at 61.9 mg/kg included slightly (4%) prolonged gestational length, increased number of post-implantation losses, increased number of dead pups, and reduced pup survival, mostly during the first four days postpartum. Pup weights were lower compared to controls at 61.9 mg/kg and a related ≤1 day delay in the auditory startle response was observed at this dose level. A marginal effect on pup weight was observed at 17.8 mg/kg. Hence, the NOAEL was 17.8 mg/kg and 4.64 mg/kg for the F0 and F1 generation, respectively.

No toxicokinetic measurements were performed but the plasma exposure levels obtained were considered to be most likely below what those obtained clinically at the MRHD. Therefore, the CHMP considered that the reproductive and developmental toxicity profile in rats and rabbits had not been fully characterised and the Applicant was requested to evaluate if additional reproductive studies in rat and rabbit with different dosing regimen could provide an exposure significantly above clinically relevant plasma exposure levels.

In the responses to the D120 List of questions, the Applicant adequately justified the low dose range used in the reproductive studies and the effects observed. The impossibility to increase exposure margins by altering dose routes or changing dosing regimens was acknowledged but the data provided were considered insufficient and not adequate to justify the use of retigabine in pregnant women. Toxic effects on the foetuses could not be excluded and a strict recommendation for not using retigabine in pregnant women and women of childbearing potential not using contraception was included in section 4.6 of the SmPC.

Toxicity studies in juvenile animals

Overall, identical target organs were identified in the juvenile and adult toxicity studies. However, based on toxicokinetic data, the studies suggested that juvenile animals were more sensitive towards RTG than adult animals. Moreover, the animal sensitivity appeared to be influenced by the post partum age of the animals. Hence, 30 mg/kg PO (gavage) RTG was associated with mortalities in post-natal day (PND) 21 rats but not in rats which were 28 days old. In addition, an increased mortality rate was observed in PND 7 rats dosed with 0.6 mg/kg RTG. The treatment-related findings consisted of clinical signs of CNS toxicity and centrilobular hypertrophy of the liver. The plasma exposure obtained in the high-dose animals corresponded roughly to what was obtained in patients treated with 1200 mg RTG. Based on CNS development, a 28 day old rat corresponds approximately to a 6 year-old child thus caution should be exercised if attempting treatment of younger children.

Local Tolerance

Local RTG effects following IV, i.a. and p.v. dosing to dogs were similar to those observed with the vehicle control, indicating that RTG has a low potential to cause local tissue toxicity.

Other toxicity studies

- **Impurities**

The Applicant provided an extensive evaluation of the genotoxicity of the impurities/potential impurities in RTG, testing the isolated impurity in concentrations ≥250 µg/plate.

Three impurities are specified in the RTG active substance specifications. Considering the structural similarities of two of these impurities, they are controlled to a combined TTC limit of <1.5 µg/day (equivalent to <1.25 µg/g [~1.2 ppm] based on the 1200 mg maximum RTG daily dose) which is defined in the CHMP Guideline on the limits of Genotoxic Impurities.

For the third impurity, taken into consideration the available non-clinical data and the As Low As Reasonable Practicable (ALARP) principle, the CHMP requested the applicant to lower the specification limit.

In the DFB micronucleus study, bone marrow exposure (i.e., systemic exposure) was not directly assessed; however, adverse CNS signs consisting of ataxia, reduced motility and dyspnoea were observed at the Maximum Tolerated Dose (MTD = 1000 mg/kg), which suggested that adequate systemic exposure had been achieved.

Negative DFB Ames data indicated that the potential for mutagenicity of DFB had been appropriately addressed. Ethyl chloroformate (ECF) was not mutagenic in the Ames test

On consideration of all data pertaining to potential genotoxic impurities, the CHMP considered that there was no genotoxicity risk with the RTG active substance.

- **Immunotoxicity**

The antigenic/allergenic potential of RTG was investigated in male Guinea pigs by the passive cutaneous anaphylaxis test. Repeated intraperitoneal injections of RTG with or without adjuvants were administered to attempt to develop an antigenic reactin. Ovalbumin was used as positive control. RTG induced no passive or active anaphylactic response under the conditions of the study.

To evaluate the potential skin-sensitizing properties of RTG, a Buehler test was performed in guinea pigs. The results indicated that RTG had no sensitizing properties on the skin of guinea pigs. No systemic toxicity was observed.

RTG was found to be non-allergenic in guinea-pigs in two different tests for immunogenicity

- **Dependence Potential**

No evidence of physical dependence to RTG was generated from a 45 day abuse potential rat study. RTG was not considered to have a significant potential for clinical dependence or abuse.

- **Metabolites**

NAMR, the N-acetyl metabolite of RTG, was the only significant non-glucuronide metabolite of RTG present in the human circulation (AUC(0-24) NAMR values at 600 mg and 1200 mg RTG are ~12700 and ~22970 ng·h/mL, respectively). The potential toxicity of NAMR was evaluated as part of nonclinical studies conducted to assess RTG toxicity in rodents.
Dogs, due to their deficiency of the N-acetyl transferase enzyme, were not systemically exposed to NAMR in toxicology studies of RTG; therefore, the potential toxicity of NAMR could not be assessed during the evaluation of RTG toxicity in dogs.

In view of this and to complement the toxicology program, two 13-week studies were conducted to evaluate the potential toxicity of NAMR following oral administration in dogs.
Significant treatment-related clinical, haematology and pathology changes were observed at daily oral dose levels of ≥30 mg/kg (AUC0-24h ≥24900 and 13500, in males and females, respectively).

The mechanism(s) underpinning the haemato-pathology changes resulting in the severe clinical signs associated with NAMR administration at ≥30 mg/kg/day in dogs have not been identified.

Overall, the pattern of clinical, haematology and pathology findings identified in dogs administered NAMR at daily dose levels of ≥30 mg/kg were not present in rats at any of the administered oral dose levels (NAMR at dose levels of ≤120 mg/kg/day (males; AUC0-24h = 155734 ng.h/mL) or ≤100 mg/kg/day (females; AUC0-24h = 167797 ng.h/mL) for 13 weeks. The toxicity observed with NAMR dosing to dogs, but not in rats, is believed to represent a species-specific toxicity. Nevertheless, clinical and hematologic changes associated with NAMR administration in dogs were periodically monitored for in clinical trials.

- **Special toxicity and Mechanistic studies**

Mechanistic studies were conducted to further investigate the relationship between RTG effects on KCNQ-related smooth muscle contraction in the urinary bladder and the gall bladder, to characterize the pathogenesis of urinary tract lesions and to evaluate the gastrointestinal and the liver toxicity of RTG.

Results of these studies demonstrated that the activation of the Kv7 channels in the gall bladder by RTG leads to a dose-dependent reduction in gall bladder contractility. Effects on urinary tract in mice were probably dependent from the effects of RTG on KCNQ channels suggesting that these effects directly inhibit bladder contractility and lead to inhibition of micturation. Effects of RTG on liver

observed in dogs are probably species specific and are due to a mechanical pressure necrosis of the liver due to the distended gall bladder.

- **Phototoxicity**

Based on data from rat distribution studies and from *in vitro* studies, it was concluded that RTG had no phototoxic potential.

- **Compatibility with human blood**

The blood compatibility of RTG was analysed *in vitro*. The results indicated that RTG was compatible with human blood at intended clinical doses.

2.3.5. Ecotoxicity / environmental risk assessment

The environmental risk assessment submitted by the Applicant as part of this application was considered insufficient by the CHMP. Based on theoretical considerations, the Applicant considered that it was unnecessary to perform a sediment toxicity study even though the conditions for such a study were met. This was not considered acceptable by the Committee and the Applicant was requested to evaluate the potential toxicity of retigabine to sediment organisms and update the PEC estimates and the respective PEC:PNEC comparisons within 1 year of approval of the present application. The MAH was also requested to undertake additional Kow testing and to provide the relevant report concurrent with the proposed sediment toxicity testing.

The results from the additional studies were not considered required by the Committee before the adoption of the positive CHMP opinion and it is confirmed that these applications comply with Article 6 of Regulation 726/2004 having regard to the requirements of Article 8(3) (ca) of Directive 2001/83.

2.3.6. Discussion on non-clinical aspects

Potassium channels are one of the voltage-gated ion channels found in neuronal cells and are important determinants of neuronal activity. In vitro studies indicate that retigabine acts primarily through opening neuronal potassium channels (KCNQ2 [Kv7.2] and KCNQ3 [Kv7.3]). This stabilises the resting membrane potential and controls the sub-threshold electrical excitability in neurons, thus preventing the initiation of epileptiform action potential bursts. Mutations in the KCNQ channels underlie several human inheritable disorders, including epilepsy (KCNQ2 and 3).

The mechanism of action of retigabine on potassium channels has been well documented, however other mechanisms by which retigabine may assert an antiepileptic effect have yet to be fully elucidated.

In a range of seizure models, retigabine increased the threshold for seizure induction produced by maximal electroshock, pentylenetetrazol, picrotoxin and N-methyl-D-aspartate (NMDA). Retigabine also displayed inhibitory properties in multiple kindling models. In addition, retigabine was effective in preventing status epilepticus seizures in rodents with cobalt-induced epileptogenic lesions, and inhibiting tonic extensor seizures in genetically susceptible mice. The relevance of these models to human epilepsy, however, is not known.

Maximum doses in repeat dose toxicity studies were limited by the exaggerated pharmacologic effects of retigabine (including ataxia, hypokinesia and tremor). At no observed effect levels, animal exposure in these studies was generally less than that reached in humans at recommended clinical doses. Distension of the gall bladder was seen in studies with dogs, but there was no evidence of cholestasis or other signs of gall bladder dysfunction, and bile ejection volume was unchanged. The gall bladder distension in the dog resulted in focal compression of the liver. No signs of gall bladder dysfunction were seen clinically.

Non-clinical data revealed no special hazard for humans based on studies of genotoxicity or carcinogenic potential.

Retigabine had no effect on fertility or general reproductive performance. However the plasma levels achieved in the reproductive toxicity studies were less than those reached in humans at recommended doses due to maternal toxicity.

It is considered problematic that retigabine has not been characterized with respect to toxicity to reproduction especially considering that it is a first-in-class compound. However, the problem cannot be resolved non-clinically as higher exposure in the animals cannot be achieved due to maternal toxicity. Epilepsy with partial onset seizures is a prevalent disease (around 0.45% of the European population) and women of child-bearing potential will undergo long-term treatment. As the risk from using retigabine during pregnancy could not be excluded, a strict recommendation for not using retigabine in pregnant women and women of childbearing potential not using contraception has been included in section 4.6 of the SmPC.
The environmental risk assessment that was provided is considered insufficient and a fully updated ERA should be provided within 1 year of approval of the present application.

2.3.7. Conclusion on the non-clinical aspects

In general, the non-clinical properties of Trobalt have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

The Applicant has submitted an application for a dose starting on 300 mg daily with increasing doses optimized to an effective dose between 600 to 1200 mg/day. However, nearly all studies conducted in order to characterize the pharmacokinetic properties of retigabine used much lower doses.

The analytical methods, the pharmacokinetic data analysis, and the statistical analysis on which this application is based have been evaluated according to best standard and were well described.

Absorption

- **Bioavailability**

In Study 3065A1-123, the absolute bioavailability of retigabine administered as an oral solution and as oral immediate release (IR) capsules were determined.

The study was conducted as a single-center, randomized, open-label, single-dose crossover study in healthy male subjects (n=12), three single doses of retigabine were administered under fasting conditions with a washout period of at least 5 days between treatments: 50 mg retigabine as an IV infusion over 15 minutes, 200 mg retigabine as 2× 100 mg IR capsules orally with 200 mL of tap water; or, 80 mg of retigabine diluted in 180 mL of apple juice.

Serial blood samples for determining retigabine concentrations were obtained from each subject up to 48 hours after the end of the 15 minute IV infusion of retigabine and up to 72 hours post-dose following oral administration of retigabine.

Plasma concentrations of retigabine increased rapidly with a Cmax being achieved at a median Tmax of approximately 0.5 h. The t1/2 values were similar for the oral and IV dosage forms (7.2–9.4 h). The absolute bioavailability (Fabs) of both the oral solution and the IR capsule of retigabine were approximately 60% and the relative bioavailability (Frel) of the capsules versus oral solution was approximately 100%, indicating that absorption of a solid dosage form of retigabine administrated as an oral IR capsule appears complete relative to solution.

In conclusion, Retigabine was rapidly absorbed following oral administration with the absolute bioavailability of retigabine from both the oral solution and the IR capsule being approximately 60%. The similar bioavailability of retigabine for the IR capsule and the solution suggests that retigabine was fully released from the capsule.

- **Bioequivalence**

The following formulations were used in clinical studies:

- Retigabine Capsules. IR capsules (formulated in 4 strengths, 25, 50, 100, and 200 mg) were used in the early Phase I and II studies, including the pivotal Phase IIb Study 205.
- Clinical Trials IR Tablets. The Clinical Trials IR tablets (50, 100 and 300mg tablets) were used in the pivotal Phase III studies (Studies 301 and 302) and for Phase I clinical pharmacokinetic and clinical pharmacology studies that were conducted after initiation of the Phase III program. The Clinical Trial IR tablets had the same tablet core composition as the initial tablet formulation with minor changes in the tablet coating to enhance the stability of the product.
- The Final Market Image IR Tablets were developed using an identical tablet core composition as was used for the Clinical Trials IR tablets, with minor changes in appearance and coating.

An Initial Immediate Release Tablet (200 mg) was also formulated but was not used in any safety or efficacy studies in patients with epilepsy.

Bioequivalence of the 200 mg initial IR tablet versus the 200 mg capsule formulation under fasting conditions was shown in Study 3065A1-110. The geometric mean ratios of Cmax and AUC were approximately 100% when the 1x 200 mg tablet was compared to 1x 200 mg capsule and the corresponding 90% CI were all within the equivalence limits of 80-125%.

Two studies were conducted to bridge between the highest intended commercial tablet strength (400 mg) and the lower strength tablets (50 and 300mg) used in the Phase III clinical trials.

Study VRX-RET-E22-105 showed that the retigabine market image tablet was equivalent to the clinical trial tablet on the basis of overall systemic exposure (AUC), but not Cmax. The upper end of the 90% confidence interval (133%) for the peak concentration (Cmax) exceeded the traditional acceptance range for equivalence (125%) and the geometric mean of the market image tablet was 16% higher than that of the clinical trial tablet. This 16% higher Cmax appeared to be driven by individuals with low Cmax values for clinical trial tablets rather than high Cmax values for the market image tablet. The clinical trial IR tablets used for this study were from a batch with the largest particle size of all active substance batches that were used in the phase III trials and it was considered that the difference in particle size could explained the difference in Cmax that was observed. In addition, it was acknowledge that this study was underpowered.

Study RTG113287 was completed after the submission of the application and submitted at D121 of the procedure. This study showed bioequivalence between the market image IR tablet and the clinical trial IR tablet since the 90% confidence intervals for AUC and Cmax values were completely contained within the range 0.80 to 1.25.

Studies investigating the bioequivalence between the market image tablets and the clinical trial IR tablets showed bioequivalence with regard to AUC, but only Study RTG113287 demonstrated bioequivalence for Cmax. As the better powered study showed robust equivalence, it was agreed by the Committee that bioequivalence had been established between the clinical trial IR and the market image tablets.

No bioequivalence studies linking the formulations used in the clinical development program were provided. This was justified by the Applicant by the fact that the only difference between the two formulations was a minor change to the tablet coating.

- **Influence of food**

The effect of administration of retigabine IR capsules with a high fat breakfast on the rate and extent of retigabine absorption was investigated in Study 3065A1-106

The results of this study showed that administration of retigabine capsules with a high fat breakfast had no significant effects on the AUC or Cmax values of retigabine relative to dosing in a fasted state. However, there was a delay in the median time to reach Cmax by approximately 2.75 h.

The effect of a high fat breakfast on the rate and extent of absorption of retigabine from the initial IR tablet was investigated in Study 3065A1-110. Administration of the initial tablet formulation with a high fat meal had no marked effects on the AUC. However Cmax was increased by 14% when retigabine was administered with a high fat meal relative to dosing in a fasted state.

In Study VRX-RET-E22-104, the effect of a high fat breakfast on the rate and extent of absorption of retigabine from the Market Image IR tablet was investigated. This study showed that food did not affect the extent of oral absorption of retigabine from the market image tablets, but did result in a 38% higher Cmax.

In those three clinical studies, food did not influence the extent of absorption of the active substance. However, food increased the Cmax of the market image tablets by 38% compared to only a 14% increase for the clinical trial tablets. It was considered that the lower inter-subject variability under fed conditions may be due to delayed gastric emptying.

Distribution

The steady-state volume of distribution (Vss) of retigabine was 2-3 L/Kg after IV administration (dose range: 1-50 mg) (Study 3065A1-117).

Retigabine binding to both human plasma proteins and human serum albumin was about 80%. Thus, the drug is essentially bound only to albumin. Binding was not concentration-dependent over a range 0.1 – 8 µg/mL for HSA and 0.1-2 µg/mL for human plasma proteins. Due to the relatively low binding, no relevant increase in free concentration is expected as a result of interactions with other drugs.

Metabolism and Elimination

Study 3065A1-108 was an open-label, non-randomized single-dose study conducted in order to characterize the mass balance, route of elimination and metabolic pathways of retigabine after single dosing.

Six healthy male subjects were enrolled and received a single oral dose of retigabine 200 mg (200 µCi [14C]-retigabine) following an overnight fast. All enrolled subjects completed the study.

Retigabine metabolic pathways were primarily formation of the N-acetyl metabolite of retigabine (NAMR), and N-glucuronidation of both retigabine and NAMR. In addition, a small amount of an N-glucoside of retigabine was observed as was a cyclised product derived from NAMR. There was no evidence of oxidative metabolism of retigabine. Retigabine or retigabine radio-equivalents did not partition preferentially into the whole blood constituents and there was no evidence for a retigabine metabolite that would be expected to accumulate to a greater degree than parent itself.

Blood, urine and fecal samples were collected up to 240 hours post-dose in order to assess the metabolic profile and the amount of drug related material that was excreted.

Comparison of plasma total [14C]-retigabine-derived radioactivity versus concentrations of retigabine and N-acetyl metabolite of retigabine (NAMR) indicated that the majority of plasma radioactivity was attributable to a retigabine metabolite other than NAMR at all sampling time. T1/2 values for retigabine (9h), NAMR (11h) and total radioactivity (8.5h) were similar indicating that none of the retigabine metabolites would be expected to accumulate to a greater extent than retigabine.

The plasma concentration time curves for both 14C-retigabine-derived radioactivity and unchanged drug showed a secondary plasma peak in all subjects, which indicates hepato-biliary re-circulation. The major metabolite identified was N-glucuronide. The secondary peak of retigabine is in agreement with the observation that glucuronide deconjugation may occur in the intestine.

The whole blood-to-plasma ratio for the radioactivity ranged from 0.55 to 0.68 indicating that retigabine did not significantly partition into cellular components of blood.

Data showed that retigabine and its metabolites were almost exclusively excreted with the urine: following oral administration of 14C-retigabine (200 mg), 84% of administered radioactivity dose was recovered in the urine (13.5% recovered in the faeces). The main retigabine-related compounds found in the urine were the unchanged drug (36% of the administered dose), the N-glucuronide M1 (17% of

the administered dose) and the acetyl metabolite M2 (18% of the administered dose). The mean recovery was 97.9% ± 4.8% after 240 h. Elimination was rather fast, 70% of the dose being excreted within 24 h and the majority (93%) of the dose within 72 h.

Dose proportionality and time dependencies

- **Dose proportionality**

After IV dosing of retigabine (1, 2.5, 5, 10, 25 or 50 mg) as a 15 minute IV infusion dose proportionality was demonstrated within the rage of 2.5-50 mg. The single oral dose pharmacokinetics of retigabine was dose-proportional over the dose range 25 mg to 600 mg. Retigabine was rapidly absorbed and elimination values were typically with t½ around 10 hours.

Retigabine pharmacokinetics was dose-proportional after both single and repeated doses of 50-200 mg BID and over a single oral dose range of 100 to 300 mg and a multiple twice-daily dose range of 100 to 350 mg BID.

Population pharmacokinetic analysis showed that the systemic exposure to retigabine was linear over the therapeutic dose range of 600 to 1200 mg /day.

- **Time dependency**

The accumulation of retigabine was shown to be moderately low with the BID regimens and there was no evidence for a time-dependency in retigabine PK indicating that retigabine did not induce or inhibit its own metabolism.

Pharmacokinetics in target population

Studies evaluating the multiple-dose PK of retigabine in epileptic patients with therapeutically resistant partial-onset seizures showed that retigabine PK were dose-proportional in patients with epilepsy over a 50 mg BID to 200 mg BID dose range. Retigabine PK parameters in patients with epilepsy were similar to respective values in healthy subjects.

Special populations

- **Impaired renal function**

Thirty-one subjects were enrolled in an open-label single-dose, parallel-group study conducted in order to evaluate the effects of renal insufficiency on the PK of retigabine and NAMR after a single oral 100-mg dose of retigabine. The subjects were assigned into the different treatment groups based on their creatinine clearance (CLcr).

Retigabine AUC values in subjects with mild renal dysfunction were approximately 30% higher than respective values in healthy subjects, and retigabine AUC values in subjects with moderate or severe renal dysfunction or ESRD were approximately 100% greater than respective values in healthy subjects. Similar results were observed with NAMR AUC parameters across the groups, although the effects observed with NAMR were more marked than those observed with retigabine. Both retigabine and NAMR t1/2 values increased with increasing degree of renal dysfunction. As expected, the renal clearance (CLR) of both retigabine and NAMR decreased with the decreasing renal function. However, percent of dose excreted as retigabine or as NAMR was not markedly different among the groups, with the exception of a reduced percentage of retigabine excreted unchanged in subjects with severe renal impairment. The effect of renal function on retigabine and NAMR PK was considered to reflect a direct effect of these analytes on the urinary elimination.

It was concluded that retigabine pharmacokinetics was dependent on renal function.

The Applicant maintained that the effect of mild renal impairment on retigabine AUC was not considered clinically significant, and therefore no adjustment of the Trobalt dose was necessary.

To support this opinion, the Applicant performed a simulation to compare Cmax and AUC(0-24) at steady-state obtained with:

1) the current dosing recommendation (no dose adjustment in patients with mild renal impairment; a 50% reduction in the initial and maintenance dose in patients with moderate to severe renal impairment);

2) reduced unit dose of retigabine (one-half of the current starting dose for mild impairment);

3) a reduced frequency in dosing (BID instead of TID). A BID dosing regimen was also applied to subjects with moderate and severe renal impairment.

In subjects with mild renal impairment, a BID dosing regimen was predicted to provide a systemic exposure more consistent with that observed for healthy subjects, with respect to the current recommendations.

However, as a BID regimen might cause confusion among the prescribers since the TID regimen is the standard for all other patient groups, it was agreed by the CHMP that the pharmacokinetic advantage was not considered to outweigh this drawback and that the TID regimen for subjects with mild renal impairment should be maintained. Consequently, no adjustment of the dose was recommended in patients with mild renal impairment.

In subjects with moderate or severe renal impairment, the predicted exposure with the current recommendations (50% reduction in the initial and maintenance dose) was only slightly higher than the predicted exposure in subjects with normal renal function. On the other hand, a reduced frequency resulted in a ~ 50% increased exposure, as compared to subjects with normal renal function. The recommendation to have a 50% decrease in the initial and maintenance dose of retigabine was confirmed.

The information on the effect of haemodialysis on the clearance of retigabine was very limited as only 6 patients with end-stage renal disease (ESRD) and requiring haemodialysis were included in the study. The Applicant committed in the Risk Management Plan to further investigate the effect of haemodialysis on the clearance of retigabine.

- **Impaired hepatic function**

Twenty-four subjects were enrolled in an open-label, single-dose, and parallel-group study conducted in order to evaluate the effects of hepatic impairment on the PK of retigabine and NAMR after a single oral 100-mg dose of retigabine. The subjects were assigned into the following treatment groups: subjects with normal liver function (n=6), with mild hepatic impairment (n=6), moderate hepatic impairment (n=6) and severe hepatic impairment (n=6).

The PK characteristics of both retigabine and NAMR were dependent on hepatic function. Retigabine AUC parameters in subjects with mild hepatic impairment were similar to respective values in healthy subjects, but retigabine AUC parameters were approximately 50% and 100% greater in subjects with moderate or severe hepatic impairment, respectively, than AUC parameters in healthy subjects. Both retigabine CL/F and retigabine CLR were similar in healthy subjects and subjects with mild hepatic dysfunction, but were decreased in subjects with moderate or severe hepatic dysfunction. There were no consistent trends in retigabine Cmax values or retigabine t1/2 values across the study groups. There were no trends in NAMR PK parameters with varying degrees of hepatic dysfunction relative to respective parameters in subjects with normal hepatic function.

No retigabine dose adjustment was considered necessary in patients with mild hepatic impairment but a 50% decrease in the initial and maintenance doses of retigabine was recommended in patients with moderate or severe hepatic impairment. Those recommendations are reflected in section 4.2 of the SmPC.

An open-label, single- and multiple-dose, parallel-group study was conducted to investigate the impact of frequently occurring genetic polymorphisms of UGT1A1 (Gilbert's Syndrome) and NAT2 (slow acetylators) on the PK of retigabine and NAMR, and its main metabolites (glucuronidation products and NAMR), and to investigate the effect of retigabine treatment on serum bilirubin concentrations. This study showed that UGT1A1 or NAT2 genotype had no effect on retigabine pharmacokinetics. No retigabine dose adjustments were considered necessary on the basis of UGT1A1 or NAT2 genotype.

- **Gender**

The results of a single dose study showed that in young adult volunteers, retigabine C_{max} was approximately 65% higher in females than in males, and in elderly volunteers (66 to 82 years of age),

retigabine C_{max} was approximately 75% higher in females compared with males. When C_{max} was normalized for weight, the values were approximately 30% higher in young females than in males and 40% higher in elderly females compared with males. However, there was no apparent gender difference in weight-normalized clearance, and since retigabine is titrated according to individual patient response and tolerability, dose-adjustments were not considered necessary on the basis of gender.

- **Race**

A meta-analysis conducted to compare retigabine CL/F parameters between healthy Black and Caucasian subjects using relevant data combined from 6 single-dose clinical pharmacology studies, demonstrated a 20% reduction in retigabine clearance in healthy black volunteers relative to healthy Caucasian volunteers. Given the modest difference in retigabine PK in Black subjects, and considering that retigabine is titrated in each patient on the basis of efficacy and tolerability, retigabine dose adjustments in Black subjects were not considered necessary.

- **Elderly**

In a single-dose study, it was shown that retigabine was eliminated more slowly by healthy elderly volunteers (66 to 82 years of age) than by healthy young adult volunteers, resulting in a higher AUC (approximately 40 to 50%). Half-life was ~30% longer in elderly compared to young subjects across males and females. Elderly subjects were shown to have an approximate 30% lower weight-normalised CL/F than young subjects.

A reduction in the initial and maintenance dose of RTG was therefore considered necessary in elderly patients (see sections 4.2 and 5.1 of the SmPC). It was recommended to have a total daily starting dose at 150 mg/day and to increase the total daily dose by a maximum of 150 mg every week during the titration period, depending on the individual patient response and tolerability.

Pharmacokinetic interaction studies

- ***In vitro***

In-vitro studies using human liver microsomes revealed little or no potential for retigabine to inhibit the major CYP isoenzymes including CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5 (D-23129/9321030009). In addition, retigabine and NAMR did not induce CYP1A2 or CYP3A4/5 in human primary hepatocytes. It was considered unlikely for RTG to have P450 mediated drug-drug interactions. Interaction of RTG with the oral absorption of other drugs P-gp substrates when co-administered was not anticipated

Retigabine binding to human serum albumin (HSA) and plasma proteins was low and did not exceed 80% in *in vitro* ultracentrifugation studies.

- ***In vivo***

Anti-epileptic drugs (AEDs):

Lamotrigine/retigabine interaction study: No clinically relevant effect on the pharmacokinetics of retigabine was shown. However, the dose of lamotrigine was subtherapeutic. Conversely, there was no clinically significant effect of retigabine on the pharmacokinetics of lamotrigine, but the retigabine dose was at the lower end of the therapeutic range.

Phenobarbital/retigabine interaction study: No clinically relevant effect on the pharmacokinetics of retigabine was shown. However, the dose of phenobarbital was at the low end of the therapeutic range. Conversely, there was no clinically significant effect of retigabine on the pharmacokinetics of phenobarbital, but again the retigabine dose was at the lower end of the therapeutic range.

Based on two phase II studies, an exploratory analysis of the impact of the co-administration of phenytoin, carbamazepine, valproic acid and topiramate on the pharmacokinetics of retigabine was conducted.

This analysis indicated that co-administration of valproic acid (750-1500 mg/day) (n=4) and topiramate (250 – 1200 mg/day) (n=5) had no impact on the pharmacokinetics of retigabine whereas carbamazepine (600 – 2400 mg/day) (n=8) and phenytoin (120 – 600 mg/day) (n=9) increased oral clearance of retigabine by approximately 27% and 36%, respectively. The results from this analysis should be treated with caution since the recommended ANOVA approach was not used and the analysis was based on a limited number of subjects.

A population pharmacokinetic analysis of the effect of other AEDs on the pharmacokinetics of retigabine was performed. This analysis was based on the pivotal clinical trials. Since the point estimate for the fractional change in retigabine clearance for each AED was less than 10% ad the outer end of the 95% confidence intervals was less than 12%, no clinically significant effects of the following AEDs on retigabine pharmacokinetics were identified: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproate.

However, even though the analysis failed to identify a clinically significant effect of inducers (phenytoin, carbamazepine and phenobarbital) on retigabine clearance, it should be noted that steady-state data from limited number of patients in smaller phase II studies indicated that:

- phenytoin can reduce retigabine AUC by 35%, ad increase retigabine clearance by 36%;
- carbamazepine can reduce retigabine AUC by 33%, and increase retigabine clearance by 27%.

An integrated analysis of the impact of retigabine on trough concentration of existing AEDs was performed based on the phase III studies 301 and 302. Retigabine did not result in clinically significant effects on the plasma trough concentrations of the following AEDs: carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate and zonisamide. The largest effect was on lamotrigine phamacokinetics where retigabine co-administration was associated with a 20% decreased in lamotrigine concentrations.

It was not considered necessary by the CHMP to warrant dose adjustments when of retigabine when co-administered with other AEDs.

Oral contraceptive steroid:

There was no evidence for induction of oral contraceptive steroid metabolism following a repeat-dose retigabine 250 mg TID regimen. Therefore, oral contraceptive products can be co-administered with retigabine 250 mg TID without compromising the oral contraceptive agent safety and efficacy. Conversely, there was no effect of norethindrone/ethinyl estradiol (1 mg/0.035 mg) daily dosing on retigabine pharmacokinetics.

Ethanol:

AUC and Cmax value were 23% and 37% higher, respectively, during coadministration with ethanol relative to administration of retigabine alone. The AUC and Cmax of ethanol were essentially identical with and without retigabine co-administration. Co-administration of ethanol (1.0 g/kg) with retigabine (200 mg) resulted in an increase in visual blurring in healthy volunteers. This has been reflected in the SmPC.

2.4.3. Pharmacodynamics

Mechanism of action

Retigabine has a novel mechanism of action for a potential antiepileptic drug. The antiepileptic activity is believed to be mediated through retigabine's ability to enhance the K+ current mediated by human KCNQ2 and KCNQ3 K+ channels. A further contribution to retigabine's antiepileptic activity may be through its ability to augment gamma aminobutyric acid (GABA) mediated neurotransmission.

Primary and Secondary pharmacology

Due to the lack of relevant pharmacodynamic endpoints with regards to epilepsy, no pharmacology study addressing efficacy endpoints has been performed in humans.

Analysis of the relationship between plasma concentrations and efficacy or safety showed that there is poor correlation between exposure and response using the responder/non responder approach. On the other hand, there was a rather good correlation between exposure and occurrence of AEs.

The effect of retigabine on QT was assessed trough a phase I QTc study in healthy subjects (Study VRX-RET-E22-103) and a population PK/PD analysis based on QT data acquired from both the phase I QTc study and the Phase III clinical studies.

Study 103 was a double-blind (except for the use of moxifloxacin), randomized, 3-arm parallel-group study, investigated the effect of retigabine at a maximum tolerated dose on QT interval corrected for heart rate (QTc) in healthy men and women, as compared with placebo and the positive control, moxifloxacin. It was conducted to determine whether retigabine had a threshold pharmacologic effect on cardiac repolarisation, as detected by QT prolongation. The assessment of the data from the overall retigabine group showed no apparent effect; however, analysis of the completer population (those subjects who achieved the dose of 1200mg/day) indicated a slight and transient QT-prolonging effect (upper 95% CI greater than 10msec, but less than 13msec, and mean values less than 7msec) within 3 hours of dosing in healthy volunteers titrated to 1200mg/day.

A *post hoc* evaluation of the 95% CIs for the ORs and RRs for exceeding ICH-E14 thresholds for absolute QT intervals and changes from baseline (Bazett's and Frederica's corrected values) indicated that there were no significant association between QTc and retigabine overall. However, the *post hoc* analyses for individual retigabine doses indicated that patients who received a 1200 mg/day dose of retigabine were significantly associated with a Bazett's QTc interval increase from baseline of >30 msec although the data for the corresponding Frederica's QTc interval increase from baseline of >30 msec did not indicate an association with the 1200mg/day dose of retigabine.

A detailed ECG safety evaluation was also conducted during the retigabine epilepsy development programme to fully evaluate the effect of retigabine on the QT interval, and the data did not demonstrate a substantial effect on cardiac conduction across the 600 mg/day to 1200 mg/day dose range. In particular, no patients treated with retigabine experienced a QT interval of greater than 480 msec or reported adverse events related to QT prolongation.

The overall assessment of the data showed no apparent effect on cardiac repolarisation. However, analysis of the complete population indicated that a small effect of retigabine on cardiac repolarisation could not be excluded. Caution was therefore recommended with Trobalt when prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients an electrocardiogram (ECG) should be recorded before initiation of treatment with Trobalt and in those with a corrected QT interval >440ms at baseline, an ECG should be recorded on reaching the maintenance dose.

2.4.4. Discussion on clinical pharmacology

There was no direct bioequivalence link from the capsules used in the phase II study and the clinical trial IR tablets used in the two phase III trials. The Applicant has shown that the phase II capsule was bioequivalent with the initial IR tablet but this tablet was not used in any efficacy and safety study in epilepsy.

According to the Applicant, the clinical trial IR tablets and the initial IR tablets can be considered bioequivalent since the core tablet composition is the same, and the only difference between the two formulations was a minor change to the tablet coating. However, the Applicant has not convincingly demonstrated that the difference in tablet coating was non-significant with regard to bioavailability. Also, other quality attributes (particle size) may have been different between the two formulations.

Two studies investigating the bioequivalence between the market image tablets and the clinical trial IR tablets have been conducted. Both of them showed bioequivalence with regards to AUC, but only one of these studies demonstrated bioequivalence for Cmax. As the better powered study showed robust equivalence, it was agreed by the Committee that bioequivalence had been established between the clinical trial IR and the market image tablets.

In a food interaction study, food increased the Cmax of the market image tablets by 38%. This is to be compared to only a 14% increase for the clinical tablets. The Applicant has provided a comprehensive overview of the biopharmaceutical properties of retigabine and how these may influence the impact of

food. The explanation that the higher Cmax and the lower intra-subject variability under fed conditions may be due to delayed gastric emptying was considered to be plausible by the CHMP.

Further, it was agreed that in the fasted state incomplete dissolution of the market image 400 mg tablet strength may have resulted in a more pronounced apparent food effect with respect to Cmax compared to the smaller 200 mg initial IR tablet. This hypothesis was supported by the Cmax data of a single-dose ascending study (Study 3065A1-101) conducted in the fasted state. It was also agreed that the study VRX-RET-E22-104 may have overestimated the food effect for the lower strengths of the market image tablet which would be used for 600 and 900 mg/day doses.

Simulations of Cmax under fasted and fed conditions at steady state conditions following a retigabine TID regimen with the market image tablet formulation has been provided. It is predicted that the fed:fasted ratio for Cmax is reduced from 1.38 after single dose to 1.14 (90% CI 1.03 – 1.26) at steady state.

Based on the proposed mechanism for the food effect, administration with food could reduce intra-individual variability. However, the potential advantage arising from reducing the variability in Cmax assuming the drug with a meal are outweighed by the disadvantages arising from uneven dosing intervals and lower flexibility for individualised dosing.

After both single and multiple oral doses, retigabine was rapidly absorbed with median t_{max} values generally between 0.5 and 2 hours. Absolute oral bioavailability of retigabine relative to an intravenous dose is approximately 60%. Administration of retigabine with a high fat meal resulted in no change in the overall extent of retigabine absorption, but food reduced the between-subject variability in C_{max} (23%) compared to the fasted state (41%), and led to an increase in C_{max} (38%). The effect of food on C_{max} under usual clinical conditions is not expected to be clinically relevant. Therefore Trobalt may be taken with or without food.

Retigabine was approximately 80% bound to plasma protein over the concentration range of 0.1 to 2 µg/ml. The steady state volume of distribution of retigabine was 2 to 3 l/kg following intravenous dosing.

Retigabine was extensively metabolised in humans. A substantial fraction of the retigabine dose was converted to inactive N-glucuronides. Retigabine was also metabolised to an N-acetyl metabolite (NAMR) that is also subsequently glucuronidated.

There was no evidence for hepatic oxidative metabolism of retigabine or NAMR by cytochrome P450 enzymes. Therefore co-administration with inhibitors or inducers of cytochrome P450 enzymes was considered unlikely to affect the pharmacokinetics of retigabine or NAMR.

In vitro studies using human liver microsomes showed little or no potential for retigabine to inhibit the major cytochrome P450 isoenzymes (including CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5). In addition, retigabine and NAMR did not induce CYP1A2 or CYP3A4/5 in human primary hepatocytes. Therefore retigabine was considered unlikely to affect the pharmacokinetics of substrates of the major cytochrome P450 isoenzymes through inhibition or induction mechanisms.

In clinical pharmacokinetic drug interaction studies, retigabine did not result in clinically significant effects on the plasma trough concentrations of the following AEDs: carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate and zonisamide. The largest effect was on lamotrigine phamacokinetics where retigabine co-administration was associated with a 20% decreased in lamotrigine concentrations. Dose adjustments of retigabine were therefore not considered necessary when co-administered with other AEDs.

Elimination of retigabine occurs via a combination of hepatic metabolism and renal excretion. A total of approximately 84% of the dose was recovered in the urine, including the N-acetyl metabolite (18%), N-glucuronides of the parent active substance and of the N-acetyl metabolite (24%), or parent active substance (36%). Only 14% of retigabine was excreted in the faeces. Retigabine has a plasma half-life of approximately 6 to 10 hours. The total clearance of retigabine from plasma following intravenous dosing is typically 0.4 to 0.6 l/h/kg.

Retigabine pharmacokinetics were essentially linear over the single dose range of 25 to 600 mg in healthy volunteers and up to 1,200 mg daily in patients with epilepsy, with no unexpected accumulation following repeated administration.

Adjustment of the Trobalt dose is recommended in patients with moderate to severe renal impairment and in patients with moderate or severe hepatic impairment and the Applicant committed to further investigate the effect of haemodialysis on the clearance of retigabine as part of the Risk Management Plan.

Since retigabine is titrated according to individual patient response and tolerability, dose-adjustments are not required on the basis of body weight.

A reduction in the initial and maintenance dose of Trobalt is recommended in elderly patients.

The pharmacokinetics of retigabine in children and adolescents have not been investigated.

No clinically significant ECG morphology changes were noted for retigabine. No gender-related difference in QTc was noted for retigabine. Analysis of the complete population indicated that a small effect of retigabine on cardiac repolarisation could not be excluded. Caution is therefore recommended with Trobalt when prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients an electrocardiogram should be recorded before initiation of treatment with Trobalt and in those with a corrected QT interval >440ms at baseline, an ECG should be recorded on reaching the maintenance dose.

As part of the Risk Management Plan, the Applicant has committed to a programme of enhanced pharmacovigilance, as well as its routine proactive pharmacovigilance to allow a more precise definition of the true level of risk of QT prolongation and sequelae and consequently permit the retigabine SmPC to be updated with appropriate guidance, if more information becomes available.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacology data submitted were considered satisfactory.

2.5. Clinical efficacy

The clinical studies supporting efficacy are summarised in the table below.

Overall, 1244 patients were randomized to treatment in the primary efficacy studies (Studies 205, 301 and 302). A total of 813 patients received retigabine in doses of 600, 900 or 1200 mg/day in the three randomized, controlled trials for 16 to 18 weeks and 427 patients received placebo.

Summary of Studies Supporting Clinical Efficacy of Retigabine in the Adjunctive Treatment of Adults with Partial Onset Seizures

Study Number	Phase	Design and Control	Primary Objectives	Duration[a] (titration and maintenance only)	Regimens	Number of Patients[c]
Primary Efficacy Studies						
205	2b	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	16 weeks (8 week titration phase and 8 week maintenance phase)	200 mg TID	101
					300 mg TID	95
					400 mg TID	106
					Placebo	97
301	3	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	18 weeks (6 week titration phase and 12 week maintenance phase)	400 mg TID	154
					Placebo	152
302	3	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	16 weeks (4 week titration phase and 12 week maintenance phase)	200 mg TID	181
					300 mg TID	179
					Placebo	179
Supportive Phase 2a Efficacy Studies						
200/201	2a	Open-label, uncontrolled, randomized, parallel group	Safety, tolerability, PK and preliminary efficacy	24 weeks	RTG BID regimen: slow titration rate (25 mg/day) up to 400 mg/day	5
					RTG BID regimen: medium titration rate (100 mg/day) up to 1200 mg/day	23
					RTG BID regimen: fast titration (200 mg/day) up to 2400 mg/day	18
202	2a	Open-label, uncontrolled, randomized, parallel group	Safety, tolerability, PK and preliminary efficacy	15 weeks	RTG (BID or TID regimen) + AED monotherapy (valproic acid) up to 1600 mg/day[b]	8
					RTG (BID or TID regimen)+ AED monotherapy (carbamazepine) up to 1600 mg/day[b]	22
					RTG (BID or TID regimen)+ AED monotherapy (phenytoin) up to 1600 mg/day[b]	19
					RTG (BID or TID regimen)+ AED monotherapy (topiramate) up to 1600 mg/day[b]	11

Continued

Summary of Studies Supporting Clinical Efficacy of Retigabine in the Adjunctive Treatment of Adults with Partial Onset Seizures (Continued)

Study Number	Phase	Design and Control	Primary Objectives	Duration[a] (titration and maintenance only)	Regimens	Number of Patients[c]
Supportive Phase 2a Efficacy Studies (Continued)						
214	2a	Double-blind, randomized, parallel group	Safety, tolerability, PK and preliminary efficacy	7 weeks	RTG (TID regimen) titration rate : 150 mg/2 days up to 1200 mg/day	24
					RTG (TID regimen) titration rate: 150 mg/4 days up to 1200 mg/day	25
					RTG (TID regimen) titration rate: 150 mg/7 days up to 1200 mg/day	24
Open-Label Extension Studies that Support long-Term Efficacy						
212	2b	Open-label, long term extension study to Study 205	Safety, tolerability, long term efficacy	540 Days (1.5 years)	RTG 900 mg/day (followed by flexible titration up to 1200 mg/day)	222
303	3	Open-label, long term extension study to Study 301	Safety, tolerability, long term efficacy	ongoing	RTG 1200 mg/day (followed by flexible titration 600 to 1200 mg/day)	181
304	3	Open-label, long term extension study to Study 302	Safety, tolerability, long term efficacy	ongoing	RTG 900 mg/day (followed by flexible titration 600 to 1200 mg/day)	375

[a]Weeks for evaluation of efficacy
[b]Amended final maximum dose
[c]Number enrolled

2.5.1. Dose response studies and main clinical studies

Three controlled studies in patients with partial-onset epilepsy, which is the topic of this application, were conducted: A Phase 2b study conducted by Wyeth, Study 205 and two Phase 3 studies conducted by Valeant, Study 301 and Study 302. All three primary efficacy studies were international, multi-centre, parallel-group randomized, double-blind, placebo-controlled studies.

Study 205 was designed to assess the efficacy and safety of 600 mg/day (200 mg TID), 900 mg/day (300 mg TID), and 1200 mg/day (400 mg TID) compared with placebo. In addition to assessment of safety/efficacy, Study 205 provides the primary dose-response data in the clinical development program.

Studies 301 and 302 were conducted by Valeant. Study 301 included assessment of retigabine (1200 mg/day; 400 mg TID) compared with placebo. Study 302 included assessment of retigabine 900 mg/day (300 mg TID) and retigabine 600 mg/day (200 mg TID) compared with placebo.

Three pivotal studies were conducted, as shown in the table below.

Outline of Pivotal Efficacy Studies 205, 301 and 302

	Study 205	**Study 301**	**Study 302**
Phase/Sponsor	IIb/Wyeth	III/Valeant	III/Valeant
Treatment Group	600, 900, 1200 mg/day, PBO	1200 mg/day, PBO	600, 900 mg/day, PBO
Dosage Forms Used	50 mg, 100 mg or 200 mg IR capsules (note: 600 mg dose = 2X100 mg capsule TID; 900 mg dose = 3X100 mg capsule TID; 1200 mg dose = 1X 200 mg and 2X 100 mg capsule TID)	50 mg, 100 mg, 300 mg IR tablets (note: 1200 mg dose = 1X 300 mg tablet and 2X 50 mg tablets TID)	50 mg and 100 mg IR tablets (note: 300 mg dose = 3X 100 mg tablets TID)
Duration of Double-blind	16 weeks	18 weeks	16 weeks
Duration of Titration	8 weeks	6 weeks	4 weeks
Duration of Maintenance	8 weeks	12 weeks	12 weeks
Countries	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland Portugal ,Slovakia, Spain, Sweden, UK, and US	Argentina, Brazil Canada, Mexico, and US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, S Africa, Spain, UK Ukraine, and US

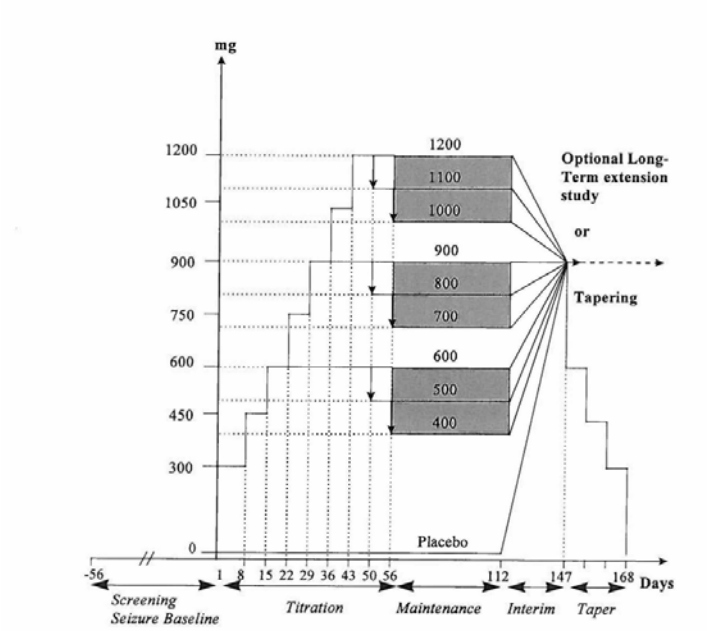
Methods

- ***Study design***

Study 205

Study 205 (3065 A1-205) was a randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of retigabine (600, 900 and 1200 mg/day) in patients (age 16 to 70 years) with partial-onset seizures. The study consisted of four phases: an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, an 8-week Titration Phase to the final targeted randomized dose and an 8-week Maintenance Phase during which patients received a fixed dose regimen (Figure 1).

Figure 1 Study Design – Study 205



The actual duration of the maintenance phase depended on the dose:
600 mg/d: 2 weeks titration and 14 weeks maintenance;
900 mg/d: 4 weeks titration and 12 weeks maintenance;
1200 mg/d: 6 weeks titration and 10 weeks maintenance; this latter scheme, thus, did not reach the full length recommended in the CHMP advice.

After completing the double-blind phase, patients could enrol in a long term, open-label, extension study (Study 3065 A1-212), after a 5-week interim phase of dose adjustment.

Patients who completed the double-blind study and who opted not to continue into the open-label extension study were discontinued from treatment by gradual down titration of study medication, over a 3-week period.

Study 301 and 302:

Studies 301 and 302 were similarly designed Phase 3 studies for assessing the efficacy and safety of retigabine (tablets) in patients with refractory partial epilepsy. Both were randomized, double-blind, placebo-controlled, multi-centre, parallel-group studies with similar inclusion and exclusion criteria.

Study 301 included assessment of retigabine (1200 mg/day; 400 mg TID) compared with placebo. Study 302 included assessment of retigabine 900 mg/day (300 mg TID) and retigabine 600 mg/day (200 mg TID), compared with placebo.

Both studies included an 8-week Baseline Phase during which patients were evaluated for seizure frequency, followed by a Titration Phase during which the retigabine dose was increased by 150 mg/week (50 mg TID) [up to 4 weeks in Study 302 and 6 weeks in Study 301]. At the end of the titration period, patients were maintained on a fixed dose for a 12-week Maintenance Period (Figure 2 and Figure 3).

Figure 2 Study Design- Study 301

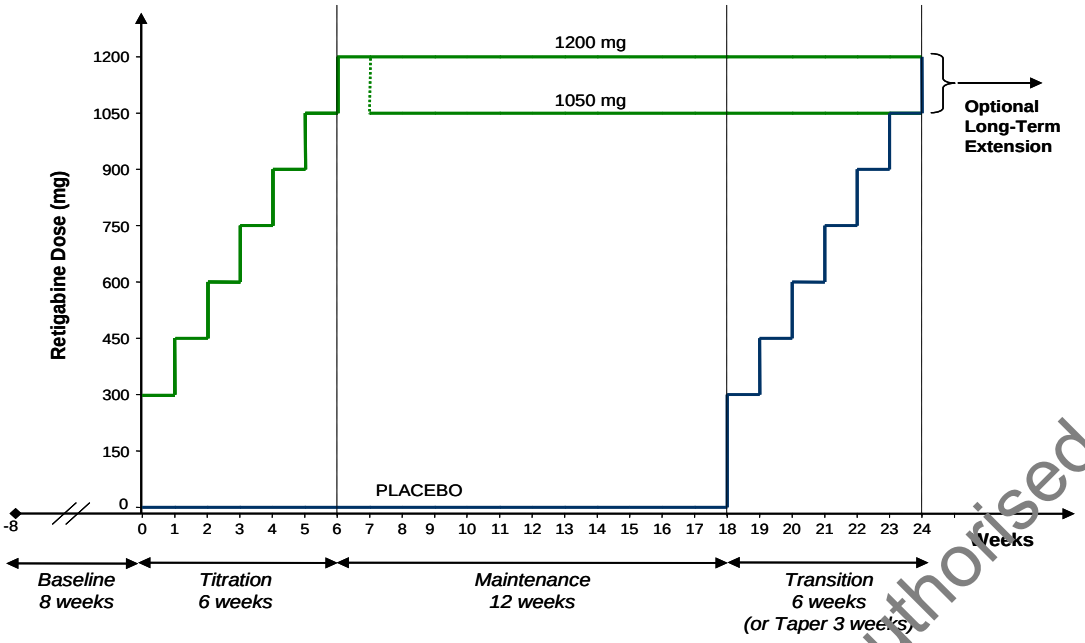
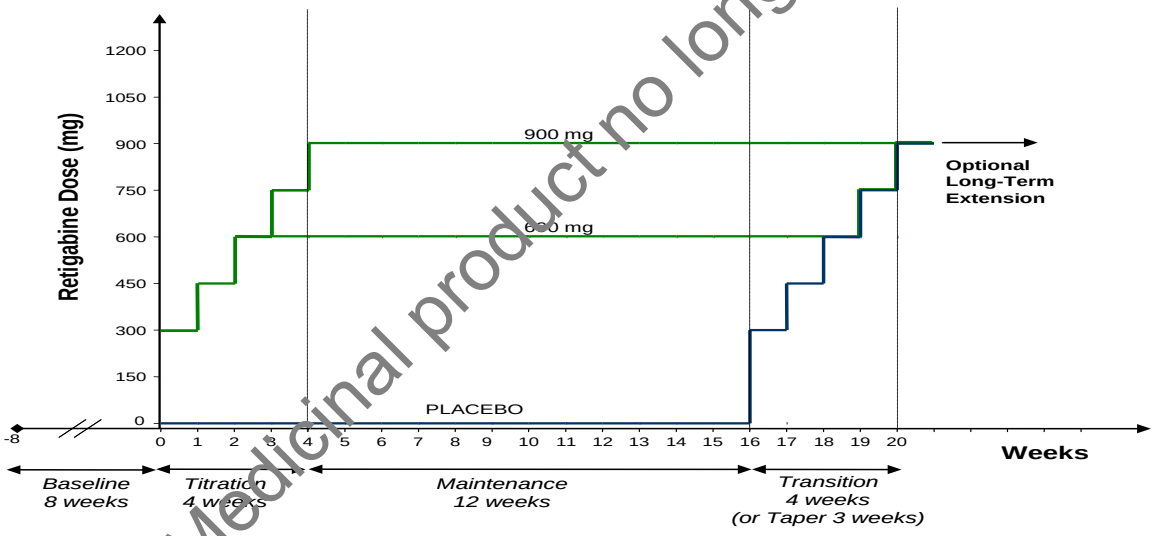


Figure 3 Study Design- Study 302



The only exception was that in Study 301 patients had a single opportunity to down titrate to 1050 mg/day at the end of Week 7, if they were unable to tolerate the targeted retigabine dose (1200 mg/day). Patients who down-titrated were then to continue at 1050 mg/day for the remainder of the maintenance period. Efficacy data were reported based on the assigned randomized dose and not on the actual dose received.

After completing the double-blind phase, patients could enrol in a long term, open-label, extension study (Study 303 for Study 301 and Study 304 for Study 302) after a transition phase of dose adjustment. In Study 301, this was a 6-week double-blind transition phase during which patients already randomized to retigabine 1200 mg/day were maintained on this dose level and patients previously on placebo during the double-blind phase, were dose escalated to retigabine 1200 mg/day in a double-blind, double-dummy manner. In Study 302, this was a 4-week double-blind transition phase during which patients already randomized to retigabine 900 mg/day were maintained on this dose level and patients previously on placebo or retigabine 600 mg/day during the double-blind phase, were dose escalated to retigabine 900 mg/day in a double-blind, double-dummy manner. In both

studies patients could be down-titrated off blinded treatment over 3 weeks, either if they chose not to continue into the open-label extension study, or if they were unable to complete the transition phase.

- ***Study Participants***

All three primary efficacy studies recruited patients with partial onset seizures (simple partial seizures and/or complex partial seizures with or without secondary generalization) in accordance with the International League Against Epilepsy (ILAE) classification criteria (Commission, 1981). Patients with simple partial seizures as their only qualifying seizure type were only eligible for study participation if there was a motor component to their seizures. The patient population in the three studies was described according to clearly defined clinical criteria.

In the Phase 2b study (Study 205) patients were eligible if:

- They were receiving up to two pre-specified AEDs at stable doses for at least 1 month prior to screening: valproic acid, carbamazepine, phenytoin, topiramate, lamotrigine, gabapentin, oxcarbazepine, benzodiazepines, or barbiturates. Vagal nerve stimulation (VNS), where applicable, was included as an AED therapy. Vigabatrin, felbamate and tiagabine were not allowed;
- They had at least four seizures per 28 days during the 8-week prospective baseline period;
- They were not seizure-free for more than 30 days during the baseline period.

In contrast, patients recruited in the Phase 3 studies (Studies 301 and 302) were only eligible if:

- They had a diagnosis of epilepsy for ≥2 years.
- They had previously received treatment with at least two AEDs, concurrently or sequentially, without significant clinical benefit (in the opinion of the investigator):
    - patients could be receiving up to three AEDs at stable doses (with or without VNS), at least 1 month prior to screening and throughout the study treatment period
    - vigabatrin and felbamate were not allowed;
- They had at least four seizures per 28 days during the 8-week prospective baseline period;
- They were not seizure-free for more than 21 days during the baseline period.

Supplementary VNS was allowed in all studies if the regimen had been initiated at least 6 months prior to study enrolment and treatment parameters were maintained constant for at least 1 month prior to screening and for the duration of the study.

Pre-specified restricted use of benzodiazepines to control flurries was allowed in the Phase 3 studies; use of benzodiazepines as background AEDs was permitted in the Phase 2 study as long as the dose was kept constant for at least 1 month before screening and for the duration of treatment. Benzodiazepine use as rescue or as last resort to control flurries was also permitted according to pre-defined criteria in this study.

Prohibited medications across all three studies included agents known to lower seizure threshold e.g., neuroleptics.

Study 205 included subjects aged between 16 and 70 years old, whereas studies 301 and 302 recruited subjects aged between 18 and 75.

Enrolment criteria excluded patients with significant medical conditions including those that would confound assessment of efficacy. Patients were excluded from study participation if they had a history of status epilepticus, seizure clusters or flurries within the 12 months prior to study entry, pseudo-seizures, non-epileptic events or any type of psychogenic seizures. Evidence of progressive central nervous system (CNS) disease (e.g., CNS lupus, tumors, multiple sclerosis, Alzheimer's) lesion or encephalopathy also precluded eligibility for study entry.

- ***Treatments***

Study 205 assessed the following dosages of retigabine (capsules): 600 mg/d (200 mg TID), 900 mg (300 mg TID), and 1200 mg/d (400 mg TID).

Study 301 assessed the following dosage of retigabine (tablets): 1200 mg/d (400 mg TID). In this trial patients were allowed to down titrate the daily dosage to 1050 mg/d if unable to tolerate the full 1200 mg/d dose.

Study 302 assessed the following dosages of retigabine (tablets): 600 mg/ (200 mg TID) and 900 mg/d (300 TID).

- ***Objectives***

Study 205: The objectives of study 205 was to evaluate the efficacy and safety of retigabine capsules 200 mg TID, 300 mg TID and 400 mg TID compared with placebo, when administered as add-on therapy in patients with partial epilepsy receiving one or two pre-specified AEDs.

Studies 301 and 302: Studies 301 and 302 aimed at assessing the efficacy and safety of retigabine tablets in the doses 1200 mg/d, or 600 mg/d and 900 mg/d, respectively in patients with refractory partial epilepsy.

- ***Outcomes/endpoints***

Primary efficacy measures

Study 205

In this study, the primary endpoint was the percentage change in total partial seizure frequency per 28 days from baseline to the double-blind phase.

Responder rate (50% reduction from baseline in partial onset seizure frequency) was not defined as a primary variable in the protocol but was identified as an efficacy variable for analysis in the statistical analyses plan (SAP) prior to unblinding of the data.

The term 'total partial seizures' was considered the primary seizure category and was defined as all simple partial and complex partial seizures with or without secondary generalization and also included status epilepticus and flurries.

Studies 301 and 302

In order to support international registration of retigabine, the primary efficacy studies included two primary objectives reflecting regulatory requirements in the US and Europe.

- The primary endpoint required by EMA guidance is based on responder rate i.e. a comparison of the percentage of responders (defined as those experiencing a ≥50% reduction in 28-day total partial seizure frequency) between baseline and maintenance phase.
- The primary endpoint required by FDA guidance is based on the percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind phase (titration and maintenance phases combined). The data are most appropriately described by the median percent value.

Secondary Efficacy Measures

For seizure categories, simple partial seizures included those with and without motor signs. Also flurries were not to be considered a separate type of seizures, but might be a secondary characteristic of other types of seizures.

Study 205

The secondary endpoints were the following:

- Median percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind (maintenance phase).
- Increase in seizure frequency categories defined as 0% to 25% and >25% to ∞. A further post-hoc analysis included assessment of seizure categories that presented the proportion of patients with a worsening of seizures.
- Percent of patients who were seizure free (all seizure types). Post-hoc analysis.
- Percent of seizure-free days (all seizure types). Post-hoc analysis.
- Number of seizure-free days per 28 days of treatment for total partial seizures and total seizures.
- Maximum number of consecutive seizure-free days for total partial seizures and total seizures.
- Incidence of new seizure types not present at baseline.
- Change in Clinical Global Impression-Improvement (CGI-I). Measures of overall response to treatment from the clinician were collected on a 7-point Likert scale where 1 indicated very much improved and 7 indicated very much worse.
- Rate (number and percent of patients) of discontinuation due to lack of efficacy.
- Time until discontinuation for patients discontinuing treatment early.
- Severity of illness.

Studies 301 and 302

The secondary endpoints included the following:

- The median percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind, here the maintenance phase.
- Percent of patients experiencing a reduction from baseline in 28-day total partial seizure frequency in categories of >75, 50-75%, <50%, <25% in addition to a category for those with no change/increase in seizures. A further post-hoc analysis included assessment of seizure categories that presented the proportion of patients with a worsening of seizures.
- Incidence of new seizure types not present at baseline.
- Percent of patients experiencing exacerbation of seizures with increase from baseline in 28-day total partial seizure frequency categories of 0-25% and >25 %.
- Change in Clinical Global Impression-Improvement (CGI-I) and Patient Global Impression-Improvement (PGIC) [Study 205 did not include PGIC]. Both measures of overall response to treatment from the clinician and patient perspective respectively, were collected on a 7-point Likert scale where 1 indicated very much improved and 7 indicated very much worse.
- Quality of Life in Epilepsy Problems (QOLIE-31P).

- ***Randomisation***

In all three studies a 1:1 randomisation for each of the doses of retigabine and placebo, respectively was issued.

- ***Blinding (masking)***

The test medication was delivered in blister cards using a double-dummy technique for the placebo.

- ***Statistical methods***

Study 205

Responder rates were analysed with logistic regression with centre and treatment as effects in the model. For the primary endpoint percent change in total partial seizures, the same closed procedure was applied. For the other secondary endpoints, pairwise comparisons were done to investigate the dose-response without any adjustments for multiplicity.

Rank analysis of covariance (ANCOVA) with treatment and pooled centres as factors in the model, and ranked baseline 28-day seizure rate as a covariate. Note: Dose response was studied by using contrasts in the rank ANCOVA, according to a closed procedure for monotonic trend. Hodges-Lehmann estimates and two-sided confidence intervals were provided for pairwise comparisons.

The following analyses were done in the integrated analyses to allow comparisons with Studies 301 and 302:

- A non-parametric rank ANCOVA, stratified by baseline seizure rate category (4-8 versus >8), was used to assess the percent change in 28-day total partial seizure rate
- The response rate was analyzed using Fisher's Exact test. Responder data, stratified by baseline seizure rate category (4-8 vs. >8), were also analyzed by Cochran-Mantel-Haenszel (CMH) test along with the Breslow-Day test of homogeneity.

301 and 302

Stratified non-parametric rank analysis of covariance was applied to assess the primary endpoint percent change in monthly seizure rate.

For the primary endpoint, the responder rates for the retigabine groups versus the placebo group were compared using Fisher's Exact test.

Further analysis of responder rates stratified by region and baseline seizure rate category was based on the CMH test along with the Breslow-Day test of homogeneity.

The FDA primary endpoint, the percent change in 28-day total partial seizure frequency, was further analyzed using the methods specified above, first stratified by geographic region only, and then stratified by baseline seizure rate category only.

Analysis of the continuous secondary endpoints employed the same methods as for the primary endpoints.

- ***Analysis Populations***

The ITT patient populations that were used to describe the primary analysis in Studies 301 and 302 differed from the pre-specified population defined in Study 205.

In Study 205, the ITT population was defined as all randomized patients who received at least one dose of study drug, had a baseline seizure evaluation, and at least one seizure evaluation on-therapy. This population was used in defining all efficacy endpoints across the double-blind phase.

A number of post-hoc analyses were conducted on unblinded data from Study 205 in order to harmonize the statistical methodology with those applied in Studies 301 and 302. The patient populations characterized for these additional post-hoc analyses were:

- An ITT (EMEA) population that was defined as all randomized patients who received at least one dose of study drug, and at least one seizure measurement recorded in the maintenance phase.
- An ITT (FDA) population that was defined as all randomized patients who received at least one dose of study drug, and had at least one seizure measurement recorded in the double-blind phase (titration and maintenance phase combined).

In Studies 301 and 302, two different ITT populations were defined with respect to the primary measure of interest for FDA and EMEA review respectively.

- The ITT (EMA) population was defined as all randomized patients who received at least one dose of study drug in the maintenance phase and had at least one seizure measurement (whether or not they had a seizure) recorded in the maintenance phase.

  This population was used in defining the primary efficacy endpoint for the EMA review. It also defined efficacy data for the maintenance phase in Study 301 and 302 and within the Summary of Clinical Efficacy is hereafter referred to as the ITT maintenance population for describing efficacy data for the maintenance phase.

- The ITT (FDA) population was defined as all randomized patients who received at least one dose of study drug.

  This population was used in defining the primary efficacy endpoint for the FDA submission. It also defined efficacy data for the titration and maintenance periods in Study 301 and 302 and within the Summary of Clinical Efficacy is hereafter referred to as the ITT double-blind population for describing efficacy data for the double-blind phase.

In addition to analyses across studies, pooled analyses were conducted for the primary efficacy studies. Pooled analyses were also conducted for the corresponding open-label extension studies of these trials.

For the integrated summaries of Studies 205, 301 and 302, two efficacy analysis populations were defined. These populations also define the phase of treatment that was assessed and are identical to the patient population definitions and associated phases describing efficacy that were pre-specified and described in Studies 301 and 302.

Results

Study 205

- **Participant flow**

Of the 537 patients who were screened, 399 were enrolled in the study and randomly assigned to treatment. Two of them did not receive any of the test capsules. These 2 patients were excluded from the safety population.

One patient (from the retigabine 200 mg TID group) who had no record of seizures during therapy was additionally excluded from the ITT population, and 396 patients were analyzed for efficacy. 279 patients completed the 8-week maintenance phase and were considered “completers.”

In all populations except the modified ITT patients had their data analyzed according to the treatment to which they were randomly assigned.

- **Recruitment**

A number of 73 centres in 19 countries participated: Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, The Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, UK, and USA.

- **Conduct of the study**

A number of protocol amendments were issued. However, these are not likely to be of major importance. More essential are the considerable amount of changes of analyses and conduct of post-hoc analyses, mainly to accommodate with the more recent pivotal trials 301 and 302. Per se these analyses therefore should be considered with caution.

- **Baseline data**

For age, gender, race, weight, and duration of the disease, no overall differences across the treatment groups were noted. The number of AEDs seemed to be distributed with numerically fewer patients in the placebo group receiving 1 concurrent AED, whereas more patients in the active groups received 2 or more AEDS. However, it is not considered likely that it will result in clinically important consequences for the results.

- **Numbers analysed**

The number of patients in each population and for each treatment dose is given below.

Population	Number (%) of Patients				
		Retigabine			
	Placebo	200 mg TID	300 mg TID	400 mg TID	Total
Enrolled	97 (100.0)	101 (100.0)	95 (100.0)	106 (100.0)	399 (100.0)
Safety	96 (99.0)	100 (99.0)	95 (100.0)	106 (100.0)	397 (99.5)
Intent to treat	96 (99.0)	99 (98.0)	95 (100.0)	106 (100.0)	396 (99.2)
Modified intent to treat[a]	78 (80.4)	83 (82.2)	74 (77.9)	67 (63.2)	302 (75.7)
Completers[b]	75 (77.3)	75 (74.3)	67 (70.5)	62 (58.5)	279 (69.9)
Per protocol	72 (74.2)	71 (70.3)	65 (68.4)	56 (52.8)	264 (66.2)
Maintenance[c]	78 (80.4)	83 (82.2)	74 (77.9)	68 (64.2)	303 (75.9)

[a] This population, also called the "as treated population" in the protocol, consisted of all the patients in the ITT population who had taken the investigational product for at least 14 days during the maintenance phase

[b] Included patients who were treated at the maintenance dose for the planned duration but who were not necessarily protocol compliant

[c] Includes patients who received at least one dosed in the maintenance phase and had at least one seizure frequency measurement.

Note: Percentages were not presented in the original table. The denominator is the number of patients enrolled in each group

A number of 126 (32%) patients were discontinued, most commonly for adverse events, reported for 87 (22 %) of the patients with an increase proportionally to the dosage regimen.

- **Outcomes and estimation**

Primary endpoint

Percent change in monthly total seizure rate from baseline to the double-blind therapy phase

Results of the original primary endpoint are shown in the table below.

Percent Change in Monthly Seizure Rate for Total Partial Seizures (ITT Population)

Phase Statistic	Placebo (N = 96)	Retigabine 200 mg TID (N = 99)	Retigabine 300 mg TID (N = 95)	Retigabine 400 mg TID (N = 106)
Titration Phase				
n	96	99	95	106
Median	-9.97	-22.27	-32.32	-31.47
Mean ± SD	3.78 ± 75.78	10.50 ± 197.12	-13.72 ± 70.60	-20.71 ± 62.93
Interquartile range	53.3	65.4	66.0	60.5
Range (min, max)	-100.0, 533.3	-100.0, 1756.3	-100.0, 303.5	-100.0, 375.0
Maintenance Phase				
n	78	83	74	68
Median	-22.94	-30.36	-35.81	-43.74
Mean ± SD	-17.48 ± 52.60	0.54 ± 193.37	-23.13 ± 63.49	-25.63 ± 88.51
Interquartile range	56.1	54.8	55.6	52.4
Range (min, max)	-100.0, 200.0	-100.0, 1652.6	-100, 291.6	-100.0, 502.6
Double-blind (Titration and Maintenance)				
n	96	99	95	106
Median	-13.10	-23.39	-29.23	-35.22
Mean ± SD	-3.33 ± 75.03	8.57 ± 190.94	-14.15 ± 70.35	-23.55 ± 64.87
Interquartile range	47.5	54.9	68.0	53.4
Range (min, max)	-100.0, 533.3	-100.0, 1703.1	-100.0, 297.6	-100.0, 375.0

Note: Summary statistics in the subgroup of patients with a non-zero baseline seizure rate for this seizure type. The primary analysis concerns the change from baseline to the "double-blind" therapy phase.
SD = standard deviation

For the original primary endpoint, the difference between the dosages of 900 mg/d (p=0.043) and 1200 mg/d (p<0.001), respectively, versus placebo were statistically significant. The 600 mg/d regimen did not reach statistical significance with regard to the primary endpoint.

The apparent dose response relationship was reproduced in analysis of the 50% responder rate endpoint (double-blind phase), where the results were consistent. However, sub-analysis restricted to the maintenance phase, showed superiority to placebo for the 1200 mg/d dose regimen, but not for the 600mg/d and 900 mg/d dose regimen. This inconsistency was further supported by an identical number of subjects discontinuing treatment because of lack of efficacy in the placebo and the 900 mg/d groups, as opposed to the two other retigabine dose regimens.

Overall the demonstrated efficacy fed within the range of results of studies of efficacy of other new antiepileptic drugs in refractory epilepsy, but was considered as modest from a clinical perspective.

Secondary endpoint

Responder rates for total partial seizures (ITT population)

A summary of the responder rates in each phase of the study is presented below.

Responder Rate for Total Partial Seizures (ITT Population)

		Retigabine		
Phase	**Placebo n / N (%)**	**200 mg TID n / N (%)**	**300 mg TID n / N (%)**	**400 mg TID n / N (%)**
Titration	13 / 96 (13.54)	28 / 99 (28.28)	26 / 95 (27.37)	35 / 106 (33.02)
Maintenance	20 / 78 (25.64)	23 / 83 (27.71)	30 / 74 (40.54)	28 / 68 (41.18)
Interim	33 / 76 (43.42)	34 / 79 (43.04)	30 / 67 (44.78)	24 / 63 (38.10)
Tapering	13 / 29 (44.83)	8 / 27 (29.63)	9 / 24 (37.50)	10 / 32 (31.25)
"Double-blind"	15 / 96 (15.63)	23 / 99 (23.23)	30 / 95 (31.58)	35 / 106 (33.02)
Summary statistics in the subgroup of patients with a non-zero baseline seizure rate for this seizure type				

The responder rates (patients whose seizure frequencies were reduced by at least 50%) during the double-blind phase were 16%, 23%, 32%, and 33% for the placebo group and the retigabine 600 mg/day, 900 mg/day, and 1200 mg/day dose groups, respectively. The results were consistent with the primary analysis for the percent change from baseline in seizure frequency. The pair-wise comparisons using the original logistic regression methodology for responder rate indicated significant linear dose trend across the tested doses that included placebo (p=0.001) and 900 mg/day versus placebo (p=0.008), but not 600 mg/day versus placebo (p=0.189).

During the maintenance phase only, the responder rate was 26% in the placebo group, 28% in the retigabine 200 mg TID group, 41% in the retigabine 300 mg TID group, and 41% in the 400 mg TID group. This rate was significantly higher in the retigabine 400 mg TID group than in the placebo group (p=0.010). The comparison between placebo and 300 mg TID retigabine is non-significant (p=0.057). The comparison between placebo and 200 mg TID retigabine is also not significant (p=0.845).

Proportion of patients who were seizure free (all seizure types)

The percent of patients who were seizure free (all seizure types) was considered to be the most important secondary endpoint. The results of this post-hoc analysis are presented in Table 26.

Percent of Patients who were Seizure Free (Maintenance Phase) – ITT Maintenance Population: Studies 205

Category	Number (%) of Patients			
	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205[a]				
N	78	83	74	68
n	78	83	74	68
Seizure-free	3(4)	2 (2)	4 (5)	6 (9)
Not seizure-free	75 (96)	81 (98)	70 (95)	62 (91)
P-value[b]		0.674	0.714	0.304

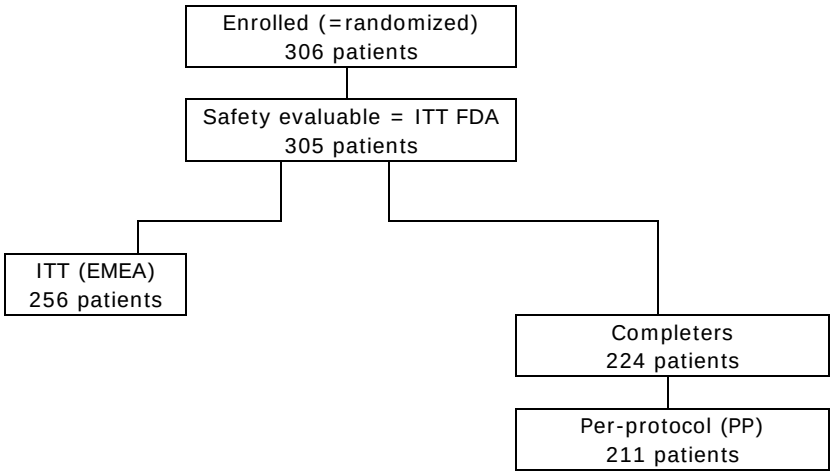
a. Post hoc analyses performed for Study 205
b. P-value from Fisher's Exact test

Study 301

Results

- **Participant flow**

The distribution of the participant flow is shown below in the figure below.



- **Recruitment**

A number of 53 centres in the USA (34), Canada, Mexico, Argentina, and Brazil contributed.

- **Conduct of the study**

A number of protocol amendments and changes of analyses was issued. The most important was the omission of a planned PQ sub-study, which in agreement with the FLA was substituted by a trial in healthy volunteers.

- **Baseline data**

There are no remarkable dissimilarities in the distribution of demographic data. A baseline imbalance was seen with respect to the percentage of patients taking 3 concomitant AEDs. However, this discrepancy did not seem to have a definite impact on the treatment response.
The demographics and baseline characteristics in the safety population are described in the table below.

	Placebo N=152	RTG 1200 mg/day N=153	Total N=305
Age, years			
Mean ± SD	36.7 ± 11.63	37.7 ± 12.55	37.2 ± 12.09
Sex, n (%)			
Male	72 (47.4)	68 (44.4)	140 (45.9)
Female	80 (52.6)	85 (55.6)	165 (54.1)
Race, n (%)			
White/Caucasian	78 (51.3)	90 (58.8)	168 (55.1)
Black	15 (9.9)	15 (9.8)	30 (9.8)
Hispanic	47 (30.9)	39 (25.5)	86 (28.2)
Asian	1 (0.7)	1 (0.7)	2 (0.7)
Other	11 (7.2)	8 (5.2)	19 (6.2)
Baseline Seizure Frequency			
N	150	151	n/a
Median	11.3	12.1	n/a
Previous AEDs tried and failed			
N	121	124	245
Mean ± SD	2.5 ± 1.64	2.6 ± 1.52	2.5 ± 1.58
Number of AEDs, n (%)			
1	21 (13.8)	32 (20.9)	53 (17.4)
2	70 (46.1)	79 (51.6)	149 (48.9)
3	61 (40.1)	42 (27.5)	103 (33.8)
Vagal nerve stimulator used, n (%)?			
Yes	17 (11.2)	12 (7.8)	29 (9.5)
No	135 (88.8)	141 (92.2)	276 (90.5)
Duration of Illness, years			
mean ± SD	23.1 ± 12.77	23.7 ± 13.00	23.4 ± 12.87

Note: All data are for Safety population, with the exception of baseline seizure rates, which are for the ITT double-blind population.
n/a= not available

- **Numbers analysed**

Populations Analyzed

Population	Number (%) of patients		
	Placebo	RTG 400 mg TID	Total
Randomized	152(100)	154(100)	306(100)
Safety	152(100)	153(99.4)	305(99.7)
Intent-to-treat population (FDA)	152(100)	153(99.4)	305(99.7)
Intent-to-treat population (EMEA)	137(90.1)	119(77.3)	256(83.7)
Completers[a]	127(83.6)	97(63.0)	224(73.2)
Per-protocol population	122(80.3)	89(57.8)	211(69.0)

EMEA=European Medicines Agency; FDA=Food and Drug Administration; RTG = retigabine, TID = three times daily
[a]ITT (FDA) patients who completed Visit 11 (Week 18) and at least 60 days of treatment in the maintenance phase.

- **Outcomes and estimation**

Primary endpoint

The responder rates between baseline and maintenance phase are presented in the table below

Maintenance Phase Responder Rate (Patients with at Least a 50 % Reduction From Baseline in 28-day Total Partial Seizure Frequency) to Maintenance Phase – ITT (EMEA) Population

	Number (%) of patients	
	Placebo (N=137)	RTG 400 mg TID (N=119)
Responders	31 (22.6)	66 (55.5)
Non-responders	106 (77.4)	53 (44.5)
p-value from Fisher's Exact test		<0.001

N = number of patients in the analysis population, n = number of evaluable patients, RTG = retigabine, SD = standard deviation, TID = three times daily

The responder rate in the maintenance phase for the ITT maintenance population was 22.6% in the placebo group and 55.5% in the retigabine 1200 mg/day group, which is a statistically and clinically significant difference (p<0.001).

Secondary endpoints

Percent Change in Total Partial Seizure Frequency – ITT (EMEA) Population

The percent change in 28-day total partial seizure frequency in the ITT (EMEA) population is shown below.

Baseline and Percent Change From Baseline in 28-day Total Partial Seizure Frequency to Maintenance Phase – ITT (EMEA) Population

	Placebo (N=137)	RTG 400 mg TID (N=119)	p-value[a]
Baseline frequency	n=137	n=119	
Mean ± SD	33.6 ± 83.81	34.2 ± 69.54	
Median	11.3	12.4	
Range	4 – 885	4 – 632	
Post-baseline frequency	n=137	n=119	
Mean ± SD	28.7 ± 56.73	23.2 ± 60.90	
Median	9.2	5.6	
Range	0 – 439	0 – 583	
Percent change from baseline	n=137	n=119	
Mean ± SD	-3.1 ± 135.74	-32.0 ± 91.86	
Median	-18.9	-54.5	<0.001
Range	-100 – 1382	-100 – 660	

[a] p-value for treatment comparison using rank analysis of covariance model with baseline seizure category and region as covariates.

N = number of patients in the population, n = number of patients with an observation, RTG = retigabine, SD = standard deviation, TID = three times daily

The median difference between retigabine and placebo treated patients was statistically and clinically significant with -54.5 % vs. 18.9 %, respectively (p<0.001).

Proportion of Patients With a Reduction or Exacerbation in 28-day Total Partial Seizure Frequency Presented by Category

Proportion of Patients With a Reduction in 28-day Total Partial Seizure Frequency From Baseline to Maintenance Phase by Reduction Categories Defined by EMEA – ITT (EMEA) Population

	Number (%) of patients	
Reduction Category	**Placebo (N=137)**	**RTG 400 mg TID (N=119)**
>75%	13(9.5)	37(31.1)
50% to 75%	18(13.1)	29(24.4)
< 50%	65(47.4)	33(27.7)
No reduction	41(29.9)	20(16.8)
p-value from Cochran-Mantel-Haenszel test	<0.001	

RTG = retigabine, TID = three times daily

There was a significant difference between treatment groups with respect to the proportion of patients in the ITT (EMEA) population with a reduction in 28-day total partial seizure frequency from baseline to maintenance phase by reduction categories defined by the EMEA guidance, with greater proportions of the retigabine group showing larger percentages of reduction in seizures ($p<0.001$). A greater proportion of patients receiving retigabine 37 (31%) experienced a greater than 75% reduction in seizure frequency compared to 13 (10%) in the placebo group. In addition, when compared to the placebo group, fewer patients in the retigabine group experienced no reduction in seizure frequency.

The percent of patients experiencing exacerbation of seizures with increase from baseline in 28-day total partial seizure frequency categories of 0 to 25% increase and >25 % increase was analysed as a post-hoc analyses. A smaller proportion of patients receiving retigabine (4, 3%) experienced a 0-25% increase in seizure frequency compared to 20 (15%) in the placebo group. In addition, when compared to the placebo group, a similar proportion of patients in the retigabine group experienced a >25% increase in seizure frequency (13% for the retigabine group and 15% for the placebo group).

Proportion of patients seizure free and percentage of seizure-free days

The proportion of patients who were seizure-free during the maintenance phase was 7.6 % in the retigabine group versus 1.5 % in the placebo group ($p=0.027$).

Percent of Patients who were Seizure-free (Maintenance Phase) – ITT Maintenance Population: Study 301

	Number (%) of Patients	
Category	**Placebo**	**RTG 1200 mg/day**
N	137	119
n	137	119
Seizure-free	2 (1.5)	9 (7.6)
Not seizure-free	135 (98.5)	110 (92.4)
P-value[b]	-	0.027

b. P-value from Fisher's Exact test.

Among secondary endpoints the proportion of seizure free subjects, during the maintenance phase, compared to that of placebo did not reach statistical significance. However, the numerical proportion of seizure free subjects on retigabine was higher than the corresponding on placebo.

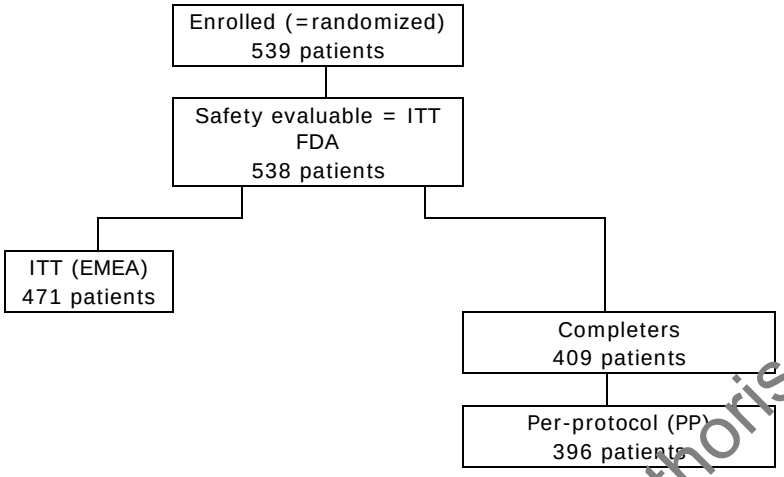
The median percentage of seizure-free days during the maintenance period was 86.9 % for the retigabine group versus 78.1 % for the placebo group ($p<0.01$).

Study 302

- **Participant flow**

The distribution of the participant flow is shown below

Number (%) of Patients in Analysis Populations



- **Recruitment**

A total of 71 centres in Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, South Africa, Spain, UK, Ukraine, and USA recruited patients.

- **Conduct of the study**

A number of protocol amendments and some changes in the analyses were issued.

- **Baseline data**

Demographic and other baseline characteristics are presented below.

Demographics and Other Baseline Characteristics – Safety Population

Variable	Placebo (N=179)	RTG 200 mg TID (N=181)	RTG 300 mg TID (N=178)	p-value
Age (years)				0.980[a]
Mean ± SD	37.7 ± 11.75	37.5 ± 12.02	37.7 ± 12.77	
Sex (n[%])				0.127[b]
Male	89 (49.7)	76(42.0)	93(52.2)	
Female	90 (50.3)	105(58.0)	85(47.8)	
Race (n[%])				0.782[b]
Caucasian	169 (94.4)	173(95.6)	170(95.5)	
African-American (black)	2 (1.1)	2(1.1)	1(0.6)	
Hispanic	0	0	0	
Asian	3 (1.7)	0	2(1.1)	
Other	5 (2.8)	6(3.3)	5(2.8)	
Height (cm)				0.944[a]
Mean ± SD	169.9 ± 9.19	169.6 ± 10.23	169.7 ± 8.92	
Weight (kg)				0.507[a]
Mean ± SD	74.8 ± 17.46	72.9 ± 15.75	73.5 ± 15.04	
BMI (kg/m^2)				0.551[a]
Mean ± SD	25.9 ± 5.93	25.3 ± 4.91	25.5 ± 4.99	

[a] p-value for treatment comparison using one-way analysis of variance model.
[b] p-value for treatment comparison using Fisher's Exact test.
BMI=body mass index; n=number of patients with the observation; N = number of patients in the population; RTG = retigabine; SD = standard deviation.

- **Numbers analysed**

A summary of patients in each analysis population is presented below.

Population	Number (%) of patients			
	Placebo	RTG 200 mg TID	RTG 300 mg TID	Total
Randomized	179 (100)	181 (100)	179 (100)	539 (100)
Safety	179 (100)	181 (100)	178 (99.4)	538 (99.8)
Intent-to-treat population (FDA)	179 (100)	181 (100)	178 (99.4)	538 (99.8)
Intent-to-treat population (EMEA)	164 (91.6)	158 (87.3)	149 (83.2)	471 (87.4)
Completers[a]	153 (85.5)	135 (74.6)	121 (67.8)	409 (75.9)
Per-protocol population	149 (83.2)	130 (71.8)	117 (65.4)	396 (73.5)

EMEA=European Medicines Agency; FDA=Food and Drug Administration; RTG = retigabine, TID = three times daily

[a] ITT (FDA) patients who completed Visit 9 (Week 16) and at least 60 days of treatment in the maintenance phase

- **Outcomes and estimation**

Primary endpoint

The responder rate in the maintenance phase for the ITT maintenance population was significantly higher in both the 600 mg/day and 900 mg/day dose groups compared to placebo, with a dose-response relationship (38.6% and 47.0% versus 18.9%, $p<0.001$ for both comparisons by Fisher's Exact test).

Responder Rate (Patients with at Least a 50% Reduction in 28-day Total Partial Seizure Frequency) From Baseline to Maintenance Phase – ITT (EMEA) Population

	Number (%) of patients		
	Placebo (N=164)	RTG 200 mg TID (N=158)	RTG 300 mg TID (N=149)
Responders	31 (18.9)	61 (38.6)	70 (47.0)
Non-responders	133 (81.1)	97 (61.4)	79 (53.0)
p-value (versus placebo) from Fisher's Exact test		<0.001	<0.001

N = number of patients in the population; RTG = retigabine.

Secondary endpoints

Percent Change in Total Partial Seizure Frequency – ITT (EMEA) Population

Baseline and Percent Change in 28-day Total Partial Seizure Frequency From Baseline to Maintenance Phase– ITT (EMEA) Population

	Placebo (N=164)	RTG 200 mg TID (N=158)	RTG 300 mg TID (N=149)
Baseline frequency			
Mean ± SD	31.0 ± 71.17	25.6 ± 70.68	23.1 ± 32.71
Median	9.2	9.8	10.1
Range (minimum, maximum)	3, 485	3, 858	3, 186
Post-baseline frequency			
Mean ± SD	28.7 ± 69.36	18.7 ± 36.54	16.9 ± 32.21
Median	8.0	6.8	5.7
Range (minimum, maximum)	0, 473	0, 336	0, 220
Percent change from baseline			
Mean ± SD	-5.1 ± 133.27	-25.0 ± 55.96	-30.9 ± 80.49
Median	-17.4	-35.3	-44.3
Range (minimum, maximum)	-100, 1589	-100, 253	-100, 714
p-value[a]	--	0.002	<0.001

[a] p-value for treatment comparison (versus placebo) using rank analysis of covariance model with baseline seizure category and region as covariates.
N = number of patients in the population; RTG = retigabine; SD = standard deviation, TID = three times daily.
Note: Only patients with baseline and maintenance phase seizure measures were included in this table.

The median percent change from baseline to maintenance phase in 28-day total partial seizure frequency in the ITT (EMEA) population was significantly greater for the 200 mg TID retigabine group (-35.3%, p=0.002) and the 300 mg TID retigabine group (-44.3%, p<0.001) compared with the placebo group (-17.4%), with a clear dose response effect.

Proportion of Patients With a Reduction or Exacerbation in 28-day Total Partial Seizure Frequency Presented by Category

The proportion of patients in the ITT (EMEA) population experiencing a reduction in 28-day total partial seizure frequency from baseline to maintenance phase by reduction categories of quartiles as defined EMEA guideline are shown below.

Proportion of Patients With a Reduction in 28-day Total Partial Seizure Frequency From Baseline to Maintenance Phase by Categories Defined by EMEA – ITT (EMEA) Population

	Number (%) of patients		
Reduction Category	Placebo (N=164)	RTG 200 mg TID (N=158)	RTG 300 mg TID (N=149)
>75%	11(6.7)	27 (17.1)	30 (20.1)
50% to 75%	20(12.2)	34 (21.5)	40 (26.8)
< 50%	83(50.6)	60 (38.0)	49 (32.9)
No reduction	50(30.5)	37 (23.4)	30 (20.1)
p-value from Cochran-Mantel-Haenszel test		<0.001	<0.001

RTG = retigabine, TID = three times daily.

When compared with placebo patients, a smaller percentage of patients in the retigabine 200 mg TID and 300 mg TID groups experienced a 0-25% increase in seizure frequency (17%, 9% and 7% for placebo, 200 mg TID and 300 mg TID, respectively). In addition, when compared to the placebo group, a similar proportion of patients in the retigabine groups experienced a >25% increase seizure frequency (13%, 15% and 13% for placebo, 200 mg TID and 300 mg TID, respectively).

Proportion of Patients Seizure Free and Percent of Seizure-free Days

The part of patients who is seizure-free is 3.2 %, and 4.7 % in the 600 mg/d and 900 mg/d dosage groups, as compared with 1.2 % in the placebo group. In both cases the difference was not significant.

Percent of Patients who were Seizure Free (Maintenance Phase) – ITT Maintenance Population: Study 302

	Number (%) of Patients		
Category	**Placebo**	**RTG 600 mg/day**	**RTG 900 mg/day**
N	164	158	149
n	164	158	149
Seizure-free	2 (1.2)	5 (3.2)	7 (4.7)
Not seizure-free	162 (98.8)	153 (96.8)	142 (95.3)
P-value[a]	-	n/a	0.091

a. P-value from Fisher's Exact test.

The median percent of seizure-free days was 82% (p=0.03) and 85% (p=<0.001) for the 600 and 900 mg/d group, respectively, as opposed to 78 % in the placebo group.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial 205

Title: A randomised, double-blind, placebo-controlled, parallel-group, multicentre, dose-ranging, efficacy and safety study of retigabine (D-23129; GKE-841) administered as add on therapy in patients with partial epilepsy.			
Study identifier	3065A1-205-AU/EU/US		
Design	This was a randomised, double-blind, placebo-controlled, multicentre, dose-ranging study of efficacy and safety in patients with epilepsy currently treated with one or two anti-epileptic drugs (AEDs). Patients were randomized (1:1:1:1) to 4 parallel groups. The study consisted of 5 phases: an 8-week screening and baseline phase, during which patients were evaluated for seizure frequency; an 8-week titration phase; an 8-week maintenance phase, during which patients received the dose reached at the end of the titration phase; and a 5-week interim phase, during which the retigabine dose was adjusted to 300 mg TID for all patients. The double-blind period consisted of the titration phase plus the maintenance phase for purposes of efficacy assessments.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	8 weeks not applicable not applicable	
Hypothesis	Superiority of retigabine (RTG) (dose-ranging assessment of efficacy i.e. seizure reduction from baseline) compared with placebo		
Treatments groups	Poo		Placebo, = 16 weeks, number randomised= 97
	RTG 600 mg/day		Retigabine 600 mg/day. 16 weeks, number randomised = 101
	RTG 900 mg/day		Retigabine 900 mg/day. 16 weeks, number randomised = 95
	RTG 1200 mg/day		Retigabine 1200 mg/day. 16 weeks, number randomised = 106
Endpoints and definitions	**Primary endpoint** Percent change in monthly total partial seizure (TPS) rate from baseline phase to the double blind phase	% change in 28-day TPS (DB phase)	Percent change in monthly total partial seizure rate from baseline phase (8-week baseline phase) to the double-blind therapy phase (including all titration and maintenance phase data).
	Secondary Responder rate in the double-blind phase	RR (DB phase)	Percentage of patients with a reduction in monthly total partial seizure frequency by at least 50% in double-blind phase from the baseline rate.

	Secondary Percent change in monthly total partial seizure (TPS) rate from baseline phase to the maintenance phase	% change in 28-day TPS (MN phase)	Percent change in monthly total partial seizure rate from baseline phase (8-week baseline phase) to the maintenance phase (excluding titration data).
	Secondary Responder rate in the maintenance phase	RR (MN phase)	Percentage of patients with a reduction in seizure frequency by at least 50% in maintenance phase from the baseline rate (excluding titration data).
Database lock	December 21, 2001		

Results and Analysis

Analysis description	**Primary Analysis**				
ITT population **Double Blind Phase**	The ITT population was defined as all randomized patients who received at least one dose of study drug, had a baseline seizure evaluation, and at least one seizure evaluation on-therapy. This population was used in defining all efficacy endpoints across the double-blind phase.				
Descriptive statistics and estimate variability	Treatment group	**Pbo**	**RTG 600mg/day**	**RTG 900mg/day**	**RTG 1200mg/day**
	Number of subjects	96	99	95	106
	% change in 28-day TPS (DB phase)				
	Mean	−3.33	8.57	−14.15	−23.55)
	SD	75.03	190.94	70.35	64.87
	Median	−13.1	−23.39	−29.29	−35.22
	Range	−100, 533	−100, 1703	−100, 298	−100, 375

Effect estimate per comparison	**% change in 28-day TPS (DB phase)**	**Comparison groups**	**RTG 600 mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	−10.29%
		variability statistic	Not Applicable
		P-value	0.199
		Comparison groups	**RTG 900 mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	−16.19%
		variability statistic	Not Applicable
		P-value	0.043
		Comparison groups	**RTG 1200 mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	−22.12%
		variability statistic	Not Applicable
		P-value	<0.001

Notes	The primary test statistic was rank analysis of covariance (ANCOVA) with treatment and pooled centres as factors in the model, and ranked baseline 28-day seizure rate as a covariate. The dose response was studied by using contrasts in the rank ANCOVA, according to a closed testing procedure for monotonic trend. The pre-specified analyses using the rank ANCOVA methodology for percent reduction in monthly total partial seizures indicated significant linear dose trend across the tested doses that included placebo ($p<0.001$) and between retigabine 900 mg/day versus placebo ($p=0.043$) and for 1200 mg versus 600 mg/day ($p=0.047$). The data at 600 mg compared with placebo were not statistically significant ($p=0.199$). The primary objective of the original planned analyses was to assess dose response using a closed testing procedure which assumed a monotonic trend. A further *post-hoc* assessment to assess the relationship between each active dose of retigabine and placebo without the assumption of monotonicity showed for the additional contrast for retigabine 1200 mg/day and placebo, a significant treatment difference in the double-blind phase ($p=0.001$)- (see Addendum to 205 CSR Section 5.1)				
Analysis description	**Secondary analysis**				
ITT population **Double Blind Phase**	The ITT population was defined as all randomized patients who received at least one dose of study drug, had a baseline seizure evaluation, and at least one seizure evaluation on therapy. This population was used in defining all efficacy endpoints across the double-blind phase.				
Descriptive statistics and estimate variability	Treatment group	**Pbo**	**RTG 600mg/day**	**RTG 900mg/day**	**RTG 1200mg/day**
	Number of subjects	96	99	95	106
	Responders (%) DB Phase	15 (15.6)	23 (23.2)	30 (31.6)	35 (33.0)
	Non-responders (%) DB Phase	81 (84.4)	76 (76.8)	65 (68.4)	71 (67.0)
Effect estimate per comparison	**Responders (%) DB Phase**	**Comparison groups**		**RTG 600 mg/day vs. Pbo**	
		Unadjusted difference from placebo in RR		7.6%	
		P-value		0.189	
		Comparison groups		**RTG 900 mg/day vs. Pbo**	
		Difference from placebo in RR		16%	
		P-value		0.008	
		Comparison groups		**RTG 1200 mg/day vs. Pbo**	
		Difference from placebo in RR		17.4%	
		P-value		0.001	
Notes	The original logistic regression analysis for responder rate indicated a significant linear dose trend across the tested doses that included placebo ($p=0.001$) and 900 mg/day versus placebo ($p=0.008$), but not for 600 mg/day versus placebo ($p=0.189$). The results of the additional *post-hoc* direct comparison of retigabine 1200 mg/day versus placebo without the assumption of monotonicity was significant ($p=0.003$) –see Addendum to 205 CSR Section 5.1.2)				
Analysis description	**Secondary analysis**				
ITT population **Maintenance Phase**	The pre-specified population for the maintenance phase analysis was based on all randomized patients who received at least one dose of study drug, and at least one seizure measurement recorded in the maintenance phase.				
Descriptive statistics and estimate variability	Treatment group				
Effect estimate per comparison	Number of subjects	**Pbo**	**RTG 600mg/day**	**RTG 900mg/day**	**RTG 1200mg/day**
	% change in 28-day TPS (MN phase)	78	83	74	68
	Mean				

	SD	-17.48	0.54	−23.13	−25.63
	Median	52.6	193.37	63.49	88.51
	Range	−22.94	−30.36	−35.81	−43.74
	% change in 28-day TPS (MN phase)	−100, 200	−100, 1653	−100, 292	−100, 503

Notes		**Comparison groups**	**RTG 600 mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	−7.42%
		Variability statistic	Not Applicable
		P-value	0.536
		Comparison groups	**RTG 900 mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	−12.87%
		Variability statistic	Not Applicable
		P-value	0.170
	The analyses using the original rank ANCOVA methodology under the assumption of monotonicity indicated a statistically significant difference between the retigabine 1200 mg/day group and placebo (p=0.008) The results of the additional *post-hoc* direct comparison of retigabine 1200 mg/day versus placebo without the assumption of monotonicity was significant (p=0.012) –see Addendum to 205 CSR Section 5.1)	**Comparison groups**	**RTG 1200 mg/day vs. Pbo**
		Difference from placebo in median percent change	−20.8%
		Variability statistic	Not Applicable
		P-value	0.008

Analysis description	**Secondary analysis**
ITT population **Maintenance Phase**	The pre-specified population for the maintenance phase analysis was based on all randomized patients who received at least one dose of study drug, and at least one seizure measurement recorded in the maintenance phase.
Descriptive statistics and estimate variability	Treatment group

Effect estimate per comparison	Number of subjects	**Pbo**	**RTG 600mg/day**	**RTG 900mg/day**	**RTG 1200mg/day**
	Responders (%) Mn Phase	78	83	74	68
	Non-responders	20 (25.6)	23 (27.7)	30 (40.5)	28 (41.2)
	Responders (%) Mn Phase	58 (74.4)	60 (72.3)	44 (59.5)	40 (58.8)

Notes		**Comparison groups**	**RTG 600 mg/day vs. Pbo**
		Unadjusted difference from placebo in RR	2.1%
		P-value	0.845
		Comparison groups	**RTG 900 mg/day vs Pbo**
		Unadjusted difference from placebo in RR	14.9%
		P-value	0.057

	In the original logistic regression analysis the results showed a significant linear dose trend across the tested doses that included placebo (p=0.010). The results of the additional *post-hoc* direct comparison of retigabine 1200 mg/day versus placebo without the assumption of monotonicity was significant (p=0.031) -see Addendum to 205 CSR Section 5.1.2)	**Comparison groups**	**RTG 1200 mg/day vs Pbo**
		Unadjusted difference from placebo in RR	15.6%
		P-value	0.010

Summary of Efficacy for trial 301

Title: A randomised, double-blind, placebo-controlled, multicentre, parallel-group phase 3 study to determine the efficacy and safety of retigabine (1200 mg/day) used as adjunctive therapy in refractory epilepsy patients with partial-onset seizures			
Study identifier	VRX-RET-E22-301		
Design	This was a randomised, double-blind, placebo-controlled, multicentre, parallel-group Phase 3 study to assess the efficacy and safety of retigabine (1200 mg/day; 400 mg TID]) compared to placebo (1:1) in patients with epilepsy who were receiving 1, 2, or 3 AEDs. Use of a vagal nerve stimulator (VNS) was also allowed in addition to as many as 3 AEDs. The study consisted of a screening visit, an 8-week baseline phase to evaluate seizure frequency; a 6-week titration phase; a 12-week maintenance phase; and a 6-week transition phase or a 3-week tapering phase. During the titration phase, patients were titrated from 300 mg/day to 1200 mg/day (400 mg TID) on blinded study drug, with weekly increases in doses of 150 mg/day over the course of 6 weeks. Patients who were unable to tolerate dose escalation were discontinued from the study. During the maintenance phase, patients who were unable to tolerate the 1200 mg/day (400 mg TID) dose were allowed to reduce their dose to 1050 mg/day at the Week 7 visit only and were to continue on that dose for the remainder of the maintenance phase. The double-blind period consisted of the titration phase plus the maintenance phase for purposes of efficacy assessments.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks Not applicable Not applicable
Hypothesis	Superiority of retigabine (RTG) i.e. seizure reduction from baseline compared with placebo		
Treatments groups	Pbo		Placebo, = 18 weeks, number randomised=152
	RTG 1200 mg/day		Retigabine 1200 mg/day. 18 weeks, number randomised = 154
Endpoints and definitions	Primary endpoint Responder rate in the maintenance phase	RR (%) MN phase	Percentage of patients with a reduction in seizure frequency by at least 50% in maintenance phase from the baseline rate (excluding titration data).
	Secondary Percent change in monthly total partial seizure (TPS) rate from baseline phase to the maintenance phase	% change in 28-day TPS (MN phase)	Percent change in monthly total partial seizure rate from baseline phase (8-week baseline phase) to the maintenance phase (excluding titration data).

	Secondary Proportion of patients by % reduction category of monthly total partial seizure (TPS) rate in the maintenance phase	Number (%) patients in 28-day TPS % reduction category (MN phase)	Proportion of patients by percent reduction category in monthly total partial seizure rate from baseline phase (8-week baseline phase) to the maintenance phase (excluding titration data).
	Secondary Percent patients seizure free in the maintenance phase	Number (%) patients seizure free (MN phase)	Proportion of patients seizure-free (prior to end of maintenance phase or drop out) during the maintenance phase.
	Secondary Percent seizure free days in the maintenance phase	% seizure free days (MN phase)	Percent seizure-free days (prior to end of maintenance phase or drop out) during maintenance
Database lock	February 1, 2008 (prior to unblinding)		

Results and Analysis

Analysis description	**Primary Analysis**			
ITT Maintenance Population	The ITT (EMEA) population was defined in the study report as all randomised patients who received at least one dose of study drug in the maintenance phase and had at least one seizure measurement (whether or not they had a seizure) recorded in the maintenance phase. It defined efficacy data for the maintenance phase. This population and definition was used in defining the primary efficacy endpoint for the EMA review. A more general term for describing efficacy during the maintenance phase i.e. ITT maintenance population is utilised below.			
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=137**	**RTG 1200mg/day N=119**	
	Number of subjects in analysis	137	119	
	Responders (%)-Mn Phase	31 (22.6)	66 (55.5)	
	Non-responders (%)- MN phase	106 (77.4)	53 (44.5)	

Effect estimate per comparison	**Primary endpoint Responders (%)-Mn Phase**		**RTG 1200mg/day vs. Pbo**
		Unadjusted difference from placebo in RR	32.9%
		variability statistic	Not Applicable
		P-value	<0.001 using Fisher's Exact test
Notes	In the pre-specified analysis, the ITT Maintenance Population did not include patients who dropped out prior to maintenance. However *post-hoc* sensitivity analyses (full details in study report) that included different imputation paradigms for missing data, demonstrated a robust treatment effect for retigabine. In the conservative imputation scheme that assumed non-responder status for patients who dropped out during the titration phase the results remained significant.		
Analysis description	**Secondary analysis**		

ITT Maintenance Population	*See above*			
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N= 137**	**RTG 1200mg/day N= 119**	
	Number of subject in analysis	137	119	
	% change in 28-day TPS (MN phase)			
	Mean	−3.1	−32.0	
	SD	135.74	91.86	
	Median	−18.9	−54.5	
	Range	−100, 1382	−100, 660	

Effect estimate per comparison	**% change in 28-day TPS (MN phase)**		**RTG 1200mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	−35.9%
		variability statistic	Not Applicable
		P-value	<0.001 treatment comparison vs. placebo using non-parametric rank ANCOVA.
Notes			

ITT Maintenance Population	*See above*		
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=137**	**RTG 1200mg/day N=119**
	Number of subject in analysis	n= 137	n=119
	Proportion of patients in 28-day TPS % reduction category (MN phase)		
	75 to 100%	13 (9)	38 (32)
	50 to <75%	18 (13)	28 (24)
	25 to <50%	31 (23)	16 (13)
	>0 to <25%	34 (25)	17 (14)
	No change or increase	41 (30)	20 (17)

Effect estimate per comparison	**Proportion of patients in 28-day TPS % reduction category (MN phase)**	Comparison groups	**RTG 1200mg/day vs. Pbo**
		test statistic i.e. treatment difference	Not Available
		variability statistic	Not Applicable
		P-value	<0.001 Categorised reductions or increases from baseline in seizure frequency were analyzed using a Cochrane Mantel Haenszel test
Notes	The data presented is from CSR source table Table 11.4.12.2.3A. A number of pre-specified analyses on percentage change by varying categories were conducted. The results of these analyses showed a statistically significant difference in the distribution profiles by categories for retigabine compared to placebo		

ITT Maintenance Population	See above			
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=137**	**RTG 1200mg/day N=119**	
	Number of subject in analysis	n= 137	n= 119	
	Number (%) patients seizure free (MN phase)			
	Seizure-free	2 (1.5)	9 (7.6)	
	Not seizure-free	135 (98.5)	110 (92.4)	

Effect estimate per comparison	**Proportion of patients seizure free (MN phase)**		**RTG 1200mg/day vs. Pbo**
		Unadjusted difference compared with Placebo	6.1%
		variability statistic	Not Applicable
		P-value	0.027 Fisher's exact test
Notes	Patients discontinued prematurely and did not have any seizure in the maintenance phase prior to discontinuation were included as seizure-free		

ITT Maintenance Population	See above			
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=137**	**RTG 1200mg/day N=119**	
	Number of subjects in analysis	n=137	n=119	
	% seizure free days (MN phase)			
	Mean	66.3	73.6	
	SD	28.26	28.60	
	Median	78.2	86.9	
	Range	0, 100	0, 100	

Effect estimate per comparison	**% seizure free days (MN phase)**		**RTG 1200mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	8.7%
		Unadjusted difference from placebo in mean percent change	7.3%
		variability statistic	Not Applicable
		P-value	<0.001 treatment comparison versus placebo using non-parametric rank ANCOVA model

Summary of Efficacy for trial 302

Title: A randomised, double-blind, placebo-controlled, multicenter, parallel-group Phase 3 study to determine the efficacy and safety of two doses of retigabine (900 mg/day [300 mg TID] and 600 mg/day [200 mg TID]) used as adjunctive therapy in refractory epilepsy patients with partial-onset seizures			
Study identifier	VRX-RET-E22-302		
Design	This was a randomised, double-blind, placebo-controlled, multicentre, parallel-group Phase 3 study to assess the efficacy and safety of retigabine dosed at 600 mg/day (200 mg TID) or 900 mg/day (300 mg TID) compared to placebo in patients with epilepsy who are receiving 1, 2, or 3 AEDs. Use of a vagal nerve stimulator (VNS) was also allowed in addition to as many as 3 AEDs. The study consisted of a screening visit, an 8-week baseline phase to evaluate seizure frequency; a 4-week titration phase; a 12-week maintenance phase; and a 4-week transition phase or a 3-week tapering phase. During the titration phase patients were titrated from 300 mg/day to 600 or 900 mg/day, with weekly increases in dose of 150 mg/day over the course of 2 to 4 weeks. Patients who were unable to tolerate the dose escalation were discontinued from the study. The double-blind period consisted of the titration phase plus the maintenance phase for purposes of efficacy assessments.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks not applicable not applicable
Hypothesis	Superiority of retigabine (RTG) i.e. seizure reduction from baseline compared with placebo		
Treatments groups	Pbo		Placebo, 16 weeks, number randomised=179
	RTG 600 mg/day		Retigabine 1200 mg/day. 16 weeks, number randomised = 181
	RTG 900 mg/day		Retigabine 1200 mg/day. 16 weeks, number randomised = 179
Endpoints and definitions	**Primary endpoint** Responder rate in the maintenance phase	RR (%) MN phase	Percentage of patients with a reduction in seizure frequency by at least 50% in maintenance phase from the baseline rate (excluding titration data).
	Secondary Percent change in monthly total partial seizure (TPS) rate from baseline phase to the maintenance phase	% change in 28-day TPS (MN phase)	Percent change in monthly total partial seizure rate from baseline phase (8-week baseline phase) to the maintenance phase (excluding titration data).
	Secondary Proportion of patients by % reduction category of monthly total partial seizure (TPS) rate in the maintenance phase	Number (%) patients in 28-day TPS % reduction category (MN phase)	Proportion of patients by percent reduction category in monthly total partial seizure rate from baseline phase (8-week baseline phase) to the maintenance phase (excluding titration data).
	Secondary Percent patients seizure free in the maintenance phase	Number (%) patients seizure free (MN phase)	Proportion of patients seizure-free (prior to end of maintenance phase or drop out) during the maintenance phase.
	Secondary Percent seizure free days in the maintenance phase	% seizure free days (MN phase)	Percent seizure-free days (prior to end of maintenance phase or drop out) during maintenance
Database lock	May 1, 2008 (prior to unblinding)		

Results and Analysis				
Analysis description	**Primary Analysis**			
ITT Maintenance Population	The ITT (EMEA) population was defined in the study report as all randomised patients who received at least one dose of study drug in the maintenance phase and had at least one seizure measurement (whether or not they had a seizure) recorded in the maintenance phase. It defined efficacy data for the maintenance phase. This population and definition was used in defining the primary efficacy endpoint for the EMA review. A more general term for describing efficacy during the maintenance phase i.e. ITT maintenance population, is utilised below.			
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=164**	**RTG 600mg/day N=158**	**RTG 900mg/day N=149**
	Number of subjects in analysis	n= 164	n=158	n=149
	Responders (%)-Mn Phase	31 (18.9)	61 (38.6)	70 (47.0)
	Non-responders (%)- MN phase	133 (81.1)	97 (61.4)	79 (53.0)
Effect estimate per comparison	**Responders (%)-Mn Phase**		**RTG 600mg/day vs. Pbo**	
		Unadjusted difference from placebo in RR	19.7%	
		variability statistic	Not Applicable	
		P-value	<0.001 using Fisher's Exact test	
			RTG 900mg/day vs. Pbo	
		Unadjusted difference from placebo in RR	28.1%	
		variability statistic	Not Applicable	
		P-value	<0.001 using Fisher's Exact test	
Notes	In the pre-specified analysis, the ITT Maintenance Population did not include patients who dropped out prior to maintenance. However *post-hoc* sensitivity analyses (full details in study report) that included different imputation paradigms for missing data, demonstrated a robust treatment effect for retigabine. In the conservative imputation scheme that assumed non-responder status for patients who dropped out during the titration phase the results remained significant.			
Analysis description	**Secondary analysis**			
ITT Maintenance Population	*See above*			
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=164**	**RTG 600mg/day N=158**	**RTG 900mg/day N=149**
	Number of subject in analysis	164	158	149
	% change in 28-day TPS (MN phase)			
	Mean	−5.1	−25.0	−30.9

	SD	133.27	55.96	80.49
	Median	−17.4	−35.3	−44.3
	Range	−100, 1589	−100, 253	−100, 714
Effect estimate per comparison	**% change in 28-day TPS (MN phase)**		**RTG 600mg/day vs. Pbo**	
		Unadjusted difference from placebo in median percent change	−17.9%	
		variability statistic	Not Applicable	
		P-value	0.002 treatment comparison vs. placebo using Non-parametric rank ANCOVA.	
			RTG 900mg/day vs. Pbo	
		Unadjusted difference from placebo in median percent change	−26.9%	
		variability statistic	Not Applicable	
		P-value	<0.001 treatment comparison vs. placebo using Non-parametric rank ANCOVA.	
Notes				
ITT Maintenance Population	*See above*			
Descriptive statistics and estimate variability	Treatment group Number of subject in maintenance population	**Pbo** **N=164**	**RTG 600mg/day** **N= 158**	**RTG 900mg/day** **N=149**
	Number of subjects in analysis	164	158	149
	Proportion of patients in 28-day TPS % reduction category (MN phase)			
	75 to 100%	11 (7)	27 (17)	30 (20)
	50 to <75%	20 (12)	34 (22)	40 (27)
	25 to <50%	32 (20)	30 (19)	36 (24)
	>0 to <25%	51 (31)	30 (19)	13 (9)
	No change or increase	50 (30)	37 (23)	30 (20)
Effect estimate per comparison	**Proportion of patients in 28-day**		**RTG 600mg/day vs. Pbo**	

	TPS % reduction category (MN phase)	test statistic	Not Available
		variability statistic	Not Applicable
		P-value	<0.001 Categorised reductions or increases from baseline in seizure frequency were analyzed using a Cochrane Mantel Haenszel test
		Comparison groups	**RTG 900mg/day vs. Pbo**
		test statistic	Not Available
		variability statistic	Not Applicable
		P-value	<0.001 Categorised reductions or increases from baseline in seizure frequency were analyzed using a Cochrane Mantel Haenszel test
Notes	The data presented is from CSR source table Table 11.4.12.2.3A. A number of pre-specified analyses on percentage change by varying categories were conducted. The results of these analyses showed a statistically significant difference in the distribution profiles by categories at all retigabine dose groups compared to placebo		
ITT Maintenance Population	See above		

Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=164**	**RTG 600mg/day N=158**	**RTG 900mg/day N=149**
	Number of subjects in analysis	n=164	n=158	n=149
	Number (%) patients seizure free (MN phase)			
	Seizure-free	2 (1.2)	5 (3.2)	7 (4.7)
	Not seizure-free	162 (98.8)	153 (96.8)	142 (95.3)

Effect estimate per comparison	**Proportion of patients seizure free (MN phase)**		**RTG 600mg/day vs. Pbo**
		Unadjusted difference compared with Placebo	2%
		variability statistic	Not Applicable
		P-value	Not available.
			RTG 900mg/day vs. Pbo
		Unadjusted difference compared with Placebo	3.5%
		variability statistic	Not Applicable
		P-value	0.091 Fisher's exact test
Notes	Patients discontinued prematurely and did not have any seizure in the maintenance phase prior to discontinuation were included as seizure-free Source Table 11.4.12.2.4		

ITT Maintenance Population	See above			
Descriptive statistics and estimate variability	Treatment group Number of subjects in maintenance population	**Pbo N=164**	**RTG 600mg/day N=158**	**RTG 900mg/day N=149**
	Number of subjects in analysis	n=164	n=158	n=149
	% seizure free days (MN phase)			
	Mean	68.7	72.3	73.4
	SD	27.02	25.22	28.42
	Median	78.1	81.6	84.5
	Range	0, 100	0, 100	0, 100

Effect estimate per comparison	**% seizure free days (MN phase)**		**RTG 600mg/day vs. Pbo**
		Unadjusted difference from placebo in median percent change	3.5%
		Unadjusted difference from placebo in mean percent change	3.6%
		variability statistic	Not Applicable
		P-value	0.003 treatment comparison versus placebo using non-parametric rank ANCOVA model
			RTG 900mg/day vs. Pbo
		Unadjusted difference from placebo in median percent change	6.4%
		Unadjusted difference from placebo in mean percent change	4.7%
		variability statistic	Not Applicable
		P-value	<0.001 treatment comparison versus placebo using non-parametric rank ANCOVA model

Integrated analyses

The applicant has provided comparisons and analyses of results across the main studies.

The results should be read in the perspective that bioequivalence between the test drugs in study 205 and 301/302 has not been established.

In addition, for the purpose of the integrated analysis across the 3 studies, the primary endpoint, i.e. responder rate during the maintenance phase for the study 205 has been "harmonised" with the results of the two other studies via pot-hoc analysis to satisfy the CHMP requirements.

The integrated analysis did not provide evidence supporting an interpretation of the efficacy of retigabine that differed from the interpretation of the results of the individual studies. The issues described for Study 205 hinder a direct comparison with studies 301 and 302, and integration of the results through post-hoc analysis calls for caution.
Due reluctance for a direct comparison across the results from the 3 trials is necessary here.

Responder Rate by Seizure Type

Of most interest were the analyses of efficacy by the seizure types, where the main findings for the maintenance phase are shown below:

Responder Rate by Seizure Type (Maintenance Phase) – ITT Maintenance Population (Studies 205, 301 and 302 Integrated)

	Placebo[a]	RTG 600 mg/day	RTG 900 mg/day	Placebo[b]	RTG 1200 mg/day
Simple partial seizures					
Patients with simple partial seizures	N=67	N=88	N=64	N=71	N=63
n	67	88	64	71	63
Responders	15 (22)	31 (35)	31 (48)	17 (24)	31 (49)
Adjusted Odds Ratio (95% CI)[c]		1.9 (0.9, 4.0)	3.6 (1.7, 7.7)		3.2 (1.5, 6.7)
P-value[c]		0.077	0.001		0.002
Patients without simple partial seizures	N=175	N=153	N=159	N=144	N=124
n	175	153	159	144	124
Responders	36 (21)	53 (35)	69 (43)	34 (24)	63 (51)
Adjusted Odds Ratio (95% CI)[c]		2.1 (1.3, 3.4)	3.0 (1.8, 4.9)		3.2 (1.9, 5.5)
P-value[c]		0.005	<0.001		<0.001
Complex partial seizures					
Patients with complex partial seizures	N=210	N=195	N=189	N=184	N=169
n	210	195	189	184	169
Responders	46 (22)	67 (34)	92 (49)	50 (27)	85 (50)
Adjusted Odds Ratio (95% CI)[c]		1.9 (1.2, 2.9)	3.5 (2.3, 5.4)		2.7 (1.7, 4.2)
P-value[c]		0.005	<0.001		<0.001
Patients without complex partial seizures	N=32	N=46	N=34	N=31	N=18
n	32	46	34	31	18
Responders	5 (16)	17 (37)	8 (24)	1 (3)	9 (50)
Adjusted Odds Ratio (95% CI)[c]		3.2(1.0, 9.8)	1.7 (0.5, 5.9)		26.2 (2.9,1276)
P-value[c]		0.047	0.415		<0.001[d]

Continued

Responder Rate by Seizure Type (Maintenance Phase) – ITT Maintenance Population (Studies 205, 301 and 302 Integrated) (Continued)

	Placebo[a]	RTG 600 mg/day	RTG 900 mg/day	Placebo[b]	RTG 1200 mg/day
Secondarily generalized seizures					
Patients with secondarily generalized seizures	N=71	N=90	N=86	N=68	N=65
n	71	90	86	68	65
Responders	15 (21)	32 (36)	33 (38)	16 (24)	23 (35)
Adjusted Odds Ratio (95% CI)[c]		2.1 (1.0, 4.2)	2.4 (1.2, 5.0)		1.8 (0.8, 3.8)
P-value[d]		0.051	0.016		0.142
Patients without secondarily generalized seizures	N=171	N=151	N=137	N=147	N=122
n	171	151	137	147	122
Responders	36 (21)	52 (34)	67 (49)	35 (24)	71 (58)
Adjusted Odds Ratio (95% CI)[c]		2.0 (1.2, 3.3)	3.7 (2.2, 6.1)		4.4 (2.6, 7.5)
P-value[d]		0.006	<0.001		<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.

a. Consists of the placebo patients corresponding to the comparison with retigabine 600 mg and 900 mg (Studies 205 and 302).
b. Consists of the placebo patients corresponding to the comparison with retigabine 1200 mg (Studies 205 and 301).
c. Comparison vs placebo is based on logistic regression.
d. Comparison vs placebo is based on exact logistic regression.

Change from Baseline in Total Partial Seizure Frequency

Percent Change from Baseline in Total Partial Seizure Frequency (Maintenance Phase) – ITT Maintenance Population: Studies 205, 301 and 302 Integrated

	Placebo[a] N=242	RTG 600 mg/day N=241	RTG 900 mg/day N=223	Placebo[b] N=215	RTG 1200 mg/day N=187
Studies 205, 301 and 302 Integrated					
n	242	241	223	215	187
Mean ± SD	-9.1 ± 113.71	-16.2 ± 122.36	-28.3 ± 75.22	-8.3 ± 112.93	-29.7 ± 90.47
Median	-18.5	-33.3	-40.3	-20.8	-50.6
Range	-100, 1589	-100, 1653	-100, 714	-100, 1382	-100, 660
P-value[c]	-	0.004	<0.001	-	<0.001

a Consists of the placebo patients corresponding to the comparison with retigabine 600 mg and 900 mg (Studies 205 and 302).
b Consists of the placebo patients corresponding to the comparison with retigabine 1200 mg (Studies 205 and 301).
c Comparison vs. placebo based on non-parametric rank ANCOVA.

The primary efficacy data by Seizure Type demonstrated that there was no statistically significant percent reduction from baseline in 28-day total partial seizure rate at any RTG dose compared with placebo for patients with secondarily generalized seizures in the double-blind phase and in the maintenance phase. The treatment effect was unexpectedly similar between 1200 mg/day and placebo in the double-blind phase. Conversely, both the Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Seizure Type (in Double-Blind Phase and in the Maintenance phase) and Responder Rate by Seizure Type (in the Maintenance Phase and in the double blind phase) showed a significant treatment effect at all doses of RTG in the cohort of patients without secondarily generalized seizures.

Percent of Patients who were Seizure Free

The analysis showed no significant difference between retigabine 600 mg/d and 900 mg/d and placebo with regard to percentage of seizure free patients, whilst the result was equivocal regarding the retigabine 1200 mg/d regimen, being superior to placebo in the study 301 but non superior in the study 205. As for the percentage of seizure–free days in the maintenance period no statistical difference versus placebo was observed for retigabine in study 205, while in the two other pivotal trials a statistical difference was observed for all dose regimens versus placebo.

In all three studies, the percent of retigabine patients in the ITT maintenance population with ≥75% reduction in seizure rate was greater than placebo, and increased with increasing dose. Conversely, the largest proportions of patients with no change or an increase in seizure frequency were larger in the placebo groups than in the retigabine groups, with the exception of the 600 mg/day group in Study 205.

Percent change in 28-day total partial seizure by quartile categories

The integrated analysis of Studies 205, 301 and 302 for percent change in 28-day total partial seizure by quartile categories in the maintenance phase showed a dose-related increase in the proportion of retigabine patients with ≥75% reduction in seizure rate compared with placebo (conversely, in each study the placebo group had the largest proportions of patients with no change or an increase in seizure frequency). The proportion of subjects experiencing no change or up to 25% increase in seizure frequency was larger in the placebo group, but there was no difference from placebo with regard to subjects with >25% increase in seizure frequency. Across all studies and all RTG doses very few seizure free patients were observed. In the RTG 600 mg/day group the number of patients seizure free is similar to placebo confirming the apparent lack of efficacy of this low dosage.
Having presented and discussed the data for the proportion of subjects with a seizure reduction and seizure worsening in the study populations in the PVTs, the Applicant concluded that the proportion of patients with seizure worsening was similar across all doses of retigabine compared to placebo. This was agreed by the CHMP.

Supportive studies

Study 200/201

Studies 200 and 201 (3065 A1-200/201; 8001/8005) were exploratory open-label, uncontrolled, multi-centre studies in patients aged 18 to 50 years with partial-onset seizures (with or without secondary generalization) who had at least 8 seizures during the preceding 2 months and who were treated with up to three AEDs.

A total of 46 patients were enrolled in these 2 studies.

Given the similarity of the protocols, the efficacy data were pooled and reported within one clinical study report. However, the PK data derived from both protocols were reported separately in consideration of the differences in the PK sampling schedule across the study protocols.

The studies were divided into three phases: Baseline (2 months), Treatment (6 months; 3-month dose-titration period followed by a 3-month maintenance period); after completion of the Treatment phase, patients were either tapered off retigabine over a period of 3 weeks (25% dose reduction every week), or entered into a long-term follow-up study (Study 8017) at the discretion of the investigator. During the treatment phases of Studies 200/201, concomitant AEDs were to remain constant.

Efficacy criteria were percent reduction from baseline in total partial seizure frequency and responder rate (≥50% reduction from baseline in seizure frequency) during the 3-month maintenance period (end of Week 24) or last study visit.

Descriptive statistics were produced across all analyses and no statistical comparisons were performed.

The seizure frequency was reduced by 36% (ITT) or 34% (PP).

These first exploratory studies for retigabine indicated that the therapeutic window for retigabine in this patient population was between 400 mg/day and 1200 mg/day, with the maximum responder rate seen with 800 mg/day to 1200 mg/day. Titration schemes of between 100 mg/day and 200 mg/day weekly increments were sufficient to reach an efficacious dose within an appropriate time frame.

Study 202

Study 202 (3065 A1-202) was an open-label, uncontrolled, multi-centre study in which, primarily, the safety, tolerability, drug- interactions, and, secondarily, the efficacy of retigabine, administered first as add-on therapy and then as monotherapy, were evaluated in patients aged 16 to 75 years with partial or generalized epilepsy. Patients had a documented seizure frequency of at least two seizures/month and were receiving monotherapy with an established AED (valproic acid, carbamazepine, phenytoin, or topiramate) at stable doses, for at least 5 weeks at the time of enrolment.

The study was divided into five phases; screening/baseline (2-3 weeks), retigabine titration (variable duration, but at least 6 weeks), AED tapering (variable duration dependent upon patient tolerability of established AED withdrawal/reduction), retigabine maintenance (2 weeks); after completion of the maintenance phase, patients either tapered off retigabine over a period of 3 weeks (25% dose reduction every week) and possibly had their established AED re-introduced, or entered into a long-term follow-up study (3065A1-208-US) at the discretion of the investigator.

Efficacy was assessed by percent reduction in total seizure frequency from both historical and pre-study baselines, and the responder rate for total seizures only (≥50% reduction from pre-study baselines in seizure frequency) during the treatment period.

A number of 60 patients were enrolled. Retigabine titrated up to 1200 mg/day (administered either as a BID or TID regimen) was associated with evidence of efficacy for total seizures. The efficacy profiles were generally similar across the four AED subgroups.

Based on the efficacy results and adverse event profile, retigabine 1200 mg/day (BID) was deemed the maximum tolerated dose in patients with epilepsy.

The results from this study were deemed relevant in informing the maximum dose selection and dosing regimen (TID) to be included in the Phase 2b dose-ranging study in patients with refractory total partial seizures.

Study 214

Study 214 (3065 A1-214) was a multi-centre, randomized, double-blind, parallel-group, exploratory study primarily comparing the safety and tolerability, and, secondarily, the efficacy, of three titration rates of retigabine (300 mg/day TID starting dose being increased by 150 mg/day every 2, 4, or 7 days; up to a maximum of 1200 mg/day) in patients aged 16 to 70 years with a diagnosis of partial epilepsy and a documented seizure frequency of ≥2 seizures per month during the 4 weeks before study evaluation. Eligible patients could be receiving one or two marketed AEDs (with the exception of vigabatrin and felbamate) at a stable dose for at least 1 month prior to screening. Patients could also be on VNS therapy and this counted as one AED towards the total of up to two AEDs.

The primary objective was to determine the acceptability of 3 titration rates of retigabine, using the discontinuation rate because of adverse events as the primary method of evaluation. The secondary objective was the efficacy of the 3 titration rates on control of seizures.

The study enrolled a number of 73 patients.

While efficacy was demonstrated across the three titration regimens, a titration scheme of 150 mg every 7 days to a maximum tolerated dose of retigabine 1200 mg/day i.e., over a 6-week titration period, was considered optimum with respect to the lowest discontinuation rates due to AEs. The results of Study 214 indicated that caution should be used if a titration scheme faster than 150 mg every 7 days is used to achieve a total daily dose of 1200 mg/day.

Long-Term Studies

A total of three open-label extension studies to the Phase 2b study (Study 205) and the Phase 3 studies (Studies 301 and 302) were conducted to assess the long-term safety of retigabine in the treatment of patients with partial-onset seizures. However, these studies did allow an assessment of persistence of efficacy.

Patients who completed Studies 205, 301 and 302 were eligible to enter long-term retigabine treatment protocols, Studies 212, 303 and 304 respectively.

Study 212 was completed in February 2002, but Studies 303 and 304 were ongoing at time of submission.

A summary of the key efficacy results from these studies are briefly presented below.

Study 212

Study 212 was an uncontrolled, open-label extension study to evaluate, primarily, the long-term safety and tolerability, and, secondarily, the long-term efficacy of retigabine in eligible patients who had successfully completed the titration and maintenance phases of Study 205.

At the end of the maintenance phase of Study 205, all patients had their study drug adjusted to 900 mg/day (300 mg TID) in a double-blind, double-dummy manner. At the end of this interim phase (i.e., when the dose of 900 mg/day was reached), patients could enter the long-term open-label extension study (Study 212). Further dose adjustments up to 1200 mg/day could be made depending on achievement of adequate efficacy and tolerability. Patients who did not tolerate further dose adjustments or did not wish to enter Study 212 had their dose progressively tapered to zero before withdrawal from the study.

The background AED therapy could be adjusted to achieve the optimal balance for efficacy and safety. The primary efficacy variable was the percent change in the monthly seizure frequency from the baseline phase to open-label treatment phase. Efficacy was assessed by comparing the baseline seizure frequency obtained during the screening period of the parent double-blind study (Study 205) with seizure frequency during retigabine treatment in the open-label phase (Study 212). Additional efficacy endpoints included assessment of responder rates based on the same criteria used in Study 205 and the number of seizure-free days for each patient assessed as a percentage of each patient's duration in the open-label phase.

A further post-hoc analysis that presented efficacy data (responder rate and percent change from baseline in 28-day total partial seizure frequency) by specified time points up to 18 months treatment, were derived.

A total of 222 of the 279 patients who completed Study 205 (79.5%) were enrolled into this open-label extension study and received retigabine at doses of up to 1200 mg/day (400 mg TID).

The median treatment duration was 358 days (mean 352.5 days ±172.1) (CSR 212, Section 5.1.5). The majority of patients (105/222, 47.3%) received retigabine 900 mg/day as their maximum dosage and a further 52 (23.4%) patients received retigabine 1200 mg/day as their maximum dosage. Twelve (5.4%) patients received doses >1200 mg/day.

The overall median percent change in total partial seizure rates was -48.3%. Efficacy data split by previous double-blind assignment in Study 205 showed that patients allocated to both placebo and retigabine 600 mg/day during the double-blind phase, showed improved efficacy during the extension study that was similar to that observed for patients that were allocated to retigabine 900 mg/day and 1200 mg/day during the previous double-blind phase.

The overall responder rate was 46% and similar conclusions on efficacy by previous double-blind treatment were observed in this analysis.

The overall mean rate of seizure-free days (in percentage of all days of observation) increased from 69.7% at baseline taken from Study 205, to 81.2% by the end of the open-label phase. The rates increased by 4% and 5% for patients previously assigned to placebo and retigabine 600 mg/day respectively.

In conclusion, retigabine administered during the open-label phase showed that seizure rates in patients who had previously received placebo or treatment with 600 mg/day during the Study 205, achieved a reduction in total and total partial seizure rates during open-label treatment of similar magnitude to that observed in the double-blind phase for retigabine 900 mg/day and 1200 mg/day. The results were supportive of the effectiveness of retigabine doses ≥900 mg/day based upon the open-label dosing schedule.

Studies 303 and 304

Studies 303 and 304 were ongoing at the time of submission. They were uncontrolled, open-label extension studies to the placebo-controlled, double-blind Studies 301 and 302, respectively.

A total 181 (81%) of the 224 patients who completed Study 301, and 375 (92%) of the 409 patients who completed Study 302 were enrolled into open-label extension studies 303 and 304, respectively.

The interim results seemed to indicate confirmation of the already discussed efficacy and tolerability results.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Of note is that the development of retigabine has a history of frequent change of sponsorship. The efficacy of retigabine was primarily investigated in a phase IIb trial (205) and two phase III trials (301 and 302). These were all multi centre, randomized, double-blinded, placebo controlled, parallel group studies randomizing totally 1244 subjects, whereof 427 to placebo and 813 to three retigabine dose regimens of respectively 600, 900 and 1200 mg daily.

The major differences among the three pivotal studies were the type of patients recruited, the duration of the maintenance period, the dose titration scheme, and the formulation of test drug.

Study 205 was conducted and the study report prepared under the sponsorship of Wyeth before the current EMA guidance was made available and therefore the prespecified primary efficacy parameters do not adhere to the guidance. In addition, this study was designed with a 8-week maintenance period only. Subsequently, Valeant updated/modified the report in order to comply with the guidelines for structure and contents of clinical study reports. Moreover, in order to improve the data presentation and harmonise the results with these of the other pivotal studies additional analyses - after unblinding – were conducted. As these analyses were conducted post hoc they are only supportive in nature.

Studies 301 and 302 recruited patients with more refractory disease as a result of protocol requirements (i.e., higher number and greater range of background AEDs allowed; stipulation of ≥2 years diagnosis of epilepsy). The majority of patients across the primary efficacy studies (76.6 %)

used at least two concurrent AED's, and the most common stable concomitant AED was carbamazepine (51.5%), followed by lamotrigine (27%), valproate (24%), topiramate (17.2%), levetiracetam (15.1%), phenytoin (12.4%), and oxcarbazepine (12.0%). Concomitant AEDs are quite similar across treatment groups except for phenytoin that was more represented in RTG 1200 mg/day group (and placebo group correlated). This discrepancy could be ascribed to Study 301 mainly enrolled US patients. Consistent with the 2000 EU CHMP Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Epilepsy Disorders, the Phase III studies were designed with a 12-week maintenance period. Both studies 301 and 302 had a forced titration scheme but Study 301 allowed a single dose reduction to 1050 mg/day downwards at the start of the maintenance period (end of Week 7) for patients who did not tolerate 1200 mg/day at the end of the forced titration scheme. Study 205 allowed down titration on up to two occasions during the titration period.

Efficacy data and additional analyses

The study 205 investigated the efficacy of retigabine 600 mg, 900 mg and 1200 mg daily compared to placebo. Of note the three retigabine treatment arms had titration and maintenance phases of different duration together comprising a double blind phase of equal duration in all three arms of 16 weeks.
With regard to the primary efficacy outcome of seizure frequency reduction, the 900 mg/d and the 1200 mg/d regimens showed superiority to placebo, but the 600 mg/d did not. Analysis of the efficacy outcome of at least 50% responder rate showed the same results comparing baseline with the whole double blind phase. However, the same efficacy outcome in analysis restricted to the maintenance phase showed superiority of the 600 mg/d and the 1200 mg/d regimens compared to placebo, but the 900 mg/d regimen did not.
Efficacy of retigabine in the study was within the range defined by similar studies of other new AEDs, but must be considered as modest.

The studies 301 and 302 were very similar with regard to design and efficacy outcomes and differed only in that study 301 investigated retigabine 1200 mg/d against placebo and study 302 investigated retigabine 600 mg/d and 900 mg/d against placebo.
In both studies and with regard to both primary efficacy outcomes of at least 50% responder rate and median percent reduction in frequency of total partial seizures, superiority of retigabine compared to placebo was statistically significant for all three dose regimens.
In Study 301, approximately one-fifth (34/153) of the patients randomized to the retigabine 1200 mg/day group had an average weekly dose of ≤1050 mg/day for at least 50% of the duration of the maintenance phase. Overall, it appeared that the efficacy of the 1050 mg/day dose was comparable to that of the retigabine 1200 mg/day group and both doses demonstrated trends and/or clinically relevant differentiation from the placebo group across primary and key secondary endpoints except for the median number of seizure free days where retigabine 1050 mg/day appears similar to placebo.

A very small number of subjects with age above 65 years was exposed to retigabine in the pivotal clinical studies (N= 8). A very different efficacy in the elderly population is, however, not anticipated.

The great majority of subjects exposed were Caucasian. This raised a concern on the generalisation of the results of the pivotal trials for populations of other racial background. However, as the dose of retigabine in clinical practice will be determined according to the individual patient response to the treatment during the titration phase, it was not considered necessary to have any specific dose adjustments according to patients' racial background.
The recommendation in the posology section of the SmPC (section 4.2) "Trobalt must be titrated according to individual patient response, in order to optimise the balance between efficacy and tolerability" was considered to adequately cover a possible race impact on efficacy.

The Applicant has provided data about efficacy and safety results by use of selected concomitant AEDs, in order to find out any possible positive or detrimental association among RTG and other AEDs.
It was concluded that concomitant use of the most common AEDs with retigabine was efficacious with no clear positive or detrimental differences between AEDs except levetiracetam. As part of the Risk Management Plan, the Applicant committed to further investigate the potential interaction between retigabine and levetiracetam.

The evaluation of long term efficacy was based on the primary variables that were defined on the basis of EMA and FDA guidance, i.e. responder rate and percent changes in seizure frequency, respectively. Both end points were analysed based upon a cumulative evaluation across specified time points

compared to changes from baseline seizure frequency, determined at the start of the double-blind period. Responder rate analysis was calculated based on the proportion of patients with at least 50% reduction in 28-day total partial seizure frequency up to the time of scheduled evaluation. Data for these endpoints were presented as side-by-side comparisons and as an integrated analysis across the 3 extension studies.
The large number of patients dropping out in open label long-term extension studies raised concerns about the long-term efficacy and the balance efficacy/adverse events over time. The submitted data (cut-off date of 30th June 2008) were considered insufficient to assess long-term maintenance of efficacy in responders to assigned treatment.
To address those concerns, the applicant conducted a more comprehensive and extended evaluation of long term efficacy up to the 2nd October 2009 extended cut-off date. The analyses included:

I. an assessment of retention rate over time
II. seizure frequency (responder rate and % change)
III. the proportion of patients achieving seizure freedom and
IV. the prescribed dose achieved at the end of the treatment period.

Retention rates described after 12 months open-label treatment with retigabine were similar across each of the open label studies. In patients exposed for at least 12 months, the probability of retention on open label treatment with retigabine varied between approximately 53% and 62% across each of the three studies; the probability of retention at 24 months was estimated to be approximately 41%. The probability of retention between the first and second year of open label treatment appeared to plateau, such that a greater proportion of patients remaining on treatment beyond 12 months treatment were retained in the study than during the first 12 months.
Efficacy was maintained in those patients who remained in the open label studies, for up to 32 months of treatment with retigabine. Moreover, there were no notable differences in the distribution of the proportion of patients across the various doses over time and by similar time points reported for efficacy.
These extension studies reflected clinical practice to the extent that dose adjustments were made according to individual subject need, and the data indicated that, in those patients retained in the study, retigabine was titrated to doses that spanned the entire recommended dose range (600 to 1200 mg/day) that balanced maintaining adequate efficacy with tolerability.
Seizure-freedom rates for any continuous 6 or 12 month period compared favourably to similar estimates calculated for a number of cited AEDs administered in long term open-label extension settings.
Those additional analyses were endorsed by the CHMP. It should however be kept in mind that the patients were selected as they were eligible for continuing the therapy and that the study was open and uncontrolled; additionally most patient received 2-3 other AEDs.

Retigabine was considered effective in the treatment of partial epilepsy. The size of the effect was similar to other marketed AEDs, in particular for the 900 and 1200 mg/day doses. For the 600 mg/day dose, the efficacy results were less robust and less convincing.

2.5.3. Conclusions on the clinical efficacy

Three multicentre, randomized, double-blind, placebo-controlled studies in a total of 1239 adult patients have been conducted to assess the efficacy of retigabine as adjunctive therapy of partial onset seizures, with or without secondary generalisation. All patients enrolled were to have had seizures that were not adequately controlled with 1 to 3 concomitant antiepileptic drugs, and more than 75% of all patients were taking ≥2 concurrent antiepileptic drugs. Across all studies, patients had a mean duration of epilepsy of 22 years and a median baseline seizure frequency ranging from 8 to 12 per 28 days. Patients were randomized to placebo or retigabine at 600, 900 or 1,200 mg/day. During an 8-week baseline period, patients had to experience ≥4 partial onset seizures per 28 days. Patients could not be seizure-free for ≥21 days. The duration of the maintenance phase was 8 or 12 weeks.

Retigabine was effective in adjunctive treatment of adults with partial onset seizures in three clinical studies. Retigabine was statistically significantly superior to placebo at 600 mg/day (one study), 900 mg/day (two studies) and 1,200 mg/day (two studies).

In open-label extensions of the three placebo-controlled studies, persistence of efficacy was maintained over an evaluation period of at least 12 months (365 patients).

2.6. Clinical safety

Patient exposure

Safety assessment of retigabine in the original submission (cut-off of 30th December 2008) was based on 2.168 exposed subjects, whereof 813 participated in the 3 placebo controlled trials 205, 301 and 302. A total of 2034 subjects were exposed to at least one dose of retigabine in the epilepsy clinical development programme. After exclusion of the transition phase, this subgroup, contributed a total of 211 exposure years, with a median drug exposure of 112 days. The total exposure to RTG (in the initial submission) in Phase II and phase III trials, was 1.131 patient-years (median 235), with 229 subjects being exposed for > 1 year. During the evaluation procedure, additional safety data from 7 pharmacology trials have been submitted (= "non-integrated clinical pharmacology"), contributing data from 196 subjects of whom 194 received retigabine. Overall, this added up to 669 subjects for the entire clinical pharmacology program.

An additional 10 patients received retigabine in the completed bipolar disorder study (Study D-23129/8040), and, further 125 patients have been exposed to retigabine in the post herpetic neuralgia (PHN) study (Study VRX-RET-E22-NP201).

The highest single oral dose administered in the clinical pharmacology studies was 900 mg and the highest IV dose was 50 mg. In the repeat dose studies, the highest retigabine daily dose administered was 1200 mg (400 mg TID). In a phase IIa study (200/20) 18 patients were exposed to a dose of up to 2400 mg/d. The longest duration of retigabine treatment was 28 days (200 mg BID).

The table below does not include the non-integrated clinical pharmacology studies submitted during the evaluation process.

Enumeration of Subjects Exposed to Study Medication

	Number of Subjects	
	Placebo	**RTG**
Phase I Studies	70[1]	669[2]
Phase II and Phase III Epilepsy Study Data Sets		
PCT (Studies 205, 301, and 302)	427	813
All Phase II and Phase III Combined	N/A[4]	1365
Total Exposures in Epilepsy Program	497[4]	2034
Other Studies		
Study VRX-RET-E22-NP201, PHN[3] [4]	62[4]	125[4]
Study D-23129/8040, Bipolar Disorder	0	10
Total Unique Exposures	559[4]	2169

1. Includes exposure in parallel group studies (3065A1-101, 3065A1-102, 3065A1-107, and VRX-RET-E22-103)
2. Includes RTG exposure numbers, regardless of formulation; subjects may have also received control drug.
3. 31st December 2008 was the submission cut-off date.
4. Only the PCTs within the All Phase II/III Combined studies were placebo-controlled.

N/A = Not Applicable

A number of 8 patients ≥ 65 years received retigabine in the pivotal clinical studies. In addition, 61 elderly patients out of the total population of 187 patients received retigabine in Study VR-RET-E22-NP201.

The presented safety results should be interpreted with caution as - most importantly - the doses were generally lower and the treatment period was shorter, respectively, than in the epilepsy studies. PHN trial used 150 mg/d - 900 mg/d as compared to 600 - 1200 mg/d in the epilepsy PVTs. The titration and maintenance phase was 10 weeks as opposed to 16 or 18 weeks in the epilepsy trials.

Adverse events

An overview of the treatment-emergent adverse events (TEAEs) is provided below, also distributed by the degree of severity.

Summary of Treatment-Emergent Adverse Events (Safety Population: PCT, All Phase II/III Combined and Integrated Clinical Pharmacology Studies)

	Number (%) of Patients						
	PCT					All Phase II/III Combined	Integrated Clinical Pharmacology Studies
	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)	RTG (N=1365)	RTG (N=469)
Any AE	318 (74.5)	207 (73.7)	223 (81.7)	227 (87.6)	657 (80.8)	1225 (89.7)	350 (74.6)
AEs by Maximum Intensity							
Mild	131 (30.7)	83 (29.5)	77 (28.2)	55 (21.2)	215 (26.4)	286 (21.0)	186 (39.7)
Moderate	144 (33.7)	97 (34.5)	114 (41.8)	121 (46.7)	332 (40.8)	633 (46.4)	118 (25.2)
Severe	43 (10.1)	27 (9.6)	32 (11.7)	51 (19.7)	110 (13.5)	281 (20.6)	46 (9.8)
Unknown	N/A	N/A	N/A	N/A	N/A	25 (1.8)	N/A
AEs Considered Related to Study Drug	206 (48.2)	177 (63.0)	197 (72.2)	212 (81.9)	586 (72.1)	1104 (80.9)	286 (61.0)
Non-Fatal SAEs	25 (5.9)	23 (8.2)	18 (6.6)	29 (11.2)	70 (8.6)	216 (15.8)	2 (0.4)
Deaths	3 (0.7)	1 (0.4)	0	1 (0.4)	2 (0.2)	5 (0.4)[1]	0
AEs Leading to Withdrawal	45 (10.5)	49 (17.4)	69 (25.3)	81 (31.3)	199 (24.5)	418 (30.6)	32 (6.8)

AE details for PCTs, All Phase II/III Combined and Integrated Clinical Pharmacology Studies can be found in the following respective Sections:
AEs by Maximum Intensity: Sections AEs Considered Related to Study Medication: Sections, and SAEs: Sections
Deaths: Sections AEs Leading to Withdrawal: Sections
There are 3 additional deaths included in this data set that are explained in Section
N/A = Not Applicable

Across all (integrated and not integrated) clinical pharmacology studies a total of 37/669 (6%) subjects reported one or more TEAE leading to discontinuation.
The severity of the reported adverse events as well as the relation to study drug is proportionally connected to the increasing dose.

The incidence of AEs in the safety population in the pivotal studies is shown below.

Incidence of Adverse Drug Reactions for Retigabine (Safety Population: PCT, Studies 205, 301 and 302)

	Number (%) of Patients				
Preferred Term	**Placebo (N=427)**	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Dizziness	38 (8.9)	41 (14.6)	64 (23.4)	84 (32.4)	189 (23.2)
Somnolence	51 (11.9)	43 (15.3)	67 (24.5)	69 (26.6)	179 (22.0)
Fatigue	25 (5.9)	45 (16.0)	40 (14.7)	34 (13.1)	119 (14.6)
Confusional state	11 (2.6)	12 (4.3)	21 (7.7)	42 (16.2)	75 (9.2)
Vertigo	9 (2.1)	22 (7.8)	21 (7.7)	24 (9.3)	67 (8.2)
Tremor	12 (2.8)	7 (2.5)	26 (9.5)	32 (12.4)	65 (8.0)
Coordination abnormal	12 (2.8)	14 (5.0)	14 (5.1)	30 (11.6)	58 (7.1)
Nausea	22 (5.2)	18 (6.4)	17 (6.2)	22 (8.5)	57 (7.0)
Diplopia	7 (1.6)	22 (7.8)	15 (5.5)	19 (7.3)	56 (6.9)
Disturbance in attention	4 (<1.0)	17 (6.0)	15 (5.5)	17 (6.6)	49 (6.0)
Memory impairment	11 (2.6)	7 (2.5)	15 (5.5)	24 (9.3)	46 (5.7)
Blurred vision	9 (2.1)	5 (1.8)	12 (4.4)	27 (10.4)	44 (5.4)
Asthenia	8 (1.9)	12 (4.3)	15 (5.5)	11 (4.2)	38 (4.7)
Dysarthria	3 (<1.0)	10 (3.6)	5 (1.8)	21 (8.1)	36 (4.4)
Gait disturbance	5 (1.2)	6 (2.1)	13 (4.8)	15 (5.8)	34 (4.2)
Aphasia	4 (<1.0)	3 (1.1)	9 (3.3)	17 (6.6)	29 (3.6)
Balance disorder	3 (<1.0)	8 (2.8)	8 (2.9)	13 (5.0)	29 (3.6)
Constipation	6 (1.4)	4 (1.4)	11 (4.0)	13 (5.0)	28 (3.4)
Paraesthesia	9 (2.1)	7 (2.5)	4 (1.5)	14 (5.4)	25 (3.1)
Anxiety	8 (1.9)	7 (2.5)	5 (1.8)	12 (4.6)	24 (3.0)
Increased liver function tests [1]	6 (1.4)	6 (2.1)	9 (3.3)	9 (3.5)	24 (3.0)
Weight increased	5 (1.2)	6 (2.1)	9 (3.3)	7 (2.7)	22 (2.7)
Amnesia	3 (<1.0)	2 (<1.0)	9 (3.3)	8 (3.1)	19 (2.3)
Dysuria	3 (<1.0)	4 (1.4)	5 (1.8)	10 (3.9)	19 (2.3)
Urinary hesitation	4 (<1.0)	6 (2.1)	3 (1.1)	9 (3.5)	18 (2.2)
Dyspepsia	7 (1.6)	7 (2.5)	4 (1.5)	7 (2.7)	18 (2.2)
Disorientation	3 (<1.0)	1 (<1.0)	1 (<1.0)	12 (4.6)	14 (1.7)
Hallucinations [1]	2 (<1.0)	3 (1.1)	4 (1.5)	7 (2.7)	14 (1.7)
Dysphasia	2 (<1.0)	3 (1.1)	3 (1.1)	7 (2.7)	13 (1.6)
Influenza [2]	9 (2.1)	10 (3.6)	3 (1.1)	12 (4.6)	25 (3.1)
Chromaturia	1 (<1.0)	2 (<1.0)	4 (1.5)	7 (2.7)	13 (1.6)
Haematuria	3 (<1.0)	6 (2.1)	3 (1.1)	4 (1.5)	13 (1.6)
Malaise	2 (<1.0)	4 (1.4)	4 (1.5)	4 (1.5)	12 (1.5)
Dry mouth	2 (<1.0)	2 (<1.0)	4 (1.5)	5 (1.9)	11 (1.4)
Increased appetite	4 (<1.0)	1 (<1.0)	4 (1.5)	5 (1.9)	10 (1.2)
Myoclonus	0	3 (1.1)	4 (1.5)	2 (<1.0)	9 (1.1)
Psychotic disorders [1, 3]	0	1(<1.0)	1 (<1.0)	7 (2.7)	9 (1.1)
Psychotic disorder [4]	0	0	1 (<1.0)	6 (2.3)	7 (<1.0)
Peripheral oedema [1]	0	3 (1.1)	3 (1.1)	3 (1.2)	9 (1.1)
Urinary retention	2 (<1.0)	1 (<1.0)	4 (1.5)	2 (<1.0)	7 (<1.0)
Hypokinesia	0	1 (<1.0)	2 (<1.0)	3 (1.2)	6 (<1.0)
Dysphagia	1 (<1.0)	0	1 (<1.0)	4 (1.5)	5 (<1.0)

Preferred Term	Number (%) of Patients				
	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Hyperhidrosis	0	0	1 (<1.0)	3 (1.2)	4 (<1.0)

1. Incidences shown reflect the overall incidence derived by grouping similar preferred terms – see m2.7.4, Appendix 7.4
2. Included in US PI as this met the 2% threshold; not included in EU SmPC as a causal relationship to treatment was not considered plausible
3. Frequency of psychotic disorders in EU SmPC is based on the overall incidence derived by combining similar terms
4. Incidence of psychotic disorder in US PI reflects the incidence for that preferred term only as this met the 2% threshold

CNS related adverse events

Of particular interest was the frequency of dizziness, somnolence, fatigue, memory and attention impairment, convulsion, diplopia, aphasia, dysarthria, speech disorder, gait disturbance and balance disorder.

The frequency of CNS related adverse events was high and appeared to be significantly higher than in the placebo group. Apart from non-specific adverse events such as dizziness, somnolence and fatigue, retigabine was associated with high occurrence of more specific adverse events impacting on cognitive function as memory and attention, as well as adverse events of significance for daily activities such as gait disturbance and language. Although in general the frequency of the adverse events appeared to be dose related, there were examples of adverse events such as attention disturbance where no dose relationship was apparent or where the pattern across retigabine dose regimens was inconsistent as with diplopia and dysarthria.

Adverse events involving the CNS are commonly associated with AEDs. The CNS adverse events associated with retigabine are not unique to retigabine, but are to a varying degree observed with all AEDs. The Applicant was requested to provide further analyses and to further discuss the CNS-related symptoms. The overview provided by the Applicant suggested that retigabine belonged to the category with the most frequent CNS adverse events. This may be due to more efficient adverse event recording practises employed in the retigabine studies compared to older studies with other AEDs. However, without any direct comparisons, it was difficult to conclude that retigabine compared favourably with other AEDs in terms of CNS adverse effects.

Renal/Urinary Events

Effects of retigabine on the renal/urinary system were expected from the pharmacological mode of action as well as from non-clinical safety studies. Renal/urinary adverse events are also reported for topimarate (nephrolithiasis, pollakiuria and dysuria listed as common and additional events listed as uncommon or rare) and zonisamide (nephrolithiasis listed as common and additional events listed as uncommon or very rare).

In the PCTs, AEs related to renal and urinary disorders were reported for greater proportions of patients in the Total RTG group than the placebo group (17% versus 13%). The relative risk of any such event was greatest for the retigabine 1200 mg/day dose group (1.9; 95% CI 1.409, 2.695).

Adverse events related to voiding dysfunction and urinary retention (e.g. dysuria, urinary hesitation, urinary retention) were reported for 5% of the Total RTG-treated group compared to 3% on placebo. Urinary hesitation was the most common adverse reported (2% total RTG versus 0.9% placebo) with no clear dose response relationship across retigabine dose groups. Generally, these events occurred during the first 8 weeks of treatment.

The incidence of AEs of Urinary Tract Infections (UTI) and related symptoms and signs were reported in the PCTs by 8% in the placebo group versus 9% in the Total RTG group, but were more common than placebo in the 1200 mg/day group. There were no reports of SAEs due to UTIs in the PCTs. A higher but similar profile for UTI-related AEs was reported for retigabine in the Phase II/III studies (14%).

There were no clear differences between placebo and retigabine groups for any renal function indices (creatinine, urea and uric acid) at baseline and there were no meaningful changes over time for creatinine and urea. There were 4 cases of nephrolithiasis in the total RTG group (all in the 1200 mg/day group). More patients reported urinary crystals in the All Phase II/III Combined population than in the PCT group (2% versus 1%).

Mean change from baseline in post-void residual (PVR) bladder volume increased in the total RTG group compared with a decrease in the placebo group. In most patients, PVR returned to baseline after discontinuation of treatment.
There was no evidence for an increased incidence of values of potential clinical concern (PCC) relating to PVR bladder ultrasound measured at any time post baseline between total RTG and placebo across the PCTs or Phase II/III combined. This suggested a worsening of effect with long term exposure to retigabine. The PVR did not return to normal in all patients.

Urinary crystals
About 15% of patients receiving retigabine had crystals with bilirubin-like appearance in the urine compared to none in patients on placebo. This finding was considered to be due to photometric properties of retigabine being similar to those of bilirubin. There were 4 cases of nephrolithiasis in retigabine-treated patients (all on the highest dose) and none on placebo. Renal colic was reported in 0.4% of retigabine-treated patients.

Renal dysfunction
Renal dysfunction/failure was reported in 4 patients on retigabine (600 and 900 mg/day groups) and in none on placebo. One of the events was reported as an SAE. Urinary retention was the dominating clinical feature.

Conclusion on renal/urinary adverse events
Although the numbers were small and the dose-response relationship not entirely clear, there were indications that retigabine may cause urinary retention/hesitation in a small proportion of patients. The potential causal relationship was supported by mechanistic and non-clinical findings. It cannot be excluded that the one SAE of renal failure was caused by the potential of retigabine to induce urinary retention.

There were also findings indicating that retigabine is associated with events caused by urinary crystals such as nephrolithiasis.

Clearly more cases of UTI and dysuria were recorded with the 1200 mg/day dose. High rates were reported from 3 Mexican sites. It is acknowledged that a more pronounced awareness at these centres could be at least part of the explanation for the more frequent reports of UTI and dysuria. It is reassuring that no cases were preceded by urinary retention. However, in the original submission, five serious cases of urinary retention required catherisation (4 of which were in patients receiving Trobalt). In one patient intermittent self-catherisation was required and non-reversible bladder dysfunction was developed. Appropriate warnings were therefore stated in section 4.4. of SmPC.

Duration of CNS and renal/urinary events

A considerable part of the adverse events must be regarded as persistent. On the other hand, adverse events, which were not ongoing at the end of the pivotal trials constituted the majority. Generally, one quarter of CNS and urinary adverse events had disappeared after one week and about half after one month, be it on retigabine or on placebo. The data included only patients where the CNS and urinary events did not lead to withdrawal.

Cardiac safety

QTc prolongation

Findings for QTc of Potential Clinical Concern (Safety Population: PCT)

	Number of Patients[2] / Number of Patients Evaluable (%)				
	Placebo (N=427)	**RTG 600mg/day (N=281)**	**RTG 900mg/day (N=273)**	**RTG 1200mg/day (N=259)**	**RTG Total (N=813)**
QTc Bazett's					
Increase >30 msec from baseline	47/403 (11.7)	41/266 (15.4)	36/255 (14.1)	42/232 (18.1)	119/753 (15.8)
Increase >30 msec and ≤60 msec from baseline	47/403 (11.7)	39/266 (14.7)	35/255 (13.7)	42/232 (18.1)	116/753 (15.4)
Increase >60 msec from baseline	2/403 (<1)	2/266 (<1)	1/255 (<1)	2/232 (<1)	5/753 (<1)
Post-baseline ≥450 msec[1]	19/403 (4.7)	5/266 (1.9)	10/255 (3.9)	12/232 (5.2)	27/753 (3.6)
Post-baseline ≥480 msec[1]	0	1/266 (<1)	0	0	1/753(<1)
Post-baseline ≥500 msec[1]	0	0	0	0	0
QTc Fridericia's					
Increase >30 msec from baseline	32/403 (7.9)	26/266 (9.8)	30/255 (11.8)	28/232 (12.1)	84/753 (11.2)
Increase >30 msec and ≤60 msec from baseline	32/403 (7.9)	26/266 (9.8)	28/255 (11.0)	28/232 (12.1)	82/753 (10.9)
Increase >60 msec from baseline	1/403 (<1)	0	2/255 (<1)	1/232 (<1)	3/753 (<1)
Post-baseline ≥450 msec[1]	4/403 (1.0)	2/266 (<1)	3/255 (1.2)	3/232 (1.3)	8/753 (1.1)
Post-baseline ≥480 msec[1]	0	1/266 (<1)	0	0	1/753 (<1)
Post-baseline ≥500 msec[1]	0	0	0	0	0

Data Source: Table 15.07
And baseline < this value or missing.
A patient may be counted more than once, if they had ECG parameters that met different criteria across various timepoints.
Data are for any post-baseline finding.

The "thorough" QTc study 103 (described in section 3.4.3 of this report) was positive in that the upper limit of the 95% one-sided confidence interval for the mean effect within 3 h of the 1200 mg/day dose on the QTc interval exceeded 10 ms. Following evaluation of the clinical database, it is noteworthy that no patient experienced QTc intervals greater than 480 ms or adverse events related to QTc prolongation.

OR and RR values for QTc interval increased greater than 30 ms relative to placebo using the Bazett and Fridericia correction methods for heart rate have been presented. For both methods, there was a trend for an effect for the overall retigabine group with the 95% confidence intervals only just including unity. For the 1200 mg/day dose, OR and RR values are about 1.5-1.7 for both correction methods with the 95% confidence interval excluding unity for the Bazett correction method.

Retigabine caused a modest dose-dependent QTc prolongation related to Cmax. The clinical significance of such a finding is difficult to determine. It appears that retigabine does not compare well with established AEDs since an association of QTc prolongation to other AEDs has not been firmly established. Warnings have been introduced in section 4.4 of the SmPC, and it is recommended that an ECG is recorded in patients at risk before initiation of treatment and in those with a corrected QT interval >440 ms at baseline, an ECG should be recorded on reaching the maintenance dose. With the modest QTc increase observed, the CHMP considered disproportionate to require recommendations of baseline ECG for all patients.

Weight gain

Retigabine was associated with a weight increase after 4 months ranging from about 1 kg on the 600 mg/day dose to about 2.5 kg on 1200 mg/day compared to 0.2 kg on placebo. The weight increase appeared to be dose-dependent and to plateau after approximately 20 weeks of treatment.

Weight gain is a well-known side effect of many (but not all) AEDs. It is particular prominent with valproate (listed as a very common effect), but also commonly observed with carbamazepine, gabapentin, levetiracetam, pregabalin and vigabatrin. The weight gain associated with retigabine was considered to be modest and probably in the same range as several other AEDs.

Suicidality

A meta-analysis conducted by the FDA for suicidality in placebo controlled trials from 11 marketed AEDs demonstrated an increase in the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication (0.43% risk in patients taking AED versus 0.22% in patients taking placebo). Based on this analysis, class labelling for marketed AEDs and suicidality was adopted by the EMA's PhVWP and the CHMP in July 2008.

In the submitted trials, there was no evidence of any increase in events of suicide, suicidality or self-injurious behaviour with retigabine. Nonetheless, class labelling related to suicidality was adopted for retigabine and Pharmacovigilance activities are planned. An appropriate class label warning has been included in section 4.4 of the SmPC.

SUDEPS

The risk of sudden unexplained deaths in epilepsy (SUDEP) with RTG treatment was lower than that with placebo and the SUDEP rate reported in the PCTs was within the range of SUDEP rates published in the literature. However, this rate was higher than SUDEP rates reported for population based epilepsy cohorts, and also high among comparable populations, i.e. cohorts with refractory epilepsy. Overall, the figures are small and a firm conclusion is difficult to draw.

Proconvulsive potential

There was no consistent difference across retigabine doses groups and placebo in distribution profile of seizure worsening by partial seizure type. Furthermore, more new seizure types were similar across retigabine treatment group compared to placebo.

Serious adverse events and deaths

In the entire retigabine epilepsy clinical development program (including deaths up to the submission cut-off and in the compassionate use program), there were 10 treatment emergent deaths in patients treated with retigabine in approximately 1400 patient-years of exposure, i.e. a rate of 7.1 per 1000 patient-years. Seven of these cases met the conservative criteria for possible, probable, or definite SUDEP. This represents an overall rate of SUDEP of 5.0 per 1000 patient-years on retigabine across the entire retigabine epilepsy program.

In the integrated safety database, 6% of placebo-treated patients and 9% of retigabine treated patients reported a TESAE in the PCTs (Studies 205, 301, and 302). TESAEs were reported for 8%, 7%, and 11% of the 600, 900, and 1200 mg/day groups, respectively.

In the PCT group, the most frequently reported TESAE was convulsions followed by psychotic disorder. The incidence of convulsion was similar between the placebo and total retigabine groups (1.2% and 1.5%, respectively) and there was no clear indication of any retigabine dose relationship.

In the PCTs, 3 (1%) patients on retigabine reported psychosis and hallucinations related SAEs, and 15 (2%) patients, all on retigabine, discontinued treatment due to psychosis and hallucinations. A review of the SAEs identified that 6/ 8 events were reported in the setting of increased seizures and/or were post-ictal psychotic events. Other events were often reported in the setting of intercurrent illness or in patients with well-documented history of psychiatric illness.

Other TESAEs were reported in a low proportion of patients (<1% of patients in any treatment group), while nausea, encephalopathy, confusional state and suicidal ideation were reported only in the retigabine 1200 mg/day group.

There was no notable difference in the reporting incidence of TESAE by phase (titration or maintenance phase) and despite there being a higher number of events reported in the 1200 mg/day group, an examination of the dose at time of occurrence of the adverse event suggests that many of these events occurred at lower doses during the course of the first 8 weeks of treatment (titration period).

Serious cases of urinary retention requiring catheterization were reported in 5 patients (1 placebo and 4 on retigabine) across the Phase II/III program. This was reversible in all but 1 patient, who

experienced persistent urinary retention, potentially as a result of a delay in reporting symptoms and it required intermittent self-catheterization, which must be considered an important adverse event.

Serious cardiac events were identified in subjects on retigabine. Among others, these events included cardiac arrest/asystole and transient non-sustained ventricular tachycardia, following single doses of 900mg in an abuse liability study conducted in subjects with a history of recreational drug use. This information is described in the SPC in Section 4.9 – Overdose.

In the PCT grouping, there were 3 deaths (including one SUDEP) out of 427 patients on placebo (0.7%) and 2 deaths (including one SUDEP) out of 813 patients in the Total RTG group (0.2%) (1 patient in the 600 mg/day group and 1 patient in the 1200 mg/day group).

Withdrawal and rebound potential

TEAEs in patients with tapers of >7 days were reported for 17% (6/36) of patients in the placebo group and 26% (44/171) of patients in the Total RTG group. Among patients in the retigabine group, the overall TEAE incidence during the tapering phase was 28%, 21%, and 28% for the 600, 900, and 1200 mg/day dose groups. Headache, dizziness, nausea and abdominal pain were the TEAEs reported in more than 2 patients in the Total RTG group (5%, 3%, 2% and 2%, respectively) during tapering. Overall, TESAEs during tapering phase were reported for 1 patient receiving retigabine (convulsion in the 600 mg/day group) and none in the placebo group.

In the PCTs abrupt withdrawal of study drug was defined as discontinuation of treatment of ≤7 days. In the PCTs, TEAEs reported upon abrupt discontinuation were reported for 42% (19/45) of patients in the placebo group and 34% (56/163) of patients in the Total RTG group. Among patients in the retigabine group, the overall TEAE incidence upon abrupt discontinuation was 39%, 30%, and 36% for the 600, 900, and 1200 mg/day dose groups. Convulsion (3%), tremor (3%), confusional state (3%), psychotic disorder (3%), dizziness (3%), somnolence (3%), vertigo (2%), coordination abnormal (2%) and aphasia (2%) were the TEAEs in more than 2 (1.2%) patients in the Total RTG group.

TESAEs upon abrupt discontinuation of study drug were reported for 7 (16%) patients in the placebo group and 21 (13%) patients in the Total RTG group. Among patients in the retigabine group, the overall TESAE incidence during tapering phase was 18%, 9%, and 13% for the 600, 900, and 1200 mg/day dose groups. In the retigabine groups, convulsion, psychotic disorder and pregnancy were TESAEs reported in more than one patient.

There was no indication of rebound (including increased seizures) or withdrawal syndrome based on adverse events reported to the end of the post-treatment period.

Comparison of TEAEs during taper versus abrupt discontinuation support a withdrawal/taper period.

Recommendation that retigabine is withdrawn over a period of at least 3 weeks, unless safety concerns require abrupt withdrawal, has been included in sections 4.2 and 4.4 of the SmPC.

Abuse Potential

Consistent with investigations conducted with other marketed AEDs retigabine has been investigated in pre-clinical studies and a formal Phase I drug abuse liability study. The results of these formed part of an 8-factor analysis which provided an established and accepted methodological framework in which to assess drug-abuse potential. The methodology also included evaluations of relevant pharmacology and scientific knowledge, any known abuse pattern, psychotropic effects or dependence liability and risk to public.

Retigabine did not demonstrate affinity for any of the receptor binding sites associated with the potential for abuse.

The abuse liability study indicated that retigabine is poorly tolerated in recreational drug users particularly when administered without dose titration at doses considered supra-therapeutic. In contrast, dose titration in patient studies (Phase II/III) to similar dose levels as achieved in the Phase I study, indicated a low incidence of adverse events typically associated with evidence of drug abuse potential.

A careful evaluation of all 8 factors and lines of evidence (particularly pre-clinical and clinical studies) indicated that the relative abuse liability of retigabine is similar to levetiracetam, which has not been associated with significant abuse. Structural similarities of retigabine to flurpitine also suggest a low

potential for abuse. The risk for abuse of retigabine and the potential for public health consequences associated with any potential abuse are considered minimal.

Overdose

There is limited experience of overdose with retigabine. A dose that would constitute an overdose of study medication was not defined in the retigabine clinical trial program, and therefore, a computerized search strategy was implemented to identify a broad list of AEs potentially indicative of overdose in association with administered retigabine doses >1200 mg. There were no deaths that resulted from an overdose with retigabine. A total of 5/1365 (0.4%) patients were determined to have had an overdose of retigabine; doses in excess of 2500 mg/day were reported. In addition to adverse reactions that are also typically seen at therapeutic doses, events reported with retigabine overdose included agitation, aggressive behaviour, and irritability. There were no reported sequelae.

These adverse reactions have been included in SmPC as specific to overdose with retigabine. In addition, coma was reported in a patient who ingested retigabine as part of a multi-drug overdose.

Pregnancies

A total of 11 pregnancies have occurred during the retigabine program to date. Eight pregnancies were reported in female patients exposed to retigabine while 3 pregnancies occurred in the female partners of male patients taking retigabine. Of the 8 female patients who reported pregnancies, 5 patients electively terminated their pregnancies, and 3 patients who had exposures for the first 9 days, 3 days, and 63 days of gestation, respectively, carried their babies to delivery. Of the 3 patients who delivered, 2 delivered full-term, healthy infants. The remaining patient, who had a 3 day exposure to retigabine, delivered a premature male infant with a patent ductus arteriosus and polydactyly at 27 5/7-weeks gestation. All 3 pregnancies occurring in the female partners of male patients resulted in normal births. There are no adequate and well-controlled studies with retigabine in pregnant women and retigabine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. This is reflected in section 4.6 of the SmPC that also recommends that Trobalt is not used during pregnancy and in women of childbearing age, not using contraception and that specialist advice should be given to women who are of childbearing potential.

Laboratory findings

The risk of haematological complications during retigabine treatment appeared low and comparable to placebo.

A clear association between retigabine therapy and liver enzyme increase has been identified already in the clinical development programme. This is reflected in section 4.8 of the SmPC and addressed in the RMP.

Please also refer to previous section on urinary/renal events.

Safety in special populations

Elderly population
Too few patients aged ≥ 65 years participated in the epilepsy programme. A number of 61 patients with PHN added to some extent experience, but both the daily retigabine dosages and the duration of exposure were clearly below that employed in the epilepsy programme.

The observed CNS adverse events, which are clearly more commonly reported in patients ≥ 65 years, i.e. somnolence 38% vs. 28%), memory impairment (10% vs. 5%), amnesia (7% vs. 5 %), tremor 5% vs. 0%), balance disorder (7% vs. 3%), and speech disorder (3% vs. 0 %) are particularly problematic in an elderly population.

In view of the worse safety and tolerability profile of retigabine in elderly patients compared to young patients, as suggested also by the study in post herpetic neuralgia patients, further specifications and tightening of the recommendations for use of retigabine in the elderly population are introduced in the SmPC. Starting, maintenance, and maximum doses are now specified in Section 4.2, Posology and Method of Administration. In particular, the proposal not to recommend doses higher than 900 mg/day is in accordance with the PK data in elderly and is endorsed. Appropriate clarifications and additions of

the QT interval issue have been included, and a paragraph on the possible increased risks in the elderly population has been introduced in the SmPC Section 4.4, Special Warnings and Precautions for Use.

Paediatric population
The lower age limit was 16 years and 18 years in the 205 and 301/302 studies, respectively, so no paediatric data are available.

Gender
No clear difference in the incidence of adverse events was noted between genders in the phase III clinical trials.

Race
Too few patients of non-Caucasian race were included to allow for conclusions on possible differences.

Safety related to drug-drug interactions and other interactions

Retigabine had little or no effects on the trough concentrations of carbamazepine, clobazam, clonazepam, gabapentin, levetiracetam, oxcarbazepine, pgenobarbital, phenytoin, pregabalin, topiramate, valproate, and zonisamide. Retigabine co-administration has been associated with a 20% decrease in lamotrigine plasma levels. In the available reports, there was no evidence that concomitant treatment with carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, or valproate have any clinically relevant effect on the clearance of retigabine. No interactions have been detected between retigabine, estrogens, progesterone and alcohol. A higher number of adverse events (88%) was reported when retigabine was associated with levetiracetam. With few exceptions (carbamazepine and, to a lesser extent, valproate, levetiracetam, lamotrigine), there were no remarkable differences in specific adverse event reports across differing drug combinations.

Discontinuation due to adverse events

In the Clinical Pharmacology Studies grouping, there has been a generally low incidence of treatment emergent adverse events leading to withdrawal (32/469, 7% of retigabine-treated subjects). The most frequent AE leading to discontinuation was rash (5 subjects, 1%). All other specific AEs led to discontinuation in <1% of subjects. AEs leading to discontinuation in more than 1 subject were chills (3 subjects), extrasystoles, ventricular extrasystoles, feeling drunk, headache, dizziness, tremor, nausea, and vertigo (each event in 2 subjects).

Most of the discontinuations in this grouping were reported in studies that evaluated higher individual doses and titration schedules, which were nearly twice as rapid as that used in patients with epilepsy.

In the pivotal controlled trials, treatment-emergent adverse events (TEAEs) leading to discontinuation were reported for greater proportions of retigabine patients than for placebo patients (11% placebo versus 25% Total RTG). The most common (>2% in Total RTG group) TEAEs leading to discontinuation were dizziness (6%), confusional state (4%), fatigue (3%), and somnolence (3%). Among the retigabine dose groups, TEAEs leading to discontinuation were reported for 17%, 25%, and 31% of the 600, 900, and 1200 mg/day groups, respectively (see Table 7).

There appeared to be a retigabine dose relationship for discontinuations due to dizziness (1%, 3%, 6%, and 8% of the placebo, 600 mg/day, 900 mg/day, and 1200 mg/day groups) and confusional state (<1%, 1%, 3%, and 8%, respectively).

The proportion of patients and preferred term categories of AEs leading to discontinuation were similar in the PCTs and all Phase II/III Combined groupings, indicating that the incidence and type of TEAEs leading to discontinuation remained similar with longer retigabine exposure.

TEAEs Leading to Discontinuation Reported by >2% of Patients in Any Treatment Group by Preferred Term (Safety Population: PCT, Studies 205, 301, and 302)

	Number (%) of Patients				
Preferred Term	**Placebo (N=427)**	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Any event leading to d/c	**45 (10.5)**	**49 (17.4)**	**69 (25.3)**	**81 (31.3)**	**199 (24.5)**
Dizziness	5 (1.2)	9 (3.2)	16 (5.9)	21 (8.1)	46 (5.7)
Confusional state	4 (<1.0)	4 (1.4)	8 (2.9)	20 (7.7)	32 (3.9)
Somnolence	4 (<1.0)	7 (2.5)	13 (4.8)	8 (3.1)	28 (3.4)
Fatigue	1 (<1.0)	9 (3.2)	12 (4.4)	6 (2.3)	27 (3.3)
Vertigo	4 (<1.0)	5 (1.8)	5 (1.8)	6 (2.3)	16 (2.0)
Coordination abnormal	3 (<1.0)	2 (<1.0)	5 (1.8)	9 (3.5)	16 (2.0)
Disturbance in attention	0	3 (1.1)	5 (1.8)	6 (2.3)	14 (1.7)
Headache	2 (<1.0)	3 (1.1)	5 (1.8)	6 (2.3)	14 (1.7)
Tremor	0	1 (<1.0)	4 (1.5)	7 (2.7)	12 (1.5)
Dysarthria	0	3 (1.1)	1 (<1.0)	6 (2.3)	10 (1.2)
Convulsion	7 (1.6)	2 (<1.0)	1 (<1.0)	6 (2.3)	9 (1.1)

Data Source: m2.7.4, Table 9.05

The rates of withdrawal and predominance of CNS-related events leading to withdrawal are comparable to other AEDs administered in this patient population.

For the ongoing open-label Phase III extension studies (Study 303 and 304), an additional 8 TEAEs leading to premature withdrawal were reported in 7 patients between the integrated safety database cut-off date (30 June 2008) and the submission cut-off date (31 December 2008). No event was reported in more than one patient. None was an SAE, and all resolved with the exception of fatigue.

The titration scheme (150 mg/7 days titration) may be the principal explanation for the number of premature discontinuations which mostly occurred during the titration period.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Safety assessment of retigabine in the originally submitted application was based on 2.168 exposed subjects, whereof 813 participated in the 3 placebo controlled trials 205, 301 and 302. A total of 2034 subjects were exposed to at least one dose of retigabine in the epilepsy clinical development program. After exclusion of the transition phase, this subgroup, contributed a total of 211 exposure years, with a median drug exposure of 112 days. The total exposure to RTG in Phase II and Phase III trials, was 1.131 years (median 235), with 229 subjects being exposed for > 1 year. During the review process, additional safety data from the 7 clinical pharmacology trials have been submitted, contributing data from 196 subjects of whom 194 received retigabine.

A very limited amount of data has been provided on persons aged 65 years and above, a population subgroup very relevant for the clinical scope of RTG. Additional data for 61 subjects $\geq$ 65 years were submitted from a study in patients with post herpetic neuralgia. However, the dose exposure in particular and the treatment duration was below that for the patients in the epilepsy program. Thus, the value of the contribution was limited. When adverse events in patients ≥ 65 years treated with retigabine were compared to adverse events in patients in the same age group treated with placebo, an overweight of findings was evident in the retigabine group. Also in the comparisons between adverse events across the age groups ≥65 and < 65 years of age, there is a distinct preponderance. Of special note is the predominance of nervous system and psychiatric events, which are noteworthy in this age group that is often fragile, especially with regard to CNS adverse effects. Relevant warnings have been included in the SmPC for the elderly patients with partial epilepsy.

In general, severity and frequency of TEAEs appeared to increase in a dose dependent manner. This pattern was recognizable with regard to the most frequent CNS related adverse events, such as

dizziness, somnolence and fatigue. Occurrence of adverse events impacting on cognitive function, like memory and attention impairment was high and adverse events of particular importance for daily life activities such as balance/gait disturbance and language were also frequent. There was agreement between the AEs considered to be treatment related and the overall reported AE incidence.

Hallucinations and psychosis were also dose-related, and visual hallucinations and psychosis were only reported with retigabine and not with placebo.

Although the numbers are small, and the dose-response relationship is not entirely clear, there are indications that retigabine may cause urinary retention/hesitation in a small proportion of patients. The potential causal relationship is supported by mechanistic and non-clinical findings. It cannot be excluded that the one SAE of renal failure was caused by the potential of retigabine to induce urinary retention.

There were also findings indicating that retigabine is associated with events caused by urinary crystals such as nephrolithiasis.

For CNS-related adverse events and renal/urinary tract adverse events, the mean duration for these adverse events was 42 days for retigabine treated patients versus 37 days for placebo treated patients. The corresponding figures for the median duration were 24 and 16 days, respectively. Thus, a distinction of the overall duration between patients treated with retigabine or placebo is clear.

A considerable part of the adverse events must be regarded as persistent. On the other hand, adverse events, which were not ongoing at the end of the pivotal trials, constituted the majority. Generally, one quarter of CNS and urinary adverse events had disappeared after one week and about half after one month, be it on retigabine or on placebo. It should be emphasised that the data included only patients where the CNS and urinary events did not lead to withdrawal.

RTG treatment was associated with a modest increase of QTc interval in a dose dependent manner. The clinical significance of this finding is uncertain. However, in SmPC section 4.4, Special warnings and Precautions for use, warnings have been introduced, and it is recommended that an ECG is recorded in patients at risk before initiation of treatment and in those with a corrected QT interval >440 ms at baseline, an ECG should be recorded on reaching the maintenance dose. With the modest QTc increase observed, it is considered disproportionate to require recommendations of baseline ECG for all patients.

Serious cardiac events were identified in subjects on retigabine. Among others, these events included cardiac arrest/asystole and transient non-sustained ventricular tachycardia. However, in the pivotal clinical trials there does not appear to be any pattern in cardiac AEs observed with retigabine when compared with placebo.

Dose dependent weight gain was observed during RTG treatment. However, the issue is considered to be modest and probably in the same range as several other AEDs.

Retigabine did not seem to possess a proconvulsive potential.

The risk of sudden unexplained deaths in epilepsy (SUDEP) with RTG treatment was lower than that with placebo and the SUDEP rate reported in the PCTs was within the range of SUDEP rates published in the literature. Overall, the figures are small and a firm conclusion is not easy to draw.

RTG treatment discontinuation related to TEAEs, ranging between 17.4 and 31.3%, was higher than in the placebo group (10.5%), and clearly dose dependent. In addition TEAE related RTG discontinuation rates are higher than those reported in clinical trials with most other AEDs marketed during recent years.

2.6.2. Conclusions on the clinical safety

A multitude of adverse events (in particular related to CNS and the renal/urinary system) are associated with retigabine. Some of them show a dose-response relationship; for some the relation to dose is less clear. None of them are unique to retigabine since they are also observed with other AEDs to the same, in a few cases to a higher degree, but in many cases to a lesser degree. Retigabine is associated with weight gain, but this issue is unlikely to be significantly different from the weight gain seen with several other AEDs. Also, a modest QTc prolongation is associated with the 1200 mg/day

dose of retigabine. This increase may be unique to retigabine compared to other AEDs. Furthermore, some cases of serious cardiac arrhythmia were seen. In keeping with this wide range of safety issues, discontinuation rate because of TEAEs was high, also in comparison with other recently marketed AEDs.

The main safety results have been addressed in the SmPC. In addition, post-authorisation studies and risk minimisation measures have been proposed by the Applicant and agreed by the CHMP.

Regarding the risk of voiding dysfunction and urinary retention an epidemiological study using a healthcare database in the US (Healthcare Inc. Research Database) has been proposed in the Risk Management Plan. A draft protocol has been submitted and the objective, practical considerations and power calculations are considered sufficient.

Regarding the risk of neuropsychiatric disorders the Applicant has proposed to further characterize these risks by close monitoring of withdrawal from future clinical studies. A potential relationship between age and the occurrence of neuropsychiatric side effects should be part of the characterization. To reduce the risk of neuropsychiatric disorders and to optimize compliance during dose titration in the first weeks of therapy, a provision of starter packs has been proposed as a risk minimisation activity. This approach was endorsed by the Committee, but the Applicant was requested to classify the treatment initiation pack as a routine risk minimisation measure, and to describe it as a routine measure.

The Pharmacovigilance actions aimed at characterising most of the important potential risks were endorsed.

Specialist prescriber education about the risk of urinary retention/voiding dysfunction and QT prolongation at the time of prescription via a one-pager outlining the risks and the need for appropriate patient information are endorsed for the safe and effective use. The risk of hallucination and psychotic disorders and the risk of accident or injury secondary to neuropsychiatric events are both well managed by SmPC/PIL in connection with the proposed treatment initiation pack as additional measure.

Regarding the lack of information on treatment of elderly subjects, the Applicant has proposed to evaluate safety in elderly patient's in future clinical studies. Data from the proposed epidemiological study will also be used in the characterization of the risk of retigabine use in the elderly.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan which included a risk minimisation plan.

Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risks		
Voiding dysfunction or urinary retention	*Routine activities*	
	• Routine pharmacovigilance • Targeted follow-up questionnaire • Evaluation of urinary effects in clinical studies	• SmPC Section 4.4: <u>Urinary retention</u> Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies with retigabine, generally within the first 8 weeks of treatment (see section 4.8). Trobalt must be used with caution in patients at risk of urinary retention, and it is recommended that patients are advised

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		about the risk of these possible effects. • SmPC Section 4.8: **Renal and urinary disorders** **Common**: Dysuria, Urinary hesitation, Haematuria, Chromaturia **Uncommon**: Urinary retention • PIL Sections 2 and 4.
	Additional measures	
	• Prospective epidemiology study of urinary retention following retigabine exposure, using the Health Inc. Research Database.	• Physician Guide for prescribers advising of the potential for urinary retention
Hallucinations and psychotic disorder	*Routine activities*	
	• Routine pharmacovigilance • Investigate for background characteristics e.g. medical history and concomitant medication that might elevate risk of events	• SmPC Section 4.4: Psychiatric disorders Confusional state, psychotic disorders and hallucinations were reported in controlled clinical studies with retigabine (see section 4.8). These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients. It is recommended that patients are advised about the risk of these possible effects. • SmPC Section 4.8: **Psychiatric disorders** **Common**: Confusional state, Psychotic disorders, Hallucinations, Disorientation, Anxiety • PIL Sections 2 and 4 • Optimise compliance with dose titration by provision of treatment initiation packs
	Additional measures	
	• Investigate whether a more flexible dosing regimen improves tolerability in study RGB113905	
Weight gain	*Routine activities*	
	• Routine pharmacovigilance • Monitoring of weight gain in the ongoing long-term clinical studies • Investigate for potential consequences of weight gain using post-marketing and observational data.	• SmPC Section 4.8: **Metabolism and nutrition disorders** Common: Weight increased, Increased appetite • PIL Section 4
Important potential risks		
QT effects	*Routine activities*	
	• Routine pharmacovigilance • Targeted follow-up questionnaire for any adverse event reports potentially related to pronged QT interval or Torsades de Pointes. • Monitoring of ECG changes at dose escalation in healthy volunteers • Formal ECG monitoring in future	• SmPC Section 4.4: QT interval A study of cardiac conduction in healthy subjects has demonstrated that retigabine titrated to 1,200 mg/day produced a QT-prolonging effect. A mean increase in Individual Corrected QT Interval (QTcI) of up to 6.7 ms (upper bound of 95% one-sided CI 12.6

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	clinical studies	ms) was observed within 3 hours of dosing. Caution should be taken when Trobalt is prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients it is recommended that an electrocardiogram (ECG) is recorded before initiation of treatment with Trobalt and in those with a corrected QT interval >440ms at baseline, an ECG should be recorded on reaching the maintenance dose. • PIL Section 2
	Additional measures	
		• Physician Guide for prescribers to inform them of the potential risk of prescribing retigabine with another medication known to prolong QT interval and to alert them to medical history that may increase the risk of QT prolongation with retigabine treatment
Cardiac arrhythmias	*Routine activities*	
	• Routine pharmacovigilance • Telemetry for 24 hours post-dose in healthy volunteers • Six-monthly cumulative review of AE reports of cardiac arrhythmia to be included and discussed in PSURs	• SmPC Section 4.9 <u>Symptoms and signs</u> There is limited experience of overdose with retigabine. Retigabine overdoses in excess of 2500 mg/day were reported during clinical studies. In addition to adverse reactions seen at therapeutic doses, symptoms of retigabine overdose included agitation, aggressive behaviour and irritability. There were no reported sequelae. In a study in volunteers, cardiac arrhythmia (cardiac arrest/asystole or ventricular tachycardia) occurred in two subjects within 3 hours of receiving a single 900 mg retigabine dose. The arrhythmias spontaneously resolved, and both volunteers recovered without sequelae. <u>Treatment</u> In the event of overdose, it is recommended that the patient is given appropriate supportive therapy as clinically indicated, including electrocardiogram (ECG) monitoring. Further management should be as recommended by the national poisons centre, where available. • PIL Sections 2 and 3
Risk of accidents secondary to neuropsychiatric effects	*Routine activities*	
	• Routine pharmacovigilance • Monitoring of reports of accident /injury to determine whether there was a neuropsychiatric cause.	• SmPC Section 4.4: <u>Psychiatric disorders</u> Confusional state, psychotic disorders and hallucinations were reported in

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	• Monitoring withdrawal from clinical studies due to CNS AEs	controlled clinical studies with retigabine (see section 4.8). These effects generally occurred within the first 8 weeks of treatment, and frequently led to treatment withdrawal in affected patients. It is recommended that patients are advised about the risk of these possible effects. • SmPC Section 4.7: Adverse reactions such as dizziness, somnolence, diplopia and blurred vision were reported in controlled clinical studies, particularly during titration (see section 4.8). It is recommended that patients are advised about the risk of such adverse reactions at treatment initiation and following each titration step, and that they are advised not to drive or operate machinery until they have established how Trobalt affects them. As there is individual variation in response to all AED therapy, it is recommended that prescribers discuss with patients the specific issues of epilepsy and driving. • SmPC Section 4.8: **Psychiatric disorders** **Common**: Confusional state, Psychotic disorders, Hallucinations, Disorientation, Anxiety **Nervous system disorders** **Very common**: Dizziness, Somnolence **Common**: Amnesia, Aphasia, Coordination abnormal, Vertigo, Paraesthesia, Tremor, Balance disorder, Memory impairment, Dysphasia, Dysarthria, Disturbance in attention, Gait disturbance, Myoclonus **Uncommon**: Hypokinesia • PIL Sections 2 and 4 • Optimise compliance with dose titration by provision of treatment initiation packs
	Additional measures	
	• Investigate whether a more flexible dosing regimen improves CMS tolerability and reduces the risk of accidental injury in study RGB113905).	
Raised liver function tests	*Routine activities*	
	• Routine pharmacovigilance • Targeted follow-up questionnaires to be used to investigate liver and hepatobiliary adverse event reports • Six-monthly cumulative review of adverse events reports related to liver function • Additional LFT monitoring in planned clinical studies	• SmPC Section 4..8: **Hepatobiliary disorders** **Common**: Increased liver function tests • PIL Section 4

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Gall bladder related disorders	*Routine activities*	
	• Routine pharmacovigilance • Ultrasound evaluation of gall bladder effects in healthy volunteers.	• None
Neutropenia	*Routine pharmacovigilance*	
	• Routine pharmacovigilance • Serious and non-serious events of absolute neutrophils count of less than $0.1x10^3$ will be reported to GSK within 24 hours. • Events of severe infection that result in discontinuation will be subject to intensive monitoring. • Evaluation of reports of haematological events to determine any potential risk factors	• None
Suicidality	*Routine activities*	
	• Routine pharmacovigilance • Targeted follow-up of any potentially suicide related adverse events from placebo controlled clinical studies • Use of the Columbia suicidality scale in planned clinical studies.	• SmPC Section 4.4: <u>Suicide risk</u> Suicidal ideation and behaviour have been reported in patients treated with antiepileptic drugs in several indications. A meta-analysis of randomised placebo-controlled trials of AEDs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Trobalt. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice if signs of suicidal ideation or behaviour emerge. • PIL Section 2

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important missing information		
Exposure during pregnancy and lactation	*Routine activities*	
	• Routine pharmacovigilance	• SmPC Section 4.6: Pregnancy There are no adequate data from the use of retigabine in pregnant women. Animal studies are insufficient with respect to reproductive toxicity because the plasma levels achieved in these studies were less than those reached in humans at recommended doses (see section 5.3). In a developmental study in rats whose mothers were treated with retigabine during pregnancy, there was a delay in auditory startle response development of the offspring (see section 5.3). The clinical significance of this finding is not known. Trobalt is not recommended during pregnancy and in women of childbearing age, not using contraception. Breastfeeding It is unknown whether retigabine is excreted in human breast milk. Animal studies have shown excretion of retigabine and/or its metabolites in breast milk (see section 5.3). A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Trobalt should be made taking into account the benefit of breast-feeding to the child and the benefit of Trobalt therapy to the woman. • PIL Section 2
	Additional measures	
	• Sponsorship of the NAAED and EURAP multi-AED pregnancy registries.	
Use in the elderly	*Routine activities*	

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	• Routine pharmacovigilance. • Active recruitment of patients aged ≥65 years into planned safety and efficacy studies to support a modified release formulation of retigabine for use in epilepsy. • Review of data from post-herpetic neuralgia study which included patients ≥65 years. • In future Phase III studies sparse sampling techniques will be used to monitor retigabine pharmacokinetics. Population PK analyses will be conducted to evaluate the impact of covariates, such as age, on retigabine clearance as part of the analyses and reporting of the Phase III studies.	• SmPC Section 4.2: 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 titration period. Thereafter, 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 (see Sections 4.4 and 5.2). • Section 4.4 Special warnings and precautions for use QT interval Caution should be taken when Trobalt is prescribed with medicinal products known to increase QT interval and in patients with known prolonged QT interval, congestive cardiac failure, ventricular hypertrophy, hypokalaemia or hypomagnesaemia and in patients initiating treatment who are 65 years of age and above. In these patients it is recommended that an electrocardiogram (ECG) is recorded before initiation of treatment with Trobalt and in those with a corrected QT interval >440ms at baseline, an ECG should be recorded on reaching the maintenance dose. Elderly (65 years of age and above) Elderly patients may be at increased risk of central nervous system events, urinary retention and atrial fibrillation. Trobalt must be used with caution in this population and a reduced initial and maintenance dose is recommended (see sections 4.2 and 5.2).
	Additional measures	
	• Descriptive analyses from the prospective epidemiology study will be used to evaluate urinary symptoms in an elderly population.	
Use in adolescents and children	*Routine activities*	
	• Routine pharmacovigilance to include monitoring of spontaneous data for off-label use of retigabine in children and adolescents. Paediatric studies will be conducted in line with the PIP.	• SmPC Section 4.2: Children and adolescents (below 18 years of age) Trobalt is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy in this population. • PIL Section 2

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Use in patients with hepatic impairment	*Routine activities*	
	• Routine pharmacovigilance	• SmPC Section 4.2: <u>Hepatic impairment</u> No dose reduction is required in patients with mild hepatic impairment (Child-Pugh score 5 to 6); see section 5.2. 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; see section 5.2). The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose is increased by 50 mg every week, to a maximum total dose of 600 mg/day. • PIL Section 2
Use in patients with renal impairment	*Routine activities*	
	• Routine pharmacovigilance	• SmPC Section 4.2: <u>Renal impairment</u> Retigabine and its metabolites are eliminated principally by renal excretion. No dose adjustment is required in patients with mild renal impairment (creatinine clearance 50 to 80 ml/minute; see section 5.2). A 50% reduction in the initial and maintenance dose of Trobalt is recommended in patients with moderate to severe renal impairment (creatinine clearance <50 ml/minute; see section 5.2). The total daily starting dose is 150 mg, and it is recommended that during the titration period, the total daily dose is 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. • PIL Section 2
	Additional measures	
	• The pharmacological activity of the N2-glucuronide will be tested in vitro against the KCNQ channels 1-5 and against the GABA (Cl^-) channel • The clearance of retigabine will be evaluated in patients with end-stage renal disease treated with haemodialysis by evaluating the pharmacokinetics of retigabine and NAMR on both a dialysis day and on a non-dialysis day.	
Potential interaction with	*Routine activities*	
	• Routine pharmacovigilance	
	Additional measures	

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
levetiracetam	• This will be assessed in study RGB113905, which will evaluate retigabine IR as adjunctive therapy to each of the following monotherapy AED treatments: carbamazepine/oxcarbazepine, lamotrigine, **levetiracetam** or valproic acid in adult subjects with partial onset seizures using a flexible dosing regimen.	[3]

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product (see as detailed in section 2.3):

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, at launch, all physicians who are expected to prescribe TROBALT are provided with a physician information pack containing the following elements:

- The Summary of Product Characteristics
- A physician's guide to prescribing including the following key messages:
    - The need to inform patients that TROBALT may cause or potentiate symptoms of urinary retention/urinary hesitation
    - The need to inform patients on adverse events related to QT interval prolongation
    - Caution when using TROBALT in patients with a cardiac disease or those taking medicines concomitantly known to cause QT prolongation
    - The need to inform patients to comply with dose titration to minimize the risk of hallucination and psychotic disorders

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

Overall the epilepsy development programme of retigabine provides evidence of efficacy in partial onset epilepsy as add-on therapy. This evidence is primarily based on one phase IIB trial (study 205) and two phase III trials (studies 301 and 302), which combined randomized 1244 subjects, 427 to placebo and 813 to three dose regimens of RTG of 600, 900 and 1200 mg daily respectively.

- Beneficial effects

It is acknowledged that there is a high medical need in the partial epilepsy patient population. Based on the integrated analysis and concerning the primary endpoint of responder rate during the maintenance phase, statistically significant superiority to placebo was demonstrated across all three dose regimens, but this was consistent only for the 1200 mg daily dose regimen, whereas superiority to placebo was shown for the two other regimens in one of the studies (302), but not in the other (205). There was a dose response effect with responder rates of 28-39% (600 mg), 40-47% (900 mg) and 41-55% (1200 mg), compared to 19-26% for placebo. For the original primary endpoint of median percent reduction in seizure frequency in study 205, superiority to placebo was demonstrated for the 900 mg and 1200 mg regimens, but not for the 600 mg. Efficacy of retigabine in the PCTs is within the range defined by similar studies of other new AEDs as add-on therapy in refractory epilepsy.

[3]

- Uncertainty in the knowledge about the beneficial effects.

The Study 205 differed somewhat from studies 301 and 302 with regard to study design, inclusion criteria and the formulation of trial medication. Integration of efficacy results across studies was achieved by post-hoc analysis in study 205, in which the per protocol primary endpoint was different from the primary endpoints in studies 301 and 302.

The unique pharmacologic mechanism of action of retigabine (first-in-class M-current potassium channel opener) does not – in itself – add positively to the benefit-risk balance unless accompanied by clinical data that point to a unique effect not accomplished with other AEDs. However, the Applicant has provided data indicating that retigabine is efficacious even in patients with inadequate seizure control on two or more AEDs.

Risks

- Unfavourable effects

Several safety issues were identified with a dose dependent pattern as their most common feature.

Retigabine treatment was associated with an increase of frequent CNS related adverse events, occurrence of visual hallucinations and psychotic disorder exclusively in the RTG treatment groups, and frequent, and in some cases serious, renal and urinary tract symptoms. There was lack of sufficient data to assess teratogenicity in humans. Other safety issues emerging from the preclinical pharmacology studies, apart from general CNS signs, were a reduction of smooth muscle contractility affecting urinary and gall bladder function, and a probable interaction with thiopental, contrary to other anaesthetic agents.

CNS related adverse events, such as dizziness, somnolence and fatigue were frequent and dose dependent. Occurrence of adverse events impacting on cognitive function, like memory and attention impairment was high and adverse events of particular importance for daily life activities such as balance/gait disturbance and language were also frequent.

Hallucinations and psychosis were also dose related, and visual hallucinations and psychosis were only reported with retigabine but not with placebo.

Renal and urinary tract related adverse events were frequent and dose related. Nephrolithiasis was reported in 4 cases occurring all in the 1200 mg RTG group. Serious urinary retention was irreversible in one case, requiring intermittent self-catheterization.

The majority of CNS and urinary adverse events not leading to withdrawal disappeared during the course of the studies. About one quarter disappeared after one week and about half after one month.

Retigabine treatment was associated with a modest increase of QTc interval in a dose dependent manner. The clinical significance of this finding is uncertain. However, in SmPC section 4.4, Special warnings and Precautions for use, warnings have been introduced, and it is recommended that an ECG is recorded in patients at risk before initiation of treatment and in those with a corrected QT interval >440 ms at baseline, an ECG should be recorded on reaching the maintenance dose. With the modest QTc increase observed, it is considered disproportionate to require recommendations of baseline ECG for all patients.

Serious cardiac events were identified in subjects on retigabine. Among others, these events included cardiac arrest/asystole and transient non-sustained ventricular tachycardia. However, in the pivotal clinical trials there does not appear to be any pattern in cardiac AEs observed with retigabine when compared with placebo.

RTG treatment discontinuation related to TEAEs, ranging between 17.4 and 31.3%, was higher than in the placebo group (10.5%), and clearly dose dependent. In addition TEAE related RTG discontinuation rates are higher than those reported in clinical trials with most other AEDs marketed during recent years.

- Uncertainty in the knowledge about the unfavourable effects

Retigabine and other AEDs share many of the same safety and tolerability problems, especially with respect to CNS effects. The Applicant has not provided additional documentation to counter the impression from the comparisons made to other AEDs that retigabine belongs to the category of AEDs with the most frequent CNS as well as other adverse events. It is agreed that in many instances the tolerability issues associated with retigabine may be manageable by slowly titrating/adjusting the dose or discontinuing the medication and shifting to another – as is the case with other AEDs.

A limited amount of data is provided on persons aged ≥ 65 years, a population subgroup relevant for the clinical scope of RTG. Additional safety and tolerability data were provided in 89 elderly patients (61 on retigabine) with post herpetic neuralgia (PHN), but with a lower dosage and shorter time of exposure than in the epilepsy programme. A poorer tolerability in the elderly compared with the younger population, in particular with regard to CNS and urinary events was suggested. The predominance of nervous system and psychiatric events, which are noteworthy in this age group that is often fragile, especially with regard to CNS adverse effects. However, appropriate strengthening and additions have been included in the SmPC text to address these concerns.

The risk of SUDEP with RTG treatment was lower than that with placebo and was within the range of SUDEP rates published in the literature, but it was much higher than SUDEP rates reported for population based epilepsy cohorts. Overall, the figures were small and firm conclusions were not easy to draw.

Benefit-risk balance

- Importance of favourable and unfavourable effects

A high medical need in the partial epilepsy patient population is undisputed, and evidence of efficacy of retigabine in patients with partial onset epilepsy as add-on therapy has been provided.

The forced titration regimens used in the clinical studies may have resulted in more pronounced tolerability problems compared to the individual titration based on each patient's efficacy and tolerability used in normal clinical practice. This is likely to result in an overestimation of adverse events compared to clinical conditions outside a study protocol where doses are likely to be titrated in a more lenient way. However, this would also be the case for adverse events rates reported from other studies with other AEDs employing forced titration regimens.

- Benefit-risk balance

Overall, there is robust evidence for a significant and clinically relevant effect of the retigabine 1200 mg/day dose. There is also evidence for significant and clinically relevant effect of the 900 mg/day dose, but this is less consistent. The effect of the 600 mg/day dose is less consistent compared to the two higher doses. The efficacy results are observed even in patients with a background treatment of two or more AEDs, i.e. patients who must be categorised as quite resistant to treatment.

As discussed above a multitude of adverse events (in particular related to CNS and the renal/urinary system) are associated with retigabine. Some of them show a dose-response relationship; for some the relation to dose is less clear. None of the CNS effects are unique to retigabine since they are also observed with other AEDs to the same, in a few cases to a higher degree, but in many cases to a lesser degree. Retigabine is associated with weight gain, but this issue is unlikely to be significantly different from the weight gain seen with several other AEDs. Also, a modest QTc prolongation is associated with the 1200 mg/day dose of retigabine.

2.8.1. Discussion on the benefit-risk balance

The efficacy of retigabine has been documented in patients with partial epilepsy in the add-on setting. With the caveat that direct, within-study comparisons have not been conducted, the efficacy at the 900 and 1200 mg/day doses is in the same range as that observed with other AEDs in the add-on setting. Clinically relevant effects were also seen in the subsets of patients who were treated with two or more AEDs, i.e. significantly refractory patients. In line with what is seen with existing AEDs, numerous CNS-related as well as other adverse events are associated with retigabine. Viewed isolated, no single safety and tolerability problem observed with retigabine should in itself preclude marketing

authorisation. But the combined evidence suggests that retigabine may belong to the worse end of the spectrum of currently marketed AEDs with respect to safety and tolerability.

However, the benefit-risk balance is considered positive despite the shortcomings mentioned above. There is a significant unmet medical need in epilepsy and treatments for patients not responding adequately to or not tolerating antiepileptic drugs are often shifted to or supplemented with other AEDs based on an individual, patient-by-patient assessment of efficacy, safety and tolerability (as well as other factors). Furthermore, patients are individually titrated to reach a satisfactory balance between seizure control and adverse events. If unacceptable side effects occur, the dose can be lowered or the drug discontinued, and since the vast majority of adverse events will be reversible, permanent harm is unlikely. Thus, retigabine with its novel mechanism of action and documented efficacy in significantly treatment resistant patients could serve as an option – a "building block" – in the armamentarium of AEDs from which the treating physician can choose in order to tailor the optimal antiepileptic treatment for a specific patient.

Retigabine is not a first-line AED, but is considered, in the adjunctive setting, capable of serving a useful purpose as one of several AEDs the neurologist can use to supplement the antiepileptic treatment and find an appropriate balance between seizure control and adverse events.

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- The following additional risk minimisation activities were required (see as detailed in section 2.3):

Prior to launch in each Member State the MAH shall agree the final educational material with the National Competent Authority.

The MAH shall ensure that, at launch, all physicians who are expected to prescribe TROBALT are provided with a physician information pack containing the following elements:

- The Summary of Product Characteristics
- A physician's guide to prescribing including the following key messages:
    - The need to inform patients that TROBALT may cause or potentiate symptoms of urinary retention/urinary hesitation
    - The need to inform patients on adverse events related to QT interval prolongation
    - Caution when using TROBALT in patients with a cardiac disease or those taking medicines concomitantly known to cause QT prolongation
    - The need to inform patients to comply with dose titration to minimize the risk of hallucination and psychotic disorders

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Trobalt in the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and above with epilepsy was favourable and therefore recommended the granting of the marketing authorisation.