19 November 2015
EMA/CHMP/822086/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Briviact

International non-proprietary name: BRIVARACETAM

Procedure No. EMEA/H/C/003898/0000

Note

Assement report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AAS	Atomic Absorption Spectrometry
ADR	Adverse Drug Reaction
AE	adverse event
AED	antiepileptic drug
ALP	alkaline phosphatase
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
AMPA	α-amino-3-hydroxy-5 -methylisoxazole-4 -propionate hydrobromide
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase/serum glutamic oxaloacetic transaminase
AUC	area under the curve
AUC_T	area under the curve over a dosing interval
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BID	Twice daily
BMI	body mass index
BOCF	baseline observation carried forward
BRV	brivaracetam
BSEP	Bile Salt Export Pump
c_{av}	average concentration
CBZ	carbamazepine
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	Total plasma clearance
c_{max}	Maximum observed plasma concentration
CNS	Central Nervous System
CT	computed tomography
CYP	Cytochrome P450
DDI	Drug-drug interaction
DMCM	methyl-6,7 -dimethoxy-4-ethyl-β -carboline-3-carboxylate
$dP/dt_{(max)}$	(maximum) rate of rise of left ventricular pressure
DRESS	drug reaction with eosinophilia and systemic symptoms
P-GES	Patient's Global Evaluation Scale
EC	European Commission
ECG	electrocardiogram
ED_{50}	dose resulting in 50% of the effect
EEG	electroencephalogram
EMA	European Medicines Agency
ERA	environmental risk assessment
ESI	Electrospray Ionisation
EQ-5D	EuroQoL-5 dimensions
EU	European Union
F_{pen}	marketing penetration factor
FDA	Food and Drug Administration
FT-IR	Fourrier Transform Infrared spectroscopy
GABA	gamma-aminobutyric acid
GC	Gas Chromatography
GCP	Good Clinical Practice
GLDH	glutamate dehydrogenase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
hERG	human ether-à-go-go related gene
HPLC	High Performance Liquid Chromatography

HRQoL	Health-Related Quality of Life
HSS	hypersensitivity syndrome
i.v.	intravenous
IC_{50}	Half-maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILAE	International League Against Epilepsy
IPC	In-process control
IR	Infrared
ITT	Intent-to-Treat
KF	Karl Fischer titration
Ki	inhibitory constant
LDPE	Low Density Polyethylene
LEV	levetiracetam
LS	least square
LTFU	long-term follow-up
LTG	lamotrigine
MATE	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
MES	maximal electroshock seizure
MRI	magnetic resonance imaging
MRP	multidrug resistance protein
MS	mass spectrometry
MTD	maximum tolerated dose
NCI	National Cancer Institute
NMDA	N-methyl-D-aspartate
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOEL	No-observed-effect-level
OAT1	Organic Anion Transporter 1
OAT3	Organic Anion Transporter 3
OATP1B1	Organic Anion Transporting Polypeptide 1B1
OATP1B3	Organic Anion Transporting Polypeptide 1B3
OCT1	Organic Cation Transporter 1
OCT2	Organic cation transporter 2
OECD	Organisation for Economic Co-operation and Development
PBO	placebo
PBPK	Physiologically Based Pharmacokinetics
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamic
PE	Polyethylene
PEC	predicted environmental concentration
P-GES	Patient Global Evaluation Scale
P-gp	P-glycoprotein
PGS	primary generalized seizures
Ph. Eur.	European Pharmacopoeia
pIC_{50}	log of the concentration causing 50% inhibition
PIP	paediatric investigation plan
PHT	phenytoin
PK	pharmacokinetic(s)
PNEC	Predicted no effect concentrations
POS	partial-onset seizure(s)
PP	Per-Protocol
PP	Polypropylene
PT	preferred term
PVC	Polyvinyl chloride
QOLIE-31-P	Patient Weighted Quality of Life in Epilepsy Inventory-Form 31
RH	Relative Humidity
SAE	serious adverse event

SD	standard deviation
SDH	sorbitol dehydrogenase
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	(MedDRA) system organ class
SUDEP	sudden unexplained death in epilepsy
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
TID	Three times daily
t_{max}	time to reach maximum plasma concentration
TPM	topiramate
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
ULD	Unverricht-Lundborg Disease
USA	United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
VNS	vagal nerve stimulation
VPA	valproate
V_z	volume of distribution
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant UCB Pharma SA submitted on 20 November 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Briviact, 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 21 November 2013.

The applicant applied for the following indication:

Briviact is indicated as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that brivaracetam was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on 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 EMA Decision(s) P/0127/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0127/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Not applicable.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance brivaracetam, contained in Briviact to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the European Union.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice/Protocol Assistance from the CHMP on 24/02/2006, 18/10/2007, 23/10/2008, 21/01/2010, 16/02/2012 and 02/09/2014. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

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 were:

Rapporteur: Filip Josephson Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 20 November 2014.
- The procedure started on 24 December 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2015.
- PRAC RMP Advice and assessment overview, adopted on 27 March 2015
- During the meeting on 23 April 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 August 2015.
- PRAC RMP Advice and assessment overview, adopted on 10 September 2015
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a List of Outstanding Issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 October 2015.
- PRAC RMP Advice and assessment overview, adopted on 06 November 2015
- During the meeting on 16-19 November 2015, 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 Briviact.
- The CHMP adopted a report on the claim of new active substance (NAS) status of Brivaracetam contained in Briviact

2. Scientific discussion

2.1. Introduction

Problem statement

Epilepsy is a disorder of the brain characterized by the recurrence of spontaneous, unprovoked seizures, i.e. seizures not provoked by transient systemic, metabolic or toxic disorders. In 2014, the International League Against Epilepsy (ILAE) furthermore proposed to define epilepsy by any of the following conditions: (i) At least two unprovoked (or reflex) seizures occurring >24 h apart, (ii) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years, or (iii) diagnosis of an epilepsy syndrome (Fisher et al, Epilepsia, 2014).

Epilepsy includes many clinical situations which differ by age of onset, type of seizures, aetiological background, resulting handicap, prognosis and response to treatment. The main groups of epilepsy are focal (or partial) onset seizures, related to a focal brain dysfunction (approximately 60 % of epilepsy cases), and generalised seizures which represent approximately 30 % of cases. In the remaining 10 % the classification is uncertain. Partial seizures used to be subdivided in Type IA simple partial seizures (consciousness not impaired), Type IB complex partial seizures (with impairment of consciousness) and Type IC partial seizures evolving to secondarily generalised seizures (ILAE 1981). However, such classification for focal seizures was subsequently abandoned by ILAE and later reports recommended instead description of manifestation or degree of disability (Berg et al. Epilepsia, 2010).

The lifetime risk of developing epilepsy (defined as a history of epilepsy regardless of the frequency of seizures or use of antiepileptic medication) is between 3% and 5%, with the highest incidence reported in neonates, young children, and the elderly (Banerjee et al, Epilepsy Research, 2009). The prevalence of active epilepsy is estimated at 5-8 per 1000 people in high-income countries and 10 per 1000 people in low-income countries. These regional differences probably result from differences in risk factors for epilepsy, including infections and inadequate antenatal and prenatal care. Similar differences exist for the incidence of epilepsy: findings from a 2011 meta-analysis showed that annual incidence is 45 per 100 000 population in high income countries and 82 per 100 000 population in low-income and middle-income countries (Moshé et al, Lancet, 2015).

The primary treatment option for epilepsy is antiepileptic drugs (AEDs) aiming at preventing or reducing seizures as quickly as possible. Improved seizure control is likely to reduce morbidity and premature mortality associated with continuing seizures, especially convulsive attacks. In addition, seizure remission is a major determinant of good quality of life (Duncan et al. 2006). It is estimated that roughly 70-80 % of adults with new onset epilepsy will become seizure free with available AEDs, although around half will experience adverse effects. Recent development of new AEDs thus aimed at improving the benefit-risk balance of existing AED therapy. Usually, new AEDs are evaluated in add-on settings in patients refractory to previous therapies.

Drug resistant epilepsy occurs in 20-30 % of patients newly diagnosed with epilepsy depending on the definition used (Schmidt et al. 2014). According to ILAE, drug-resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen AED schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom (Kwan et al., Epilepsia, 2010). This definition was however not available at the time of inception of the brivaracetam clinical development program.

About the product

Briviact is a new AED containing the active substance brivaracetam ((2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide), a 2-pyrrolidone derivative with affinity for synaptic vesicle protein 2A (SV2A). Brivaracetam (also referred to as BRV in this report) binds to SV2A in the brain, which is believed to be the primary mechanism for its anticonvulsant activity.

Brivaracetam is proposed for use as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy. The applicant proposed a starting dose of 100 mg/day to be followed by further adjustment of the dose between 50 mg/day and 200 mg/day based on individual patient response. The application concerns film coated tablets (10 mg, 25mg, 50 mg, 75mg and 100 mg), an oral solution (10 mg/ml) as well as a solution for injection/infusion (10 mg/ml).

Type of Application and aspects on development

The application for Briviact was a complete and independent application under Article 8.3 of Directive 2001/83/EC. New active substance status was claimed by the applicant based on the quality properties of brivaracetam.

During the development, protocol assistance and scientific advice was obtained from the CHMP on multiple occasions concerning quality, non-clinical and clinical aspects of the development program including advice on the design, conduct and analysis of the main studies supporting this application.

The main support for this application is derived from 3 pivotal clinical trials. Traditionally, newer AEDs have been evaluated in add-on studies in patients refractory to previous therapies. This strategy is also followed for the application for brivaracetam, which is in line with the relevant CHMP guideline on clinical investigation of medicinal products in the treatment of epileptic disorders (CHMP/EWP/566/98 Rev.2/Corr).

2.2. Quality aspects

2.2.1. Introduction

The finished product is available in three distinct dosage forms, containing brivaracetam as active substance: film-coated tablets (10, 25, 50, 75 and 100 mg); an oral solution (10 mg/ml); a solution for injection/infusion (10 mg/ml).

Other ingredients vary by dosage form and are listed below. Packaging is also described by dosage form as described in section 6.5 of the SmPC.

Film-coated tablets:

Tablet core: croscarmellose sodium, lactose monohydrate, betadex, anhydrous lactose and magnesium stearate.

Film coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc and iron oxides (E172) – black (25, 75 and 100 mg tablets), red (50 and 75 mg tablets) and yellow (25, 50, 75 and 100 mg tablets).

Tablets are available in PVC/PCTFE/alu blisters and PVC/PCTFE/alu perforated unit dose blisters.

Oral solution:

Sodium citrate, anhydrous citric acid, methyl parahydroxybenzoate (E218), carmellose sodium, sucralose sorbitol liquid, glycerol (E422), raspberry flavour and purified water.

The oral solution is available in amber glass bottles (type III) with white child resistant polypropylene closures. 10 ml Graduated oral dosing syringes (polypropylene, polyethylene) and adaptors for the syringes (polyethylene) are also provided.

Solution for injection / infusion:

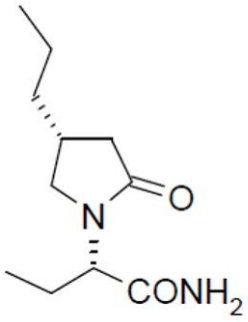
Sodium acetate trihydrate, glacial acetic acid, sodium chloride and water for injections.

The solution for injection/infusion is available in packed in glass vials (type I) with siliconized bromobutyl rubber stoppers and sealed with aluminium/polypropylene tear off caps.

2.2.2. Active Substance

General information

The chemical name of brivaracetam is (2*S*)-2-[(4*R*)-2-oxo-4-propyltetrahydro-1*H*-pyrrol-1-yl]butanamide. It has the molecular formula $C_{11}H_{20}N_2O_2$ corresponding to a relative molecular mass of 212.29 g/mol and has the following structure:



The structure of brivaracetam was inferred from the route of synthesis and confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis and XRPD.

The active substance is a white to off-white non-hygroscopic crystalline solid, very soluble in aqueous media across the physiological pH range and also in polar organic solvents. The physicochemical properties of brivaracetam render it suitable for all three proposed dosage forms.

Brivaracetam exhibits stereoisomerism due to the presence of two chiral centres. Limits for stereomeric impurities have been.

Two solid phases of brivaracetam are known. The manufacturing process generates only the desired solid phase 1. Solid phase 2 is an iso-solvate with non-polar organic molecules. Stability studies indicate that no solid phase interconversion occurs in the drug substance throughout the proposed re-test period. The second solid phase is, however, partially formed during tablet production but does not impact the performance of the finished product as dissolution is rapid and stability has been demonstrated.

Brivaracetam is considered a new active substance from a quality perspective. The applicant compared its structure with structurally-related active substances within authorised products in the EU and demonstrated

that it is not a salt, ester, ether, isomer, mixtures of isomers, complex or derivative (e.g. pro-drug or metabolite) of any of them.

Manufacture, characterisation and process controls

Brivaracetam is synthesized in two synthetic steps followed by resolution using well-defined starting materials with acceptable specifications. Different manufacturers are used for the individual steps. One chiral centre originates in a starting material whilst the other is generated during the synthetic process. One impurity known to be genotoxic is present in a starting material. However, batch analysis data shows efficient purging and since it has never been detected above 30% of the TTC in the active substance, it is deemed to be efficiently purged by the process and no limit is set in the active substance specification. The crystallisation conditions for isolation of the active substance have been designed in such a way that only the desired solid form is thermodynamically accessible.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Only minor changes to the synthetic process were made and these do not impact the quality of the API. Active substance used in phase III studies was made by the proposed commercial manufacturing route. The active substance is packaged in transparent LDPE bags which comply with EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

Different tests are applied to brivaracetam batches depending on whether they are destined for oral or intravenous use. The specification for both uses of active substance includes tests for appearance (solid and in solution), identity (IR), assay (HPLC), impurities (HPLC), stereoisomeric impurities (chiral HPLC), residual solvents (GC), water content (KF), heavy metals (Ph. Eur.), catalyst content (AAS), residue on ignition (Ph. Eur.) and microbiological purity (Ph. Eur.). Brivaracetam for oral use also includes a test for particle size distribution (laser diffraction) whilst brivaracetam destined for the IV formulation has more stringent microbiological limits and a test for bacterial endotoxins (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. Appropriate limits for impurities have been set for starting materials and intermediates and form part of the control strategy, ensuring the quality of brivaracetam.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 68 batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on twenty three production scale batches of brivaracetam from the proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions (25 °C / 60% RH), up to 12 months under intermediate conditions (30 °C / 65% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The following parameters were

tested: appearance (solid and in solution), assay, impurities, stereoisomeric impurities, water content and microbiological quality. In addition, batches of brivaracetam to be used for solution for injection/infusion were tested for bacterial endotoxins. The analytical methods used were the same as for release and are stability indicating. All tested parameters were well within specification at all time-points and no significant trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch and the active substance shown not to be photosensitive.

Solid state stress testing was carried out at a range of temperatures and humidities. Brivaracetam is stable to heat exposure but degrades and picks up water when exposed to both high temperature and humidity.

Forced degradation was carried out in aqueous solution at a variety of pHs from 1 to 11 and in aqueous hydrogen peroxide. Brivaracetam degrades under strongly acidic and strongly basic conditions. It is considered stable under oxidative conditions.

The stability results indicate that the active substance made by the proposed manufacturers is sufficiently stable. The stability results justify the proposed retest in the proposed container.

2.2.3. Finished Medicinal Product

Film-coated Tablets

Description of the product and pharmaceutical development

The aim of development was to identify an immediate release solid oral dosage form of brivaracetam. As such, film-coated tablets have been developed in five strengths: 10, 25, 50, 75 and 100 mg. The four highest strengths are made from a common blend and are thus quantitatively proportional, whilst the 10 mg tablet contains a lower proportion of active substance and different proportions of the same excipients. Tablets are debossed and distinguishable by size and colour.

The active substance is highly soluble in physiologically relevant media and highly permeable and thus labelled as BCS I. The manufacturing process was designed to take into account the physicochemical properties of brivaracetam.

All excipients are well known pharmaceutical ingredients and their quality is compliant with either Ph. Eur. or in-house standards (for the film-coating agents). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The compatibility of brivaracetam with the proposed excipients was tested in a series of binary mixtures. It was found that partial conversion from polymorph I to polymorph II occurs on formulation. However, it was shown that this has no impact on the finished product dissolution characteristics and thus doesn't affect bioavailability.

Various formulations were used during clinical development. Bioequivalence was shown *in vivo* with each change in formulation and bioequivalence of the proposed commercial formulation has been demonstrated with the phase III formulation.

The rapid dissolution of all formulations across the physiologically relevant pH range means that a disintegration test can be used instead of the standard dissolution test. Accordingly, no discriminatory dissolution method has been developed.

Critical quality attributes of the finished product were identified as disintegration, assay, uniformity of dosage units and degradation products. The likely impact of manufacturing steps was assessed by risk assessment, the outcome of which was used to guide formulation development. Set-points for critical process parameters and in-process controls are used to control critical steps and their levels are justified.

The primary packaging is PVC/PCTFE – aluminium blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: de-lumping and mixing of brivaracetam and intra-granular excipients; roller compaction; milling and blending with extra-granular excipients; compression to form tablet cores; film-coating. The process is considered to be a standard manufacturing process.

An acceptable validation scheme has been submitted applicable to all strengths. It has been demonstrated that the manufacturing process is capable of producing finished product of the intended quality in a reproducible manner. The in-process controls are adequate for this dry granulation process.

Product specification

The finished product release specification includes appropriate tests for film-coated tablets and includes tests for appearance, identification (IR), assay (HPLC), degradation products (HPLC), water content (KF), uniformity of dosage units (Ph. Eur.), disintegration (Ph. Eur.) and microbiological quality (Ph. Eur.). The use of a disintegration test as a surrogate for a dissolution test is justified according to the criteria outlined in ICH Q6A. Stability studies indicate that no epimerisation occurs during formulation and storage and so no test for stereoisomeric impurities is included.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for sixteen pilot scale batches of finished product, used in stability and clinical bioequivalence studies and manufactured using the proposed commercial process, formulation and image were provided: four batches each of the 10, 25 and 100 mg strengths and two each of the 50 and 75 mg strengths. In addition, data on four batches of a prototype formulation with the same tablet cores but different film-coating and no debossing, along with thirty five batches of the phase III formulation was provided as supporting data. All of the batches met with the proposed specification and thus confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

A bracketing approach was taken to assess the stability of the strengths derived from a common blend. Three batches each of the 25 and 100 mg strengths were studied, along with a single batch each of the 50 and 75 mg strengths. Three batches of the 10 mg strength were also included. All batches were manufactured on pilot scale. Stability data was generated with finished product stored for up to 24 months under long term conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) in line with the ICH guidelines. The batches of Briviact are identical to and packed in the same primary packaging as those proposed for marketing.

Samples were tested for appearance, water content, dissolution, assay and degradation products. In addition, disintegration results were reported. The analytical procedures used are stability indicating. All results remained

within specification throughout the studies and no trends were observed, save for a slight increase in water content over time.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed to any of the monitored parameters and thus Briviact tablets are not considered to be photosensitive.

Thermal cycling studies were also carried out over three weeks between -20 ^{o}C and 40 ^{o}C / 75% RH. No changes to any of the tested parameters were observed.

Finally, bulk stability studies were carried out on one 10 mg batch and one 25 mg batch. The 25 mg tablet is considered the worst case scenario as it has the highest surface area to weight ratio. No changes to any of the tested parameters were observed over the twelve month study and thus, a bulk holding time of one year is acceptable.

Based on available stability data, the proposed shelf-life of 36 months and without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose and lactose monohydrate are produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that they have been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

The magnesium stearate is of vegetable origin.

Oral Solution

Description of the product and Pharmaceutical development

A non-sterile oral solution was developed to cater for patients who have difficulty swallowing tablets. The formulation was developed in order to create a solution of acceptable taste, consistency and stability. Brivaracetam is highly water-soluble and the commercial formulation has a concentration well below its aqueous solubility. Therefore, particle size and polymorphic form are not considered important for this formulation. Brivaracetam has a bitter taste so various sweeteners and flavourings were tested for palatability. A combination of sucralose and raspberry flavour was selected. Additional excipients were chosen to ensure a desirable consistency and buffering agents were added to control solution pH to ensure stability whilst maintaining palatability. A preservative was added and the levels minimised to allow dosing to paediatric patients whilst ensuring suitable microbiological quality throughout shelf-life.

All excipients are well known pharmaceutical ingredients used in pharmaceutical products and their quality is compliant with either Ph. Eur. or in-house standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The manufacturing process was developed in order to ensure complete dissolution of the various excipients. The formulation used during clinical studies is the same as that intended for marketing. Bioequivalence with the tablet formulation was demonstrated in a clinical study.

The primary packaging is an amber glass bottle (type III) with a white polypropylene (PP) child-resistant closure. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

A CE-marked PP/PE 10 ml graduated oral dosing syringe is supplied with the product. Accuracy and compatibility of the syringe was demonstrated in line with Ph. Eur. requirements.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: dissolution of the active substance and excipients in purified water; filtration; filling of the bottle; closure of the bottle. The process is considered to be a standard manufacturing process. Nonetheless, traditional process validation has been carried out on three consecutive commercial scale batches of Briviact oral solution. The process parameters for mixing time, speed and temperature ensure complete dissolution. Dissolution of all components is monitored throughout the process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance (colour and opalescence, Ph. Eur.), identification (HPLC, chiral HPLC), identification of preservative (HPLC), relative density (Ph. Eur.), pH (Ph. Eur.), degradation products (HPLC), assay of active substance (HPLC), assay of preservative (HPLC) and microbiological quality (Ph. Eur.). No test for stereoisomeric impurities is included since studies show no epimerization occurs during formulation or storage. A risk assessment on introduction of elemental impurities was carried out and the conclusion was that no test is needed for the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for fourteen pilot to commercial scale batches, demonstrating the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on six commercial scale batches of finished product stored for up to 36 months under long term conditions (25 °C / 60% RH), up to 36 months under intermediate conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) in line with the ICH guidelines was provided. The batches of Briviact are identical to and packed in the same primary packaging as those proposed for marketing. Data was generated with batches stored both upright and horizontally.

Samples were tested for appearance, water content, pH, density, assay of brivaracetam, degradation products (including stereoisomers), assay of preservative, microbiological quality, and antimicrobial effectiveness. The analytical procedures used are stability indicating. All results remained within specification throughout the studies and no trends were observed indicating the product is stable over the periods tested.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed to any of the monitored parameters and thus it is concluded that the amber bottle provides adequate protection for the oral solution.

Forced degradation studies show that Briviact oral solution is stable to thermal stress, but unstable in the presence of strong acid, strong base, or strong oxidants.

Thermal cycling studies were also carried out over three weeks between -20 °C and 40 °C / 75% RH. No changes to any of the tested parameters were observed.

An in-use stability study was carried out over a 150 day period on three batches of finished product to simulate patient use. Batches of Briviact were up to three years old, having been used in long-term stability studies, at the start of the study. Again, no trends were observed to any of the measured parameters and thus, in-use stability has been demonstrated for up to five months.

Based on available stability data, the proposed shelf-life of 36 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

Solution for Injection / Infusion

Description of the product and Pharmaceutical development

The aim was to develop a sterile preservative-free solution for injection/infusion. Brivaracetam is highly water-soluble and the commercial formulation has a concentration well below its aqueous solubility. Excipients were chosen in order to produce a stable buffered solution and sodium chloride is added as a tonicity agent. The formulation composition was optimised in order to afford acceptable osmolarity properties. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The finished product is subjected to terminal sterilisation as brivaracetam is thermally stable. Extractables and leachables from the proposed container closure system were investigated over a six month period. Safety data on the compounds identified was provided, indicating that there is no toxicological concern with any of the potential extractables and leachables.

Compatibility with perfusion equipment was investigated. Stability of the finished product in different perfusion diluents (0.9% saline solution, 5% glucose solution, lactated Ringer's solution) at various concentrations and in either PVC or polyolefin perfusion bags was tested. The product is stable for up to 72 hours under such conditions. In addition, no loss of active substance is observed to the perfusion kit. Finally, compatibility with polyurethane and silicon feeding tubes was demonstrated.

The primary packaging is type I glass vials with siliconized bromobutyl rubber stoppers sealed with aluminium/propylene tear off caps. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: dissolution of active substance excipients and adjustment of pH; filtration; filling into bottles; closure of bottles; terminal sterilisation; visual inspection. The process is considered to be a standard manufacturing process. Nonetheless, traditional process validation has been carried out on three consecutive commercial scale batches of Briviact solution for injection/infusion using a bracketing

approach to cover the manufacturing scales applied for. Processing parameters have been defined and in process controls are included in order to produce Briviact solution for infusion of suitable quality. Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance (colour and opalescence, Ph. Eur.), identification (HPLC, chiral HPLC), assay (HPLC), degradation products (HPLC), pH (Ph. Eur.), osmolarity (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), sub-visible particles (Ph. Eur.), extractable volume (Ph. Eur.) and microbiological quality (Ph. Eur.). No test for enatiomeric impurities is included since studies show that no epimerization occurs during formulation or storage. A risk assessment on introduction of elemental impurities was carried out and the conclusion was that no test is needed for the finished product. Uniformity of dosage units is ensured by the process and therefore no test is included in the release specifications.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional data from six pilot scale clinical batches and three batches from an alternative supplier used in earlier development was provided and supports the proposed specification and limits.

Stability of the product

Stability data on three commercial scale batches of finished product stored for up to 36 months under long term conditions (25 °C / 60% RH), up to 36 months under intermediate conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) in line with the ICH guidelines was provided. These batches were manufactured by a different manufacturer but are considered representative of the commercial process and were packed in the same primary packaging as those proposed for marketing. In addition, 36 months of long term data and 6 months of accelerated data were provided for one pilot scale batch from the commercial manufacturer. Studies on three additional commercial scale batches from the commercial manufacturer are underway and 6 months of data was provided on batches stored under intermediate and long term conditions. All data was generated with batches stored both upright and inverted.

Samples were tested for appearance, assay, degradation products (including stereoisomers), sterility, bacterial endotoxins, particulate contamination, pH, container closure integrity and extractable volume. The analytical procedures used are stability indicating. All results remained within specification throughout the studies and no trends were observed indicating that the product is stable over the period investigated.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes were observed to any of the monitored parameters. Forced degradation studies show that Briviact solution for injection/infusion is stable to thermal stress, but unstable in the presence of acid, base, or strong oxidants.

Thermal cycling studies were also carried out over three weeks between -20 ^{o}C and 40 ^{o}C / 75% RH. No changes to any of the tested parameters were observed.

Based on available stability data, the proposed shelf-life of 36 months without specific storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and three presentations of finished product has been presented in a satisfactory manner. The results of tests carried out indicate 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 clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of these products is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the products have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development program of brivaracetam (BRV) for chronic use by oral and intravenous administration comprised a battery of tests including the investigation of primary pharmacodynamics (PD) in rodent models of seizures and epilepsy and mechanisms of action studies exploring the affinity and binding properties of BRV to the SV2A protein as well as the effect of BRV on various voltage-gated ion channel currents and ligand-gated receptor currents. Secondary pharmacodynamics has been investigated in pharmacology models beyond epilepsy including animal models of pain, essential tremor, mania and migraine.

For safety pharmacology, effects of BRV on the central nervous system (CNS), cardiovascular system and respiratory system, as well as the gastrointestinal system, were investigated. In addition to the pharmacokinetics (PK) studies, toxicokinetic data were generated in the frame of the toxicity studies, including single and repeated dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, mechanistic toxicity, local tolerance and drug abuse and dependency studies. In addition, toxicity studies in juvenile animals were performed.

All main safety pharmacology and toxicology studies, including the determination of plasma concentrations of BRV, were carried out in conformance of Good Laboratory Practice (GLP) standards. Only a few early, toxicity studies were performed non-GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

- *In vitro* studies

The *in vitro* affinity of BRV was investigated against a variety of conventional and putative drug targets and against rat and human SV2A in radioligand binding studies. The studies showed that BRV had affinity to SV2A, but not to 50 other binding sites tested including receptors, ion channels and transporters. The affinity to SV2A was higher for BRV (pIC_{50} ≈7) than for levetiracetam (pIC_{50} ≈6).

The ability of BRV to modify voltage-gated fast and persistent Na^+ currents was investigated in cultured neurons, a neuroblastoma cell line, CA1 pyramidal neurons and in entorhinal cortex neurons from non-epileptic and epileptic mice. The ability of BRV to modify voltage-gated Ca^{2+}, K^+ and delayed rectifier currents was investigated in hippocampal neurons and (Ca^{2+} only) dorsal root ganglia neurons. In some assays, BRV seemed to have some effect on voltage-gated Na^+ currents, which was not considered clinically relevant by the applicant due to the absence of effects on sustained repetitive firing in neurons together with the inconsistent and moderate magnitude of effect of BRV across various assays on fast and persistent Na^+ currents. BRV did not modulate voltage-gated Ca^{2+} or K^+ currents at therapeutic relevant concentrations.

Excitatory NMDA-induced currents were inhibited by BRV from 100 µM in tests on cultured mouse hippocampal neurons, which is equivalent to an exposure of 21.1 µg/ml, compared to a clinical c_{max} after oral administration of 3.5 µg/ml. However, BRV did not modify excitatory currents induced by AMPA or kainate, neither did it modify currents induced by the inhibitory amino acids GABA and glycine.

Binding properties were also investigated for the abundant hydroxy-acid metabolite of BRV, ucb-107092-1, which represents 15 % of the administered dose recovered in urine over 48 h in humans. Contrarily to BRV, ucb-107092-1 up to the maximum tested concentration of 10µM did not bind to either rat or to human SV2A.

- *In vivo* studies

In a radioligand binding study in mice BRV showed affinity to SV2A, displaying 50% occupancy of central SV2A at 3.3 µmol/kg (0.7 mg/kg intraperitoneal) and dose-dependently occupied central SV2A proteins after systemic administration.

In addition to this binding study, the *in vivo* primary pharmacodynamics of BRV were evaluated in a large number of animal models of seizures and epilepsy including acute seizure models in rodents with induced convulsions and several models of acquired and genetic epilepsy.

The maximal electroshock seizure (MES) test and a test for chemically induced seizures by pentylenetetrazol in male NMRI mice are common models for the detection of compounds able to inhibit seizure spread. In contrast to many approved AEDs, BRV showed protective effects in these two models only at high doses (ED_{50}-values of 113 and 30 mg/kg, respectively). In other chemically induced seizures tests using various chemoconvulsants including DMCM, 3-mercaptopropionic acid, AMPA, NMDA and kainic acid, BRV also only showed protective effects at high doses (ED_{50}-values of 30, 254, 42, 76 and 89 mg/kg, respectively).

A number of studies were conducted to test the protective effect of BRV against seizures with focal onset. BRV protected against secondarily generalized seizures in fully 6 Hz- and corneally kindled mice with ED_{50} values of 3.5 and 1.2 mg/kg, respectively. BRV also increased the after discharge- and seizure threshold by 73% at a dose of 0.68 mg/kg and 51% at 21 mg/kg in amygdala kindled rats. Furthermore, in the same model, BRV increased the generalized seizure threshold current by 623% at the highest dose tested (21 mg/kg). Using

supra-threshold stimulation, the ED_{50} value against secondarily generalized motor seizures was 44mg/kg. Protective effects of BRV were also observed against partial seizures induced by 6Hz stimulation in mice (ED_{50}=4.4 mg/kg) and against secondarily generalized seizures induced by supra-threshold stimulation in phenytoin-resistant amygdala kindled mice (~90% reduction at 210 mg/kg, ED50=68 mg/kg).

Protection by BRV against primary generalized seizures was investigated in a genetic absence epilepsy model in rats and in a genetically sound-sensitive mice model. In the genetic absence epilepsy model BRV produced a suppression of spontaneous cortical and wave discharges (ED_{50}=2.6 mg/kg). A statistical significant suppression was evident from a dose of 6.8mg/kg. In the genetically sound-sensitive mice model, BRV dose-dependently protected against wild-running, clonic and tonic convulsions, ED_{50}-values were 37, 2.4 and 1.4 mg/kg, respectively.

Protection by BRV against status epilepticus was investigated as intravenous monotherapy treatment and combination treatment with diazepam in a rat model of self-sustained status epilepticus, where BRV was shown to shorten the duration of seizures in a dose-dependent manner. A synergistic effect of BRV and diazepam was shown when given in combination. At doses of 10 mg/kg BRV and 1 mg/kg diazepam in combination, a reduction of the number of seizures from 72 to 6.8, of the duration of status epilepticus from 20 to 1.6 hours and of the cumulative seizure time from 32 to 3 minutes was observed, whereas the same doses when given alone had a much smaller and not significant effect on status epilepticus.

Potential antiepileptogenic effects of BRV were demonstrated in a corneal kindling model in mice where a delay in kindling acquisition was observed, measured as a reduced incidence of generalized seizures.

Protection of BRV against myoclonus was investigated in a rat model of post-hypoxic myoclonus where reductions of post-hypoxic seizures from 0.3 mg/kg and post-hypoxic myoclonus at 0.3 and 3 mg/kg were demonstrated.

Effects on clonic convulsions by the main metabolites of BRV were investigated in a model using sound sensitive mice. The ketone metabolite ucb 47074 was the only metabolite showing a protective effect with an ED_{50} of 52 mg/kg compared to anED_{50} value of 2.4 mg/kg for BRV. The other metabolites tested, ucb-100406-1 (hydroxy metabolite), ucb-100023-1 (diastereoisomer of the hydroxy metabolite), ucb-42145 (acid metabolite) and ucb 107092-1 (hydroxy-acid metabolite) were inactive. Furthermore, no effects were found with any of the metabolites tested in the maximal electroshock test in mice, in an amygdala kindling test in rats nor in a test involving clonic convulsions induced by pentylenetetrazol in mice.

Secondary pharmacodynamic studies

The secondary pharmacodynamics of BRV has been evaluated in various *in vitro* and *in vivo* models with the purpose to characterize its analgesic properties, potential against tremor, mania and migraine as well as impact on cognitive function. An effect of BRV was shown in some of the tests conducted including the ability to attenuate peripheral neuropathic pain and the mechanical allodynia in rats, reduction of β-carboline harmaline alkaloid-induced elicited tremor in rats and an anti-mania effect.

The observed effects did not related to the therapeutic target subject to the present application and are therefore no further discussed.

Safety pharmacology programme

Effects on the CNS were evaluated in rats and mice. In rotarod performance tests in rodents BRV dose-dependently impaired the performance of fully corneally kindled mice and fully amygdala-kindled rats and genetic absence epilepsy rats from Strasbourg. Margins between doses inducing seizure protection (ED_{50} values

1.2 mg/kg, 44 mg/kg and 6.8 mg/kg, respectively) and motor adverse effects (ED_{50} values 55 mg/kg, 163 mg/kg and 177 mg/kg, respectively) were 46, 3.7 and 26 in corneally kindled mice, amygdala-kindled rats and genetic absence epilepsy rats from Strasbourg, respectively.

Spontaneous locomotor activity was shown to be decreased by BRV in rats at doses from 118 mg/kg .

In Irwin test in rats (oral gavage, single dose) signs of CNS depression including apathy and decreased alertness were observed in male animals at doses of 100 mg/kg. At 300 mg/kg, decreased alertness occurred in both sexes and males also displayed decreased grooming. In addition to these effects, mild changes in neuromuscular function, sensorimotor function and autonomic function were observed. Similar, moderate signs of CNS depression were seen in females at 600 mg/kg. At 1000 and 1500 mg/kg marked changes in autonomic (including salivation), sensorimotor (including decreased pain responses) and neuromuscular (decreased grip strength) functions and abnormal respiration were seen.

The impact of BRV on learning and memory functions was investigated *in vitro* on long-term potentiation in rat hippocampus and *in vivo* in normal and fully amygdala-kindled rats in the Morris water maze test. BRV up to a concentration of 30 µM (=6.37 µg/ml) had no effect on long-term potentiation parameters in rat hippocampal tissue suggesting that it might not affect memory function. This is in line with the results from the study on spatial learning using the Morris water maze model where BRV did not affect spatial reference memory of normal or amygdala-kindled rats.

Cardiovascular effects of BRV were evaluated *in vitro* and *in vivo*. *In vitro*, no significant effects on hERG potassium channels or human cardiac sodium and L-type calcium channels were observed up to 100 µM (=21.2 µg/ml, compared to clinical c_{max} of 3.5 µg/ml after oral administration). In dog Purkinje fibres no statistically significant effects on the intracellularly recorded action potential parameters were observed up to a concentration of 200 µg/ml. However, at a supra-therapeutic concentration of 200 µg/ml, a small, not statistically significant, decrease in action potential duration (at 60% repolarization) was observed (around 12%).

In anaesthetized dogs (males and females) no biologically relevant effects on cardiac, systemic, renal and pulmonary haemodynamics and on the main parameters of the electrocardiogram, including QTc, were observed up to an intravenous (i.v.) dose of 45 mg/kg. In another study in anaesthetized male dogs a dose–related decrease in heart rate was seen at i.v. doses from 50 mg/kg. At 150 mg/kg, i.v., increases in QT and QTc intervals, decreases in peak positive and negative rate of rise of left ventricular pressure (dP/dtmax+, dP/dtmax-) and a transient reduction in arterial blood pressure and left ventricular systolic pressure were observed. Plasma concentration 60 minutes after the start of a 10-minute infusion at 50 and 150 mg/kg was 79.9 and 308 µg/ml, respectively. In female telemetered conscious dogs, after oral (gavage) dosing, there was a decrease in blood pressure, an increase in heart rate and a reduction in RR interval (i.e. QTc prolonged) from 50 mg/kg. At 150 mg/kg the PR interval was shortened. Plasma concentrations 2 hours post-dose at 50 and 150 mg/kg were 61 and 174 µg/ml, respectively, compared to clinical c_{max} after oral administration of 3.5 µg/ml. However, no clear dose response was observed for these changes. Furthermore, these changes were not observed in the repeat-dose toxicity studies (see section 2.3.4.) and no effects on QTc were observed in a clinical QT-study (see section 2.4.3.) where BRV at 150 and 800 mg/day were given for 7 days.

Effects of BRV on respiratory function were investigated in anesthetized dogs and in rats. In dogs an increase in respiratory rate and minute volume at and above i.v. doses of 50 mg/kg was seen (plasma concentration at 50 mg/kg was 79.9 µg/ml 60 minutes after a 10-minute infusion). In male rats a single, oral dose of BRV had a slight respiratory stimulant effect at and above 100 mg/kg (corresponding to a plasma concentration of approximately 60 µg/ml). However, no substantial effects on inspiratory time, peak inspiratory and expiatory

flow, respiratory rate, pause and enhanced pause were observed and no toxic effects were seen on the respiratory system in the repeat-dose toxicity studies.

The safety with regards to the gastrointestinal system were studied in male rats. A delayed stomach emptying and a reduction in gastrointestinal transit were seen at single, oral (gavage) doses of 300 mg/kg (corresponding to a plasma concentration of approximately 90 µg/ml). In the repeat-dose toxicity study, however, no marked toxic effects on the gastrointestinal system were observed.

Safety pharmacology studies with metabolite ucb-107092-1 and impurity ucb 34713 showed no or very mild effects.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed other than the study on self-sustaining status epilepticus seizures in rats, which investigated the effect of BRV in monotherapy and in combination with diazepam. In this study a synergistic protective effect was observed when the two compounds were given together (see primary PD *in vivo* studies for details).

2.3.3. Pharmacokinetics (PK)

The PK of BRV has been studied following oral and/or i.v. administration in mice, rats, dogs and monkeys. *In vitro* studies were performed to investigate the intestinal absorption of BRV, its plasma protein binding, its metabolism, and its potential to produce drug interactions.

Absorption

PK studies showed that BRV was completely and rapidly absorbed across species after oral administration. Plasma concentrations were maximal within one hour after oral dosing and oral bioavailability was ≥100% in rodents and dogs, indicating complete absorption and low first-pass effect. These species were also characterized by low total plasma clearance. Co-administration with food had limited effects on BRV exposure, if any (rodent data). Cynomolgus monkeys provided contrasting data with extensive first-pass effect, high total plasma clearance and low oral bioavailability (<10%).

Distribution

Irrespective of the type of species, BRV displayed a volume of distribution (Vz) close to total body water content (ca 0.6 L/kg).

In vitro distribution studies showed that BRV (from 0.5-1 to 100 µg/mL) distributed evenly between blood cells and plasma with blood-to-plasma ratios close to one (0.83 to 0.95), and had a low plasma protein binding in the range of 12-27% (approximately 20% in humans, see section 2.4.2.), irrespective of the tested concentration or species.

Distribution studies in pigmented rats showed that ^{14}C-BRV distributed rapidly throughout the body following oral administration with the highest concentrations found in the organs generally involved in drug absorption (gastrointestinal tract), biotransformation (liver) and excretion (kidney), but also in the preputial and clitoral glands. The elimination of radioactivity from tissues generally paralleled that from plasma, with levels returning to background by maximum 24h. Elimination from the preputial and clitoral glands required more time, ca 72h. The affinity for the preputial and clitoral glands was shown to be rat-specific and was not observed in mice, was fully reversible, associated with the parent drug (i.e., not with the metabolites), and not involving any covalent binding. Data indicated that neither BRV nor its metabolites bind to melanin.

PK/PD studies in audiogenic seizure-prone mice showed that BRV distributed rapidly to the target brain tissues. Brain concentrations peaked at 15 minutes after oral dosing and directly paralleled pharmacological activity, without any time delay or hysteresis.

In mice and rats, brain-to-plasma ratios equilibrated very rapidly and were close to unity irrespective of the dosing route or gender or sampling time.

In rats, BRV was shown to readily cross the placenta. From 1h post-dose, radioactivity levels in foetuses, amniotic fluid and placenta were similar to those in maternal blood.

Metabolism

BRV was the predominant radioactive component in plasma in all species with the exception of Cynomolgus monkeys (≤5%), due to the higher metabolic clearance in that particular species.

The major metabolic route was found to involve stereoselective hydroxylation of the penultimate carbon of the propyl chain to produce ucb-100406-1, both in animals and human subjects. The other identified metabolic routes involved the hydrolysis of the acetamide moiety to form the acid derivative ucb-42145, which in turn can be hydroxylated into ucb-107092-1. The enzymes involved were CYP2C19, amidase E.C.3.5.1.4 and CYP2C9, respectively. In some cases, the hydroxy derivative ucb-100406-1 was also found to be oxidized into the corresponding ketone ucb-47074.

In rodents and monkeys, ucb-100406-1 was the only metabolite exceeding 10% of the total circulating material. In dogs, major metabolites included both ucb-100406-1 and ucb-102993-1, a derivative resulting from the hydroxylation of the butyramide side-chain. The fraction of the dose excreted as ucb-102993-1 is up to 20% in dogs whereas in other species, ucb-102993-1 accounts for at most 3% of the dose.

No chiral inter-conversion of BRV was detected in rats or dogs.

None of the identified metabolites contained structural alerts suggesting toxicity although it was speculated by the Applicant that bioactivation via oxidation of the butyramide side chain as in ucb-102993-1 may lead to the formation of a reactive intermediate assumed to be involved in dog liver porphyria (see section 2.3.4. for further discussion).

Excretion

BRV was mainly eliminated by metabolism, with only a small fraction of the dose excreted unchanged. The level of unchanged BRV recovered in excreta was found to be low, with values of 5% in mice, 6% in rats and, 4% in dogs and 0% in Cynomolgus monkeys.

Following oral administration, the balance of excretion of radioactivity was over 90% of the dose in mouse, rat, dog and monkey at 48h or 168h post-dose, and shown to be independent of gender, dose route, dose-level and/or pregnancy state. Most of the radioactivity was excreted by the renal route with minimal biliary excretion (rodent data).

Following single oral dosing of ^{14}C-BRV at 5 mg/kg to lactating female rats, radioactivity was secreted in milk to rapidly reach levels similar to those in plasma.

2.3.4. Toxicology

The toxicological profile of BRV was evaluated in a comprehensive set of non-clinical studies including single- and repeat-dose oral toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, juvenile

toxicity, dependency and mechanistic studies. In addition, the metabolite ucb-107092-1 was investigated in repeat-dose, genotoxicity and reproductive toxicology studies, as there was inadequate safety coverage for this metabolite based on concentrations observed in subjects with severe renal impairment. The diastereoisomer of BRV, ucb-34713, which presents as an impurity in BRV batches, was also tested in genotoxicity and repeat-dose toxicity studies.

Rat and dog were initially selected as the main species for the toxicology evaluation based on *in vitro* and *in vivo* PK and metabolism studies, showing that these species were exposed to the main human metabolites (hydroxy metabolite ucb-100406-1, acid metabolite ucb-42145, and hydroxy-acid metabolite ucb-107092-1). Furthermore, in pharmacological studies it was demonstrated that mice and rats were responsive to the primary PD effect of BRV. Following the observation of severe liver porphyria in dogs (see summary of results below), toxicology studies were also performed in Cynomolgus monkeys to further evaluate the appearance of similar liver findings in another non-rodent species. A dose-finding study in mice was conducted to establish suitable dose levels in the carcinogenicity study.

Single dose toxicity

Acute oral toxicity was studied in rats who received a single dose of 0 (water), 500, 1000 and 2000 mg/kg and were followed for a period of 14 days. In this study, the acute toxicity of BRV was low with the maximum non-lethal oral dose being ≥1000 mg/kg and a no-observed-effect-level (NOEL) of 500 mg/kg.

Repeat dose toxicity

The repeat-dose toxicity of BRV after oral administration was investigated in a number of studies for up to 26 weeks in the rat and dog and for up to 39 weeks in monkeys. Due to the short half-life of BRV, toxicology studies after oral dosing were performed using multiple daily dosing, usually twice a day (bid), three times a day (tid), or bid coupled with dietary administration to ensure adequate exposure throughout the whole day. BRV was also administered intravenously to rats and dogs for up to 4 weeks to support development of an i.v. formulation. Liver, thyroid gland and kidney were identified as the main target organs.

Pre-terminal mortalities

Pre-terminal deaths considered BRV-related occurred in all species used in the repeat-dose toxicology program. Other than mortality in mice, pre-terminal deaths were seen in the preliminary dose-finding studies.

Mice were terminated for welfare reasons and/or found dead at exposures equivalent to approximately ≥9-fold clinical exposure based on AUC. The cause of death was not determined. Prior to sacrifice, adverse clinical signs were observed and some mice had swollen abdomen and intestinal distension with gas noted at necropsy. Rats were terminated for welfare reasons and/or found dead at exposures equivalent to approximately ≥21-fold clinical exposure based on AUC. The cause of death was not determined. One dog was terminated for welfare reasons at exposures equivalent to approximately 28-fold clinical exposure based on AUC. Necropsy revealed a dark abnormal liver and a gall bladder with dark abnormal contents correlating with microscopic findings in the liver and gall bladder. The moribund condition of this dog was considered likely associated with the observed liver toxicity. Finally, one monkey was terminated for welfare reasons at exposures equivalent to approximately 16-fold clinical exposure based on AUC. Necropsy revealed dark areas in the stomach and a marked erosion of the cardiac region correlating with hemorrhage in the stomach noted at the microscopic examination. The moribund condition of this monkey was considered likely associated with the marked local toxicity in the stomach.

CNS

CNS clinical signs were observed in all species at high dose levels. In the repeat-dose studies, the signs were mainly seen during the first days of dosing indicating tolerance development. In mice and rats, unsteady gait was commonly observed at exposures of about 21-fold the clinical $c_{max.}$ In dogs, observed signs included partially closed and closed eyes, hypoactivity, lethargy, incoordination and unsteady gait at exposures of about 14-fold the clinical $c_{max.}$ In monkeys, CNS clinical signs seen in a few animals included sleepiness or sleeping and drooping eyelids. More common signs observed were slow or clumsy movements, poor motor coordination, loss of balance and decreased motor activity at exposures of about 34-fold the clinical $c_{max.}$

Liver findings in rats, monkeys and dogs

In rats and monkeys, chronic administration of BRV (26- and 39-week, respectively) caused adaptive metabolic hepatic responses with no evidence of hepatotoxicity at exposures corresponding to 5- to 8-fold and 42-fold clinical exposure based on AUC, respectively. In rats dosed up to 450 mg/kg/day (26-week study) or in monkeys dosed up to 900 mg/kg/day (39-week study) liver findings included increased organ weight, with centrilobular (rats) or diffuse (monkeys) hepatocyte hypertrophy and deposits of brown pigments in hepatocytes. The pigments were stained with Schmorl's staining and identified as lipofuscin in the 13-week rat study. These findings occurred at all doses in rats and only at the top dose in monkeys with slight increases in triglycerides and cholesterol in rats and in alanine aminotransferase (ALT), triglycerides and glutamate dehydrogenase (GLDH) in primates. The increased liver weight and hepatocyte hypertrophy were shown to be reversible following a treatment-free recovery period. BRV was shown to induce liver Cytochrome P450 (CYP) activity including CYP2B and CYP3A, in both rodent and non-rodent toxicity studies, whereby only minimal changes were observed in Cynomolgus monkey.

In addition to the liver effects described above, there were also findings concerning the bile ducts in some rat studies.

In one 4-week study, minimal porphyrin deposits associated with minimal hyperplasia, peribiliary inflammation and minimally elevated liver enzymes (ALT and aspartate aminotransferase, AST) in several males at ≥1000 mg/kg/day and peribiliary inflammation in one male at 300 mg/kg/day and in one female at 1500 mg/kg/day. In another 4-week study, brown pigment, not further characterized, associated with peribiliary inflammation was observed in one male at 1300 mg/kg/day, and peribiliary inflammation only in another male at the same dose level. More pronounced liver porphyrin deposits associated with additional microscopic alterations was seen in dogs. Chronic administration in dogs induced hepatotoxicity consisting of porphyrin deposits in the hepatocytes, Kupffer cells, and canaliculi with centrilobular fibrosis and hyperplasia of oval cells/bile ducts gallbladder concretions, single cell necrosis of hepatocytes, multifocal mononuclear inflammatory cell infiltrate, and elevated levels of some liver enzymes, mainly alkaline phosphatase (ALP), ALT, sorbitol dehydrogenase (SDH), and 5'-nucleotidase. Based on these liver findings the NOAEL was set at 15 mg/kg/day, corresponding to 0.6-fold clinical exposure based on AUC.

Thyroid gland findings in rats and dogs

Effects on the thyroid gland were observed in some of the rat studies, and mainly in male rats. In a 4-week study, dose-related increases of thyroid gland weight was seen and microscopic alterations included minimal to slight diffuse follicular cell hypertrophy at doses ≥1000 mg/kg/day, in some cases accompanied by colloid depletion and/or mineralization. In the 26-week toxicity study, diffuse follicular cell hypertrophy was seen in a small number of male rats in all BRV-treated groups, which in some cases were associated with brown pigment in follicular cells. Altered colloid with basophilic deposits was seen in animals of all groups but the incidence and severity were greater compared to the controls in males receiving doses ≥230 mg/kg/day. A minimum or slight increase in follicular diameter was seen in 3 of 19 males at 450 mg/kg/day. The findings indicate a mildly

increased metabolic activity of the thyroid glands in male rats. A minor effect on the thyroid gland was also observed in one dog study (4 weeks), where a minimal follicular hypertrophy was observed. In addition, in a juvenile dog study, partially to fully reversible decreases in thyroid hormone T4 level were seen mainly in females at 100 mg/kg.

Kidney findings in rats

In the kidney, proximal tubule hyaline droplets were seen in male rats across dose levels of oral BRV (100 to 1000 mg/kg/day) and were accompanied in some studies by proximal cell degeneration, shown as basophilic tubules and granular casts, and renal tubular vacuolation. Mechanistic studies showed that the hyaline droplets most likely were made up of α-2μ-globulin and that BRV induced a prominent accumulation of the protein in epithelial cells of the renal proximal tubules of male but not female rats, with individual levels correlating with the severity scores of the hyaline droplets observed in the proximal tubules following histopathological examination. Kidney proximal tubule hyaline droplets and evidence of α-2μ-globulin nephropathy is a well-known male rat-specific finding and was not considered relevant to man.

Other findings

There were no other consistent findings from the repeat-dose toxicity studies performed. In rats only, inconsistent and minor findings in the spleen were observed. These comprised a small increase in brown pigment in the spleen red pulp (from oral doses ≥150 mg/kg/day after 26-week treatment), extramedullary hematopoiesis in females only at oral doses of 400 mg/kg/day after 13 weeks and hyperplasia of splenic germinal centers (at an oral dose of 1000 mg/kg/day after 4 weeks). These changes were not considered as toxicologically significant. Additional changes were seen after 4-week oral administration in rats only and included findings in the thymus (at 1000 mg/kg/day), prostate and seminal vesicles, male mammary gland, uterus, salivary glands and mesenteric lymph nodes (at 1500 mg/kg/day). These findings were observed above the maximum tolerated dose (MTD) and are most likely related to the poor health status of the animals leading to their early sacrifice.

Genotoxicity

The set of genotoxicity studies with BRV included test for gene mutations and chromosomal aberrations *in vitro*, and chromosomal aberrations *in vivo*.

In the *in vitro* genotoxicity assays, BRV was negative in the Ames assay. Weakly positive and equivocal findings were obtained in two in vitro mammalian cell assays (mouse lymphoma mutation in the absence of metabolic activation and CHO cell chromosomal aberration in the presence of metabolic activation) at concentrations >2000 μg/mL, which is at least 10-fold in excess of the current recommendation in the relevant ICH guideline ICHS2(R1). According to the International Workshop on Genotoxicity Testing biological significance should be given to increases in mutant fraction that exceed the Global Evaluation Factor of 126 mutants per million (Moore et al., Mutation Res., 2007). In the mouse lymphoma assay, there was only one result exceeding the Global Evaluation Factor which was obtained at a cytotoxicity level well above the current recommendations, as were the equivocal results in the chromosomal aberration assay. Additional data from two *in vivo* assays showed an absence of genotoxic activity in the rat bone marrow micronucleus assay, tested up to the MTD of 2000 mg/kg for 2 days, and an absence of mutagenic activity in liver and bone marrow of the Muta^{TM} mouse, tested up to the MTD of 1350 mg/kg/day for 28 days, which represents at least 9-fold the clinical AUC (based on $AUC_{6\text{-}24h}$).

Carcinogenicity

The carcinogenic potential of BRV was evaluated in two 2-year carcinogenicity studies in mice and rats.

In mice, BRV caused an increased incidence of hepatocellular tumors in males at doses of 550 and 700 mg/kg/day corresponding to 2.4- and 4.5-fold the clinical exposure based on AUC, respectively. No increased incidence was seen in males at 400 mg/kg/day (1.5-fold clinical exposure based on AUC) or in females at any dose level. There was also a significant trend for both benign luteomas and benign Sertoli cell tumors in female mice. The incidence of benign luteomas was 1/60 (1.7%), 0/60, 6/60 (10%) and 4/60 (6.7%) at doses of 0, 400, 550 and 700 mg/kg/day, respectively. According to historical control data, incidences ranging from 0.8 to 6.0% are observed in female CD-1 mice. For the benign Sertoli cell tumors, the incidence was 3/60 (5.0%) at 700 mg/kg/day with none seen in controls and the other dose groups. According to historical control data, Sertoli cell tumors are only reported in 2 mice in one study representing an incidence of 1.7%.

In rats, benign or malignant thymomas were seen in a small number of animals from all dose groups with a significant trend compared to controls as a result of a higher incidence in females receiving BRV doses of 700 mg/kg/day. The incidence of benign or malignant thymomas in females were 2/50 (4.0%), 3/48 (6.2%), 4/48 (8.3%), 5/50 (10%) and 11/50 (22%) at 0, 150, 230, 450 and 700 mg/kg/day, respectively. Malignant thymomas were diagnosed in one female rat given the lowest dose of 150 mg/kg/day and in one control male. Benign thymomas were observed in female rats with the following incidence; 2/50 (4.0%), 2/48 (4.2%), 4/48 (8.3%), 5/50 (10%) and 11/50 (22%) at 0, 150, 230, 450 and 700 mg/kg/day, respectively. There were no increased incidences of benign thymomas observed in the mouse carcinogenicity study (incidences of 1, 1, 0, and 1 in female mice at 0, 400, 550 and 700 mg/kg/day, respectively). Historical control data collected between 2005 and 2009 in the same laboratory conducting the carcinogenicity test showed incidences ranging from 5.9% to 10.0% in female Wistar rats. Historical control data from another laboratory (3695 female rats) reported incidences up to 17%. In the literature, incidences of up to 16% have been reported in female Wistar rats (Walsh and Poteracki, Fundam Appl Toxicol., 1994). Thus, the incidence in female control rats in the BRV study (4.0%) was lower than spontaneous incidence range reported from the same laboratory during a relevant time period, and incidences seen in the low (4.2%) and intermediate (8.3%) dose groups are also lower or fall within historical control values. The exposure in the intermediate and highest doses group of 450 and 700 mg/kg/day, corresponds to 9- and 11-fold clinical exposure based on AUC. Only the incidence at the high dose of 700 mg/kg/day (22%) was outside the historical control range in the same laboratory at a relevant time period and higher but close to incidences reported in the literature and other laboratories.

In rats, there was also a positive trend in the combined sex incidence of thyroid gland follicular adenomas and carcinomas, with some increase at 230, 450 and 700 mg/kg/day without a clear dose-response relationship. Combined sex incidences were 1/100, 2/100, 8/100, 7/100 and 7/99 at 0, 150, 230, 450 and 700 mg/kg/day, respectively. According to historical control data, incidences for thyroid gland adenomas and carcinomas range from 0% to 10% and 0% to 5.8%, respectively. The observed incidences for thyroid gland adenomas and carcinomas in the BRV rat carcinogenicity study range from 0% to 10%, and 0 to 2%, respectively, and therefore fell within the historical control range in the same laboratory.

Reproduction Toxicity

BRV was tested for toxicity on fertility, early embryonic, embryo-fetal development and pre-/postnatal development including maternal function, using rats and rabbits, and for developmental toxicity using juvenile rats and dogs although the sought indication was restricted to an age cut-off of 16 years. Several studies, not performed according to GLP, were conducted in order to select suitable dosage for the main studies.

Fertility and early embryonic development

One fertility study was conducted in female and male rats that were dosed orally up to 400 mg/kg BRV, twice daily with 6 hours apart. Mild clinical signs in both sexes and slight increases in absolute liver weights from 200

mg/kg were seen. All other parameters studied were unaffected by treatment with BRV. The NOAEL for female and male fertility and early embryonic development was therefore set to 400 mg/kg. At 400 mg/kg, the margin to maximum human exposure was 18 based on c_{max} values.

Embryo-foetal development

In rat studies, time-mated females were dosed orally up to 600 mg/kg, twice daily with 6 hours apart. At doses ≥150 mg/kg, an increased body weight gain was observed and at 600 mg/kg the dams displayed salivation and partially closed eyes and a slightly reduced food consumption. All other parameters studied were unaffected by treatment with BRV. The NOAEL for maternal toxicity was set to 300 mg/kg, giving a 19-fold margin to maximum human exposure based on AUC values. The NOAEL for embryo-fetal effects and teratogenicity was set to 600 mg/kg, yielding a margin to maximum human exposure of 32, based on AUC values.

In rabbits, females were dosed with BRV orally up to 240 mg/kg, twice daily. A general body weight loss, decreased body weight gain and food consumption in treated rabbits, mainly during the first half of the dosing period, was observed. In all dose groups, an increased number of foetuses with 27 pre-sacral vertebrae were detected: 6, 13, 22, 26 and 31 at 0, 30, 60, 120 and 240 mg/kg, respectively. This finding resulted mainly from an increased number of foetuses with 13 thoracic vertebrae and 7 lumbar vertebrae. Following the revision of historical control data at the facility in which the study was performed, the increased number of foetuses with an additional 13^{th} rib at 60 and 120 mg/kg/day represented a normal variation in the rabbit. Furthermore, it was within the prevalence of supernumerary presacral vertebrae in adult rabbits. At 240 mg/kg, an increased incidence of incomplete or absence of ossification of the epiphysis or phalanges of the fore- or hind limb was seen, and, in addition, an increased post-implantation loss (-24.6% compared to -13.7% in controls) and consequently a decrease in the number of live foetuses per dam (6.6 compared to 7.3 controls) was observed. Also, a decreased foetal bodyweight (-6% compared to controls) was observed at this dose. Literature data and re-analysis of the study data confirmed that the minor skeleton abnormalities observed at high dose in presence of reduced weight of foetuses are mainly due to slight developmental delay. A NOAEL for maternal toxicity was not established. The NOAEL for embryo-fetal effects and teratogenicity was set to 120 mg/kg/day, yielding a margin to maximum human exposure of at least 3.5, based on AUC_{0-12h} values derived from bid treatment every 6 hours in rabbits.

Prenatal and postnatal development, including maternal function

Rats were dosed orally up to 600 mg/kg, twice daily with 10 hours apart, from gestation day 6 to day 20 of lactation. The F1 pups were exposed to BRV and to its metabolites irrespective of the dose administered to the mothers indicating that BRV and possibly metabolites were present in the mother's milk. An increased liver weight was noted from 300 mg/kg in the F0 generation. In the F1 generation, at BRV doses of 600 mg/kg, up to 13% lower body weight loss was observed during PND 10-14 and 14-17 resulting in lower body weight of up to - 5.2% on post-natal day 17 and lower mean body weights during the post-weaning period. In addition, the mean age of attainment of vaginal patency was delayed 2 days compared to controls at 600 mg/kg. The NOAEL for F0 maternal effects, F0 and F1 generation reproductive toxicity and F1 generation functional/neurobehavioral development was set to 600 mg/kg, giving a margin to maximum human exposure of 17. The NOAEL for female F1 generation neonatal/postnatal development is 300 mg/kg due to slightly delayed vaginal patency, and for males the NOAEL was set to 600 mg/kg, giving a margin to maximum human exposure of 6 and 17, respectively.

Studies with offspring (juvenile animals)

Juvenile rats and dogs were evaluated from postnatal day 4-70 and 4-276, respectively, corresponding to neonatal to early (0 to 12 years) and adolescent (12 to 18 years) stages of development in humans.

Juvenile rats were dosed by oral gavage at 150, 300 and 600 mg/kg between postnatal day 4 to 70, followed by a 30-day recovery period. The main findings were lower absolute brain weights, -5.2% to -11.4% at 600 mg/kg in males and females on postnatal days 22, 71 and 100, corresponding with shorter brain length and width. At 150 mg/kg and 300 mg/kg, the lower absolute brain weights were of lesser amplitude (-0.1% to -6.5%). There were no relevant differences in relative brain weights between control and treated groups and there was no histopathology observed at any dose. In addition, there were no adverse effects in any of the behavioral tests performed, apart from a slightly increased startle response on postnatal day 78 in males and females in the high-dose group. An additional study in rats at postnatal days 22, 71 and 100 showed that mean absolute and relative (to final body weight) brain weights were similar within sexes in untreated animals on the three days studied. The percentage of variation between maximum and minimum absolute brain weight values within the three evaluation ages ranged from -12% to -26% for males and from -14% to -19% for females. Thus, the differences seen in the BRV treated juvenile rats were within the range of differences seen interindividually at the same developmental ages in untreated rats.

Reversible centrilobular hepatocellular hypertrophy, accompanied with higher liver weights, was observed in both sexes. The size and number of hyaline droplets in the kidneys of males given 300 mg/kg or 600 mg/kg increased on postnatal day 71, a finding that was no longer present on postnatal day 100. The hyaline droplets were considered a male rat-specific change. Lower prostate weight in males given 600 mg/kg, only on postnatal day 71, was without concurrent histological findings. All the findings in the liver and kidney were also seen in repeat-dose toxicity studies in adult rats. The NOAEL for rat pup growth and development, including CNS development, was set at 150 mg/kg in females and 300mg/kg in males, giving exposure margin to maximum human exposure of 4. The NOAEL for reproductive toxicity was 600 mg/kg, giving an exposure to maximum human exposure of 10. Exposure margins in adult rats, based on NOAEL and AUC values derived from the main repeat-dose toxicity study, generate a margin to clinically relevant exposure of approximately 5-8.

In addition to studies in rats, juvenile dogs were dosed by oral gavage at 15, 30 and 100 mg/kg between postnatal day 4 to 276 (9 months duration), followed by a 56-day recovery period. The main findings concerned a partially to fully reversible decrease in thyroid hormone T4 level, seen mainly in females given 100 mg/kg. At the same dose, changes in the liver parameters were noted, as well as brown pigment accumulation (most likely porphyrin), centrilobular and periportal fibrosis, bile duct hyperplasia, hepatocellular hypertrophy and degeneration, associated with higher liver weights and concretion in the gall bladder. The effects on the liver were partially or fully reversible, apart from the brown pigment accumulation and concretion in the gall bladder. A reversible decrease in thymus weight in females was also seen and was accompanied by a slight increase in severity of thymic atrophy. All the findings in the liver, thyroid and thymus were also seen in repeat-dose toxicity studies in adult dogs. In another study in juvenile dogs, the pups were dosed at 15, 50 and 100 mg/kg between postnatal days 4 to 31. In males only, a lower bone mineral content, bone area and bone mineral density in femur was seen, as well as a shorter femoral length, lower bone mineral content and density in L3-L5 lumbar vertebral column. However, these effects were not seen in the longer duration, main 9-monthstudy in juvenile dogs using the same dosage regimen. The NOAEL for dog pup growth and development, including CNS development, was set at 30 mg/kg, giving no margin to maximum human exposure. Similarly, in adult dogs, based on NOAEL and AUC values derived from the pivotal repeat-dose toxicity study, no margin was observed to clinically relevant exposure.

Toxicokinetic data

Toxicokinetic data were generated within the frame of the toxicity studies including repeat-dose toxicity and reproductive toxicity. Relevant data are summarized in the respective section.

Local Tolerance

BRV at a concentration of 10 mg/mL caused little or no local irritation or tolerance effects when tested via intravenous, intramuscular, intra-arterial or perivenous routes in rabbits. A haemolytic potential assay using human whole blood showed that BRV at concentrations of 10-20 mg/mL had no hemolytic effect, while hemolysis was seen at 30 to 50 mg/mL.

Other toxicity studies

Phototoxicity

After single oral dose administration of ^{14}C-BRV to rats, the level of radioactivity in pigmented and non-pigmented eyes and skin were not significantly different from the levels measured in whole blood (within the range of 2-fold difference). Sampling at various post-dosing times showed that radioactivity measured in the eyes and skin declined in parallel to whole blood without any evidence of accumulation. In addition, BRV did not absorb UV-B, UV-A, or visible radiation in the range from 290 - 700 nm and is not expected to possess any photosensitizing properties.

Immunotoxicity

No dedicated immunotoxicity studies were conducted with BRV.

Dependence

Three drug dependence studies in rats have been performed, one self-administration study, one withdrawal study and one drug discrimination study. BRV at doses of 0.32 to 10 mg/kg/infusion did not have positive reinforcing effects in rats conditioned to self-administer cocaine. Neither did BRV at doses up to 450 mg/kg/day (oral gavage and in diet, c_{max}=39.4 µg/ml) induce any withdrawal symptoms over a withdrawal phase of 7 days after chronic treatment of BRV for 30 days. BRV administered intraperitoneally up to a behaviourally toxic (i.e. ataxia) test dose of 320 mg/kg (c_{max}=322 µg/ml), only partially generalized to the training drug chlordiazepoxide. There was a graded increase in the percentage of drug-appropriate responding by increasing dose of BRV. Approximately 62% drug-appropriate responding in 3 of the 8 animals tested was produced at 320 mg/kg. Complete generalization (>80% drug-appropriate responding) was not observed. At the lower doses of BRV (1, 10 and 32 mg/kg) predominantly 'saline-appropriate' responding was observed, drug-appropriate responding being around 20%, 30% and 20%, respectively, and around 10% at 0 mg/kg (i.e. vehicle). C_{max} at 32 mg/kg was 35.4 µg/ml and c_{max} at 320 mg/ml was 322 µg/ml, compared to clinical c_{max} (oral) of 3.5 µg/ml. Thus, the safety margins between the exposure levels showing generalization and the maximal clinical oral exposure were in the order of 10-100 times the c_{max}.

In addition, no specific binding of BRV was observed in a binding profile assay, screening 50 receptors, ion channels and uptake systems within the CNS including common abuse and dependence-related molecular targets.

Metabolites

In human subjects with normal renal function there were no major metabolites identified. However, in subjects with severe renal impairment, the plasma AUC for ucb-42145, ucb-100406-1 and ucb-107092-1 was 3, 4 and 21.5 fold, respectively, the value in healthy subjects, while the AUC was unchanged for BRV (see also section 2.4.2.). All three metabolites are devoid of pharmacological activity. The plasma AUC was >10% for the metabolites ucb-100406-1 and ucb-107092-1 and <10% for ucb-42145 while this metabolite was the most abundant metabolite found in human urine (34.2%).

Although no formal toxicological characterisation was needed for ucb-42145, it was qualified based on exposure at NOAELs in repeat-dose toxicity studies in rat and monkey where exposure was >1 and 6.6- fold versus

exposure in renally impaired subjects. Ucb-100406-1 was also qualified within the performed non-clinical studies.

Ucb-107092-1 was also evaluated in safety pharmacology studies *in vitro* and *in vivo* addressing potential effects on CNS, the cardiovascular system, respiratory and gastro-intestinal organ systems with no remarkable effects. Furthermore, ucb-107092-1 was tested negative in a complete package of genotoxicity studies. The 13-week continuous i.v. administration rat study was not considered valid due to high pre-terminal mortality and procedure-related complications. However, ucb-107092-1 was further tested in the 39-week monkey study. At the NOAEL of600 mg/kg/day for BRV, the mean male and female monkey plasma exposure (AUC_{0-24}) to ucb-107092-1 was 31.9 µg·h/mL, approximately similar to that observed in severe renally impaired subjects (35.8 µg·h/mL). In the rat embryo-foetal development study, no effects were seen on any of the standard parameters studied and the NOAEL for maternal and embryo/fetal developmental toxicity was set to 1000 mg/kg/day, corresponding to 22-fold the plasma AUC in severe renally impaired patients.

Impurities

The impurity ucb-34713 (diastereoisomer of BRV) was toxicologically qualified at the proposed specification limit. It tested negative *in vitro* in an Ames test and in a chromosomal aberration study. In the 13-week rat study, findings were limited to the dose of 200 mg/kg/day (i.e., clinical signs, increased body weight in females, increased cholesterol and triglycerides, centrilobular hepatocellular hypertrophy and occurrence of hyaline droplet nephropathy in males) with a NOAEL of 40 mg/kg/day. The findings were essentially similar to those observed with BRV. Ucb-34713 was also evaluated in two safety pharmacology studies in vitro (cardiac action potential in canine Purkinje fibres and hERG potassium channels) with no effects.

2.3.5. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) was carried out by the Applicant in accordance with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00 corr2). The *n*-octanol/water partition coefficient was estimated at log Kow=1.5 which is below the threshold of 4.5, thus not requiring further persistence, bioaccumulation and toxicity assessment. In the Phase I assessment, the predicted environmental concentration (PEC) in the surface water ($PEC_{SURFACEWATER}$) was calculated based on the default value for the marketing penetration factor (F_{pen}=0.1) at 1µg/L, which was above the action limit of 0.01µg/L, thus triggering Phase II environmental fate and effect analysis. Tier A analysis showed that BRV was not readily biodegradable. It is not expected to bioaccumulate in aquatic systems. BRV is degraded in water-sediment system to one extractable metabolite and several polar metabolites. Predicted no effect concentrations (PNEC) were calculated including ground and surface water, microorganisms and sediment. The resulting PEC:PNEC ratios indicated that BRV was unlikely to be a concern for the aquatic environment or for the sediment compartment. The PEC:PNEC ratio for microorganisms indicates that BRV is unlikely to be a concern in sewage treatment works.

In summary, the environmental risk assessment showed that BRV is unlikely to represent a risk to the environment under the proposed conditions of use. However, it was noted that several metabolites were detected at a concentration higher than 10% in the total water-sediment system at one or more sampling points of the degradation study. According to OECD308, the degradation products should be identified unless reasonably justified. As relevant samples had already been discarded at the time of this report, the CHMP recommended that the water-sediment study should be repeated in line with OECD308 and additional information on degradation metabolites M1, M2, M3, M4 and M5 should be submitted by the Applicant post-approval.

Table 1 - Summary of main ERA study results

Substance (INN / Invented Name): Brivaracetam					
CAS-number (if available): NA					
PBT screening		**Result**			**Conclusion**
Bioaccumulation potential log K_{ow}	OECD117	1.5 at pH=7			Potential PBT - No
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	logK_{ow}	N/A			not B
	BCF	N/A			not B
Persistence	DT50 or ready biodegradability	See OECD 301B in Phase II below			P
Toxicity	NOEC or CMR	See Phase II below			not T
PBT-statement :	The compound is not considered a PBT nor vPvB. However, a ready biodegradability test (see Phase II assessment) showed that it is not biodegradable, and hence should be considered persistent.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	1	µg/L			> 0.01 threshold - Yes
Other concerns (e.g. chemical class)	N/A	N/A			N/A
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	Koc = 20.9 mL/g			Max value: 10000
Ready Biodegradability Test	OECD 301B	<60% degradation over 10 days			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 14.1-15.1 days $DT_{50, sediment}$ = 14.3-21.2 days $DT_{50, whole\ system}$ = 16.5-18.8 days % shifting to sediment >10% after 14 days			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	100	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	10	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	mg/L	
Phase IIb Studies					
Sediment dwelling organism	OECD219	NOEC	100	mg/L	*Chironomus riparius*

2.3.6. Discussion on non-clinical aspects

The non-clinical documentation was comprehensive and the majority of the studies were conducted in accordance with relevant guidelines and GLP. The choice of non-clinical species was considered acceptable by the CHMP. Overall, the non-clinical part of the dossier was considered to be adequate.

Pharmacology

Pharmacology studies showed potent and significant seizure suppression by BRV in animal models of partial, drug-resistant and generalized epilepsy. The postulated primary mechanism of action through SV2A was reflected in a high and selective affinity for rat and human SV2A and occupancy of central SV2A in mice after systemic administration of anticonvulsant doses. The primary pharmacological anticonvulsant effect of BRV appeared to derive from the parent compound as only one minor metabolite revealed very weak anticonvulsant activity.

The Applicant claimed some pharmacological differences between BRV and levetiracetam (LEV), both in mechanism of action and in the effect in some in vivo animal models. Differences shown in non-clinical studies included higher selectivity and affinity for SV2A associated with a more potent and complete seizure suppression as well as no involvement of inhibition of high-voltage activated calcium currents and AMPA-gated currents for BRV. However, the extent of these differences, and if they would have any clinical relevance are difficult to assess based on non-clinical data alone. The CHMP was of the view that any claimed differences between BRV and LEV need to be demonstrated in the clinical setting.

The effects on central nervous, cardiovascular, respiratory, and gastrointestinal systems were investigated in a battery of standard safety pharmacology studies. The predominant effects were CNS-related and included transient CNS depression and decreased spontaneous locomotor activity. BRV was not considered to alter cognitive function. BRV was furthermore considered unlikely to affect cardiac conduction, depolarization and repolarization. The cardiovascular effects that were observed at doses ≥50 mg/kg in the dog, at plasma levels much higher than the c_{max} at the maximum recommended human dose of 200 mg/day, were not dose-related, inconsistent between sexes and were not observed in the repeated-dose toxicity studies. Effects on respiratory and gastrointestinal function were limited to a slight respiratory stimulant effect at doses above 100 mg/kg and delayed stomach emptying and slower gastrointestinal transit at 300 mg/kg. Safety pharmacology studies with metabolite ucb-107092-1 and impurity ucb 34713 showed no or very mild effects.

Pharmacokinetics

BRV is a high permeability drug with a rapid and unrestricted absorption across species with little food effect. In rat and dog, oral bioavailability was close to 100%, whereas Cynomolgus monkeys displayed an extensive first-pass effect. In all species, BRV was rapidly and evenly distributed in most tissues. BRV was mainly eliminated by oxidative metabolism, with only ca 5-10% of the dose eliminated in excreta as unchanged drug. The main biotransformation routes include the hydroxylation into ucb-100406-1, hydrolysis of the amide group into ucb 42145, and the combination of the 2 pathways into the hydroxy-acid metabolite ucb-107092-1.

Toxicology

One concern arising from the toxicology studies was the observation of hepatobiliary porphyrin deposits associated with adverse liver effects in dogs but also to a lesser degree seen in rats and potentially in other species, which has not been seen with the structurally related compound LEV. Porphyrins are intermediates in the synthesis of heme and can be deposited in the liver and bile canaliculi of rodents or dogs following administration of a xenobiotic (Greaves, 2007). Drug-induced protoporphyria in the dog is described in the literature (Greijdanus-van der Putten et al., Toxicol Pathol, 2005). Interference with or blocking of the activity of the enzyme ferrochelatase, which catalyses the last step in the formation of the heme moiety, is the most common mechanism of drug-induced protoporphyria (Greaves, 2007). Upon request by the CHMP, the Applicant provided a detailed discussion on the hepatobiliary pigment deposits in BRV-treated rats, dogs and monkeys. The Applicant provided a plausible scenario involving a cascade of events leading to porphyrin accumulation with hepatotoxic consequences only in dogs. The scenario was supported by internal investigative and mechanistic

data (Nicolas et al, 2014) for another compound, ucb-101747-1, which is also a SV2A ligand and has structural similarities to BRV and similar dog liver findings. For ucb-101747-1, it was shown that dog porphyria developed due to a number of combined events including a) bioactivation via oxidation of the butyramide side chain leading to the formation of a reactive metabolite which has structural similarities to known porphyrogenic agents, b) alkylation of CYPs by this reactive metabolite, resulting in N-alkylprotoporphyrin (N-alkylPP) formation, CYP inactivation and presumably in nonlinear pharmacokinetics, and c) induction of heme synthesis. The inhibition of ferrochelatase, the last enzyme in the heme biosynthetic pathway, by N-alkylPP and the CYP inactivation lead to accumulation of porphyrin precursors, namely protoporphyrin. This accumulation of protoporphyrin is also accelerated by the up-regulation of the heme biosynthetic pathway, through CYP induction.

Given the structural similarities, the Applicant claimed that the mechanisms outlined for ucb-101747-1 likely also applied to BRV. The dog is the only species where ucb-102993-1, a derivative resulting from the hydroxylation of the butyramide side-chain which can be regarded as a surrogate of the bioactivation of the butyramide side-chain, exists as a major circulating metabolite (≥10% total) on top of ucb-100406-1. All the other species (mice, rat and monkey) have only ucb-100406-1 as major circulating metabolite. Furthermore, the induction of CYP2B11 in BRV-treated dogs indicated a bell-shape dose-response curve, suggesting inactivation of CYP2B11 in dogs, not observed in rats or monkeys. After single intravenous dosing to dogs, the elimination of BRV from plasma did follow non-linear PK, whereas in rats, Cynomolgus monkeys and humans, BRV was eliminated according to a mono-exponential first-order kinetics. In *in vitro* assays, no N-alkylPP formation and protoporphyrin IX accumulation was detected with BRV or ucb-101747-1 although positive reference porphyrogenic agents were found to induce N-alkylPP formation when incubated with recombinant dog CYPs or to increase protoporphyrin IX levels when incubated with hepatocytes. The Applicant argued that the metabolic turnover of BRV and ucb-101747-1 *in vitro* was too small to allow their bioactivation into porphyrogenic metabolites. In humans, there is no evidence of a similar bioactivation as ucb-102993-1 was not detected in human plasma, urine or *in vitro* incubates and no non-linear PK was observed.

The CHMP therefore agreed with the Applicant that the dog liver porphyria is likely not relevant to humans. Taking into account that administration of BRV (up to 200 mg a day) to over 2300 human subjects did not reveal any concern in terms of hepatotoxicity based on liver function tests nor hepatic adverse events, the Applicant´s justification for not pursuing hepatic porphyrin in the clinical setting was considered acceptable by the CHMP.

However, the question remained why liver porphyria has not been observed in LEV non-clinical or clinical studies, although LEV contains the same structural feature as BRV, the butyramide side-chain, which is postulated to be key to the cascade of events leading to porphyrin pigment deposition in dogs. The Applicant explained the differences in metabolism of BRV and LEV whereby LEV is less prone to oxidative metabolism. The lack of butyramide side chain oxidation with LEV (which occurs with BRV) both in humans and across non-clinical species, including dogs, was considered the key factor explaining the lack of liver porphyria in dogs exposed to LEV.

Other liver findings in rats and monkeys included increased organ weight with hepatocyte hypertrophy and deposits of lipofuscin in the hepatocytes. Microsomal enzyme induction with associated hepatocellular hypertrophy, in the absence of hepatocellular damage, is considered to be an adaptive change in response to a xenobiotic (Greaves, Histopathology of Preclinical Toxicity Studies: Interpretation and Relevance in Drug Safety Evaluation, 3rd ed. Elsevier/Academic Press 2007). Lipofuscin is a natural pigment occurring in several organs and tissues and accumulates with age. Its accumulation in the liver of rodents, dogs and monkeys has been shown to be accelerated by drug treatment as a result of breakdown of smooth endoplasmic reticulum in secondary lysosomes (Greaves, 2007). Therefore, the Applicant concluded that the formation of lipofuscin

pigment was an adaptive response to the induction of drug metabolism enzymes and associated proliferation of smooth endoplasmic reticulum and not regarded as adverse, which was found acceptable by the CHMP.

There were also some thyroid findings in male rats and to a lesser degree in dogs including increased thyroid gland weight and hypertrophy. These findings were considered to represent a negative feedback response due to the adaptive liver changes and were not considered relevant to man. It is well documented that a close metabolic relationship exists between the liver and the thyroid gland via the pituitary-thyroid-liver axis and that the rat is a particularly sensitive species. Male rats are often more susceptible than females due to higher circulating thyroid-stimulating hormone levels. Regarding the 39-week repeat-dose study in monkeys, the NOAEL was set at 900 mg/kg/day by the Applicant. However, given the CNS clinical signs seen sporadically at 600 and more commonly at 900 mg/kg/day (prostrate, loss of balance, clumsy movements) it would be more appropriate to set the NOAEL at 600 mg/kg/day.

With regards to genotoxicity, based on the results obtained from both *in vitro* and *in vivo* assays, the CHMP considered that BRV does not carry a significant genotoxicity risk.

There were, however, some positive trends in the mouse and rat carcinogenicity studies. In mice, a male-specific increase in liver tumor incidence was observed. The increase was considered consistent with a non-genotoxic mechanism of induction, most likely caused by the hypertrophic changes in the liver and induction of hepatic drug metabolism enzymes. Rodent hepatic tumors caused by this mechanism are not considered relevant to humans. There was also a significant trend for both benign luteomas and benign Sertoli cell tumors in female mice. However, based on the lack of dose-exposure relationship and since the incidences were close and just outside the reported historical control range, the occurrence of benign luteoma were not considered related to BRV-treatment and most likely represent spontaneous tumors occurring in aged mice. With regards to ovarian tumors, a potential mechanism leading to the induction is hormonal dysregulation. However, there were no significant alterations in the female reproductive tract in rat carcinogenicity study and in all repeated dose toxicity and reproductive studies. Therefore, due to the lack of a consistent pattern of hormonal dysregulation and as BRV is devoid of genotoxic potential, the Sertoli cell tumours seen in 3 mice were considered likely spontaneous in nature and not related to BRV treatment.

In the rat carcinogenicity study, there was a significant trend for benign thymomas in female rats with an incidence of 22% at the highest dose tested (700 mg/kg/day, corresponding to 11-fold clinical exposure based on AUC), which was outside the historical control range. Benign thymoma is a very common spontaneous tumour in aging female Wistar rats. Potential mechanisms for the findings with BRV discussed by the Applicant include disruption of hormone homeostasis or immunosuppression, although there was no strong evidence for either. No toxicity to thymic epithelial cells was evident during the BRV non-clinical programme. There were no increased incidences of benign thymomas observed in the mouse carcinogenicity study. In the clinical safety data pool of Phase III studies (Pool S1), only one thymoma was observed in the placebo group while none occurred in the BRV treated groups. Taken together, the increased incidence of benign thymomas in female rats given 700 mg/kg/day likely represents an unusual incidence most likely spontaneous in nature and was not considered relevant to man.

There was also a positive trend for thyroid gland follicular adenomas and carcinomas in rats. Although the incidences among the BRV treated animals fell within the historical control range, the CHMP was of the view that a relationship to BRV could not be excluded as increased incidence rates were observed in BRV-treated animals versus the study control animals, which was most prominent for thyroid adenomas and especially in males given 230, 450, or 700 mg/kg/day. However, rat thyroid tumors likely represent an adaptive response to the enhanced metabolism and clearance of thyroxine due to liver enzyme induction and were not considered relevant to man.

With regards to the reproductive and developmental toxicity studies, the CHMP considered that the doses chosen for the main studies were appropriate. In the rabbit embryofoetal development study, skeletal variations were observed. However, literature data and re-elaboration of study data confirmed that the minor skeletal abnormalities in presence of reduced weight of foetuses are mainly due to slight developmental delay and not due to a direct BRV effect. Apart from the skeletal variations as well as increased post-implantation loss in rabbits due to maternal toxicity, the reproductive toxicity program did not reveal any serious toxicity with regard to fertility, early and late embryo-fetal development, prenatal and postnatal development and development in juvenile animals. Findings in the liver and kidney in juvenile rats as well as findings in the liver, thyroid and thymus of juvenile dogs were also seen in repeat-dose toxicity studies with adult rats and dogs, respectively. Based on the calculated NOAELs and exposure margins, the juvenile rat appeared to be equally or slightly more sensitive than the adult animal with regards to growth and development, while juvenile and adult dogs seemed equally sensitive to BRV treatment.

Local tolerability was generally good with haemolytic effects only observed at concentrations beyond the intended clinical i.v. formulation. BRV did not absorb UV-B, UV-A, or visible radiation in the range from 290 to 700 nm and is therefore not expected to possess any photosensitizing properties.

The lack of immunotoxicity studies was considered acceptable by the CHMP. Evaluation of the standard parameters in repeat-dose toxicity studies did not identify any significant immunotoxicity concerns.

Based on the results of the dependence studies performed the abuse liability potential of BRV appeared to be low. The Applicant argued that the observed partial generalization of the control substance chlordiazepoxide in one of the studies most likely was a result of direct drug-induced changes in motor function or muscle relaxant properties, common effects of both BRV and chlordiazepoxide, which was agreed by the CHMP to be a likely explanation of the results.

Relevant metabolites including ucb-107092-1 as well as the impurity ucb-34713, a diastereoisomer of BRV, were considered adequately qualified from a non-clinical perspective.

ERA

BRV is not readily biodegradable and is not expected to bioaccumulate in aquatic systems. Furthermore, BRV does not persist in water-sediment systems, and is degraded to one extractable metabolite and several polar metabolites. Overall, the CHMP concluded that BRV is unlikely to represent a risk to the environment under the proposed conditions of use. However, the CHMP recommended that the water sediment degradation study be repeated and additional information on the identity of metabolites appearing at a concentration higher than 10% in the total water-sediment system at one or more sampling points be submitted post-authorization.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical development program for Briviact was comprehensive and broadly in line with relevant guidelines and GLP. No major concern arose from the data that would be expected to be of clinical relevance. However, while Briviact was considered unlikely to represent a risk to the environment under the proposed conditions of use, the CHMP recommended that the water sediment degradation study be repeated post-authorization to provide additional information on the identity of relevant metabolites.

Overall, the CHMP concluded that the non-clinical data were adequate to support the Application for Briviact tablets, oral solution and solution for injection/infusion as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy. The SmPC

correctly reflects the results from the non-clinical studies and provides relevant information to prescribers.

2.4. Clinical aspects

2.4.1. Introduction

In support of this application, the applicant provided the results of the clinical development program comprising clinical pharmacology studies aiming at investigating bioequivalence, bioavailability, tolerability, PK, and PD of BRV as well as Phase II/III epilepsy studies to explore the efficacy, safety, and tolerability of BRV. An overview of the clinical studies is provided below.

A tabular overview of the main phase II/III clinical trials provided in support of this application is provided in section 2.5. of this report (Table 2 and Table 3).

Good Clinical Practice (GCP)

According to the Applicant, the clinical trials were performed in accordance with GCP.

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 clinical pharmacology program aimed at describing the absorption and disposition of BRV, identifying sub-groups of patients in which exposure might be altered and revealing potential interactions with food and with other medical products. Twenty-seven (27) Phase I trials have been completed to investigate the clinical pharmacology of BRV. Furthermore, population pharmacokinetic analyses, PK/PD and statistical meta-analyses have been performed using data pooled from the Phase II and III studies in POS patients (N01114, N01193, N01252, N01253, and N01358). In addition, about 20 in vitro studies using human biomaterial have been performed to investigate the characteristics of BRV.

For the quantification of BRV, ucb 42145 (carboxylic acid metabolite), ucb-107092-1 (hydroxyacid metabolite) and ucb-100406-1 (hydroxymetabolite) in human samples, liquid chromatography coupled to ESI-MS or ESI-MS/MS was used. Overall, the bioanalysis was GLP-compliant and validations of methods were satisfactory. Standard non-compartmental analysis was used for analysis of PK parameters in phase I studies.

The population PK model used plasma concentration data for BRV from the completed fixed-dose Phase II studies N01114 and N01193 as well as the Phase III studies N01252, N01253, and N01358. Overall, the model was based on 1248 patients on active treatment and 5820 BRV concentration records. Using non-linear mixed effects modeling (NONMEM®) software, a model consisting of first order absorption, single compartment distribution, and first order elimination components was fit to the data. The resulting model provided an adequate description of the sparse data, as was confirmed based on goodness of fit and visual predictive checks..

Absorption

BRV was rapidly absorbed, with a median t_{max} of 1 h (range 0.5-3 h) following a single dose of 100 mg of the commercial tablet in fasting healthy subjects. *In vitro* studies showed that BRV is highly permeable. BRV was furthermore shown to have a high solubility and to be completely absorbed after oral administration of a 10 mg

or a 100 mg tablet with an absolute bioavailability of approximately 100%. Complete and rapid absorption was also observed after administration of [^{14}C]-BRV in the radioactive mass balance study. According to *in vitro* studies, BRV is a not a substrate of P-glycoprotein (P-gp) transport protein.

The intra- and inter-subject variability was found to be low in healthy volunteers. Both intra- and inter-subject variability was generally below 20% and 35%, respectively, for c_{max} and AUC.

Finally, the influence of food on BRV PK was evaluated in a two food interaction studies. A high fat meal delayed t_{max} (median 3 h) and reduced c_{max} 30-40% while AUC was unchanged.

Distribution

The plasma protein binding was found to be low (~20%) in both *in vitro* and *ex-vivo* human studies and independent of concentration. The blood-to-plasma ratio ranged between 0.83 - 0.90. The volume of distribution was determined at 0.55 L/kg after i.v. administration and was similar after oral and i.v. administration.

Elimination

Plasma concentrations of BRV decline mono-exponentially after oral or i.v. administration. Based on the population PK analysis, clearance (CL) and half-life in patients with POS were determined to be approximately 3.6 L/h and 9 h, respectively. Based on these results, clearance in a typical patient with POS and without concomitant enzyme inducing AEDs was similar to CL in healthy volunteers. In patients with concomitant enzyme inducing AEDs (carbamazepine, phenytoin, and phenobarbital) the CL was 24-35% higher compared to healthy volunteers, leading to an approximate 20-25% decrease in exposure to BRV. The inter-individual variation (%CV) was 25% for CL and 30.5% for volume. The residual error was 21% which suggests a low intra-individual variation.

Metabolism

In a radioactive mass balance study in healthy male subjects, parent drug represented 83 to 99% of the circulating radioactivity in plasma up to 24h after administration. The metabolites ucb-100406-1 and ucb-42145 were also identified as circulating species, representing 7 and 5% of the radioactivity, respectively. No unique human metabolites were identified.

In vivo studies furthermore showed that BRV is extensively biotransformed before being excreted renally. The major metabolic pathway for the elimination of BRV is acetamide hydrolysis to the carboxylic acid metabolite ucb 42145 (ca. 60% of BRV elimination) and in a secondary step a hydroxylation of the propyl chain forming ucb 107092-1. Another pathway for the elimination of BRV is hydroxylation of the propyl chain as the first step forming ucb -100406-1 (ca. 30% of BRV elimination) to be further hydrolysed to the carboxylic acid ucb 107092-1 in a second step (Figure 2). All three major metabolites are pharmacologically inactive.

The hydroxylation of BRV to form ucb -100406-1 is primarily mediated by CYP2C19 as demonstrated in a pharmacogenetic study in CYP2C19 poor and extensive metabolisers. There was a 10-fold decrease in formation of ucb -100406-1 in poor metabolisers compared to extensive metabolisers, while the exposure to BRV was increased by 42% in poor metabolisers. The increase of exposure of metabolite ucb-100406-1 was moderate at ~20% when co-administered with carbamazepine and two to three-fold when co-administered with rifampicin).

The metabolite ucb 42145 was formed after incubation of BRV in whole blood and in liver homogenate. The enzyme found to mediate this reaction was amidase (E.C.3.5.1.4). *In vitro* data with microsomes indicated that CYP2C9 is primarily involved in the hydroxylation of ucb 42145 to form ucb 107092-1. In an *in vivo* study with the CYP2C8/CYP2C9 inhibitor (gemfibrozil) the formation of ucb 107092-1 decreased by 33% (AUC), while BRV

exposure was unaffected.

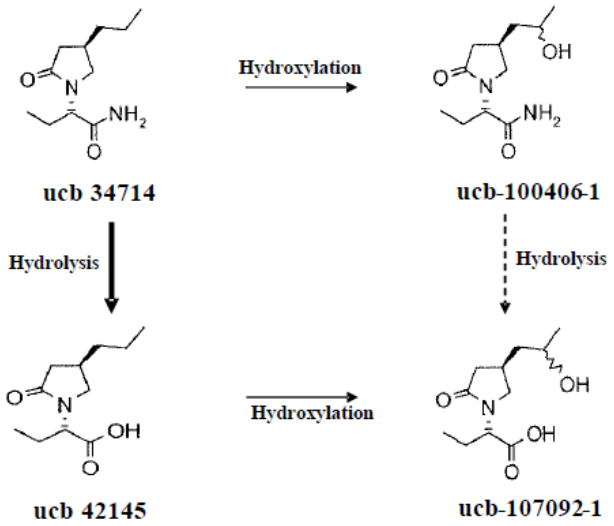


Figure 1 - Main metabolic pathways for BRV (ucb 34714) in humans

Excretion

In the human mass balance study the total mean recovery of the administered radioactive dose was 98%, with relative recovery of <1% in faeces and 97% in urine. Similar results were also observed in other clinical pharmacology studies. Overall, ucb 42145 accounted for 34% of the excreted dose, while the two other metabolites ucb -100406-1 and ucb 107092-1 accounted for 16% and 15% of the dose, respectively. The parent compound (unchanged BRV) accounted for 9% of the excreted dose. All other identified metabolites were minor (n=11, each accounting for 0.03 - 3.8%). The plasma half-lives of total radioactivity and parent compound were similar 8-9 h.

Dose proportionality and time dependencies

The exposure of BRV was found to increase approximately in proportion to the dose after single dose administration over a range of 10 to 1400 mg.

No time dependence of the BRV exposure was observed at doses of 100 and 200 mg bid. At the highest dose tested, 400 mg bid, there was a 14% increase in the apparent total body clearance and a decrease of 22% of evening trough levels when comparing Day 14 and Day 1. This indicate a slight auto induction at a supra therapeutic dose.

Bioequivalence

Four clinical pharmacology studies were conducted to compare the PK of different BRV formulations. The PK of BRV tablet formulation F4, which has been used in the pivotal clinical trials (see section 2.5.2.), was compared to the commercial tablets and bioequivalence of the 10 mg, 75 mg and 100 mg commercial tablet formulation with the 50 mg F4 tablet was shown. Cross comparison of the three formulations (tablet, oral solution and solution for injection/infusion) did not indicate any difference in systemic exposure, except for c_{max} after i.v. administration, which was found to be 20-30% higher compared to oral formulation after single administration.

Special populations

In patients with severe renal impairment, following administration of a single dose of 200 mg BRV, the AUC for ucb 42145, ucb-100406-1 and ucb-107092-1 was 3-, 4- and 21.5-fold, respectively, compared to healthy subjects, while the AUC of BRV remained relatively unchanged (small increase of 21%).

In patients with hepatic impairment the exposure to BRV increased 50-60%, independent of Child-Pugh score. BRV exposures in patients with Child Pugh A, B and C (mild, moderate, and severe hepatic impairment, respectively) were 50% (90% CI 1.17; 1.93), 57% (90% CI 124; 2.01) and 59% (90% CI 1.24; 2.02), respectively. The exposure to metabolites ucb-100406-1 and ucb-107092-1 were generally in the same range or lower in hepatically impaired subjects compared to healthy subjects, while the exposure of ucb 42145 was slightly increased.

The influence of CYP2C19 polymorphism on the BRV exposure was investigated in healthy Japanese volunteers (n=36) including 10 subjects who were homozygous extensive metabolisers, 17 heterozygous extensive metabolisers and 9 poor metabolisers. BRV $AUC_{(0-t)}$ increased by approximately 40% (90% CI 1.29; 1.50) in poor metabolisers compared to homozygous extensive metabolisers, while the hydroxy metabolite (ucb-100406-1) decreased more than 10-fold in poor metabolisers. In heterozygous extensive metabolisers BRV $AUC_{(0-t)}$ was increased by approximately 20% compared to homozygous extensive metabolisers. The carboxylic acid metabolite (ucb-42145) behaved similar to the parent compound, while for the hydroxyacid metabolite (ucb-107092-1) the AUCs were slightly modified but not consistently among the 3 genotypes.

Gender, race, or age (≥16-80 years) had no clinically relevant effect on the PK of BRV in adults in pharmacology studies. This was supported by the results from population PK modeling.

In the population PK model, body weight was found to be a significant covariate of BRV clearance. Across a weight range from 46 to 115 kg, BRV population average CL for a patient without additional covariate effects was estimated to change from 2.82 to 4.74 mL/min (a 68% increase leading to an approximately 40% decrease in exposure).

The applicant also provided the results an open-label, single-arm, multicentre study evaluating the PK, safety, and efficacy of the oral solution formulation of BRV in paediatric subjects with epilepsy ≥1 month and <16 years of age, which was included in the PIP. Population PK simulations in children (≥1 m to <16 years) suggest that an age-independent dose of 2.0 or 2.5 mg/kg bid (depending on co-treatment) results in exposures similar to those in adult patients given 100 mg bid. The model furthermore indicated that lean body weight was a better predictor of clearance compared to body weight in this population.

Pharmacokinetic interaction studies

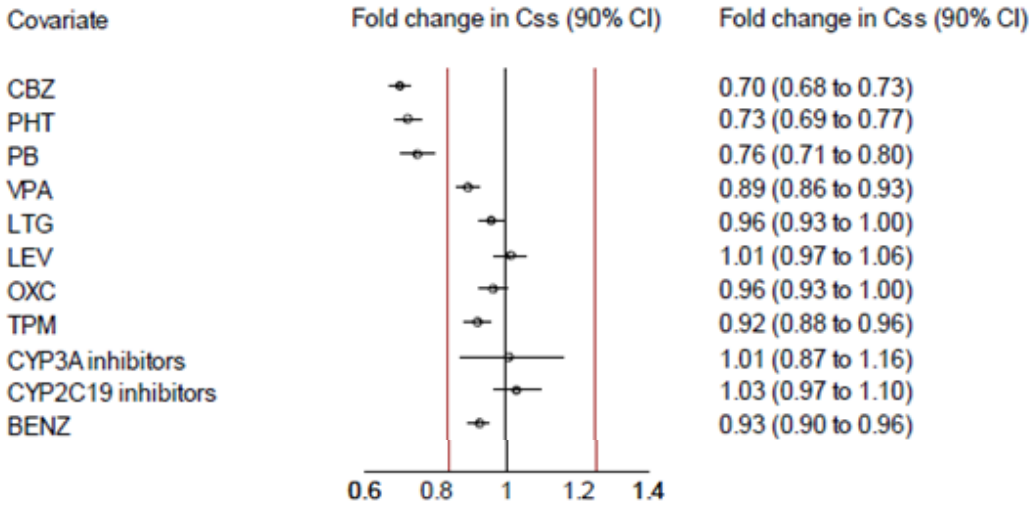
Effect of other medical products on the PK of BRV

In vitro data indicate that BRV is a substrate of amidase which mediates the formation of the major excretory metabolite ucb 42145. As discussed under elimination, CYP2C19 and CYP2C9 are also involved, but not as major pathways for the elimination of BRV and thus no clinically relevant interaction with the corresponding CYP inhibitors was expected.

BRV did not show substrate activity against P-glycoprotein (P-gp), multidrug resistance protein (MRP) 1, and MRP2 *in vitro*. BRV is highly permeable and has shown a very low liver-to-plasma ratio in distribution studies in animals. Based on this, BRV is not likely to be a substrate of organic anion transporters (OAT) P1B1 or OATP1B3. In addition, no increase of BRV exposure was observed in a clinical drug-drug interaction (DDI) study with gemfibrozil (CYP2C8, CYP2C9 and OATP1B1 inhibitor).

Three clinical DDI studies have been performed to investigate the effect of ethanol, rifampicin and carbamazepine (CBZ) on exposure of BRV. There was no PK interaction when oral BRV was co-medicated with i.v. ethanol. Concomitant enzyme inducers like rifampicin and CBZ decreased BRV exposure. . Although, the duration of the rifampicin dosing was likely too short (5 days at 600 mg) to obtain the full enzyme induction effect, the plasma clearance of BRV was increased 1.8-fold, leading to a 45% decrease of AUC (point estimate 0.55; 95% CI 0.53-0.58) and c_{max} by 11% (point estimate 0.89; 95% CI 0.83-0.95). When co-medicated with CBZ (up titrated to 300 mg bid for >14 days) in healthy volunteers, BRV clearance was increased 1.4-fold and BRV AUC decreased by 29% (point estimate 0.71; 90% CI 0.67-0.75) and c_{max} by 13% (point estimate 0.87; 90% CI 0.74-1.02).

The effect of concomitant medication was also tested as co-variates in the population PK analysis (Figure 2). The result is in good agreement with the DDI study for CBZ and the analysis is likely to describe an accurate effect for other enzyme inducers like phenytoin (PHT) and phenobarbital. However, estimating an effect of CYP inhibitors was more difficult since the relative timing of dosing of the compounds is often important. The data from the study in CYP2C19 poor metabolisers showed an increase of BRV exposure of approximately 40%. A similar change would be expected with a strong CYP2C19 inhibitor, but was not captured in the population PK covariate analysis although strong CYP2C19 inhibitors like fluvoxamine were included as co-medication. Consequently no firm conclusions regarding interaction with CYP inhibitors should be drawn from these data.



Red lines indicate the fold change associated with 20% change in CL

Figure 2 - Forest plot of covariate effects (concomitant medication) on fold change in BRV steady state plasma concentration with 90% CI

Effect of BRV on the PK of other medical products

The potential of BRV to inhibit and/or induce CYPs has been investigated *in vitro* with relevant enzymes. In addition, *in vivo* DDI studies with midazolam (CYP3A4 probe) and medical products relevant as common concomitant medications, including carbamazepine, lamotrigine, topiramate, phenytoin and oral contraceptives, were performed. A retrospective meta-analysis of interactions with AEDs from phase II and III study data was also performed.

When tested against CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/5, no signal of *in vitro* CYP inhibition by BRV was observed in the concentration range studied (up to 650 µM), except for CYP2C19 where a competitive

inhibition with a Ki of 314 µM was reported. No time dependent CYP inhibition has been found. CYP induction was observed *in vitro* for CYP3A4 and CYP2B6. CYP3A4 induction was investigated *in vivo* using midazolam as a marker probe. No effect on midazolam was observed in this study, however, the BRV dose was slightly low (75 mg bid) and the duration short (5 days). At doses of 50 or 150 mg/day midazolam AUC was not affected but c_{max} was slightly increased (18% and 49%, respectively).

No or only moderate inhibition by BRV of P-gp, breast cancer resistance protein (BCRP), MRP2, multidrug and toxin extrusion transporter MATE-1 and MATE-K, OATP1B1, OATP1B3, OAT1, OCT1, OCT2 and bile salt export pump (BSEP) was observed in the concentration range studied (up to 6500 µM). However, inhibition of substrates of uptake transporter OAT3 was caused by BRV with an IC_{50} of 540 µM. *In vitro*, BRV was furthermore found to be an epoxide hydroxylase inhibitor (IC_{50}=108 µM in microsomes).

Two DDI studies were performed in young fertile, non-smoking, and non-obese female subjects taking a single type of oral contraceptives containing 30µg ethinylestradiol and 150 µg levonorgestrel. At the BRV 50 mg bid dose level no clinically relevant change in ethinylestradiol and levonorgestrel levels was found, but at the supra-therapeutic dose of 200 mg bid there was a slight decrease in ethinylestradiol and levonorgestrel exposure (point estimates c_{max} 10-15% and $AUC_{(0-24)}$ 22-27% decrease). There was no change in the mean profiles of the PD markers estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone and sex hormone binding globulin with and without BRV. No ovulation occurred during the study.

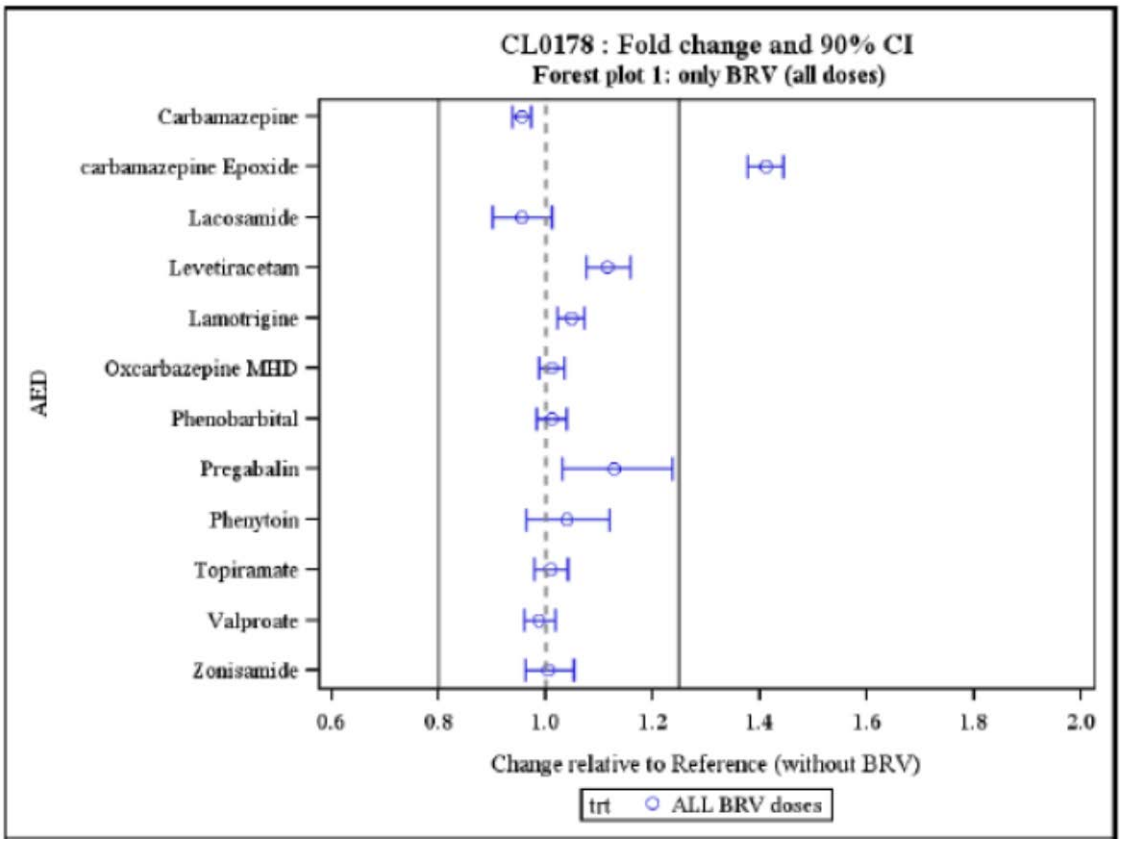
In the DDI studies performed, BRV had no effect on the exposure of lamotrigine (LTG) or topiramate (TPM).

In a DDI study with PHT, epilepsy patients stable on PHT monotherapy for at least 3 months and having plasma concentrations of PHT within the target range (7 – 23 µg/mL) were included. BRV was up-titrated to 200 mg bid (400 mg/day) during the maintenance period (Day 4 - 24); the mean BRV trough plasma concentrations were 1.8 µg/mL (8.5 µM). At the end of the maintenance period, the geometric means of c_{max} and AUC_{τ} of PHT were increased by approximately 20% compared to baseline (point estimates c_{max} 1.20; 95% CI 1.03-1.40 and AUC_{τ} 1.20; 95% CI 1.02-1.42). PHT is a CYP2C19 substrate and a signal of CYP2C19 inhibition by BRV has been observed *in vitro* and this may be the mechanism for the observed interaction. In the retrospective meta-analysis of PK drug-drug interactions (see below) also a slight increase of PHT plasma concentration (12-15%) from baseline was found when co-medicated with BRV.

Two DDI studies were performed with CBZ, one in healthy volunteers and one in epilepsy patients stable on CBZ (≥600 mg daily dose). In the healthy volunteer study BRV at 200 mg bid dosing did not alter CBZ exposure (AUC_{τ} and c_{max}) to any relevant extent (ca. 10% decrease), but resulted in a 2.6-fold increase of both AUC_{τ} and c_{max} for CBZ-epoxide. In the study with patients, BRV was up-titrated from 50 mg bid (Day 1–7) to 100 mg bid (Day 8-14) and 200 mg bid (Day 15–21). A reduction in trough concentration of CBZ (17%) and CBZ-diol (27%) and an increase of CBZ-epoxide (2.2-fold) was found after 200 mg bid BRV dosing. The increase of CBZ clearance at supra therapeutic dose level of BRV (200 mg bid) may be caused by the slight enzyme inducing properties of BRV as observed *in vitro* and *in vivo* (see also effect on oral contraceptives above). At the therapeutic dose levels, up to 100 mg bid, BRV did not have an effect on CBZ exposure. However, the trough concentration of CBZ-epoxide was found to be elevated by 57% and 98% at 50 mg bid and 100 mg bid, respectively. This is likely to be due to the inhibitory effect of BRV on epoxide hydrolase. A BRV dose related effect on the plasma concentration of CBZ-epoxide was also found in the retrospective PK drug-drug interaction meta-analysis (see below). At 50 mg/day, 100 mg/day and 200 mg/day, the mean increase was 37%, 62% and 98%, respectively.

The PK drug-drug interaction meta-analysis was performed using data from the 5 clinical phase II and III studies with POS patients taking one or two AEDs (n=1771). A clinically significant AED concentration change was

excluded if both limits of 90% CI of the geometric least square (LS) means ratio were within the predefined 0.8-1.25 boundaries. About 70% of the patients in the meta-analysis received BRV (5, 20, 50, 100, 150 or 200 mg/day) and 30% received placebo. CBZ (41% of subjects) was the most common AED co-medication, followed by LTG (25%), valproate (VPA) (19%), oxcarbazepine (15%) and TPM (13%), LEV (11%), PHT (10%), phenobarbital (6%), lacosamide (6%), pregabalin (4%), zonisamide (5%) and primidone (1%). For some AEDs, such as primidone and benzodiazepines, there was too limited data for assessing possible interactions. The influence of BRV on the AED steady state plasma concentrations is shown in Figure 4. The plot provides an overview of the effect of all doses combined and thus, the effect may be underestimated, as the highest BRV dose is more likely to result in a larger interaction. However, when analysing the individual BRV dose levels, the meta-analysis seemed to be in good agreement with data on available AEDs from DDI studies performed with single drugs. The only obvious dose dependent effect of BRV in the meta-analysis was for the CBZ-epoxide, which was found to be outside the 90% CI 0.8-1.25 boundaries.



AED=antiepileptic drug; BRV=BRV; CI=confidence interval; MHD=mono-hydroxy derivative; trt=treatment

Figure 3 - Forest plot of fold change in plasma concentrations at steady state by AED (BRV all doses combined from 5mg/day to 200 mg/day)

Pharmacokinetics using human biomaterials

Relevant results from in vitro studies using human biomaterial are summarised in the relevant section(s) above.

2.4.3. Pharmacodynamics

Mechanism of action

BRV has been shown to display high and selective affinity for synaptic vesicle protein 2A in the brain, the same binding site as targeted by the structurally related antiepileptic compound LEV. Binding to SV2A is believed to be the primary mechanism for BRV anticonvulsant activity. SV2A is a membrane glycoprotein localised in both neurons and endocrine cells. It is ubiquitously expressed in presynaptic terminals and is believed to be involved in normal synaptic vesicle function. Although the exact role is still to be elucidated, there is some evidence suggesting an involvement in neurotransmitter release through modulation of exocytosis.

Primary and Secondary pharmacology

Several studies were conducted to investigate the PD of BRV, including a number of clinical pharmacology studies. In a PD study exploring the electroencephalographic (EEG) response to BRV in subjects with photosensitive epilepsy, BRV was shown to suppress the photoparoxysmal EEG response at the tested doses (BRV 10 mg to 80 mg), with BRV 80 mg being the most effective dose. The study thus provided first evidence of dose-response in epilepsy and information for dose selection in the initial Phase II studies.

The studies also included exploratory psychometric and neurological tests. The results of these studies indicated a dose-related increase of sedation and a decrease of alertness after administration of BRV. The effect of BRV on cognitive performance was only evaluated at the very low dose of 10 mg, which was too low to provide useful information on the possible cognitive impairment related to therapeutic doses.

Since BRV and LEV both bind to the same target structure, SV2A, there is a PD interaction between these drugs. The results from the pivotal clinical studies N01252 and N01253 (see section 2.5.2.) indicated that subjects treated with concomitant LEV at baseline did not show any additional efficacy benefit from the addition of BRV. As a consequence, concomitant LEV use was not allowed in study N01358. With regards to PD interactions, a study with ethanol showed that BRV increased the effects of ethanol on psychomotor function, attention and memory in the absence of a relevant PK interaction, generally in an additive manner.

To investigate if BRV had an effect on cardiac repolarisation, a thorough QT study in healthy subjects was conducted. There was no effect of either therapeutic (BRV 150 mg/day) or supra-therapeutic (BRV 800 mg/day) doses on cardiac repolarisation, as measured by QT_c prolongation.

The effect of BRV on pain and essential tremor was investigated in two studies, but the development of BRV for these indications were halted.

Relationship between plasma concentration and effect

A population exposure-response model was developed to describe the correlation between changes in seizure rate and average BRV concentration during treatment (c_{av}) using the data from the Phase II and III studies in POS patients (N01114, N01193, N01252, N01253, and N01358). The relationship between c_{av} and daily seizure rate was best described by an E_{max} model. A mixture model with two populations was applied, separating subjects into a responder population and a placebo-like population. Visual predictive checks showed that the model provided an adequate description of the data.

The results suggested that in the overall population, maximum response is reached by 50 mg/day. However, the results from the mixture model indicated that patients in the responder subpopulation might benefit from a higher dose, since a further increase in response was predicted to occur beyond 50 mg/day. The exposure response correlation furthermore suggested that the median c_{av} for patients receiving 100 mg/day resulted in

effects close to E_{max}, but increased efficacy was observed in the model up to 200 mg/day.

Covariate analysis indicated that LEV co-administration effectively reduced the fraction of subjects in the responder population to close to zero. It also indicated that subjects with high baseline seizure rates had a lower probability of being a responder. The analysis did not identify any PD interactions with other chronically prescribed co-medications (CBZ, PHT, phenobarbital or primidone, VPA, LTG, oxcarbazepine, TPM, GABAergic drugs, benzodiazepines, and traditional sodium channel blockers).

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology of BRV has been investigated in a comprehensive set of studies as well as related meta-analyses and population PK and PK/PD models involving both healthy volunteers and patients with POS.

In PK studies, BRV was found to be highly permeable in in vitro studies and also has a high solubility. After oral administration, BRV is rapidly and completely absorbed from the gastrointestinal tract and the intra- and inter-subject variability was low. The influence of food on rate and extent of BRV exposure was limited and considered not to be clinically relevant, thus enabling intake with and without food. Furthermore, studies showed bioequivalence of the tablet formulation used during clinical development and the commercial formulation as well as between different formulations and relevant strengths (tablets, oral solution and solution for injection/infusion). The only exception was a small difference in c_{max} for the 10 mg/ml solution for injection/infusion when compared to BRV 100 mg and 50 mg tablets in one study, which was not considered clinically relevant by the CHMP in light of the clinical safety data (see section 2.6.).

BRV is extensively biotransformed before being excreted renally. Non-renal (hepatic) clearance accounts for around 90% of the plasma clearance. Metabolism of BRV involves both hydrolysis and hydroxylation, whereby the main metabolic pathway consists of hydrolysis to the carboxylic acid metabolite ucb 42145, which is mediated by the enzyme amidase. All major metabolites are pharmacologically inactive.

No clinically meaningful time dependency of BRV exposure was found and exposure was dose proportional.

Gender, race, or age (≥16-80 years) had no clinically relevant effect on the PK of BRV. However, in subjects with severe renal impairment a very large increase of exposure to the metabolites (up to 21-fold after a single dose) was observed. All metabolites have been adequately characterised in non-clinical toxicological studies including at the exposure levels estimated after multiple doses in severe renally impaired patients and assuming linear PK of the metabolites. The data shows the importance of renal elimination for the metabolites. However, as the metabolites are not pharmacologically active, no dose adjustment is needed in patients with impaired renal function. Furthermore, exposure to BRV increased by 40-60% both in subjects with hepatic impairment (independent of severity grade) and poor CYP2C19 metabolisers. As a result of this finding, a maximum dose of 150 mg/day is recommended in patients with hepatic impairment, whereas no dose adjustment is needed in poor metabolizers as the uncertainty of exposure was less compared to the fragile hepatically impaired population as reflected by the CI intervals. Finally, a body weight effect was found in the population PK analyses whereby increasing weight led to increased BRV clearance. However, the extent of the BRV exposure increase was not considered to be of clinical relevance.

With regards to drug-drug interactions, there was no clinical evidence in the scientific literature at the time of this report of PK interactions on the main metabolic pathway (hydrolysis), which is mediated by amidase and CYP-independent. Given the clinical experience with LEV, which shares the hydrolytic pathway with BRV and since amidase is ubiquitously distributed in tissue, the risk for interactions was considered to be likely low. The CHMP noted the applicant's plan to further investigate such risk in physiologically-based PK modeling. CYP2C19

is also involved in the BRV metabolism (hydroxylation), but not as a major pathway for the elimination and thus no clinically relevant interaction was expected. Co-administration with enzyme-inducers reduced BRV exposure as shown both in pharmacology studies and the population PK model. While no dose adjustment is needed with enzyme-inducing AEDs such as carbamazepine, phenobarbital or phenytoin, prescribers should consider adjusting the BRV dose in patients starting or ending treatment with rifampicin.

No signal of *in vitro* CYP inhibition/induction by BRV was observed, except for an inhibition of CYP2C19 as well as an induction of CYP3A4 and CYP2B6, whereby the effect on CYP3A4 was not confirmed *in vivo*. No reliable *in vivo* data were available for CYP2B6, however, since there are only few clinically relevant interactions known for CYP2B6, the CHMP was of the view that no further studies were needed. Based on the *in vitro* signal, induction of CYP2B6 could not be excluded and the CHMP considered that relevant information should be presented in the SmPC. Competitive inhibition of CYP2C19 was observed with an IC_{50} of 909 µM a Ki of 314 µM. Furthermore, when co-administered with PHT, a slight numerical increase of PHT exposure was observed and CYP2C19 inhibition might explain this effect of BRV. In the course of this procedure, the applicant performed physiologically based PK (PBPK) modelling, which predicted only a 4% increase of the CYP2C19 substrate omeprazole by BRV 100 mg bid. However, the CHMP considered that, in order to draw any conclusions, further support was needed for the predictive performance of the PBPK modelling when applied for simulating CYPC19 mediated interactions. At the time of this report a potential risk of increased exposure to CYP2C19 substrates upon co-administration with BRV could not be excluded and relevant information should be reflected in the SmPC until further information is available.

In vitro data furthermore indicated that there was low risk of clinically relevant inhibition by BRV of the transporters P-gp, BCRP, BSEP, MRP2, MATE-1, MATE-K, OATP1B1, OATP1B3, OAT1, OCT1 and OCT2. However, a risk of *in vivo* inhibition of uptake transporter OAT3 by BRV could not be excluded and the CHMP therefore considered that this information should be added to the SmPC, including the potential of BRV to increase plasma concentrations of medicinal products transported by OAT3.

A BRV dose related effect on the plasma concentration of CBZ-epoxide was found in interaction studies as well as a retrospective PK drug-drug interaction meta-analysis. This is likely caused by an inhibitory effect of BRV on epoxide hydrolase. While no apparent safety concern arose from the available clinical data, interaction with other medical products metabolised via epoxide hydrolase could not be excluded. No other effect on AEDs was observed, but for some AEDs there was too limited data to reliably assess the interaction potential.

From the available studies there was no indication that BRV impaired contraceptive efficacy of low-dose combination oral contraceptives. Alcohol did not affect BRV PK, but BRV increased the CNS effect of alcohol. Therefore, intake of BRV with alcohol is not recommended.

Finally, first evidence for dose-response response relationship in epilepsy was provided in PD studies as well as a population exposure-response model. As could be expected, there was a PD interaction between BRV and LEV, with both compounds binding to the same site, SV2A. Patients already treated with LEV in the phase III studies N01252 and N01253 had no additional benefit from BRV. This was confirmed in the population exposure-response model, which did not reveal any other PD interaction with chronically prescribed co-medications.

2.4.5. Conclusions on clinical pharmacology

Overall, the CHMP was of the view that the available clinical pharmacology data were sufficient to support the Application for Briviact tablets, oral solution and solution for injection/infusion as adjunctive therapy in the

treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy. The clinical pharmacology properties of BRV have been adequately characterized and relevant information was reflected in the SmPC.

2.5. Clinical efficacy

The clinical efficacy of BRV was investigated in 2 phase II dose finding studies (N01114 and N01193) and 6 phase III trials of which 3 were considered pivotal for this application (N01252, N01253, and N01358). Patients who completed the pivotal studies could enrol in long-term follow up (LTFU) studies, which were on-going at the time of this report (N01125, N01199, and N01379).

Additional supportive data were available from 3 phase III trials (N01254, N01258 and N01395), primarily aiming at evaluating the safety of BRV. Studies N01258 and N01395 are discussed in section 2.6. (clinical safety). Supportive efficacy data were available from study N01125.

BRV was also studied as conversion to monotherapy in 2 Phase III studies (N01276 and N01306). These studies were stopped prematurely after an interim analysis and unblinded review of study data revealed the study was unlikely to attain a positive outcome for the efficacy analysis. No safety concerns were detected. At the time of this report, some of the patients were still participating in the related LTFU study N01315.

2.5.1. Dose response study(ies)

Two dose-ranging studies, N01114 and N01193, were conducted (Table 1). The selection of the doses in these studies was based on the pharmacologically active dose range predicted from animal models of epilepsy, on toxicological findings, and on the results of a PD study exploring the EEG response to BRV in subjects with photosensitive epilepsy.

Table 2 – Overview of the dose-ranging Phase II studies N01114 and N01193

Study number (design)	**No of subjects receiving BRV**	**No of subjects receiving PBO**	**Maximum duration of treatment**
N01114 (randomized, double-blind, PBO-controlled, dose-ranging)	50 mg/day=53 150 mg/day=52	52	12 weeks[a]
N01193 (randomized, double-blind, PBO-controlled, dose-ranging)	5mg/day=50 20 mg/day=52 50 mg/day=52	54	7 weeks[b]

Note: The number of subjects in each study is based on the Intent-To-Treat (ITT) population, defined as all the randomized subjects who received at least 1 dose of study drug.
[a] Maximum duration of treatment included a 10-week Treatment Period (3-week Up-Titration Period and a 7-week Maintenance Period [fixed dose]), followed by a 2-week Down-Titration Period.
[b] Maximum duration of treatment included a 7-week Treatment Period (fixed dose).

N01114 investigated the high end of the dose range (BRV 50 mg/day and 150 mg/day versus PBO)), while N01193 investigated the low end of the dose range (BRV 5mg/day, 20 mg/day, and 50 mg/day versus PBO). Doses of BRV 50 mg/day were investigated in both dose ranging studies in order to bridge them. N01114 was

conducted only in countries of the European Union (EU), whereas N01193 was conducted in Brazil, India, Mexico, and the United States of America (USA).

Subjects were male or female, age 16 to 65 years with refractory epilepsy suffering from POS, whether or not secondarily generalized. Randomization in both studies was stratified for the intake of LEV and CBZ.

- Study N01114

Study title: A multicenter, double-blind, randomized, placebo-controlled, 3 parallel groups, dose-ranging trial evaluating the efficacy and safety of ucb 34714 (BRV) used as adjunctive treatment at doses of 50 and 150 mg/day in bid administration (oral capsules of 25 mg) for a maximum of 12 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized.

In study N01114, 157 subjects were randomised in a 1:1:1 fashion to receive BRV 50 mg/day, BRV 150 mg/day, or PBO during a 10-week treatment period (3-week up-titration period and a 7-week maintenance period). A total of 157 subjects were randomized all of whom were included in the ITT population. At the end of the treatment period, subjects either entered the LTFU study (N01125) at the recommended starting dose of BRV 100 mg/day (2-week conversion period), or entered a 2-week down-titration period followed by a 2-week study drug-free period.

The primary endpoint was POS frequency per week (type I) over the maintenance period. Secondary efficacy variables included the rate of responder with a ≥ 50% reduction in POS (type I) frequency per week over the maintenance period compared to baseline, seizure frequency per week for all seizures (types I+II+III), reductions and percentage reductions from Baseline in seizure frequency per week for POS (type I) and for all seizures (types I+II+III) and percentage of seizure-free subjects over the maintenance period.

For the primary efficacy variable, the estimated percent reduction over PBO in the POS frequency per week was 14.7% in the BRV 50 mg/day group and 13.6% in the BRV 150 mg/day group. The differences were not statistically significant. For the secondary endpoint, the 50 % responder rates in the PBO, BRV 50 mg/day, and BRV 150 mg/day groups were 23.1% (12/52), 39.6% (21/53) and 33.3% (17/51), respectively. The odds ratios of being a 50% responder over the maintenance period were 2.16 (p=0.077) and 1.66 (p=0.261) in the BRV 50 mg/day and BRV 150 mg/day groups, respectively. The proportion of seizure-free subjects was higher in the active groups than in the PBO group. An unexpected finding in study N01114 was that consistently across most primary and secondary outcome measures the lower BRV dose of 50 mg/day tended to be more effective than the higher 150 mg/day dose.

- Study N01193

Study title: A multicenter, double-blind, randomized, placebo-controlled, 4 parallel groups, dose-ranging trial evaluating the efficacy and safety of brivaracetam used as adjunctive treatment at doses of 5, 20 and 50 mg/day in bid administration (oral tablets of 2.5 or 10 mg) for a maximum of 7 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized.

In study N01193, after a baseline period of 4 weeks, 210 patients were randomised 1:1:1:1 to receive BRV 5 mg/day, 20 mg/day, 50 mg/day or PBO for a 7-week fixed dose treatment period without any up-titration. A total of 210 subjects were randomized and of these 208 subjects were included in the ITT population. At the end of the treatment period, the patients entered either the LFTU study N01199 or entered a 2-week study drug-free period.

The endpoints were similar to study N01114. The primary endpoint of percent reductions over PBO in POS frequency per week over the treatment period were 9.8% (2-sided 95% CI -7.2%, 24.0%), 14.9% (-0.8%,

28.2%), and 22.1% (7.6%, 34.3%) in the BRV 5mg/day, BRV 20 mg/day and BRV 50 mg/day groups, respectively. For the 50 mg/day dose the reduction over PBO was statistically significant (p=0.004). For BRV 20 mg/day, the reduction approached statistical significance (p=0.062). The 50 % responder rates (secondary efficacy variable) in the PBO, BRV 5 mg/day, 20 mg/day, and BRV 50 mg/day groups were 16.7% (9/54), 32.0% (16/50), 44.2% (23/52)and 55.8% (29/52), respectively. The probability of being a 50% responder was modelled using a logistic regression analysis with treatment group and stratum (LEV use, concomitant use of CBZ) as factors and baseline seizure frequency as covariate. The model estimated that the odds of being a 50% responder in the BRV 5 mg, 20 mg/day and 50 mg/day groups were 2.66, 4.27, and 7.21 times those in the PBO group. These results were statistically significant for all the investigated doses of BRV.

Both country (p=0.0244) and treatment-by-country interaction (p=0.0203) were statistically significant. These exploratory results appeared to be mainly driven by the results for Brazil (n=18) where a worsening in POS was reported in all active groups. Compared to PBO (n=5), POS frequency was increased by 105%, 72% and 71% in the BRV 5mg/day (n=2), 20 mg/day (n=5) and 50 mg/day (n=6) groups, respectively.

2.5.2. Main study(ies)

The Phase III BRV POS program was initiated presuming 50 mg/day as the optimal dose. Doses of BRV 20 mg/day, 50 mg/day, or 100 mg/day and 5mg/day, 20 mg/day, or 50 mg/day were investigated in two parallel studies, N01252 and N01253, with the same design. In both studies approximately 20% of subjects were using concomitant LEV.

Following the completion of N01252 and N01253, a meta-analysis across the fixed dose Phase II/III studies was performed to confirm the effect of BRV treatment and to examine possible variables contributing to the effect sizes. Based on the meta-analysis results, the applicant concluded that the use of concomitant LEV may have influenced the overall therapeutic response in these studies. The applicant decided that BRV 100 mg/day would be tested in a third efficacy study, N01358, and that subjects with concomitant use of LEV would be excluded. Following a scientific advice, BRV 200 mg/day was added to obtain data on the upper end of the dose response curve.

The three pivotal Phase III studies were randomized, double-blind, PBO-controlled, parallel-group, fixed dose, multicentre studies. An overview of trials is provided in Table 3.

Table 3 – Overview of the pivotal Phase III trials N01252, N01253 and N01358

Study number (study title)	**No of subjects**	**LEV use[a]**		**No of subjects in treatment groups**		**Maximum duration of treatment[b]**
		Use	**No use**			
N01252: A multi-center, double-blind, parallel-group, PBO-controlled, randomized study: Evaluation of the efficacy and safety of brivaracetam in subjects (≥16 to 70 years old) with POS	398	76	322	BRV20 mg/day=99 BRV 50 mg/day=99 BRV 100 mg/day=100 PBO=100		14 weeks
N01253: An international, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with POS	396	76	320	BRV 5mg/day=97 BRV 20 mg/day=100 BRV 50 mg/day=101 PBO=98		13 weeks
N01358: A randomized, double-blind, PBO-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of brivaracetam in subjects (≥16 to 80 years old) with POS	764	NA[c]		BRV 100 mg/day=253 BRV 200 mg/day=250 PBO=261		16 weeks
Total	**1558**			**1099**	**459**	

Note: The number of subjects in each study was based on the Safety Population, defined as all the randomized subjects who received at least 1 dose of study drug. For N01252 and N01253, the Safety Population was the same set of subjects as the ITT Population.

[a] LEV use (or not) was collected at study entry and was restricted to 20% of randomized subjects. The incidence of LEV use was similar across treatment groups, ranging from 18.0% to 20.2% in N01252 and 18.6% to 20.0% in N01253.

[b] For each study, the maximum duration of treatment comprised of a 12-week Treatment Period (fixed dose of BRV), followed by a Down-Titration Period.

[c] LEV use was not permitted within 90 days of study entry and as a concomitant medication during the study.

2.5.2.1. Methods

Study Participants

Main inclusion criteria

- Subjects were from 16 to 70 years (*16 to 80 years in study N01358*), both inclusive. Subjects under 18 years of age were only included where legally permitted and ethically accepted.
- Subjects with well-characterized focal epilepsy or epileptic syndrome according to the ILAE classification.
- Subjects had a history of POS whether or not secondarily generalized (Type I seizures according to the ILAE classification).

  (In study N01358: Presence of an electroencephalogram (EEG) reading compatible with the clinical diagnosis of focal epilepsy within the last 5 years AND presence of a brain magnetic resonance imaging (MRI)/computed tomography (CT) scan performed within the last 2 years.)
- Subjects had at least 2 POS whether or not secondarily generalized per month during the 3 months preceding Visit 1.

- Subjects had at least 8 POS during the 8-Week Baseline Period *(Study N1358: with at least 2 Type I seizures during each 4-week interval of the Baseline Period)*
- Subjects were uncontrolled while treated by 1 to 2 permitted concomitant AED(s). Vagal nerve stimulation was allowed. *In studies N01252 and N01253, VNS was not counted as a concomitant AED*.
- The dosage of permitted concomitant AEDs and VNS was kept stable and optimal for at least 1 month (3 months for PB and primidone, *and PHT - N01358 only*) prior to study entry and Treatment Period, *and throughout the Baseline Period - N01358 only*.

Main exclusion criteria:

- Seizure Type IA nonmotor as only seizure type.
- History or presence of seizures occurring only in clusters (too frequently or indistinctly separated to be reliably counted).
- History or presence of status epilepticus during the year preceding Visit 1 or during Baseline.
- History or presence of pseudo-seizures.
- Subjects had a history of cerebrovascular accident, including transient ischemic attack, in the last 6 months.
- *Study N01358 only: Subject was currently treated with LEV* (the number of subjects using LEV as a concomitant AED was limited to 20% of the total study population of N01252 and N01253).
- *Study N01358 only: Subject had taken LEV within 90 days prior to Visit 1.*

Treatments

All three studies consisted of 2 phases: An 8-week baseline (pre-randomization) period, during which subjects remained on a stable dose of their present AEDs and maintained a seizure diary, and a double-blind 12-week treatment period. These periods were followed by either a LTFU study or a down-titration period (2 weeks for N01252, 1 week for N01253 and 4 weeks for N01358) for those subjects who either withdrew from the studies prematurely or completed the double-blind phase, but did not consent to enter the LTFU studies.

At the end of the baseline period, patients were randomized to receive either placebo or BRV at a fixed dose without titration. The daily dose was administered in 2 equal intakes, morning and evening. Oral tablets of BRV (2.5mg/day, 10 mg/day, and 25mg/day, as well as 50mg/day in study N01358) and matching PBO were used in the studies.

In study N01252, patients were randomized in a 1:1:1:1 fashion to 1 of 4 treatment arms (BRV 20 mg/day, 50 mg/day, 100 mg/day, or PBO).

In study N01253, subjects were randomized in a 1:1:1:1 fashion to 1 of 4 treatment arms (BRV 5mg/day, 20 mg/day, 50 mg/day, or PBO).

In study N01358, subjects were randomized 1:1:1 to 1 of 3 treatment arms (PBO, BRV 100 mg/day, or BRV 200 mg/day).

A schematic diagram of study N01358 is provided in **Figure 5** as an example for the conduct of the studies.

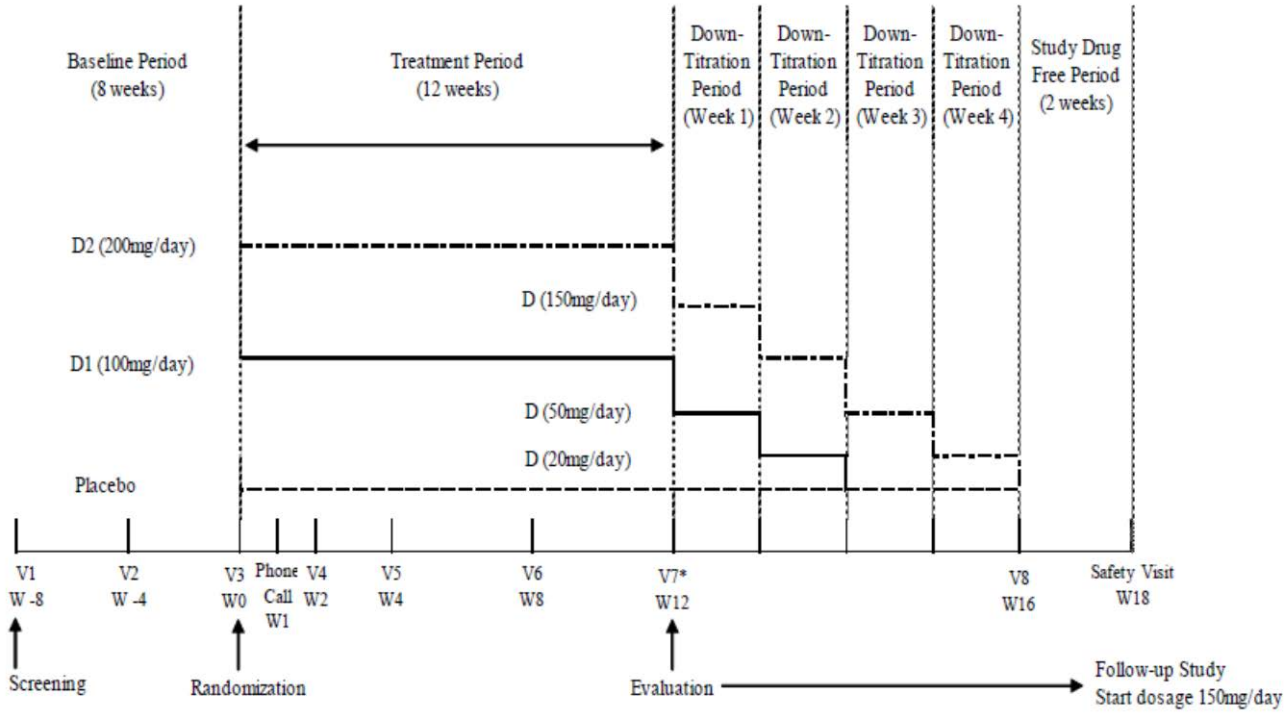


Figure 4 – Schematic diagram of study N01358

Objectives

The primary objective of the studies was to evaluate the efficacy of BRV in reducing seizure frequency in subjects with POS not fully controlled despite optimal treatment with 1 to 2 concomitant AEDs, compared with PBO.

A secondary objective of all studies was to assess the safety and tolerability of BRV.

In addition, studies N01252 and N01253 had the following secondary objectives:

- To confirm the dose/clinical response relationship
- To assess the effects of BRV on Type IC seizures
- To assess the effects of BRV on different dimensions of patients' functioning and Health Related Quality of Life (HRQoL)

Exploratory objectives of all studies were:

- To obtain a description of the subjects' self-reported health status
- To explore direct medical resources use and indirect cost parameters

Study N01358 additionally investigated the effects of BRV on HRQoL (secondary objective for the other 2 studies).

Studies N01252 and N01253 also had the following secondary objectives:

- To explore the population PK of BRV and identify relevant covariates and to assess the impact of BRV on concomitant AED plasma levels

- To collect blood samples for genotyping of SV2-and epilepsy-related genes (for a pooled analysis at the program level)

Outcomes / endpoints

In studies N01252 and N01253, the primary endpoint was the POS (Type I) frequency per week over the Treatment Period. Responder rate (the proportion of subjects who had a ≥50% reduction in seizure frequency per week from Baseline) for POS (Type I) over the Treatment Period was a secondary endpoint.

For study N01358, the primary efficacy variable was the POS (Type I) frequency per 28 days during the 12-week Treatment Period. The primary efficacy outcome for European authorities was the 50% responder rate based on percent reduction in POS (Type I) frequency from Baseline to the 12-week Treatment Period. The primary endpoint in the USA, percent reduction in POS (Type I) frequency over PBO, was a secondary endpoint for the European evaluation.

Other secondary endpoints were:

All three studies

- All seizure frequency (Type I+II+III) per week over the Treatment Period
- Categorized percentage reduction from Baseline in seizure frequency for POS (Type I) over the Treatment Period.
- Seizure freedom rate (all seizure types) over the Treatment Period.
- Time to nth (n=1, 5, 10) Type I seizure during the Treatment Period.

Studies N01252 and N01253 only:

- Percent reduction for POS (Type I) frequency per week from Baseline to the Treatment Period.
- Reduction of seizure frequency ratio (Type IC/Type I) from Baseline to the Treatment Period.
- Total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score (*other efficacy variable in N01358*).
- Seizure Worry QOLIE-31-P score.
- Daily Activities/Social Functioning QOLIE-31-P score.
- Remaining QOLIE-31-P domain scores (Energy/Fatigue, Emotional Well-being, Cognitive Functioning, Overall Quality of Life and Medication effects).
- Hospital Anxiety and Depression Scale (HADS) scores (*other efficacy variable in N01358*).
- Patient's Global Evaluation Scale (P-GES) (*other efficacy variable in N01358*).
- Investigator's Global Evaluation Scale (I-GES) (*other efficacy variable in N01358*).

Other/exploratory efficacy variables included:

- EuroQoL-5 dimensions (EQ-5D) items (*N01252 and N01253 only*).
- Indirect cost parameters: number of working or school days lost by the subject and/or caregiver (*N01252 and N01253 only*).

- Direct cost parameters: concomitant medications, medical procedures, healthcare provider consultations not foreseen by the protocol, hospitalizations (*N01358: Number of hospital stays, healthcare provider consultations not foreseen by the protocol, and medical procedures during the study period*).
- Socioprofessional data (driver's license, employment status, etc.).

Sample size

Studies N01252 and N01253: With a power of 90% and a 2-sided level of significance of 5%, 87 subjects per arm were required to detect a treatment difference of 20% reduction in seizure frequency over PBO. Since the 3 doses of BRV were tested hierarchically at the 5% significance level starting with BRV 50 mg/day, power was lost for the other two dose groups. In order to compensate for this loss in power, 100 subjects per arm were included.

Study N01358: The sample size was calculated based on the 50% responder outcome in the European primary efficacy analysis. Assuming responder rates of 20% and 35% for PBO and BRV, 231 analysable subjects per treatment group were required to provide 90% power to detect a 15% difference between BRV and PBO at the 0.025 significance level. A total of 693 analysable subjects were required across all treatment groups. Because some randomized subjects may not have qualified for the primary analysis, 240 subjects were randomized in each arm, for a total of 720 randomized subjects across all 3 treatment groups.

Randomisation

A 1:1:1:1 (studies N01252 and N01253) and 1:1:1 (N01358) central randomization (random permuted blocks) was used in the studies. Eligible subjects were assigned to one of the treatment groups using an Interactive Response System

To ensure overall balance across the different treatment groups, the studies were stratified as follows:

Studies N01252 and N01253 were stratified by

- geographical region [study N01252: Eastern Europe, Western Europe, Rest of the World (only India), study N01253 North America: (US and Canada) and Australia, Latin America (Mexico and Brazil), Rest of the World]
- concomitant LEV use at study entry (yes/no)

Study N01358 was stratified by

- country
- LEV status (never used LEV vs prior LEV use only)
- number of previous AEDs (≤2/>2) based on AEDs previously used and discontinued prior to Visit 1.

Blinding (masking)

All studies were double-blind with double-dummy administration of study treatment. BRV was supplied as white, film-coated, oral tablets, with matching PBO and were packaged in wallet cards. Patients were taking 3 tablets in the morning and the evening. All Sponsor, Investigator sites, and CRO staff involved with the study were blinded to the treatment code except for staff directly involved in the packaging of product or in the management of the IVRS including reporting of serious adverse event (SAE) to regulatory authorities, as well as central laboratory staff who performed study medication assays and in case of a medical emergency.

Statistical methods

POS (Type I) frequency was calculated for each subject as 'Total number of Type I seizures over the Treatment Period' divided by 'Total number of days with no missing seizure count in the Treatment Period' times the relevant number of days (1 week in case of studies N01252 and N01253; 28 days in case of study N01358). This variable was transformed prior to being analysed using the logarithmic transformation loge [x+1] (where x is the seizure frequency per week). The log-transformed POS frequency per week over the Treatment Period was analysed applying an analysis of covariance (ANCOVA) model, including treatment and stratification effect as factors and the log-transformed Baseline seizure frequency as covariate.

The analysis of 50% responder outcome (primary efficacy analysis in study N01358) was based on a logistic regression model with an effect for treatment as well as a stratification effect, and log-transformed Baseline POS frequency as a continuous covariate. Odds ratios and corresponding 95% confidence intervals (Wald method) were calculated.

Multiplicity

In studies N01252 and N01253, in order to control the overall Type I error rate to 0.05, the 3 doses of BRV were tested at the 5% significance level against PBO, according to a predefined hierarchical sequential rejective testing procedure. For Step 1, the hierarchical testing procedure began with the BRV 50 mg/day dose versus PBO. If the comparison was not statistically significant, the procedure stopped and no groups were declared different from PBO. If the comparison was statistically significant, the BRV 50 mg/day group was considered different from PBO and the procedure continued with the second step. Step 2 tested PBO against BRV 100 mg/day (N01252) or 20 mg/day (N01253) in a similar manner to Step 1, and if the comparison was statistically significant, Step 3 tested PBO against BRV 20 mg/day (N01252) or 5mg/day (N01253). This procedure strongly controlled the overall Type I error rate to 0.05.

The evaluation of statistical significance for the primary analysis in study N01358 was based on a Hochberg multiple comparison procedure. Both multiplicity-adjusted p-values and unadjusted p-values were calculated.

Withdrawals and handling of missing data

Missing seizure diary days were not considered in the calculation of seizure frequency. Sensitivity analysis were performed to investigate the impact of missing diary data. If a subject withdrew from the study before the end of the Treatment Period, the seizure information collected up until the time of withdrawal was used to calculate the seizure frequency per week over the Treatment Period.

Analysis sets

Intent-To-Treat (ITT) Population

The ITT Population was defined as all randomized subjects who received at least 1 dose of study medication. In study N1358, subjects in the ITT population also had to have had at least 1 post-Baseline seizure diary entry. The primary efficacy analysis and all secondary efficacy analyses were performed on the ITT Population and subjects were analysed according to the randomized treatment.

In study N01253, a modified ITT (mITT) Population was defined as all subjects in the ITT population, but excluding all 3 randomized subjects from one study site as well as one other subject due to serious and persistent noncompliance.

Per Protocol (PP) Population

The PP Population was a subset of the ITT Population, consisting of those subjects who had no major protocol deviations affecting the primary efficacy variable.

Selected supportive efficacy analyses were carried out using the PP Population. In studies N01252 and N01253, primary efficacy analysis was planned to be performed if more than 10% of the ITT Population were totally or partially excluded from the PP Population.

Safety Population

The Safety Population was comprised of the same set of subjects as the ITT Population

Subgroups

Several subgroup analyses were conducted including geographical region, LEV status (concomitant LEV use in studies N01252 and N01253; prior LEV use in study N01358), gender, age, race, number of previous AEDs, etc.

2.5.2.2. Results for Study N01252

Participant flow / numbers analysed

A total of 486 subjects were screened for this study. A total of 399 subjects were randomized to either PBO or one of 3 BRV doses (20 mg/day, 50 mg/day, or 100 mg/day). Of these randomized subjects, 1 subject randomized to the BRV 50 mg/day group was excluded from the ITT Population. The ITT and Safety Populations were identical and consisted of all randomized subjects who received at least 1 dose of study medication (N=398). Of the 398 subjects in the ITT Population, 367 subjects (92.2%) completed the study. A total of 31 subjects (7.8%) discontinued the study.

Table 4 – Disposition of Subjects in Study N01252

Screened subjects **Screen failures** **Randomised subjects** **ITT population**	n= 486 n=87 [ineligibility n=62, withdrawal of consent n=15, other reasons n=10] n=399 [Failure to take study medication n=1] n=398			
Study arm	**PBO**	**BRV 20 mg/day**	**BRV 50 mg/day**	**BRV 100 mg/day**
ITT	n=100	n=99	n=99	n=100
Discontinued **Adverse event** **Lack of efficacy** **Other reasons**[a]	n=8 n=4 n=0 n=4	n=6 n=4 n=0 n=2	n=11 n=6 n=0 n=5	n=6 n=5 n=0 n=1
Completed[b]	n=92	n=93	n=88	n=94
Entered LTFU study	n=88	n=87	n=82	n=88

[a]Includes lost to follow-up, withdrawal of consent, and other reasons.
[b]Patients who completed the 12-week treatment period.

Recruitment

The first subject was enrolled on 10 Sep 2007 and the last subject completed the study on 9 Feb 2009. The study was initiated in 88 sites (71 sites having randomized at least 1 subject) in 12 European countries: Belgium, Switzerland, Germany, Finland, France, Hungary, India, Italy, Netherlands, Poland, Spain, United Kingdom, Denmark. Sites in Denmark did not enrol subjects due to study refusal by the central ethics committee (due to comparison of active drug to PBO).

Conduct of the study

There were two protocol amendments. Amendment #1 was issued prior to enrolment of any subjects and concerned an extension of the storage period of DNA samples, the rationale for collecting the race and clarification of the electrocardiogram tracings retrieval. The second amendment followed a recommendation from the US Food and Drug Administration (FDA) and included the addition of an additional 1 week step at 20 mg/day to the Down-Titration Period, a clinic visit 2 weeks after randomization and microscopy evaluations for all urinalysis. Other changes included the addition of specifications for the handling of missing data.

Baseline data

The demographics of the patients recruited in study N01252 are summarised in Table 5. The treatment groups were generally balanced with regard to most demographic parameters. Only 11 subjects were ≥65 years old.

Table 5 – Demographic Characteristics of Study N01252 (ITT)

Characteristics[a]	Descriptive statistics	PBO	BRV			Overall
			20 mg	50 mg	100 mg	
		(N=100)	(N=99)	(N=99)	(N=100)	(N=398)
Gender						
Female	n (%)	46 (46.0)	38 (38.4)	45 (45.5)	42 (42.0)	171 (43.0)
Male	n (%)	54 (54.0)	61 (61.6)	54 (54.5)	58 (58.0)	227 (57.0)
Age (years)	n	100	99	99	100	398
	Mean (SD)	36.36 (12.97)	35.71(12.48)	38.93 (13.56)	37.97 (13.13)	37.24 (13.05)
	Min - Max	16.2-68.9	16.2-68.2	18.2-71.1	17.6-70.8	16.2-71.1
Class of age (years)						
<18	n (%)	2 (2.0)	2 (2.0)	0	1 (1.0)	5 (1.3)
18-<30	n (%)	40 (40.0)	34 (34.3)	31 (31.3)	33 (33.0)	138 (34.7)
30-<50	n (%)	39 (39.0)	50 (50.5)	45 (45.5)	46 (46.0)	180 (45.2)
50-<65	n (%)	17 (17.0)	10 (10.1)	20 (20.2)	17 (17.0)	64 (16.1)
≥65	n (%)	2 (2.0)	3 (3.0)	3 (3.0)	3 (3.0)	11 (2.8)
Race						
Caucasian	n (%)	77 (77.0)	76 (76.8)	76 (76.8)	76 (76.0)	305 (76.6)
Black	n (%)	0	0	0	0	0
Asian	n (%)	23 (23.0)	22 (22.2)	23 (23.2)	24 (24.0)	92 (23.1)
Native Hawaiian/ other Pacific Islander	n (%)	0	0	0	0	0
American Indian/ Alaskan Native	n (%)	0	0	0	0	0
Mixed race	n (%)	0	1 (1.0)	0	0	1 (0.3)
Weight (kg)	n	100	99	99	100	398
	Mean (SD)	70.1 (17.3)	72.3 (18.5)	71.1 (14.4)	72.0 (18.1)	71.4 (17.1)
	Min - Max	43-122	45-118	45-105	45-140	43-140
Height (cm)	n	97	99	98	98	392
	Mean (SD)	167.8 (9.2)	169.9 (9.7)	168.3 (8.5)	168.9 (9.2)	168.7 (9.2)
	Min - Max	149-197	148-195	151-187	141-189	141-197

Characteristics[a]	Descriptive statistics	PBO	BRV			Overall
			20 mg	50 mg	100 mg	
		(N=100)	(N=99)	(N=99)	(N=100)	(N=398)
BMI (kg/m^2)	n	97	99	98	98	392
	Mean (SD)	24.79 (5.22)	24.87 (5.19)	25.10 (4.15)	25.21 (5.26)	24.99 (4.96)
	Min - Max	16.9-44.8	15.6-38.5	14.2-36.0	14.7-44.9	14.2-44.9

Max=maximum; Min=minimum; SD=standard deviation; V=visit
[a] Age (years) at first study medication dispensation, body weight (kg) at Randomization Visit (V3), height at Screening Visit (V1), BMI=10000 * weight (kg) / [height (cm)]^2.

The mean duration of epilepsy at randomization was 22 years, and the mean age at onset of the first seizure was 15 years old. Subjects had spent approximately 59% of their lives with epilepsy. Five per cent of subjects had a history of status epilepticus. The most common aetiologies of epilepsy in all subjects were unknown (43.7%), "other" (14.1%), and congenital malformation (11.1%). The history of epilepsy and the aetiology of epilepsy appeared balanced between groups.

Seizure types were similar across all treatment groups. All subjects had partial seizures with a total of 84.2% who had experienced during their lifetime complex partial seizures, 67.1% partial seizures with secondary generalization, and 32.7% simple partial seizures. Less than 10% of subjects had had generalized seizures (6.0%), clusters (1.3%), and unclassifiable epileptic seizures (0.5%). Regarding epileptic syndromes, most were classified as localization-related – symptomatic (51.5%), followed by localization-related – cryptogenic (34.7%), and localization-related – congenital (8.3%). Epileptic syndromes were unknown in 5.5% of subjects.

Overall, 334 subjects (83.9%) had a history of taking at least 1 previous AED. The most frequently used previous AEDs were: CBZ (32.4%), TPM (27.9%), VPA (25.9%), LEV (25.6%), and LTG (20.4%). The incidence of previous use of these AEDs was generally similar across treatment groups, with the exception that a lower percentage of subjects in the BRV 100 mg/day group took VPA, compared to the other treatment groups. The numbers of subjects taking 0 to 1, 2 to 4, or 5 or more previous AEDs were similar across treatment groups. Approximately half of all subjects took 2 to 4 previous AEDs (51.0%), while 31.9% of subjects took 0 to 1 previous AEDs, and 17.1% took 5 or more previous AEDs.

All subjects were taking at least 1 concomitant AED at Baseline. The majority (77.9%) of subjects were taking 2 concomitant AEDs at Baseline. The most frequently used concomitant AEDs were: CBZ (46.5%), VPA (22.4%), LTG (20.9%), and OXC (20.4%). Concomitant LEV was used by 76 (19.1%) patients. Slight imbalances occurred in the use of concomitant AEDs at baseline. CBZ was taken by more subjects in the BRV 20 mg/day (55.6%) group compared with the other treatment groups (range 40.0% to 48.5%). VPA was taken by more subjects in the BRV 50 mg/day (28.3%) and BRV 100 mg/day (28.0%) groups compared with the PBO (17.0%) and BRV 20 mg/day groups (16.2%). For TPM, more subjects were taking concomitant TPM in the PBO group (22.0%) than in the BRV groups (range 3.0% to 13.0%). Nineteen subjects (4.8%) had VNS implants and 2 subjects (0.5%) had VNS implants removed prior to Baseline.

Overall, 196 subjects (49.2%) took at least 1 concomitant non-AED during the Treatment Period. The most frequently used concomitant non-AEDs overall were: paracetamol (8.5%), ibuprofen (5.0%), and acetylsalicylic acid (2.8%), levothyroxine (2.8%),metoprolol (2.8%), and omeprazole (2.8%).

Outcomes and estimation

Primary efficacy analysis: % reduction over PBO in the POS frequency per week over the Treatment Period

The primary efficacy analysis was performed on the ITT and PP Populations since more than 10% of the ITT Population was totally or partially excluded from the PP Population. The results for the ITT population are summarised in Table 6.

Table 6 - Primary Efficacy Analysis: Treatment Comparison of POS Frequency per Week over the Treatment Period in Study N01252 (ITT Population, ANCOVA)

Statistics	PBO	BRV		
		20 mg	50 mg	100 mg
	(N=100)	(N=99)	(N=99)	(N=100)
LS means (log transformed) (SE)	1.167 (0.042)	1.096 (0.042)	1.099 (0.042)	1.042 (0.042)
LS means (back transformed)	2.211	1.993	2.002	1.836
Treatment comparison vs PBO				
% reduction over PBO		6.8	6.5	11.7
95% confidence interval		-4.8, 17.1	-5.2, 16.9	0.7, 21.4
p-value[a]		0.239	0.261	0.037[b]

SE=standard error
[a] Statistical significance against PBO was tested according to a predefined hierarchical sequential testing procedure starting with 50 mg, then 100 mg, and finally 20 mg, only moving to the next test if the previous one was significant at the 0.050 level.
[b] Nominally statistically significant.

The per cent reductions over PBO in the POS frequency per week over the Treatment Period were 6.8%, 6.5%, and 11.7% in the BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day groups, respectively. The primary outcome for study N01252 did not achieve statistical significance based on the sequential testing procedure, which required statistical significance at the 0.050 level for BRV 50 mg/day versus PBO prior to the testing of BRV 100 mg/day and BRV 20 mg/day in sequence. The comparison of BRV 100 mg/day versus PBO was nominally statistically significant. Results of the primary efficacy analysis on the PP Population showed no statistically significant differences between any BRV group and the PBO group.

Secondary efficacy variables

All secondary efficacy analyses were performed on the ITT Population only.

- 50% responder rate

The results for subjects with ≥50% reduction in POS frequency per week over the Treatment Period were similar to those for the primary efficacy endpoint. In the PBO group, 20 out of 100 patients (20.0%) were responders compared to 27 out of 99 patients (27.3%) in the BRV 20 mg/day group, 27 out of 99 patients (27.3%) in the BRV 50 mg/day group and 36 out of 100 patients (36.0%) in the BRV 100 mg/day group. The 50% responder rate for the BRV 50 mg/day group was not statistically significantly different compared with the PBO group (27.3% versus 20.0%, p=0.372), while statistical significance was achieved with BRV 100 mg/day versus PBO for the 50% responder rate (36.0% vs 20.0%, p=0.023).

- Other secondary efficacy variables

Similar results as for the primary efficacy analysis and 50% responder rate were also observed for other secondary endpoints including changes in all (Type I+II+III) seizure frequency, seizure frequency of all types, and percent reduction from Baseline in partial (Type I) seizure frequency.
The analysis for the categorized response rate in partial (Type I) seizure frequency per week revealed that an overall larger proportion of subjects in the PBO group showed <-25% and -25% to <25% response compared with all 3 BRV groups. In addition, no subjects in the PBO group achieved 100% response, as compared with

7 subjects in the 3 BRV groups. Seizure freedom (in all seizure types, Type I+II+III) during the Treatment Period was achieved for 4 subjects in the BRV 100 mg/day group and 2 subjects in the BRV 20 mg/day group. Furthermore, 1 subject in the BRV 50 mg/day group experienced no seizures, but this subject did not complete the study. Median times to n^{th} Type I seizure were generally similar between treatment groups. There were no statistically significant differences in the hazard ratio between any of the BRV dose groups and the PBO group in the time to the 1^{st} or 5^{th} POS. There was a statistically significant difference in the time to the 10^{th} POS in the BRV 50 mg/day group compared with the PBO group (p=0.0312).

There were no meaningful differences in health-related quality of life or indirect or direct cost parameters between any BRV dose group and PBO. There was no treatment effect for any BRV dose over PBO for the HADS subscales of anxiety and depression. Results of the P-GES and I-GES were generally similar; both subjects and Investigators considered that more subjects in the BRV groups improved (slight, moderate, or marked improvement) compared with PBO. Comparison of each BRV dose to PBO showed a statistically significant difference for BRV 100 mg/day over PBO for both the I-GES and P-GES.

Ancillary analyses

- Concomitant LEV use

Concomitant LEV use at study entry was limited to 20% of the total study population, per protocol. In the PBO, BRV 20 mg/day, BRV 50 mg/day and 100 mg/day groups, 18, 18, 20 and 20 patients had used LEV during the treatment period, respectively. Primary ANCOVA analysis of treatment-by-concomitant LEV use interaction was not significant at the 0.10 level. However, results of the primary analysis showed greater per cent reductions over PBO in log-transformed POS frequency per week in subjects in all 3 BRV dose groups without concomitant LEV use at study entry (range 9.5% to 16.5%) compared with subjects with concomitant LEV use at study entry (range -6.6% to -12.2%).

- Regional effect

The statistical analysis showed that the treatment-by-region interaction was significant at the 0.10 level. Results of the primary efficacy analysis reduction in weekly POS frequency suggested a positive treatment effect for the 3 BRV dose groups in subjects from Eastern Europe and India whereas for subjects from Western Europe, the results showed no observable treatment effect for any BRV dose. Results for 50 % responder rate were of similar magnitude for Eastern and Western Europe, with no observable beneficial effect of any BRV dose, whereas the rates for Indian subjects were generally higher in all active groups and driving the overall results.

2.5.2.3. Results for Study N01253

Participant flow / numbers analysed

A total of 509 subjects were screened for this study. A total of 400 subjects were randomized to either PBO or one of 3 BRV doses (5mg/day, 20 mg/day, or 50 mg/day). Four subjects were excluded from the ITT Population, due to failing to take study medication or erroneous randomisation nut never dispensed study medication. The ITT and Safety Populations were identical and consisted of all randomized subjects who received at least 1 dose of study medication (N=396). Of these, 361 subjects (91.2%) completed the study. A total of 35 subjects (8.8%) discontinued the study. See section 'Methods' for the definition of the mITT population.

Table 7 – Disposition of Subjects in Study N01253

Screened subjects **Screen failures** **Total patients randomised** **ITT population** **mITT population**	n= 509 n=109 [ineligibility n=83, withdrawal of consent n=12, other reasons n=14] n=400 [Failure to take study medication n=1, randomised but not dispensed study medication n=3] n=396 n=392 [compliance issues n=3, seizure type eligibility n=1]			
Study arm	**PBO**	**BRV 5 mg/day**	**BRV 20 mg/day**	**BRV 50 mg/day**
mITT	n=96	n=96	n=99	n=101
Discontinued **Adverse event** **Lack of efficacy** **Other reasons**[a]	n=5 n=2 n=1 n=2	n=15 n=8 n=0 n=7	n=7 n=5 n=0 n=2	n=8 n=6 n=0 n=2
Completed[b]	n=93	n=82	n=93	n=93
Entered LTFU study	n=86	n=79	n=91	n=91

[a]Includes lost to follow-up, withdrawal of consent, and other reasons.
[b]Patients who completed the 12-week treatment period.

Recruitment

The first subject enrolled on 7 September 2007 and the last subject completed the study on 2 January 2009. This study was conducted at 85 sites in 5 countries: Australia, Brazil, Canada, Mexico, and the United States.

Conduct of the study

In response to FDA comments, a protocol amendment was issued prior to subject enrolment (see changes including other changes described for study N01252).

Baseline data

The demographics of subjects in study N01253 are displayed in Table 8. The treatment groups were balanced with regard to most demographic parameters. Only 7 subjects were ≥65 years old.

Table 8 – Demographic Characteristics of Study N01253 (ITT)

Characteristics[a]	**Descriptive statistics**	**PBO**	**BRV**			**Overall**
			5mg	**20 mg**	**50 mg**	
		(N=98)	**(N=97)**	**(N=100)**	**(N=101)**	**(N=396)**
Gender						
Female	n (%)	55 (56.1)	48 (49.5)	48 (48.0)	50 (49.5)	201 (50.8)
Male	n (%)	43 (43.9)	49 (50.5)	52 (52.0)	51 (50.5)	195 (49.2)
Age (years)	n	98	97	100	101	396
	Mean (SD)	37.45 (12.56)	38.89 (11.61)	37.32 (13.33)	38.88 (12.29)	38.13 (12.45)
	Min - Max	16.5-66.5	18.3-69.3	14.4-69.4	16.6-69.9	14.4-69.9
Class of age (years)						
<18	n (%)	7 (7.1)	0	5 (5.0)	2 (2.0)	14 (3.5)
18-<30	n (%)	23 (23.5)	26 (26.8)	31 (31.0)	27 (26.7)	107 (27.0)
30-<50	n (%)	51 (52.0)	55 (56.7)	43 (43.0)	50 (49.5)	199 (50.3)
50-<65	n (%)	16 (16.3)	14 (14.4)	19 (19.0)	21 (20.8)	70 (17.7)
≥65	n (%)	1 (1.0)	2 (2.1)	2 (2.0)	1 (1.0)	6 (1.5)

Characteristics[a]	Descriptive statistics	PBO	BRV			Overall
			5mg	20 mg	50 mg	
		(N=98)	(N=97)	(N=100)	(N=101)	(N=396)
Race						
Caucasian	n (%)	66 (67.3)	73 (75.3)	70 (70.0)	77 (76.2)	286 (72.2)
Black	n (%)	4 (4.1)	5 (5.2)	5 (5.0)	2 (2.0)	16 (4.0)
Asian	n (%)	1 (1.0)	0	2 (2.0)	3 (3.0)	6 (1.5)
Native Hawaiian/ other Pacific Islander	n (%)	0	1 (1.0)	0	1 (1.0)	2 (0.5)
American Indian/ Alaskan Native	n (%)	13 (13.3)	8 (8.2)	9 (9.0)	8 (7.9)	38 (9.6)
Mixed race	n (%)	14 (14.3)	10 (10.3)	14 (14.0)	10 (9.9)	48 (12.1)
Weight (kg)	n	98	97	99	101	395
	Mean (SD)	77.0 (21.4)	76.6 (18.7)	76.6 (20.4)	75.0 (20.1)	76.3 (20.1)
	Min - Max	45-170	42-126	46-172	41-161	41-172
Height (cm)	n	96	97	99	99	391
	Mean (SD)	165.6 (9.5)	166.7 (9.9)	165.7 (11.0)	166.2 (9.1)	166.0 (9.9)
	Min - Max	147-191	130-190	130-195	142-191	130-195
BMI (kg/m^2)	n	96	97	99	99	391
	Mean (SD)	28.01 (6.94)	27.52 (6.28)	27.88 (7.08)	27.06 (6.42)	27.62 (6.67)
	Min - Max	18.0-59.1	15.2-47.3	18.2-68.0	15.6-57.0	15.2-68.0

Max=maximum; Min=minimum; SD=standard deviation; V=visit
[a] Age (years) at first study medication dispensation, body weight (kg) at Randomization Visit (V3), height at Screening Visit (V1), BMI=10000 * weight (kg) / [height (cm)]^2.

History of epileptic seizures and seizure types were generally similar across the treatment groups.

The mean duration of epilepsy was 24 years, and the mean age at onset of the first seizure was 14 years old. Overall, subjects had spent approximately 64% of their lives with epilepsy. Ten percent of subjects had a history of status epilepticus. The most common aetiologies of epilepsy in all subjects were unknown (44.4%), “other” (18.9%), and congenital malformation (10.4%).

All subjects had partial seizures. Eighty-eight percent of subjects had complex partial seizures, 59% had partial seizures with secondary generalization, and 46% had simple partial seizures. Less than 10% of subjects experienced generalized seizures (7.3%), clusters (0.8%), and unclassifiable epileptic seizures (0.5%). A lower percentage of subjects in the BRV 5mg/day group (35%) had simple partial seizures compared with subjects in the PBO (49%), BRV 20 mg/day (51%) and BRV 50 mg/day groups (48%). Half of the epileptic syndromes were classified as localization related–symptomatic (50.0%), followed by localization related–cryptogenic (24.2%), and localization related–idiopathic (16.4%); epileptic syndromes were unknown in 9.3% of subjects. No generalized epileptic syndromes (idiopathic, symptomatic, or cryptogenic) were confirmed or suspected at Baseline.

Overall, 328 subjects (82.8%) had a history of taking at least 1 previous AED. The most frequently reported previous AEDs were: CBZ (24.7%), VPA (24.2%), PHT (24.0%), LEV and TPM (22.5% each). The incidence of previous use of these AEDs was generally similar across treatment groups, with the exception of the BRV 20 mg/day group where a higher percentage of subjects took TPM (31.0%) or LTG (27.0%) compared with other

treatment groups. The numbers of subjects taking 0 to 1, 2 to 4, or 5 or more previous AEDs were generally similar across treatment groups. Approximately half of all subjects (46.0%) took 2 to 4 previous AEDs, while 37.4% of subjects took 0 to 1 previous AEDs, and 16.7% took 5 or more previous AEDs.

All but 1 subject were taking at least 1 concomitant AED at Baseline. The majority of subjects (78.3%) were taking 2 concomitant AEDs at Baseline. The most frequently used concomitant AEDs were: CBZ (40.4%), LTG (27.8%), LEV (19.2%), and PHT (17.2%). The proportion of subjects taking different types of concomitant AEDs showed slight variations between groups but overall the use of different concomitant AEDs was balanced between groups. The number of concomitant AEDs taken at Baseline was also generally similar across treatment groups, although a lower percentage of subjects in the BRV 20 mg/day group were taking 2 AEDs compared with the other treatment groups. Sixty-six subjects (16.7%) had VNS implants and 2 subjects (0.5%) had VNS implants removed prior to Baseline.

Overall, 300 subjects (75.8%) took at least 1 concomitant non-AED during the Treatment Period. The most frequently used concomitant non-AEDs overall were: paracetamol (18.7%), ibuprofen (15.2%), folic acid (9.3%), metamizole sodium (9.1%), and multivitamins (8.3%).

Outcomes and estimation

Primary efficacy analysis: % reduction over PBO in the POS frequency per week over the Treatment Period

The results for the mITT population are summarised in Table 9.

Table 9 - Primary Efficacy Analysis: Treatment Comparison of POS Frequency per Week over the Treatment Period in Study N01253 (mITT Population, ANCOVA)

Statistics	PBO	BRV		
		5mg	20 mg	50 mg
	(N=96)	(N=96)	(N=99)	(N=101)
LS means (log transformed) (SE)	1.418 (0.044)	1.427 (0.044)	1.376 (0.044)	1.282 (0.043)
LS means (back transformed)	3.131	3.168	2.961	2.602
Treatment comparison vs PBO				
% reduction over PBO		-0.9	4.1	12.8
95% confidence interval		-13.9, 10.6	-8.1, 15.0	1.7, 22.6
p-value[a]		0.885	0.492	0.025

SE=standard error
[a] Statistical significance against PBO was tested according to a predefined hierarchical sequential testing procedure starting with 50 mg, then 20 mg, and finally 5mg, only moving to the next test if the previous one was significant at the 5% level.

The primary efficacy analysis showed a statistically significant effect of the 50 mg dose but not for the lower doses. Sensitivity analyses to evaluate the impact of exclusion of subjects from the ITT population showed consistent results with the analysis conducted on the mITT population.

Secondary efficacy variables

- 50% responder rate

The results for subjects with ≥50% reduction in POS frequency per week over the Treatment Period were similar to those for the primary efficacy endpoint. In the PBO group, 16 out of 96 patients (16.7%) were responders compared to 21 out of 96 patients (21.9%) in the BRV 5mg/day group, 23 out of 99 patients (23.2%) in the BRV

20 mg/day group and 33 out of 101 patients (32.7%) in the BRV 50 mg/day group. Only the 50 mg dose was statistically significantly different from PBO (p=0.008).

- Other secondary efficacy variables

Similar results as for the primary efficacy analysis and 50% responder rate were also observed for other secondary endpoints including changes in all (Type I+II+III) seizure frequency, seizure frequency of all types, and percent reduction from Baseline in partial (Type I) seizure frequency.

The analysis for the categorized response rate in partial (Type I) seizure frequency per week revealed that an overall larger proportion of subjects in the PBO group showed -25% to <25% response compared with all 3 BRV groups. The proportion of subjects showing 25% to 75% response was similar across all groups. Larger proportions of subjects in the 3 BRV groups showed 75% to 100% and 100% responses compared with the PBO group. In addition, no subjects in the PBO group achieved 100% response, as compared with 7 subjects in the 3 BRV groups. Seizure freedom in all seizure types (type I+II+III) during the Treatment Period was achieved for 1 subject in the BRV 5mg/day and BRV 20 mg/day groups each and 4 subjects in the BRV 50 mg/day group. Median times to n^{th} POS were generally similar between treatment groups. Statistically significant differences in the hazard ratios between all BRV dose groups and the PBO group were observed in the time to the 1^{st} or 5^{th} POS. In the time to 10^{th} POS, statistically significant differences in the hazard ratios between the BRV 5mg/day and BRV 50 mg/day dose groups and the PBO group were observed.

The QOLIE-31-P results showed that mean change from Baseline to the last assessment in the Treatment Period for the Total score was similar between the PBO group (3.88) and BRV overall group (4.03). Mean change in HADS anxiety subscale scores from Baseline to the last assessment of the Treatment Period were statistically different between the PBO and BRV 50 mg/day groups (p=0.020); however, the difference was not clinically meaningful. There were no statistically significant differences in the mean changes from Baseline between treatment groups for the depression subscale.

Results from the P-GES showed that similar proportions of subjects in the PBO and BRV groups considered that their disease improved (slight, moderate, marked improvement) after treatment. Results from the I-GES showed that a larger proportion of subjects were considered by the Investigator to have improved (slight, moderate, or marked improvement) after treatment with BRV compared with PBO. For the P-GES or I-GES, no BRV group achieved statistical significance compared with PBO.

Ancillary analyses

- Concomitant LEV use

As in study N01252, concomitant LEV use at study entry was limited to 20% of the total study population, per protocol. In the PBO, BRV 5mg/day, BRV 20 mg/day and 50 mg/day groups, 19, 18, 19 and 19 patients had used LEV during the treatment period, respectively. In all 3 BRV dose groups without concomitant LEV use at study entry there were greater reductions over placebo in POS frequency per week compared with subjects with concomitant LEV use at study entry. Specifically for subjects in the BRV 50 mg/day group without concomitant LEV use, there was a 16.0% reduction over PBO for the primary efficacy analysis of POS frequency per week over the Treatment Period, while there was no observable treatment effect in subjects with concomitant LEV use (- 0.9%). Similar findings were observed with the secondary efficacy endpoints of 50% responder rate whereby no benefit compared to PBO was observed for patients with concomitant LEV use (15.8% PBO versus 16.7%, 10.5% and 5.3% for BRV 5mg/day, BRV 20 mg/day and 50 mg/day), while patients without concomitant LEV use more patients responded to BRV treatment (16.9% PBO versus 23.1%, 26.3% and 39.0% for BRV 5mg/day, BRV 20 mg/day and 50 mg/day).

Primary ANCOVA analysis of the log-transformed POS frequency per week over the Treatment Period, showed that the treatment-by-region interaction was not significant at the 0.10 level (p=0.310).

- Regional effect

Primary ANCOVA analysis of the log-transformed POS seizure frequency per week over the Treatment Period, including a treatment-by-region interaction term, showed that the treatment-by-region interaction was not significant at the 0.10 level. However, for each dose of BRV the reduction in seizure frequency was higher in Latin America than in North America/Australia. For North America/Australia the reduction for 50 mg/day was 8.9% and for Latin America 18.1%.

2.5.2.4. Results for Study N01358

Participant flow / numbers analysed

A total of 1045 subjects were screened for this study. A total of 768 subjects were randomized to either PBO or one of 2 BRV doses (100 mg/day, or 200 mg/day). Eight subjects were excluded from the ITT Population (see footnote of Table 10 for details). The ITT Population consisted of all randomized subjects who received at least 1 dose of study medication (N=760). Of these, 696 subjects (90.6%) completed the study. A total of 72 subjects (9.4%) discontinued the study. The Safety Population was comprised of 764 subjects; 4 subjects received at least 1 dose of study drug (and were included in the Safety Population) but did not have at least 1 post-Baseline seizure diary day and were therefore excluded from the ITT Population.

Table 10 - Disposition of Subjects in Study N01358

Screened subjects **Screen failures** **Total patients randomised** **ITT population**	**n= 1045** **n=277** [ineligibility n=222, withdrawal of consent n=31, adverse event n=8, lost to follow-up n=5, other reasons n=11] **n=768** [Eight randomised subjects were excluded from the ITT population[a]) **n=760**		
Study arm	**PBO**	**BRV 100 mg/day**	**BRV 200 mg/day**
ITT	n=259	n=252	n=249
Discontinued Adverse event Lack of efficacy Protocol violation Lost to follow-up Consent withdrawn Other reasons	n=17 n=10 n=1 n=0 n=0 n=2 n=4	n=29 n=21 n= 1 n=3 n=1 n=2 n=1	n=26 n=17 n=0 n=1 n=3 n=4 n=1
Completed	n=246	n=225	n=225
Entered LTFU study	n=237	n=219	n=220

[a] 4 subjects in the PBO group (2 prior to study drug administration, 1 due to consent withdrawn, 1 due to TEAE), 2 subjects in the BRV 100 mg/day group (1 prior to study drug administration, 1 due to TEAE), 2 subjects in the BRV 200 mg/day group (1 prior to study drug administration, 1 lost to follow-up)

Recruitment

The first subject enrolled on 10 December 2010 and the last subject completed the study on 22 May 2014. This study was conducted at 208 sites in 27 countries including countries in Europe, Asia as well as north and South America.

Conduct of the study

The protocol was amended once globally (concerning safety aspects) and had 12 country-specific amendments. The changes were considered by the CHMP not to affect the efficacy evaluation.

Baseline data

The demographics of subjects in study N01358 are displayed in Table 11. The treatment groups were generally balanced with regard to most demographic parameters. There were more female patients in the BRV 100 mg/day group compared to the other two groups.

Table 11 – Demographic Characteristics of Study N01358 (ITT)

Characteristics	Descriptive statistic	PBO N=261	BRV 100 mg/day N=253	BRV 200 mg/day N=250	All subjects N=764
Age (years)	n	261	253	250	764
	Mean (SD)	39.8 (12.5)	39.1 (13.4)	39.8 (12.8)	39.5 (12.9)
	Min, Max	16, 77	16, 80	16, 73	16, 80
Age category (years)					
<17	n (%)	3 (1.1)	2 (0.8)	3 (1.2)	8 (1.0)
≥17 to <65	n (%)	253 (96.9)	240 (94.9)	241 (96.4)	734 (96.1)
≥65	n (%)	5 (1.9)	11 (4.3)	6 (2.4)	22 (2.9)
Gender					
Male	n (%)	133 (51.0)	102 (40.3)	133 (53.2)	368 (48.2)
Female	n (%)	128 (49.0)	151 (59.7)	117 (46.8)	396 (51.8)
Overall racial group					
White	n (%)	189 (72.4)	182 (71.9)	182 (72.8)	553 (72.4)
Black	n (%)	11 (4.2)	8 (3.2)	7 (2.8)	26 (3.4)
Asian	n (%)	32 (12.3)	32 (12.6)	29 (11.6)	93 (12.2)
Other	n (%)	26 (10.0)	29 (11.5)	29 (11.6)	84 (11.0)
Ethnicity					
Hispanic or Latino	n (%)	40 (15.3)	40 (15.8)	36 (14.4)	116 (15.2)
Not Hispanic or Latino	n (%)	217 (83.1)	210 (83.0)	210 (84.0)	637 (83.4)
Weight (kg)	n	261	253	249	763
	Mean (SD)	76.1 (20.0)	74.1 (16.8)	75.4 (19.0)	75.2 (18.7)
	Median	74.0	74.0	72.0	73.6
	Min, Max	42, 158	40, 145	42, 176	40, 176
Height (cm)	n	258	250	249	757
	Mean (SD)	168.3 (10.0)	166.6 (9.8)	168.7 (9.9)	167.9 (9.9)
	Median	168.0	165.3	168.0	167.1
	Min, Max	141, 198	138, 192	142, 203	138, 203
BMI (kg/m^2)	n	258	250	248	756
	Mean (SD)	26.7 (5.7)	26.7 (5.7)	26.4 (6.0)	26.6 (5.8)
	Median	25.8	25.8	24.9	25.6
	Min, Max	15, 51	15, 51	16, 52	15, 52

Max=maximum; Min=minimum; SD=standard deviation

All treatment groups were generally balanced with respect to subjects' history and aetiologies of epilepsy. The mean duration of epilepsy for subjects at randomization was 23 years, and the mean age at onset of the first seizure was 17 years of age. Subjects had spent approximately 57% of their lives with epilepsy. Overall, 5% of subjects had a history of status epilepticus. The most common aetiologies of epilepsy in all subjects were congenital (16.1%), "other" (10.9%), and cranial trauma (8.6%).

Seizure types were similar across all treatment groups. All subjects had POS. A total of 85% of subjects had experienced complex partial seizures, 58% had experienced partial seizures evolving to secondarily generalization, and 47% had experienced simple partial seizures during their lifetime. Less than 10% of subjects had experienced generalized seizures (5.9%), clusters (3.9%), and unclassifiable epileptic seizures (0.4%).

Overall, 707 subjects (93.0%) had a history of taking at least 1 previous AED. The most frequently used previous AEDs were: LEV (54.2%), VPA (49.6%), CBZ (48.6%), TPM (40.0%), and PHT (38.0%). The prevalence of previous use of these AEDs was similar across treatment groups. Around half of the patients (47.2%) had taken ≥5 previous AEDs, while 33.8% of subjects took 2 to 4 previous AEDs and 18.9% took no or only 1 previous AEDs. The numbers of subjects taking 0 to 1, 2 to 4, or ≥5 previous AEDs were similar across treatment groups.

All subjects had taken at least 1 AED at study entry and during treatment. The most frequently used AEDs at study entry were: CBZ (37.2%), LTG (25.9%), and VPA (21.8%). AEDs taken concomitantly (i.e., during treatment) were similar to those taken at study entry. Use of AEDs was generally similar across treatment groups. The number of subjects taking AEDs at study entry was similar across regions. Overall, there were 11 subjects (1.4%) with active VNS and 21 subjects (2.8%) whose VNS were inactive.

Overall, 384 subjects (50.3%) took at least 1 concomitant non-AED at study entry. The most frequently used concomitant non-AEDs overall were: ibuprofen (5.0%), paracetamol (4.7%), levothyroxine sodium (3.9%), folic acid (3.7%), and acetylsalicylic acid (3.4%).

Outcomes and estimation

Primary efficacy analysis: 50% responder rate

The median Baseline POS frequency was similar across treatment groups for Type I seizures, reported for 760 subjects with a median of 9.5 POS per 28 days for all subjects. It was similar across the PBO, BRV 100 mg/day, and BRV 200 mg/day groups (10.0, 9.5, and 9.3 POS, respectively). During the Treatment Period, median POS frequency decreased to 8.7 POS in the PBO group, 6.3 POS in the BRV 100 mg/day group, and 5.8 POS in the BRV 200 mg/day group.

The results for the EU primary endpoint, the 50% responder rate based on % reduction in POS (Type I) frequency from Baseline to the 12-week Treatment Period, are summarised in Table 12.

Table 12 - 50% responder outcome for POS frequency in Study N01358 (ITT Population)

Statistics	PBO N=259	BRV 100 mg/day N=252	BRV 200 mg/day N=249
Number of subject analysed	259	252	249
Responders, n (%)	56 (21.6)	98 (38.9)	94 (37.8)
Non-responders, n (%)	203 (78.4)	154 (61.1)	155 (62.2)
Odds ratio (BRV vs PBO)	-	2.39	2.19
95% CI (LL, UL)	-	(1.6, 3.6)	(1.5, 3.3)
p-value[a]	-	<0.001*	<0.001*
p-value[b]	-	<0.001*	<0.001*

CI=confidence interval; LL=lower limit; UL=upper limit
* Statistically significant with control of Type I error rate based on a Hochberg multiple comparison procedure.
[a] p-values were not adjusted for multiplicity.
[b] Multiplicity-adjusted p-values were based on a Hochberg multiple comparison procedure.

The 50% responder outcomes in both the BRV 100 mg/day and 200 mg/day groups (38.9% and 37.8%, respectively) were greater than in the PBO group (21.6%). The odds ratios for the BRV 100 mg/day and 200 mg/day groups were 2.39 and 2.19, respectively; the difference compared to PBO was statistically significant for both BRV groups (p<0.001), regardless of whether the data were adjusted for multiplicity. No dose response was demonstrated for the BRV groups.

Secondary efficacy variables

- % reduction over PBO in the 28-day adjusted POS frequency over the Treatment Period

The 28-day adjusted frequency of POS (back-transformed LS means) were 9.2, 6.9 and 6.8 for the PBO, BRV 100 mg/day and the BRV200 mg/day groups. The percent reduction in the 28-day adjusted POS frequency over PBO in the BRV 100 mg/day and 200 mg/day groups was similar (22.8% and 23.2%, respectively) with no dose response. The differences compared to PBO were statistically significant for both BRV groups (p<0.001); p-values were the same regardless of whether the data were adjusted for multiplicity.

- Seizure freedom for all seizure types

Thirteen subjects (5.2%) in the BRV 100 mg/day group and 10 subjects (4.0%) in the BRV 200 mg/day group were seizure free during the Treatment Period compared with 2 subjects (0.8%) in the PBO group. The difference to PBO was statistically significant for both BRV groups.

- All seizure frequency (Type I+II+III) during the Treatment Period

Seizure frequency for the 28-day duration was reduced in the Treatment Period compared with the Baseline Period in both the BRV 100 mg/day group (from 9.5 to 6.3 seizures) and the BRV 200 mg/day group (from 9.3 to 5.8 seizures). The percent reduction over PBO was 22.6% and 22.8% in the BRV 100 mg/day and 200 mg/day groups, respectively, both of which were statistically significant (p<0.001).

The 50% responder outcome for seizure frequency for all seizure types in the BRV 100 mg/day and 200 mg/day groups was 38.5% and 37.8%, respectively, compared with the PBO group (21.6%) (p<0.001).

- Other secondary efficacy variables

The analysis for the categorized response rate in partial (Type I) seizure frequency per week showed overall, a larger proportion of subjects in the PBO group with percent reductions in POS frequency of <-25% and -25% to

<25% compared with the BRV groups. Larger proportions of subjects in the BRV 100 mg/day and 200 mg/day groups showed 50% to <75% and 75% to <100% reductions compared with the PBO group. The same proportion of subjects showed 100% seizure reduction in the BRV groups (6.0%, 15 patients each), which was greater than the PBO group (0.8%, 2 patients). Statistical analysis showed that the responses in the BRV 100 mg/day and 200 mg/day groups across the 6 categories were statistically significant ($p<0.001$) compared with the responses in the PBO group.

The median number of days to the 1st, 5th and 10th POS were consistently higher in the BRV groups compared with the PBO group. Statistically significant differences in the hazard ratios between all BRV dose groups and the PBO group were observed in the time to the 1st, 5th and 10th POS ($p \leq 0.009$).

Ancillary analyses

- Regional effect

For the regional subgroup analyses (North America, Latin America, Europe EU member states, Europe non-EU member states, Asia/Pacific/Other), the odds ratios (BRV versus PBO) for the 50% responder outcomes in the BRV 100 mg/day group were high for Latin America (4.61) and Asia/Pacific/Other (3.68) regions. The odds ratios were lower for Europe EU (2.29) and for North America (1.84). In the BRV 200 mg/day group, the odds ratios were generally high across North America (3.76), Latin America (4.66), and Asia/Pacific/Other (3.92) regions. The odds ratio was low in the region Europe EU (1.26).

- LEV status (never used LEV vs prior LEV use only)

For LEV-naïve subjects, the median difference versus PBO in POS frequency from Baseline was similar in the BRV 100 mg/day and 200 mg/day groups (23.4% and 20.7%, respectively). For subjects with prior LEV use, the differences were smaller; in the BRV 100 mg/day group the difference was 7.4% and in the 200 mg/day group it was 14.8%. The odds ratios for the 50% responder outcomes for subjects who had never used LEV were 2.70 and 2.12 for the BRV 100 mg/day and 200 mg/day groups, respectively. For subjects with prior LEV use, the odds ratios were 2.04 and 2.22 in the BRV 100 mg/day and 200 mg/day groups, respectively.

- Prior use of AEDs

The odds ratios for the 50% responder outcomes for subjects who used ≤2 previous AEDs were higher in the BRV 100 mg/day group (2.39) compared with the BRV 200 mg/day group (1.83). For subjects who had used >2 previous AEDs, the odds ratios were similar in the BRV 100 mg/day and 200 mg/day groups (2.39 and 2.43), respectively.

- Gender

The median % reduction in POS frequency from Baseline was lower in females compared with males. The median differences for the BRV 100 mg/day and 200 mg/day groups were in males 23.3% and 21.5%, and for females 10.7% and 13.9%, respectively.

2.5.2.5. Summary of main study(ies)

The following tables (Table 13, Table 14 and Table 15) 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).

Table 13 – Summary of efficacy for trial N01252

Title: A multi-center, double-blind, parallel-group, placebo-controlled, randomised study: Evaluation of the efficacy and safety of brivaracetam in subjects (≥16 to 70 years old) with partial-onset seizures						
Study identifier	N01252 (Clinical Trial Registry: NCT00490035)					
Design	Phase 3, therapeutic confirmatory, double-blind, parallel-group, placebo-controlled, randomised study					
	Duration of main phase:		12 weeks			
	Duration of Run-in phase:		8 weeks (baseline period; no treatment)			
	Duration of Extension phase:		4 weeks (including 2 weeks down-titration and 2 weeks study-drug free period). Long-term follow-up studies (optional after 12 weeks treatment period): N01125/N01199.			
Hypothesis	Superiority					
Treatments groups	BRV 20		BRV 20 mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 99 patients randomized.			
	BRV 50		BRV 50 mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 100 patients randomized.			
	BRV 100		BRV 100 mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 100 patients randomized.			
	PBO		Placebo tablets, 2 oral intakes over 12 weeks, 100 patients randomized.			
Endpoints and definitions	Primary endpoint	POS frequency	POS type I frequency per week (log transformed)			
	Secondary endpoint	50% POS responder rate	Proportion of subjects who had a ≥50% reduction in POS type I frequency per week from Baseline			
	Secondary endpoint	% reduction in POS frequency	Percent reduction for POS type I frequency per week from Baseline			
	Secondary endpoint	Seizure freedom rate	Seizure freedom rate (all seizure types)			
Database lock	09 Feb 2009 (last subject completed)					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Intent to treat (ITT); 12 weeks					
Descriptive statistics and estimate variability	**Treatment group**	**BRV 20**	**BRV 50**	**BRV 100**	***PBO***	
	Number of subjects (ITT)	**99**	**99**	**100**	***100***	
	POS frequency (median / LS means back transformed)	1.34 / 1.99	1.49 / 2.00	1.26 / 1.84	*1.75 / 2.21*	
	Q1, Q3 (median)	0.70, 3.12	0.69, 2.78	0.52, 2.93	*0.76, 5.12*	

	50% POS responder rate, n (%)	27 (27.3)	27 (27.3)	36 (36)	*20(20.0)*
	% reduction in POS frequency (median)	30.03	26.83	32.45	*17.03*
	Q1, Q3	2.11, 55.99	-6.32, 60.5	-0.04, 72.51	*-17.59, 40.27*
	Seizure freedom rate, n (%)	2 (2)	0 (0)	4 (4)	*0 (0)*

Effect estimate per comparison (according to hierarchical testing order)	Primary endpoint: POS frequency	Comparison groups	(1) BRV 50 vs PBO (2) BRV 100 vs PBO (3) BRV 20 vs PBO
		% reduction over PBO	(1) 6.5 (2) 11.7 (3) 6.8
		95% CI	(1) -5.2, 16.9 (2) 0.7, 21.4 (3) -4.8, 17.1
		P-value	(1) 0.261 (2) 0.037 [a)] (3) 0.239
	Secondary endpoint: 50% POS responder rate	Comparison groups	(1) BRV 50 vs PBO (2) BRV 100 vs PBO (3) BRV 20 vs PBO
		Odds ratio	(1) 1.36 (2) 2.13 (3) 1.39
		95% CI	(1) 0.69, 2.66 (2) 1.11, 4.10 (3) 0.71, 2.72
		P-value	(1) 0.372 (2) 0.023 [a)] (3) 0.339
	Secondary endpoint: % reduction in POS frequency	Comparison groups	(1) BRV 50 vs PBO (2) BRV 100 vs PBO (3) BRV 20 vs PBO
		Median difference	(1) -10.98 (2) -19.35 (3) -14.23
		95% CI	(1) -24.03, 1.74 (2) -32.75, -6.22 (3) -26.16, -2.46
		P-value	(1) 0.092 (2) 0.004[a)] (3) 0.019[a)]
	Secondary endpoint: Seizure freedom rate	Comparison groups	(1) BRV 50 vs PBO (2) BRV 100 vs PBO (3) BRV 20 vs PBO
		P-value	(1) n/a (2) 0.121 (3) 0.246
Notes	[a)] Nominally statistically significant outcome, but according to hierarchical testing, none of the groups were considered different from PBO. The number of subjects using LEV as concomitant AED was limited to 20% of the total study population (due to suspected PD interactions).		

Analysis description	The 3 doses of BRV were tested at the 5% significance level against PBO, according to a predefined hierarchical sequential testing procedure (control for multiplicity). The hierarchical testing procedure began with the BRV 50 mg/day dose versus PBO. If the comparison was not statistically significant, the procedure stopped and no groups were declared different from PBO. If the comparison was statistically significant, the BRV 50 mg/day group was considered different from PBO and next PBO was tested against BRV 100 mg/day dose in a similar manner. If the comparison was statistically significant, PBO was tested against BRV 20 mg/day. For the primary analysis, log-transformed POS frequency per week over the treatment period was analysed applying an analysis of covariance (ANCOVA) model, including treatment and a stratification effect combining study region and concomitant levetiracetam use as factors and the log-transformed Baseline seizure frequency per week as covariate. The primary analysis was performed on the ITT and PP population. The secondary analyses were performed on the ITT population.

Table 14 - Summary of efficacy for trial N01253

Title: An international, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with Partial Onset Seizures			
Study identifier	N01253 (Clinical Trial Registry: NCT00464269)		
Design	Phase 3, therapeutic confirmatory, double-blind, parallel-group, placebo-controlled, randomized study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 8 weeks (baseline period; no treatment) 3 weeks (including 1 week down-titration and 2 weeks study-drug free period). Long-term follow-up studies (optional after 12 weeks treatment period): N01199.
Hypothesis	Superiority		
Treatments groups	BRV 5		BRV 5mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 99 patients randomized.
	BRV 20		BRV 20 mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 100 patients randomized.
	BRV 50		BRV 50 mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 102 patients randomized.
	PBO		Placebo tablets, 2 oral intakes over 12 weeks, 99 patients randomized.
Endpoints and definitions	Primary endpoint	POS frequency	POS type I frequency per week (log transformed)
	Secondary endpoint	50% POS responder rate	Proportion of subjects who had a ≥50% reduction in POS type I frequency per week from Baseline
	Secondary endpoint	% reduction in POS frequency	Percent reduction for POS type I frequency per week from Baseline
	Secondary endpoint	Seizure freedom rate	Seizure freedom rate (all seizure types)
Database lock	02 Jan 2009 (last subject completed)		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Modified Intent To Treat (mITT); 12 weeks				
Descriptive statistics and estimate variability	**Treatment group**	**BRV 5**	**BRV 20**	**BRV 50**	***PBO***
	Number of subjects (ITT)	**96**	**99**	**101**	***96***
	POS frequency (median / LS means back transformed)	1.80 / 3.17	1.96 / 2.96	1.70 / 2.60	*2.15 / 3.13*
	Q1, Q3 (median)	0.99, 5.59	1.05, 5.45	0.91, 4.80	*1.43, 4.15*
	50% POS responder rate, n (%)	21 (21.9)	23 (23.2)	33 (32.7)	*16 (16.7)*
	% reduction in POS frequency (median)	19.95	22.52	30.47	*17.75*
	Q1, Q3	-12.96, 45.15	-4.56, 46.51	11.40, 59.78	*-5.11, 37.07*
	Seizure freedom rate, n (%)	1 (1)	1 (1)	4 (4)	*0 (0)*

Effect estimate per comparison (according to hierarchical testing order)	Primary endpoint: POS frequency	Comparison groups	(1) BRV 50 vs PBO (2) BRV 20 vs PBO (3) BRV 5 vs PBO
		% reduction over PBO	(1) 12.8 (2) 4.1 (3) -0.9
		95% CI	(1) 1.7, 22.6 (2) -8.1, 15.0 (3) -13.9, 10.6
		P-value	(1) 0.025 (2) 0.492 (3) 0.885
	Secondary endpoint: 50% POS responder rate	Comparison groups	(1) BRV 50 vs PBO (2) BRV 20 vs PBO (3) BRV 5 vs PBO
		Odds ratio	(1) 2.51 (2) 1.53 (3) 1.41
		95% CI	(1) 1.27, 4.96 (2) 0.75, 3.13 (3) 0.68, 2.91
		P-value	(1) 0.008 (2) 0.239 (3) 0.353
	Secondary endpoint: % reduction in POS frequency	Comparison groups	(1) BRV 50 vs PBO (2) BRV 20 vs PBO (3) BRV 5 vs PBO

		Median difference	(1) -15.69 (2) -4.50 (3) -0.14
		95% CI	(1) -27.00, -5.21 (2) -15.83, 6.65 (3) -11.60, 11.95
		P-value	(1) 0.003 (2) 0.386 (3) 0.991
	Secondary endpoint: Seizure freedom rate	Comparison groups	(1) BRV 50 vs PBO (2) BRV 20 vs PBO (3) BRV 5 vs PBO
		P-value	(1) 0.122 (2) >0.999 (3) >0.999
Notes	The number of subjects using LEV as concomitant AED was limited to 20% of the total study population (due to suspected PD interactions).		
Analysis description	The 3 doses of BRV were tested at the 5% significance level against PBO, according to a predefined hierarchical sequential testing procedure (control for multiplicity). The hierarchical testing procedure began with the BRV 50 mg/day dose versus PBO. If the comparison was not statistically significant, the procedure stopped and no groups were declared different from PBO. If the comparison was statistically significant, the BRV 50 mg/day group was considered different from PBO and next PBO was tested against BRV 20 mg/day dose in a similar manner. If the comparison was statistically significant, PBO was tested against BRV 5mg/day. For the primary analysis, log-transformed POS frequency per week over the treatment period was analysed applying an analysis of covariance (ANCOVA) model, including treatment and a stratification effect combining study region and concomitant levetiracetam use as factors and the log-transformed Baseline seizure frequency per week as covariate. The primary analysis was performed on the mITT and PP population. The secondary analyses were performed on the mITT population.		

Table 15 - Summary of efficacy for trial N01358

Title: A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group Study to Evaluate the Efficacy and Safety of Brivaracetam in Subjects (≥16 to 80 Years Old) with Partial-onset Seizures		
Study identifier	N01358 (Clinical Trial Registry: NCT01261325, EudraCT-Number: 2010-019361-28)	
Design	Phase 3, therapeutic confirmatory, double-blind, parallel-group, placebo-controlled, randomised study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks 8 weeks (baseline period; no treatment) 6 weeks (including 4 weeks down-titration and 2 weeks study-drug free period). Long-term follow-up studies (optional after 12 weeks treatment period): N01379
Hypothesis	Superiority	
Treatments groups	BRV 100	BRV 100 mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 254 patients randomized.
	BRV 200	BRV 200 mg/day, 2 equal oral intakes (tablets) in the morning and the evening over 12 weeks, 251 patients randomized.

	PBO		Placebo tablets, 2 oral intakes over 12 weeks, 263 patients randomized.
Endpoints and definitions	Primary endpoint	50% POS responder rate	50% responder rate based on percent reduction in POS (Type I) frequency from Baseline
	Secondary endpoint	28-day adjusted POS frequency	POS type I frequency per 28 days
	Secondary endpoint	% reduction in POS frequency	Percent reduction for POS type I frequency from Baseline
	Secondary endpoint	Seizure freedom rate	Seizure freedom rate (all seizure types)
Database lock	22 May 2014 (last subject completed)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT) 12 weeks			
Descriptive statistics and estimate variability	**Treatment group**	**BRV 100**	**BRV 200**	***PBO***
	Number of subjects (ITT)	**252**	**249**	***259***
	50% POS responder rate, n (%)	98 (38.9)	94 (37.8)	*56 (21.6)*
	28-day adjusted POS frequency (LS mean back transformed)	6.9	6.8	*9.2*
	% reduction in POS frequency (median)	37.2	35.6	*17.6*
	Q1, Q3	0.1, 69.4	4.8, 66.2	*-8.3, 46.0*
	Seizure freedom rate, n (%)	13 (5.2)	10 (4.0)	*2 (0.8)*

Effect estimate per comparison	Primary endpoint: 50% POS responder rate	Comparison groups	(1) BRV 100 vs PBO (2) BRV 200 vs PBO
		Odds ratio	(1) 2.39 (2) 2.19
		95% CI	(1) 1.6, 3.6 (2) 1.5, 3.3
		P-value	(1) <0.001 (2) <0.001
	Secondary endpoint: 28-day adjusted POS frequency	Comparison groups	(1) BRV 100 vs PBO (2) BRV 200 vs PBO
		% reduction over PBO	(1) 22.8 (2) 23.2
		95% CI	(1) 13.3, 31.2 (2) 13.8, 31.6
		P-value	(1) <0.001 (2) <0.001
	Secondary endpoint: %	Comparison groups	(1) BRV 100 vs PBO (2) BRV 200 vs PBO

	reduction in POS frequency	Median difference	(1) 15.8 (2) 18.1
		95% CI	(1) 7.6, 24.2 (2) 10.4, 26.4
		P-value	(1) <0.001 (2) <0.001
	Secondary endpoint: Seizure freedom rate	Comparison groups	(1) BRV 100 vs PBO (2) BRV 200 vs PBO
		P-value	(1) 0.003 (2) 0.019
Notes	Subjects currently receiving LEV were excluded from this study due to potential PD interactions.		
Analysis description	The primary analysis was based on a logistic regression model with an effect for treatment, an effect for country, and an effect for the 4 combination of levels for levetiracetam status and number of previous AEDs (≤2 vs >2), and log-transformed Baseline POS frequency as a continuous covariate. Odds ratios and corresponding 95% 2-sided Wald CIs were provided. The evaluation of statistical significance for the primary analysis was based on a Hochberg multiple comparison. Both multiplicity-adjusted p-values and unadjusted p-values were presented. Both primary and secondary analyses were performed on the ITT population. All statistical testing was carried out at a 2-sided 0.05 significance level unless otherwise indicated.		

2.5.2.6. Analysis performed across trials (pooled analyses and meta-analysis)

The data from the clinical trials were combined in 3 pools:

- The primary efficacy study pool, designated as **Pool E1**, consisted of subjects included in the primary efficacy analyses for N01252, N01253, and N01358 but excluded subjects receiving LEV at the time of study entry for N01252 and N01253.
- A supportive efficacy study pool, designated as **Pool E2**, consisted of subjects included in the primary efficacy analyses for N01252 and N01253. Both subjects receiving and not receiving LEV at the time of study entry were included.
- Long-term efficacy was evaluated using **Pool E3**, which consisted of subjects with focal epilepsy with uncontrolled POS receiving BRV in LTFU studies N01125, N01199, and N01379 (subjects entered these studies from N01114, N01193, N01252, N01253, N01254, and N01358).

All pooled study summaries for the evaluation of % reduction of POS frequency over PBO were based on 28-day adjustment (as compared to 7-days used in studies N01252 and N01253).

Pool E1

Study Pool E1 consisted of subjects included in the primary efficacy analyses for N01252 (ITT), N01253 (mITT) and N01358 (ITT). Subjects receiving LEV at the time of study entry for N01252 and N01253 were excluded from this study pool to ensure consistency, since N01358 did not allow enrolment of subjects receiving LEV at study entry.

Pool E1 comprised 418 PBO subjects and 903 BRV subjects. The demographic characteristics for the groups in Pool E1 showed that overall, the mean age of subjects was 38.2 years, ranging from 16 to 80 years, with the majority of subjects within the 17 to <65 year age category (96.3%). Approximately half of subjects were male (50.1%), and the majority of subjects were White (72.1%). The mean BMI was 26.3kg/m^2, with the majority of

subjects within the 18.5 to <25kg/m^2 BMI category. Overall, the demographic characteristics of the groups in Pool E1 with regard to age, gender, racial group, weight, height, and BMI were balanced across treatment groups.

Overall, at study entry in Pool E1, more than one-half of subjects (56.2%) had never used LEV and 43.8% of subjects had previously used LEV. A total of 39.3% of subjects had previously taken 2 to 4 AEDs, 35.5% had previously taken at least 5 AEDs, and 25.2% of subjects had previously taken and discontinued none or 1 AED. Slight differences were noted in the 20 mg and 50 mg groups, where the proportion of subjects who never had used LEV was higher (70-71%) than in the other groups (46-54%). The 20 and 50 mg groups had also a higher proportion of subjects with AED inducer at study entry (77-79% versus 64-66% in the other groups). Seizure types were generally similar across all treatment groups.

Summaries for Pool E1 present results for PBO and BRV 20 mg/day, 50 mg/day, 100 mg/day, and 200 mg/day. The results for BRV 5mg/day, which was included only in study N01253, were not presented.

- 50% responder rate

The results of the analysis for the 50 % responder rate for BRV doses in the range of 20 mg/day to 200 mg/day for each of the 3 primary efficacy studies and the primary efficacy study pool, Pool E1, are presented in Table 16. The individual results for N01252 and N01253 are based on the entire population studied, including subjects receiving LEV at study entry.

Table 16 – 50% Responder Rate in POS frequency over the Treatment Period in N01252, N01253, N01358, and Pool E1

Statistics	PBO	BRV (mg/day)			
		20	50	100	200
N01252 (ITT Population)					
n/N (%)	20/100 (20.0%)	27/99 (27.3%)	27/99 (27.3%)	36/100 (36.0%)	--
Odds ratio	--	1.39	1.36	2.13	--
95% CI	--	0.71, 2.72	0.69, 2.66	1.11, 4.10	--
p-value	--	0.339	0.372	0.023[f]	--
N01253 (mITT Population)					
n/N (%)	16/96 (16.7%)	23/99 (23.2%)	33/101 (32.7%)	--	--
Odds ratio	--	1.53	2.51	--	--
95% CI	--	0.75, 3.13	1.27, 4.96	--	--
p-value	--	0.239	0.008[g]	--	--
N01358 (ITT Population)					
n/N (%)	56/259 (21.6%)	--	--	98/252 (38.9%)	94/249 (37.8%)
Odds ratio	--	--	--	2.39	2.19
95% CI	--	--	--	1.6, 3.6	1.5, 3.3
p-value	--			<0.001[g]	<0.001[g]
Pool E1[e]					
n/N (%)	85/418 (20.3%)	46/146 (28.6%)	55/161 (34.2%)	131/332 (39.5%)	94/249 (37.8%)
Odds ratio	--	1.62	2.15	2.56	2.27
95% CI	--	1.0, 2.6	1.3, 3.4	1.8, 3.6	1.5, 3.3
p-value	--	0.04886	0.00150	<0.00001	<0.00003

[e] Odds ratio, CIs, and p-value for the treatment effect on percent responders based on a logistic regression model with effects for treatment and study, and log-transformed Baseline partial seizure frequency as covariate.
[f] Statistically significant at the 0.050 significance level without control for multiplicity (individual studies only).
[g] Statistically significant with control for multiplicity.

All BRV group doses showed statistical superiority over PBO, although the result for BRV 20 mg/day (28.6%) was of borderline statistical significance. A trend for dose-response was seen in the interval from 20 mg/day to 100 mg/day.

- % reduction in POS seizure frequency

The baseline median POS frequency for Type I seizures was similar across treatment groups in Pool E1, with 9.6, 7.9, 8.9, 8.9 and 9.3 seizures (28-day adjusted) for PBO, BRV 20 mg/day, BRV 50 mg/day, BRV 100 mg/day and BRV 200 mg/day, respectively. During treatment, the seizure frequency was reduced over PBO by 11.7%, 19.5%, 24.4% and 240% in the BRV 20 mg/day, BRV 50 mg/day, BRV 100 mg/day and BRV 200 mg/day groups, respectively. The difference over PBO was statistically significant for all but the BRV 20 mg/day group (p=0.0674).

The percentage of patients by category of reduction from baseline in POS frequency per 28 days in Pool E1 is shown in Table 17.

Table 17 – Categorised Response in POS frequency (per Week) over the Treatment Period in Pool E1

Category	PBO	BRV			
		20 mg/day	50 mg/day	100 mg/day	200 mg/day
Pool E1					
N	417	161	161	332	249
<-25%	68 (16.3)	20 (12.4)	18 (11.2)	42 (12.7)	27 (10.8)
-25% to <25%	174 (41.7)	53 (32.9)	47 (29.2)	95 (28.6)	73 (29.3)
25% to <50%	90 (21.6)	42 (26.1)	41 (25.5)	64 (19.3)	55 (22.1)
50% to <75%	56 (13.4)	29 (18.0)	34 (21.1)	60 (18.1)	45 (18.1)
75% to <100%	27 (6.5)	13 (8.1)	16 (9.9)	52 (15.7)	34 (13.7)
100%	2 (0.5)	4 (2.5)	5 (3.1)	19 (5.7)	15 (6.0)
p-value	--	0.00757	0.00025	<0.00001	<0.00001

Note: Subjects with zero seizure frequency per week at Baseline are classified in the <-25% category

The percentages of patients with at least a 50% reduction in POS frequency were 20.3%, 34.2%, 39.5%, and 37.8% for placebo, 50 mg/day, 100 mg/day, and 200 mg/day, respectively.

- Seizure freedom from all seizure types (type I+II+III) during the treatment period

In Pool E1, 1.9% (3/161), 2.5% (4/161), 5.1% (17/332) and 4.0% (10/249) of the patients on BRV 20 mg/day, 50 mg/day, 100 mg/day and 200 mg/day respectively achieved seizure freedom from all seizure types (Type I+II+III) during the 12-week treatment period compared with 0.5% (2/418) on placebo. A total of 31 subjects achieved seizure freedom in the proposed therapeutic dose range of 50 mg/day to 200 mg/day.

- Response to treatment by region

Response to treatment by region for Pool E1 is presented in Table 18 for the 50% responder rate. Similar trends for the 50% responder rate and reduction in seizure frequency per 28 days from baseline were observed with regards to regional effects.

In general, a trend towards a numerically lower response rate was seen in Europe (EU) than in most other regions for the proposed therapeutic dose range of 50 mg/day to 200 mg/day. A similar trend for lower response rates or lower reduction in POS seizure frequency in Europe (EU) was reported in the pivotal studies N01252 and N01358. Furthermore, a smaller effect size was observed in the 200 mg/day group in Europe (EU) compared to the effect observed in all the other regions as well as the 100 mg/day group in Europe (EU).

Table 18 – 50% Responder Outcome for POS frequency by Region (Pool E1)

Region	PBO N=418	BRV (mg/day)			
		20 N=161	50 N=161	100 N=332	200 N=249
North America					
Number of subjects analyzed	87	29	32	64	61
Responders n (%)	15 (17.2)	8 (27.6)	14 (43.8)	20 (31.3)	30 (49.2)
Odds ratio (BRV vs PBO)	--	2.85	6.40	1.84	3.77
Latin America					
Number of subjects analyzed	71	43	43	27	28
Responders n (%)	13 (18.3)	11 (25.6)	17 (39.5)	13 (48.1)	14 (50.0)
Odds ratio (BRV vs PBO)	--	1.73	3.31	3.42	3.73
Europe (EU)					
Number of subjects analyzed	185	59	53	175	125
Responders n (%)	44 (23.8)	15 (25.4)	13 (24.5)	68 (38.9)	36 (28.8)
Odds ratio (BRV vs PBO)	--	1.07	1.07	2.17	1.21
Europe (non-EU)					
Number of subjects analyzed	11	0	5	13	7
Responders	3 (27.3)	0	2(40.0)	7 (53.8)	3 (42.9)
Odds ratio (BRV vs. PBO)	--	--	1.04	3.24	2.19
Asia/Pacific/Other					
Number of subjects analysed	64	30	28	53	28
Responders	10 (15.6)	12 (40.0)	9(32.1)	23 (43.4)	11 (39.3)
Odds ratio (BRV vs PBO)	--	3.84	2.38	3.95	4.18

- Other subgroup analyses

In Pool E1, the 50% responder rates were higher across the PBO group and all BRV groups for subjects who had never used LEV compared with subjects who had previously used LEV. For subjects who had never used LEV, the 50% responder rates were 28.9%, 37.2%, 48.3%, and 45.2% for BRV 20 mg/day, BRV 50 mg/day, BRV 100 mg/day, and BRV 200 mg/day, respectively, compared with PBO (22.5%). The 50% responder rates in subjects who had previously used LEV were 27.7%, 27.1%, 29.7%, and 31.3% for BRV 20 mg/day, BRV 50 mg/day, BRV 100/mg/day, and BRV 200 mg/day respectively, compared with PBO (17.8%).

No differences in efficacy were observed within the dose range of 50 mg/day to 200 mg/day when BRV was combined with inducing or non-inducing AEDs. Median % reductions in seizure frequency per 28 days from baseline for BRV 50 mg/day, 100 mg/day and 200 mg/day were 34.4% (n=124), 37.1% (n=213) and 38.4% (n=162) for patients using AEDs inducers at study entry and 36.0% (n=37), 40.2% (n=119) and 33.8% (n=87) for patients for patients who did not take any AED inducers.

With regards to the impact of gender, the results for mean percent reduction of seizure frequency from baseline were similar for male and female subjects for PBO and BRV 50 mg/day. For the 100 mg/day and 200 mg/day doses men had a higher mean seizure frequency reduction (35.4%, n=147 for BRV 100 mg/day; 34.1%, n=133 for BRV 200 mg/day) than women (24.6%, n=185 for BRV 100 mg/day; 26.9%, n=116 for BRV 200 mg/day).

The majority of subjects were White. Asians had numerically higher seizure reductions than Whites in the interval 20 mg-100 mg/day, but not for the 200 mg/day dose. The number of Black subjects was too low to permit any conclusions.

Pool E2

Study Pool E2 consisted of all subjects included in the primary efficacy analysis for N01252 and N01253 irrespective of LEV use at the time of study entry. Pool E2 was primarily defined for the evaluation of subgroup effects for subjects using and not using LEV at the time of study entry.

Pool E2 comprised 196 PBO subjects and 498 BRV subjects. The average age of subjects in Pool E2 was 36.9 years , 53.7% were male, and 46.3% were female. The majority of subjects (74.8%) were white.

- 50% responder rate and % reduction in POS seizure frequency

The pooled analysis of studies N01252 and N01253 showed statistically significant results compared to PBO for BRV 50 mg/day and BRV 100 mg/day for both % reduction in 28 day adjusted POS frequency and 50% responder rate, whereas the result for the 20 mg/day dose were non-significant. The % reduction in the 28-day adjusted POS frequency compared to PBO (9.9%, 16.4%, and 22.5% for BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day, respectively) was similar between Pool E1 and Pool E2. The 50% responder rates were 18.4 (36/196), 25.3% (50/198), 30.0% (60/200), and 36.0% (36/100) in the PBO, BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day groups, respectively.

- Efficacy results by LEV status

The % reduction over placebo in 28–day adjusted POS frequency by LEV use at study entry is shown in Table 19. No seizure reduction was observed in subjects treated with LEV at core study entry. In subjects with previous LEV only, seizure reductions were numerically lower compared to subjects who never used LEV.

Table 19 - % Reduction over Placebo in 28-Day adjusted POS Frequency by LEV Status (Pool E2)

Statistics	PBO	BRV (mg/day)		
		20	50	100
LEV at core study entry				
n	37	37	39	20
% reduction over PBO	--	-8.0	-7.2	-13.9
Previous LEV only				
n	49	47	48	22
% reduction over PBO	--	10.4	8.2	24.6
Never used LEV				
n	109	114	113	58
% reduction over PBO	--	15.3	26.6	31.1
No LEV at core study entry				
N	158	161	161	80
% reduction over PBO	--	13.5	21.1	29.3
95% CI	--	1.1, 24.4	9.7, 31.1	15.9, 40.6
p-value	--	0.03459	0.00059	0.00010

With regards to the 50% responder rate, for subjects who had never used LEV, the rates were 17.3%, 28.9%, 37.2%, and 43.1% for PBO, BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day, respectively. The odds ratios were 2.06, 3.09, and 3.69 for BRV 20 mg/day, BRV 50 mg/day, BRV 100 mg/day, respectively. The 50% responder rates in subjects who had previously used LEV were 20.4%, 27.7%, 27.1%, and 36.4% for PBO, BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day, respectively. The odds ratios were 1.46, 1.45, and 2.50 for the BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day, respectively.

Pool E3

Pool E3 consisted of subjects who received BRV in open label follow-up studies N01125, N01199 and N01379 (see section 2.5.2.8. for a brief summary of the individual study data). The presented data are based on a clinical cut-off date of 17 January 2014, except for some of the exposure data, which were provided upon request by the CHMP with a later cut-off at 1 October 2014. By this time, of the 1904 subjects included in Pool E3, more than half had discontinued. The most common reason for discontinuation was lack of efficacy (n=499, 26.2%) followed by AEs (n=211, 11.1%). The study was ongoing for 870 subjects at the time of cut-off.

Subjects who were taking LEV at core study entry had the option to discontinue LEV or add other AEDs during the LTFU. The majority of subjects (86.4%) was not using LEV at core study entry and had never used LEV (55.2%). The most common AEDs taken at study entry were CBZ (42.5%) followed by LTG (24.6 %), VPA (22.5 %), OXC (16.2 %) and TPM (15.3 %). Use of AEDs at study entry was generally similar between Pool E1 and Pool E3.

The median % reduction of POS increased over time through the 96-month cohort (from 48.8% in the 6 month cohort to 66.7% in the 96-month cohort per 28-day period). The same tendency was seen for the proportion of 50% responders. For the subjects who remained in the study and on BRV treatment, the percentages of 50% responders increased at each efficacy time interval assessed through 90 months (range: 49.3% to 73.3%).

Of subjects exposed to BRV for 6 months (N=1500), 12 months (N=1188), and 24 months (N=847), the percentages of seizure-free subjects were 5.3 %, 4.6 % and 3.7, respectively.

As of 1 Oct 2014, the proportions of subjects exposed to BRV for ≥6 months by modal dose were 11.7%, 19.6%, 42.0%, and 22.7% at 50mg/day, 100mg/day, 150mg/day, and 200mg/day, respectively.

2.5.2.7. Clinical studies in special populations

Elderly patients

No specific efficacy study was performed in the elderly population. In the phase II/III studies, there were 44 elderly subjects with epilepsy (39 subjects between 65 and 74 years of age, and 5 subjects between 75 and 84 years of age, whereas no subject was 85 years or older). Data from an additional 16 subjects aged 65 to 74 years and 6 subjects aged 75 to 84 years were available from clinical pharmacology studies.

Renally and hepatically impaired patients

See section 2.4. for a summary of relevant clinical PK data.

2.5.2.8. Supportive studies

Supportive efficacy data were available from study N01254, a PBO controlled flexible dose study. Furthermore, supportive data from long-term follow-up studies and conversion to monotherapy studies were provided.

Study N01254

Study N01254 was a randomised, double-blind, parallel-group, PBO-controlled, flexible dose study with the primary objective of assessing the safety and tolerability of BRV at doses from 20 to 150 mg/day in subjects aged 16 to 70 years and suffering from localization-related or generalized epilepsy. A secondary objective was to investigate the efficacy of BRV on POS (Type I) frequency in subjects suffering from localisation related epilepsy. An exploratory objective of the study was to explore the efficacy of BRV in reducing Type II seizure

days in subjects suffering from generalized epilepsy. The inclusion criteria for this study were similar to the three pivotal studies, however both subjects with focal and generalised epilepsy were included. Subjects with generalised epilepsy were limited to 20% of the study population.

After completing a 4-week baseline period, a total of 480 subjects were centrally randomized 3:1 to one of two treatment arms (BRV 20 mg/day or matching PBO) and entered an 8-week dose-finding period. During the dose-finding period, subjects either remained at the BRV 20 mg/day dose or were up-titrated to either BRV50 mg/day, BRV 100 mg/day, or BRV 150 mg/day in a stepwise manner. Up-titration was based on the investigators assessment of efficacy and tolerability. One fall-back option was offered at doses ≥50 mg/day. Subjects then entered an 8-week maintenance period at the last dose reached in the dose-finding period.

The primary analysis was done on the ITT population, which consisted of all randomized subjects who received at least 1 dose of study medication (n=480 total, n=121 PBO, and n=359 BRV). The ITT POS population included 431 subjects and the ITT PGS (primary generalised seizures) population 49 subjects. The percentages of subjects receiving during the maintenance period BRV doses of 20, 50, 100, and 150 mg/day were 5.8%, 15.6%, 23.4%, and 48.2%, respectively.

In subjects suffering from localization-related epilepsy, the main efficacy variable was the POS frequency per week over the treatment period (dose-finding and maintenance period). The primary efficacy endpoint, % reduction over PBO of POS frequency was 7.3%, which was not a statistically significant difference (p=0.125). Additional sensitivity analyses were consistent with the primary ANCOVA analysis. Contrary to the results for the primary efficacy endpoint, the secondary endpoint 50% responder rate over the treatment period was statistically significantly different for BRV (30.3%, 98/323) compared with PBO (16.7%, 18/108) (p=0.006). Due to the small number of patients enrolled with PGS, the results were explored by descriptive analysis only. The median % reduction from baseline in PGS days per week over the treatment period was higher in the BRV group (42.6%) than in the PBO group (20.7%). The 50% responder rate in generalised seizure days per week over the treatment period was 15.4% (2/13) for the PBO group and 44.4% (16/36) for the BRV group.

Long-term follow-up studies

Long-term efficacy data were available from 3 open label follow-up studies N01125, N01199 and N01379, which were ongoing at the time of the submission of this application. These studies comprised patients who participated in and completed studies N01114, N01193, N01252, N01253, N01254, and N01358 and opted to enrol in a LTFU study thereafter. Only limited efficacy data are available from these studies. The presented data are based on a clinical cut-off date of 17 January 2014.

Studies N01125 and N01199 (LTFU for studies N01252 and N01253) initially provided for a maximum dose of BRV 150 mg/day. When the maximum dose was increased to BRV 200 mg/day in study N01358, the protocols for the LTFU studies N01125 and N01199 were amended to also allow for a maximum dose of BRV 200 mg/day. Subjects who were taking LEV at core study entry had the option to discontinue LEV or add other AEDs during the LTFU.

Study N01125 was an open-label, multicentre study to evaluate long-term safety and maintenance of efficacy of BRV oral tablets used as adjunctive treatment at a flexible dose up to a maximum of 200 mg/day. This study enrolled subjects with epilepsy aged 16 years or older who participated in studies N01252 (Europe only), N01114, or N01254 (Europe and Asia only). The individual starting dose of each subject was the dose recommended at the end of the previous study prior to enrolment in N01125. A total of 853 subjects were enrolled in this study. By the clinical cut-off date of 17 January 2014, there were 293 subjects on-going. The most common reason for discontinuation was lack of efficacy (337 subjects [39.5%]), followed by AEs (90 subjects [10.6%]). There was up to 96 months of exposure to BRV treatment in the study as of the clinical

cut-off. Subjects with POS on treatment reported a median reduction in POS frequency from Baseline of 41.5% per 28-day period. Subjects who remained in the study and on BRV treatment reported increasing median per cent reductions from Baseline at each efficacy time interval assessed through 24 months (reduction range: 47.6% to 59.0%) and remained stable at about 60% thereafter. Overall, 42.9% of all subjects with POS on treatment were 50% responders. For the subjects who remained in the study and on BRV treatment, the percentages of 50% responders increased consistently at each efficacy time interval assessed through 24 months (range: 46.7% to 61.1%) and remained stable at about 60% thereafter. Overall, 2.4% of the subjects with POS treated with BRV for at least 6 months were seizure free for the first 6 months of treatment. In the 48-month cohort, 4.1% of the subjects were continuously seizure free for 42 months and 2.4% of the subjects were continuously seizure free for 48 months).

Study N01199 was an open-label, multicentre, LTFU study to evaluate long-term safety and maintenance of efficacy of BRV used as adjunctive treatment at a flexible dose up to a maximum of 200 mg/day. The individual starting dose of each subject was the dose recommended at the end of the previous study prior to enrolment in N01199. This study enrolled subjects with epilepsy aged 16 years or older who participated in core studies N01193, N01252, N01253, and N01254. From these trials, a total of 668 subjects were enrolled. At the time of the clinical cut-off date, there were 239 subjects on-going in the study. Overall, the most common reason for discontinuation was lack of efficacy (150 subjects [22.5%]), followed by AEs (100 subjects [15.0%]). As of the clinical cut-off date, there was up to 90 months of exposure to BRV treatment in the study. Subjects on treatment reported a median reduction in POS frequency from Baseline of 54.6% per 28-day period. Subjects who remained in the study and on BRV treatment reported increasing median % reductions from Baseline at each efficacy time interval assessed through 48 months (reduction range: 44.4% to 68.9%). Overall, 53.9% of all subjects on treatment were 50% responders. For the subjects who remained in the study and on BRV treatment, the percentages of 50% responders increased at each efficacy time interval assessed through 48 months (range: 43.8% to 71.4%). A total of 28.2% of the subjects on BRV treatment were seizure free for any continuous 6-month period.

Study N01379 was an open-label, multicentre, LTFU study to evaluate long-term safety and efficacy of BRV used as adjunctive treatment at a flexible dose up to a maximum of 200 mg/day. The majority of subjects enrolled in N01379 had POS and came from primary efficacy study N01358. Other patients with localization related or generalized epilepsy came from N01258. Subjects from N01358 were started on a BRV dose of 150 mg/day at study entry. A total of 627 subjects were enrolled and by the clinical cut-off date of this submission, 431 subjects were ongoing in the study. The most common reason for discontinuation was lack of efficacy (74 subjects [11.8%]), followed by AEs (60 subjects [9.6%]). As of the clinical cut-off date, there was up to 30 months of exposure to BRV. Subjects on treatment reported a median % reduction in POS frequency from Baseline of 52.2% per 28-day period. Subjects who remained in the study and on BRV treatment reported increasing median percent reductions from Baseline at each efficacy time interval assessed through 18 months (reduction range: 51.9% to 69.7%). Overall, 51.2% of all subjects on treatment were 50% responders. For the subjects who remained in the study and on BRV treatment, the percentage of 50% responders increased consistently at each efficacy time interval assessed through 18 months (range: 53.2% to 72.7%). A total of 16.9% of the subjects on BRV treatment were seizure free for any continuous 6-month period of treatment.

Conversion to monotherapy studies

Two double-blind, randomised, multicentre, parallel-group historical-control conversion to monotherapy studies have been conducted (N01276 and N01306) in subjects with uncontrolled POS. These studies were terminated prematurely upon a recommendation from the Independent Data Monitoring Committee, as an interim analysis using predefined criteria indicated futility.

2.5.3. Discussion on clinical efficacy

The main evidence for efficacy for BRV in the treatment of refractory POS was derived from two phase II dose-finding studies and three pivotal phase III studies investigating BRV as add-on treatment to baseline AED therapy. Supportive efficacy data were available from three ongoing long-term follow-up studies as well as a flexible dose study with the primary objective to investigate safety and tolerability. In these studies, BRV doses from 5 mg/day to 200 mg/day given in two equal doses in the morning and in the evening were explored.

Design and conduct of clinical studies

The conduct and design of the two dose-finding studies were generally considered acceptable, including the choice of the patient populations, treatment duration and endpoints. The studies differed in the dose ranges investigated and countries where the studies were conducted. The study exploring the lower end of the dose range (5, 20 and 50 mg/day) was conducted in countries in America and Asia, while the study investigating the upper end of the dose range (50 and 150 mg/day) was carried out in EU countries.

On the basis of the Phase II study results, the Phase III BRV POS program was initiated presuming 50 mg/day as the optimal dose. Two of the three phase III trials had identical designs, but evaluated different doses of BRV, 20, 50 and 100 mg/day in study N01252 and 5, 20 and 50 mg/day in N01253. There was no up-titration of the dose at treatment start. In these studies, use of LEV as a concomitant medication was allowed but limited to no more than 20% of the total study population. The third phase III study, N01358, restricted the population to subjects without concomitant or recent use of LEV. This decision was made further to a meta-analysis of the two previous phase III trials, which showed that the use of LEV may have influenced the overall therapeutic response in these studies. Study N01358 explored the upper dose range of BRV at doses of 100 and 200 mg/day. Overall, the approach for the clinical efficacy evaluation was considered acceptable.

All three pivotal phase III studies were designed as multicentre, randomized, double-blind add-on studies comparing BRV to PBO in addition to an existing AED regimen. Subjects were aged 16-80 years and were uncontrolled with regards to their POS while treated with 1 to 2 permitted concomitant AEDs, which is in line with the indication as claimed by the applicant. The choice of the study population was not surprising for a new antiepileptic agent, which are traditionally first tested in adult patients with POS despite treatment with other AEDs. As the studies were initiated prior to the ILAE 2010 definition of treatment resistant epilepsy, the inclusion criteria did not require failure of two adequate trials of AED schedules. However, the patient population enrolled was drug resistant by generally accepted criteria at the time of study initiation, including a high baseline seizure frequency and inadequate seizure control with at least one AED trial.

Concomitant AEDs were to be kept stable throughout the baseline and treatment period of all studies. Upon an enquiry by the CHMP, the applicant confirmed that the number of patients who changed type and number of AEDs during the study periods were few and sensitivity analyses, excluding patients who modified the dose of concomitant AEDs during the study period, provided consistent results compared to the original analyses.

Overall, the design of all pivotal studies was essentially in accordance with the CHMP guideline on clinical investigation of medicinal products in the treatment of epileptic disorders, with the exception that in the first two pivotal trials (N01252 and N01253) the primary endpoint was the change in POS frequency per week over the treatment period and not a responder outcome, which is recommended in the guideline. The 50% responder rate, i.e. rate of patients with at least 50% reduction in POS frequency over the treatment period, was however included as secondary endpoint. In the third study, N01358, different primary endpoints were defined for the USA and Europe. In line with the guideline, in Europe the primary endpoint was the 50% responder rate, whereas reduction in POS frequency was included as secondary endpoint (primary endpoint in USA).

Efficacy data and additional analyses

For all phase II and III studies, no major concerns arose from the study conduct and numbers of patients analysed. Baseline characteristic were generally balanced between groups with few exceptions, which are discussed as relevant in the context of the trials' outcome below. Only few subjects recruited were 65 years and older and the limited experience in elderly was reflected in SmPC section 4.2.

The dose-finding study exploring the lower end of the dose range of BRV indicated a numerical dose response relationship for the investigated daily doses of 5, 20 and 50 mg. While only the 50 mg/day dose group showed a statistically significant higher % reduction over PBO in POS frequency, all BRV groups were statistically superior to PBO with regards to the 50% responder rate. In one of the participating countries, Brazil, the results showed an unexpected worsening of seizure frequency in all of the active treatment groups. However, given the small numbers of subjects recruited from Brazil (18) and the exploratory nature of the analysis, it could not be excluded that this outcome was a chance finding. In the other dose-response study, in both the 50 and 150 mg/day groups, numerical improvements compared to PBO were observed both in % reductions in POS frequency and 50% responder rates, but statistically significant superiority over PBO was not reached. The extent of the improvements was similar in both dose groups and thus, no additional benefit of the BRV 150 mg/day dose compared to BRV 50 mg/day could be derived from these results. The applicant suggested that a higher baseline seizure frequency in the 150 mg/day group (2.94 versus 1.75) and differences in epilepsy aetiologies between the two groups (9 patients in the 50 mg/day dose group had cerebral neoplasm, cerebrovascular accident or cerebral infection but none of the patients receiving 150 mg/day BRV) could have contributed to this finding. The CHMP furthermore noted that this study was conducted in Europe, where a lower response to BRV compared to other regions and particularly for BRV 200 mg/day compared to 100 mg/day was observed in the pivotal studies (see discussion below).

In the first pivotal study N01252, BRV doses of 20 mg, 50 mg and 100 mg or PBO were added to baseline medication. The study failed to reach statistical significance on the primary endpoint, POS (Type I seizure) frequency per week, based on a sequential testing procedure which required superiority of BRV 50 mg/day over PBO prior to testing BRV 100 mg/day and BRV 20 mg/day in sequence. For 100 mg/day, however, the results were nominally significant (% reduction over PBO was 11.7%, p= 0.037). Similar results were obtained for the 50% responder rate. However, study N01253, with an identical design to N01252, but testing a lower dose range (BRV 5 mg, 20 mg or 50 mg/day) succeeded in its primary endpoint with a reduction in POS over PBO of 12.8% in patients receiving BRV 50 mg/day (p=0.025). No statistically significant effect was seen in the 5 mg/day or 20 mg/day dose groups. Similar results were observed for the 50% responder rates.

When the results of both studies, N01252 and N01253, were pooled (pool E2), both reduction in POS frequency and 50% responder rate were statistically significant in favour of BRV at doses of 50 mg/day and 100 mg/day, but not for the BRV 20 mg/day dose. Both the % reduction over PBO in POS frequency (9.9%, 16.4%, and 22.5% for BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day, respectively) and the 50% responder rate (18.4%, 25.3%, 30.0%, and 36.0% in the PBO, BRV 20 mg/day, BRV 50 mg/day, and BRV 100 mg/day groups, respectively) increased with dose. Furthermore, analysis of POS frequency by LEV status showed that subjects with concomitant LEV use had no benefit from BRV, which may be due to a competition of both compounds at the SV2A binding site. This may also explain that in subjects who previously used but then stopped LEV, seizure reduction with BRV was numerically lower than in LEV-naïve subjects. However, this finding might also be explained by baseline imbalances in the number of prior AEDs used and partial seizure frequency between patients with prior LEV exposure and LEV-naïve patients. The CHMP considered that the information on prior and concomitant use of LEV was relevant to prescribers and should be reflected in the SmPC.

The third pivotal study N01358, evaluating BRV 100 mg/day and 200 mg/day, included considerably more subjects in each treatment group compared to studies N01252 and N01253. The 50 % responder rates in this study were 38.9% and 37.8% for BRV 100 mg/day and BRV 200 mg/day, respectively, both being statistically significantly higher than the responder rate of 21.6% in the PBO arm. Results for % POS reduction were in line with the responder findings.

When pooling the results of the three pivotal studies (Pool E1), patients receiving LEV at the time of study entry (only allowed in studies N01252 and N01253) were excluded. This was considered acceptable by the CHMP as indeed previous findings from studies N01252 and N01253 had shown there was no beneficial effect in adding BRV to an AED regime containing LEV. The efficacy evaluation for Pool E1 showed that, all BRV doses from 20 mg/day to 200 mg/day were superior to PBO for the 50% responder rate and there was a dose-response relation in the interval of 20 mg/day to 100 mg/day. Compared to a 50% responder rate of 20.3% (85/418) in the PBO pool, 28.6% (46/146), 34.2% (55/161), 39.5% (131/332) and 37.8% (94/249) of the patients receiving 20mg/day, 50 mg/day, 100 mg/day and 200 mg/day, respectively, were responders. The effect size for the proposed effective dose range of 50-200 mg/day, with difference in responder rate of 14-19% compared to PBO, was of comparable magnitude tor other AEDs approved in recent years, and was considered by the CHMP to be of clinical relevance. Similar results were obtained for the % POS frequency reduction over PBO, which was statistically significant for all but the BRV 20 mg/day group. Further support for a beneficial treatment effect of BRV was provided by the rates of seizure free patients during the treatment period, which were consistently higher in the BRV groups compared to PBO with 2 (0.5 %), 3 (1.9 %), 4 (2.5 %), 17 (5.1 %) and 10 (4.0 %) patients in the PBO, BRV 20 mg/day, BRV 50 mg/day, BRV 100 mg/day and BRV 200 mg/day groups, respectively.

Contrary to use of LEV, in Pool E1, administration of AED inducers at study entry did not affect the median percent reduction in seizure frequency from baseline.

With regards to the upper end of the proposed dose range, the CHMP noted that there was no clear additional benefit of the 200 mg/day dose compared to 100 mg/day and no single patient characteristic could be determined that would help define a subgroup likely to benefit from BRV doses above 100 mg/day. However, there was a trend in some analyses for increased efficacy at 200 mg/day including patients with prior LEV therapy and those with type IC seizures. Furthermore, PK/PD modelling results suggested that patients in the responder population may benefit from a dose higher than 100 mg/day. Finally, in long-term follow-up studies, the majority of subjects received a dose higher than 100 mg/day (65% of subjects were exposed for at least 6 months to a dose of 150 or 200 mg/day). This suggests that some patients may have additional benefit from doses beyond 100 mg/day. Therefore, and in light of the safety profile of the 200 mg/day dose (which was comparatively benign for an AED, see discussions on clinical safety), the CHMP agreed to recommend doses up to 200 mg/day, whereby the dose should be gradually further increased based on individual response and tolerability.

With regards to the lower end of the proposed therapeutic dose interval, the CHMP noted that the efficacy data for BRV 50 mg/day were inconsistent across the dose-finding and pivotal studies N01114, N01193, N01252 and N01253. Compared to PBO, there was a statistically significant difference for the 50% responder rate and % reduction in POS frequency in favour of BRV 50mg/day in studies N01193 and N01253, but not in N01114 and N01252. Further analyses did not identify a single reason that might explain this variability across studies. Nevertheless, the CHMP considered that there was sufficient evidence supporting efficacy of the 50 mg/day dose, particularly since even when nominal statistical significance was not reached, there was still a consistent trend towards a favourable effect of BRV 50 mg/day in all studies (% reductions in POS frequency over PBO were 14.7%, 22.1%, 6.5% and 12.8% in N0114, N01193, N01252 and N01253, respectively). Furthermore, in the

long-term follow-up studies, approximately one third of subjects remained on BRV 50 mg/day dose as their effective dose.

Having identified BRV 50 mg/day as the lowest effective dose, the CHMP was furthermore of the view that this dose should be used when initiating treatment with BRV, in line with common clinical practice in the therapy of epilepsy. The applicant however also proposed a starting dose of BRV 100 mg/day without prior titration as differences in tolerability were small and the efficacy at 100mg/day is higher in the fixed dose clinical trials. The CHMP agreed that a higher initial dose could be considered at the possible expense of a worse safety profile in case of a clinical need to quickly reach an optimal control of seizures. Therefore, it is recommended to initiate BRV treatment with either 50 mg/day or 100 mg/day, whereby the choice of the starting dose should be based on the physician's assessment of required seizure reduction versus potential side effects thus taking into account the individual patient's needs.

The CHMP furthermore discussed the variability of the efficacy of BRV observed in the pivotal trials for different geographical regions. The pooled analysis (Pool E1) confirmed the findings of the individual trials in that responder rates were in general lower in Europe than in other geographical regions. Factors which may possibly have contributed to the regional differences include the lower number of previous AEDs and lower frequency of previous LEV use in Latin America. Furthermore, it could not be excluded that at least part of the differences between regions may be related to chance. This was supported by forest plots provided by the applicant in response to a request by CHMP, showing overlapping confidence intervals for the vast majority of the regional subgroups. In particular, the lower effect of BRV 200 mg/day in the EU population compared to all other regions including North America remained unexplained, but this too might have been a chance finding. Future studies within the clinical development program for Briviact in epilepsy, involving the 200mg/day dose and different geographic regions, will help to gather additional data on this subject and the applicant is expected to monitor and discuss any difference observed, in particular any findings of a reduced effect size in the EU population.

Another subgroup analysis in study N01358 and Pool E1 showed that in women, the % reduction in POS frequency was slightly lower than in men for both BRV 100 mg/day and 200 mg/day doses. A possible explanation might be baseline differences in previous AED use and Type I seizure frequency which suggested that women might have had more pharmacoresistant epilepsy compared to men. In other individual BRV studies (N01252, N01253 and N01254), there were no clinically relevant gender differences in efficacy identified for BRV 50 mg/day and BRV 100 mg/day. Taking into account that the observed differences were relatively small, the finding was not considered by the CHMP to be of clinical relevance.

Maintenance of the treatment effect was shown over the entire treatment period in the pivotal trials. While initially an analysis performed in study N01358 by monthly increments for both the 50% responder rate and 28-day adjusted POS frequency gave the impression of a progressive decrease in BRV treatment effect over time, the applicant showed that this observation was mainly driven by an increase in the PBO response and, overall, the effect of BRV was maintained over the total duration of 3 months. This was agreed by the CHMP. Additional evidence for persistence of the effect over time was available from long-term follow-up studies, which were ongoing at the time of this report. However, interim results from these studies showed that a high proportion of subjects discontinued in the open-label extension studies due to lack of efficacy. A selection bias may therefore have occurred, because the patients who stayed on in the studies may have responded better than those who had terminated prematurely. Therefore, efficacy results from these studies should be interpreted with caution.

Finally, there were some uncertainties regarding the quality of the diary data from the study participants which formed the basis of the primary efficacy variable in the 3 pivotal studies. However, the applicant demonstrated that the occurrence of missing diary days was low and similar across the BRV dose groups in each study. In all

3 studies, diary compliance was very high with a mean compliance rate of ≥98% in the PBO and BRV overall groups and the vast majority of subjects being 95-100% compliant in completing their seizure diary during the Treatment Period. To explore the impact of missing data, the applicant furthermore provided several sensitivity analyses including a baseline observation carried forward (BOCF) approach, removal of baseline seizure frequency from the set of covariates and a longitudinal linear mixed-effects model. These analyses were generally in line with the primary ANCOVA analyses, thereby confirming the robustness of the study results and the lack of bias in favour of BRV treatment due to missing data. In particular, the sensitivity analyses based on the BOCF method, which is considered a worst-comparison type of sensitivity analysis, were reassuring.

2.5.4. Conclusions on the clinical efficacy

The CHMP was of the view that the clinical development program was generally in line with relevant guidelines and adequate to support the application for BRV. Based on the available clinical efficacy data, the CHMP was of the view that there was sufficient evidence for a clinically relevant benefit of BRV at doses from 50 mg/day to 200 mg/day in the add-on treatment of partial-onset seizures with or without secondary generalisation in patients from 16 years of age with epilepsy. Treatment should be initiated either with 50 mg/day or 100 mg/day depending on the physician's assessment weighing the need for rapid seizure reduction against a possible increase in side effects. No effect on seizures was observed for BRV in subjects receiving concomitant treatment with LEV, which was likely due to the similar mode of action of LEV and BRV. Furthermore, BRV was less effective in patients previously treated with LEV, compared to LEV-naïve patients. This information as well as other relevant clinical efficacy data has been adequately reflected in the SmPC.

2.6. Clinical safety

The full safety analysis for the BRV program included review of safety data from all clinical studies. Supportive data were available in particular from study N01258 evaluating the safety and tolerability of BRV 200 mg/day administered i.v. as an infusion or a bolus injection during repeated dosing. In addition, study N01395 investigated the reduction of non-psychotic behavioural side effects in subjects with epilepsy who switched to BRV 200 mg/day after discontinuing LEV 1g/day to 3g/day as well as the overall safety and tolerability of BRV. Patients from study N01395 were eligible to enrol in the LTFU study N01372 upon study completion.

Data were combined in several integrated safety analysis pools, as follows:

- Pool S1: The primary study pool used to support the safety of BRV for the proposed target population consists of subjects who received study drug in the PBO-controlled, fixed dose, Phase III studies in subjects ≥16 years of age with epilepsy (N01252, N01253, and N01358). Pool S1 was used as the basis for the proposed labelling of adverse drug reactions (ADRs).
- Pool S2: This supportive study pool consists of subjects ≥16 years of age with epilepsy who received study drug in the 2 PBO-controlled Phase II studies (N01114 and N01193).
- Pool S3: This supportive study pool consists of subjects who received study drug in N01114, N01193, and the Phase III PBO-controlled, fixed-dose studies N01252, N01253, and N01358, as well as the flexible-dose study N01254.
- Pool S4: An additional study pool for safety analysis consisting of all subjects ≥16 years of age with focal or generalized epilepsy who received BRV in a Phase II or Phase III study. This pool is also referred to as the All-treated Epilepsy Pool. Pool S4 includes subjects from studies N01114, N01193, N01252,

N01253, N01254, N01358, and N01395 and LTFU studies N01125, N01199, N01372, and N01379, excluding subjects in N01372 who enrolled from N01394 (an exploratory Phase II study aiming at investigating i.v. BRV in the treatment of non-convulsive electrographic seizures, which at the time of the submission of this application had no subjects enrolled) as well as any subjects from the conversion to monotherapy studies.

- Pool i.v.: This pool consisted of healthy subjects and subjects with epilepsy who received i.v. BRV in Phase I studies using the i.v. formulation (N01256 and EP0007) and Phase IIIa study N01258.

Other supportive safety data pools included paediatric subjects (Pool Paediatric) and subjects in other studies including Pool Monotherapy, Pool Unverricht Lundborg Disease, and Pool Other (including studies in subjects with essential tremor and with postherpetic neuralgia), and safety data for subjects in Pool Phase I studies.

The assessment of safety was mainly based on data from Pool S1. Relevant additional information from other safety pools and individual studies is summarised in this report as relevant.

Patient exposure

Overall, 3673 subjects have been exposed to BRV in the clinical development program, and of these, 2481 were diagnosed with POS. The maximum duration of exposure was 84 months and the mean age of BRV-treated subjects was 37.0 years. Patient exposure for safety analysis is described in Table 20.

Patient distribution regarding age, sex and ethnicity was similar across all BRV doses tested and similar to PBO.

Table 20 – Overview of BRV Exposure in the BRV Development Program

Population	Total No. of unique BRV exposures
Total number of BRV exposed subjects[a]	3673
Clinical pharmacology exposures (Pool Phase I subjects plus subjects from non-pooled studies)[b]	754
Subjects enrolled in adult Phase II/III epilepsy studies[a]	2551
Subjects with POS	2481
Subjects enrolled in adjunctive treatment studies (from Pool S4)	2319
Subjects enrolled in conversion to monotherapy studies (Pool Monotherapy)	150
Subjects in iv study (N01258) who did not continue into LTFU study (N01379)[c]	12
Subjects with other seizure types	70
Subjects enrolled in adjunctive studies (from Pool S4)	69
Subjects in iv study (N01258) who did not continue into LTFU study (N01379)[c]	1
Subjects enrolled in paediatric epilepsy studies (N01263 and N01266)	120
Subjects with Unverricht-Lundborg Disease (Pool ULD)	102
Subjects with postherpetic neuralgia (from Pool Other)	102
Subjects with essential tremor (from Pool Other)	44

[a] Does not include subjects from N01394 (exploratory Phase II iv study that had not enrolled subjects at time of clinical cutoff for this submission [17 Jan 2014]).
[b] Pool Phase I did not include subjects from 3 studies due to inherent differences in these populations (elderly and renal/hepatic insufficient patients).
[c] Subjects from N01258 who did continue into N01379 are included in Pool S4 exposures.

In the primary safety pool (Pool S1), 1099 subjects were exposed to BRV and 459 subjects were exposed to PBO. The mean duration of exposure was similar across BRV dose groups, with the mean of 83.0 days for subjects receiving BRV doses ≥50mg and mean of 83.1 days for BRV Overall. In total, Pool S1 included 249.9 subject-years of BRV exposure.

Compared to Pool S1, exposure in Pool S4 was much larger including 2388 patients exposed to BRV. Pool S4 included subjects who participated for up to 8 years in BRV clinical studies with a total of 5558 subject-years of exposure. Amongst the subjects included in Pool S4, 2319 subjects had POS and 69 subjects had other seizure types. Overall, 29 subjects were <17 years of age, 2315 subjects were 17 to <65 years of age, 39 subjects were 65 years to <75 years of age, 5 subjects were 75 years to <85 years of age, and 0 subjects were ≥85 years of age. A total of 1,740 patients have been treated for ≥6 months, 1,363 for ≥12 months, 923 for ≥24 months and 569 for ≥60 months (5 years).

Across the clinical development program, a total of 150 subjects aged 65 years and older was exposed to BRV including 130 subjects that were exposed to multiple BRV doses. Amongst these were 51 epilepsy patients with POS. In other indications, 79 elderly subjects were exposed to BRV (up to very high doses of 800mg/day). Overall, only 30 patients were aged between 75 and 84 years (5 in the phase II/III epilepsy studies and 25 in other neurological conditions).

The data in Table 21 show that a majority of subjects received 100 – 150 mg/day dose. Exposures to BRV 200 mg/day appear to be lower, but this dose was initiated later in the development program, with study N01358.

Table 21 – Overview of Exposure to BRV by Modal Daily Dose (S4)

	BRV modal dose/day[b]						BRV Overall (N=2388)[b]
	5mg (N=53)	20mg (N=149)	50mg (N=319)	100mg (N=544)	150mg (N=869)	200mg (N=454)	
Subject years of exposure[a]	14.3	204.3	791.1	1341.7	2700.1	506.5	5558.0
Number of subjects exposed, n (%)	53 (2.2)	149 (6.2)	319 (13.4)	544 (22.8)	869 (36.4)	454 (19.0)	2388 (100)
Number of subjects exposed by duration of exposure							
≥1 month, n (%)	32 (1.4)	130 (5.6)	306 (13.3)	531 (23.0)	863 (37.4)	443 (19.2)	2305 (96.5)
≥3 months, n (%)	22 (1.1)	106 (5.2)	272 (13.3)	445 (21.7)	828 (40.4)	374 (18.3)	2047 (85.7)
≥6 months, n (%)	11 (0.6)	67 (3.9)	225 (12.9)	364 (20.9)	768 (44.1)	305 (17.5)	1740 (72.9)
≥12 months, n (%)	2 (0.1)	41 (3.0)	181 (13.3)	305 (22.4)	634 (46.5)	200 (14.7)	1363 (57.1)
≥18 months, n (%)	2 (0.2)	34 (3.0)	159 (14.2)	255 (22.7)	538 (48.0)	133 (11.9)	1121 (46.9)
≥24 months, n (%)	0	31 (3.4)	146 (15.8)	220 (23.8)	468 (50.7)	58 (6.3)	923 (38.7)
≥36 months, n (%)	0	25 (3.4)	119 (16.2)	187 (25.5)	389 (53.1)	13 (1.8)	733 (30.7)
≥48 months, n (%)	0	23 (3.6)	98 (15.2)	167 (25.9)	344 (53.3)	13 (2.0)	645 (27.0)
≥60 months, n (%)	0	18 (3.2)	82 (14.4)	150 (26.4)	306 (53.8)	13 (2.3)	569 (23.8)
≥72 months, n (%)	0	8 (5.4)	15 (10.1)	42 (28.2)	81 (54.4)	3 (2.0)	149 (6.2)
≥84 months, n (%)	0	6 (5.5)	11 (10.0)	35 (31.8)	56 (50.9)	2 (1.8)	110 (4.6)
≥96 months, n (%)	0	0	1 (2.4)	12 (29.3)	27 (65.9)	1 (2.4)	41 (1.7)
≥102 months, n (%)	0	0	0	1 (33.3)	2 (66.7)	0	3 (0.1)

[a] Subject years of exposure by modal daily dose is the total subject years of exposure of subjects within that modal daily dose category.
[b] Percentages for the BRV Overall column are relative to the number of subjects in the study pool. Percentages for the modal dose columns are relative to the number of subjects in the same row from BRV Overall column

Adverse events

In the clinical trials with BRV, an adverse event (AE) was defined as any untoward medical occurrence in a subject administered a pharmaceutical product that did not necessarily have a causal relationship with this treatment. An AE could therefore have been any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the product.

Treatment-emergent AEs (TEAEs) were defined differently at different times in the clinical program. For the Phase II POS studies (N01114, N01193) and Phase III Unverricht-Lundborg Disease studies (N01187, N01236), TEAEs were defined as AEs that had onset on or after the date of randomization. For all other Phase II and Phase III studies, including the 3 pivotal Phase III studies in adults with POS, TEAEs were defined as AEs that had onset on or after the date of first dose of study drug.

For all studies, the relationship of an AE to the study drug was based on the Investigator's assessment of causality. Drug-related AEs were those TEAEs for which the relationship to study drug was classified as related or as possible, probable, or highly probable. If the relationship to study drug was unspecified, the TEAE was considered to be drug-related.

Table 22 provides an overview of the TEAEs in Pool S1. In general, there were more reports of TEAEs (68.3%) in BRV overall group compared to the PBO group (62.1%) in Pool S1. The results for Pool S2 and Pool S3 are

similar to those for Pool S1. The number of patients reporting TEAE was also higher in all-epilepsy patients (84.8%; Pool S4) compared to Pool S1.

Table 22 - Overview of TEAEs for subjects in Pool S1

	PBO (N=459) n (%) [#]	BRV dose/day					BRV Overall (N=1099) n (%) [#]
		5mg (N=97) n (%) [#]	20mg (N=199) n (%) [#]	50mg (N=200) n (%) [#]	100mg (N=353) n (%) [#]	200mg (N=250) n (%) [#]	
Any TEAE	285 (62.1) [841]	69 (71.1) [243]	136 (68.3) [511]	142 (71.0) [599]	236 (66.9) [730]	168 (67.2) [512]	751 (68.3) [2595]
Discontinuation due to TEAE[a]	18 (3.9) [36]	9 (9.3) [13]	11 (5.5) [13]	10 (5.0) [16]	27 (7.6) [37]	17 (6.8) [29]	74 (6.7) [108]
Drug-related TEAE[b]	139 (30.3) [315]	44 (45.3) [97]	71 (35.7) [208]	94 (47.0) [298]	141 (39.9) [332]	109 (43.6) [281]	459 (41.8) [1216]
Severe TEAE	19 (4.1) [26]	7 (7.2) 11]	7 (3.5) [8]	12 (6.0) [21]	17 (4.8) [24]	16 (6.4) [25]	59 (5.4) [89]
Treatment-emergent SAE	13 (2.8) [15]	1 (1.0) [1]	2 (1.0) [2]	6 (3.0) [8]	9 (2.5) [12]	9 (3.6) [11]	27 (2.5) [34]
Drug-related treatment-emergent SAE	2 (0.4) [2]	0	0	1 (0.5) [1]	3 (0.8) [3]	2 (0.8) [4]	6 (0.5) [8]
Deaths[c]	1 (0.2)	0	1 (0.5)	1 (0.5)	0	2 (0.8)	4 (0.4)

Note: n is the number of subjects who reported a TEAE for the specified category; # is the number of individual TEAEs.
[a] Discontinuation due to TEAE includes the cases where study drug was permanently discontinued due to a TEAE. Subjects who temporarily stopped study drug for any reason are not included.
[b] Drug-related TEAEs were determined by the Investigator.
[c] The summary for deaths considers all TEAEs with fatal outcome which had onset during the core study regardless of the study period in which they occurred.

Common TEAEs, i.e. AEs reported in ≥5% of BRV subjects, in Pool S1 were somnolence, dizziness, headache, and fatigue. Somnolence, dizziness, and fatigue were reported more frequently in the BRV Overall group (14.3%, 11.0%, and 8.2% of subjects, respectively) compared with the PBO group (8.5%, 7.2%, and 3.7% of subjects, respectively); the incidence of headache was similar for the BRV Overall and PBO groups (10.0% and 10.2%, respectively). There was an apparent relationship between BRV dose and the incidences of somnolence and fatigue across the proposed therapeutic range (BRV 50mg/day to BRV 200mg/day). Results for Pool S2 and S3 were similar to those observed in Pool S1.

In Pool S4, the most frequently reported common TEAEs for the BRV Overall group were headache (20.9%), dizziness (17.3%), somnolence (15.2%), nasopharyngitis (12.7%), and fatigue (11.5%). Among these most frequently reported TEAEs, onset occurred early during treatment, typically during the first 3 months. Relatively few TEAEs had onset later in treatment and there were no events that had increased frequency over time.

With regards to the incidence of AEs in other safety data pools, the following TEAEs were reported more frequently in the Pool monotherapy, compared to Pool S4: back pain (10.7% in pool monotherapy versus 6.3% in pool S4), rash (9.3% versus 3.0%), decreased appetite (8.7% versus 3.8%), pain in extremity (6% versus 4.1%), chest pain (6.0% versus 1.9%). When considering only drug-related TEAEs as determined by the Investigator, differences in the incidences of drug related TEAEs between Pool Monotherapy and Pool S4 became

less apparent, however, decreased appetite maintained a high frequency (6.7% in Pool Monotherapy, compared to 2.4% in Pool S4). In Pool S1 decreased appetite had an incidence in BRV overall group which was higher than for PBO (1.4% versus 0.7%).

For Pool S1, the incidence of TEAEs that occurred in at least 2% of subjects in any BRV dose arm, BRV Overall, or combined BRV doses ≥50mg/day and with greater incidence than PBO are summarized in Table 23. These were the TEAEs mainly considered for the determination of adverse drug reactions (ADRs) by the applicant.

Table 23 – Summary of TEAEs with Incidence of ≥2% in any BRV Arm and Greater than PBO (Pool S1)

MedDRA (Version 15.0) Primary SOC PT	PBO (N=459) n (%)	BRV randomized dose/day					BRV Overall (N=1099) n (%)
		5mg (N=97) n (%)	20mg (N=199) n (%)	50mg (N=200) n (%)	100mg (N=353) n (%)	200mg (N=250) n (%)	
Ear and labyrinth disorders							
Vertigo	10 (2.2)	1 (1.0)	2 (1.0)	4 (2.0)	12 (3.4)	6 (2.4)	25 (2.3)
Eye disorders							
Vision blurred	3 (0.7)	1 (1.0)	3 (1.5)	4 (2.0)	3 (0.8)	4 (1.6)	15 (1.4)
Diplopia	4 (0.9)	1 (1.0)	3 (1.5)	4 (2.0)	2 (0.6)	1 (0.4)	11 (1.0)
Gastrointestinal disorders							
Nausea	11 (2.4)	5 (5.2)	7 (3.5)	8 (4.0)	15 (4.2)	9 (3.6)	44 (4.0)
Diarrhoea	13 (2.8)	4 (4.1)	5 (2.5)	7 (3.5)	6 (1.7)	8 (3.2)	30 (2.7)
Vomiting	4 (0.9)	3 (3.1)	3 (1.5)	9 (4.5)	5 (1.4)	3 (1.2)	23 (2.1)
Constipation	1 (0.2)	4 (4.1)	2 (1.0)	6 (3.0)	4 (1.1)	6 (2.4)	22 (2.0)
Abdominal pain upper	4 (0.9)	0	3 (1.5)	6 (3.0)	4 (1.1)	3 (1.2)	16 (1.5)
Toothache	5 (1.1)	1 (1.0)	2 (1.0)	3 (1.5)	1 (0.3)	4 (1.6)	11 (1.0)
Abdominal pain	8 (1.7)	2 (2.1)	1 (0.5)	3 (1.5)	3 (0.8)	1 (0.4)	10 (0.9)
Gastritis	4 (0.9)	2 (2.1)	2 (1.0)	0	4 (1.1)	0	8 (0.7)
Dyspepsia	2 (0.4)	1 (1.0)	3 (1.5)	1 (0.5)	0	2 (0.8)	7 (0.6)
General disorders and administration site conditions							
Fatigue	17 (3.7)	3 (3.1)	17 (8.5)	14 (7.0)	27 (7.6)	29 (11.6)	90 (8.2)
Irritability	5 (1.1)	2 (2.1)	4 (2.0)	10 (5.0)	9 (2.5)	7 (2.8)	32 (2.9)
Asthenia	7 (1.5)	0	3 (1.5)	4 (2.0)	6 (1.7)	2 (0.8)	15 (1.4)
Pyrexia	2 (0.4)	2 (2.1)	5 (2.5)	1 (0.5)	1 (0.3)	0	9 (0.8)
Chest pain	2 (0.4)	2 (2.1)	0	2 (1.0)	0	0	4 (0.4)
Infections and infestations							
Nasopharyngitis	14 (3.1)	2 (2.1)	13 (6.5)	6 (3.0)	12 (3.4)	9 (3.6)	42 (3.8)
Influenza	6 (1.3)	9 (9.3)	8 (4.0)	4 (2.0)	6 (1.7)	2 (0.8)	29 (2.6)
Urinary tract infection	12 (2.6)	2 (2.1)	7 (3.5)	2 (1.0)	12 (3.4)	3 (1.2)	26 (2.4)
Upper respiratory tract infection	9 (2.0)	5 (5.2)	6 (3.0)	1 (0.5)	8 (2.3)	5 (2.0)	25 (2.3)
Pneumonia	1 (0.2)	2 (2.1)	0	1 (0.5)	2 (0.6)	1 (0.4)	6 (0.5)
Oral herpes	0	0	0	3 (1.5)	0	1 (0.4)	4 (0.4)
Injury, poisoning and procedural complications							

MedDRA (Version 15.0) Primary SOC PT	PBO (N=459) n (%)	BRV randomized dose/day					BRV Overall (N=1099) n (%)
		5mg (N=97) n (%)	20mg (N=199) n (%)	50mg (N=200) n (%)	100mg (N=353) n (%)	200mg (N=250) n (%)	
Contusion	8 (1.7)	1 (1.0)	0	3 (1.5)	7 (2.0)	3 (1.2)	14 (1.3)
Fall	5 (1.1)	1 (1.0)	2 (1.0)	3 (1.5)	4 (1.1)	3 (1.2)	13 (1.2)
Head injury	4 (0.9)	2 (2.1)	2 (1.0)	3 (1.5)	2 (0.6)	1 (0.4)	10 (0.9)
Laceration	1 (0.2)	0	5 (2.5)	1 (0.5)	2 (0.6)	2 (0.8)	10 (0.9)
Excoriation	6 (1.3)	0	1 (0.5)	3 (1.5)	2 (0.6)	1 (0.4)	7 (0.6)
Ligament sprain	1 (0.2)	1 (1.0)	3 (1.5)	0	2 (0.6)	1 (0.4)	7 (0.6)
Investigations							
Weight decreased	1 (0.2)	1 (1.0)	3 (1.5)	3 (1.5)	3 (0.8)	3 (1.2)	13 (1.2)
Gamma-glutamyltransferase increased	5 (1.1)	1 (1.0)	3 (1.5)	3 (1.5)	2 (0.6)	3 (1.2)	12 (1.1)
Weight increased	3 (0.7)	2 (2.1)	4 (2.0)	3 (1.5)	1 (0.3)	1 (0.4)	11 (1.0)
Metabolism and nutrition disorders							
Decreased appetite	3 (0.7)	0	3 (1.5)	6 (3.0)	2 (0.6)	4 (1.6)	15 (1.4)
Hyponatraemia	2 (0.4)	0	1 (0.5)	0	4 (1.1)	4 (1.6)	9 (0.8)
Musculoskeletal and connective tissue disorders							
Back pain	4 (0.9)	3 (3.1)	1 (0.5)	6 (3.0)	4 (1.1)	2 (0.8)	16 (1.5)
Myalgia	6 (1.3)	0	2 (1.0)	6 (3.0)	4 (1.1)	2 (0.8)	14 (1.3)
Pain in extremity	6 (1.3)	3 (3.1)	2 (1.0)	5 (2.5)	2 (0.6)	2 (0.8)	14 (1.3)
Muscle spasms	0	3 (3.1)	1 (0.5)	2 (1.0)	3 (0.8)	2 (0.8)	11 (1.0)
Arthralgia	3 (0.7)	0	5 (2.5)	2 (1.0)	2 (0.6)	1 (0.4)	10 (0.9)
Nervous system disorders							
Somnolence	39 (8.5)	14 (14.4)	21 (10.6)	23 (11.5)	57 (16.1)	42 (16.8)	157 (14.3)
Dizziness	33 (7.2)	12 (12.4)	19 (9.5)	23 (11.5)	31 (8.8)	36 (14.4)	121 (11.0)
Headache	47 (10.2)	13 (13.4)	20 (10.1)	32 (16.0)	26 (7.4)	19 (7.6)	110 (10.0)
Convulsion	7 (1.5)	3 (3.1)	7 (3.5)	5 (2.5)	9 (2.5)	3 (1.2)	27 (2.5)
Paraesthesia	6 (1.3)	2 (2.1)	2 (1.0)	3 (1.5)	4 (1.1)	1 (0.4)	12 (1.1)
Tremor	6 (1.3)	0	3 (1.5)	3 (1.5)	2 (0.6)	4 (1.6)	12 (1.1)
Memory impairment	5 (1.1)	2 (2.1)	1 (0.5)	3 (1.5)	1 (0.3)	3 (1.2)	10 (0.9)
Balance disorder	1 (0.2)	0	1 (0.5)	3 (1.5)	2 (0.6)	3 (1.2)	9 (0.8)
Ataxia	3 (0.7)	1 (1.0)	1 (0.5)	3 (1.5)	1 (0.3)	2 (0.8)	8 (0.7)
Syncope	3 (0.7)	1 (1.0)	3 (1.5)	0	1 (0.3)	1 (0.4)	6 (0.5)
Sedation	0	0	1 (0.5)	0	0	4 (1.6)	5 (0.5)
Psychiatric disorders							
Insomnia	7 (1.5)	2 (2.1)	6 (3.0)	10 (5.0)	7 (2.0)	6 (2.4)	31 (2.8)
Depression	5 (1.1)	4 (4.1)	4 (2.0)	9 (4.5)	4 (1.1)	3 (1.2)	24 (2.2)
Anxiety	6 (1.3)	2 (2.1)	4 (2.0)	4 (2.0)	5 (1.4)	7 (2.8)	22 (2.0)
Nervousness	2 (0.4)	0	3 (1.5)	3 (1.5)	3 (0.8)	1 (0.4)	10 (0.9)

MedDRA (Version 15.0) Primary SOC PT	PBO (N=459) n (%)	BRV randomized dose/day					BRV Overall (N=1099) n (%)
		5mg (N=97) n (%)	20mg (N=199) n (%)	50mg (N=200) n (%)	100mg (N=353) n (%)	200mg (N=250) n (%)	
Aggression	2 (0.4)	0	4 (2.0)	1 (0.5)	1 (0.3)	2 (0.8)	8 (0.7)
Renal and urinary disorders							
Nephrolithiasis	1 (0.2)	2 (2.1)	0	1 (0.5)	0	0	3 (0.3)
Respiratory, thoracic and mediastinal disorders							
Cough	7 (1.5)	1 (1.0)	5 (2.5)	3 (1.5)	9 (2.5)	4 (1.6)	22 (2.0)
Dyspnoea	0	1 (1.0)	1 (0.5)	3 (1.5)	1 (0.3)	2 (0.8)	8 (0.7)
Skin and subcutaneous tissue disorders							
Pruritus	4 (0.9)	1 (0.1)	4 (2.0)	3 (1.5)	3 (0.8)	4 (1.6)	15 (1.4)
Rash	6 (1.3)	0	4 (2.0)	4 (2.0)	5 (1.4)	2 (0.8)	15 (1.4)

Based on a medical review performed by the applicant taking into account plausibility in light of the medicine's known pharmacology, occurrence at a frequency above that expected in the treated population, occurrence of an event typical of drug-induced adverse reactions, occurrence of even a single serious event that is typical of drug-induced adverse reactions as well as severity of AEs and discontinuation rates, the following events were identified as ADRs and proposed for inclusion in SmPC section 4.8:

- Common ADRs: vertigo, nausea, vomiting, constipation, fatigue, irritability, influenza, insomnia, anxiety, depression, and cough.
- Very common ADRs: somnolence, dizziness.

Other AEs were excluded if considered adequately demonstrated to be unrelated to BRV, if the terms were similar in meaning to those already included and whose inclusion would offer no further information, or if the AEs occurred with some meaningful background frequency in the target population and were not plausibly associated with the known mechanism of action of BRV.

Based on a review of data from across the program, the applicant identified additional ADRs which did not meet the statistical threshold set in the table above:

- Blood and lymphatic disorders: Neutropenia (uncommon). See 'AEs of special interest' for details.
- Infections and infestations: Upper respiratory tract infection (common)

  The incidence of upper respiratory tract infection was greater in the BRV Overall group than PBO (2.3% and 2.0%, respectively) in Pool S1. In the BRV Overall group, the incidence by severity of upper respiratory tract infection were <0.1% for severe AEs and 0.3% for moderate AEs compared with 0.7% moderate AEs for PBO. No subject in Pool S1 had an SAE or discontinuation because of upper respiratory tract infection. Upper respiratory tract infection is a broad term that could also encompass nasopharyngitis and it is likely that there was inconsistency in the terms reported. Although the number of events reported as nasopharyngitis was higher, as there were no SAEs for nasopharyngitis compared to 2 SAEs of upper respiratory tract infection, the applicant proposed inclusion of the term upper respiratory tract infection.
- Psychiatric disorders: Aggression (uncommon), and suicidal ideation (uncommon). See 'AEs of special interest' for details.

Adverse events during down-titration

In Pool S4, TEAEs during the Down-Titration Period were reported by 106 subjects (12.3%). TEAEs potentially associated with seizure worsening were reported by 9 subjects in the BRV overall group including 3 subjects reporting convulsions, 2 with grand mal convulsion, and 1 subject each with sudden unexplained death (SUDEP), epilepsy, complex partial seizure, and aura. The most frequently reported TEAEs during the Down-Titration Period for the BRV Overall group were headache (1.5%), nasopharyngitis (1.3%), and dizziness (0.8%). Laceration and nausea were both reported by 0.6% of the subjects. A total of 202 subjects (17.3%) reported TEAEs during the Post-Treatment Period.

Severity of adverse events

In Pool S1, most subjects reported TEAEs with a maximum intensity of mild (165 subjects [35.9%] in the PBO group and 401 subjects [36.5%] in the BRV Overall group) or moderate (101 subjects [22.0%] in the PBO group and 291 subjects [26.5%] in the BRV Overall group). Nineteen subjects (4.1%) in the PBO group and 59 subjects (5.4%) in the BRV Overall group reported TEAEs with a maximum intensity of severe. There was no apparent relationship between BRV dose and the incidences of severe TEAEs across the proposed therapeutic range (BRV 50mg/day to BRV 200mg/day). Severe TEAEs were most frequently reported in the SOC of nervous system disorders. The most frequently reported TEAEs in the SOC of nervous system disorders with a maximum intensity of severe in the BRV Overall group were headache (9 subjects [0.8%]), somnolence (3 subjects [0.3%]), dizziness (2 subjects [0.2%]), grand mal convulsion (2 subjects [0.2%]), tremor (2 subjects [0.2%]), and status epilepticus (2 subjects [0.2%]).

In Pool S4, similar to what was observed in Pool S1, most subjects in the BRV Overall group reported TEAEs with a maximum intensity of mild (643 subjects [26.9%]) or moderate (912 subjects [38.2%]). A total of 472 subjects (19.7%) in the BRV Overall group reported TEAEs with a maximum intensity of severe. Severe TEAEs were most frequently reported in the SOC of nervous system disorders. The most frequently reported TEAEs in the SOC of nervous system disorders with a maximum intensity of severe in the BRV Overall group were headache (54 subjects [2.3%]), convulsion (42 subjects [1.8%]), and dizziness (21 subjects [0.9%]).

Adverse events of interest

A list of AEs of interest was identified by the applicant after consideration of rare events which were more likely to be drug-induced, anticipated events for the population of interest (patients with epilepsy), predicted events for AEDs (including the SV2A mechanism of action), identification of ADRs reported in the BRV program.

A summary of the most relevant AEs of interest is provided below. Other AEs of special interest identified by the applicant including cognitive impairment, severe cutaneous adverse reactions, acute pancreatitis, renal impairment, Torsade de pointes and other significant cardiac arrhythmias, anaphylaxis and injection site reactions were reviewed and no relation between BRV exposure and such events was apparent.

- Suicidality

The applicant stated that in Pool S1, 3 subjects (0.3%) in the BRV Overall group and 3 subject (0.7%) in the PBO group reported TEAEs of suicidal ideation, and 1 subject (0.2%) in the PBO group reported TEAEs of intentional self-injury (which was not of suicidal nature).

In Pool S4, for the BRV Overall group, 45 subjects (1.9%) reported TEAEs of suicidal ideation, 13 subjects (0.5%) reported TEAEs of suicide attempt, 2 subjects (<0.1%) reported TEAEs of self-injurious ideation, and 1 subject (<0.1%) each reported depression suicidal and intentional self-injury. There was a tendency of dose relationship and suicidal ideation with the highest proportion in the 200mg dose group (5 cases (1.6%) for 50mg

8 cases (1.5%) for 100mg, 21 cases (2.4%) for 150mg and 9 cases (2.0%) for 200mg). Treatment emergent SAEs of suicidal ideation and suicide attempt were reported for 12 subjects (0.5%) each and of self-injurious ideation was reported for 1 subject (<0.1%) in the BRV Overall group. Treatment emergent SAEs of completed suicide were reported for 1 subject (0.2%) in the BRV 100mg/day group who had a history of depression and 1 subject (0.1%) in the BRV 150mg/day group who had poor seizure control in the preceding days. Both subjects had been exposed to BRV for more than 6 months with no recent dose change.

For Pool S4, the incidence of subjects with at least 1 TEAE of interest potentially associated with suicidality or suicidal ideation was highest during the 1 to 3 month safety time interval (85 subjects [3.6%]). The incidence of TEAEs of suicidal ideation was low, but slightly higher in the 4 to 6 month safety time interval (12 subjects [0.6%]) than in the other safety time intervals up to 69 months (all ≤0.3%). Based on the observations in Pool S4, the applicant provided an updated suicidality incidence rate (cut-off Oct 2014) considering only completed suicide and suicide attempts of 3.2 per 1000 subject-years (95% [CI: 2.1, 5.0]).

For one subject who drowned during the study duration, the applicant excluded suicidality as the event was witnessed by the subject's parents and since the subject had not consumed alcohol that day and did not have any history of psychiatric disorder nor did he show signs of a psychiatric problem or suicidal intention during participation in the trial. Additionally, suicidality was excluded for two subjects killed by trains, which instead were codified by the applicant as accidents. Although limited information was available, the respective investigators specifically reported in both cases that there was no psychiatric history and no recent change in behaviour suggesting a suicidal tendency. In one case, the event was captured on Closed Circuit Television and the investigator believed that automated behaviour preceding the accident was compatible with his usual behaviour during seizure. With regards to the other patient who was hit by the train while crossing the railway track dying on the spot, the possibility of a suicide may however not be definitely excluded due to lack of witnesses and lack of available information.

- Behavioral disorders, including hostility and aggression

In Pool S1, 49 subjects (4.5%) in the BRV Overall group and 9 subjects (2.0%) in the PBO group reported at least 1 TEAE of interest potentially associated with behavioral disorders; there was no apparent relationship of BRV dose and incidence across the proposed therapeutic range (BRV 50mg/day to BRV 200mg/day). The most commonly reported TEAEs of interest potentially associated with behavioral disorders were irritability (32 subjects [2.9%] in the BRV Overall group and 5 subjects [1.1%] in the PBO group), aggression (8 subjects [0.7%] in the BRV Overall group and 2 subjects [0.4%] in the PBO group), and agitation (6 subjects [0.5%] in the BRV Overall group and no subjects in the PBO group); the highest incidence for TEAEs of irritability was in the BRV 50mg/day group (10 subjects [5.0%]) and no subjects in the BRV 200mg/day group reported TEAEs of agitation. For TEAEs of interest potentially associated with hostility or aggression, the most commonly reported TEAEs also included laceration (10 subjects [0.9%) in the BRV Overall group and 1 subject [0.2%] in the PBO group). Three subjects (0.3%) in the BRV Overall group and no subjects in the PBO group reported TEAEs of abnormal behavior, and 3 subjects (0.3%) in the BRV Overall group and 2 subjects (0.4%) in the PBO group reported TEAEs of anger.

One subject (0.2%) in the BRV 100mg/day group had agitation reported as treatment-emergent SAE.

Higher rates of irritability and aggression were reported in BRV treated patients compared to PBO. With regards to aggression, severity was slightly worse for BRV (<0.1% severe, 0.5% moderate, and 0.2% mild for BRV Overall, and 0.4 % moderate for PBO). In addition, 0.3% of subjects in the BRV Overall group discontinued because of aggression compared with zero in the PBO group. Several cases were suggestive with regard to time

to onset and positive dechallenges. Both terms were listed in SmPC section 4.8. Aggression was furthermore included in the RMP as an identified risk.

Study N01395 investigated the reduction of non-psychotic behavioural side effects in subjects with epilepsy who switched to BRV 200 mg/day after discontinuing LEV 1g/day to 3g/day as well as the overall safety and tolerability of BRV. This was a small open-label study which enrolled 29 patients. Of these 26 (89.7%) completed the study. The applicant stated that results suggested that patients who experience behavioural AEs leading to the discontinuation of LEV treatment might benefit from a switch to BRV. However, the results should be interpreted with caution owing to the small sample size, lack of baseline prospective seizure data, short treatment period and open-label nature of the study.

- Psychosis

For Pool S1, 2 subjects (0.2%) in the BRV Overall group and 1 subject (0.2%) in the PBO group reported a TEAE of psychotic disorder, 1 subject (<0.1%) in the BRV Overall group and 1 subject (0.2%) in the PBO group reported TEAEs of epileptic psychosis. There was also 1 subject (<0.1%) in the BRV Overall group reporting illusion. Two subjects (0.2%) in the BRV Overall group had psychotic disorder reported as treatment emergent SAEs and 1 subject (0.3%) in the BRV 100mg/day group had epileptic psychosis reported as a treatment emergent SAE. BRV treatment was stopped in all three cases and the one patient with psychotic disorder and the patient with epileptic psychosis recovered after some days despite other AED treatment was continued. There were no SAEs reported for patients in the PBO group.

- Anxiety

In Pool S1, anxiety (22 subjects [2.0%] in the BRV Overall group and 6 subjects [1.3%] in the PBO group), nervousness (10 subjects [0.9%] in the BRV Overall group and 2 subjects [0.4%] in the PBO group), and agitation (6 subjects [0.5%] in the BRV Overall group and no subjects in the PBO group) were reported. There was a slightly higher incidence of anxiety in the BRV 200mg/day group (7 subjects [2.8%]) than in the other groups in the proposed therapeutic range (4 subjects [2.0%] in the BRV 50mg/day group and 5 subjects [1.4%] in the BRV 150mg/day group). In pool S4, the most commonly reported treatment-emergent SAE potentially associated with anxiety in the BRV Overall group was anxiety (3 subjects [0.1%]; 1 subject [0.1%] in the BRV 100mg/day group and 2 subjects [0.2%] in the BRV 150mg/day group).

- Depression

For Pool S1, the TEAEs of interest potentially associated with depression were depression (24 subjects [2.2%] in the BRV Overall group and 5 subjects [1.1%]) in the PBO group) and depressed mood (5 subjects [0.5%] in the BRV Overall group and 1 subject [0.2%] in the PBO group). No subjects in either the BRV Overall group or the PBO group had reports of treatment emergent SAEs potentially associated with depression. In pool S4, the most commonly reported treatment-emergent SAE was depression (7 subjects [0.3%)] in the BRV Overall group); no subjects in the BRV 5mg/day, BRV 50mg/day, or BRV 200mg/day groups had reports of this SAE.

- Seizure worsening

In Pool S1, 47 subjects (4.3%) in the BRV Overall group and 25 subjects (5.4%) in the PBO group reported at least 1 TEAE of interest potentially associated with seizure worsening; there was no apparent relationship between BRV dose and incidence across the proposed therapeutic range. The most commonly reported TEAE was convulsion (27 subjects [2.5%] in the BRV Overall group and 7 subjects [1.5%] in the PBO group). Two subjects (0.2% of the BRV Overall group) reported TEAEs of status epilepticus; no subjects in the PBO group reported TEAEs of status epilepticus. Two subjects (0.2% of the BRV Overall group) and 1 subject (0.2%) in the PBO group reported TEAEs of seizure cluster.

The incidence of convulsion was decreasing with increasing doses within the therapeutic interval with 2.5% for the 50mg/day dose, 2.5% for 100mg/day and 1.2% for 200mg/day. A similar tendency was observed in Pool S4. The incidence of the TEAE convulsion was highest during the time interval of 1-3 months (2.4%) and 4-6 months (2.3%), then gradually declining over time.

In Pool S1, at least 1 treatment emergent SAE potentially associated with seizure worsening was reported by 7 subjects (0.6%) in the BRV Overall group and 6 subjects (1.3%) in the PBO group. The most commonly reported treatment emergent SAEs in the BRV Overall group were grand mal convulsion (2 subjects [0.2%]) and status epilepticus (2 subjects [0.2%]). The most commonly reported treatment emergent SAE in the PBO group was convulsion (3 subjects [0.7%]). One subject (0.2%) in the PBO group had grand mal convulsion reported as a treatment-emergent SAE and no subjects in the PBO group had reports of treatment emergent SAEs of status epilepticus. One subject in the BRV 200mg/day group reported a treatment emergent SAE of seizure cluster.

- Abuse potential

TEAEs potentially associated with abuse potential, related to overdose and events that might indicate diversion were assessed across the BRV clinical development program. There were no reports of abuse, misuse, dependence or withdrawal with BRV. Across all study pools, dizziness, somnolence, fatigue, and asthenia were the most common CNS events of interest. The incidence of euphoric mood and feeling drunk was low in subject populations but higher in the Phase I population. Reports of hallucinations, stimulant-related, dissociative/psychotic, mood disorders, and motor/cognitive impairment events were infrequent in most populations. There are no data on single intakes exceeding BRV 1400mg. There were no reports of diversion during the clinical development of BRV.

In the 3 primary PBO-controlled studies, most subjects (87% to 88%) continued into a long-term extension study. Therefore, there was limited information from which to assess possible withdrawal effects and these have not been formally evaluated. In Pool S4 (the All-treated Epilepsy Pool), the incidence of events that occurred during down-titration and post-treatment was very low, and much lower compared to on-treatment. More importantly, the pattern of events did not change from on-treatment to down-titration to post-treatment, rather the incidence of events simply decreased across these periods.

- Falls

In Pool S1, the incidences of TEAEs associated with falls and injuries with and without concurrent Type IB or IC seizure were similar between the BRV Overall group and the PBO group. The rate of subjects with at least one TEAE associated with falls and injuries without concurrent type IB or IC seizure were 3.7% in the PBO group and 4.2% in the BRV Overall group; with concurrent type IB or IC seizure, the rates were PBO 4.8% versus BRV Overall 4.0%. The incidences of treatment emergent SAEs associated with falls and injuries irrespective of concurrent Type IB or IC seizure were also comparable between the BRV Overall group and the PBO group (PBO: 0.4%; BRV overall: 0.3%). However 3 cases of SAEs of fall were reported in the BRV group while no SAE of fall occurred in the PBO group. Two of those cases occurred in 200mg/day dose group and one in the 100mg/day dose group. All 3 SAEs were associated with seizure activity.

In Pool S4 the incidences of TEAEs associated with falls and injuries were generally higher compared to Pool S1, which was expected due to the longer observation period. Unexpectedly however, in Pool S4, TEAEs associated with falls and injuries were reported at a higher incidence without concurrent Type IB or IC seizure (15% [n=358]) than with concurrent Type IB or IC seizure (12%, [n=286]) in the BRV Overall group. The event of fall was reported at a similar incidence with (2.0%) or without (2.5%) concurrent Type IB or IC seizure in the BRV Overall group. The incidence of SAEs associated with falls and injuries, with and without concurrent Type IB or IC seizure were 2.0 and 2.3% respectively. Ten (10) (0.4%) cases of SAEs of falls were reported, most

frequently in the dose group of 150mg/day (n=5) and two cases in the dose group 200mg/day potentially indicating an increasing risk of falls in patients treated with higher BRV doses.

Both in Pool S1 and in Pool S4, there was no apparent relationship between BRV dose and incidence of TEAEs associated with falls and injuries with and without concurrent Type IB or IC seizure across the proposed therapeutic range.

There is a reasonable possibility that fall directly or indirectly led to at least 2 deaths. A 72-year old male died from septic shock following surgery on hip fracture secondary to fall, and a 43-year old male died from head trauma after fall because he slipped on a bathroom floor.

- Postural hypotension

In Pool S1, 1 subject (0.5%) in the BRV 20mg/day group reported a TEAE of hypotension and 1 subject (0.3%) in the BRV 100mg/day group reported a TEAE of orthostatic hypotension. Neither of the events was an SAE or led to permanent discontinuation of study drug.

- Blood dyscrasia

In PBO controlled studies (Pool S1), the most commonly reported TEAEs were neutropenia (6 subjects [0.5%] in the BRV Overall group and no subjects in the PBO group), neutrophil count decreased (3 subjects [0.3%] in the BRV Overall group and 2 subjects [0.4%] in the PBO group), and white blood cell count decreased (2 subjects [0.4%] in the PBO group and 1 subject in the BRV Overall group [<0.1%]). For the cases of neutropenia, BRV treatment was continued. No clinical signs of fever or infection were reported and neutropenia resolved in 4 out of the 6 patients. No subjects in either the BRV Overall group or the PBO group had reports of treatment emergent SAEs potentially associated with blood dyscrasia or TEAEs of interest potentially associated with blood dyscrasia that led to study drug discontinuation.

In Pool S4, the most commonly reported TEAEs in the BRV Overall group were neutropenia (46 subjects [1.9%]) and neutrophil count decreased (17 subjects [0.7%]). The majority of subjects (47.2%) had a decrease in neutrophils that met the National Cancer Institute (NCI) Grade 2 criteria (moderate severity, equivalent to the neutrophil count being <1,500 to 1,000/mm^3), with minimal intervention indicated and with some limitation of activities. The maximum severity grade reached at any time point was Grade 3 (severe, neutrophil count being <1,000 to 500/mm^3) and occurred in 5.7% of subjects in Pool S4 (4 cases).

- HSS/DRESS

In Pool S1, 1 subject in the BRV 100 mg/day group and 1 subject in PBO group and in Pool S4, 19 (0.8%) subjects in BRV-treated subjects experienced TEAEs potentially associated with HSS/DRESS. Additionally, there were 3 BRV-treated subjects (2.0%) in the Pool Pediatric and 1 subject each in the Pool Monotherapy and Pool ULD. However, none of the algorithmically identified cases of potential HSS/DRESS was considered HSS/DRESS based a medical review by the applicant.

The applicant excluded events linked to medications taken for more than 2 months or initiated less than 2 weeks before the onset of DRESS since it was not possible to a priori reject the possibility that BRV could be causative drug if assumed in a different time window. The CHMP requested to also include in the total count of potential HSS/DRESS, events falling in the broader timeframe of less than 2 weeks and more than two months and to combine events and their time of onset, ranging from 0.5 to 16 weeks in order to eliminate any potential temporal relation among the two. RegiSCAR scoring system should also be used to grade HSS/DRESS cases as “no,” “possible,” “probable,” or “definite” and concomitant drugs should be specified.

This additional analysis was provided by the applicant in the course of the assessment. In addition, the applicant applied an alternative approach to identify cases of HSS/DRESS in line with the publication by Kardaun et al. (Br J Dermatol., 2007), with a refined scoring table and taking into account the whole clinical picture of patients with an SAE or a TEAE leading to discontinuation in the 2 relevant SOCs of 'Immune system disorders' and 'Skin and subcutaneous tissue disorder'. Among the previously identified 19 TEAEs potentially associated with HSS/DRESS for Pool S4 in these two SOCs, none of them could be confirmed as being associated with HSS/DRESS with the new algorithm and the alternative approach led to similar results as in the original analysis, except for the identification of 1 subject in Pool Other (N01162-073-0850) for whom the scoring criteria (<2) did not allow consideration of this case as a DRESS event.

Serious adverse event / deaths / other significant events

In Pool S1, a total of 13 subjects (2.8%) in the PBO group and 27 subjects (2.5%) in the BRV Overall group reported SAEs. Treatment-emergent SAEs were reported most frequently under the SOCs terms nervous system disorders (n=7, 0.6%), Injury, poisoning and procedural complications and Psychiatric disorders (N=5, 0.5% each). Treatment-emergent SAEs of fall were reported for 3 subjects in the BRV Overall group (2 subjects in the BRV 200mg/day group and 1 subject in the BRV 100mg/day group). Treatment-emergent SAEs of humerus fracture, grand mal convulsion, status epilepticus, adjustment disorder, and psychotic disorder were each reported in 2 subjects in the BRV Overall group. No other SAEs were reported for more than 1 subject.

In Pool S4, a total of 433 subjects (18.1%) in the BRV Overall group reported SAEs. The percentage of patients reporting treatment emergent SAE were lowest in the highest dose group (200 mg/day, 13.4%) compared to the low dose (50 mg/day, 20.7%). The most frequently reported SAEs for subjects in the BRV Overall group were convulsion (60 subjects [2.5%]), status epilepticus (20 subjects [0.8%]), pneumonia (13 subjects [0.5%]), epilepsy (13 subjects [0.5%]), suicidal ideation (12 subjects [0.5%]), suicide attempt (12 subjects [0.5%]), and grand mal convulsion (11 subjects [0.5%]). The majority of SAEs occurred during the LTFU studies.

In the BRV overall group treatment emergent SAEs occurred in one patient in the first 7 days of treatment (corresponding to an exposure adjusted incidence of occurrence 7 times higher than in the ≥8 days' time period). The corresponding exposure-adjusted incidences among subjects in the 18 to 65 year age group indicated an occurrence 2 times higher than in the ≥8 days' time period (0.003547 compared to 0.001512).

Deaths

Overall, deaths of adult subjects >16 years of age as of the clinical cut-off date of 17 Jan 2014 was reported at a mortality rate of 5.9 per 1000 subject-years (95% CI: 4.1-8.3). An updated rate of 5.4 per 1000 subject-years (95% CI: 3.8-7.6) was calculated for the updated cut off of 01 Oct 2014. The mortality rate observed in Pool S4 did not exceed the range of rates observed in published data on pooling of add-on AEDs clinical trials provided by the applicant.

Five deaths occurred in the placebo controlled studies including 4 cases (0.4%) in the BRV group (1 with the 20 and 50 mg/day doses each and 2 with the 200 mg/day dose) and 1 case in the PBO group. Three (3) out 4 cases in the BRV group were classified as sudden unexplained death in epilepsy (SUDEP) and 1 case as drowning, even though seizure related activity could not be excluded because of insufficient information. These three cases of SUDEP occurred within 3 months from the start of BRV treatment.

Using methodology proposed by Ryvlin et al. (2011), among the 5558 subject-years of exposure (Pool S4) there were 8 deaths considered to be definitely due to SUDEP, 4 deaths considered probably due to SUDEP and 4 deaths were considered to be possibly due to SUDEP. The majority of subjects were taking ≥2 other AEDs. Five

subjects were taking 1 other AED. The durations of exposure to BRV varied from 4.3 weeks to 65.5 months. A total of 5 cases reported within the first 6 months of BRV exposure.

Six subjects died from carcinoma (3 due to lung cancer and one case each due to oesophageal cancer, ovarian cancer and astrocytoma). All cases of carcinoma occurred after more than 16 months of BRV exposure (range 16.6 to 60.8).

Laboratory findings

There were no clinically meaningful differences in Baseline haematology parameters or vital signs, nor in the mean changes from Baseline to the Last Value across the treatment groups in Pool S1 for vital signs and the majority of haematology parameters. . For neutrophils, there was a small downward trend under treatment with BRV compared to PBO (mean change from Baseline for BRV Overall: -0.12G/L versus 0.05G/L under PBO).

With regards to clinical chemistry parameters, the numbers and incidences of subjects who shifted from normal values at Baseline to abnormal high or low values at the Last Value were generally small. Overall, no clinically relevant shifts in clinical chemistry parameters were observed.

Evaluation of ECG outcomes (normal, abnormal but not clinically significant, and clinically significant) was based on the Investigator's assessment. Overall, incidences of clinically significant ECG abnormalities in Pool S1 were low and comparable across all treatment groups. There was no trend over time.

A QT study in healthy subjects was conducted. The results of this study is summarised in section 2.4.3.

Safety in special populations

Renal impairment

In an open-label clinical pharmacology study in both healthy subjects with normal renal function and patients with renal function impairment, the most frequent TEAEs observed were somnolence and dizziness. Somnolence was reported by 5 subjects (55.6%) in both groups of severe renally impaired subjects and healthy subjects. Dizziness was reported by 4 (44.4%) severe renally impaired subjects and 2 (22.2%) healthy subjects. Both these AEs occurred immediately or shortly after study drug administration, were mild, and were of limited duration. Clinical laboratory evaluations indicated abnormal values for most severe renally impaired subjects. The Investigator considered these abnormalities as typical for this chronic pathology. Healthy subjects did not show any clinically significant abnormal laboratory value. Slightly elevated systolic and diastolic blood pressure values were recorded in severe renally impaired subjects, when compared to healthy subjects. However, severe renally impaired subjects had increase values already at Baseline. Blood pressure and heart rate were slightly and similarly decreased in both groups immediately or shortly after study drug administration. Recovery of pre-dose values was achieved within 48 hours post-dose. With the exception of 1 subject who exhibited sinus bradycardia reported as an AE, all other ECG abnormalities were considered as not clinically significant by the Investigator.

Hepatic impairment

In an open-label clinical pharmacology study, healthy subjects and subjects with impaired liver function (Group A: Child-Pugh class A (Child-Pugh score: 5 to 6), Group B: Child-Pugh class B (Child-Pugh score: 7 to 9), Group C: Child-Pugh class C (Child-Pugh score: 10 to 15), and Group D: healthy subjects matched for gender, age, and weight) received a single oral administration of BRV 100mg. A total of 19 subjects (73.1%) reported at least 1 TEAE. All the TEAEs reported were mild to moderate. The incidence of subjects experiencing at least 1 TEAE was similar in the 4 groups of subjects studied. No SAE was reported. The most frequent TEAEs reported were

somnolence (reported by 11 subjects [42.3%]), orthostatic hypotension (7 subjects [26.9%]), vertigo (6 subjects [23.1%]), and hypotension (3 subjects [11.5%]).

Elderly subjects

In the entire BRV clinical development program, including indications other than POS, there were 165 subjects ≥65 years of age. In Pool S1 there were 30 BRV-treated and 8 PBO subjects ≥65 years of age. These patients reported generally similar TEAEs compared to patients <65 years old.

In Pool S4, 44 subjects were ≥65 years of age. An overview of the safety data for elderly patients is provided in Table 23. The TEAEs profile was consistent with the TEAEs observed in subjects 17 to <65 years of age, and with those observed in Pool S1. Exposure adjusted incidence of TEAEs in subjects ≥65 years of age were higher in the first 7 days of treatment compared to ≥8 days both for BRV overall group and for PBO (approximately 4 fold higher during the first 7 days of exposure compared to the ≥8 days period). The corresponding exposure-adjusted incidences among subjects in the 18 to 65 year age group, indicated an exposure adjusted incidence of occurrence 5 times higher than in the ≥8 days' time period (0.366085/ 0.031119). Furthermore, the available data indicate that TEAEs leading to permanent discontinuation and SAEs occurred more frequently in the first 7 days of treatment than in the subsequent period. The increase in occurrence of treatment emergent SAE and AE leading to permanent discontinuation in the first 7 days of treatment compared to the ≥8 days' time period is relatively higher for patients aged ≥65 years compared to the overall age group (18-65 years).

In the Pool Other, there were 112 subjects ≥65 years of age; 79 subjects received BRV and 54 subjects received PBO. Pool Other included the highest BRV doses in the primary and supportive safety pools in the clinical development program of BRV of up to 800mg/day.

The TEAE with the highest incidence in subjects ≥65 years of age in Pool Other was somnolence, which occurred in 20.9% of BRV-treated subjects and 7.7% of PBO subjects.

Table 24 - Overall BRV safety data for elderly subjects by age category (Pool S4)

	BRV Overall		
	Age category		
	≥65-74 years	75-84 years	≥85 years
At least 1 TEAE	34 (87.2)	4 (80.0)	--
Treatment-emergent SAEs (total)	11 (28.2)	1 (20.0)	--
TEAEs leading to permanent discontinuation	6 (15.4)	2 (40.0)	--
TEAEs with a maximum intensity of mild[a]	9 (23.1)	3 (60.0)	--
TEAEs with a maximum intensity of moderate[a]	14 (35.9)	0	--
TEAEs with a maximum intensity of severe[a]	11 (28.2)	1 (20.0)	--
Common TEAEs (MedDRA Version 15.0)[b] Primary SOC/ PT			
Cardiac disorders			
Bradycardia	2 (5.1)	0	--
Ear and labyrinth disorders			
Vertigo	2 (5.1)	0	--
Eye disorders			
Vision blurred	3 (7.7)	0	--
Gastrointestinal disorders			
Abdominal pain upper	4 (10.3)	0	--
Diarrhoea	3 (7.7)	0	--
Vomiting	2 (5.1)	0	--
General disorders and administration site conditions			
Fatigue	4 (10.3)	0	--
Asthenia	3 (7.7)	0	--
Irritability	3 (7.7)	0	--
Gait disturbance	2 (5.1)	1 (20.0)	--
Malaise	2 (5.1)	0	--
Infections and infestations			
Nasopharyngitis	4 (10.3)	0	--
Urinary tract infection	4 (10.3)	0	--
Cystitis	3 (7.7)	0	--
Pharyngitis	2 (5.1)	0	--
Herpes zoster	2 (5.1)	0	--
Injury, poisoning, and procedural complications			
Fall	4 (10.3)	1 (20.0)	--
Investigations			
Blood cholesterol increased	2 (5.1)	0	--
Blood triglycerides increased	2 (5.1)	0	--
Metabolism and nutrition disorders			
Hyponatraemia	2 (5.1)	0	--
Musculoskeletal and connective tissue disorders			
Back pain	4 (10.3)	0	--
Pain in extremity	4 (10.3)	0	--
Arthralgia	2 (5.1)	0	--

	BRV Overall		
	Age category		
	≥65-74 years	75-84 years	≥85 years
Muscle spasms	2 (5.1)	0	--
Musculoskeletal pain	2 (5.1)	0	--
Nervous system disorders			
Convulsion	7 (17.9)	0	--
Headache	6 (15.4)	0	--
Somnolence	6 (15.4)	1 (20.0)	--
Dizziness	5 (12.8)	1 (20.0)	--
Tremor	3 (7.7)	0	--
Balance disorder	2 (5.1)	0	--
Paraesthesia	2 (5.1)	1 (20.0)	--
Syncope	2 (5.1)	0	--
Psychiatric disorders			
Insomnia	4 (10.3)	0	--
Depression	3 (7.7)	0	--
Anxiety	2 (5.1)	0	--
Suicidal ideation	2 (5.1)	0	--
Skin and subcutaneous disorders			
Pruritis	2 (5.1)	0	--
Vascular disorders			
Hypertension	3 (7.7)	0	--

Safety assessments in paediatric subjects

Pool Paediatric includes subjects from paediatric epilepsy studies (N01263 and N01266) and subjects <17 years of age who participated in other BRV clinical studies. Overall, in the BRV clinical development program, 152 subjects were <17 years of age. There were 29 subjects <2 years of age, 9 subjects 2 to <4 years of age, 55 subjects 4 to <12 years of age, and 59 subjects ≥12 years of age.

In Pool S1, there were 10 BRV-treated and 6 PBO subjects <17 years of age. In Pool S4, 29 subjects were <17 years of age.

In general, the side effect profile was as anticipated, though respiratory and gastrointestinal AEs appeared to have relatively higher incidences in the younger pediatric age categories.

Safety related to drug-drug interactions and other interactions

The results from clinical pharmacology studies which evaluated interactions of BRV with combination oral contraceptives as well as concomitant use of AED inducers are summarized in section 2.4.

With regards to concomitant use of LEV, LEV status did not appear to have an effect on the incidences of most common TEAEs in the integrated safety analysis pools of subjects with epilepsy (Pool S1, Pool S2, Pool S3, and Pool S4) or subjects in conversion to monotherapy studies (Pool Monotherapy). However, in Pool S1, the observed rates of convulsion were higher in subjects who used LEV at core study entry (2.7% PBO compared with 6.1% BRV Overall) compared to subjects who did not use LEV at core study entry (1.4% PBO compared with 2.0 % BRV Overall).

In the All-treated Epilepsy Pool (Pool S4), there were 2029 BRV-treated subjects who were LEV naïve and 359 subjects who were LEV users at core study entry. LEV users had a higher discontinuation rate than LEV naïve subjects at core study entry. In LEV users, lack of efficacy was the main reason for discontinuation, while in LEV naïve subjects, AEs and lack of efficacy were both reasons with similar frequency.

Discontinuation due to adverse events

A total of 18 subjects (3.9%) in the PBO group and 74 subjects (6.7%) in the BRV Overall group reported TEAEs leading to permanent discontinuation of study drug. Dizziness, convulsion, depression, fatigue and headache were the most frequently reported TEAEs leading to discontinuation, and these were reported more frequently by subjects in the BRV Overall group (0.8%, 0.8%, 0.5%, 0.5%, and 0.4%, respectively) compared with the PBO group (0.2%, 0.4%, 0.2%, 0.4%, and 0%, respectively). In general, the incidences of TEAEs leading to discontinuation were similar across BRV groups. The discontinuation rate due to ADRs was 3.5%, 3.4% and 4.0% for patients randomized to BRV at doses of 50 mg/day, 100 mg/day and 200 mg/day, respectively and 1.7 % for patients randomized to PBO.

A total of 2.5% of BRV Overall subjects discontinued during the first 7 days versus 6.7% at any time point during the study (Pool S1). Rates for PBO discontinuations were 1.5% subjects discontinued in the first 7 days of treatment versus 3.9% PBO subjects at any time point. When the incidences were adjusted for exposure, TEAEs resulting in permanent discontinuation of study drug occurred approximately 7 times more frequently during the first 7 days compared to the ≥8 days' period, both for the BRV overall group and for the PBO group.

In Pool S4, amongst the 2388 subjects who received BRV, at the time of the clinical cut-off date, 1293 (54.1%) discontinued from either a core study or LTFU. The primary reasons for discontinuation were AE (342 subjects, 14.3%) and lack of efficacy (542 subjects, 22.7%). In Pool S4, TEAEs resulting in permanent discontinuation of study drug occurred approximately 27 times more frequently during the first 7 days of exposure compared to the ≥8 days' period, with no evidence of a dose related increase.

In both Pools (S1 and S4), there was no evidence of a dose-related increase in exposure-adjusted incidences of TEAEs leading to permanent discontinuation of study drug for BRV during either time periods.

Safety of solution for injection/infusion

The safety of the solution for injection/infusion formulation was investigated in several Phase I studies as well as a safety Phase III study (N01258). Study N01258 was a Phase III randomized, open-label, parallel-group multicenter study designed to evaluate the safety and tolerability of bid i.v. administration of BRV in subjects 16 to 70 years of age with epilepsy (focal onset or generalized). After a double-blind run-in period of 1 week, during which subjects either received PBO or oral BRV 200 mg/day, subjects entered the open-label evaluation period and received repeated doses of BRV 200 mg/day (100 mg twice a day) over 4.5 days either as 2-minute bolus or 15-minute infusion, depending on their random assignment. A total of 105 subjects were randomized, with 104 subjects receiving i.v. BRV. The majority of subjects (67.6%) reported a TEAE during the Evaluation Period (i.e., during i.v. BRV treatment), and the most common TEAEs during this period were somnolence (21.9%) and dizziness (7.6%). The incidences of these TEAEs were similar across treatment groups (somnolence: 19.2% in the bolus group and 25.0% in the infusion group; dizziness: 9.6% in the bolus group and 5.8% in the infusion group). In general, the overall incidence and type of drug-related TEAEs was similar whether BRV was administered as a bolus or infusion. The incidence of injection-related TEAEs was similar whether BRV was administered as a bolus or infusion (9.6% vs 11.5%).

A comparison of TEAEs reported by subjects during the first 7 days of BRV treatment by method of administration showed that a greater percentage of subjects receiving an i.v. formulation reported adverse

events compared with the oral formulation. However, the types and severity of adverse events reported were similar, with the increase for the i.v. formulations being mainly due to events that could be expected, i.e., injection related events such as injection site extravasation and infusion site pain. The incidence of such events was low (10.5%).

In Pool i.v., a total of 124 subjects (70.1%) in the BRV Overall group reported TEAEs. Most TEAEs in Pool i.v. were reported by subjects in the BRV 100 mg group. The BRV 100mg group was comprised predominantly of subjects with epilepsy from study N01258 (104 subjects). In addition, the BRV 100mg group included 31 healthy subjects from other studies. All other dose groups included healthy subjects only. Two subjects (1.1%) in the BRV Overall group administering BRV as an infusion reported a TEAE that led to discontinuation. Overall, 55.9% of subjects in the BRV Overall group reported a TEAE considered related to study drug by the Investigator. One subject (0.6%) in the BRV Overall group reported at least 1 severe TEAE. No treatment-emergent SAEs or deaths were reported.

Post marketing experience

No post-marketing data were available for BRV as the product had not been launched on any market at the time of this report.

2.6.1. Discussion on clinical safety

The BRV safety database covered 3673 patients in the overall clinical development program and 2481 patients with POS exposed to BRV, which was considered adequate by the CHMP. Safety information was collected from several studies including phase III clinical trials in patients with POS as well as long term follow up studies. A total of 1363 patients were exposed to BRV for more than 12 months and 1320 of these were exposed to doses of 50 and 200 mg/day for at least 12 months. The extent of exposure was considered adequate by the CHMP. However, the 200mg/day dose was tested only in one pivotal clinical trial and, therefore, the exposure to this dose beyond 24 months was limited.

Patient distribution regarding age, sex and ethnicity was similar across all BRV doses tested and similar to PBO.

The safety analysis focused on Pool S1, which included subjects who received study drug in the PBO-controlled, fixed dose, Phase III studies. An additional study pool consisted of all subjects ≥16 years of age with focal or generalized epilepsy who received BRV in a Phase II or Phase III adult study and in subsequent long-term follow-up studies (Pool S4). Other safety Pools were considered supportive. This approach was considered adequate by the CHMP.

The rate of TEAES, both in terms of number of individuals reporting a TEAE and number of actual events, was higher in patients treated with BRV, irrespective of the dose (BRV overall group), compared to PBO. The number of patients reporting TEAE was higher in all-epilepsy patients Pool S4 compared to Pool S1, which was to be expected due to the substantially larger exposure in Pool S4, which included subjects treated up to 8 years (249.9 subject-years of BRV exposure in Pool S1 versus 5558 subject-years in Pool S4).

Most reported AEs were mild or moderate in intensity. The most commonly reported TEAEs in clinical studies were somnolence, dizziness, fatigue and headache in all analysed safety Pools. Except for headache, these AEs were more frequently reported in the BRV group compared to PBO and were included in SmPC section 4.8.

Not unexpectedly, a high overall discontinuation rate was observed with 54.1% in Pool S4. However, similar rates of around 50% have been previously observed in long-term studies with other AEDs described in literature (e.g. Husain A et al., 2012; Bauer J et al., 2006). The profile of TEAEs leading to discontinuation of treatment

was broadly similar to the most commonly reported TEAEs. In Pool S1, the discontinuation rate due to ADRs was 3.5%, 3.4% and 4.0% for patients randomized to BRV at doses of 50 mg/day, 100 mg/day and 200 mg/day, respectively, and 1.7 % for patients randomized to PBO. Dizziness, convulsion, depression, fatigue and headache were the most frequently reported TEAEs leading to discontinuation at frequencies of 0.8%, 0.8%, 0.5%, 0.5%, and 0.4%, respectively.

The number of treatment emergent SAEs were similar between the patients receiving BRV and PBO. The most common SAEs reported in the BRV overall group, but not in the PBO group, were under the MedDRA SOCs Psychiatric disorders and General disorders.

With regards to psychiatric and behavioral disorders, higher rates of irritability, aggression, anxiety and depression were reported in BRV treated patients compared to PBO. With regards to aggression, severity was slightly worse for BRV than for PBO and more patients on BRV discontinued because of aggression. Several cases were suggestive with regard to time to onset and positive de-challenge. Furthermore, amongst the reports of behavioral disorders for BRV treated patients, there were also cases of agitation including one serious case. For these reasons, the CHMP considered that depression, anxiety and irritability should be added as common ADRs in SmPC section 4.8 and aggression and agitation as uncommon ADRs. Aggression was furthermore included in the RMP as an identified risk.

Psychosis is known to be more common in subjects with epilepsy compared to the general population and AEDs have been shown to be able to induce psychotic disorders. Given that 3 SAEs of psychotic events were reported in the BRV treatment group and none in the PBO group and that two of the three SAEs were cases of possible positive de-challenge, the CHMP was of the view that a causal relationship to BRV use could not be excluded. The CHMP noted that in all 3 cases, patients were concomitantly taking other AEDs having the potential to cause a psychotic reaction. However, this was not surprising considering that BRV was investigated as add-on therapy and, such co-medication did not allow excluding a casual relationship with BRV. There is also the possibility for BRV to augment the probability of inducing psychotic disorders in an add-on setting. Therefore, the CHMP concluded that psychotic disorder should be included in SmPC section 4.8.In general, the use of AEDs is associated with a risk of suicidal ideation and behaviour in epilepsy patients. Cases of suicidal ideation and behaviour have also been reported in patients using BRV. Overall, the incidence rate of suicidality related events observed in the BRV program falls within the range reported in community based epidemiological studies in epilepsy patients. An observational study conducted in the UK (Arana et al., 2010), showed an incidence of suicide-related events among patients with epilepsy receiving AEDs of 0.482 per 1000 person-years. This incidence rate is lower than the one observed in Pool S4 considering only completed suicide and suicide attempts (3.3 per 1000 subject-years). However possible under-reporting of suicide has been hypothesized by the authors of the publication. Furthermore, this study did not confirm the finding that treatment with AEDs confers an additional risk of suicide-related events among patients with epilepsy. When considering another study conducted by Patorno et al. (2010), the incidence rate of attempted or completed suicide observed in Pool S4 did not exceed the range of rates observed in this study with other AEDs (range 3.7 – 33 per 1000 patients years). Based on the known risk of suicidal ideation and behaviour for AEDs in general and since the mechanism of this risk is not known and the available data for BRV did not exclude the possibility of an increased risk in particular during the first 6 months of treatment, an important identified risk was included in the RMP. Suicidal ideation was also listed as uncommon ADR in section 4.8 of the SmPC. In addition, a class warning for AEDs on suicidal ideation and behaviour was included in SmPC section 4.4.

Potential for abuse is an important potential risk for drugs with a CNS mechanism of action, which was reflected in the RMP of BRV. However, based on the data from the phase III clinical trials with BRV, a significant concern for BRV was considered unlikely. While there was only limited information on possible withdrawal effects, as

most patients in the phase III trials continued in a long-term extension study, there was no evidence for a withdrawal syndrome with BRV. In line with clinical practice, all pivotal studies provided for down-titration schedules and the CHMP considered it appropriate to recommend gradual withdrawal of 50 mg/day on a weekly basis with a final week of treatment at 20 mg/day, in case of treatment discontinuation.

More patients reported adverse events of convulsion in the BRV overall group compared to the PBO group, in particular early during treatment. The highest incidence of convulsion was in a dose group of 50mg/day and lowest in 200mg/day group. While it was acknowledged that that the term convulsion describes both changes of seizure type and inadequate control of seizure activity, the CHMP considered that it was not possible to exclude that treatment with BRV treatment was causally related to some of the events and consequently SmPC section 4.8 was updated to updated to include convulsion as a common ADR.

A similar incidence of TEAEs associated with falls and injuries was observed in patients treated with BRV and PBO. Three serious cases of fall were reported in patients receiving BRV at doses of 150 and 200mg/day, but no case occurred in the PBO group. At least two of these events were considered drug related. However, since all three cases were related to seizure activity, addition of convulsion to SmPC section 4.8 was considered by the CHMP sufficient to address the concern.

Blood dyscrasia was amongst the AEs of interest identified by the applicant. A review of the available data revealed a number of cases of neutropenia and neutrophil count decreased reported with the use of BRV. The majority of changes were within NCI Grade 2, but there were 4 subjects with severe changes of neutrophil count according to NCI Grade 3 criteria. Cases of this severity, although not life-threatening require hospitalization. While the CHMP recognized that BRV is used as adjunctive treatment and that other AEDs may have contributed to the development of neutropenia, a causal role of BRV could not be excluded. The CHMP considered that prescribers should be informed of this risk, in particular in patients who already present with neutropenia or neutrophil count decrease at the time of treatment initiation. For this reason, neutropenia was included in SmPC section 4.8 as an uncommon ADR and in the RMP as important potential risk.

Other TEAES that were more frequently reported in patients receiving BRV compared to PBO included nausea, vomiting, constipation, influenza, insomnia, cough and upper respiratory tract infection, which were consequently labelled as ADRs in SmPC section. Furthermore, cases of vertigo considered drug-related were also reported.

Some TEAEs were reported more frequently in the Pool Monotherapy compared to Pool S4, including a higher incidence of drug related TEAEs of decreased appetite. Although it is acknowledged that Pool Monotherapy comprised only a small number of subjects (150), this finding lends support to a possible causal association with BRV for this AE. Furthermore, in the pool of PBO-controlled Phase III studies, decreased appetite was also more frequently reported in patients receiving BRV compared to PBO. For these reasons, and taking into account that related events are already listed ADRs for LEV (weight decreased) and for BRV (nausea), the CHMP was of the view that decreased appetite should be added to the SmPC section 4.8.

Five deaths occurred in the placebo controlled studies including 4 cases of patients receiving BRV treatment. Of these, 3 cases were classified as SUDEP and 1 case as drowning, even though seizure related activity could not be excluded because of insufficient information. These three cases of SUDEP occurred within 3 months from the start of BRV treatment. Overall, the incidence rate of SUDEP using Ryvlin criteria (2011, definite, probable or possible) reported in the BRV program (2.2 per 1000 subject-years) falls within the range reported in other AED development programs and community based epidemiological studies (range from 0.9 to 3.8 per 1000 subject-years). A further 6 subjects died from carcinoma. All cases of carcinoma occurred after more than 16 months of BRV exposure (range 16.6 to 60.8). Available non-clinical BRV data did not show any evidences of

carcinogenicity. For LEV, which is structurally related and acts on the same SV2 receptors, no signal of carcinogenicity has emerged since its authorization in the EU in 2000, neither in the clinical development program nor in post-marketing. Furthermore, the cancer mortality rate observed in Pool S4 was similar to what would be expected in the target population of BRV, as was confirmed by comparing the standardized mortality ratio with the published cancer mortality rates by the International Agency for Research on Cancer (GLOBOCAN). Thus, there was no indication for an increase in cancer mortality in BRV treated patients. Nevertheless, potential occurrence of cancer with BRV will be monitored in upcoming periodic safety update reports (PSURs).

With regards to special populations, based on the available data, the safety in elderly patients appeared similar compared to patients aged less than 65 years. A total of 130 subjects aged 65 years and older were exposed to multiple doses of BRV, including 51 epilepsy patients. Only 30 patients were aged between 75 and 84 years (5 in the phase II/III epilepsy studies and 25 in other neurological conditions). Based on the small numbers of elderly subjects enrolled in the POS studies, the CHMP considered that the clinical experience with BRV in patients ≥65 years was limited and no definitive conclusions could be drawn.

Furthermore, based on the safety results from a clinical pharmacology study in healthy subjects and subjects with impaired liver function, the CHMP concluded that a single oral dose of 100 mg BRV, as applied in the study, was safe and well tolerated in subjects suffering from hepatic impairment (Child-Pugh scores A, B and C). As discussed in section 2.4.3. , a maximum daily dose of 150mg/day is recommended in hepatically impaired patients due to an increased exposure to BRV. Relevant information including a warning on the limited experience in patients with pre-existing hepatic impairment and the need for dose adjustment was incorporated in the SmPC.

In the PBO-controlled studies, the incidence of the common and very common adverse events fatigue and somnolence were dose-related (incidence for 100 mg/day 7.6 % and 14.2 %, respectively and for 200 mg/day 10.4% and 16.8 %, respectively). There was also a trend for more frequent reporting of treatment-emergent SAEs of injury (i.e. fall, fractures etc.) in the high dose groups than in low dose groups. Nevertheless, although there was a dose-related increase in certain adverse events, overall, the safety profile of BRV was considered manageable across the proposed therapeutic dose range up to the maximum daily dose of 200 mg. The CHMP therefore agreed that initial dose titration to an effective dose is not required for tolerability.

Finally, additional discussion was requested by the CHMP on the safety of the solution for injection/infusion in light of the PK finding of an approximately 20-30% higher c_{max} and shorter t_{max} resulting from i.v. application of BRV compared to BRV tablets. Supportive data were available mainly from a phase III study which evaluated the safety and tolerability of BRV i.v. bolus and 15 minute infusions. The data of this study showed that the adverse event profile of BRV in the first 7 days of treatment was similar regardless of the method of administration used (oral, i.v. bolus or infusion). It was furthermore noted that i.v. administration is only intended as an alternative for patients when oral administration is temporarily not feasible and would take place in a healthcare setting, adding additional risk mitigation.

2.6.2. Conclusions on the clinical safety

The CHMP considered the extent of the safety database to be adequate to support the application for BRV. No major safety concern has been identified in clinical trials with BRV. The most common ADRs observed with the use of BRV were somnolence, dizziness, and fatigue. Adverse events were mostly mild and moderate in intensity and appeared to be generally manageable. Overall, for an AED, the safety profile of BRV was considered

comparably benign within the proposed dose range and in line with what could be expected based on the experience with LEV, another SV2A targeting compound approved for the treatment of POS.

The CHMP concluded that the available safety data were suitable to support the application for BRV as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in patients from 16 years of age with epilepsy at the dose range from 50 mg/day to 200 mg/day. Relevant safety information was adequately reflected in the SmPC.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report (i.e. removing the list of paediatric studies in the pharmacovigilance plan).

The applicant implemented the changes in the RMP as requested by PRAC and aligned the RMP with the SmPC and therefore the CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 5 with the following content:

Safety concerns

Important identified risks	• Suicidality (class label for anticonvulsant products) • Aggression
Important potential risks	• Neutropenia • Worsening of seizures (as an anticonvulsant) • Abuse potential (as a CNS-active product) • Off-label use for unapproved epilepsy indications (including preterm neonates to children aged < 16 years)
Missing information	• Data during pregnancy and lactation • Data in patients with pre-existing hepatic impairment • Data in patients with pre-existing end stage renal impairment requiring dialysis • Data on elderly • Clinical outcome after an overdose • Long-term safety

Pharmacovigilance plan

Study / activity type, title, and category (1 to 3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Participation in and sponsorship of EURAP (Category 3)	Collect data on pregnancy	Pregnancy and lactation	Planned	Ongoing – will be discussed in PSURs
Participation in and sponsorship of the North American AED Pregnancy Registry (Category 3)	Collect data on pregnancy	Pregnancy and lactation	Planned	Ongoing – will be discussed in PSURs

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Suicidality (class label for anticonvulsant products)	Available by prescription only Packaging: The brivaracetam oral tablet pack contains unit-dose packaging (blister) that requires a sequential withdrawal of the tablets, which could interfere with accomplishment of suicidal thoughts. Intravenous formulation is provided in vials containing 50mg of brivaracetam in total, and the administration will be performed by a health care professional and not the patient. Oral solution is packaged in bottles with 300mL fill volumes with a concentration of brivaracetam 10mg/mL. This corresponds to 3g of brivaracetam if the entire volume is taken. Once placed, the adaptor for the oral-dosing syringe is difficult to remove, thus limiting the ability to drink significant volume. The oral solution, although flavoured, does not have a pleasant taste due to the bitter tasting drug substance. SmPC Section 4.4: Special warnings and precautions for use SmPC Section 4.8: Undesirable effects	None
Aggression	Available by prescription only SmPC Section 4.8: Undesirable effects	None
Neutropenia	Available by prescription only SmPC Section 4.8: Undesirable effects	None
Worsening of seizures (as an anticonvulsant product)	Available by prescription only	None
Abuse potential (as a CNS-active product)	Available by prescription only	None

Off-label use for unapproved epilepsy indications (including preterm neonates to children aged <16 years)	Available by prescription only SmPC Section 4.1: Therapeutic indications SmPC Section 4.2: Posology and method of administration SmPC Section 4.8: Undesirable effects SmPC Section 5.1: Pharmacodynamic properties SmPC Section 5.2: Pharmacokinetic properties	None
Data during pregnancy and lactation	Available by prescription only SmPC Section 4.6: Fertility, pregnancy and lactation	None
Data in patients with pre-existing hepatic impairment	Available by prescription only SmPC Section 4.2: Posology and method of administration SmPC Section 4.4: Special warnings and precautions for use SmPC Section 5.2: Pharmacokinetic properties	None
Data in patients with pre-existing end stage renal impairment requiring dialysis	Available by prescription only SmPC Section 4.2: Posology and method of administration SmPC Section 5.2: Pharmacokinetic properties	None
Data in elderly	Available by prescription only SmPC Section 4.2: Posology and method of administration	None
Clinical outcomes after an overdose	Available by prescription only SmPC Section 4.2: Posology and method of administration SmPC Section 4.9: Overdose	None
Long-term safety	Available by prescription only SmPC Section 4.8: Undesirable effects	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet of Brivact oral solution 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.*

No full user consultation with target patient groups on the package leaflet of the tablets and solution for injection/infusion has been performed on the basis of bridging reports making reference to Briviact oral solution. The bridging reports submitted by the applicant have been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Briviact (brivaracetam) is included in the additional

monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The evaluation of the benefits of BRV treatment was mainly based on the outcome of three pivotal fixed-dose phase III studies in patients aged 16 years and older with refractory POS. In these studies BRV was compared to PBO as add-on treatment to an existing AED regimen for relevant endpoints including the rate of patients with at least 50% reduction in POS frequency over the treatment period as well as reduction of adjusted POS seizure frequency. Overall, the patient population was considered representative of the target population in line with the claimed indication of adjunctive therapy of POS with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy.

The first study N01252 failed its primary endpoint, % reduction in adjusted POS frequency over PBO for the 50 mg/day dose, which was 6.5 % (95 % CI [-5.2, 16.9], p=0.261). However, the result for the 100 mg/day dose was nominally statistically significant, with 11.7 % (95 % CI [0.7, 21.4], p=0.037) and there was a numerical trend in favour of all BRV dose groups.

The second study N01253 reached its primary endpoint, % reduction in adjusted POS frequency over PBO for the 50 mg/day dose (12.8 %, 95% CI [1.7, 22.6], p=0.025) whereas no difference was seen for the lower doses 20 mg/day or 5 mg/day. Similar results as for POS frequency reduction were obtained for the 50% response rate in both study N01252 and study N01253.

The third pivotal study, which was the largest of the three trials, investigated BRV doses of 100 mg/day and 200 mg/day. For both doses a statistically significantly higher proportion of 50% responders were observed (38.9 % and 37.8%, respectively, versus PBO 21.6 %, p<0.001). The % reductions in adjusted POS frequency over PBO were also statistically significant with no difference between the 100 mg/day and 200 mg/day doses (22.8 % and 23.2 %, respectively, p<0.001).

Pooling of the data from the three pivotal studies excluding patients receiving LEV at the time of study entry demonstrated a statistically significant difference in favour of BRV for the 50 % responder rate for doses from 20 mg/day to 200 mg/day, and for the % reduction in adjusted POS frequency for BRV doses 50 mg/day to 200 mg/day, with a dose-response relation in the interval from 20 mg/day to 100 mg/day. The effect size for the proposed effective dose range of 50-200 mg/day, with a difference in responder rate of 14-19% compared to PBO, was of a similar magnitude as for other AEDs, and was considered by the CHMP of clinical relevance.

Furthermore, the number (%) of subjects who were seizure-free during the 12-week treatment period in the pooled pivotal studies was 2 (0.5%), 3 (1.9 %), 4 (2.5 %), 17 (5.1 %) and 10 (4.0 %) in the PBO, BRV 20 mg/day, BRV 50 mg/day, BRV 100mg/day and BRV 200 mg/day groups, respectively, and thus consistently higher in all BRV groups compared to PBO.

Uncertainty in the knowledge about the beneficial effects

Generally, the study populations across the clinical development program were representative of the intended target population, however, only few subjects recruited were 65 years and older. While PK analysis did not reveal the need for dose adjustment, the limited experience in elderly was reflected in SmPC section 4.2.

The primary and main secondary endpoints were based on diary data collected by the patients at home. Initial uncertainties of the quality of the diary data were addressed by the applicant who documented that across the 3 studies, diary compliance was very high (mean compliance was ≥98% in the PBO and BRV Overall groups) and the occurrence of missing diary days was low. Additional sensitivity analyses to explore the impact of missing data on the study outcome, including a worst-case BOCF approach, confirmed the robustness of the original results and showed that missing data did not significantly bias the results.

Analysis by LEV status showed that subjects with concomitant LEV use did not derive any benefits from BRV treatment, which may reflect competition of both compounds at the SV2A binding site. There was also a numerically lower seizure reduction in patients who previously used but then stopped LEV compared to LEV-naïve subjects. However, the latter finding might also be explained by baseline imbalances in the number of prior AEDs used and partial seizure frequency. The CHMP considered that the information on prior and concomitant use of LEV was relevant to prescribers and should be reflected in the SmPC.

With regards to the proposed therapeutic dose range from 50 mg/day to 200 mg/day, the CHMP noted that efficacy data for the lower end of the range, BRV 50 mg/day, were inconsistent in the two dose-finding studies N01114 and N01193 as well as the two pivotal studies N01252 and N01253 in which 50 mg BRV has been evaluated. However, overall, there was a consistent trend of at least a numerical advantage of BRV 50 mg/day over PBO throughout all studies. Further support for the efficacy of the 50mg/day dose was provided from long-term follow-up studies, where approximately one third of the patients remained on this dose as their maintenance dose. With regards to the upper end of the dose range, study N01358 as well as the pooled data analysis from all three pivotal trials showed no further increase in efficacy for the 200 mg/day dose compared to 100 mg/day. While it was not possible to identify a single prognostic factor for a better response with BRV 200 mg/day compared to100 mg/day, there was a trend in some analyses for increased efficacy at 200 mg/day and PK modelling results also suggested that patients in the responder population may benefit from doses higher than 100 mg/day. Furthermore, in long-term follow-up studies, the majority of patients received a dose of 150 or 200 mg/day as their maintenance dose. Taken together, the available data suggest that some patients may have additional benefit from doses beyond 100 mg/day.

Some uncertainty arose from the finding that efficacy of BRV varied between different geographical regions. In Study N01358 and in the pooled analysis of the phase III trials, the percentage of responders was lower in Europe than in other geographical regions. A number of factors might possibly have contributed to these differences including the lower number of previous AEDs and lower frequency of previous use of LEV in Latin America. It could also not be excluded that at least part of the differences between regions were chance findings. In particular, the lower effect of BRV 200 mg/day in the EU population compared to all other regions including North America remained unexplained. It is therefore expected that in future studies within the clinical development program for Briviact in epilepsy, involving the 200mg/day dose and different geographic regions, the applicant will monitor and discuss any difference observed, in particular any findings of a reduced effect size in the EU population.

Finally, in study N01358, there was an increase in the PBO response over time, which initially gave the impression of an attenuation of the BRV treatment effect with time. Additional analyses provided by the applicant were reassuring with regards to the maintenance of the effect of BRV over the total duration of

treatment for 3 months. Additional evidence for persistence of the effect over time was available from long-term follow-up studies, all of which were ongoing at the time of this report. However, interim results from these studies showed that a high proportion of subjects discontinued at some point during the extension phase due to lack of efficacy which may have introduced selection bias. Therefore, efficacy results from these studies should be interpreted with caution.

Risks

Unfavourable effects

The safety database of BRV included 2388 epilepsy patients receiving BRV in controlled and uncontrolled trials and, amongst these, 1320 patients who were exposed to BRV doses between 50 and 200 mg/day for at least 12 months. The evaluation of risks focused on the pool of safety data derived from the three pivotal Phase III studies, comprising 1099 and 459 patients receiving BRV and PBO, respectively.

Overall, the incidence of TEAEs was higher in BRV treated patients compared to PBO. The majority of adverse events were mild to moderate in intensity. Most frequently reported ADRs in BRV treated patients were somnolence (14.3%), dizziness (11.0%), and fatigue (8.2%).

Some unfavourable effects believed to be related to AEDs in general or to LEV, the only other compound approved for epilepsy treatment with a similar mechanism of action, were also observed with BRV. This includes the risk of suicidality and worsening of seizures, which are considered to be common concerns for AEDs. Consequently, suicidal ideation was included as an important identified risk in the RMP of BRV and an ADR in the SmPC which also includes the related class labelling for AEDs on suicidal ideation and behaviour. Worsening of seizures was considered an important potential risk in the RMP and convulsion was added as a common ADR in SmPC section 4.8. Furthermore, decreased appetite was identified as an ADR of BRV.

Risks related to behaviour and psychiatric disorders including anxiety, aggression, irritability, depression agitation and psychotic disorder were also identified in the development program of BRV and included in the product information. Aggression was also considered an important identified risk which was included in the RMP.

Other important potential risks in the RMP include neutropenia, off-label use for unapproved epilepsy indications and abuse potential as a CNS-active drug. Routine pharmacovigilance was considered sufficient to address all safety concerns in the RMP.

Finally, the potential of BRV for drug-drug interactions appeared to be generally low. Relevant information on PD and PK interactions was incorporated in SmPC section 4.5.

Uncertainty in the knowledge about the unfavourable effects

Even though the safety database was generally considered sufficient in terms of patient numbers and exposure duration, it was too limited to allow detection of rare ADRs. In particular, with regards to the safety in the elderly population uncertainties remained since very few subjects ≥65 years of age have been enrolled in BRV clinical trials. Safety data in subjects older than 75 years were very limited and, except for one patient, come from healthy volunteers. Only limited data were also available for patients with hepatic impairment for whom a starting dose of 50 mg/day is advised with a maximum daily dose of 150 mg. Information on the limitations of the safety database were considered relevant for healthcare professional and thus was included in the SmPC.

For somnolence and fatigue, incidence rates increased with the BRV dose within the proposed dose range of 50 mg/day to 200 mg/day. However, overall, the CHMP considered the safety profile across the proposed therapeutic dose range to be manageable and comparably benign for an AED, including the proposed maximum

daily dose of 200 mg.

Other missing information listed in the RMP included long-term safety, clinical outcomes after overdose and certain specific populations such as pregnant and lactating women, and patients with end-stage renal impairment.

Benefit-risk balance

Importance of favourable and unfavourable effects

BRV has been developed for the adjuvant treatment of epilepsy patients with refractory POS, which comprises a patient population inadequately controlled in their seizures by their existing AED regimen. For these patients, efficient treatment options are needed including regimens of one or more AED to reduce the occurrence of seizures and ideally achieve seizure freedom. In the pivotal clinical trials conducted with BRV, BRV has been effective in improving seizure control in patients with refractory POS, as demonstrated by a statistically significant difference in favour of BRV compared to PBO for the 50% responder rate, and for the % reduction of POS frequency within the recommended dose range. The effect size expressed as 50% responder rate of 14-19% more responders compared to PBO in the therapeutic dose range from 50 mg/day to 200 mg/day is of similar magnitude as for other AEDs, and represents a clinically relevant effect.

The safety profile of BRV did not raise particular concerns and was considered relatively benign for an AED across the therapeutic dose range. Most ADRs were mild to moderate in intensity and are considered manageable. The risks of suicidal ideation, behaviour abnormalities and seizure worsening appear similar to what is known for other approved AEDs.

Benefit-risk balance

Based on the available quality, efficacy and safety data at the time of the report, the CHMP considered that the benefits of adjunctive BRV therapy outweighed its risks in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy. The benefit-risk balance was considered favourable.

Discussion on the benefit-risk balance

The results in individual clinical studies and the pooled analysis of the data from the pivotal trials support a favourable effect of BRV in the treatment of POS at doses of 50 mg/day to 200 mg/day. Despite some inconsistencies in the results across individual studies for the 50 mg/day dose, sufficient evidence was provided supporting this dose as the lowest effective dose of BRV. Treatment should be initiated either with 50 mg/day or 100 mg/day depending on the physician's assessment weighing the need for rapid seizure reduction against a possible increase in ADRs.

Beyond the dose of 100 mg/day there was no increase in efficacy in the randomized clinical trials. However, the upper end of the dosing interval was still agreed at 200 mg/day given the manageable safety profile at this dose level and since the totality of the data suggested that individual patients may indeed benefit from doses higher than 100 mg/day. Nevertheless, there was an increased incidence of some adverse events including somnolence and fatigue with increasing doses of BRV. Therefore, it is recommended to further adjust the dose within the range of 50 mg/day to 200 mg/day based on individual patient response and tolerability.

Limited data were available for long-term efficacy and safety. Reassurance on the maintenance of efficacy over the treatment period of 3 months in the pivotal clinical trials was provided by the applicant, but data from the long-term follow-up studies should be interpreted with caution as the high rate of discontinuations over time due

to lack of efficacy, while not unusual for such study, may have introduced selection bias.

There was only limited data for elderly patients ≥ 65 years and patients with hepatic impairment, which was reflected in the SmPC. While no dose adjustment was necessary in older patients, a starting dose of 50 mg/day and a maximum daily dose of 150 mg were advised for hepatically impaired patients.

Finally, regional differences in efficacy were observed in the clinical studies with a trend for lower efficacy in Europe compared to other regions. Factors which may possibly have contributed to such differences are the lower number of previous AEDs used, and the lower frequency of previous use of LEV in regions outside Europe, for example in Latin America. It was also not possible to exclude that at least part of the differences between regions was related to chance. In particular, the lower effect for BRV 200 mg/day in the EU patient population compared to North America remained unexplained. It is expected that in future studies within the clinical development program of Briviact in epilepsy, involving the 200 mg/day dose and different geographic regions, the applicant will monitor and discuss any difference observed, in particular any findings of a reduced effect size in the EU population.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Briviact as adjuvant therapy in the treatment of partial-onset seizures with or without secondary generalisation in adult and adolescent patients from 16 years of age with epilepsy is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that brivaracetam is qualified as a new active substance.