European Medicines Agency

WITHDRAWAL ASSESSMENT REPORT

FOR

Lunivia

International Non-proprietary Name: eszopiclone

Procedure No. EMEA/H/C/000895

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1. Submission of the dossier

The applicant Sepracor Pharmaceuticals, Ltd. submitted on 23 July 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Lunivia, 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 EMEA/CHMP on 27 February 2007.
The legal basis for this application refers to:

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

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

The application submitted is a complete dossier:

Composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies

The applicant applied for the following indication treatment of insomnia.

Licensing status:
Lunivia has been given a Marketing Authorisation in US on 15 December 2004 (marketed as product called Lunesta).

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur:	Dr David Lyons	**Co-Rapporteur:**	Prof Cristina Sampaio

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 23 July 2007.
- The procedure started on 15 August 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 November 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 November 2007. In accordance with Article 6(3) of Regulation (RC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 10-13 December 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 14 December 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 28 March 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 12 May 2008.
- During the CHMP meeting on 27-29 May 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- During the CHMP meeting on 22-25 September 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 20-23 October 2008, 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 Lunivia on 23 October 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 17 October 2008.

1.3. Steps taken for the re-examination procedure

- The applicant submitted written notice to the EMEA on 04 November 2008 to request a re-examination of the Lunivia CHMP positive opinion of 23 October 2008.
- During its meeting on 15-18 December 2008, the CHMP appointed Dr. K. Broich as Rapporteur and Dr Votava as Co-Rapporteur.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the re-examination evaluation teams were:

Rapporteur:	Dr Karl Broich	**Co-Rapporteur:**	Dr Martin Votava

- The detailed grounds for the re-examination request were submitted by the applicant on 23 December 2008. The re-examination procedure started on 23 December 2008.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 28 January 2009. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 23 January 2009.
- During its meeting on 19-22 January 2009, the CHMP adopted a List of Participants for the Scientific Advisory Group (SAG) meeting on Clinical Neuroscience meeting to be held on 5 February 2009.
- During the SAG meeting on 5 February 2009, experts were convened to consider the grounds for re-examination. During this meeting the applicant presented an oral explanation. A report of this meeting was forwarded to the CHMP.
- The Rapporteurs' Joint Assessment Report was circulated to all CHMP members on 11 February 2009.
- During the CHMP meeting on 16 - 19 February 2009, the applicant presented an oral explanation before the CHMP on 16 February 2009.
- During the meeting on 16 – 19 February 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final Opinion confirming the favourable benefit/risk balance of Lunivia as determined in the original opinion of October 2008. However, the CHMP also reconfirmed its opinion of October 2008, concluding that no meaningful clinical difference could be established between eszopiclone and zopiclone regarding safety and efficacy and therefore recommending the refusal of the New Active Substance Status to eszopiclone. The applicant provided the revised letter of undertaking on the follow-up measures to be fulfilled on 19 February 2009.

2. SCIENTIFIC DISCUSSION

2.1. Introduction

Sepracor Pharmaceuticals Ltd. has submitted an application for a marketing authorisation through the centralised procedure for Lunivia 2 mg and 3 mg film coated tablets.
Racemic zopiclone is already marketed in Europe, and eszopiclone is approved on the market in the United States of America.
The product contains the active substance eszopiclone. Racemic zopiclone is a mixture of the enantiomers (S)-zopiclone and (R)-zopiclone whereas eszopiclone is comprised of pure (S)-zopiclone, a single isomer associated with hypnotic activity.

The applied indication for Lunivia is for *the treatment of insomnia, including difficulty falling asleep, nocturnal awakening or early awakening, in adults, usually for short term duration.*

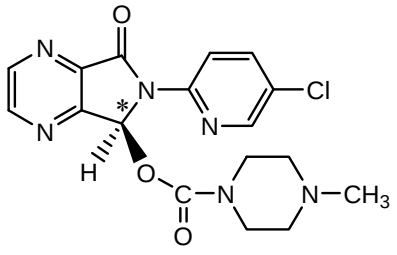
Insomnia is a heterogeneous condition featuring reduced quality, duration, or efficiency of sleep; it is a common condition characterised by sleep disruption lasting at least one month. Disruption of sleep may include difficulty initiating sleep, difficulty maintaining sleep, or early morning awakening. An additional complaint is diminished sleep quality or non-restorative sleep and may cause consequent daytime impairment or distress with fatigue and poor concentration.

2.2. Quality aspects

Introduction
Sepracor Pharmaceuticals Ltd. has submitted an application for a marketing authorisation through the centralised procedure for Lunivia 2 mg and 3 mg film coated tablets.
The product contains the active substance eszopiclone which is pure (S)-zopiclone, a single isomer associated with hypnotic activity.
The proposed commercial product is provided in polyvinylchloride (PVC)/polymerized chlorotrifluoroethylene (PCTFE) blisters.

Active Substance

The chemical structure of Eszopiclone (INN/USAN) or (+)-(5*S*)-6-(5-chloropyridin-2-yl)-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methylpiperazine-1-carboxylate (INN) is presented thereafter.



* = chiral centre

Physico-chemical properties of eszopiclone such as pH, crystallinity, hygroscopicity, optical rotation, particle size of the milled substance have been described. Eszopiclone has one single chiral centre. The substance is non hygroscopic and only one form has been observed during development.

- Manufacture

The commercial manufacturing process has been adequately described. The synthesis consists of two main steps.

Appropriate control of starting materials, reagents, solvents as well as intermediates has been carried out.

TSE declarations have been provided for all starting materials and reagents, this is satisfactory.

The manufacturing process has been successfully validated and reproducibly demonstrated.

The chemical structure of eszopiclone has been fully elucidated by elemental analysis UV, IR, ^{1}H NMR, ^{13}C NMR, MS and X-ray crystallography. Results of structural and polymorphism studies (such as X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetry, hot stage microscopy, moisture sorption, solution ^{1}H NMR, IR and Raman spectroscopy) have been presented. It has been demonstrated that no polymorphism was observed during stability studies. Furthermore, the route of synthesis/resolution supports the chemical structure assigned.

An extensive discussion on impurities has been presented and is acceptable. Impurities including those present in the starting materials and reagents or process derived impurities were removed and controlled during the synthesis. Impurity levels found in pre-clinical and clinical batches were also similarly low and did not present any toxicological issues.

Similarly, residual solvents were satisfactorily controlled and results remained below ICH limits. Studies confirmed the ability of the eszopiclone process to remove these solvents.

Although no inorganic materials were used, the applicant has included a heavy metals test (PhEur 2.4.8). This is acceptable.

- Specification

The proposed specification for the active substance Eszopiclone is satisfactory and adequately justified. Parameters tested include appearance (PhEur 2.2.1 and 2.2.2), identification (IR and chiral HPLC), enantiomeric purity (enantioselective HPLC), assay (HPLC), impurities (HPLC), water content (Karl-Fisher method, PhEur), sulfated ash (PhEur 2.4.14), heavy metals (PhEur 2.4.8), particle size (laser diffraction), residual solvents (GC), microbial contamination (PhEur 2.6.12 and 2.6.13).
Analytical methods have been sufficiently described and non compendial methods validated in accordance with ICH requirements.

Batch analysis data have been presented for 33 batches including development and commercial/full size batches. Data presented confirm batch-to-batch consistency of the proposed process and uniformity of the active substance regardless the source of the starting material zopiclone. The level of total impurities found was low and did not raise any safety concern. Also, Impurity levels in pre-clinical, clinical and full scale batches were comparable, i.e. impurity level in all batches was below the reporting threshold.

The active substance is stored in double low density polyethylene (LDPE) bags which are then stored in high density polyethylene (HDPE) drums (for storage and transport). The bags conform to the food directives in 2002/72/EC. The container closure system is satisfactorily described. The containers proposed for routine storage are those which have been used in the stability studies supporting the re-test period.

- Stability

Stability studies were carried out on four commercial batches of eszopiclone kept in the packaging similar to the commercial container under ICH conditions (60 months at 25°C/60% RH and 6 months at 40°C/75% RH). Parameters performed were appearance, water content, assay (HPLC), enantiomeric purity, impurities, particle size distribution and microbial examination. Analytical methods and specifications were the same as those used for release testing.
Results demonstrate the chemical and physical stability of eszopiclone under long term and accelerated conditions. Additionally, results show that racemization does not occur during storage.

Furthermore, photostability testing was conducted for one batch in accordance with guideline ICH Q1B (option 2 conditions). The substance was found to be light sensitive. Studies conducted when the product is kept in the packaging demonstrated the suitability of the packaging.
Stability studies conducted under forced conditions (acid, basic and oxidative conditions) allowed establishing the main degradation pathways of the molecule. The decomposition pathways observed in the forced degradation studies were not observed in the other stability studies.
Based on the stability results, a re-test period of 24 months for eszopiclone is proposed when stored in the commercial packaging and with no special precautions of storage.

Medicinal product

The proposed commercial medicinal product consists of round, biconvex, immediate release film-coated tablets containing 2 mg or 3 mg of eszopiclone per tablet. The tablets presented in the dossier are debossed with GS" on one side and "11N" and "KUU" on the other side for the 2 and 3 mg tablets, respectively. The tablets are packaged in thermoformed PVC/PCTFE blisters with aluminium lidding.

The tablet cores of both strengths are identical, apart from a slight difference in the amount of active ingredient, which is quantitatively offset by an equivalent amount of Microcrystalline Cellulose to maintain a target core weight.
The following compendial excipients used in the core formulation: microcrystalline cellulose as a diluent, dibasic calcium phosphate anhydrous as a diluent, croscarmellose sodium as a disintegrant, silica colloidal anhydrous as a glidant, magnesium stearate as a lubricant. The film-coating, intended for taste masking and product differentiation, is given by white (2.0 mg tablet) or dark blue (3.0 mg tablet). All the excipients are described in the PhEur. except the indigotine (E132), which complies with the specifications set in the Directive 95/45/EC (as amended by Directive 99/75/EC).
A certificate of analysis is provided for each excipient.

- Pharmaceutical Development

Formulation development
The formulation development for those immediate release tablet and selection of excipients were satisfactorily described.
The active substance eszopiclone is closely related to the authorised racemic zopiclone. Eszopiclone is comprised of pure (S)-zopiclone. Eszopiclone is a white to light-yellow powder. It is non hygroscopic, but it degrades in contact with water. Only one form has been observed during development. Based on development studies and the stability data, it has been shown that the active substance is compatible with the formulation excipients. Since the dose is small, maintenance of the dosage uniformity has been investigated and adequately controlled.
The effect of particle size distribution upon the medicinal product formulation and performance has been extensively studied and that the medicinal product performance is essentially unaffected by active substance particle size distribution (e.g dissolution profiles are comparable). After 60 months of storage of eszopiclone at 25°C/60% RH, the particle size distribution remains essentially unchanged, demonstrating that storage does not affect particle size.

Quantity of the excipients is the same for both strengths apart from Microcrystalline Cellulose (diluent) to offset the incremental differences in active ingredient in order to maintain a target core weight.
The excipients were unchanged throughout development and will be used for the proposed commercial formulation. With the exception of the blue colour (E132; indigotine) used in the coating agent (Opadry), all excipients used throughout development conform to the corresponding PhEur monographs and are routinely used in similar conventional solid oral dosage formulations. The excipients were selected because of their compatibility with eszopiclone and to achieve a short tablet disintegration time and to mask the bitter taste of the active ingredient.

Manufacturing Process Development
An immediate release tablet, with rapid disintegration characteristics in aqueous solution, was selected as the dosage form for development.
A dry blend, direct compression process was utilized in lieu of a wet granulation due to the potential for hydrolysis of Eszopiclone

Appropriate in-process controls were performed during manufacturing process development

Container Closure System
The packaging material chosen was satisfactory and supported by stability data. A PVC/ PCTFE film was selected. Certificates of analysis for the primary packaging materials have been provided.

- Adventitious Agents

None of the excipients is from human or animal sources. BSE/TSE signed declaration from the manufacturer is provided in Section 3.2.R and are maintained by Sepracor and available upon request from all qualified suppliers.

- Manufacture of the Product

The manufacturing procedures for both tablet strengths are identical, utilizing dry blending/ compression/ film coating (2.0 mg = white; 3.0 mg = dark blue) with identical tablet weights and with the slight change in active ingredient.
Appropriate control of critical steps has been carried out.

The medicinal product manufacturing process has been validated on 3 commercial batches for each strength. Validation of blending, compression and coating steps was carried out by the proposed commercial medicinal product manufacturer. The results provided by the applicant demonstrate the reproducibility of the manufacturing process.

- Product Specification

Release and end-of-shelf-life finished product specification for 2.0 mg and 3.0 mg tablets includes the following parameters: appearance, identification (chiral HPCL for eszopiclone and achiral HPLC for racemic zopiclone), assay (HPLC), related substances (HPLC), enantiomeric purity, water content (PhEur Karl Fisher), uniformity of dosage units (PhEur 2.9.40), dissolution (PhEur 2.9.3), microbial quality (PhEur 2.6.12 and 2.6.13).

Analytical methods have been sufficiently described and non-compendial methods have been validated in accordance with ICH requirements

Batch analysis data are submitted for 31 commercial scale batches (2 mg and 3 mg strengths) manufactured at the proposed commercial manufacturing site.
All batches met the specification and results confirm the consistency and uniformity of the product and that the product is under control.

The primary packaging of Lunivia tablets (2 mg and 3 mg) consists of 10 and 15-count blisters made of polyvinyl chloride (PVC)/polymerized chlorotrifluoroethylene (PCTFE) and aluminium foil lidding. Blister cards will be supplied in a carton (secondary packaging), which does not contribute to product integrity. The resins/additives and vinyl coating used in the primary packaging components conform to the food grade Directive 2002/72/EC, as amended; the vinyl coating meets the compositional requirements of PhEur 3.1.11. Suitability of the blister is further supported by the medicinal product stability data provided in this submission.

Appropriate characterisation and analysis of the packaging materials have been presented.

- Stability of the Product

Stability data based on ICH Q1A(R2) requirements have been presented for 12 batches kept in the commercial container closure systems as follows. All batches were manufactured at the commercial facility via the commercial processes.
For each strength, 2 mg tablets and 3 mg tablets: – 3 pilot batches (36 months at 25°C/60% RH and 30°C/60%RH and 6 months at 40°C/75% RH) and 3 commercial batches (30 months at 25°C/60% RH and 6 months at 40°C/75% RH).
In addition, photostability testing data based on ICH Q1B requirements using one batch of each strength were included. Studies revealed that medicinal product stability is not affected by exposure to light.

The following parameters were tested: appearance, water content, assay (HPLC), impurities, and dissolution,: enantiomeric purity, and microbial examination.
Analytical methods were the same as those used for the control of the finished product.

All the results were found within the shelf life specifications, hence "No storage conditions necessary" could possibly be assigned in line with the current Guidance. However, it is evident that the rate of change for most of the stability attributes increases at 30°C/ 60% RH and further at 40°C/ 75% RH and based on the stability data from the long-term storage condition and the statistical analysis of impurity formation, the applicant has opted to stringent storage conditions to "Do not store above 25 °C".
Based on the stability data, a shelf-life in accordance with the precautions of storage as defined in the SPC can be granted.

Discussion on chemical and pharmaceutical aspects
Information on development, manufacture and control of the active substance eszopiclone and the medicinal product Lunivia 2mg and 3 mg tablets has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of the important product quality characteristics and in turn lead to the conclusion that the product should have a satisfactory and uniform, performance in the clinic.

2.3. Non-clinical aspects

Introduction

Pivotal safety pharmacology studies and toxicology studies (including toxicokinetic arm of each study) have been performed to good laboratory practice (GLP). All pivotal safety pharmacology endpoints have been sufficiently addressed either as dedicated safety pharmacology studies or as endpoints within pivotal toxicology studies. A number of safety pharmacology studies were submitted that were not performed to GLP, but these studies are not considered pivotal.

Pharmacology

- Primary pharmacodynamics

The mechanism of action of eszopiclone has been appropriately studied in dedicated studies addressing zopiclone and R-zopiclone as well as the active metabolite (S)-DMZ. *In vitro* studies have shown and characterised the selective binding activity for $GABA_A$ receptor subtypes, for receptor - associated ion chloride channels and ion current.

Different molecular pharmacology at GABAA alpha subunits is shown in the table below.

Table: human recombinant GABA receptor subtypes in *Xenopus* oocytes

Compound	EC_{50} (nM)			
	α1β2γ2	α2β2γ2	α3β2γ2	α5β2γ2
Eszopiclone	240	99	102	25
(R)-Zopiclone	787	-	>10,000	>10,000
Zopiclone	97	600	117	97
Zolpidem*	78 ± 10	470 ± 110	750 ± 160	-
Zaleplon*	169 ± 4	1360 ± 300	2150 ± 300	2600 ± 700

- = no response or not measurable. EC_{50} is the concentration that resulted in 50% of maximum potentiation of GABA evoked Cl^- current. Data from Sepr. Doc. 190-435 and *Sanna et al. 2002.

The S-isomer (eszopiclone) presents higher affinity either to the receptor or to the ion channel as compared to the racemate or to the R enantiomer. Ranking the affinity values (IC_{50}) of the different test compounds for the receptor subtype or for the associated chloride currents, different results are obtained:

Eszopiclone (IC50 for receptor subtype): α5= α1> α2> α3
Eszopiclone (IC50 for chloride channel current): α5> α2=α3> α1
Zopiclone (IC50 for receptor subtype): α1> α2> α5> α3
Zopiclone (IC50 chloride channel current): α1= α5> α3> α2

In addition, the IC50 for α5 mediated chloride current is of the same magnitude as that for receptor binding at α5 and α1 subtypes. Put together, this could suggest that the activity of eszopiclone (linked to chloride currents) is primarily mediated by α5 receptor subtype. The same cannot be concluded for the racemate, possibly due to the influence of the R-enantiomer in the results.
In vivo, anxiolytic and sedative effects were observed for eszopiclone, zopiclone and the R-enantiomer (at higher doses than those observed for eszopiclone and zopiclone) in different animal models using rodents and non-rodents. In a conflict model in Rhesus monkeys, a profile consistent with a separation between doses that induce anxiolytic effects and those having sedative-motor effects was observed for eszopiclone, being the anxiolytic effect observed at doses lower than the sedative effect.
The affinities of (S)-DMZ and N-oxide zopiclone (two major metabolites) to the central BZD receptor site were > 20-fold and >250-fold lower than (S)-zopiclone. (S)-DMZ was shown to enhance $GABA_A$ current by increasing the affinity of receptors for GABA but dose dependently inhibited agonist evoked currents at both NMDA (glutamate) and nACh (acetylcholine) receptors, an effect that was mimicked by zopiclone. Inhibitory actions at NMDA and nACh receptors are also evident at a 20 µM, a concentration 900-fold higher than the eszopiclone's Ki at the central benzodiazepine site [22 nM]. At this concentration, zopiclone potentiated GABA-evoked currents from GABA-A receptors by up to 787% (Fleck, 2002). Based on the presented data the hypothesis that (S)-zopiclone is the primary component of Zopiclone responsible for its efficacy is considered acceptable. However based on the *in vitro* and *in vivo* it is not demonstrated that removal of the (R)-enantiomer alters either the safety or efficacy at clinically relevant doses.
It is asserted that the (S)-zopiclone is the primary component responsible for the pharmacological activity of zopiclone and that the (R) component does not add significant benefit. Based on the receptor binding pharmacodynamic studies (primary and secondary) this statement is considered true. Furthermore it is hypothesised that removal of (R)-zopiclone (and resultant decreased in (S)-DMZ exposure) may result in notable pharmacological differences and that removal is likely to be beneficial. This is considered theoretical because these differences have not been sufficiently demonstrated and the exposures required to cause an off target effect are considerably higher than those expected following administration of the current clinical dose of zopiclone.

- Secondary pharmacodynamics

Studies addressed the binding affinity of eszopiclone, zopiclone and the R enantiomer as well as (S)-DMZ for multiple central and peripheral receptors. The affinity for and the activity associated to muscarinic and nicotinic receptors was very low with EC50 values well beyond those for $GABA_A$ receptor. Some affinity was identified for NMDA receptor.
Investigation of anticholinergic effects did not reveal any significant effects on induced salivation or mydriasis and previous publications have failed to document any effect on gastrointestinal motility, bile flow, uterine motility (pregnant and non-pregnant rabbits) or diaphragmatic twitch tension.

- Safety pharmacology programme

Relevant effects on the cardiovascular and respiratory functions were investigated and not identified for eszopiclone, zopiclone and the R-enantiomer at exposures that might be of relevance as compared to those to be reached at the therapeutic doses. Binding to HERG channels was also not observed at concentrations which might be relevant for the clinical situation.
The potential for inducing physical dependence has been addressed in some studies in the literature and other conducted by Sepracor in rodents. The tests described suggest that eszopiclone, zopiclone and (S)-DMZ displayed a very low potential to induce physical dependence after acute to short term administration. A study by Yanagita 1983 revealed that discontinuing high doses of chronically administered zopiclone to Rhesus monkeys (16 or 32 mg/kg b.i.d for 4 weeks) resulted in a withdrawal syndrome manifested by tremor, muscle rigidity, apprehension, piloerection, and hyperirritability. The withdrawal signs were similar in intensity to those produced by nitrazepam, but less than those produced by diazepam. The doses evaluated in this study, on a mg/kg basis, are greater than 250-fold than those administered clinically (equivalent dose of 16 mg/kg/day eszopiclone as compared to a maximum human dose of 3 mg/day or 0.06 mg/kg/day). Systemic exposures were not described. Signs of withdrawal were not evident in clinical studies following treatment of up to 12-months duration with eszopiclone. In conclusion, effects after long term administration were not addressed, despite the intended chronic use being applied for eszopiclone. However, since clinical data were made available, the discussion on dependence potential should be continued in the clinical setting and in principle, additional pharmacological studies are not considered as needed.

- Pharmacodynamic drug interactions

A justification was provided for the lack of specific pharmacodynamic drug interaction studies: the pharmacological profile of racemic zopiclone in animals is well understood and, since removal of the (R)-isomer did not unmask any new pharmacologic or toxicologic properties of eszopiclone, additional risks of pharmacodynamic interactions were not expected. Also, the potentials for pharmacodynamic drug interactions were evaluated in multiple clinical studies and the results of these trials did not suggest the need for additional nonclinical investigations.

Pharmacokinetics

The non-clinical file is limited in what concerns the pharmacokinetic profile of eszopiclone in animals and human, making difficult the assessment since almost exclusively zopiclone data are presented. The company submitted a series of pharmacokinetic studies for zopiclone with the assertion that pharmacokinetic studies with zopiclone are representative of eszopiclone and presented *in vitro* studies to indicate that the presence of the (R)-enantiomer does not alter the metabolism of zopiclone and therefore there is no need for pharmacokinetic studies with (S)-zopiclone. However, part of the argumentation with respect to eszopiclone being a new chemical entity is based on pharmacokinetic differences and these differences are supported by toxicokinetic data from the 1- and 3-month toxicology studies in the rat and the dog. Furthermore, comparative toxicokinetic analysis was performed with three doses of (S)-zopiclone *versus* a single high dose of zopiclone. It is unclear if the toxicokinetics performed at such higher doses in the toxicity studies completely reflect the pharmacokinetics at lower doses and if a single

high dose of zopiclone is sufficient for comparative assessment. A comparative study of zopiclone with eszopiclone should have been performed to clarify the effect of the presence of the (R)-enantiomer.
Zopiclone Absorption, Distribution, Metabolism, Excretion (ADME) is extensively described and clearly, a high number of studies are available, showing it is well absorbed in animals and humans, widely distributed and excreted almost totally within 96 hours. It reaches brain regions as expected and crosses the placenta. The major metabolic pathways in rats and dogs involved decarboxylation (accounting for more than 50% of the dose), and in humans involved N-oxidation and N-demethylation in the side chains (accounting for more than 30% of the dose in urine). Fecal and renal excretion of metabolites and parent compound are the main routes and negligible pulmonary excretion is observed. Excretion in maternal milk is described in nursing women.
In vitro investigations revealed that (S)-zopiclone to be highly permeable across intestinal cell monolayer via transcellular pathway which corresponds with the high absorption of (RS)-zopiclone. (RS)-zopiclone was demonstrated to undergo extensive first pass metabolism and *in vitro* investigation with cytochrome P450 isoforms indicated that CYP2E1 and CYP3A4 may be responsible for the metabolism of (S)-zopiclone. Additional studies conducted as part of the three month toxicology studies to evaluate the liver microsomal cytochrome P450 and UDP-glucuronosyl-transferase enzymes in mice (190-819A1) and rats (190-818A1) indicated that (S)-zopiclone was a moderate phenobarbital-type inducer and are further discussed in the toxicology section below.
Since a comprehensive information regarding eszopiclone ADME was not submitted, the applicant was requested by the CHMP to describe the ADME profile of eszopiclone in the relevant species used for nonclinical assessment and in humans.
No new information has been provided with respect to pharmacokinetics of eszopiclone; however the applicant has compiled and presented all the relevant pharmacokinetic information in the dossier with respect to eszopiclone and its ADME profile in the relevant species. It was concluded that the ADME program with racemic zopiclone was an adequate surrogate for eszopiclone assessment, and the CHMP agreed with this conclusion.

Toxicology

- Single dose toxicity

The major clinical findings that were observed in mice with oral administration included decreased activity, muscle tone, laboured respiration, abnormal gait and stance were noted at all dose levels. Shut eyes and prostration were observed at ≥1500 mg/kg. Following macroscopic examination animals that received ≥ 1200 mg/kg demonstrated pale liver and kidneys with dark spots together with distended stomachs and fluid filled intestines. Based on mortality in this acute study in mice (S)-zopiclone appears to be the most toxic component.
In a intravenous study with albino rats, there were sporadic occurrences of urinary, renal, gastrointestinal, splenic and/or external findings noted at necropsy in rats that died in all dose groups, with all deaths occurring within one hour post-dose. Clinical findings were related to the known pharmacological action of the agent with the exception of convulsions, tail-findings, self-mutilation, soft faeces, ptosis. No clear target organ toxicity was identified. A number of these findings are similar to those observed in mice.

- Repeat dose toxicity (with toxicokinetics)

Based on the findings observed in the repeat dose toxicity studies and the carcinogenicity studies the NOAELS and indicated safety margins based on systemic exposure are outlined in the Table below.

Species	**Mouse**		**Rat**		**Dog**	
Gender	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
MTD/NOAEL	>200	>200	25	100	2.5	10
(S)-zopiclone (ng.h/ml)	29430	28167	9157	67203	5884	25,574
Safety Margin	154	147	48	352	31	134
(S)-Zopiclone and (S)-DMZ (ng.h/ml)	35,152	29,539	20353	110,563	7,050	28,308
Safety Margin	153	129	89	481	31	123

- Genotoxicity

Genotoxic potential of eszopiclone was assessed in several studies: *in vitro* bacterial and mammalian mutation assays, *in vitro* chromosome aberration assays, *in vivo* mouse micronucleus test, and *in vivo* unscheduled DNA synthesis in rat hepatocytes.
The overall results are exposed in the Table below.

Assays	Eszopiclone	(S)-DMZ	Study Numbers
In Vitro			
Ames	Negative	Negative	190-811, 192-807
Chromosome aberrations	Negative *	Positive **	190-808, 190-815A1, 192-805, 192-810
Mouse lymphoma	+ / - ***	NT	190-816A1, 190-864A2
In vitro DNA binding ^{32}P	NT	Negative	192-818A1
In Vivo			
Mouse micronucleus	Negative	Negative	190-820A1, 192-806
Mouse chromosome aberration	NT	Negative	192-806
Rat liver UDS	Negative	Negative	192-816A2
Transgenic $p53^{+/-}$ mouse	Negative	Negative	190-838, 192-821

* Two studies performed: One study (190-808) was considered invalid due to inadequate sample size and excessive cytotoxicity, the second study (190-815A1) was considered negative and adequate.
** Positive; however, supplemental results support an indirect, non-DNA binding mechanism for the chromosome damage.
*** One study with eszopiclone was negative (190-816A1), but a supplemental study of eszopiclone plus impurities (190-864A1) produced a weak positive response.
NT = test not performed.

From the test battery performed, positive clastogenic activity was observed at high concentrations of eszopiclone for nonactivated (-S9) condition in one of two CHO chromosomal aberration studies.
The concentrations at which positive clastogenic effects were seen (1200 and 1400 µg) were higher than the cytotoxic ones (>240 µg/L).
Other *in vitro* and *in vivo* assays performed were negative, including the *in vitro* mouse lymphoma, *in vivo* mouse bone marrow micronucleus, and unscheduled DNA synthesis in rat hepatocytes studies. Also the *in vivo* 6-month oncogenicity study in p53+/- transgenic mice, a model recognized for its sensitivity to mutagenic carcinogens was negative (no induced tumours where observed).

- Carcinogenicity

The carcinogenic potential of eszopiclone of investigated in 2-year bioassays by oral gavage in mice and rats (190-830A1 and 190-823A1) and a 6-month study in p53+/- transgenic mice (190-838). Additionally, a 6-month study in p53+/- transgenic mice (192-821) with (S)-DMZ has been performed.

Long-Term Studies
2-Year carcinogenicity in mice (190-830A1)
The exposures to total eszopiclone in mice were approximately 90 times higher than those observed in humans after the maximum recommended dose of 3 mg eszopiclone per day.
The parameters evaluated included mortality, clinical signs, detailed physical examination (including palpable masses), body weights, food consumption, ophthalmology, haematology, gross necropsy, and histopathology.
Survival was similarly affected in control and treated groups.
There were no reported treatment-related neoplastic findings at any dose level. Body weights, food consumption, haematology parameters (white blood cell counts), and ophthalmology were unaffected by

treatment with eszopiclone. There were no test-article-related findings in palpable mass, gross necropsy, or histopathology.

2-Year carcinogenicity in rats (190-823A1)
Exposures to total eszopiclone in male and female rats were approximately 21 and 89--times higher, respectively, than those observed in humans after the maximum recommended dose of 3 mg eszopiclone per day.
Assessment parameters included mortality, clinical signs, detailed physical examination including palpable masses, body weights, food consumption, ophthalmology, haematology, gross necropsy, organ weights, and histopathology.
There were no eszopiclone-related increases in tumour incidences for any tissue of either gender.
There were no treatment-related effects in haematology parameters, ophthalmology, palpable mass, organ weights, or macroscopic or microscopic findings at any dose level for either gender. Also, there were no effects on the male reproductive system (testes/epididymides) at any dose level.

Short or medium-term studies
6-Month carcinogenicity in p53+/- transgenic mice (190-838)
Heterozygous p53+/- transgenic mice in C57BL/6 strain background (B6.129-Trp53tm1 N5) were used because of the model sensitivity to genotoxic carcinogens. An additional positive control group with p-cresidine was included.
Mortality: 25 animals (distributed across all groups including controls) died during the study

- 9 were due to tumours,
- 4 were due to non-neoplastic findings,
- 12 deaths were either undetermined or oral gavage procedure error.

The deaths in the eszopiclone dose groups were not treatment-related. There were no clinical signs, macroscopic or microscopic findings indicative of toxicity as the cause of lethality in eszopiclone treated mice.
There were no treatment-related neoplastic findings in any of eszopiclone groups. In contrast, p-cresidine treated groups showed a marked and high incidence of neoplastic lesions in the urinary bladder.

- Reproduction Toxicity

Fertility and early embryonic development
The reproductive toxicity of eszopiclone was studied according to the current ICH guidelines recommendations.
Three studies were performed using 1) treated males and females, 2) nontreated males and treated females and 3) treated males and nontreated females.
Treated males mated with treated females – in this study were observed reduced spermatogenic effects with subsequent reductions in fertility indices in the mid- and high-dose eszopiclone treated animals. Similar treatments with zopiclone at 15 mg/kg/day in males and 120 mg/kg/day in females were associated with decreased sperm motility but no discernible effects on sperm production rate or on mating or fertility indices. The NOAEL for male systemic and reproductive findings was considered to be <5 mg/kg/day.
Treated females mated to non-treated males – the study demonstrated reduced fertility rates (not statistically significant) and increased preimplantation loss. The NOAEL for maternal systemic toxicity and female reproductive toxicity was 5 mg/kg/day and the NOAEL for early embryonic developmental toxicity was 25 mg/kg/day.
Treated males mated to non-treated females – he study was performed with the active metabolite (S)-DMZ where eszopiclone was included as one treatment group. No negative effects were reported with eszopiclone. In male rats, epididymal pathologic and spermatogenic changes along with low fertility or pre-implantation loss were observed with (S)-DMZ at ≥12 mg/kg/day. Dose levels of 5 mg/kg/day eszopiclone and 6 mg/kg/day (S)-DMZ were considered to be the NOAEL for male reproductive toxicity.

Embryo-foetal development
In studies with rats, weight loss of the dams was observed in the post-treatment period. Mean foetal body weights were reduced, which correlates with intrauterine growth retardation. No other significant effects on intrauterine parameters were observed. In rabbits, neither foetal body weights reduction nor other alterations of intrauterine parameters were reported.

Prenatal and postnatal development, including maternal function
Toxicity in the F0 and F1 generations were observed, which included decreased litter size, post natal survival and body weight gains. F1 reproductive performance was not altered by maternal treatment. F2 toxicity was not observed. The NOAEL of eszopiclone based on results from studies performed and from literature data (for pre and post natal toxicity) was estimated as 5mg/Kg/day.

- Local tolerance

A guinea pig local tolerance and sensitization test revealed that eszopiclone possesses little irritation and no sensitization potential in the Magnusson and Kligman Maximization test.
10 Harley guinea pigs/sex aged six weeks were dosed with multiple intradermal injections (1% w/v eszopiclone) on study day 0 and topical application (50% w/v eszopiclone) on study day 7 to attempt to induce a sensitized state for evaluation of delayed contact hypersensitivity. Freund's complete adjuvant was injected intradermally on study day 0. Fourteen days after topical induction, challenge topical dosing (50% w/v eszopiclone) for detection of sensitization was performed. The incidence index for the test group was 0% (0/20) following challenge dosing. Based on this value, the test article, eszopiclone, was nonsensitizing in guinea pigs under the conditions of this study, and was essentially nonirritating.

- Other toxicity studies

A guinea pig local tolerance and sensitization test revealed that eszopiclone possesses little irritation and no sensitization potential in the Magnusson and Kligman Maximization test.
10 Harley guinea pigs/sex aged six weeks were dosed with multiple intradermal injections (1% w/v eszopiclone) on study day 0 and topical application (50% w/v eszopiclone) on study day 7 to attempt to induce a sensitized state for evaluation of delayed contact hypersensitivity. Freund's complete adjuvant was injected intradermally on study day 0. Fourteen days after topical induction, challenge topical dosing (50% w/v eszopiclone) for detection of sensitization was performed. The incidence index for the test group was 0% (0/20) following challenge dosing. Based on this value, the test article, eszopiclone, was nonsensitizing in guinea pigs under the conditions of this study, and was essentially nonirritating.

Ecotoxicity/environmental risk assessment

The submitted environmental risk assessment includes a phase I analysis (Log Kow of 1.38) where a worst-case $PEC_{surface\ water}$ of 0.015 µg/L and a revised $PEC_{surface\ water}$ of 0.00854 µg/L, based on sales forecast, were calculated. However, any refinement data at this stage are only acceptable based on published data, e.g. epidemiological studies. The CHMP pointed out that according to the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, EMEA/CHMP/SWP/4447/00, 01 June 2006, a Phase II environmental fate and assessment analysis is needed for compounds exceeding the 0.01 µg/mL threshold. The applicant committed to completing the Phase II environmental risk assessment in accordance with the above mentioned guideline by conducting a series of studies (see section 2.7, Follow-up measures following Marketing Authorisation).

Discussion on the non-clinical aspects

The CHMP noted that the ADME parts of the non clinical file were limited and asked the applicant to describe the ADME profile of eszopiclone in the relevant species used and in humans. No new information has been provided with respect to pharmacokinetics of eszopiclone; however the applicant has compiled and presented all the relevant pharmacokinetic information in the dossier with respect to

eszopiclone and its ADME profile in the relevant species. It was concluded that the ADME program with racemic zopiclone was and adequate surrogate for eszopiclone assessment, and the CHMP agreed with this conclusion.

The CHMP also requested the applicant further information with regard to the ERA, and in response the applicant committed to completing the Phase II environmental risk assessment in accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use by conducting a series of studies after the marketing authorisation.

2.4. Clinical aspects

Introduction

Eszopiclone is a positive allosteric agonist at gamma-aminobutyric acid type A receptors (GABAA). Racemic zopiclone is a 1:1 mixture of the enantiomers (S)-zopiclone and (R)-zopiclone. Racemic zopiclone (also referred to as (RS)-zopiclone is a short-acting hypnotic agent already marketed in Europe. Sepracor, the applicant of the marketing authorisation applicantion for Lunivia, has developed eszopiclone as a treatment for the relief of insomnia in adult patients, at a proposed dosage of 3.0 mg OD (immediately before bedtime). A reduced dosage of 2.0 mg OD is proposed in elderly patients (≥ 65 years of age).

The eszopiclone pharmacology programme consists of *in vitro* studies of human biomaterials as well as *in vivo* human pharmacokinetic and pharmacodynamic studies. The clinical pharmacology development programme for eszopiclone conducted by Sepracor is comprised of 16 studies in human subjects. Clinical development of eszopiclone was undertaken to optimise the dose required for efficacy in reducing sleep latency and night-time awakenings and increasing total sleep time, while minimising next day effects.

The approved therapeutic indication is,

LUNIVIA is indicated for the treatment of insomnia, including difficulty falling asleep, nocturnal awakening or early awakening, in adults, usually for short term duration.

GCP

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

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

Pharmacokinetics

Analytical methods for the determination of eszopiclone, (R)-zopiclone, (R)- and (S)-desmethylzopiclone, and N-oxide-zopiclone have been validated for specificity, sensitivity, linearity, precision, accuracy, recovery, and stability.
A validated chiral method was applied to Sepracor Studies 190-001, 190-002, 190-005, and 190-010 measuring each enantiomer, i.e., (R)-zopiclone, eszopiclone, and (S)- and (R)-desmethylzopiclone. Since there was no evidence of *in vivo* chiral inversion, an achiral method was also developed and validated for measuring zopiclone and desmethylzopiclone, and applied to the rest of the studies. Other methods applied to analysing olanzapine, lorazepam, paroxetine, (R)- and (S)-warfarin and ketoconazole were also validated in each corresponding lab.
All analyses including sample handling, sample preparation, instrumental analysis and data reporting have been conducted according to the principles of GLP as applied to bioanalytical chemistry.

- Absorption

An evaluation of permeability classification for eszopiclone using the Caco-2 *in vitro* model of human epithelial monolayers was conducted. Eszopiclone did not have any effect on the integrity of the tight cellular junctions between the Caco-2 cell monolayers at the highest test concentration. Eszopiclone exhibited high absorptive and secretory permeability, but did not exhibit any active transport mechanisms in either the absorptive or secretory directions.

The pharmacokinetic profiles of eszopiclone, and its metabolites, (S)-DMZ and zopiclone N-oxide were determined following single administration of eszopiclone oral solution (1.0 to 7.5 mg) in a double-blind, placebo-controlled, single-dose, dose-escalation study (Study 190-001). Dose proportionality of eszopiclone was evaluated following a single-dose administration of eszopiclone in solution at 1.0, 2.0, 2.5, 3.0, 3.75, 5.0 and 7.5 mg.
Eszopiclone was rapidly absorbed following oral administration, with tmax occurring at 1 hour post-dose in healthy subjects. The plasma concentration profile of eszopiclone was characterized by a bi-exponential decline with an apparent terminal phase $t_{½}$ of approximately 6 hours. Eszopiclone exhibited dose-proportional pharmacokinetics over the range of 1.0 to 6.0 mg once daily (QD).

The bioavailability of the clinical trial tablet formulation relative to the oral solution formulation that was used in early clinical studies was established in the combined bioavailability & bioequivalence study 190-010 (101%). Additionally, following QD dosing for four days, eszopiclone 3.5 mg tablet and (RS)-zopiclone 7.5 mg tablet formulations exhibited bioequivalent eszopiclone pharmacokinetics. Thus, the absence of the (R)-isomer does not generally impact the human exposure to eszopiclone in terms of C_{max} and AUC. Removal of the R-isomer at steady-state, however, did result in a reduction in exposure to (S)-desmethylzopiclone [(S)-DMZ], the primary metabolite – with a relative bioavailability of 83% compared to (RS)-zopiclone. The confidence interval for the $AUC_{(0-\tau)}$ comparison was outside the standard range of 80%-125% (reported 90% CI 71.7%-95.0%). Although the Applicant stated in the dossier that this would not be expected to impact the metabolism of eszopiclone, it was unclear in the application what the clinical significance of this reduction in exposure to the primary metabolite is. The applicant was requested to clarify accordingly by the CHMP. The response was that the applicant conducted a pharmacokinetic study (190-010) designed to examine the impact of the removal of the R-enantiomers upon exposure to (S)-zopiclone and its primary metabolite, (S)-desmethylzopiclone [(S)-DMZ] when compared to racemic zopiclone. This study was conducted at steady-state in healthy subjects and used a validated chiral bioanalytical method (LOQ ~ 1 ng/mL). Healthy subjects were given either 3.5 mg of eszopiclone or 7.5 mg of racemic zopiclone over a 4 day period. Blood samples were obtained for plasma concentration assays of (S)- zopiclone, (S)-desmethylzopiclone, N-oxide-zopiclone, (R)-Zopiclone and (R)-desmethylzopiclone following single and multiple dose administration. Pharmacokinetic parameters were derived from these data. Following once daily dosing for four days, the S-zopiclone/racemate ratio for Cmax was 99.0 and for AUC was 99.5 for S-desmethylzopiclone the equivalent ratios were 96.9 and 82.5.
The information requested was provided and indicated that the exposure to S-desmethylzopiclone is less than with the racemic substance; thus the CHMP judged the question as resolved.

Study 190-002 investigated the effect of food on the pharmacokinetics of eszopiclone. The results of this study demonstrated that eszopiclone can be taken with or without food , but a delay in Tmax is observed following a high-fat meal.

- Distribution

Racemic zopiclone is widely distributed with an absolute volume of distribution of approximately 90 L. eszopiclone would be expected to exhibit similar distributive properties, based on the similarity of the pharmacokinetics (clearance) of eszopiclone.

The percent of binding of [^{14}C]-eszopiclone to protein in mouse, rat, dog and human plasma was determined in study 190-528 using ultrafiltration methods. *In vitro* protein binding of eszopiclone in human plasma was 52.2-58.9% over the concentration range of 5-500 ng/mL of [^{14}C]-eszopiclone. Non-specific binding of eszopiclone was less than 5% at concentrations of 1000 ng/mL or below. The relatively low plasma protein binding suggest that reduction in albumin concentration typically observed in severe renal and liver diseases would be expected to result in a negligible change in unbound eszopiclone concentration.

- Elimination

Excretion

Renal excretion is the principal route of elimination of eszopiclone and its metabolites. Up to 75% of an oral dose of racemic zopiclone is excreted in the urine primarily as metabolites. A similar excretion profile would be expected for eszopiclone, because of the observed equivalency in the metabolic clearance of eszopiclone in the presence or absence of (R)-zopiclone and the formation of the same metabolites. Less than 10% of the dose was excreted in the urine as unchanged drug.

The plasma concentration profile of eszopiclone was characterized by a bi-exponential decline with an apparent terminal phase $t_{½}$ of approximately 6 hours. Eszopiclone exhibited dose-proportional pharmacokinetics over the range of 1.0 to 6.0 mg QD. No accumulation of eszopiclone was observed following 7 days of once daily drug administration.

Metabolism
The ability of different CYP450 isoforms to metabolise eszopiclone was determined in study 190-516 by incubating eszopiclone and human liver microsomes in the presence or absence of selective CYP450 isoform inhibitors. The metabolism of eszopiclone was catalysed by CYP3A4 and CYP2E1. Metabolism by CYP2E1 is a rare metabolic pathway for most drugs used clinically. Ethanol is partially metabolised by CYP2E1. No pharmacodynamic interaction was observed upon co-administration of ethanol and eszopiclone in Study 190-015.

The potential of eszopiclone to inhibit human liver CYP450 isoforms 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 was determined in study 190-518 in cryopreserved human hepatocytes in the presence and absence of standard probe substrates, the outcome is shown in Table 6 below.

Table 6: The effect of eszopiclone on CYP450 isoenzymes

Substrate	Isoenzyme	Outcome
coumarin 7-hydroxylation	2A6	No effect
on Smephenytoin 4-hydroxylation	2C19	No effect
chlorzoxazone 6-hydroxylation	2E1	No effect
6α-testosterone	3A4	No effect
7-ethoxyresorufin Odealkylation	1A2	Dose dependent inhibition
tolbutamide 4-hydroxylation	2C9	Dose dependent inhibition
dextromethorphan Odemethylation	2D6	Dose dependent inhibition

Eszopiclone did not cause inhibition of the metabolism of specific substrates of the CYP450 isoforms 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 in human hepatocytes at concentrations up to 100 µM. This demonstrated that eszopiclone was not a CYP450 inhibitor.

The *in vitro* metabolism of [^{14}C]-eszopiclone was compared in study 190-536 in human hepatocytes in the absence or presence of (R)-zopiclone. Examination of radio-HPLC chromatograms showed that the radioactivity profiles of [^{14}C]-eszopiclone were very similar between the incubation mixtures with or

without (R)-zopiclone, indicating that (R)-zopiclone did not affect the rate of *in vitro* metabolism of [^{14}C]-eszopiclone.

Inter-conversion
No interconversion from eszopiclone to (R)-zopiclone was observed in the combined bioavailability & bioequivalence Study (Study 190-010) or in Study 190-001.

Pharmacokinetics of metabolites
Study 190-001 determined the pharmacokinetic profile of eszopiclone and its metabolites both alone and in the presence of (R)-zopiclone and the pharmacodynamic profiles of eszopiclone, (RS)-zopiclone and zolpidem. Pharmacokinetic analyses were performed on all subjects who received eszopiclone and (R)-zopiclone and who had evaluable concentration-time profiles for each measured PK analyte.

Eszopiclone and its primary metabolites appeared rapidly in the systemic circulation following oral administration of either eszopiclone or the racemic mixture. Exposure to eszopiclone and its metabolites increased with dose. The change in exposure was essentially dose proportional with the exception of zopiclone N-oxide, which did not increase consistently with all dose levels following oral administration of eszopiclone.

- Dose proportionality and time dependencies

Study 190-002 was a Phase I, two-centre, daytime administration, randomised, double-blind, placebo-controlled, parallel-group, multiple daily dose study in healthy male and female volunteers. Forty-eight subjects were randomised into 12 blocks of 4 patients. There were two study periods: during period 1, subjects were administered either, eszopiclone (1, 3 or 6 mg) as an oral solution or placebo in a 3:1 ratio following a high fat breakfast. PK samples were collected and subjects were discharged following their 48-hour PK blood sample and safety assessments. Subjects returned on Day 7 of Period 1 to complete Period 2 Day –1 assessments.

On days 1-7 of Period 2, subjects in the fasted state were dosed with either eszopiclone (1, 3 or 6 mg) or placebo in a 3:1 ratio as in Period 1. PK blood samples were collected on Day 1 of Period 2 for 24 hours and on Day 7 of Period 2 both prior to and up to 48 hours post-dose.

The pharmacokinetic parameters for eszopiclone and its metabolites (S)-DMZ and zopiclone N-oxide, were determined following a single dose in the fed or fasted state and following 7 daily doses in the fasted state. Pharmacokinetic analyses were performed for all subjects who received active treatment.

Eszopiclone demonstrated dose proportional pharmacokinetics (AUC_{0-24} and C_{max}) following both single and multiple dosing. Its metabolite, (S)-DMZ, approximated dose-proportional pharmacokinetics. However, no conclusions could be drawn regarding the dose proportionality of zopiclone N-oxide AUC_{0-24} due to variable results, while C_{max} showed a less than dose proportional increase (1.49- and 1.56-fold mean increases in C_{max} with two-fold increase in dose). The data is summarised in Table 7 below.

Table 7: Pharmacokinetic Parameters of Eszopiclone and its Metabolites Following Single and Multiple doses in the Fed/Fasted State

Analyte	Parameter	Single Dose Period 1, Day 1 (Fed)			Single Dose Period 2, Day 1 (Fasted)			Multiple Dose Period 2, Day 7 (Fasted)		
		1 mg	3 mg	6 mg	1 mg	3 mg	6 mg	1 mg	3 mg	6 mg
Eszopiclone	C_{max}	6.15	19.88	40.28	10.29	25.48	54.68	9.58	26.18	59.63
	AUC_{0-24}	54.76	166.21	338.26	62.96	187.76	379.04	66.05	191.07	409.31
(S)-DMZ	C_{max}	NC	1.94	4.32	NC	2.74	4.93	1.64	2.78	5.83
	AUC_{0-24}	NC	28.42	55.92	NC	34.46	63.73	NC	38.66	86.67
Zopiclone N-Oxide	C_{max}	6.01	12.80	28.31	10.31	10.20	25.04	15.92	12.12	23.52
	AUC_{0-24}	NC	125.69	20.18	NC	NC	230.90	NC	NC	206.10

Note: Results are the group means and are expressed as ng/mL for C_{max} and ng·h/mL for AUC_{0-24}.
NC = not calculated

Intra- and inter-individual variability
The pharmacokinetic parameters appeared consistent across studies; however the applicant was requested to provide coefficients of variation for intersubject and intra-subject variability.
The response was that the inter-subject variability of pharmacokinetic (PK) parameters for eszopiclone was assessed in two studies with repeat dose administration, based on Cmax and AUC(0-24). Study 190-010 was a three-way cross-over study in healthy adults. Subjects received 3 mg eszopiclone in liquid form, eszopiclone 3 mg as a tablet, or 7.5 mg racemic zopiclone as a tablet on Day 1 of each period. The withinsubject (Vw) and between-subject variance components (Vb) were identified on the log scale. The total variability, Vt = Vb + Vw, was computed. For Cmax, the overall CV was 30.0%. The subject and residual CVs were 18.5% and 22.4%, respectively. For AUC(0-24), the overall CV was 24.4%, and the subject and residual CVs were 19.7% and 13.6%, respectively. This analysis was repeated excluding the racemic zopiclone data, and very similar results were obtained. The CHMP agreed that the data provided by the applicant were satisfactory.

Pharmacokinetic in target population
PK studies have not been conducted in subjects with insomnia. This was considered as acceptable given the available data and the underlying condition.

- Special populations

Impaired renal function
Study 190-014 was an open evaluation of the pharmacokinetics, tolerability and safety of eszopiclone in patients with mild to severe renal impairment; it was conducted at three investigative sites in the US. The principal pharmacokinetic parameters and demographic details are shown in Table 8.

Table 8: Demographics and pharmacokinetic parameters for eszopiclone by degree of renal impairment. Data are mean (s.d.) unless otherwise stated

	Normal n = 16	Mild n = 8	Moderate n = 8	Severe n = 8
Age years mean (s.d.)	43.6 (11.2)	50.1 (9.4)	49.3 (9.8)	51.8 (11.1)
Gender (No. Male)	9	6	6	5
C_{max} ng/mL	36.7 (11.4)	43.1 (10.6)	32.4 (7.8)	43.4 (15.4)
$AUC_{0\rightarrow t}$ (ng.h/mL)	271.0 (87.3)	372.3 (118.2)	304.7 (77.8)	385.6 (139.4)
t_{max} (h) median	1.25	1.0	1.0	1.0
range	0.50 – 4.08	0.50 – 1.5	0.50 – 4.00	0.50 – 2.00
$t_{1/2}$ (h)	6.12 (1.94)	7.30 (1.09)	7.60 (1.66)	8.18 (2.59)
Cl_r (L/h)	0.811 (0.5)	0.564 (0.6)	0.614 (0.4)	0.496 (0.4)

Exposure to (S)-DMZ was also affected by renal impairment. Cmax increased by 22%, 17% and 43% in subjects with mild, moderate and severe renal impairment, and AUC(0-last) increased by 41%, 59% and 139% in subjects with mild, moderate and severe renal impairment, respectively, compared to normal subjects. The (S)-DMZ terminal phase t½ was increased by 2-7 hr in subjects with renal disease. Renal clearance was reduced by 49-83% in subjects with renal impairment. However, AUC(0-last) increased by 2.4-fold compared to a 5.7-fold decline in renal clearance in subjects with severe renal disease, which suggested that additional clearance pathways may be involved in the disposition of this metabolite.
Systemic exposure increased by 47% in subjects with severe renal impairment. The applicant's view was that no dosage adjustment appeared necessary in subjects with renal impairment, and that these subjects should be closely monitored. By comparison the applicant considered a decrease of eszopiclone dose from 3.0 to 2.0 mg is warranted in the elderly as systemic exposure increased by 41% in the elderly (≥ 65 years of age) compared to non-elderly adults. The applicant was requested by the CHMP to comment on the requirement for a similar dose reduction in patients with severe renal impairment. The applicant considered that there is no clinically relevant relationship between the degree of renal impairment and increase in eszopiclone exposure. The pattern of adverse events in renal impairment did not show a trend in relation to the severity of renal impairment. However it will be recommended in the SPC that eszopiclone is contraindicated for patients with severe renal impairment. On the basis of this argumentation, the CHMP considered the issue as resolved.

Study 190-013 was an evaluation of the pharmacokinetics, tolerability and safety of eszopiclone in patients with mild to moderate and moderate to severe hepatic impairment; it was conducted at five investigative sites in the US. The principal pharmacokinetic parameters are shown in Table 9.

Table 9: Demographics and pharmacokinetic parameters for eszopiclone by Child-Pugh class – data are mean (s.d.) unless otherwise stated.

	Normal n = 16	Mild/Mod n = 8	Mod/Severe n = 8	Severe n = 8
Age years mean (s.d.)	42.1 (12.0)	47.6 (10.5)	57.5 (6.5)	46.6 (3.5)
Child-Pugh class (min – max)	NA	5 – 5	7 – 9	9 – 11
C_{max} ng/mL	25.1 (8.0)	23.0 (7.0)	20.6 (6.7)	20.5 (9.3)
$AUC_{0\rightarrow t}$ (ng.h/mL)	172.2 (72.2)	165.0 (50.1)	195.2 (75.6)	325.6 (204.8)
t_{max} (h) median	1.01	1.0	1.0	1.5
range	0.5 – 2.0	0.5 – 1.97	0.5 – 2.0	0.5 – 6.0
$t_{1/2}$ (h)	6.7 (2.1)	6.8 (1.8)	11.05 (5.6)	15.3 (6.1)
Cl_r (L/h)	0.73 (0.39)	0.90 (0.40)	0.68 (0.32)	0.46 (0.32)

The pharmacokinetics of a single 2.0 mg eszopiclone dose were affected by hepatic impairment. Eszopiclone C_{max} decreased by 13%, 29% and 25% in mild, moderate and severe hepatically impaired subjects, respectively. $AUC_{(0\text{-last})}$ was unchanged in subjects with mild and moderate hepatic impairment, but was increased by 74% in subjects with severe hepatic impairment compared to normal subjects. The elimination half-life increased from 6.5 hr in subjects with normal hepatic function to 9.6 hr and 14.3 hr

in subjects with moderate and severe hepatic impairment, respectively. Since more than 90% of eszopiclone is metabolized, this route of elimination would be expected to have a major impact on exposure. Exposure to (S)-DMZ was also affected by hepatic impairment. The formation of (S)-DMZ was substantially reduced in subjects with moderate and severe hepatic impairment.

Hepatic disease had no clinically relevant effect on exposure to eszopiclone in subjects with mild and moderate hepatic disease. Thus, no dosing adjustment is warranted in subjects with mild or moderate hepatic disease. The mean increase in exposure to eszopiclone reached 74% in subjects with severe hepatic impairment. Eszopiclone treatment was generally well-tolerated in subjects with severe hepatic impairment. Eszopiclone treatment in subjects with severe hepatic impairment was not associated with clinically significant changes in the number or severity of adverse events, changes in laboratory parameters, vital signs, or ECG measures. However, eszopiclone is contraindicated in subjects with severe hepatic impairment.

Elderly

Study 190-005 was a Phase I two-centre, daytime administration, randomised, double-blind, placebo-controlled, rising, multiple-dose study to determine the pharmacokinetic profile of eszopiclone in healthy elderly subjects (aged 65 to 79 years). In addition, the effect on daytime sleepiness and psychomotor performance of a once daily dose of eszopiclone administered for 7 days was evaluated.
Table 11.2-1 shows the summary of subjects' demographic and baseline characteristics.

Table 11.2-1: Demographic and Baseline Characteristics

Characteristic		Treatment Group				
		Placebo (N=12)	(S)-Zopiclone 1 mg (N=6)	(S)-Zopiclone 2 mg (N=6)	(S)-Zopiclone 3 mg (N=6)	(S)-Zopiclone 5 mg (N=6)
Gender N (%)	Female	6 (50%)	2 (33.3%)	0 (0%)	5 (83.3%)	4(66.7%)
	Male	6(50%)	4(66.7%)	6(100%)	1 (16.7%)	2(33.3%)
Race N (%)	Caucasian	12(100%)	6(100%)	6(100%)	6(100%)	6(100%)
Age (yrs)	Mean (± SD)	70.2 (3.6)	69.2 (3.5)	68.5 (3.4)	73.8 (4.7)	72.2 (4.4)
	Min, Max	65, 77	65, 75	65, 73	67,79	68,78
Height (cm)	Mean (± SD)	168.7 (10.6)	173.6 (8.9)	176.3 (2.7)	163.4 (6.5)	167.6 (10.1)
	Min, Max	147, 180	163, 183	173, 180	154, 173	158, 180
Weight (kg)	Mean (± SD)	75.5 (14.2)	79.4 (12.1)	86.6 (7.8)	69.3 (9.4)	67.6 (12.5)
	Min, Max	47, 94	66, 96	74, 95	57, 84	54, 83
BMI (kg/m*2)	Mean (± SD)	26.2 (2.5)	26.2 (2.3)	27.9 (2.6)	26.0 (3.6)	23.8 (1.8)
	Min, Max	22, 31	23, 29	24, 30	22, 30	22, 26

Pharmacodynamic evaluation indicated that the effect of the daytime administration of eszopiclone on Digit Symbol Substitute Test (DSST) scores was negligible in the 1.0, 2.0 and 3.0 mg single dose groups. No drug effect was evident following multiple doses of eszopiclone 1.0 and 2.0 mg, however, a small but statistically significant effect was observed following daily administration of eszopiclone 3.0 mg on Day 7. Subjects administered 5.0 mg eszopiclone exhibited a more pronounced decrease in DSST scores. The maximum effect was reached approximately 2 hours post-dose, with a gradual return to baseline by 8 hours after dosing. The time to reach the maximum DSST score effect was slightly delayed in comparison with the time to reach maximum plasma concentration.

A negative correlation was found between the pharmacodynamic parameters (E_{max} and AUC_{DSST}) and their corresponding eszopiclone pharmacokinetic parameters (C_{max} and AUC_{0-8}). However, despite a trend toward increasing effect with dose, the DSST results did not clearly demonstrate that eszopiclone exhibited a clinically meaningful impact on DSST scores at doses lower than 5.0 mg in elderly subjects.
The effect of 1.0 mg eszopiclone on Stanford Sleepiness Scale (SSS) scores was regarded as similar to placebo after single or multiple doses. Sleepiness generally increased with increasing doses of eszopiclone from 2 to 3 mg. However, there was a general decrease in sleepiness with 5 mg eszopiclone

comparative to the 3 mg dose and at several time-points comparative to placebo. The effect of eszopiclone on SSS scores were maximal within1 hour post-dose and this effect was maintained for up to 4 hours. SSS scores generally returned to baseline within 8 to 10 hours post-dose at all doses.

In summary, daytime administration of eszopiclone was safe and well tolerated in doses up to 5.0 mg in elderly healthy subjects. The exposure in healthy elderly subjects was approximately 50% greater than the exposure observed in healthy adults (study 190-002). For this reason, the recommended therapeutic dose in elderly should be reduced. This has been taken into account in the SPC.

The CHMP was concerned by the finding of a statistically significant effect, albeit small, on DSST scores on Day 7 of daily administration of eszopiclone 3.0 mg, and therefore requested the applicant to comment further. The applicant did not consider detriments in psychomotor function to be of clinical significance within the initial hours following dosing, as the intended use of eszopiclone is for nighttime administration to promote sleep. However, effects at later time points post dose may represent residual daytime effects following night time administration. Appropriate changes to the SPC were proposed to duly reflect this information and to provide adequate warning. The CHMP considered the changes to the SPC as an appropriate response to this issue.

Children/Gender/ethnicity/weight
Specific studies have not been conducted in children. The applicant has also analysed the effect of gender, race, and weight on the pharmacokinetics of eszopiclone and found no meaningful differences.

- Pharmacokinetic interaction studies

In vitro
The potential of eszopiclone to inhibit human liver CYP450 isoforms 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4 was determined in study 190-518 in cryopreserved human hepatocytes in the presence and absence of standard probe substrates. Results demonstrated that eszopiclone was not a CYP450 inhibitor.

In vivo
Table 10: Summary of *in vivo* drug-drug interaction studies

Study ID	Interaction	Format	Outcome
190-018	Olanzapine 10 mg	Four arm, Pbo; E; O; E + O; four day dosing n = 40	No PK interaction Significant potentiation of psychomotor impairment 3 hrs post-dose
190-019	Lorazepam 2 mg	Four arm, Pbo, E; L; E + L; three day dosing n = 36	Reduction of 23% in Cmax E with coadministration – DSST not quite additive
190-020	Paroxetine 20 mg	Four arm, Pbo, E; P; E + P; three day dosing n = 40	No PK or PD interaction
190-021	Warfarin 25 mg single dose	Four arm, Pbo, E; W; E + W; five day eszopiclone dosing n = 12	No PK or PD interaction
190-022	Digoxin 1 gm loading then 0.25 mg for six days	Four arm, Pbo, E; D; E + D; seven day dosing n = 12	No PK interaction
190-023	Ketoconazole 400 mg	Three way crossover, E; K; E + K five day dosing n = 18	125% increase in eszopiclone AUC and 43% Cmax and 13% reduction in ketoconazole AUC and 18% Cmax

Study 190-015 was a single centre four way crossover evaluation of the potential pharmacodynamic interaction between eszopiclone and ethanol. The study demonstrated that there was psychomotor performance impairment following co-administration of eszopiclone and alcohol that was approximately additive. These effects were most apparent during the approximate period of peak drug effect (1 to 4 hours post-dosing) and diminished with time. Additive effects were expected based on the pharmacology of the individual active treatments, and therefore the results meriting particular attention were potential synergistic effects that were greater than the combined individual effects. With respect to the potential for synergistic effects, three results fall into this category (spatial working memory, word recognition, and quality of secondary working memory) and these occurred during the approximate peak drug effect.

A reduction in eszopiclone dose to 2.0 mg is endorsed upon co-administration with potent CYP 3A4 inhibitors (i.e., inhibition constant ≤ 1 μM). Rifampicin, a potent inducer of CYP3A4, was shown to substantially decrease exposure to racemic zopiclone and to some measures of its pharmacological activity. A similar effect may also occur with eszopiclone. A dose adjustment for warfarin or digoxin is not required when co-administered with eszopiclone. Co-administration of lorazepam or paroxetine and eszopiclone did not have a clinically meaningful effect. Significant impairment of psychomotor performance was, however, observed when eszopiclone was co-administered with olanzapine. This pharmacodynamic effect is detailed in the proposed SPC. As might be anticipated from its mechanism of action, downward dose adjustment of eszopiclone may be necessary when eszopiclone is administered with agents having known CNS-depressant effects. In line with the findings of the interaction study of eszopiclone and ethanol, Section 4.5 of the proposed SPC advises against concomitant use with alcohol as the sedative effect of eszopiclone may be enhanced.

Pharmacodynamics

- Mechanism of action

The applicant presented no new studies of the mechanism of action of eszopiclone. However, the mechanism of action of zopiclone is well-established and it is accepted that the desired pharmacologic activity of the racemic drug resides primarily with eszopiclone.

A series of *in vitro* and *in vivo* binding studies and *in vitro* functional assays demonstrate that the mechanism of action of zopiclone is to allosterically modulate the effects produced by central $GABA_A$ receptor activation via binding to a central binding site or one that is closely linked to benzodiazepine receptors. The net result of zopiclone's interactions with the $GABA_A$ receptor macromolecular complex is the augmentation of GABA-induced chloride conductance, resulting in inhibition of neurotransmission. Evidence indicates that potentiation of inhibitory synaptic transmission mediated by GABA acting at $GABA_A$ receptors is one of the primary mechanisms of action of drugs with sedative/hypnotic properties. Several studies have shown that zopiclone was not bound to the benzodiazepine receptor, *per se*, but rather it interacted with yet another distinct site on the $GABA_A$ receptor complex. This binding and receptor activation of zopiclone is attributed to the binding of eszopiclone, as (R)-zopiclone demonstrates minimal binding to the central benzodiazepine site.
The binding affinity of the two major metabolites of both zopiclone and eszopiclone, namely desmethylzopiclone (DMZ) and zopiclone N-oxide, have also been investigated. The affinities of (S)-DMZ and (S)-zopiclone N-oxide for the central benzodiazepine site are >20-fold and >250-fold lower than that of eszopiclone, respectively.

- Primary and Secondary pharmacology

Two studies were conducted evaluating the next-day performance effects of single doses of eszopiclone in healthy subjects (Study 190-024) and in subjects with primary insomnia (Study 190-025).

In study 190-024 on healthy volunteers, next-day performance effects of single doses of eszopiclone and flurazepam *versus* placebo were evaluated.

Eszopiclone 2 mg and 3 mg and flurazepam 30 mg did not demonstrate significant effects on the primary measure, Power of Attention, compared with placebo at 9.5 or 12.5 hours post-dose.
Eszopiclone 2 mg and 3 mg demonstrated a slight decline in Speed of Memory (a secondary composite measure) that was significant at 9.5 hours, but not at 12.5 hours, after dosing, while flurazepam significantly reduced Speed of Memory at both post-dose timepoints. The effect with eszopiclone was also smaller in magnitude than the effect seen with flurazepam 30 mg. Neither eszopiclone dose had a significant effect on any of the other three secondary composite measures (Quality of Working Memory, Quality of Secondary Memory, and Continuity of Attention).
Contrary to flurazepam, eszopiclone did not demonstrate psychomotor impairment (measured by DSST scores) compared with placebo.

In study 190-025 with insomniac patients, eszopiclone 2 mg and 3 mg and flurazepam 30 mg did not demonstrate significant effects on the primary measure, Power of Attention, compared with placebo at 9.5 or 12.5 hours post-dose. Eszopiclone 3 mg significantly reduced Quality of Secondary Memory (a secondary composite measure) at 12.5 hours, but not at 9.5 hours, post-dose. Neither eszopiclone dose had a significant effect on any of the other three secondary composite measures (Speed of Memory, Quality of Working Memory, and Continuity of Attention). Flurazepam 30 mg did not demonstrate significant effects on the secondary composite measure, Quality of Secondary Memory. Eszopiclone 2 mg and 3 mg did not demonstrate psychomotor impairment as measured by significant changes in DSST scores compared with placebo.

Clinical efficacy

Eleven studies have been conducted to investigate the efficacy of Lunivia in the treatment of insomnia, five of them short-term in subjects with transient (1) or primary insomnia (4), two long-term in subjects with primary insomnia and the remaining four in subjects with comorbid insomnia. A total of 2463 subjects were exposed to night-time doses of 3 mg Lunivia, and a total of 1802 subjects received placebo in these studies. These are summarised in Table 1.

Table 1: Efficacy Studies of Eszopiclone

Study	Diagnosis	N	Treatment duration	Eszopiclone dose (mg)	Comparator	Type of Assessment	Endpoints
Transient Insomnia							
190-026	Transient insomnia (first night model)	436	Single Dose	1.0, 2.0, 3.0, 3.5	Placebo	PSG and Clinical	1°: objective latency to persistent sleep (LPS) Key 2nd: objective sleep efficiency
Primary Insomnia							
190-045	Adults with primary insomnia	65	2 days	1.0, 2.0, 2.5, 3.0	Placebo, Zolpidem 10 mg	PSG and Clinical	1°: objective LPS Key 2nd: objective sleep efficiency, objective WASO
190-046	Adults with primary insomnia	308	44 days	2.0, 3.0	Placebo	PSG and Clinical	1°: objective LPS Key 2nd: objective sleep efficiency, objective WASO
190-047	Elderly patients with primary insomnia.	264	2 weeks	1.5, 2.0[a]	Placebo	PSG and Clinical	Co-primary: objective LPS and objective sleep efficiency Key 2nd: objective WASO
190-048	Elderly patients with primary insomnia.	231	2 weeks	1.0, 2.0	Placebo	Clinical	1°: sleep latency Key 2nd: total sleep time
190-049	Adults with primary insomnia	788	52 weeks (26 wks DB + 26 wks OL)	3.0	Placebo	Clinical	1°: sleep latency Key 2nd: total sleep time
190-050	Adults with primary insomnia	828	26 weeks	3.0	Placebo	Clinical	1°: sleep latency Key 2nd: total sleep time
Comorbid Insomnia							
190-052	Adults with insomnia and MDD	543	8 weeks	3.0	Placebo	Clinical	1°: mean WASO Key 2nd: time to onset of 30% antidepressant response and % subjects which achieved 30% antidepressant response.
190-902	Adults with insomnia and GAD	593	8 weeks	3.0	Placebo	Clinical	1°: change from baseline mean sleep latency over DB treatment. Key 2nd: 1) total sleep time; 2) total HAM-A score; 3) CGI-Severity; 4) 50% anxiolytic response (HAM-A); 5) time to onset of anxiolytic response (CGI-I)
190-054	Patients with insomnia and menopausal symptoms	407	4 weeks	3.0	Placebo	Clinical	1°: mean daily sleep latency during week 1. Key 2nd: Mean WASO during week 1.
190-055	Patients with insomnia and RA	153	4 weeks	3.0	Placebo	Clinical	1°: subjective mean WASO during week 1

DB = double-blind, OL = open-label, GAD = Generalized Anxiety Disorder, MDD = Major Depressive Disorder, RA = Rheumatoid Arthritis; PSG = polysomnography; Clinical = patient reported. [a]1.5 mg dose removed per protocol amendment 2, n=28 received 1.5 mg dose

- Dose response study(ies)

Study 190-045 was a randomised prospective six-way crossover comparison of eszopiclone 1 mg, 2 mg 2.5 mg 3.0 mg, placebo and zolpidem 10 mg. The study took place at seven US centres.
Patients between 21 and 64 years old with DSM-IV criteria for insomnia who reported sleeping no more than 6.5 hours per night and taking at least thirty minutes to fall asleep were eligible; patients were required to show evidence of insomnia on screening polysomnography. Each dosing period consisted of a single bedtime dose of study drug for two consecutive nights followed by a washout period of three to seven days.
Efficacy variables of interest were; latency to persistent sleep (LPS), sleep efficiency (total sleep time as a percentage of total recording time), wake time after sleep onset (WASO) number of awakenings.

The efficacy data from the study are presented in Table 2.7.3.2-5. In terms of the primary efficacy measure, all doses of Lunivia and zolpidem 10 mg significantly decreased objective LPS relative to placebo ($p \leq 0.0001$ for each dose).

Table 2.7.3.2-5: Efficacy Results from Study 190-045

Sleep Category	Efficacy Measure	PBO (n=63)	Eszopiclone				Zolpidem 10.0 mg (n=64)
			1.0 mg (n=63)	2.0 mg (n=63)	2.5 mg (n=65)	3.0 mg (n=64)	
Induction	Obj LPS – Primary Measure (min)	29.0	16.8**	15.5**	13.8**	13.1**	13.1**
	Sub Sleep Latency (min)	47.5	27.5**	25.0**	25.0**	25.0**	25.0**
	Obj Wake Time Before Persistent Sleep (min)	27.0	13.8**	12.0**	10.3**	10.8**	9.3**
Duration	Obj SE – Key Secondary Measure (%)	86.0	88.6**	89.6**	90.4**	92.0**	89.1**
	Sub Total Sleep Time (min)	375.0	382.5	412.5**	420.0**	420.0**	411.3**
Maintenance	Obj WASO – Key Secondary Measure (min)	39.0	35.5	30.5	29.5*	25.3*	30.5
	Obj Number of Awakenings	6.5	7.5	6.5	7.0	5.3**	6.8
	Sub WASO (min)	42.5	35.0	27.5**	25.0**	28.8**	30.0*
	Sub Number of Awakenings	3.5	3.0	3.0*	3.0*	2.5**	2.5**
	Wake Time After Sleep (min)	0.3	0.5	0.0	0.3	0.5	0.3
	Obj Wake Time During Sleep (min)	30.8	28.0	26.0	25.3*	23.3**	27.4
Quality	Quality of Sleep[a]	43.5	47.0*	58.0**	55.0**	62.0**	56.0**
	Depth of Sleep[b]	40.3	46.0*	56.5**	53.0**	59.5**	56.5**

*$0.01<p\leq0.05$; **$p\leq0.01$. The pairwise comparison with placebo was performed using the appropriate contrast from an ANOVA model on rank-transformed data with treatment, sequence, and visit as fixed effects and subject nested within sequence as a random effect. All values refer to group medians.

a. On a scale of 0 = poor and 100 = excellent. **b.** On a scale of 0 = very light and 100 = very deep.

Note: PBO = placebo; SE = sleep efficiency; Obj = objective; Sub = subjective.

Study 190-045 in primary insomnia is the only trial in the whole programme that includes a comparative arm. The chosen comparator was zolpidem 10 mg. This choice is acceptable however the CHMP considered regrettable that comparative data in the Lunivia clinical development programme are limited to this small-size, short-term, crossover trial. Even if there is no formal comparison between zolpidem and Lunivia yet the data suggest that zolpidem 10 mg is similar to Lunivia 3 mg in induction of sleep but probably superior to Lunivia 2 mg. In maintenance of sleep Lunivia 3 mg seems to be more effective.

- Main studies

Transient insomnia

Study 190-026 was a randomised prospective double blind parallel group comparison of Lunivia 1 mg, 2 mg 3 mg, 3.5 mg and placebo: treatments were administered as 25 mL oral solutions. The study took place at five US centres.

Healthy male and female volunteers who where willing to be randomised and to spend a night (12 – 14) hours were eligible, they needed to have normal sleep patterns and no history of insomnia or other significant illness. The disturbance of undergoing polysomnography in an unfamiliar setting the 'first night effect' acts as a model of transient insomnia. Treatments were administered 30 minutes before the subjects' mean 'lights out' time.

Efficacy variables of interest were; latency to persistent sleep (LPS), sleep efficiency (total sleep time as a percentage of total recording time), wake time after sleep onset (WASO) number of awakenings. Demographics and results are presented in Table below.

Table 11 Demographics and main outcomes of Study 190-026

	Placebo	1 mg	2 mg	3 mg	3.5 mg
Demographic outcomes					
Number recruited	98	47	97	98	96
Age mean s.d (years).	32.6 (6.8)	33.6 (7.0)	35.4 (7.7)	33.2 (6.9)	33.8 (8.1)
Proportion (%) male	40.8	51.1	38.1	50.0	38.5
BMI (Kg/m^2)	24.5 (3.0)	24.6 (3.1)	24.3 (3.4)	24.7 (3.5)	24.7 (3.5)
Efficacy outcomes					
LPS (minutes)	17.90 (16.39)	15.27 (22.11)	10.08 (11.81)	9.10 (10.85)	6.62 (6.79)
Sleep efficiency	87.88 (8.24)	91.78 (4.90)	91.72 (5.73)	93.02 (4.48)	94.01 (4.00)
WASO (minutes)	42.93 (32.27)	26.74 (17.45)	31.16 (21.16)	26.31 (19.08)	23.03 (17.67)
Number of awakenings	6.01 (2.98)	5.62 (4.00)	5.42 (3.30)	4.84 (3.11)	4.71 (2.91)
Sleep architecture outcomes					
% of time in REM sleep	18.7 (5.7)	19.9 (6.0)	18.3 (4.8)	17.11 (5.5)	17.1 (4.8
Latency to REM sleep	97.3 (45.6)	100.3 (44.0)	107.5 (42.4)	121.7 (55.5)	123.97 (52.5)

Primary insomnia

Study 190-046 examined the safety and efficacy of eszopiclone 2.0 mg and 3.0 mg taken for 44 days by adult patients with primary insomnia: following the end of active treatment there was a two night placebo treatment. The study was a prospective parallel group placebo controlled trial and was conducted at 51 US centres. Patients between 21 and 64 years old with DSM-IV criteria for insomnia who reported sleeping no more than 6.5 hours per night and taking at least thirty minutes to fall asleep were eligible; patients were required to show evidence of insomnia on screening polysomnography. Efficacy variables of interest were; latency to persistent sleep (LPS), sleep efficiency (total sleep time as a percentage of total recording time), wake time after sleep onset (WASO) number of awakenings. The trial evaluated whether tolerance and rebound insomnia occurred. Patients were admitted to a sleep laboratory for baseline, night 15 and night 29 polysomnography. Evaluation at night 45 and 46 was by response to a questionnaire.

The sample size of 270 patients was based on the aim to achieve a 90% power to detect a treatment difference of 15 minutes for LPS and 6.25% in sleep efficiency with standard deviations of 35 minutes and 11.5% respectively; α was 0.05. Significance testing was by ANOVA using the MIXED procedure for efficacy variables. The Wilcoxon signed-rank test was used to evaluate the presence of rebound insomnia at nights 45 and 46. Demographic data and results are presented in Table 12.

Table 12 Demographics and main outcomes of Study 190-046

	Placebo	2 mg	3 mg	p value
Demographic outcomes				
Number randomised	99	104	105	
Age mean s.d (years).	40.8 (11.8)	40.6 (11.5)	38.0 (11.7)	0.11
Proportion (%) male	43.4	36.5	26.7	0.03
BMI (Kg/m^2)	26.1 (4.5)	28.0 (6.7)	27.1 (6.1)	0.05
Efficacy outcomes				
LPS (minutes) night 1	35.2 (28.0)	21.4 (27.6)	17.5 (20.2)	<0.001
LPS (minutes) night 29	30.2 (28.2)	24.0 (35.8)	18.1 (26.1)	<0.001
LPS (minutes) night 45/46*	59.9 (43.0)	36.0 (34.2)	34.7 (36.1)	0.004
Sleep efficiency night 1	83.8 (9.2)	89.3 (7.0)	90.6 (6.2)	<0.001
Sleep efficiency night 29	82.9 (11.7)	86.2 (9.6)	88.4 (8.5)	<0.001
WASO (minutes) night 1	47.1 (37.3)	32.4 (24.0)	31.7 (24.7)	0.002
WASO (minutes) night 29	49.6 (42.1)	52.9 (41.3)	43.8 (39.1)	0.025
WASO (minutes) night 45/46*	44.0 (34.9)	40.6 (49.8)	42.5 (52.8)	
Number of awakenings night 1*	3.3 (2.4)	2.6 (2.0)	2.5 (2.0)	0.01
Number of awakenings night 29*	3.4 (2.3)	3.2 (2.1)	3.4 (2.3)	> 0.6
Number of awakenings night 45/46*	2.2 (1.2)	2.3 (1.8)	2.4 (2.6)	~ 0.2

*measured subjectively n = 30 to 40 across treatment arms for day 45/46 data

Study 190-049 was an evaluation of the safety and efficacy of eszopiclone 3.0 mg taken for twelve months by adult patients with primary insomnia. Eligible patients were between 21 and 64 years old and met DSM-IV criteria for primary insomnia and had a sleep onset time of at least thirty minutes and a total sleep time of no more than six and a half hours. The study was a prospective parallel group placebo controlled trial. In a six-month blinded phase patients received eszopiclone 3 mg or placebo, in a subsequent six month open phase patient received eszopiclone 3 mg. The study was conducted at seventy centres in the US. The primary efficacy criterion was change in subjective sleep latency for the month 4-6 average as measured by sleep questionnaires reported by an Interactive Voice Response System (IVRS). A secondary criterion was change from baseline in total sleep time and wake time after sleep onset.

The sample size was based on the wish to obtain six months exposure data in at least 300 patients and twelve months exposure data in at least 100 patients. In order to achieve this, 600 patients were to be enrolled into the eszopiclone arm and 200 to the placebo arm. A formal statistical power calculation was not made. Statistical analysis was by ANOVA on ranked data with treatment and site as fixed effects. Demographics and main results are displayed in the table below.

Table 13 Demographics and main outcomes of Study 190-049

	Placebo	Eszopiclone 3 mg	p value
Number studied	195	593	
Number studied in open extension	---	471	
Age mean (s.d.) years	43.2 (11.1)	44.3 (11.4)	
Proportion male (%)	35.9	37.1	
BMI (Kg/m^2)	27.8 (6.5)	29.5 (7.2)	
Sleep latency month 1 (minutes)	71.3 (59.8)	44.3 (36.5)	< 0.001
Sleep latency average months 4 – 6 (minutes)	64.7 (56.4)	46.7 (45.6)	< 0.001
Total sleep time month 1 (minutes)	333.1 (69.8)	373.9 (67.5)	< 0.001
Total sleep time average months 4 – 6 (minutes)	341.1 (72.4)	377.3 (69.2)	< 0.001
WASO month 1 (minutes)	62.8 (77.2)	47.4 (77.7)	< 0.001
WASO average months 4 – 6 (minutes)	52.5 (63.0)	43.0 (58.6)	< 0.001

Study 190-050 was an evaluation of the safety and efficacy of eszopiclone 3.0 mg taken for six months by adult patients with insomnia. Eligible patients were between 21 and 64 years old and met DSM-IV criteria for primary insomnia and had a sleep onset time of at least thirty minutes and a total sleep time of no more than six and a half hours. The study was a prospective parallel group placebo controlled trial with randomisation 2:1 to active and placebo treatments and was conducted at multiple centres in the US. The primary efficacy criterion was change in sleep latency from baseline to month 4-6 as measured by sleep questionnaires reported by an IVRS; change from baseline in total sleep time and WASO were secondary criteria.

The sample size of 450 patients completing the six months was based on the aim to achieve a 90% power to detect a treatment difference of 0.13 ($\log_e$) for sleep latency with a standard deviation of 0.40; α was 0.05. Significance testing was by ANOVA using the MIXED procedure for efficacy variables. Demographics and results are showed in the table below.

Table 14 Demographics and main outcomes of Study 190-050

	Placebo	Eszopiclone 3 mg	p value
Number studied	280	548	
Age mean (s.d.) years	44.7 (11.8)	46.0 (11.8)	
Proportion male (%)	39.6	38.7	
BMI (Kg/m^2) (male)	28.7 (4.9)	28.5 (5.9)	
BMI (Kg/m^2) (female)	28.2 (7.5)	28.5 (6.9)	
Sleep latency baseline (minutes)	83.2 (55.04)	76.9 (47.95)	
Sleep latency average months 4 – 6 minutes	59.0 (47.3)	38.5 (32.5)	$p < 0.001$
Total sleep time baseline (minutes)	300.22 (62.28)	309.42 (61.84)	
Total sleep time average months 4 – 6 (minutes)	346.1 (75.4)	390.5 (66.2)	$p < 0.001$
WASO baseline (minutes)	51.2 (38.78)	47.69 (38.46)	
WASO average months 4 – 6 (minutes)	41.0 (41.8)	23.9 (32.1)	$p < 0.001$

Comorbid insomnia

Study 190-052 was a comparison of the safety and efficacy of Lunivia 3.0 mg taken for eight weeks by adult patients with *insomnia secondary to major depressive disorder*. Eligible patients were between 21 and 64 years old and met DSM-IV criteria for major depressive disorder with the current episode having duration of at least two weeks but no more than six months. Insomnia eligibility criteria were a sleep onset time of at least thirty minutes, a wake time after sleep onset of at least forty-five minutes, no more than six and a half hours of total sleep time. The study was a prospective parallel group placebo controlled trial. All patients received fluoxetine ad an initial dose of 20 mg titrating to 40 mg at week four if deemed clinically necessary, they were randomised to placebo or eszopiclone 3 mg as 'add on' treatment. The primary efficacy criterion was subjective wake time after

sleep onset (WASO) during the first study week, important secondary variables were time to onset of 30% antidepressant response as indicated by patient reported Hamilton-D- 6 (HAM-D-6) questionnaire on two successive visits, and proportion of patients achieving a 30% reduction in Hamilton-D- 6 (Bech) score. Secondary insomnia efficacy criteria were WASO at later time points and sleep latency. Following the eight week double blind period there was a two week single blind washout period.

The sample size of 360 patients was based on the aim to achieve a 90% power to detect a treatment difference of 0.3 ($\log_e$) for WASO with a standard deviation of 0.87; α was 0.05. Significance testing was by ANOVA using the MIXED procedure for efficacy variables.
Demographics and main results are displayed in the table below.

Table 15 Demographics and main outcomes of Study 190-052

	Placebo + Fluoxetine	Eszopiclone 3 mg + Fluoxetine	p value
Number studied	274	269	
Age mean (s.d.) years	40.4 (11.3)	41.6 (10.7)	0.15
Proportion male (%)	33.6	33.1	0.89
BMI (Kg/m^2) (male)	29.5 (5.9)	30.0 (6.4)	0.51
BMI (Kg/m^2) (female)	30.9 (8.0)	31.4 (9.1)	0.51
WASO baseline	90.8 (71.3)	92.0 (79.4	
WASO week 1 (minutes)	63.6 (61.1)	51.2 (55.6)	< 0.001
WASO week 8 (minutes)	46.3 (61.3)	22.7 (49.4)	< 0.001
Sleep latency baseline (minutes)	198.7 (166.9)	196.2 (171.2)	
Sleep latency week 1 (minutes)	148.9 (151.3)	102.3 (127.3)	< 0.001
Sleep latency week 8 (minutes)	112.1 (153.9)	79.2 (126.0)	< 0.001
Total sleep time baseline (minutes)	218.1 (117.9)	228.8 (127.1)	
Total sleep time week 1 (minutes)	278.2 (121.3)	337.6 (116.9)	< 0.001
Total sleep time week 8 (minutes)	331.8 (141.5)	376.1 (129.7)	< 0.001
30% reduction in HAM-D-6	144 (56.3%)	143 (56.1%)	0.76
50% reduction in HAM-D-6	95 (37.1%)	107 (42.0%)	0.009

Study 190-902 was a comparison of the safety and efficacy of eszopiclone 3.0 mg taken for eight weeks by adult patients with *insomnia secondary to generalised anxiety disorder*. Eligible patients were between 18 and 64 years old and met DSM-IV criteria for generalised anxiety disorder had a score of at least 10 on the subject administered HADS anxiety subscale and a clinician administered Hamilton anxiety (HAM-A) score of at least twenty. Insomnia eligibility criteria were a sleep onset time of at least thirty minutes and a total sleep time of no more than six and a half hours. The study was a prospective parallel group placebo controlled trial and was conducted at 69 centres in the US. All patients received escitalopram 10 mg daily for 10 weeks (including during the two week placebo washout) and were randomised to placebo or eszopiclone 3 mg as 'add on' treatment. The primary efficacy criterion was change from baseline in subjective sleep latency over the average in the double blind treatment period. A secondary insomnia efficacy criterion was change from baseline in total sleep time. Anxiety criteria were change in HAM-A and in Clinical Global Impression of anxiety. Following the eight week double blind period there was a two week single blind washout period.

The sample size of 420 patients was based on the aim to achieve a 90% power to detect a treatment difference of 0.15 ($\log_e$) for sleep latency with a standard deviation of 0.45; α was 0.05. Significance testing was by ANCOVA using the MIXED procedure for efficacy variables. Demographic data and results are presented in the table below.

Table 16 Demographics and main outcomes of Study 190-902

	Placebo + escitalopram	Eszopiclone 3 mg + escitalopram	p value
Number studied	299	294	
Age mean (s.d.) years	39.7 (11.6)	40.2 (11.9)	0.6
Proportion male (%)	33.8	34.0	0.9
BMI (Kg/m^2) (male)	27.01 (4.23)	27.14 (4.01)	0.6
BMI (Kg/m^2) (female)	28.11 (6.94)	27.03 (6.30)	< 0.05
Sleep latency baseline (minutes)	101.07 (103.26)	93.12 (84.04)	
Sleep latency double blind (minutes)	73.41 (85.95)	51.29 (48.20)	<0.001
Total sleep time baseline (minutes)	328.14 (94.38)	327.57 (84.93)	
Total sleep time double blind (minutes)	369.48 (91.31)	398.92 (76.55)	<0.001
HAM-A total score baseline	22.36 (6.00)	21.77 (6.33)	
HAM-A total score week 8	11.54 (7.82)	9.84 (6.62)	0.007
CGI-S baseline	4.39 (0.70)	4.30 (0.68)	0.029
CGI-S week 8	2.83 (1.19)	2.64 (1.10)	0.12

Study 190-054 examined the safety and efficacy of eszopiclone 3.0 mg taken for four weeks by adult female *patients with menopausal or perimenopausal insomnia* as defined by the Stages of Reproductive Aging workshop.[1] The study was a prospective parallel group placebo controlled trial and was conducted at multiple US centres. Patients between 40 and 60 years old with a total sleep time of no more than 6.0 hours per night at least three times per week over the previous month and taking at least forty-five minutes to fall asleep were eligible. The primary and key secondary efficacy variables were; subjective sleep latency during the first week of double blind treatment, subjective wake time after sleep onset during the first study week. There was a 3 – 7 day single blind run in period to establish baseline values prior to randomisation. Following the four week double blind period there was a one week single blind washout period.

The sample size of 352 patients was based on the aim to achieve a 90% power to detect a treatment difference of 0.185 ($\log_e$) for WASO with a standard deviation of 0.534; α was 0.05. Significance testing was by ANOVA using the MIXED procedure for efficacy variables.

Table 17 Demographics and main outcomes of Study 190-054

	Placebo	Eszopiclone 3 mg	p value
Number studied	208	199	
Age mean (s.d.) years	48.9 (3.9)	49.3 (4.1)	
BMI (Kg/m^2)	28.2 (6.2)	28.2 (5.9)	
Sleep latency baseline (minutes)	104.1 (111.3)	110.8 (125.6)	
Sleep latency week 1 (minutes)	77.3 (87.7)	59.2 (84.3)	< 0.001
Sleep latency week 4 (minutes)	67.0 (88.6)	58.7 (100.5)	< 0.001
WASO baseline (minutes)	68.4 (54.9)	74.5 (54.8)	
WASO week 1 (minutes)	53.9 (51.3)	33.5 (33.8)	< 0.001
WASO week 4 (minutes)	40.2 (45.2)	30.0 (36.7)	< 0.001
Total sleep time baseline (minutes)	315.0 (100.4)	312.2 (105.8)	
Total sleep time week 1 (minutes)	346.9 (90)	392.8 (88.5)	< 0.001
Total sleep time week 4 (minutes)	365.1 (93.6)	396.1 (94.2)	< 0.001
Physician global assessment week 1 (score)	3.73 (0.71)	3.76 (0.72)	----
Physician global assessment week 4 (score)*	3.26 (1.14)	2.65 (1.18)	< 0.001

* The score on menopausal symptoms ranges from 1 = very much improved to 7 = very much worse

[1] Soules MR et al. Fertility and Sterility 2001 76(5) 874 - 78

Study 190-055 examined the safety and efficacy of eszopiclone 3.0 mg taken for four weeks by adult patients with *insomnia related to rheumatoid arthritis* diagnosed on the basis of the American College of Rheumatology criteria. The study was a prospective parallel group placebo controlled trial and was conducted from February 2004 to November 2004 at multiple US centres. Patients between 25 and 64 years old with wake time after sleep onset of at least 45 minutes and no more than 6.5 hours per night at least three times per week over the previous month were eligible. Symptoms of insomnia must have post-dated the onset of rheumatoid arthritis. Anti-arthritis medication had to be stable for 90 days prior to study entry. The primary efficacy criterion was wake time after sleep onset during the first week of double blind treatment. There was a 3 – 7 day single blind run in period to establish baseline values prior to randomisation. Following the four week double blind period there was a two week single blind washout period.

The original plan and power calculation called for a sample size of 440 patients; however, due to slow recruitment the study was closed after inclusion of 153 patients, it is estimated to have a 65% power to a treatment difference of 0.185 ($\log_e$) for WASO. Demographic data and results are presented in the table below.

Table 18 Demographics and main outcomes of Study 190-055

	Placebo	Eszopiclone 3 mg	p value
Number studied	76	77	
Age mean (s.d.) years	51.9 (9.5)	52.8 (8.1)	
Proportion male (%)	18.4	7.8	
BMI (Kg/m^2) (male)	30.8 (4.9)	27.4 (3.6)	
BMI (Kg/m^2) (female)	30.7 (6.6)	31.0 (9.6)	
Sleep latency week baseline (minutes)	88.3 (84.5)	99.0 (89.2)	
Sleep latency week 1 (minutes)	68.3 (68.8)	99.0 (89.2)	< 0.001
Sleep latency week 4 (minutes)	63.0 (81.9)	39.4 (48.3)	< 0.001
WASO baseline	72.9 (56.9)	77.2 (59.6)	
WASO week 1 (minutes)	56.8 (50.9)	33.9 (40.6)	< 0.001
WASO week 4 (minutes)	39.5 (37.7)	31.3 (37.9)	< 0.001
Total sleep time baseline (minutes)	329.7 (85.8)	328.2 (84.5)	
Total sleep time week 1 (minutes)	350.1 (87.2)	397.2 (63.1)	< 0.001
Total sleep time week 4 (minutes)	370.8 (88.8)	394.9 (67.3)	0.014
SF-36 Acute Health Survey change from baseline (upward change indicates benefit)	+ 0.8	+ 2.4	0.2

- Clinical studies in special populations

Study 190-047 was a multicentre randomised prospective two-week parallel group evaluation of the safety and efficacy of Lunivia 2 mg and placebo in <u>elderly patients</u>.
Patients 65 to 85 years old with DSM-IV criteria for insomnia who reported sleeping no more than 6.5 hours per night and taking at least thirty minutes to fall asleep were eligible; patients were required to show evidence of insomnia on screening polysomnography. The first two dosing nights and last two dosing nights were at a sleep lab with polysomnography intermediate doses were at home and efficacy was recorded by the patient using subjective criteria by questionnaire. The presence of significant comorbidity was an exclusion criterion.

The main efficacy variables were; latency to persistent sleep (LPS), sleep efficiency wake time after sleep onset (WASO). The sample size was based on the assumption of a treatment difference of 15 minutes (s.d. 30 minutes for LPS and a difference of 5% (s.d.) 10% for sleep efficiency, with 80% power and $\alpha = 0.05$ the number of patients required was 270. Demographic data and main results are showed in the table below.

Table 19 Demographics and main outcomes of Study 190-047

	Placebo	2 mg
Demographic outcomes		
Number randomised	128	136
Age mean s.d (years).	70.7 (4.9)	71.5 (5.2)
Proportion (%) male	28.9	36.0
BMI (Kg/m^2)	26.3 (4.2)	26.9 (4.0)
Efficacy outcomes		
LPS (minutes) night 1	42.1 (33.3)	17.7 (18.6)
LPS (minutes) night 14	39.0 (38.5)	21.0 (20.8)
Sleep efficiency night 1	73.4 (11.1)	81.3 (8.3)
Sleep efficiency night 14	73.5 (11.2)	77.5 (8.4)
WASO (minutes) night 1	93.2 (40.3)	76.0 (35.2)
WASO (minutes) night 14	94.3 (39.0)	91.0 (36.5)
Sleep architecture outcomes		
% time in REM sleep night 1	19.2 (19.0)	18.0 (17.6)
% time in REM sleep night 14	19.0 (18.5)	17.9 (17.5)
Next day function		
Morning sleepiness week 1	6.7	7.3
Morning sleepiness week 2	6.7	7.0
Daytime alertness week 1	7.1	7.4
Daytime alertness week 2	7.2	7.2
Symptomatic outcome		
Change in total insomnia score	-3.8 (5.3)	-5.8 (5.0)

The main efficacy results are generally highly statistically significant $p < 0.001$ ANOVA MIXED procedure. The reduction in REM sleep and the increase in morning sleepiness at week 1 were statistically significant $p < 0.05$

Study 190-048 was a multicentre randomised prospective two-week parallel group evaluation of the safety and efficacy of Lunivia 1 mg, 2 mg, and placebo in elderly patients.
Patients 65 to 85 years old with DSM-IV criteria for insomnia who reported sleeping no more than 6.5 hours per night and taking at least thirty minutes to fall asleep were eligible. The presence of significant comorbidity was an exclusion criterion.

The main efficacy variables were subjective latency to persistent sleep (LPS). The sample size was based on previous studies of zolpidem assuming a standard deviation of 36 minutes; with 80% power and $\alpha = 0.05$ the number of patients required was 225. Demographics and results are presented in the table below.

Table 20 Demographics and main outcomes of Study 190-048

	Placebo	1 mg	2 mg	p value
Demographic outcomes				
Number randomised	80	72	79	0.73
Age mean s.d (years).	72.0 (5.0)	72.7 (4.5)	72.2 (5.3)	
Proportion (%) male	38.8	43.1	45.5	0.68
BMI (Kg/m^2)	27.0 (5.0)	27.2 (4.5)	26.3 (3.7)	0.50
Efficacy outcomes				
LPS (minutes) week 1	100.7 (116.3)	60.8 (71.6)	50.0 (62.5)	0.008
LPS (minutes) week 2	64.7 (65.3)	45.7 (55.1)	47.9 (58.3)	0.08
Total sleep time (minutes) week 1	316.4 (102.2)	345.8 (79.8)	372.9 (76.2)	0.0002
Total sleep time (minutes) week 2	346.5 (72.6)	357.4 (71.8)	379.1 (68.4)	0.002
WASO (minutes) week 1	83.7 (63.3)	78.0 (55.4)	63.0 (54.9)	0.02
WASO (minutes) week 2	67.4 (56.2)	63.0 (54.5)	54.1 (60.9)	0.04
Number of awakenings week 1	2.0 (1.1)	2.2 (1.2)	1.8 (1.0)	0.1
Number of awakenings week 2	1.0 (1.8)	1.0 (1.7)	1.1 (1.4)	0.04
Quality of sleep week 1	6.0	6.4	7.3	0.01
Quality of sleep week 2	6.5	6.7	7.5	0.01
Next day outcomes				
Morning sleepiness week 1	6.5 (2.1)	6.7 (1.8)	7.1 (1.8)	0.05
Morning sleepiness week 2	6.9 (1.9)	7.1 (1.7)	7.5 (1.7)	0.07
Daytime alertness week 1	6.8 (2.6)	6.9 (4.0)	7.7 (2.3)	0.04
Daytime alertness week 2	7.1 (1.5)	7.4 (1.5)	7.7 (1.6)	0.02

- Discussion on clinical efficacy

Across all the efficacy clinical studies Lunivia 2 mg and 3 mg consistently showed statistically significant improvement of the primary variable – latency to persistent sleep – measured either objectively or subjectively, and both in the short- and in the long-term.
Efficacy was also consistently demonstrated with regard to the secondary efficacy measures, which measured sleep maintenance, sleep quality and daytime functioning.
Lunivia 3 mg also improved insomnia associated to the co-morbid conditions, major depression, generalised anxiety, menopausal symptoms and rheumatoid arthritis.

The derived differences between Lunivia and placebo for each endpoint for all efficacy studies are shown in Table 11 below. The clinical patient reported outcomes were used in order to provide consistency of the comparison across all studies. The calculations were weighted averages based on the overall sample size of the study.

Table 11: Summary of Treatment Effect versus Placebo for Sleep Parameters and the Difference between Eszopiclone and Placebo Results

Study	Sleep Latency (Minutes)			WASO (Minutes)			TST (Minutes)		
	PBO	ESZ 3.0mg	Δ	PBO	ESZ 3.0mg	Δ	PBO	ESZ 3.0mg	Δ
Short Term Insomnia									
190-045	47.5 *n=65*	**25.0** *n=64*	22.5	30.8 *n=65*	**23.3** *n=64*	7.5	375.0 n=65	**420.0** n=64	45
190-046	46.0 *n=99*	**27.7** *n=105*	18.3	44.1 *n=99*	**33.8** *n=105*	10.3	366.0 n=99	**406** *n=105*	40
190-047 (*2 mg)	55.0 *n=128*	**26.5*** *n=136*	28.5	91.2 *n=128*	**81.7*** *n=136*	9.5	324.4 *n=128*	**386.9*** *n=136*	62.5
190-048 (*2 mg)	52.0 *n=80*	**36.2*** *n=79*	15.8	58.1 *n=80*	**49.5*** *n=79*	8.6	345.0 *n=80*	**383.2*** *n=79*	38.2
190-049 4 weeks	52.5 *n=195*	**31.3*** *n=593*	21.2	36.7 *n=195*	**23.8*** *n=593*	12.9	337.5 *n=195*	**375.0*** *n=593*	37.5
190-050 4 weeks	52.5 *n=280*	**28.8*** *n=548*	23.7	32.5 *n=280*	**17.5*** *n=548*	15	336.8 *n=280*	**390.0*** *n=548*	53.2
Ave. Diff. between ESZ and Placebo			**19.0**			**10.9**			**43.8**
Long-Term Insomnia									
190-049	64.7 *n=195*	**46.7** *n=593*	18	35.7 *n=195*	**22.5** *n=593*	13.2	345.1 *n=195*	**381.7** *n=593*	36.6
190-050	59.0 *n=280*	**38.5** *n=548*	20.5	26.1 *n=280*	**14.7** *n=548*	11.4	345.0 *n=280*	**396.5** *n=548*	51.5
Ave. Diff. between ESZ and Placebo			**19.2**			**12.3**			**44.0**
Comorbid Insomnia									
190-054	38.6 *n=186*	**26.3** *n=181*	12.3	27.5 *n=183*	**15.0** *n=177*	12.5	377.3 *n=186*	**411.4** *n=181*	34.1
190-055	32.7 *n=56*	**22.2** *n=66*	10.5	27.9 *n=67*	**15.0** *n=76*	12.9	383.5 *n=68*	**400.8** *n=76*	17.3
190-052	47.5 *n=261*	**30.0** *n=253*	17.5	26.7 *n=255*	**8.75** *n=249*	18	360.0 *n=261*	**405.0** *n=253*	45
190-902	42.0 *n=299*	**30.2*** *n=294*	11.8	18.9 n=297	**13.0** *n=294*	5.9	398.6 *n=299*	**421.2** *n=294*	22.6
Ave. Diff. between ESZ and Placebo			**13**			**11**			**38**

A *post hoc* responder analysis was also performed, using the criterion where responders were defined as achieving an improvement of 10 minutes or more on sleep latency or 10 minutes or more on WASO or 20 minutes or more on TST.
A responder analysis is regarded as useful in judging the clinical relevance of the benefit observed on the pivotal efficacy measures. The results are shown in Table 10 below.

Table 10: Responder Analysis for Sleep Parameters in Eszopiclone Development

Study	Sleep Latency (% Responders)			WASO (% responders)			TST (% responders)		
	PBO	ESZ 3.0mg	Δ	PBO	ESZ 3.0mg	Δ	PBO	ESZ 3.0mg	Δ
Primary Insomnia									
190-045	58.7 *n=65*	85.9 *n=64*	27.2	41.3 *n=65*	70.3 *n=64*	29	61.9 n=65	76.2 n=64	14.3
190-046	52.1 *n=99*	76.0 *n=105*	23.9	54.3 *n=99*	52 *n=105*	-2.3	59.6 n=99	69 *n=105*	9.4
190-049 4 week	56.6 *n=195*	75.9 *n=593*	19.3	43.3 *n=195*	67.6 *n=593*	24.3	57.0 *n=195*	78.7 *n=593*	21.7
190-050 4 week	58.2 *n=280*	82.8 *n=548*	24.6	48.4 *n=280*	66.1 *n=548*	17.7	58.7 *n=280*	84.6 *n=548*	25.9
190-047 (*2 mg)	50.4 *n=128*	65.9* *n=136*	15.5	57.0 *n=128*	59.8* *n=136*	2.8	53.7 *n=128*	63.6* *n=136*	9.9
190-048 (*2 mg)	52.9 *n=80*	56.3* *n=79*	3.4	39.7 *n=80*	62.9* *n=79*	23.2	50.0 *n=80*	74.6* *n=79*	24.6
Ave. Diff. between ESZ and PBO % Responders			**20.5**			**17.5**			**20.6**
Long-Term Insomnia									
190-049 6 month	60.8 *n=195*	73.8 *n=593*	13	53.3 *n=195*	69.9 *n=593*	16.6	55.4 *n=195*	78.4 *n=593*	23
190-050 6 month	60.9 *n=280*	77.9 *n=548*	17	57.1 *n=280*	71.4 *n=548*	14.3	62.1 *n=280*	80.6 *n=548*	18.5
Ave. Diff. between ESZ and PBO % Responders			**15.0**			**15.4**			**20.7**
Comorbid Insomnia									
190-054	55.4 *n=186*	73.9 *n=181*	18.5	63 *n=183*	74.1 *n=177*	11.1	59.7 *n=186*	76.7 *n=181*	17
190-055	60.7 *n=56*	73.8 *n=66*	13.1	67.2 *n=67*	77.3 *n=76*	10.1	55.9 *n=68*	68.0 *n=76*	12.1
190-052	73.9 *n=261*	80.8 *n=253*	6.9	70.7 *n=255*	84.4 *n=249*	13.7	79.6 *n=261*	83.2 *n=253*	3.6
190-902	65.7 *n=299*	72.1 *n=294*	6.4	66.1 n=*297*	73.2 *n=294*	7.1	68.2 *n=299*	81.3 *n=294*	13.1
Ave. Diff. between ESZ and PBO % Responders			**9.9**			**10.4**			**10.9**

Based on the above results, it can be concluded that in adults Lunivia 2 mg and above consistently produced statistically significant improvements in sleep induction and quality of sleep measures. By contrast, only the recommended dose of 3 mg consistently produced significant improvements in sleep maintenance parameters, including several improvements that were not achieved with the comparator zolpidem 10 mg. For the primary and key secondary measures in adult studies investigating primary insomnia, the 3 mg Lunivia consistently produced numerically better improvements than the 2 mg dose. Results were sustained throughout each month of the long-term studies for up to 12 months. In elderly subjects, the 2 mg dose appeared more effective than the 1 mg dose. For these reasons, it is believed that nighttime administration of Lunivia 3 mg for adults and 2 mg for elderly subjects will provide effective hypnotic activity.

The data from trials in insomnia as co-morbid condition are also supportive of efficacy.

Clinical data presented suggest there is a positive impact in quality of life and day functioning.

Overall the efficacy data of the clinical program support the maintenance of effect and the claimed indication for the treatment of insomnia, including difficulty falling asleep, nocturnal awakening or early awakening, in adults, usually for short term duration.

Clinical safety

A total of 34 Lunivia studies were conducted in the clinical development programme for Lunivia. The vast majority of these studies were conducted in the United States. Two of these studies were conducted in the United Kingdom.
Safety was evaluated in all studies via routine physical and neurological examinations, adverse events, vital signs, clinical laboratory parameters, and electrocardiograms.
Several special studies specifically evaluated withdrawal, next-day performance effects, next-day driving ability, cognitive function, and psychomotor performance.

- Patient exposure

For overall summaries on subject disposition, demographics and study drug exposure, data were pooled, without weighting, from 27 of 34 clinical studies. Data from the remaining studies were not appropriate to pool because they were special population studies, studies to evaluate effects on driving performed in the U.K., or where Lunivia was not administered as a monotherapy during the study.
For summaries of deaths, serious adverse events (SAEs), adverse events (AEs), clinical laboratory parameters, electrocardiograms (ECGs), and vital signs, data from studies of similar population (healthy volunteers versus subjects with insomnia; elderly versus non-elderly), administration time (daytime versus nighttime), and dosing duration (short-term, chronic-dosing, long-term) were pooled to form groups of homogeneous studies (study types; defined in Table 2.7.4.1.1.1-1). Data from the remaining studies were not appropriate to pool, because they were special population studies, studies performed in the U.K., eszopiclone was not administered as a monotherapy during the study, or there was only one study of its kind.Data from Study 190-003 were not pooled with other short-term studies in healthy volunteers, because this study was intended to extrapolate data to a foreign market (Japan). Data from 4 other studies (190-013, 190-014, 190-016, and 190-028) were not pooled, because they were special populations. Data from the drug-drug interaction Study 190-022 were not pooled, because eszopiclone was not administered as a monotherapy during the study. Data from Study 190-055 were not pooled, because it was the only study in subjects with comorbid insomnia and rheumatoid arthritis and it captured adverse events uniquely associated with that disease and/or its treatment. Data from Studies 190-059 and 190-060 were not pooled, because the study design dictated the times when subjects were administered drug, awakened, and outside the clinic at a driving track. Further, regional (U.K.) differences in the collection and handling of adverse events may have occurred, compared with the U.S.

Table 2.7.4.1.1.1-1: Study Type Categorization

Study Type	Studies Included
HEALTHY VOLUNTEERS	
Daytime Dosing	
Pooled short-term (1-7 days) studies	190-001, 190-002, 190-005, 190-010, 190-011, 190-012, 190-015[a], 190-018[a], 190-019[a], 190-020[a], 190-021[a], and 190-023[a]
Nighttime Dosing	
Pooled short-term (1-7 days) studies	190-024[b] and 190-026
Chronic-dosing (12 weeks) study	190-029
SUBJECTS WITH INSOMNIA	
Nighttime Dosing	
Pooled short-term (1-7 days) studies in non-elderly adults	190-025[b] and 190-045
Pooled chronic-dosing (2 weeks) studies in elderly subjects	190-047 and 190-048
Pooled chronic-dosing (4-6 weeks) studies in non-elderly adults	190-046 and 190-054
Pooled chronic-dosing (8 weeks) studies coadministered with an SSRI (non-elderly adults with insomnia and in comorbid MDD/GAD)	190-052 (MDD) and 190-902 (GAD)
Pooled long-term (6-month double-blind) studies in non-elderly adults	190-049[c] (refers to the 6 months of placebo-controlled, double-blind data only) and 190-050

MDD=Major Depressive Disorder; GAD=Generalized Anxiety Disorder SSRI=Selective Serotonin-Reuptake Inhibitor.

[a] For Study 190-021, only safety data from the first four days of the (RS)-Warfarin combination treatment period were pooled, because this period represents eszopiclone monotherapy prior to the addition of (RS)-Warfarin on Day 5. For the remaining drug-drug interaction studies (190-015, 190-018, 190-019, 190-020, and 190-023), safety data on eszopiclone monotherapy were pooled. However, safety data on eszopiclone combination therapy were not pooled, because of treatment confounding. For this study, the CSR summary in Module 5.3 was referenced to support the conclusions of the pooled data.

[b] For Studies 190-024 and 190-025, all safety data collected in the completed studies were pooled, except for the next-day effect data that were referenced from the CSRs in Module 5.3.

[c] For Studies 190-049 and 190-050, 6 months of safety data from the placebo-controlled, double-blind period were pooled.

Overall, 79.2% of subjects completed the studies. Over 75% of subjects completed the study in each Lunivia dose category (1 mg, 2 mg, 2.5 mg, 3 mg, and ≥3.5 mg). Discontinuation rates were between 19.4% for Lunivia overall and the 21.9% for placebo group. There was a slightly higher discontinuation rate in the Lunivia 3 mg group (24.9%) due to the contribution of subjects from the 6- and 12-month studies to this dose category. The table below summarises exposure data for Lunivia.

Population exposure

Duration of Treatment by Average Daily Dose (mg/day) for Pooled Studies (ITT Population)

	Average Daily Dose (mg/day)						
Duration of Treatment Subject n (%)	**Placebo (N=1971)**	**Lunivia ≤1.75 mg (N=261)**	**>1.75 to 2.25 mg (N=630)**	**>2.25 to 2.75 mg (N=286)**	**>2.75 to 3.25 mg (N=1972)**	**>3.25 mg (N=232)**	**All Active (N=3381)**
1-7 days	389 (19.7)	83 (31.8)	185 (29.4)	40 (14.0)	249 (12.6)	195 (84.1)	752 (22.2)
>1 to 4 weeks	499 (25.3)	122 (46.7)	270 (42.9)	42 (14.7)	246 (12.5)	17 (7.3)	697 (20.6)
>1 to 6 months (>4 to 24 weeks)	843 (42.8)	40 (15.3)	140 (22.2)	100 (35.0)	862 (43.7)	13 (5.6)	1155 (34.2)
>6 to 12 months (>24 to 48 weeks)	240 (12.2)	8 (3.1)	18 (2.9)	56 (19.6)	390 (19.8)	5 (2.2)	477 (14.1)
>1 year (>48 weeks)	0	8 (3.1)	17 (2.7)	48 (16.8)	225 (11.4)	2 (0.9)	300 (8.9)

- Adverse events

For the healthy volunteers/daytime-dosing in the pooled short-term (1-7 days) studies, a higher rate of Lunivia-treated subjects (82.7% and 75.6% for 2 mg and 3 mg, respectively) reported at least one treatment emergent adverse event than placebo-treated subjects (44.4%). This was largely driven by the high frequency of unpleasant taste.
Unpleasant taste, a known side effect of Lunivia, was also reported in placebo subjects, because the placebo solution in these studies was designed to be bitter tasting.
Most of the TEAEs were potentially related (possible, probable, definite, or unknown relationship) to study drug (33.1%, 82.7%, and 73.3% of placebo-, 2 mg Lunivia-, and 3 mg Lunivia-treated subjects, respectively).
For the healthy volunteers/nighttime-dosing in the pooled short-term (1-7 days) studies, there were higher incidences for Lunivia-treated subjects with respect to the overall incidence of TEAEs (20.9%, 32.1%, and 34.5% for placebo, Lunivia 2 mg, and Lunivia 3 mg, respectively), driven by the higher number of subjects experiencing unpleasant taste. This trend is also present among the potentially related TEAEs (18.2%, 30.3%, and 30.9%, respectively). Higher incidence of potentially related unpleasant taste was observed for the Lunivia groups (21.1% and 20.9% for 2 mg and 3 mg, respectively) as compared with placebo (7.3%).

For the healthy volunteers/nighttime-dosing in the chronic-dosing (12 weeks) study, there were no notable differences between placebo- and 3 mg Lunivia-treated subjects with respect to the overall incidences of TEAEs (44.7% and 47.9%, respectively) and potentially related TEAEs (10.6% and 12.5%, respectively), or the observed adverse event profile. While headache was most prevalent, it was similar between active and placebo treatment groups.

For the subjects with insomnia/nighttime-dosing in the pooled short-term (1-7 days) studies in non-elderly adults, there were no notable differences between placebo- and Lunivia-treated subjects with respect to the overall incidences of TEAEs (25.0%,25.3%, and 30.3% for placebo, Lunivia 2 mg, and Lunivia 3 mg, respectively) and potentially related TEAEs (17.1%, 18.7%, and 22.4%, respectively). Potentially-related unpleasant taste (0%, 6.7%, and 6.6%) and somnolence (3.9%, 2.7%, and 7.9%) were more prevalent among one or more Lunivia groups. Pharyngitis was also uniquely associated with Lunivia treatment in a small number of subjects.

In elderly subjects with insomnia/nighttime-dosing in the pooled chronic-dosing (2 weeks) studies, placebo-treated and 2 mg Lunivia-treated subjects were similar with respect to the overall incidences of TEAEs (43.8% and 46.5% for placebo and Lunivia 2 mg, respectively). Treatment emergent adverse events assessed as potentially related were slightly more prevalent in the 2 mg Lunivia group (25.5% and 31.2% for placebo and Lunivia 2 mg, respectively). Specifically, dizziness (2.4% and 5.1%), dry mouth (1.9% and 5.6%), and unpleasant taste (0.5% and 12.1%) were more prevalent among 2 mg Lunivia-treated subjects. Although not considered potentially related by the investigators, accidental injury was more prevalent among 2 mg Lunivia-treated subjects than placebo-treated subjects (2.8% and 1.0%).

For the subjects with insomnia/nighttime-dosing in the chronic-dosing (4-6 weeks) studies in non-elderly adults, a higher rate of Lunivia-treated subjects (64.4% and 62.5% for 2 mg and 3 mg, respectively) reported TEAEs than placebo-treated subjects (47.2%). Most of these TEAEs were assessed as potentially related to study drug (27.0%, 42.3%, and 47.7% of placebo-, 2 mg Lunivia-, and 3 mg Lunivia-treated subjects, respectively).

Table 2.7.4.2.1.1.2-3: All Treatment Emergent Adverse Events with an Incidence >2% in Either Active Group, and the Percent Potentially Related for the Subjects with Insomnia/Nighttime-Dosing in the Chronic-Dosing (4-6 Weeks) Studies in Non-Elderly Adults (COSTART Coding) (ITT Population)

BODY SYSTEM Preferred Term Subject n (%)	All TEAEs			Potentially Related TEAEs		
	Placebo (N=307)	ESZ 2 mg (N=104)	ESZ 3 mg (N=304)	Placebo (N=307)	ESZ 2 mg (N=104)	ESZ 3 mg (N=304)
AT LEAST ONE AE	145 (47.2)	67 (64.4)	190 (62.5)	83 (27.0)	44 (42.3)	145 (47.7)
BODY AS A WHOLE	91 (29.6)	34 (32.7)	90 (29.6)	51 (16.6)	16 (15.4)	45 (14.8)
Headache	44 (14.3)	22 (21.2)	47 (15.5)	31 (10.1)	13 (12.5)	32 (10.5)
Pain	14 (4.6)	5 (4.8)	13 (4.3)	3 (1.0)	0	6 (2.0)
Back pain	9 (2.9)	2 (1.9)	14 (4.6)	5 (1.6)	1 (1.0)	7 (2.3)
Accidental injury	6 (2.0)	3 (2.9)	6 (2.0)	1 (0.3)	0	1 (0.3)
Viral infection	5 (1.6)	3 (2.9)	6 (2.0)	3 (1.0)	0	1 (0.3)
DIGESTIVE	44 (14.3)	17 (16.3)	51 (16.8)	27 (8.8)	7 (6.7)	41 (13.5)
Dry mouth	6 (2.0)	5 (4.8)	15 (4.9)	5 (1.6)	5 (4.8)	14 (4.6)
Dyspepsia	9 (2.9)	4 (3.8)	12 (3.9)	4 (1.3)	0	6 (2.0)
Nausea	10 (3.3)	3 (2.9)	11 (3.6)	7 (2.3)	2 (1.9)	8 (2.6)
Diarrhoea	8 (2.6)	4 (3.8)	7 (2.3)	6 (2.0)	0	6 (2.0)
Vomiting	1 (0.3)	3 (2.9)	0	0	1 (1.0)	0
MUSCULOSKELETAL	19 (6.2)	5 (4.8)	16 (5.3)	7 (2.3)	1 (1.0)	5 (1.6)
Myalgia	11 (3.6)	3 (2.9)	7 (2.3)	2 (0.7)	0	0
NERVOUS	28 (9.1)	24 (23.1)	51 (16.8)	20 (6.5)	20 (19.2)	45 (14.8)
Somnolence	5 (1.6)	10 (9.6)	15 (4.9)	4 (1.3)	9 (8.7)	15 (4.9)
Dizziness	8 (2.6)	5 (4.8)	12 (3.9)	8 (2.6)	3 (2.9)	10 (3.3)
Nervousness	5 (1.6)	5 (4.8)	3 (1.0)	3 (1.0)	5 (4.8)	3 (1.0)
Depression	0	4 (3.8)	2 (0.7)	0	3 (2.9)	2 (0.7)
Abnormal dreams	4 (1.3)	3 (2.9)	1 (0.3)	4 (1.3)	3 (2.9)	1 (0.3)
RESPIRATORY	33 (10.7)	14 (13.5)	37 (12.2)	11 (3.6)	2 (1.9)	12 (3.9)
Infection	9 (2.9)	4 (3.8)	18 (5.9)	3 (1.0)	0	4 (1.3)
Pharyngitis	12 (3.9)	5 (4.8)	13 (4.3)	4 (1.3)	2 (1.9)	3 (1.0)
Rhinitis	10 (3.3)	5 (4.8)	4 (1.3)	1 (0.3)	0	1 (0.3)
SPECIAL SENSES	11 (3.6)	23 (22.1)	79 (26.0)	6 (2.0)	18 (17.3)	75 (24.7)
Unpleasant taste	4 (1.3)	18 (17.3)	72 (23.7)	4 (1.3)	18 (17.3)	71 (23.4)
UROGENITAL	12 (3.9)	7 (6.7)	15 (4.9)	4 (1.3)	1 (1.0)	7 (2.3)
Gynaecomastia*	0	1 (2.6)	0	0	1 (2.6)	0
Dysmenorrhoea*	4 (1.5)	2 (3.0)	1 (0.4)	1 (0.4)	0	0

*indicates a gender-specific adverse event, where percentages were based on the number of subjects in the appropriate gender and treatment group.

TEAE=treatment emergent adverse event; ESZ=eszopiclone.

Note: Includes Studies 190-046 and 190-054.

Note: Treatment emergent adverse events include those events that occurred or worsened upon or after administration of the first dose of double-blind study medication. Subjects were counted only once within each body system and each preferred term.

Note: Potentially related TEAEs include those events with a definite, possible, probable, or unknown relationship to study drug.

Reference: Module 5.3.5.3 Tables 4.1.1 and 4.2.1

For TEAEs assessed as potentially-related, somnolence (1.3%, 8.7%, and 4.9%), nervousness (1.0%, 4.8%, and 1.0%), and dry mouth (1.6%, 4.8%, and 4.6%) were more prevalent among one or more Lunivia groups. Higher incidences of unpleasant taste were observed for the Lunivia groups (17.3% and 23.4% for 2 mg and 3 mg, respectively) as compared with placebo (1.3%), with a clear dose-response relationship.

The pooled data include Study 190-054 that enrolled perimenopausal/postmenopausal women, which contributed to the higher observed frequency of dysmenorrhoea.

Results for the chronic-dosing (4 weeks) study (190-055) in non-elderly adults with insomnia and comorbid rheumatoid arthritis were generally similar to the results for the pooled chronic-dosing (4-6

weeks) studies in non-elderly adults, with the following exceptions. In this study, asthenia (1.3% and 6.5%), pharyngitis (0% and 5.2%), and rheumatoid arthritis (9.2% and 18.2%) were also more prevalent among 3 mg Lunivia-treated subjects compared with placebo-treated subjects. None of the rheumatoid arthritis adverse events were assessed as potentially related to study medication. An in-depth examination of the rheumatoid arthritis (RA) events revealed that the vast majority were less than 48 hours in duration. Only 2 events (one in each treatment group) required a change in RA treatment medications. Overall, there was no change in RA disease indices (AM stiffness, CRP, swollen joint count), and tender jointcounts actually decreased on Lunivia treatment. Thus, treatment with Lunivia 3 mg did not result in any symptomatic change of the underlying RA in these subjects.

For the subjects with insomnia/nighttime-dosing in the pooled chronic-dosing (8 weeks) studies coadministered with an SSRI (non-elderly adults with insomnia and in comorbid MDD/GAD), the incidence of TEAEs for 3 mg Lunivia-treated subjects (76.9%) was slightly higher than that for placebo-treated subjects (69.6%). A similar pattern was observed for potentially related TEAEs (65.2% for 3 mg Lunivia-treated subjects and 53.6% for placebo-treated subjects). Unpleasant taste (23.3% and 2.3%), dry mouth (12.1% and 9.2%), dizziness (6.6% and 3.8%), nervousness (6.0% and 3.5%), somnolence (11.0% and 8.6%), and asthenia (6.6% and 4.9%) were more prevalent among 3 mg Lunivia-treated subjects. Also, there was a higher frequency of overall events known to occur with an SSRI, including impotence, dry mouth, anorexia, and decreased libido. There were three potentially related events of accidental injury.

For the subjects with insomnia/nighttime-dosing in the pooled long-term (6-month double-blind) studies in non-elderly adults, a higher rate of 3 mg Lunivia-treated subjects (78.5%) reported TEAEs than placebo-treated subjects (63.8%). Most of these TEAEs were assessed as potentially related to study drug (35.6% and 55.1% of placebo-treated and 3 mg Lunivia-treated subjects, respectively).

Table 2.7.4.2.1.1.2-5: All Treatment Emergent Adverse Events with an Incidence >2% in Either Active Group, and the Percent Potentially Related for the Subjects with Insomnia/Nighttime-Dosing in the Pooled Long-Term (6-Month Double-Blind) Studies in Non-Elderly Adults (COSTART Coding) (ITT Population)

BODY SYSTEM Preferred Term Subject n (%)	All TEAEs			Potentially Related TEAEs		
	Placebo (N=475)	ESZ 2 mg (N=0)	ESZ 3 mg (N=1141)	Placebo (N=475)	ESZ 2 mg (N=0)	ESZ 3 mg (N=1141)
AT LEAST ONE AE	303 (63.8)	--	896 (78.5)	169 (35.6)	--	629 (55.1)
BODY AS A WHOLE	189 (39.8)	--	518 (45.4)	86 (18.1)	--	231 (20.2)
Headache	79 (16.6)	--	199 (17.4)	55 (11.6)	--	125 (11.0)
Pain	41 (8.6)	--	115 (10.1)	4 (0.8)	--	18 (1.6)
Back pain	26 (5.5)	--	74 (6.5)	3 (0.6)	--	22 (1.9)
Accidental injury	28 (5.9)	--	70 (6.1)	2 (0.4)	--	2 (0.2)
Abdominal pain	20 (4.2)	--	68 (6.0)	13 (2.7)	--	33 (2.9)
Asthenia	19 (4.0)	--	47 (4.1)	13 (2.7)	--	35 (3.1)
Flu syndrome	20 (4.2)	--	42 (3.7)	5 (1.1)	--	9 (0.8)
Viral infection	10 (2.1)	--	34 (3.0)	1 (0.2)	--	4 (0.4)
Chest pain	10 (2.1)	--	31 (2.7)	6 (1.3)	--	11 (1.0)
DIGESTIVE	98 (20.6)	--	322 (28.2)	47 (9.9)	--	208 (18.2)
Nausea	20 (4.2)	--	84 (7.4)	13 (2.7)	--	52 (4.6)
Dyspepsia	28 (5.9)	--	75 (6.6)	14 (2.9)	--	49 (4.3)
Diarrhoea	17 (3.6)	--	68 (6.0)	9 (1.9)	--	38 (3.3)
Dry mouth	11 (2.3)	--	60 (5.3)	11 (2.3)	--	53 (4.6)
Constipation	4 (0.8)	--	28 (2.5)	0	--	20 (1.8)
Vomiting	8 (1.7)	--	27 (2.4)	2 (0.4)	--	13 (1.1)
MUSCULOSKELETAL	39 (8.2)	--	148 (13.0)	10 (2.1)	--	38 (3.3)
Myalgia	17 (3.6)	--	60 (5.3)	4 (0.8)	--	17 (1.5)
Arthralgia	10 (2.1)	--	35 (3.1)	2 (0.4)	--	4 (0.4)
NERVOUS	75 (15.8)	--	324 (28.4)	55 (11.6)	--	249 (21.8)
Somnolence	14 (2.9)	--	102 (8.9)	14 (2.9)	--	95 (8.3)
Dizziness	15 (3.2)	--	79 (8.9)	13 (2.7)	--	63 (5.5)
Depression	5 (1.1)	--	39 (3.4)	3 (0.6)	--	22 (1.9)
Anxiety	5 (1.1)	--	33 (2.9)	2 (0.4)	--	16 (1.4)
Nervousness	8 (1.7)	--	33 (2.9)	5 (1.1)	--	27 (2.4)
Abnormal dreams	11 (2.3)	--	29 (2.5)	11 (2.3)	--	29 (2.5)
RESPIRATORY	103 (21.7)	--	356 (31.2)	21 (4.4)	--	57 (5.0)
Infection	45 (9.5)	--	174 (15.2)	5 (1.1)	--	9 (0.8)
Pharyngitis	21 (4.4)	--	92 (8.1)	5 (1.1)	--	19 (1.7)
Rhinitis	17 (3.6)	--	68 (6.0)	5 (1.1)	--	13 (1.1)
Sinusitis	22 (4.6)	--	50 (4.4)	6 (1.3)	--	7 (0.6)
Bronchitis	3 (0.6)	--	24 (2.1)	0	--	0
SKIN & APPENDAGES	32 (6.7)	--	115 (10.1)	12 (2.5)	--	43 (3.8)
Rash	10 (2.1)	--	46 (4.0)	3 (0.6)	--	19 (1.7)
SPECIAL SENSES	35 (7.4)	--	315 (27.6)	23 (4.8)	--	278 (24.4)
Unpleasant taste	14 (2.9)	--	263 (23.0)	14 (2.9)	--	260 (22.8)
UROGENITAL	32 (6.7)	--	119 (10.4)	11 (2.3)	--	41 (3.6)
Dysmenorrhoea*	5 (1.7)	--	20 (2.8)	0	--	5 (0.7)

*indicates a gender-specific adverse event, where percentages were based on the number of subjects in the appropriate gender and treatment group.

TEAE=treatment emergent adverse event; ESZ=eszopiclone.

Note: Includes Studies 190-049 and 190-050.

Note: Treatment emergent adverse events include those events that occurred or worsened upon or after administration of the first dose of double-blind study medication. Subjects were counted only once within each body system and each preferred term.

Note: Potentially related TEAEs include those events with a definite, possible, probable, or unknown relationship to study drug.

Reference: Module 5.3.5.3 Tables 4.1.1 and 4.2.1

For TEAEs assessed as potentially-related, unpleasant taste (2.9% and 22.8%), somnolence (2.9% and 8.3%), pain/back pain (1.4% and 3.5%), nausea/vomiting (3.1% and 5.7%), somnolence (2.9% and 8.3%), dizziness (2.7% and 5.5%), nervousness (1.1% and 2.4%), anxiety (0.4% and 1.4%), and dry mouth (2.3% and 4.6%) were more prevalent among 3 mg Lunivia-treated subjects. Gastrointestinal events including both diarrhoea and constipation were also more prevalent in the 3 mg Lunivia group.
For all cases of rash, which included the verbatim term (2.0% and 4.0%), as well as investigator exam findings, the majority were localized and no pattern suggestive of a drug eruption was evident in the data.
In Study 190-049-a total of 81.1% and 75.2% of 3 mg Lunivia-treated subjects reported TEAEs during the 6-month double-blind and open-label periods, respectively. Overall, the trend in the pattern of adverse events observed during the open-label period was similar to the trend observed during the double-blind period. There was a lower incidence of unpleasant taste during open-label 3 mg Lunivia treatment (6.8%) than during double-blind 3 mg Lunivia treatment (26.1%).

Potentially Related Treatment Emergent Adverse Events by Demographic Subgroup

By Age

An evaluation of the AE profile for elderly (65-74 years) and very elderly (≥75 years) subjects following 2 weeks of dosing was performed. This was compared to the AE profile observed in younger subjects following both 4-6 weeks of dosing and long-term dosing (6-12 months) in older (60-65 years) and non-elderly (<60 years) adults.
The most frequently reported potentially related adverse events with an incidence ≥2% in either active group are summarised by age group for the subjects with insomnia/nighttime-dosing in the pooled chronic-dosing (2 weeks) studies in elderly subjects in Table 2.7.4.2.1.1.4-1.

Table 2.7.4.2.1.1.4-1: Potentially Related Treatment Emergent Adverse Events with an Incidence ≥2% in Either Active Group by Age Group for the Subjects with Insomnia/Nighttime-Dosing in the Pooled Chronic-Dosing (2 Weeks) Studies in Elderly Subjects (COSTART Coding) (ITT Population)

BODY SYSTEM	Age <75 Years			Age ≥ 75 Years		
Preferred Term Subject n (%)	Placebo (N=155)	ESZ 1 mg (N=50)	ESZ 2 mg (N=149)	Placebo (N=53)	ESZ 1 mg (N=22)	ESZ 2 mg (N=66)
AT LEAST ONE AE	35 (22.6)	14 (28.0)	44 (29.5)	18 (34.0)	8 (36.4)	23 (34.8)
BODY AS A WHOLE	17 (11.0)	9 (18.0)	19 (12.8)	9 (17.0)	3 (13.6)	5 (7.6)
Headache	13 (8.4)	7 (14.0)	13 (8.7)	6 (11.3)	3 (13.6)	2 (3.0)
Asthenia	5 (3.2)	1 (2.0)	4 (2.7)	0(0.0)	1 (4.5)	1 (1.5)
Abdominal pain	2 (1.3)	1 (2.0)	3 (2.0)	2 (3.8)	0	1 (1.5)
DIGESTIVE	10 (6.5)	4 (8.0)	13 (8.7)	4 (7.5)	3 (13.6)	5 (7.6)
Dry mouth	4 (2.6)	1 (2.0)	8 (5.4)	0 (0.0)	1 (4.5)	4 (6.1)
Dyspepsia	1 (0.6)	2 (4.0)	2 (1.3)	2 (3.8)	1 (4.5)	0
Nausea	2 (1.3)	2 (4.0)	2 (1.3)	2 (3.8)	1 (4.5)	0
Diarrhoea	2 (1.3)	1 (2.0)	1 (0.7)	0	1 (4.5)	0
Vomiting	0 (0.0)	1 (2.0)	0 (0.0)	0	0	0
MUSCULOSKELETAL	3 (1.9)	1 (2.0)	2 (1.3)	2 (3.8)	1 (4.5)	0
Leg Cramps	3 (1.9)	1 (2.0)	0 (0.0)	2 (3.8)	0	0
Myalgia	0	0	1 (0.7)	1 (1.9)	1 (4.5)	0
NERVOUS SYSTEM	15 (9.7)	6 (12.0)	17 (11.4)	3 (5.7)	4 (18.2)	10 (15.2)
Somnolence	12 (7.7)	2 (4.0)	6 (4.0)	1 (1.9)	3 (13.6)	6 (9.1)
Dizziness	4 (2.6)	1 (2.0)	9 (6.0)	1 (1.9)	0	2 (3.0)
Abnormal Dreams	0 (0.0)	2 (4.0)	2 (1.3)	0	0	0
Nervousness	2 (1.3)	0 (0.0)	3 (2.0)	1 (1.9)	0	1 (1.5)
Memory Impairment	0 (0.0)	1 (2.0)	1 (0.7)	0	0	1 (1.5)
Anxiety	0 (0.0)	1 (2.0)	0 (0.0)	0	0	1 (1.5)
Vertigo	0	0	1 (0.7)	0	1 (4.5)	0
SKIN & APPENDAGES	3 (1.9)	1 (2.0)	2 (1.3)	1 (1.9)	1 (4.5)	3 (4.5)
Pruritus	1 (0.6)	1 (2.0)	1 (0.7)	1 (1.9)	1 (4.5)	2 (3.0)
SPECIAL SENSES	3 (1.9)	5 (10.0)	23 (15.4)	3 (5.7)	1 (4.5)	6 (9.1)
Unpleasant taste	1 (0.6)	5 (10.0)	22 (14.8)	0	1 (4.5)	4 (6.1)

TEAE=treatment emergent adverse event; ESZ=eszopiclone.
Note: Includes Studies 190-047 and 190-048.
Note: Treatment emergent adverse events include those events that occurred or worsened upon or after administration of the first dose of double-blind study medication. Subjects were counted only once within each body system and each preferred term.
Note: Potentially related TEAEs include those events with a definite, possible, probable, or unknown relationship to study drug.
Reference: Module 5.3.5.3 Table 4.2.2

In general, the AE profile in the very elderly (≥75 years) is similar to the elderly (<75 years). Headache, asthenia, somnolence, and unpleasant taste were most prevalent. Asthenia (fatigue) was higher for the ≥75 years-old group, while unpleasant taste was somewhat lower, both expected changes in the very elderly. The sample of included patients had no comorbidities at the moment of inclusion.

By Gender

There were somewhat higher incidences of females reporting at least one potentially related TEAE (Studies 190-047 and 190-048: 27.9% placebo and 36.8% Lunivia overall; Studies 190-049 and 190-050: 39.8% placebo and 61.2% Lunivia overall) as compared with males (Studies 190-047 and 190-048: 20.6% placebo and 22.4% Lunivia overall; Studies 190-049 and 190-050: 28.7% placebo and 45.1% Lunivia overall). However, there were no clinically relevant differences in the distribution of adverse events between males and females. (Module 5.3.5.3 Table 4.2.3)

By Race

Due to small treatment group sizes in the Asian and Other race categories, only adverse events for the Caucasian, Black, and Hispanic race categories were examined for the subjects with insomnia/nighttime-dosing in the pooled long-term (6-month double-blind) studies in non-elderly adults (Studies 190-049 and 190-050). The incidences of potentially related TEAE and the distribution of adverse events were similar across the racial categories. Additionally, Study 190-003 showed no clinically relevant differences in safety profiles between Japanese subjects compared with Caucasian subjects following 7 days of dosing. No conclusions regarding racial subgroups could be reached for the elderly subjects with insomnia/nighttime-dosing in the pooled chronic-dosing (2 weeks) studies (Studies 190-047 and 190-048) due to extremely low subject numbers in all of the race categories, except Caucasians.

By BMI
The potentially related TEAE incidences and the distribution of adverse events were similar across the BMI subgroups for both study types.
This is supported by the pharmacokinetic analysis of demographic factors, demonstrating no difference in Cmax or AUC based on body weight.

In summary, there were no apparent differences in adverse event profiles when considering age, gender, race, and BMI.

- Serious adverse event/deaths/other significant events

In total, 18 placebo-treated subjects and 30 Lunivia-treated subjects experienced serious adverse events (SAEs). This includes the double-blind period of the long-term safety studies 190-049 and 190-050. Of these 48 subjects, four experienced serious adverse events in the nighttime, 2-week studies in elderly subjects with insomnia (Studies 190-047 and 190-048), where the incidence was similar between the placebo group (1.0%; 2/208) and the Lunivia group (0.7%; 2/277). During the two night-time 6 month double-blind studies, 190-049 and 190-050, similar rates of SAEs were observed with 24 subjects (2.1%) treated with Lunivia 3 mg experiencing 25 SAEs and 10 subjects (2.1%) treated with placebo experiencing 10 SAEs. The most common serious adverse events were accidental injury, chest pain, and gastrointestinal disorder, each observed in 0.3% of Lunivia subjects.
Only accidental injury had an event rate greater than the placebo event rate. The incidence of SAEs observed in the 8 week studies in subjects with MDD or GAD were similar for the Lunivia group (7 subjects, 1.2%) and the placebo group (8 subjects, 1.4%). Finally one Lunivia subject with hepatic impairment in study 190-013 reported an SAE of gastroenteritis and one placebo subject in study 190-054 reported bladder carcinoma.

No deaths occurred in subjects who received Lunivia during any of the clinical trials. Two subjects died during the screening phase of a protocol, prior to treatment with any study medication. The first death occurred during Study 190-048; a 78-year-old male suffered a fatal myocardial infarction while swimming. The second death occurred in Study 190-049; a 41-year-old female with no contributory medical history or medication use experienced sudden death. Her death was thought to be related to a myocardial infarction, but this was not confirmed.

Because of the pharmacologic class, additional adverse events of parasomnia, hallucinations, worsening of depression, overdose, suicide, amnesia, accidental injury and convulsions were evaluated more in depth.
A low incidence of parasomnia was observed in the 6 month long-term studies in both Lunivia 3 mg (0.4%) and placebo subjects (0.2%), as well as in Lunivia subjects with MDD or GAD studies (0.4% Lunivia; 0% placebo). Parasomnia was not observed in any other study.
Hallucinations were reported in 15 subjects (0.8%; 15/1839). Daytime hallucinations were observed only in subjects taking supratherapeutic doses. Reports of hallucinations at recommended doses were typically similar to a migraine aura or hypnogogic visual hallucinations (occurring at the time of sleep onset) or sleep-onset dreaming.
There were no occurrences of potentially related treatment emergent accidental overdose, intentional overdose or suicide attempt reported. Regarding depression, a slightly higher incidence of placebo subjects (1.0%) reported depression compared to Lunivia 3 mg subjects (0.5%) in the MDD/GAD

studies. In other pooled studies, the incidence of depression was 1.5% (28/1836) with the highest rate occurring in the long-term studies.
The incidence of accidental injury ranged from 0% to 1.5% for placebo subjects compared to the range of 0% to 0.8% for Lunivia subjects.
There were no reports of convulsion in any of the studies.

- Laboratory findings

Most of the subjects in each population group who were normal at baseline remained in the normal range at the end of the study for haematology, serum chemistry, and urinalysis parameters. For the parameters with shifts, there were minor differences in rates between placebo and Lunivia. There was no evidence of a clinically meaningful drug effect on any parameter.
There were a few incidences of potentially clinically significant (PCS) elevated liver enzymes, specifically AST and ALT. The majority of these were isolated high values that did not persist despite continued dosing or were noted on the last day of dosing, or corresponded to small changes in subjects with elevated AST or ALT at baseline. Only one subject had an ALT/AST value that exceeded 1000 U/L (Study 190-049, open label period). It was determined that this subject had underlying Hepatitis B infection. A few subjects had PCS low platelet values. All but one were isolated values suggestive of laboratory error or clotted samples. One occurrence (Study 190-048) was noted in an elderly subject with a baseline platelet count of 291,000/mm3, and a platelet count of 15,000/mm3 recorded two days after the last dose of Lunivia 2 mg. She experienced adverse events suggestive of a viral infection (fatigue, headache, rhinitis, dizziness, and shortness of breath) just prior to the low platelet count, all of which were reported as mild and resolved without treatment.
There were occasional occurrences of PCS low white blood counts (WBC). The majority of these were isolated high values that did not persist despite continued dosing or corresponded to small changes in subjects with low WBC counts at baseline. One subject (Study 190-049) entered the study with a WBC count of 4.24 103/mm3 that decreased to 1.54 one month after the start of dosing, without an associated adverse event. She was discontinued from the study due to this neutropenia. Three weeks after the last dose of Lunivia 3 mg the WBC count had increased to 2.66 103/mm3 and remained in that range 5 weeks later at her last visit

Vital Signs, Postural Blood Pressure and ECG Monitoring
There was no evidence of a clinical meaningful drug effect on vital signs (i.e. heart rate, blood pressure, respiration rate or body temperature), postural blood pressure or electrocardiograms.
There were a few, isolated episodes of orthostatic hypotension, all asymptomatic, in adult subjects at doses up to 7.5 mg, with no dose response observed. There were a few episodes in elderly subjects at doses of 1 and 2 mg, with slightly higher rates at 3 and 5 mg. The 3 and 5 mg doses represent dose increases of 1.5- to 2.5-fold greater than the recommended doses in the elderly. Most events were isolated instances, and only two events were associated with dizziness.
Approximately 4300 ECGs were collected during the double-blind period of Study 190-049, subjects with insomnia/nighttime-dosing in the long-term (6-month double-blind) study in non-elderly adults
There were similar rates of abnormal ECG parameters between treatment groups at each month and no increases in rates of abnormalities over time.
The greatest treatment difference was for conduction abnormalities at Month 6 (placebo, 8.0%; Lunivia 3 mg, 4.8%). The greatest treatment difference where the Lunivia 3 mg incidence was higher than the placebo incidence was for conduction abnormalities at Month 2 (placebo, 3.2%; Lunivia 3 mg, 5.9%). This result appears to be due to variability as this imbalance between groups was reversed at other months, such as at Month 6 and the last on-treatment visit (placebo, 8.3%; Lunivia 3 mg, 6.2%). The most common conduction abnormalities at Month 2 in the Lunivia 3 mg group were first degree block and left anterior hemiblock; note that many of these subjects had identical abnormalities at baseline.

- Safety in special populations

Renal Insufficiency
Lunivia was generally safe and well tolerated in subjects with impaired renal function. No subject in any renal function group died or had an AE that caused discontinuation. There were no treatment-emergent SAEs or severe AEs reported in any group. Somnolence and unpleasant taste were the most frequently reported AEs for the normal, moderate, and severe renal function groups. Somnolence was the most frequently reported AE for the mild renal function group. Somnolence was expected and consistent with the pharmacology of the drug administered during the daytime.
Unpleasant taste was expected from previous experience with Lunivia. Treatment with Lunivia was not associated with any clinically important changes in vital sign, laboratory, or electrocardiogram parameters.

Hepatic Insufficiency
The safety profile of Lunivia in subjects with hepatic impairment was similar to that for subjects with normal hepatic function. There were no deaths or adverse events leading to discontinuation following Lunivia treatment. One serious adverse event occurred, which was considered unrelated to study medication. The most common potentially related adverse events were somnolence, unpleasant taste, and memory impairment. Somnolence was expected based on the pharmacology of Lunivia and daytime administration of the drug. Unpleasant taste was also expected from previous experience with Lunivia. All episodes of memory impairment were short-term, resolved without treatment, and did not result in the withdrawal of any subject.
No clinically significant changes in any laboratory, vital sign, ECG, or physical examination parameter resulted from Lunivia use. Further, examination of the incidence of hepatobiliary adverse events and hepatic function test results suggested no additional safety concerns regarding the use of Lunivia in patients with hepatic impairment.

Studies in Subjects with Co-morbid Diseases
There was no evidence of negative effect of Lunivia 3 mg on the background diseases studied.

- Safety related to drug-drug interactions and other interactions

The applicant has conducted several studies to evaluate the interaction of Lunivia with different substances. They are discussed in the section *Pharmacokinetic interaction studies* above in the report.
Of particular interest was study 190-015, conducted to assess the effect of the interaction of Lunivia with alcohol (ethanol), that demonstrated a psychomotor performance impairment following co-administration of Lunivia and alcohol that was approximately additive. Co-administration with lorazepam and ketoconazole produced changes to PK parameters of Lunivia that however did not affect the adverse event profile, neither clinically or with regard to laboratory measures.

- Withdrawal, Rebound and other relevant safety studies

This section presents discontinuation effects that were evaluated through an examination of new withdrawal adverse events following discontinuation of study treatment and rebound insomnia analyses following both short-term and long-term treatment.

Withdrawal- and Rebound-Associated Post-treatment AEs
For the chronic-dosing (4-8 weeks) studies, there were similar overall incidences of withdrawal AEs (12.8%, 8.2%, and 13.7% of placebo, 2 mg Lunivia, and 3 mg Lunivia subjects, respectively). With respect to events that are recognized to occur in association with termination of a benzodiazepine, there were few reports of anxiety (0.1%, 2.1%, and 0.3%), and insomnia (0.1%, 0%, 0.3%), and no reports of convulsions, hallucinations, or perceptual disturbances. A higher incidence of nausea (0.6%, 2.1%, and 0.4%) was observed in at least one Lunivia dose group compared with the placebo group, although this was not consistent across dose groups. These trends are not clinically different from that observed duringdouble-blind treatment.

Study 190-050 included a single-blind wash-out phase after 6 months of long-term double-blind dosing with Lunivia 3 mg.
Longer-term treatment (6 months) did not result in higher overall rates of withdrawal adverse events compared to placebo (14.8% and 13.4% of placebo- and 3 mg Lunivia-treated subjects). Similar to the data following short-term administration, there were few reports of insomnia (0% and 0.6% for placebo and 3 mg Lunivia, respectively), and no reports of anxiety, convulsions, hallucinations, or perceptual disturbances. Report of pain including back pain, chest pain, and abdominal pain were more frequent following Lunivia use, however, this is similar to that observed during the active-treatment phase of the study. In comparison to shorter-term withdrawal effects, long-term Lunivia treatment did not increase the prevalence of any withdrawal adverse event commonly associated with termination of a sedative hypnotic.

Benzodiazepine Withdrawal Symptom Questionnaire
The Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ) was collected from subjects at the end-of-study visit in Study 190-050. The BWSQ is a subjective assessment of symptoms the subject may be experiencing after discontinuing study medication. There was no significant difference (p=0.1167) between the Lunivia 3 mg group (2.96) and the placebo group (2.26) for the total score outcome of the BWSQ.

Rebound insomnia
Rebound insomnia has been defined as the exaggerated expression of the original condition sometimes experienced by subjects following immediate cessation of an effective treatment. For purposes of these analyses, the applicant has defined rebound insomnia as a dose-dependent temporary worsening in sleep parameters compared with baseline following discontinuation of treatment.
Occurrence of rebound effects was assessed by objective parameters from polysomnography in study 190-046 (44 days duration) and by subjective parameters in study 190-050 (26 weeks duration). The data collected suggested that rebound insomnia is mostly limited to the first night. The data available covers both short-term and long term use of Lunivia. Given the PK characteristics and the known pharmacology of Lunivia it is unlikely that withdrawal and rebound will manifest after the 2 weeks that were studied in this clinical program. Further discussion on tolerance and rebound insomnia is presented in the discussion on clinical Safety.

Abuse potential
Abuse potential was evaluated with a study (190-016) conducted in patients with a history of benzodiazepines abuse and which included diazepam as active control. The results of the trial did not raise a particular concern but they were not fully conclusive either. Particularly because the active control, diazepam, could not be fully discriminated from placebo. These studies in known abusers are prone to this type of results since the endpoints are highly subjective and the numbers tested small.
The CHMP considered that post-marketing data will usefully complete the assessment of the abuse potential.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability
Lunivia 3 mg did not impair healthy volunteers' ability to function on a variety of tasks related to everyday life, including the skilled task of on-the-road driving (Brake Reaction Time) ability. Study 190-060, conducted in subjects with primary insomnia, demonstrated that nighttime administration of Lunivia 3 mg improved next-morning subjective ratings of sleep quality and ease of getting to sleep in patients. Furthermore, while sleep appeared to be improved, there were no residual impairing effects on car-driving ability or cognitive and psychomotor performance the next day.

Adverse Events of Drowsiness Reported in the Pooled Studies
For the pooled studies with nighttime administration, potentially related treatment emergent somnolence was reported in 7 study types. The incidence of somnolence in each Lunivia group was similar to or lower than the incidence in the placebo group for the following study types:
• Healthy volunteers in the short-term (1-7 days) studies (3.6% *versus* 4.3%, 5.5%, 3.6%, and 2.1% for placebo and Lunivia 1 mg, 2 mg, 3 mg, and ≥3.5 mg, respectively);
• Healthy volunteers in the chronic-dosing (12 weeks) study (2.1% *versus* 0% for placebo and Lunivia 3 mg, respectively);

• Subjects with insomnia in the chronic-dosing (2 weeks) studies in elderly subjects (6.3% *versus* 6.9% and 5.6% for placebo and Lunivia 1 mg and 2 mg, respectively);

The incidence of somnolence in at least one Lunivia group was somewhat higher than the incidence in the placebo group for the following study types:
• Subjects with insomnia in the short-term (1-7 days) studies in non-elderly adults (3.9% for placebo *versus* 3.2%, 2.7%, 3.1%, and 7.9% for Lunivia 1 mg, 2 mg, 2.5 mg, and 3 mg, respectively);
• Subjects with insomnia in the chronic-dosing (4-6 weeks) studies in non-elderly adults (1.3% *versus* 8.7% for placebo and Lunivia 3 mg, respectively);
• Subjects with insomnia in the chronic-dosing (8 weeks) studies coadministered with an SSRI (non-elderly adults with insomnia and in comorbid MDD/GAD) (8.6% *versus* 11.0% for placebo and Lunivia 3 mg, respectively);
• Subjects with insomnia in the long-term (6-month double-blind) studies in non-elderly adults (2.9% *versus* 8.3% for placebo and Lunivia 3 mg, respectively);

The data collected concerning detrimental effects in the ability to perform are reassuring as they support the notion that that ability is minimal affected by the use of Lunivia at nighttime. However there are some instances where a reduction of ability or excessive somnolence was noted. Therefore, appropriate warnings will be included in the SPC.

- Discontinuation due to adverse events

In the nighttime 4-6 week studies in non-elderly adult subjects with insomnia (Studies 190- 046 and 190-054), there were slightly higher rates of subjects who discontinued due to adverse events in the Lunivia groups (2.3% Lunivia 3 mg; 1.9% Lunivia 2 mg) compared to the placebo group (0.7%). The incidence of subjects discontinuing due to individual adverse events was less than 1% for each event with the exception of headache, in the Lunivia 2 mg group. However, no one discontinued due to headache in the Lunivia 3 mg group.
In the nighttime, 2-week studies in elderly subjects with insomnia (Studies 190-047 and 190- 048), the incidence of subjects who discontinued due to an AE was slightly lower in the Lunivia group (1.4% for Lunivia 2 mg and 2.3% for Lunivia 3 mg) than in the placebo group (3.8%).
In the nighttime, 6-month double-blind studies in non-elderly adult subjects with insomnia (Study 190-049 and Study 190-050), there were slightly higher rates of subjects who discontinued due to adverse events in the Lunivia group (11.1%) than in the placebo group (7.6%). The most common reason for discontinuation in the Lunivia group was somnolence (2.0%) followed by unpleasant taste (1.2%) and depression (1.1%). During the open-label phase of Study 190-049, 18 subjects (3.8%) discontinued due to adverse events.
Of these subjects, 7 previously received double-blind placebo treatment and 11 previously received double-blind Lunivia.
In studies 190-052 and 190-902 in MDD or GAD patients co-administered an SSRI, slightly lower rates of subjects who discontinued were observed in the Lunivia group (5.7%) compared to the placebo group (6.1%). There was no increased incidence of discontinuation due to treatment emergent depression or anxiety in the Lunivia group relative to the placebo group.
In Study 190-055 in rheumatoid arthritis patients, there was a lower rate of discontinuation in the Lunivia group (1.3%) compared to placebo (3.9%).
In general, adverse events leading to discontinuation did not raise any safety concerns

- Post marketing experience

The overall post-market safety profile of Lunivia, marketed in the U.S. under the trade name of Lunesta, has demonstrated the following.
• Based on prescription sales data, post-marketing experience with Lunivia exceeds 900,000 person years of patient exposure.
• The safety profile has been very consistent with that identified during the clinical development programme and described in the proposed Summary of Product Characteristics.

• The most frequently reported serious adverse events have been overdoses of Lunivia with no fatal overdoses of Lunivia alone. Overdose of Lunivia up to 270 mg has been reported with no long-term sequelae. Fatal overdoses of Lunivia involved overdose with other medications taken concomitantly.
• Reports suggesting tolerance to Lunivia remain low and appear in part to be related to concomitant psychiatric disease.
• Reports of diversion, abuse, or dependence have remained very low.
• There are no new or emerging safety risks evident in these data.

Table 2.7.4.6.2-1: All Lunesta Post-Marketing Adverse Reactions Reported in ≥1% of Cases as of 14 March 2007 (MedDRA coding)

System Organ Class/ Preferred Event Term	No. of Events	% of Events	% of Cases
Gastrointestinal Disorders	**860**	**5.35**	**8.29**
Nausea	245	1.52	3.15
Dry mouth	99	0.62	1.28
General Disorders and Administration Site Conditions	**4097**	**25.50**	**49.34**
Drug ineffective	3177	19.77	41.05
Paradoxical drug reaction	175	1.09	2.26
Drug effect decreased	164	1.02	2.12
Fatigue	96	0.60	1.24
Nervous System Disorders	**4566**	**28.42**	**52.24**
Dysgeusia	3207	19.96	41.42
Somnolence	370	2.3	4.78
Headache	332	2.07	4.29
Dizziness	210	1.31	2.70
Psychiatric Disorders	**5214**	**32.45**	**59.55**
Insomnia	2538	15.80	32.78
Middle insomnia	938	5.84	12.13
Initial insomnia	703	4.38	9.08
Nightmare	117	0.73	1.51
Anxiety	93	0.58	1.20
Abnormal dreams	88	0.55	1.14
Hallucination	82	0.51	1.06
Depression	79	0.49	1.02
Total	**16068**	**100.00**	**100.00**

Reference: Section 2.7.4.7.2 Table A4

The majority of serious adverse events received in post-marketing reports have involved intentional overdoses of Lunivia, often in association with multiple other drugs in a suicide attempt.

- Discussion on clinical safety

The CHMP was concerned that safety of Lunivia for long term treatment of insomnia had not been sufficiently evaluated and was of concern particularly the potential for the development of dependence, tolerance, rebound insomnia, and withdrawal effects. These phenomena are likely to develop with long term use. The applicant was therefore requested to provide detailed justification for the grounds for long-term use.
The applicant referred to the fact that in a sub-set of patients insomnia, either primary or secondary, is a chronic condition requiring more than a few days or weeks treatment and that it carries with it various co-morbidities. Current guidelines for use of hypnotics in the European Union limit the treatment duration of hypnotics to a maximum of four weeks. In the absence of appropriate guidelines for long-term use, prescribers must either discontinue treatment or recommend longer treatment off-label and without sufficient data upon which to assess continued risk/benefit. The company argued that the clinical studies conducted in the development of Lunivia constitute an important advance in the knowledge of the benefits and risks of the product over a time frame extending up to 12 months. Further justification was provided by the applicant with regard to the risk of dependence, the post-marketing experience and the proposed mitigation of the risk of dependence as detailed below,

Risks of Dependence and Duration of Treatment
Tolerance was evaluated by the examination of group and individual data in studies of up to 12 months treatment duration.

- Tolerance was not apparent in any of the sleep parameters for up to 12 months treatment duration.

Withdrawal was evaluated utilizing the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ; in Study 190-050) and the observation of new or worsening adverse events following abrupt discontinuation of treatment in six studies ranging from 4 weeks to 6 months of double blind treatment.

- The total score for the BWSQ was very low and not significantly different when comparing Lunivia (2.96 ± 4.46) and placebo (2.26 ± 3.58) subjects.
- The overall incidence of adverse events observed in either Lunivia or placebo treatment groups following discontinuation of treatment ranged from 10% to 20% in any study.
- The incidence of withdrawal adverse events following Lunivia treatment was not different from placebo.
- Treatment duration from 4 weeks to 6 months did not affect the incidence of withdrawal adverse events.

Rebound insomnia was extensively evaluated to characterise the type of rebound insomnia (e.g. rebound in sleep latency), the incidence of rebound insomnia, when rebound occurs and the impact of duration of treatment on rebound.

- Only 4 out of 1,123 (0.4%) adult subjects evaluated reported experiencing a new occurrence of insomnia during the single blind washout period following abrupt discontinuation of double-blind treatment and independence of treatment duration.
- Rebound insomnia occurs as a worsening of sleep latency, not sleep maintenance.
- Rebound typically occurs on the first or second night following discontinuation of treatment.
- 31-38% of Lunivia subjects experienced rebound insomnia in the form of a worsening of sleep latency beyond baseline values on Night 1 of the discontinuation period compared with 12-18% of placebo subjects. Only 11-16% of Lunivia subjects experienced rebound insomnia on Nights 1 and 2 compared with 4-5% of placebo subjects.
- For those patients who did experience rebound insomnia, resolution typically occurred within one to two nights without intervention. A small number of patients experienced long-lasting rebound which could be interpreted as relapse of their chronic disease.
- Duration of treatment (i.e. 6 months compared to 6 weeks) did not increase the incidence of subjects experiencing rebound insomnia following discontinuation of Lunivia.

Post Marketing Experience
In the US where Lunivia is authorised without a treatment duration recommendation patient usage data based on 1.39 million person-years exposure indicate the following.

- The average duration of Lunivia use is 82 days and the majority of patients discontinue use after 2 months.
- At the end of 12 months, only 7.4% of patients prescribed Lunesta remain on the drug.
- Only 17 cases [0.18% of total cases] of tolerance have been reported. Eighteen cases (0.19%) of withdrawal syndrome have been reported and 31 cases of rebound effect (0.33%). Similarly, reports of dependence have been very low (10 cases; 0.11%).

Proposals for the Mitigation of the Risk of Dependence
The Applicant proposes that for the subset of patients having chronic insomnia for which long-term treatment with a hypnotic may be warranted, the risks of dependence associated with Lunivia can be communicated and mitigated through the following points:

- The Applicant seeks to work with the CHMP to provide additional discussion of the risks of long-term use in Sections 4.2 (Posology and method of administration) and Section 4.4 (Special warnings and precautions for use) of the SPC.
- The Applicant proposes to conduct enhanced post marketing surveillance, the form of which can be further discussed and agreed with CHMP.
-
- The Applicant will also make available smaller pack sizes of 10, 15 or 20 tablet count in addition to the 30 counts pack size to account for both short term and longer term use.

The Applicant's contention that a sub-set of patients suffering from insomnia may need long term pharmacological treatment is considered founded. The clinical trial database gives relevant information for the use of Lunivia for up to 12 months. This is however due to the fact the applicant has conducted long term studies, despite regulatory constraint, than to any intrinsic safety or efficacy advantage over equivalent agents

2.5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan.

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimization activities (routine and additional)**
Rebound insomnia	• Routine pharmacovigilance activities	• Rebound Insomnia is described in section 4.4 the SPC: "*Rebound Insomnia*: Rebound insomnia manifested as an increase in sleep latency for one to two nights has been observed following cessation of LUNIVIA treatment. These events resolved without intervention. It is important that patients be aware of the possibility of rebound phenomena, thereby minimizing anxiety should such symptoms develop when the medicinal product in discontinued."
Depression/ Worsening of depression	• Routine pharmacovigilance activities • Study 190-062	• Under section 4.4 of the SPC, Special warnings and precautions for use; "*Depression*: Benzodiazepines and benzodiazepine-like agents, such as LUNIVIA, are not to be used alone to treat patients with depression or anxiety associated with depression (suicide may be precipitated in such patients). Since these disorders may be associated with suicidal tendencies, the least feasible amount of

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		LUNIVIA is to be supplied to these patients because of the possibility of intentional overdose (see section 5.1.)" • Under section 4.8 of the SPC (section 2 and 4 in PL), Undesirable effects
Anxiety	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Nightmare	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Insomnia	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Agitation	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Hallucination	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Bradyphrenia	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Confusional state	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Emotional distress	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Euphoric mood	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Panic reaction	• Routine pharmacovigilance activities	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;
Paradoxical reaction	• Routine and enhanced pharmacovigilance activities • Subject of TMEs	• Under section 4.8 of the SPC (section 4 in PL), Undesirable effects;

Overdose	• Routine and enhanced pharmacovigilance activities • Subject of TMEs • Trending and analysis of this issue in the PSUR	• Under section 4.9 of the SPC; "*Overdose*; Overdose is most likely to present as central nervous system depression ranging from drowsiness to coma depending on the quantity ingested. Symptomatic and supportive treatment is indicated in a suitable clinical environment. Particular attention should be paid to cardiovascular and respiratory functions. Gastric lavage is useful only when performed soon after ingestion. Although not evaluated, haemodialysis is not expected to be of value due to the large volume of distribution of eszopiclone. Flumazenil may be a useful antidote." In clinical trials with eszopiclone, one case of overdose with up to 36 mg of eszopiclone was reported in which the subject fully recovered. Since commercial marketing began in foreign markets, spontaneous cases of overdose up to 270 mg have been reported. Fatal overdose is more likely to occur when eszopiclone is taken in combination with other CNS depressants including alcohol. Subjects have recovered from overdose with up to 270 mg of eszopiclone alone." Under section 4.2 of the SPC: "In all cases, the length of treatment should be for the minimum duration necessary for effective treatment. Pack sizes are available for different durations of treatment (see section 6.5).", and under section 6.5 of the SPC.
Suicide	• Routine and enhanced pharmacovigilance activities • Trending and analysis of this issue in the PSUR • Subject to TMEs	• Under section 4.4 of the SPC, Special warnings and precautions for use; "*Depression:* Benzodiazepines and benzodiazepine-like agents are not to be used alone to treat patients with depression or anxiety associated with depression (suicide may be precipitated in such patients). Since these disorders may be associated with suicidal tendencies, the least feasible amount of LUNIVIA is to be supplied to these patients because of the possibility of intentional overdose (see section 5.1)." • Under section 2 of PL

Diversion	• Routine and enhanced pharmacovigilance activities. • Diversion Risk Management Program • Subject of TMEs • Trending and analysis of this issue in the PSUR	While diversion is not specifically listed in the SPC, abuse and dependence are. • Under section 4.4. Special warnings and precautions of use; "Risk of dependence": "Use of benzodiazepines and benzodiazepine-like substances (even at therapeutic doses) may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment, and is greater in patients with a history of alcohol and/or drug abuse or those with marked personality disorders. The decision to use any hypnotic agent in such patients should be taken only with this clearly in mind."
Dependence	• Routine and enhanced pharmacovigilance activities • Subject of TMEs • Trending and analysis of this issue in the PSUR • Modified PEMS	• Under section 4.4 of the SPC: "*Risk of Dependence*": "Use of benzodiazepines and benzodiazepine-like substances may lead to the development of physical and psychological dependence upon these products. The risk of dependence increases with dose and duration of treatment, and is greater in patients with a history of alcohol and/or drug abuse or those with marked personality disorders. If physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms which may include headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures." • Under section 4.4 of the SPC: "Patients requiring extended treatment (see section 4.2) are to be regularly monitored and evaluated for potential signs of dependence (e.g. taking the medication in larger amounts or over a longer period than was intended, a persistent desire or unsuccessful efforts to cut down or control medication use) and managed according to clinical need." • Under section 4.2 of the SPC: "In all cases, the length of treatment should be for the minimum duration necessary for effective treatment. Pack sizes are available for different durations of treatment (see section 6.5).", and under section 6.5 of the SPC. • Under section 2 and 3 of PL

Convulsions	• Routine and enhanced pharmacovigilance activities • Subject of TMEs • Trending and analysis of this issue in the PSUR	• Under section 4.4. Special warnings and precautions of use; "Risk of dependence: If physical dependence has developed, abrupt termination of treatment will be accompanied by withdrawal symptoms which may include headaches, muscle pain, extreme anxiety, tension, restlessness, confusion and irritability. In severe cases the following symptoms may occur: derealisation, depersonalisation, hyperacusis, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact, hallucinations or epileptic seizures."
Memory impairment	• Routine pharmacovigilance activities • Subject of TMEs • Trending and analysis of this issue in the PSUR	• Under section 4.4. Special warnings and precautions of use; "Memory and psychomotor impairment: Benzodiazepines or benzodiazepine-like agents may induce anterograde amnesia and psychomotor impairment. The condition occurs most often several hours after ingesting the product and therefore patients are to ensure they will have a sleep period of 7-8 hours (see section 4.7)." • Under section 4.8 of the SPC (sections 2 and 4 in PL), Undesirable effects
Parasomnias	• Routine and enhanced pharmacovigilance activities • Subject of TMEs	• Under section 4.4. Special warnings and precautions of use; "Psychiatric and "paradoxical" reactions: restlessness, nightmares, parasomnias," • Under section 4.8 of the SPC (sections 2 and 4 in PL), Undesirable effects
Respiratory compromise	• Routine and enhanced pharmacovigilance activities • Subject of TMEs • Trending and analysis of this issue in the PSUR	• Under section 4.3 of the SPC (section 2 in PL) contraindications: "respiratory failure"
Psychomotor performance -falls	• Routine and enhanced pharmacovigilance activities • Subject of TMEs • Trending and analysis of this issue in the PSUR	• Under section 4.8 of the SPC, undesirable effects – incoordination

Psychomotor performance – motor vehicle accidents	• Routine and enhanced pharmacovigilance activities • Subject of TMEs • Trending and analysis of this issue in the PSUR	• Under section 4.7 of the SPC: "LUNIVIA has a moderate influence on the ability to drive and use machines, for several hours following administration. Sedation, amnesia, eye disorders, impaired concentration and impaired muscular function may adversely affect the ability to drive or to use machines. If insufficient sleep duration occurs, the likelihood of impaired alertness may be increased. Patients are to be advised not to drive or operate machinery if they experience any of these effects the day after treatment with LUNIVIA." • Under section 2 in PL
• Exposure during pregnancy/ lactation	• Routine pharmacovigilance activities • Trending and analysis of this issue in PSURs	• Under Section 4.6 Pregnancy and lactation; "Pregnancy: Use of eszopiclone in pregnancy is not recommended. There are no adequate data from the use of eszopiclone in pregnant women. If the medicinal product is prescribed to a woman of child-bearing potential, she is to contact her physician if she intends to become or suspects that she is pregnant. Studies in animals have shown developmental toxicity at exposures considered sufficiently in excess of maximum human exposure (see section 5.3). The potential risk for humans is unknown. Breast-feeding: Use of eszopiclone in breast-feeding mothers is not recommended. It is not known whether eszopiclone is excreted in human breast milk. The excretion of eszopiclone in milk has not been studied in animals. However, animal and human studies did demonstrate transfer of racemic zopiclone into breast milk" • Under section 2 in PL
• Children	• Routine pharmacovigilance activities • Studies of pharmacokinetics, safety and efficacy in children with insomnia associated with ADHD are being planned to support paediatric development in accordance with a Written Request issued by the U.S. FDA. • Trending and analysis of this issue in PSURs	• Under section 4.2 Posology and method of administration; "Children and adolescents: LUNIVIA is not recommended for use in children and adolescents due to a lack of data on safety and efficacy." • Under section 2 in PL

• Elderly.	• Routine pharmacovigilance activities • Study 190-904	• Under section 4.2 Posology and method of administration; "Elderly: The recommended dose in elderly patients aged 65 or older is 2 mg immediately before bed time." • Under section 5.2 Pharmacokinetic properties; "Special Populations: "Age: compared with non-elderly adults, subjects 65 years and older had an increase of 41% in exposure (AUC) and a slightly prolonged elimination of eszopiclone (t1/2 approximately 9 hours). Cmax was unchanged. Therefore, in elderly patients the dose of LUNIVIA should not exceed 2 mg."
• Racial and ethnic subgroups - Asian	• Routine pharmacovigilance activities • Study 190-101 • Further studies in Japanese subjects	• Under section 5.2 Pharmacokinetic properties; "Special Populations: "Race: The pharmacokinetics for all races studied appear similar."

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product Lunivia is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The mechanism of action of eszopiclone has been appropriately studied in dedicated studies addressing zopiclone and R-zopiclone as well as the active metabolite (S)-DMZ. The S-isomer (eszopiclone) presents higher affinity either to the receptor or to the ion channel as compared to the racemate or to the R-enantiomer.

Relevant effects on cardiovascular and respiratory functions were investigated and not identified for eszopiclone.

Pharmacokinetic characteristics were mainly extrapolated from zopiclone ADME profile, and showed that it is well absorbed in animals and humans, widely distributed and excreted almost totally within 96 hours. Fecal and renal excretion of metabolites and parent compound are the main routes, while negligible pulmonary excretion is observed.

The overall toxicology data indicate that eszopiclone, in the appropriate posology will not present higher risk in humans than the racemic zopiclone.

Efficacy

In adults, Lunivia 2 mg and 3 mg consistently produced statistically significant improvements in sleep induction and quality of sleep measures.

The derived differences between Lunivia and placebo for each endpoint for all efficacy studies

- in short-term primary insomnia trials for both adults (3 mg) and elderly (2 mg) were in sleep latency (SL) 19 minutes (range 15.8 – 28.5), in wake time after sleep onset (WASO) 10.9 minutes (range 7.5 - 15) and in total sleep time (TST) 43.8 minutes (range 37.5 – 62.5).
- in long-term primary insomnia studies in SL were 19.2 minutes (range 18 – 20.5), in WASO 12.3 minutes (range 11.4 – 13.2) and in TST 44 minutes (range 36.6 – 51.5).
- in co-morbid insomnia studies in SL were 13 minutes (range 10.5 – 17.5), in WASO 11 minutes (range 5.9 - 18) and in TST 38 minutes (range 17.3 - 45).

Overall the efficacy data presented by the applicant support the claimed indication, "LUNIVIA is indicated for the treatment of insomnia, including difficulty falling asleep, nocturnal awakening or early awakening, in adults, usually for short term duration."

Safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

The safety database for Lunivia includes thorough testing in controlled clinical trials that exceed the ICH minimum requirements.
The most common of AEs were unpleasant taste (dysgeusia). Other common adverse events include dizziness, somnolence, and dry mouth, consistent with the known pharmacology of non-benzodiazepines. Headache, dyspepsia, and pain including back pain, have also been frequently observed, however, the incidence of these have not been as notably different from placebo treatment groups in clinical trials.
Evaluation of central nervous system and other potentially related effects such as orthostatic hypotension and falls demonstrates that the likelihood of clinically meaningful increase in risk is low. However orthostatic hypotension might be seen as a problem rarely in particularly sensitive patients. An array of psychomotor performance evaluations were performed, including effects on driving ability, all of which show no clinically meaningful next-day effects.
Long-term use has been evaluated in two large controlled clinical trials and the safety profile, including risk of dependence, is not different from that observed with shorter-term use of Lunivia. Withdrawal effects have been examined following both short-term and long-term use. The data demonstrate a low frequency of potential withdrawal effects (e.g., anxiety and insomnia) following discontinuation of Lunivia after both short-term and long-term use. Analysis of aggregate data does not demonstrate the presence of rebound insomnia overall after short-term or long-term use. Examination of individual subject data demonstrates that when rebound insomnia does occur, it is mild and self-limited, lasting one to two nights. The post marketing data support these findings in the development plan.
There is no pattern of adverse events suggestive of increased abuse potential, and evaluation in a population of benzodiazepine-experienced subjects did not raise new concerns. However the data of this study was not completely conclusive because it failed to discriminate the active comparator from placebo. The pro-active monitoring of abuse potential is endorsed.

Clinical results in elderly patients were collected exclusively over short-term and in patients with no relevant co-morbidity at the time of inclusion.

In general the post marketing safety data confirm the safety profile established in the clinical development plan.
The CHMP concluded that the safety profile as described is acceptable for the approved indication.

3.7 New Active Substance status (NAS)

According to the Notice to Applicants Volume 2A, Chapter 1, annex III a New Active Substance (NAS) is defined as follows:

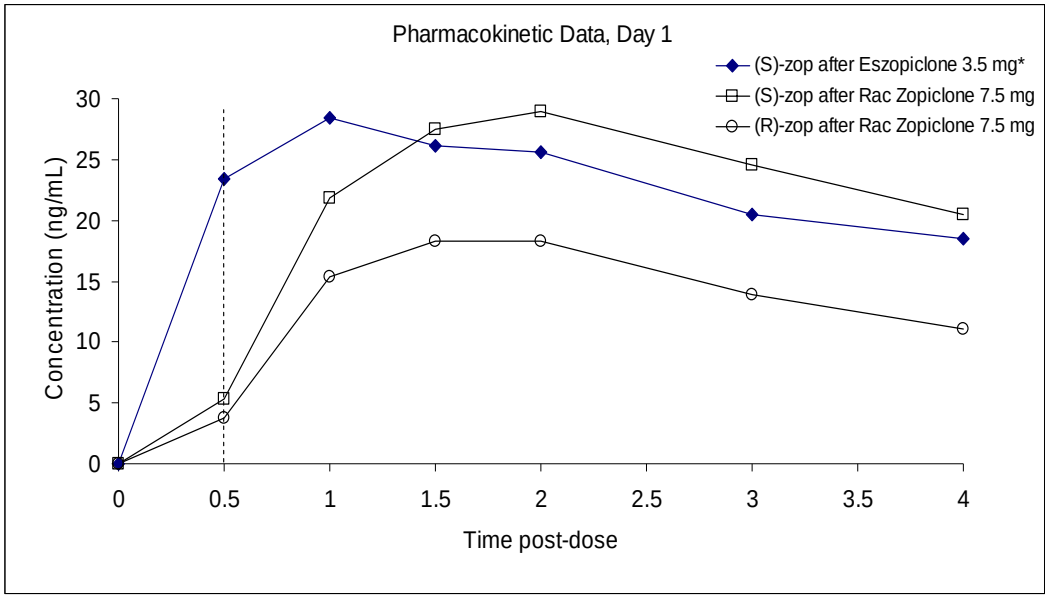
"……A new chemical, biological or radiopharmaceutical active substance includes: an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regard to safety and efficacy from that chemical substance previously authorised…"

The applicant claimed that eszopiclone should be regarded as a NAS as it was considered that meaningful differences have been demonstrated between the properties of eszopiclone and racemic zopiclone, including in comparative studies.

Pharmacokinetic
The applicant provided data from two head-to-head studies which evaluated the pharmacokinetics and tolerability of eszopiclone and racemic zopiclone. Study 190-001 evaluated single doses of eszopiclone oral solution (1 mg to 7.5 mg) and racemic zopiclone (2.5 mg to 7.5 mg) oral solution in a parallel group design, enrolling 6 patients per group.
Study 190-010 was a formal bioequivalence study, evaluating single and multiple doses of eszopiclone 3.5 mg oral solution and 3.5 mg tablet formulations and the commercially available racemic zopiclone (Imovane) 7.5 mg tablet formulation in a 3-sequence cross-over design, enrolling 18 subjects.

The data showed that eszopiclone is associated with a significant decrease in Tmax (1.0 hr) compared with the (S)-isomer of racemic zopiclone (1.5 hr) in Study 190-010.
Figure 1 shows the plasma concentrations of (S)-zopiclone and (R)-zopiclone following single dose (Day 1) administration of 3.5 mg eszopiclone and 7.5 mg zopiclone as measured in Study 190-010.

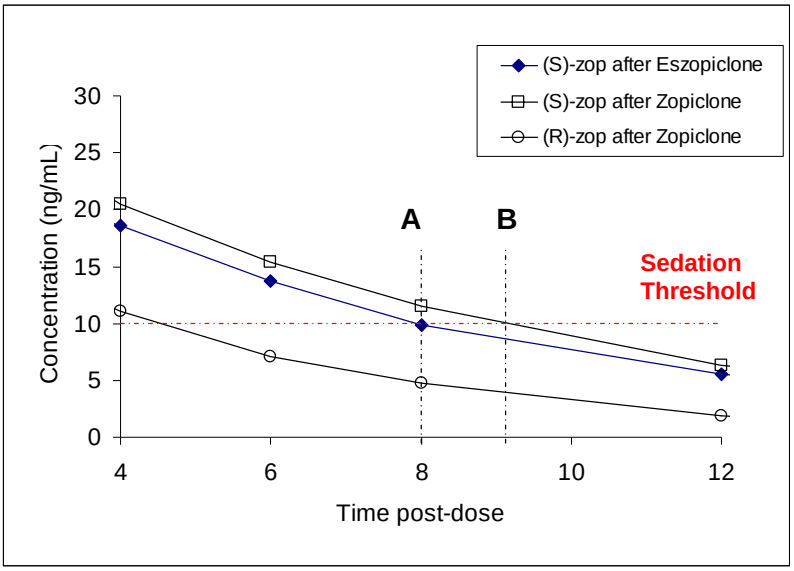
Figure 1 Mean (S)-Zopiclone and (R)-Zopiclone Plasma Concentrations by Time (0-4 hours) - Day 1



From these data, it emerged that the plasma concentration of (S)-zopiclone is approximately 4-fold greater at 30 minutes (p=0.0001) following administration of eszopiclone compared with racemic zopiclone.

Figure 2 shows the mean plasma concentrations of (S)-zopiclone following administration of eszopiclone and racemic zopiclone between 4 and 12 hours post-dose.

Figure 2 Mean (S)-Zopiclone Plasma Concentrations by Time (4-12 hours) - Day 1



*The values for eszopiclone tablet 3.5 mg in this figure are normalized to represent the equivalent administration of 3.75 mg eszopiclone. Actual values for the eszopiclone tablet were 7% lower.

Data from Study 194-026 suggested that when eszopiclone plasma levels are below 10 ng/ml, minimal hypnotic effects are observed on EEG and little cognitive impairment is observed. The point at which (S)-zopiclone plasma concentrations fall to 10 ng/ml is approximately 8 hours for 3.5 mg eszopiclone (Line A) compared to > 9 hours for 7.5 mg racemic zopiclone (Line B). This suggests that patients may be at a greater risk for residual effects for at least an hour longer in the morning following administration of racemic zopiclone as compared to eszopiclone.

Taste distortion

In study 190-010, utilizing a crossover, random sequence design, unpleasant taste was reported in 31% of subjects administered eszopiclone tablets and in 41% of subjects administered racemic zopiclone tablets. The severity of events was reduced following eszopiclone (1/5 subject reporting moderate severity) compared to racemic zopiclone (3/7 subjects reporting moderate severity).

Number of Subjects Reporting Unpleasant Taste following Administration of Eszopiclone 3.5 mg or Racemic Zopiclone 7.5 mg Tablets (Study 190-010)

	Eszopiclone 3.5 mg (N=16)	Zopiclone 7.5 mg (N=17)
Total	5 (31%)	7 (41%)
Mild	4	4
Moderate	1	3
Severe	0	0

Table 3.4 displays the incidence of subjects reporting unpleasant taste for comparative doses of (S)-zopiclone following administration of racemic zopiclone or eszopiclone. Most notably, the incidence of unpleasant taste is dose-related in the eszopiclone subjects, whereas all (100%) subjects at all doses of racemic zopiclone experienced bitter taste.

Table 3.4: Number of Subjects Reporting Unpleasant Taste following Administration of Eszopiclone or Racemic Zopiclone both in Oral Solution*(Study 190-001)

Dose of (S)-zopiclone (mg)	Racemic Zopiclone n/N (%)	Eszopiclone n/N (%)
1.0	--	0/6 (0)
1.25	6/6 (100%)	--
2.0	--	0/6 (0)
2.5	6/6 (100%)	3/6 (50%)
3.0	--	6/6 (100%)
3.75	6/6 (100%)	6/6 (100%)
5.0	--	6/6 (100%)
7.5	--	7/10 (70%)

Pharmacology at the GABA receptor
Based on the EC_{50} data (study 190-435), racemic zopiclone has its highest potency for α1 and α5 receptors with a potency at α1 that is similar to that of zolpidem. In contrast, eszopiclone has its highest potency at α5 and then α2 and α3 receptors, and is least potent at α1 (e.g. eszopiclone is 3.4 times less potent than zolpidem at α1). Based on the % maximal current data, racemic zopiclone has its maximal effectiveness at α1 and α5 receptors, whereas eszopiclone has its maximal effectiveness at α2 and α3 receptors.
GABA subunit α1 has been implicated in the development of psychological dependence. In particular, α1-selective agents zolpidem and zaleplon, have been demonstrated to be self-administered in non-human primates in a way that was greater than benzodiazepines and was in fact comparable to barbiturates. Further studies of these compounds suggest that α1 subunit changes are involved in the development of physical dependence and can be associated with the withdrawal syndrome. Conversely, α2-selective agents do not appear to lead to self-administration or withdrawal phenomena.

According to the applicant, and in relation to the data provided by the above studies, improvement in the benefit risk profile is therefore attributable to the following differences:
1. Fundamentally different pharmacology at $GABA_A$ receptor subtypes
2. Altered pharmacokinetics of eszopiclone compared with racemic zopiclone
3. Elimination of undesirable risks presented by the (R)-isomer impurity.

According to the applicant together these would lead to:
- improved pharmacological characteristics promoting physiological sleep rather than sedation;
- reduction in the administered dose of eszopiclone [3.0 mg] compared to racemic zopiclone [3.75 mg of the (S)-isomer];
- improved pharmacokinetics associated with the absence of the (R)-isomer
    - shorter latency [more than 30 min reduction compared with racemic zopiclone] to therapeutic plasma concentrations of eszopiclone and shorter Tmax;
    - reduction in the residual next day plasma concentrations of eszopiclone;
    - reduction in the amount and duration of exposure to (S)-desmethylzopiclone [(S)-DMZ], the active metabolite of eszopiclone.
- reduction in residual next day effects as evidenced by driving studies
- reduced incidence and severity of bitter taste and dry mouth; and
- demonstrated safety and effectiveness in the treatment of primary and co-morbid insomnia as evaluated in studies up to 12 months duration without tolerance or significant risk of dependence, which has not been demonstrated for racemic zopiclone.

The CHMP review of those studies comparing the pharmacodynamics and pharmacokinetics of eszopiclone and racemic zopiclone suggested that they are equivalent on a 1 to 2 mg dose ratio. There are no comparative studies of the therapeutic safety and efficacy of eszopiclone and racemic zopiclone.

More in detail, the CHMP argued as follows,

- **Pharmacokinetics** – there is reasonable evidence that the absorption curve of eszopiclone is shifted to the left by about thirty minutes with respect to the racemate and therefore the 'sleep threshold' would be reached earlier. However, the CHMP could not entirely agree upon this argument as the data supporting the evidence for a sleep threshold were not presented in any detail.
  For drug elimination, plasma concentrations of eszopiclone are about 20% lower at eight hours post dose with eszopiclone than with racemate (on a ~ 1:2 mg dosing basis). The CHMP disagreed that this could constitute an advantage with respect to unwanted next-day effects given that no actual data were presented. In fact, both the onset and offset arguments are based on small studies, the PK PD data presentation are sparse and the consequential clinical benefits are therefore theoretical.
- **Taste distortion** – the CHMP concluded that there are too few data from the head to head results to make an adequate analysis of the issue. It is possible that there is an advantage for eszopiclone but, if so, it was impossible to establish what its magnitude may be. The use of historical data for zopiclone as a comparator is not appropriate.
- **Pharmacology at the GABA receptor** – the CHMP concluded that even though the arguments deployed by the applicant were of considerable scientific interest, they did not comprise a discussion on the possible impact on clinical safety or efficacy benefit.

The lack of comparative data between eszopiclone and the racemate make the evaluation of relative clinical benefit of the former impossible. The best case which can be made is based on modest pharmacokinetic differences upon which are imputed with many assumptions, clinical benefits. In the circumstances it is not possible to consider that eszopiclone is a new active substance; it appears to be a modification of an old active substance. Despite eligibility was granted under Article 3 (2) (a) of Regulation (EC) No 726/2004, New Active Substance, following the scientific assessment the CHMP concluded that the Safety and Efficacy of eszopiclone did not differentiate from that of racemic zopiclone.

- User consultation

The user test consultation provided is satisfactory.

Risk-benefit assessment

The applicant has demonstrated in a series of well conducted clinical studies that Lunivia has a rapid onset of action, has an apparently linear dose response curve over the dose range tested, and has a relatively short plasma half life (in the region of six hours) leading to little carry over effect on the day after dosing. Although the mechanism of action is incompletely understood at a molecular level it can be assumed to be similar to that of the racemic substance zopiclone.

The applicant has studied Lunivia in a variety of clinical settings involving primary insomnia, and insomnia secondary to various chronic conditions such as rheumatoid arthritis, generalised anxiety disorder, and major depressive illness. The results across studies are consistent and demonstrate shorter sleep latency, longer sleep time, and less wakening after the onset of sleep compared to placebo.
Considering the primary endpoint (sleep latency) in primary insomnia studies, Lunivia in adults (3 mg) and elderly (2 mg) reduced time to sleep onset by 19 minutes (range 15.8 – 28.5) as compared to placebo in short-term trials and, at a dose of 3 mg in adults, Lunivia reduced time to sleep onset by 19.2 minutes (range 18 – 20.5) as compared to placebo in long-term trials.
Lunivia was demonstrated to be an effective hypnotic. Long term studies of six months or more do not suggest that the development of tolerance is such as to lead to loss of efficacy. However, the lack of comparison to other agents in this well populated field makes it difficult to identify whether it has any significant advantage over other hypnotics with half-lives of similar length.

Lunivia is associated with well defined but moderate adverse effects; the most common being fatigue, asthenia, headache, nausea, abnormal unpleasant taste and/or dry mouth.
As with all hypnotic drugs there will be a potential for abuse and dependence, though the applicant has conducted a study which suggests that this is no worse than for benzodiazepines.

Indeed, it was not proven that eszopiclone had any advantages over zopiclone as the putative advantages were advanced on theoretical grounds, and no prospective comparison has been made. For these reasons the CHMP concluded that eszopiclone cannot be considered as a New Active Substance.

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

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Lunivia in the treatment of insomnia, including difficulty falling asleep, nocturnal awakening or early awakening, in adults, usually for short term duration was favourable and therefore recommended the granting of the marketing authorisation.

3. RE-EXAMINATION OF THE CHMP OPINION

3.1. Grounds for re-examination

Further to the positive CHMP opinion dated 23 October 2008, Sepracor Pharmaceuticals, Ltd is requesting re-examination of the CHMP's recommendation not to classify eszopiclone as a new active substance. In addition the applicant asked for a discussion of these issues by the Clinical Neuro Sciences (CNS) Scientific Advisory Group (SAG). In summary, the grounds for the re-examination are as follows:

The Applicant is of the opinion that eszopiclone differs from the racemate, zopiclone with respect to properties relating to safety and efficacy. According to them the available evidence included head-to-head comparisons of pharmacokinetics, pharmacodynamics and tolerability of eszopiclone and zopiclone and the CHMP was not able to conclude in its initial assessment that these data established that eszopiclone is sufficiently different from zopiclone so as to be considered an NAS.

Based on the feedback the applicant received at the oral explanation meeting during the first round of assessment, they presented supportive evidence that in his view eszopiclone is in fact not the same as zopiclone, on both a scientific basis and within the intent of the applicable legislation. In particular, supportive results of a recent head-to-head comparison including statistical evaluation (ESZ111503 have been provided to address limitations of the data set raised by the CHMP). According to the Applicant these additional, supportive results should be regarded as proof to the CHMP that the identified differences between eszopiclone and zopiclone are clinically meaningful, reliable and reproducible.

The Applicant proposes that there are several key questions of relevance when considering whether eszopiclone is an NAS:

1. **Are there sufficient differentiating properties between eszopiclone and the racemate?**
2. **Are the differences reproducible?**
3. **Are the differences relevant and clinically meaningful?**

In the applicant's view it is fundamentally important to understand that (R)-zopiclone is not an inert isomer, and in the MAA they describe the manner in which it affects the pharmacokinetic and

pharmacodynamic characteristics of zopiclone. Eszopiclone, the (S)-isomer, possesses the desired therapeutic activity and it has been clearly established that it can be effectively and safely administered as a single-isomer drug. They do not claim that the racemate, zopiclone, is either unsafe or ineffective. However, the applicant is of the opinion that the (R)-isomer is in fact sufficiently active, in a manner that does not contribute to the desired therapeutic effect, such that its removal unmasks a more effective and safer drug having different pharmacologic properties as well. The removal of the (R)-isomer permits a lower dose of the (S)-isomer, eszopiclone, to be more effective for sleep onset and at least as effective for sleep maintenance, while at the same time providing safety benefits resulting from lower morning serum levels.

In support to the re-examination request, the Applicant has presented an additional report of the three main findings that they consider significant to demonstrate a clinical difference between Zopiclone and Eszopiclone:

I. **Pharmacokinetic differences and effect on sleep onset:**
Comparative clinical studies of eszopiclone and racemic zopiclone demonstrate differences in the Tmax of the (S)-isomer such that the Tmax of eszopiclone is 30 minutes faster than racemic zopiclone (1 hour v. 1.5 hours, respectively). Data are presented to further support the conclusion that these pharmacokinetic differences lead to pharmacodynamic differences in efficacy – namely faster onset of sleep.

II. **Next day residual effects:**
Comparative clinical studies of eszopiclone and racemic zopiclone illustrate that plasma concentrations of the (S)-isomer at approximately 8 hours post dose are lower when eszopiclone is administered alone than when administered in an equivalent amount as racemic zopiclone. Data are presented to further support the conclusion that this reduction in overall exposure contributes to an improved safety profile – namely a reduction in observed next-day residual effects.

III. **Pharmacological differences:**
Pharmacology studies evaluating the effects of eszopiclone, (R)-zopiclone and racemic zopiclone on the GABA receptors demonstrate differences in the relative activity at various alpha subunits (α1, α2, α3 and α5). Data are presented to further support the conclusion that these differences at the receptor level contribute to differences in pharmacological activity including effects on memory, anxiety, depression and pain.

The removal of the (R)-isomer permits, in the view of the Applicant, a significant reduction in the effective dose, which has been reduced from 7.5 mg of racemic zopiclone (which contains 3.75 mg of (R)-zopiclone and 3.75 mg of (S)-zopiclone) to 3 mg of eszopiclone.

Table summarising the overall findings as they relate to differences in the overall risk benefit profile of eszopiclone compared with racemic zopiclone.

	Differential findings	Evidence initially submitted	Confirmatory Analyses submitted in the re-examination procedure
Tmax	Eszopiclone Tmax of 1 hour is shorter than zopiclone Tmax of 1.5 hours	• Head-to-head comparative PK studies 190-010 and 190-001; • Corroborated by historical literature and label statements	
Sleep onset	Latency to persistent sleep is faster with a lower dose of eszopiclone than racemic zopiclone.	• Comparison of studies of similar design: 190-045 and Lamphere et al. • Corroborated by historical literature	• ESZ111503 head-to-head comparative study, which provides comparative measures of variability for this parameter as requested at the OE. o As we noted at the OE, statistical comparisons between eszopiclone (study 190-045) and zopiclone (Lamphere) were not possible, as measures of variability are not provided in the publication by Lamphere (1989) and are not available from the author.
Residual Plasma Concentration.	Plasma concentrations of the (S)-isomer at approximately 8 hours post dose are lower when eszopiclone is administered alone than when administered in an equivalent amount as racemic zopiclone	• Head-to-head comparative PK studies 190-010	
Residual effects	Eszopiclone showed a reduction in the magnitude of residual effects relative to zopiclone e.g. driving, co-ordination, reaction time	• Comparison of studies of similar design: 190-024 and 190-025 (eszopiclone) with 190-027 (zopiclone) • Corroborated by historical literature and data from studies 190-024, 190-025, 190-027, 190-059 and 190-060	• ESZ111503 head-to-head comparative study
	Fewer detrimental effects on memory compared with zopiclone, related to the lower efficacy at the $\alpha 5$ and $\alpha 1$ subunits relative to the other subunits.	• Comparative pharmacology study 190-435. • Corroborated by published literature.	• ESZ111503 head-to-head comparative study

	Differential findings	Evidence initially submitted	Confirmatory Analyses submitted in the re-examination procedure
Pharmacology	Eszopiclone is associated with greater relative effects at the α2 and α3 receptor subtypes compared with racemic zopiclone which has a greater relative effect at the α1 and α5 receptors.	• Comparative pharmacology study 190-435.	
Anxiolytic, antidepressant and antinociceptive activity	Eszopiclone is associated with beneficial effects on anxiety, mood and pain whereas racemic zopiclone and α1-selective agents demonstrate no relevant therapeutic activity at comparable doses.	• Comparative animal studies – Carlson 2001 • Corroborated by historical zolpidem and zopiclone literature and data from studies 194-026, 190-902, 190-052, 190-054 and 190-055.	• Corroborated by published literature

3.2. Detailed Positions

I. Grounds for Re-examination 1: **Pharmacokinetic differences and effect on sleep onset**

Detailed Applicant's position:
In the section below, the position of the applicant on Comparative Pharmacokinetics of Eszopiclone and Racemic Zopiclone is presented.

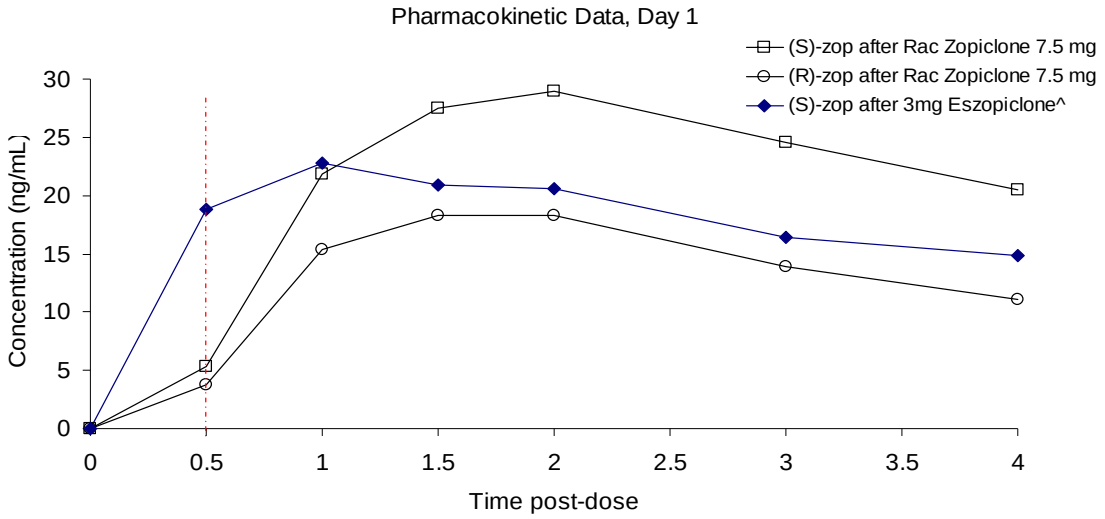
Head-to-head data regarding the pharmacokinetic differences between eszopiclone and racemic zopiclone and their clinically relevant impact on the pharmacodynamic outcomes are proposed::

- Eszopiclone leads to a faster rise in the plasma concentration of the (S)-isomer compared with that following administration of racemic zopiclone.
- This faster rise in plasma concentration leads to shorter sleep latency associated with eszopiclone as measured by:
    - Head-to-head data from a 91 patient crossover study of eszopiclone, racemic zopiclone and placebo utilising actigraphy.
    - Historical comparison of identically designed polysomnography studies evaluating eszopiclone and placebo compared with racemic zopiclone and placebo.
    - Review of the literature with respect to the relationship between Tmax and sleep latency.

Pharmacokinetic (PK) studies revealed differences regarding the impact of delivering (R)-zopiclone and (S)-zopiclone together in a racemic mixture compared with the (S)-isomer alone. Most notably, the Tmax of eszopiclone is 1 hour, whereas the Tmax of racemic zopiclone is approximately 1.5 hours. [Carlson, 2001; IMOVANE® (zopiclone) SPC; Fernandez, 1993; Houghton, 1985]. Therefore, the presence of the (R)-enantiomer delays the rate of absorption by 30 minutes, a delay that is clinically meaningful for a hypnotic drug. However, the impact of differences in pharmacokinetics for a sleep drug may not be appreciated if only the standard PK parameters of AUC and Tmax are evaluated, even though they may be significantly different. For a sedative hypnotic, the most relevant time points to evaluate are onset (during the first hour), and offset (during the last few hours).

Study 190-010 allows for a direct comparison of the PK of racemic zopiclone with eszopiclone. Figure 1 presents the mean plasma levels of (S)-zopiclone following the recommended dose of eszopiclone (3mg) compared with the levels of (S)-zopiclone following the recommended dose of racemic zopiclone over the first 4-hours following dosing. The PK curve for eszopiclone is shifted to the left, indicating more rapid absorption of the single isomer eszopiclone, despite the lower total dose. Thus, at 30 minutes post dose (indicated by the red vertical line), there is a 3.5-fold higher plasma level of (S)-zopiclone at a clinically relevant time point after administration of eszopiclone, the time point during which sleep onset occurs. In contrast, the plasma levels of (S)-zopiclone following racemic zopiclone at 30 min post-dose are significantly lower ($p<0.001$), even though the total dose administered with racemic zopiclone is 2.5-fold greater, with a 1.25-fold greater amount of the (S)-isomer. In fact, the median plasma concentration for racemic zopiclone is below the limit of quantification. The levels of (R)-zopiclone are also delayed, reaching a maximum concentration at 1.5 to 2 hours post dose, and approaching concentrations that are similar to the concentration of (S)-zopiclone following eszopiclone.

Figure 1. Comparison of mean plasma concentrations over the first 4 hours for eszopiclone 3 mg and zopiclone 7.5 mg



^Dose adjusted based on eszopiclone 3.5 mg data and linear pharmacokinetics (Study 190-010)

CHMP position:

In the section below, the position of the CHMP on Comparative Pharmacokinetics of Eszopiclone and Racemic Zopiclone is presented.

The observed differences in study 190-010 and the conclusions drawn by the applicant are not fully conclusive as other data are available as well (as outlined in the assessment of the original rapporteurs).

In study 190-010 Imovane (7.5 mg of racemic zopiclone) was taken as a single tablet, eszopiclone was taken as three tablets (two 1.0 mg and one 1.5 mg tablet). This factor may be responsible for the observed differences, and the total number of tablets taken was not discussed by the applicant. It can be assumed, that three immediate release tablets will have shorter disintegration times due to larger surface area than single Imovane tablet. There is also missing the assessment of the composition and manufacturing process of the tablets, which also plays role in the dissolution profile and can be attributable to the observed differences in Tmax. However, the real impact of this finding on T_{max} is uncertain as both formulations show very fast disintegration and dissolution properties. Though disintegration of Lunivia tablets was slightly faster compared to Imovane (<1 min. versus 4-8 min, respectively), the dissolution rates are very high for both formulations (>80% after 10 min for Lunivia; about 100% for Imovane after 15 min.).

The differences, as presented by the applicant (190-010 study), reflect rather the differences of the pharmaceutical form (different strength, different composition, different number of tablets) than differences in the absorption characteristic between eszopiclone and racemic zopiclone.

The other pharmacokinetic parameters in study 190-010 don't show major differences between eszopiclone and the racemate as outlined in the following table:

Table 11.4.2.1.2-2 Relative Bioavailability Between Multiple Doses of Tablet (S)-Zopiclone and Tablet Racemic Zopiclone: Analyte – (S)-Zopiclone

Parameter[1]	Comparison	Tablet (S)-Zopiclone Geometric LSMean	Tablet Racemic Zopiclone Geometric LSMean	Ratio[2]	90% CI	P-Value[3]
C_{max}	(S)-Zopiclone/Racemic Zopiclone	34.1	34.4	99.0	86.9, 112.8	0.8937
$AUC_{(0-\tau)}$	(S)-Zopiclone/Racemic Zopiclone	237.1	238.3	99.5	90.7, 109.1	0.9229
$t_{1/2}$	(S)-Zopiclone/Racemic Zopiclone	6.9	7.3	93.7	84.8, 103.4	0.2631
t_{max}[4]	(S)-Zopiclone/Racemic Zopiclone	1.0	1.5	--	--	0.0585
R_{Cmax}	(S)-Zopiclone/Racemic Zopiclone	1.2	1.1	105.8	99.6, 112.4	0.1227
R_{AUC}	(S)-Zopiclone/Racemic Zopiclone	1.0	1.0	96.8	79.4, 118.0	0.7735

[1] Units: $AUC_{(0-\tau)}$ is measured in ng*hr/mL, C_{max} in ng/mL, and $t_{1/2}$ and t_{max} in hr.
[2] Ratio (%) of geometric means (LSMeans) for the $\log_e$-transformed analysis.
[3] P-value for treatment effect from the ANOVA model.
[4] Values of t_{max} were rank-transformed prior to the analysis and the medians of the original values were reported for the treatments.
Note: Values were dose adjusted per Section 9.7.2.2.
Reference: Table 14.4.3.

Therefore the CHMP considers that it cannot be concluded that a distinct enantiomeric effect on absorption and distribution after oral administration of eszopiclone and the racemate has been undoubtedly demonstrated. Independently from these arguments, such pharmacokinetic differences should be established in terms of differences in clinical outcomes as well, in order to be relevant.

Detailed Applicant's position:

In the section below, the position of the applicant on Relationship between PK and Pharmacodynamics - Comparative Sleep Onset Efficacy of Eszopiclone and Racemic Zopiclone, and Sleep Onset in Normal Volunteers is presented.

According to the applicant, the pharmacokinetic differences between eszopiclone and racemic zopiclone seen in the first 30 minutes are striking (see Figure 1) and predict a difference in pharmacodynamics, specifically for sleep onset. To examine this, preliminary results from a head-to-head study in healthy volunteers recently conducted by the Applicant's EU licensing partner were submitted, as well as a comparison of data from the literature evaluating effects in studies of similar design in patients with primary insomnia.

The study (ESZ111503) was a randomised double-blind, double-dummy, 3-way cross-over in-clinic study evaluating eszopiclone 3 mg, zopiclone 7.5 mg and placebo. Ninety-one male and female healthy volunteers (aged 25-40) were dosed at 22.45 in the sleep laboratory, with lights out at 23.00. After 7 hours of time in bed, subjects were awakened at 06.00 the following morning.

The primary objective of the study was to evaluate the time course of potential residual effects seen the next day following night-time dosing, between 7.5 to 11.5 hours post dose. However, this study also utilised actigraphy as a means to monitor sleep during the night. Actigraphy was employed using an Actiwatch, which is an electronic device worn like a wrist watch that measures and records physical movement. Actigraphy is widely accepted as a non-invasive tool for assessing sleep (Ancoli-Israel 2003; Sadeh 1995; Littner 2003) and is well-correlated with PSG (Kushida 2001; Morgenthaler 2007). Evidence from healthy volunteers and psychiatric patients (Cole 1992) indicate a strong concordance ($p<0.0001$) between actigraphy outcomes and PSG findings, with a correlation

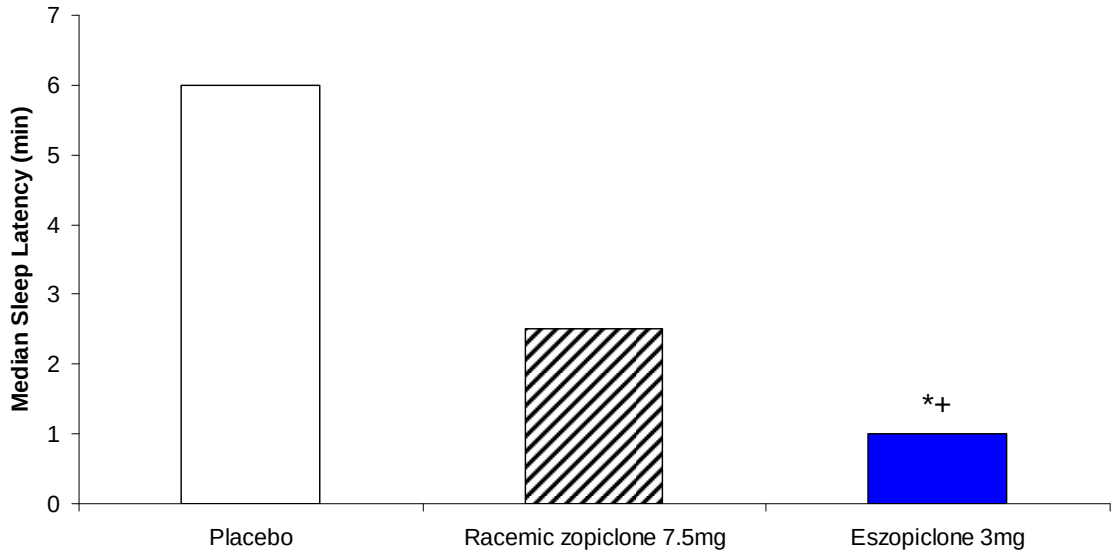
coefficient (Pearson r) for sleep latency of 0.9. Though actigraphy was used in the study for subject selection and protocol compliance, because the Actiwatch was worn throughout the trial, post-hoc evaluation is possible to determine the impact of eszopiclone and zopiclone on sleep outcomes in the laboratory in a direct head-to-head comparison.

To evaluate the impact of treatment on sleep induction two separate analyses were undertaken:

1) a comparison of the sleep latency values, derived from the Actiwatch software; and
2) a comparison of the total activity count from the Actiwatch during the first hour of sleep. In order to determine if there were differential effects in the early time periods post-dose, the first hour was further divided into 15-minute epochs and analysed specifically for the period immediately post lights-out (ie 23.00 – 23.14).

The results indicated that the median sleep latency is significantly lower for eszopiclone when compared with both placebo and racemic zopiclone ($p<0.05$; Figure 2). Sleep onset associated with racemic zopiclone trended toward statistical significance when compared to placebo ($p=0.056$). While these differences in sleep latency may appear small, they are noteworthy given that these results were obtained in healthy volunteers.

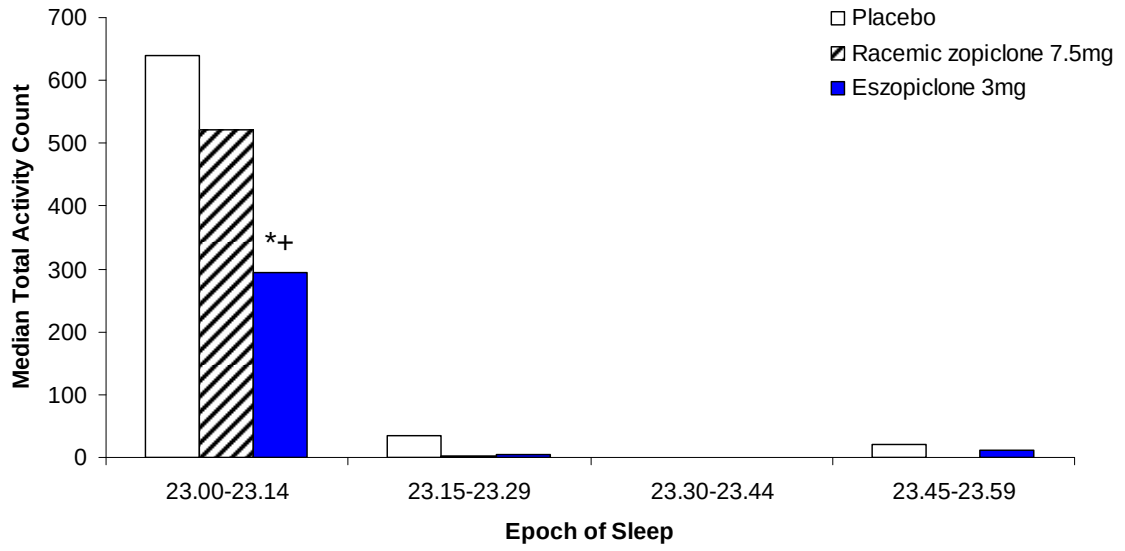
Figure 2. Median sleep latency values utilising actigraphy in healthy volunteers



*p<0.001 vs placebo
+p<0.05 vs racemic zopiclone

Figure 3 presents the analysis of total activity counts by 15-minute epochs during the first hour of the night (Figure 4). During the first 15-minute epoch, the total activity count was statistically significantly lower for the eszopiclone group compared with racemic zopiclone ($p=0.036$). Racemic zopiclone was of borderline significance from placebo ($p=0.054$). However, the total activity count for the eszopiclone group was significantly less than the placebo group ($p<0.001$).

Figure 3. Total activity count utilising actigraphy during the first four 15-minute epochs of the night in healthy volunteers



*p<0.001 vs placebo
+p<0.05 vs racemic zopiclone

In the view of the Applicant, these findings demonstrate that the differences seen in the faster Tmax of eszopiclone translate into significantly faster sleep onset for eszopiclone compared with racemic zopiclone. Statistical differences were evident even in healthy volunteers, and despite the lower dose of eszopiclone administered (3 mg eszopiclone compared with 3.75 mg (S)-zopiclone in racemic zopiclone 7.5 mg). The statistical separation from zopiclone for sleep onset was evident at 15-30 minutes post dose, corresponding with the observed separation in plasma kinetics for the (S)-isomer when the agent is dosed as eszopiclone, relative to when it is dosed as racemic zopiclone (Figure 1). The 5-minute difference in sleep latency noted between eszopiclone and placebo is similar to the 7-minute difference from placebo noted in another study of eszopiclone in normal volunteers (190-026), supporting the consistency of the eszopiclone treatment effect. Data from healthy volunteer studies such as Study 190-026 and patient studies such as Study 190-045 and 190-046 demonstrate consistent effects of eszopiclone on sleep latency such that meaningful differences observed in healthy volunteers are predictive of the conclusion of meaningful differences in patients.

CHMP position:

In the section below, the position of the CHMP on Relationship between PK and Pharmacodynamics - Comparative Sleep Onset Efficacy of Eszopiclone and Racemic Zopiclone, and Sleep Onset in Normal Volunteers is presented.

To address efficacy differences in Latency to Sleep Onset (LSO) ideally differences would have been shown in a prospective study in the natural setting and in patients with insomnia.
Unfortunately this study was planned not for efficacy by the applicant but it was intended to generate data to support market access and pricing issues. The study was performed in the artificial setting of a sleep laboratory and such studies are only considered as supportive evidence with regard to efficacy questions. Moreover, the study has been performed in healthy volunteers and it is questionable whether the small differences reported are meaningful in a patient population with insomnia.
Some general remarks must be considered: the results of this study on LSO are based on post-hoc evaluations; they have not been preplanned in the protocol. Moreover a final study report is not available.

As outlined earlier these evaluations are preliminary and have not been pre-specified in the study protocol, so the data can be considered at best as hypothesis generating.

Moreover, actigraphy cannot be considered as the ideal tool to estimate LSO as outlined in the papers by Buysse et al. (Sleep 2006, 29, 1155-1173) and Morgenthaler et al. (Sleep 2007, 30, 519-529). In

both papers it is clearly stated that additional research is needed on the influence of different actigraphy devices, on the reliability and validity of actigraphy compared to reference standards and particularly more research is needed to establish standards for setting start and stop times of the sleep and wake periods with use of actigraphy. Actigraphy is an appropriate tool to assess roughly the abnormalities in the activity level or habitual sleep pattern of patients with circadian rhythm disorders.

Therefore the CHMP considers that the data presented cannot be considered as proof of a clinically meaningful difference in LSO between eszopiclone and the racemate due to the several methodological limitations.

Detailed Applicant's position:

In the section below, the position of the applicant on Sleep Onset **in Patients** with Primary Insomnia is presented

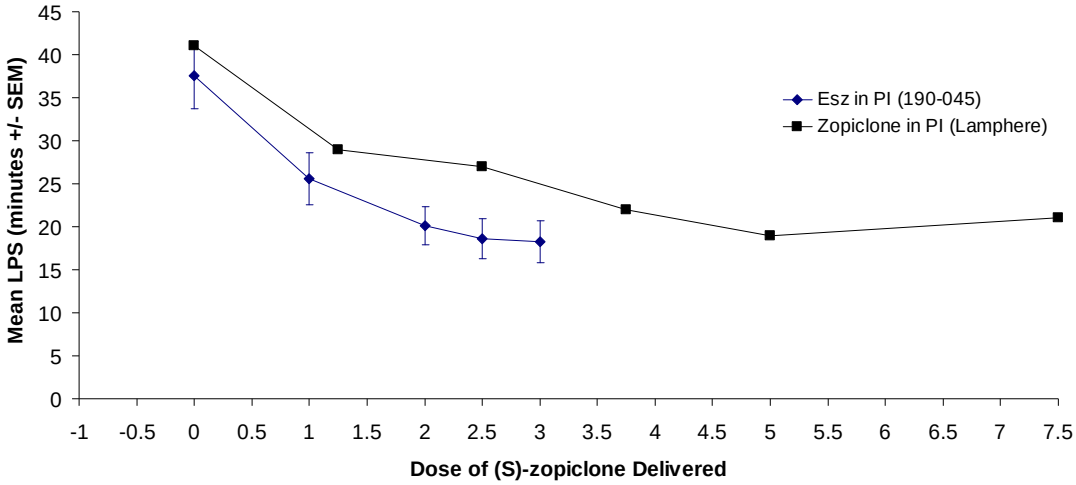
Both eszopiclone and racemic zopiclone have also been evaluated in identically designed studies in patients with primary insomnia. A comparison of the studies is provided below in Table 1. The dose ranging study of zopiclone conducted by Lamphere (1989) is the standard model for an evaluation of the dose-response of a hypnotic compound. The comparable study of eszopiclone (Study 190-045) was purposely modeled on the zopiclone study, and the senior researcher who conducted the Lamphere study assisted with the designed of Sepracor Study 190-045. Both were placebo-controlled cross-over designs, utilised objective measures of sleep via polysomnography (PSG), incorporated a wide range of doses encompassing the therapeutic window, and both used comparable patient populations who met the same criteria for entry. Finally, the sleep onset values were determined using the same methods.

Table 1: Overview of dose-response studies of eszopiclone and racemic zopiclone

	Eszopiclone (190-045)	**Zopiclone (Lamphere 1989)**
Design	5-way randomised crossover	6-way randomised crossover
Patients	Primary Insomnia (N=64) Mean age 41 +/- 10 yrs	Primary Insomnia (N=12) Mean age 36 +/- 10 years
PSG Entry Criteria	SL>20 minutes TST< 7 hours or WASO >20 min	SL >20 minutes TST < 7 hours
Treatments	Placebo, 1, 2, 2.5, and 3 mg eszopiclone	Placebo, 2.5, 5, 7.5, 10, and 15 mg of zopiclone

The data for sleep onset measured by PSG for eszopiclone and racemic zopiclone are shown in Figure 4. The baseline data are similar, likely due to the nearly identical entry criteria of the studies. The dose-response curve for eszopiclone is shifted down and to the left when compared with racemic zopiclone's dose-response curve, indicating that lower doses of the single isomer produce more rapid induction of sleep. If there was no difference in sleep onset for racemic zopiclone compared with eszopiclone, then one would expect to see the dose-response curves superimposed.

Figure 4. Evaluation of dose response data using LPS: Comparison of two identically designed studies of eszopiclone and racemic zopiclone in patients with insomnia



Note: During the first Oral Explanation the Applicant was asked to provide measures of variability. These are incorporated for the data from 190-045. However, no measure of variability was provided in the publication by Lamphere (1989) and are not available from the author.

The comparison of these two studies is important as it provides a comparison of two identical doses of eszopiclone and racemic zopiclone containing the same amount of (S)-zopiclone (2.5 mg of eszopiclone and 5 mg of racemic zopiclone). At these identical doses, a difference of ~10 minutes in LPS is noted when (S)-zopiclone is delivered as the single isomer, eszopiclone, compared with (S)-zopiclone delivered as part of the racemic compound, zopiclone i.e. an improvement in sleep onset by approximately 10 minutes over a 30 minute sleep latency, (33%). A difference of ~10 minutes in LPS when comparing two active drugs is clinically meaningful, given that the overall mean decrease in LPS by hypnotic drugs is about 11 minutes when compared with placebo (Youngstedt, 2003). In the eszopiclone program, differences from placebo in PSG studies were ~16 minutes.

These findings demonstrate that the differences seen in the earlier rise in therapeutic plasma concentrations of eszopiclone translate into faster sleep onset for eszopiclone compared with racemic zopiclone. In the head-to-head study, the statistical separation between treatments was evident even though the study was conducted in healthy volunteers. A comparison of studies in patients having nearly identical design, confirms the reproducibility of the outcomes. Taken together, these results confirm that the pharmacokinetic profile of eszopiclone gives rise to faster onset of sleep induction, compared with zopiclone.

CHMP position:

In the section below, the position of the CHMP on Sleep Onset in **Patients** with Primary Insomnia is presented

These studies are not directly comparable in the view of the CHMP, and this has been already outlined by the original assessment.

However, even if these studies would be considered as comparable, taking into account the different baseline levels the curves look more similar than different. So in the CHMP view this is more a proof of clinical similarity than difference in sleep onset.

Moreover, the comparison of the racemate zopiclone to other hypnotics, (the applicant also provided in their documentation a summary of Tmax and half-life for common hypnotics) is not helpful for solving the CHMP question, whether there are clinically meaningful differences between eszopiclone and the racemate zopiclone or not. This question can only be addressed by an adequate planned direct head-to-head-study on efficacy and safety between comparable dosages of eszopiclone and the racemate zopiclone.

II. Ground for re-examination 2: Pharmacokinetic Differences Related to Next Day Residual Effects

Detailed Applicant's position:

In the section below, the position of the applicant on Pharmacokinetic Differences Related to Next Day Residual Effects and the comparison of next day residual effects, Analysis of the Primary Outcome and Analysis of the Secondary Outcomes is presented

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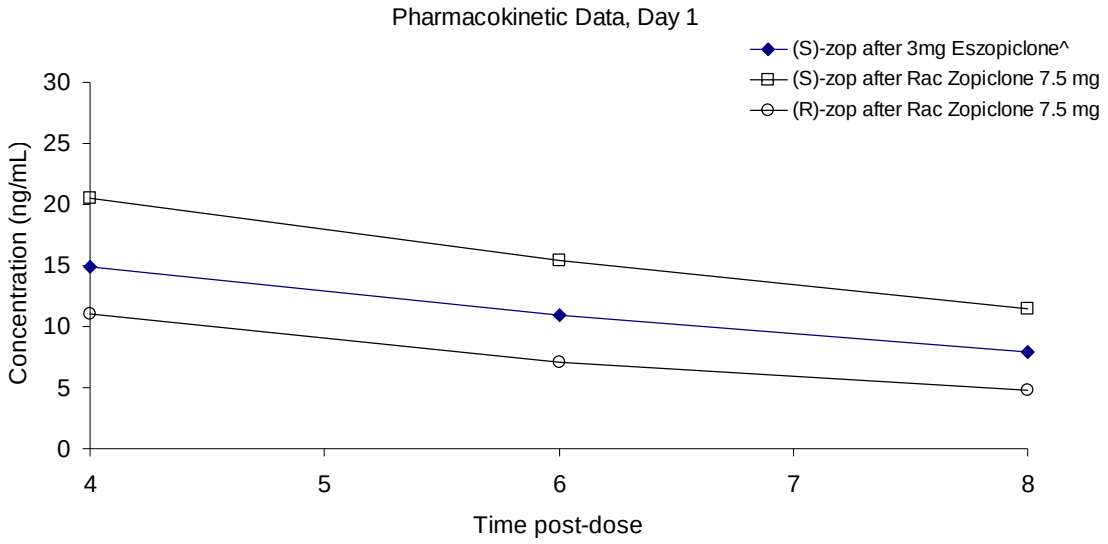
The removal of the (R)-isomer as well as the 20% reduction in dose of the (S)-isomer, may have the clinically relevant effect of reducing next day impairment following administration of eszopiclone compared to racemic zopiclone. Similar to the analysis performed at 30 minutes, one can also examine (S)-zopiclone plasma levels at 6 and 8 hours post dose in Study 190-010 as an indicator of the risk of next day residual effects. Mean (S)-zopiclone plasma levels are ~40% higher 6 and 8 hours post dose of 7.5 mg racemic zopiclone when compared with (S)-zopiclone levels following 3 mg of eszopiclone ($p<0.004$, each timepoint; Figure 6). Differences in plasma levels at hours 6 and 8 are clinically relevant, given that this is the period when most people are awakening from sleep.

Figure 6. Comparison of mean plasma concentrations over hours 4-8 for eszopiclone 3 mg and zopiclone 7.5 mg



^Dose adjusted from eszopiclone 3.5 mg based on linear pharmacokinetics (Study 190-010)

Comparison of next day residual effects

As noted in section 2.3.1, Study ESZ111503 was conducted by the Applicant's EU licensing partner, which allows the residual effects of the racemic compound (zopiclone) to be directly compared with the single isomer (eszopiclone). The study involved a 3-way cross-over design, comparing placebo, eszopiclone and zopiclone on measures of memory and psychomotor function. The study was designed to evaluate the course of potential residual effects seen the next-day (7.5 to 11.5 hours) following night-time dosing. Assessments were chosen to include measures which are sensitive to the known residual effects of zopiclone and other sedative hypnotics.

Ninety-one male and female healthy volunteers (aged 25-40) were randomised to a double-blind, double-dummy, 3-way cross-over sleep-laboratory study evaluating the potential existence and time-course of next day residual effects with eszopiclone 3mg, zopiclone 7.5 mg and placebo. The doses selected for the trial were those which have been recommended for adult patients for both treatments. Zopiclone was included in this study not only as the most relevant comparator for eszopiclone, but also it provided a positive control for determining the assay sensitivity of the study as an established hypnotic with known residual effects.

Subjects were dosed at 10.45pm in the sleep laboratory and then allowed 7 hours to sleep between 11pm and 6am. A battery of 4 short, cognitive and psychomotor tasks, as well as subjective ratings of sedation, mood and coordination, was administered at half-hour intervals between 7.5 and 11.5 hours post dose. The test battery comprised:

- The Continuous Tracking Test (CTT): This interactive task of psychomotor function (Parkin, 1998) entails using a slider to keep a cursor in alignment with a horizontally moving target on a visual display unit screen. Demands on the subject's attention are also made by requiring the subject to respond to a stimulus presented in the periphery of vision, while simultaneously attending to the tracking test. The primary outcome defined in the protocol was the mean tracking error from this task averaged over the first 5 timepoints (7.5 to 9.5 hours post dose) and the primary comparison of interest was between eszopiclone and zopiclone.
- The Critical Flicker Fusion Test (CFF) of perceptual information processing speed.
- The Digit Symbol Substitution Test (DSST) of visuomotor coordination and sustained attention.
- The N-Back tasks (visual 1- and 3-back versions) of working memory.
- Ten separate 10cm Linear Analogue Rating Scales (LARS) evaluating subjective feeling relative to the subjects' usual state of mind before treatment. Three core measures of sedation, mood and coordination are derived from the 10 individual scales.

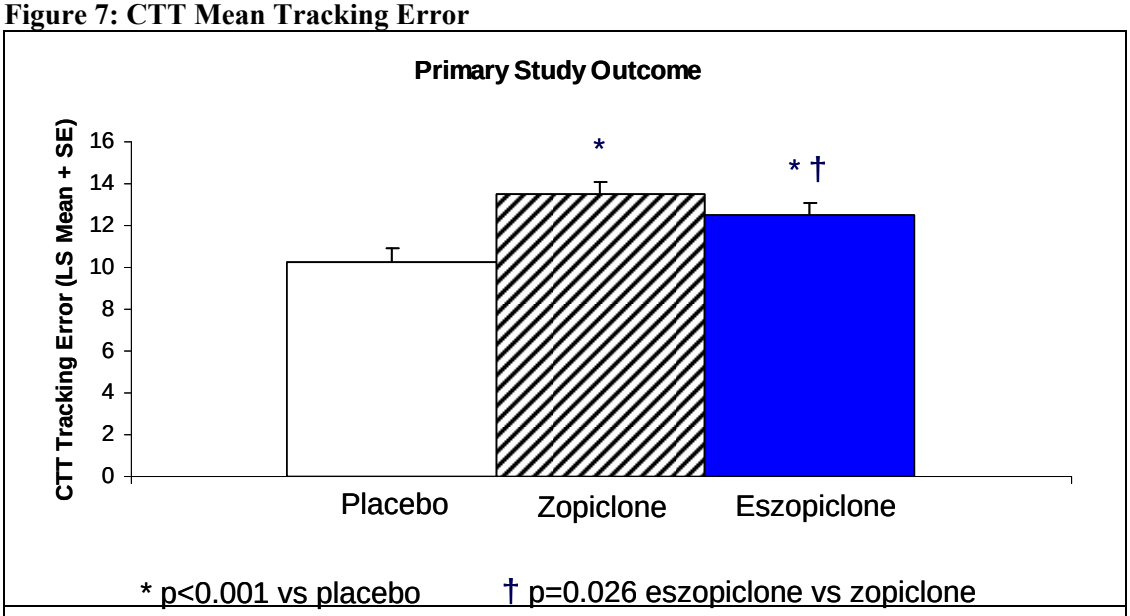
Analysis of the Primary Outcome

As specified in the study analysis plan the primary endpoint was evaluated with analysis of variance techniques. However, the assumptions of the model were seriously violated (non-normal residuals and non-constant variance). *A priori* stipulations in the study analysis plan stated that if the assumptions were seriously violated, a transformation of the endpoint, or a non-parametric method would be considered to assess the robustness of the analysis and an appropriate transformation would be undertaken if required. Exploratory investigations indicated a reciprocal transformation was appropriate and diagnostic plots confirmed it to be so.

Analysis of the reciprocal-transformed data gave a statistically significant difference favouring eszopiclone between the 2 active treatments ($p=0.026$; Figure 7) and significant differences between both active treatments and placebo ($p<0.001$). Thus, whilst the study shows both treatments produced evidence of next-day residual effects, analysis of the primary outcome indicates this detriment was greater for zopiclone. A rank-transformed analysis, which approximates a non-parametric analysis, was broadly supportive of this conclusion although the difference between eszopiclone and zopiclone was of borderline significance at the 5% level ($p=0.061$) and active treatments continue to separate from placebo ($p<0.001$).

As mentioned above the model assumptions of the original analysis were seriously violated. However for completeness, the preliminary analysis of the untransformed data demonstrated there was no significant difference between eszopiclone and zopiclone on the primary outcome measure (LS mean difference = -0.99, 95% CI= (-2.74, 0.76), $p=0.267$).

Figure 7: CTT Mean Tracking Error



CTT Mean Tracking Error (LS means and SE of the primary outcome from the untransformed analysis). Significance values are presented from the ANCOVA of reciprocally-transformed data. Subjects demonstrated a significantly greater mean tracking error on active treatment relative to placebo ($p<0.001$). The difference between active treatments was also statistically significant showing a reduction in the magnitude of residual effects for eszopiclone relative to zopiclone ($p=0.026$)

Analysis of the Secondary Outcomes

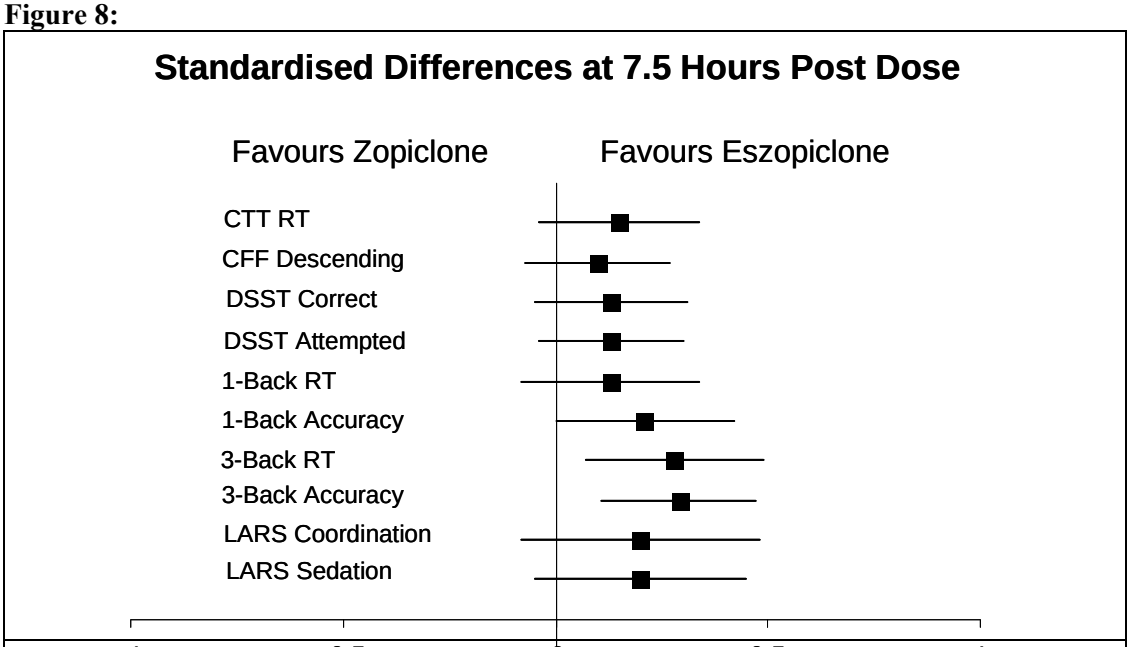
Compared with placebo, zopiclone caused statistically significant impairments at some timepoints on all outcomes except the CFF ascending threshold and the LARS evaluation of mood, thus establishing the assay sensitivity of 11 endpoints. Eszopiclone did not demonstrate statistically significant differences from placebo on these 2 outcomes and in addition there were no statistically significant differences between eszopiclone and placebo for LARS sedation, LARS coordination and 1-Back accuracy at any timepoint.

When zopiclone and eszopiclone were analysed in a post-hoc repeated measures analysis over all 9 timepoints across the 7.5 to 11.5 hour post-dose period, statistical differences ($p<0.01$) favouring eszopiclone (i.e. indicating a reduction in residual effects) were demonstrated on two of the measures (1-Back and 3-Back accuracy in memory tasks). The measure of subjective sedation (LARS) also approached significance ($p=0.054$).

When examining the individual timepoints a numerical separation indicating a reduction in impairment for eszopiclone relative to zopiclone was seen on all 11 endpoints that showed assay sensitivity and at the majority of timepoints. These differences were generally greater in the period between 7.5 and 9 hours post dose, although there was still some evidence of separation extending out to 11.5 hours post dose. Statistically significant differences in favour of eszopiclone were seen at the following endpoints; CTT-tracking error (7.5 hours), CTT-reaction time (11.5), 1-Back accuracy (7.5 hrs, 8 hrs, 9 hrs), 3-Back accuracy (7.5 hrs, 8 hrs), 3-Back reaction time (7.5 hrs), LARS sedation (8 hrs) and LARS coordination (8.5hrs and 11.5 hrs).

For illustration, standardised differences and confidence limits for the secondary outcomes demonstrating assay sensitivity are presented at the earliest assessment timepoint (7.5 hours post dose) in Figure 8.

Figure 8:



Standardised differences = Treatment difference /√(Within-subject variance component + Between-subject variance component). Note that significance cannot be determined by whether or not 0 is included within the confidence interval.

There has been no adjustment for multiplicity in the analyses of the secondary outcomes nor were these analyses necessarily powered sufficiently but it is notable that the pattern of results is consistently in favour of eszopiclone as showing a reduction in residual effects compared with zopiclone. Statistically significant differences were seen for both active treatments versus placebo but consistently the differences were numerically greater for zopiclone and statistically significant differences favouring eszopiclone over zopiclone were also demonstrated. Statistically significant separation between active treatments was seen particularly for the N-Back tasks and at the earlier timepoints. The N-Back tasks assess working memory and make substantial demands on a subject's attentional resource, arguably more so than the other outcomes employed in this battery and it is noteworthy that these measures have demonstrated the greatest separation between treatments.

CHMP position:

In the section below, the position of the CHMP on Pharmacokinetic Differences Related to Next Day Residual Effects and the comparison of next day residual effects, Analysis of the Primary Outcome and Analysis of the Secondary Outcomes is presented

Again the CHMP considered that the shown differences in the pharmacokinetic parameters might be more a consequence of the different dosages than a consequence of different enantiomeric properties. The curve of eszopiclone in the Figure 6 of the response document of the applicant is "adjusted" to 3-mg dose and therefore the differences in 4-8 hours post-dose are graphically presented as greater than were measured in the study. Based on this calculation, the applicant concludes that "*Mean (S)-zopiclone plasma levels are ~40% higher 6 and 8 hours post dose of 7.5 mg racemic zopiclone when compared with (S)-zopiclone levels following 3 mg of eszopiclone...*". The CHMP cannot accept this statement, since different doses were compared. It would be more helpful to adjust the curve to the other direction, i.e. to compared 3.75 mg of eszopiclone with 7.5 mg of zopiclone in order to see comparable results (despite the different pharmaceutical formulations). Actually the recalculation of the results (i.e. the dose of eszopiclone of 3.5 mg was adjusted to 3.75 mg), brings to the conclusion that the differences after 4-8 hours after acute administration are only about 10 % higher for racemic zopiclone.

The data described in the grounds for refusal have been complemented by a presentation of the applicant in a teleconference, the minutes of the teleconference and the presentation slides are available and have been considered. Primary objective of the study was to evaluate existence and time

course of potential next-day residual psychomotor effects of a single evening dose of 3mg eszopiclone, 7.5 mg zopiclone, and placebo as measured by the mean tracking error of the Continuous Tracking Test (CCT). The primary analysis was performed on the mean of 5 assessments conducted 7.5, 8, 8.5, 9 and 9.5 hours post-dose (protocol page 28) for the primary comparison of eszopiclone versus zopiclone 7.5mg on day three of each period in the ITT population at alpha=0.05. The primary comparison was alsoperformed in the PP and completers population.
The study is a randomized, double-blind, double-dummy, 3-way cross-over study employing a placebo and a positive control. Subjects are randomized in balanced order using a Williams Design to one of 6 possible sequences of the three treatments (one treatment in each treatments session) at visit 3. Subjects received single-blind placebo on Night 1 of each of the three 2-night crossover treatment sessions, and double-blind investigational product on Night 2 of each of the three 2-night crossover sessions.
Due to uncertainty around the standard deviation estimate, a blinded review of the data of study ESZ111503 was undertaken to estimate standard deviation when approximately 30-50% of randomizes subjects have completed the Three 2-night crossover treatment.

The CHMP noted that:

- The statistical analysis plan (SAP) was not available. Therefore it is unknown whether there are relevant changes to the primary analysis defined in the protocol, especially whether the primary analysis has been specified in detail within the SAP. As a consequence the adequacy of the presented primary analysis cannot be finally evaluated.
- A blinded sample size adjustment has been done. The method used for this and whether the method has an impact on the type-I-error cannot be assessed due to no available information on this issue. If the applicant proceeded as planned in the protocol and violations of the assumptions of the statistical model used for the primary analysis will lead either to transformations of variables or to a non-parametric approach, adjustment for multiplicity is necessary (PtC on multiplicity issues in clinical trials, 2.3, p4/10). To our knowledge no adjustment for multiplicity has been employed.
- There are three different baselines for each subject, one for each period. Strictly speaking only the baseline before the start of the first treatment is a true baseline. “Baselines” taken at the beginning of each period may reflect the previous treatment caused by carry-over effects. A subject level baseline is defined in the protocol as the average of the three baseline values of the subject. An adjusted period-specific baseline will also be defined as the baseline for each period minus the associated subject baseline. The subject level baseline and the adjusted period specific baseline will be fitted in the analysis model. It is unclear whether the different baselines reflect possible carry-over effects. They have not been reported. Additionally, a sensitivity analysis based on the “true baseline” is considered helpful.
- A discussion/reporting of possible sequence effects, period effects, carry-over, missing periods for subjects and information on how they were incorporated into the analysis, is missing, but necessary for the evaluation of the results.
- The unsatisfactory reporting on the primary analysis (provided as a powerpoint presentation) does not allow to assess the underlying assumptions of the model. The model itself has not been reported. Since the SAP is missing, it remains unknown whether the specific transformation of some data (which ones?) that has been used (reciprocally transformed data) has been pre-specified in the SAP. Further, for the primary analysis no confidence intervals, no missing values, no analysis for completers, for PP population etc. are reported.

The CHMP concluded that in the primary analysis no difference on next day residual effects between eszopiclone and the racemate of zopiclone has been established. In further analyses with transformed data significant differences are claimed by the applicant, however, due to the methodological questions these data are considered more than preliminary. Overall the insufficient and inadequate reporting of results does not allow assessing the validity of the presented study results.

The unsigned Reporting and Analysis Plan (13-11-2009) was subsequently provided by the applicant (but not the Final Clinical Study Report with its appendices)

The CHMP commented as follows:

1. The primary statistical null hypothesis is that there is no difference between eszopiclone 3mg and zopiclone 7.5mg in the mean tracking error assessed during the Continuous Tracking Test (CTT) using the mean of the 5 assessments conducted 7.5, 8, 8.5, 9, and 9.5 hours post dose in the intend-to-treat (ITT) population (RAP, p 11).The applicant defines: „*The primary population will be the ITT population, defined in section 6.1, and the comparisons will be made using the observed cases (OC) dataset, defined in Section 6.5)*" That is: "*Datasets will be based on the actual data collected (observed cases [OC] data). No technique (such as Last Observation Carried Foreward [LOCF] or others) will be used to replace missing values). The primary dataset is based on the mean of the 5 assessments conducted 7.5, 8, 8.5, 9 and 9.5 hours post-dose (double-blind) on Day 3*." The definition of the intention to treat population made by the applicant cannot be accepted since it is based only on observed data in contrast to the stronger requirement of ICH E9, p. 24/37 that the ITT population should include all randomized subjects. The definition for the per-protocol population is not in accordance with the requirements of ICH E9 (i.e. subjects who do not participate in all three double-blind periods are not excluded from the analysis) and likewise not acceptable from a statistical point of view. (Reporting and Analysis Plan, p.19f.). Further, arguments to motivate why the ITT population should be the more conservative population within the context of the primary testing problem have neither in the study protocol nor in the RAP been brought forward. However, in principle reporting of the primary result based on the per protocol population as well as for the intention to treat population are necessary for assessment and had been expected.

2. The CHMP shares the position of the applicant that there is only one pre-planned primary comparison (Reporting and Analysis Plan, p 49 „*However, the primary inference will be based on the primary model with any influential outliers included*"), and since there is only one primary endpoint (RAP, p 22) multiplicity adjustment is indeed unnecessary. All other presented calculations (for instance using a non-parametric approach, using transformed variables etc) were solely planned to be conducted for establishing robustness of the primary analysis (for example, RAP, p.49 "*Error diagnostics from the residuals will be examined to ensure that the assumptions of the model are valid. If the assumptions are seriously violated, a transformation of the endpoint or non-parametric methods will be considered to assess the robustness of the analysis. This will be carried out in addition to the parametric analysis.*" RAP12.1.6 Robustness of the primary analysis, p49-51). That is, the different approaches and analyses calculated for the primary endpoint were planned to establish robustness of a primary statistically significant result obtained by a possibly misspecified model and as such were explicitly not designed as pre-tests which would have been part of a two-stage primary analysis strategy, which in contrast would have made adjustment for multiplicity necessary. It remains an open question whether the primary analysis based on PP and ITT populations as required by ICH E9 would deliver statistically significant results, and whether the model assumptions are met in these populations. However, based on the reported results, the primary pre-planned analysis does not reach statistical significance in the first place and the additionally conducted analyses cannot compensate this result, and therefore the study has failed.

3. A blinded sample size adjustment has been done. The used method and its possible impact on the type-I-error cannot be assessed due to none available information on this issue. It can be learned that also in the RAP the method used for the blinded sample size adjustment has not been specified. It is unclear if the requirements of ICH E9 have been fulfilled (ICH E 9 p21/37, 4.4. sample size adjustment) "*A revised sample size may then be calculated using suitably modified assumptions, and should be justified and documented in a protocol amendment and in the clinical study report. The steps taken to preserve blindness and the consequences, if any, for the type I error and the width of confidence intervals should be explained. The potential need for re-estimation of the sample size should be envisages in the protocol whenever possible*."

The following issues remained open since they are untouched by the new availability of the RAP:

- The Final Clinical Report is missing.
- There are three different baselines for each subject, one for each period. Strictly speaking only the baseline before the start of the first treatment is a true baseline. "Baselines" taken at the beginning of each period may reflect the previous treatment caused by carry-over effects. A subject level baseline is defined in the protocol as the average of the three baseline values of the subject. An adjusted period-specific baseline will also be defined as the baseline for each period minus the associated subject baseline. The subject level baseline and the adjusted period specific baseline will be fitted in the analysis model. It is unclear whether the different baselines reflect possible carry-over effects. They have not been reported. Additionally, a sensitivity analysis based on the "true baseline" is considered helpful.
- A discussion/reporting of possible sequence effects, period effects, carry-over, missing periods for subjects and information on how they were incorporated into the analysis, is missing, but necessary for the evaluation of the results.
- For the primary analysis no confidence intervals, no missing values, no analysis for completers, for PP population etc. are reported.

In conclusion based on the accessible information, the CHMP draw the conclusion that the study has failed to reject the pre-specified primary null hypothesis and that the additionally conducted analyses cannot compensate this flaw. However, the Final Clinical Report is not available and thus the biometrical assessment can only be preliminary by nature.

Detailed Applicant's position:
In the section below, the position of the applicant on Review of residual effects data is presented.

Review of residual effects data

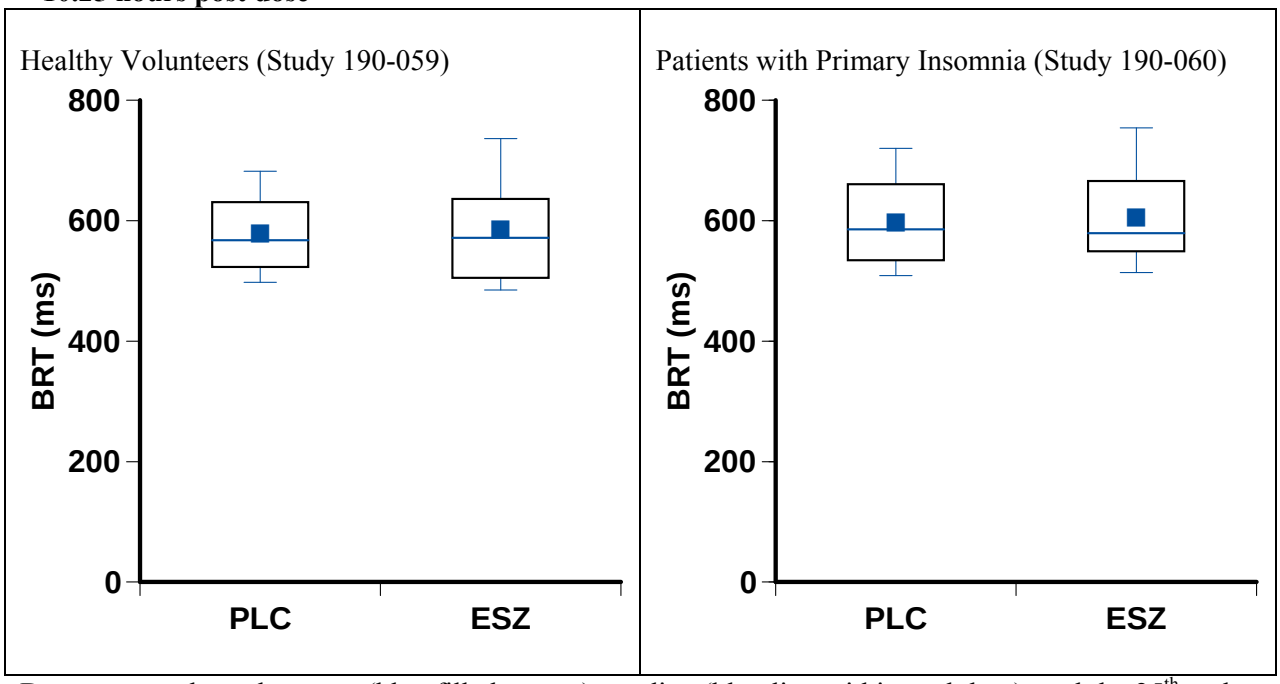
Residual daytime sleepiness and associated impairment of psychomotor and cognitive functioning the day after bedtime dosing, or 'hangover effects', constitute a major problem associated with hypnotic use (Vermeeren 2004.) Reduced alertness and slowed reactions increase a person's risk of becoming involved in accidents at home, at work, or while driving.
A large UK study (Barbone 1998), which linked the prescription records of 410,306 individuals to police records of road accidents between 1992 and 1995, showed a significant increased risk of accident for zopiclone (odds ratio 4.0). The increased risk for zopiclone shown for accidents is supported by experimental studies, showing significant residual impairment on driving performance, using a standardised highway driving test, between 10 and 11 hours after bedtime dosing (Volkerts and O'Hanlon, 1988; Vermeeren 1998; Vermeeren 2002; Vermeeren 2008). The effects of different hypnotics on this test can be compared against the known effects of different blood alcohol concentrations (BAC) on the primary performance parameter, standard deviation of lateral position (SDLP). In summary, drugs such as zaleplon and zolpidem 10mg had no significant residual effect, whereas the following agents, when tested in the morning or afternoon, had residual effects equivalent to BACs between 0.5 and 0.8 g/L: nitrazepam 10 mg, flunitrazepam 2 mg, oxazepam 50 mg, lormetazepam 2mg, flurazepam 15 mg and zopiclone 7.5 mg (Vermeeren 2004). On this basis, the dose of 7.5 mg of zopiclone is now employed as a positive control in driving studies such as these, as its residual effects have been demonstrated with sufficient consistency to be regarded as reliable and expected (Vermeeren 2008).
In 2006 Verster et al. performed a meta-analysis of on the road driving studies of different hypnotics and presented effect sizes for treatment placebo differences on the SDLP measure. The effect size (ES) for a morning driving impairment (10-11 hours post dose) was not significant for either zaleplon or zolpidem 10mg but it was large for zopiclone 7.5 mg (ES=0.89, CI =0.54-1.23).
In addition to the significant issues which have been demonstrated for zopiclone in relation to driving and the known risks associated with long-acting hypnotics and falls in the elderly, residual effects for zopiclone have also been evaluated experimentally for a number of different cognitive and psychomotor outcomes. A statistically significant detriment for zopiclone (7.5 mg or below) has been demonstrated (8-13 hours post dose) for tasks assessing psychomotor and information processing

speed, attention, memory and alertness (Lader 1983, Billiard 1987, Vera 2001, Nicholson 1982, Bocca 1999, Bocca 2000, Vermeeren 2002, Allain 2003, Silva 2003, Vermeeren 1998).

Taken together, the epidemiological, driving and experimental data provide a consistent picture, clearly indicating that whilst zopiclone provides robust sleep maintenance effects this benefit is at the cost of significant next-day residual effects. The relevance of these findings should not be overlooked, neither for the patient nor society in general, since they have important health and safety implications for the insomniac and for all those who potentially suffer from the hazardous consequences that these effects can cause.

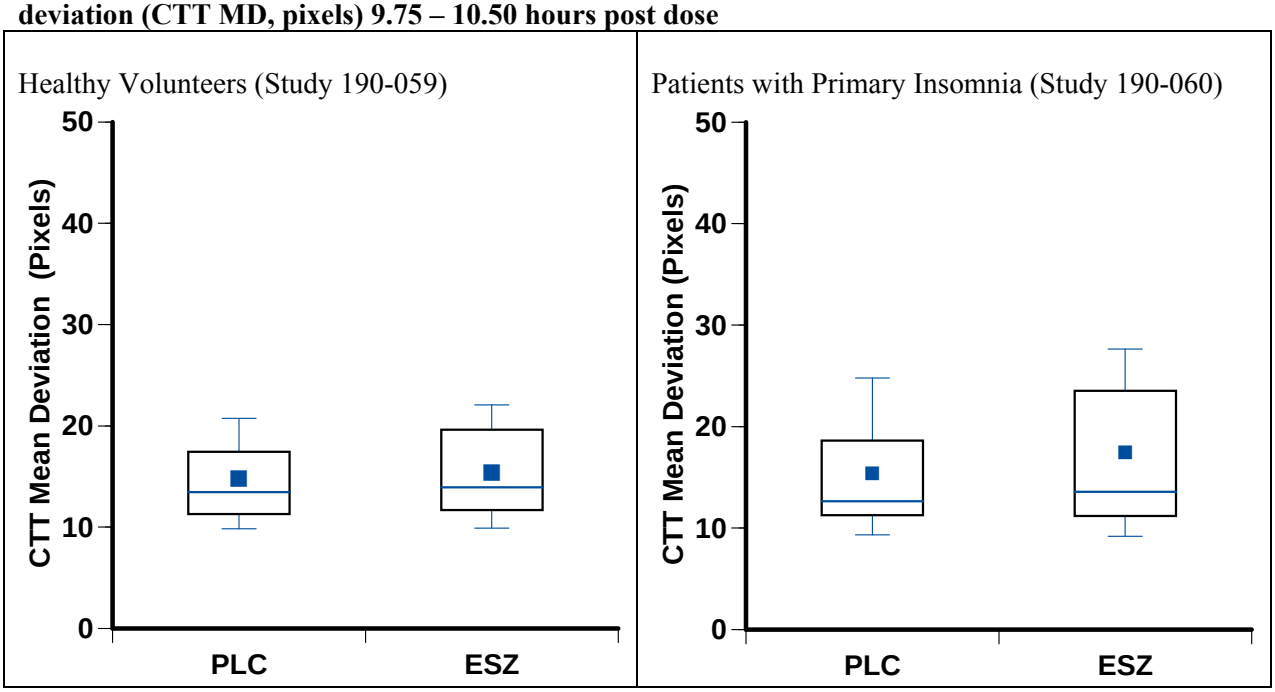
In contrast to the established next-day impairments which exist for racemic zopiclone, the evidence does not consistently demonstrate a similar detriment for the single isomer eszopiclone. Two separate studies have been conducted specifically to evaluate residual effects with eszopiclone on driving performance and cognitive and psychomotor effects 9-11 hours after bedtime administration (Studies 190-059 and 190-060; Boyle et al 2008). One study was conducted in healthy volunteers (n=31) and another in patients with primary insomnia (n=31). There was no statistical difference from placebo in either subject population on the driving assessment utilizing brake reaction time (Figure 9), continuous tracking test (Figure 10), or on any of the other psychometric measures. Healthy subjects did report a significant sense of sedation on one visual analogue scale (p=0.04).

Figure 9. Effect of eszopiclone 3mg (ESZ) and placebo (PLC) on brake reaction time (BRT) 9.50 – 10.25 hours post dose



Data presented are the mean (blue filled square), median (blue line within each box), and the 25th and 75th percentile for each treatment

Figure 10. Effect of eszopiclone 3mg (ESZ) and placebo (PLC) continuous tracking, mean deviation (CTT MD, pixels) 9.75 – 10.50 hours post dose



Data presented are the mean (blue filled square), median (blue line within each box), and the 25th and 75th percentile for each treatment

The next day effects of eszopiclone were also evaluated in study 190-024 in healthy normal subjects and in study 190-025 in insomnia patients following a single night-time dose. These studies demonstrated no significant effect of eszopiclone 3 mg on Digit Symbol Substitution Test (DSST) at 9.5 hours post dose. In contrast, racemic zopiclone 7.5 mg demonstrated statistically significant impairment on DSST at both 9 and 10 hours post dose in study 190-027.

Taken together, the data from the literature along with the recent head-to-head study confirm that differences in properties exist between eszopiclone and zopiclone, giving rise to an improved safety profile for eszopiclone compared with zopiclone that is manifested in a reduction in the probability of patients experiencing residual effects.

CHMP position:
In the section below, the position of the CHMP on review of residual effects data is presented.

Again this indirect evidence does not allow the conclusion that eszopiclone and zopiclone show clinically meaningful differences.

III. Grounds for re-examination 3: Pharmacology at the GABA receptor

Detailed applicant's position:
In the section below, the position of the applicant on differences in pharmacology between eszopiclone and zopiclone is presented.

In addition to the PK differences discussed above, differences in the pharmacology at the GABA receptor have been observed. With respect to these differences, the final assessment report for Lunivia stated that "the CHMP concluded that even though the arguments deployed by the applicant were of considerable scientific interest, they did not comprise a discussion on the possible impact on clinical safety or efficacy benefit." The following section briefly reviews the differences in receptor pharmacology between eszopiclone and zopiclone. The following section provides additional discussion on "the possible impact on clinical safety or efficacy benefit".

Differences in pharmacology between eszopiclone and zopiclone

Benzodiazepines and other sedative hypnotics are thought to promote sleep by potentiating the GABAergic neurotransmission through allosteric modulation of GABA type A ($GABA_A$) receptors. [Kopp 2004, Mohler 2006] It has been determined that the target receptors for benzodiazepine and non-benzodiazepine hypnotics are those that contain the $\alpha 1$, $\alpha 2$, $\alpha 3$ and $\alpha 5$ subunits in combination with β and γ_2 subunits. Within the last decade the subtype-selective effects of benzodiazepine modulation on receptors containing different alpha subunits has been investigated utilizing knock-in and knock-out genetically altered mice in comparison with their wild-type (control) mice. [Mohler 2008] It is apparent from these and parallel behavioral studies utilizing new selective agents that the various alpha subunits mediate selective properties of benzodiazepine receptor agonists.

Table 3 summarizes the effects modulated by compounds selective for each of the alpha subunits. [Mohler 2008, Tobler 2001, Kopp 2004, Dias 2005, Nutt 2006, Savic 2005, Sieghart 2006]

Table 3 – Selective modulatory effects of benzodiazepines on GABA alpha subunits

GABA Alpha Subunit	**$\alpha 1$**	**$\alpha 2$**	**$\alpha 3$**	**$\alpha 5$**
Modulator Effect	Sedation; Memory Impairment; Anticonvulsant	Modulation of EEG; Anxiolysis; Myorelaxation	Anxiolysis; Myorelaxation; Analgesia	Impairs cognition; Memory Impairment

$GABA_A$ receptor subunit isoforms demonstrate distinct regional and cellular distribution patterns within the brain suggesting that the location of each $GABA_A$ receptor variant may determine its function. [Seighart, 2006] Of the various subunits, $\alpha 1$ is the most abundant and is widely distributed throughout the brain particularly in the cerebral cortex. Alpha2 and $\alpha 3$ subunits are also quite prevalent but have more discrete distributions in areas of the brain, being particularly expressed in those areas associated with the sleep circuit (i.e. the brainstem and hypothalamus) and emotional responses of anxiety or depression (e.g. amygdala, hippocampus, dorsal raphe nucleus, etc). [Wafford 2008, Mohler 2006, Langen 2007]

The relative binding affinities and efficacies of benzodiazepine and non-benzodiazepine compounds to the different alpha subtypes of $GABA_A$ receptors play an important role in the nature of their sedative and hypnotic effects, their anxiolytic and mood effects, and other properties. Small but important differences between the pharmacological effects of various compounds have been shown to have clinically relevant differences in functional activity.

Table 4 summarises the relative receptor potencies (EC_{50} for $GABA_A$ potentiation) and effectiveness (percent of maximum achievable stimulation - %I in brackets) in potentiating ion channel current for eszopiclone, (R)-zopiclone, racemic zopiclone, (S)-DMZ (active metabolite), and zolpidem (Sepracor Doc. No. 190-435). These data are graphically displayed in Figures 11 and 12. This study allows the direct comparison of the receptor pharmacology related to eszopiclone and racemic zopiclone. Importantly, these data show marked differences in the modulatory actions of eszopiclone and racemic zopiclone at each receptor subunit.

Table 4: **Modulatory Actions of Selected Benzodiazepine Site Ligands at α1β2γ2, α2β2γ2, α3β2γ2 and α5β2γ2 $GABA_A$ Receptors Expressed in *Xenopus* Oocytes**

Compound	α1β2γ2		α2β2γ2		α3β2γ2		α5β2γ2	
	EC_{50}	%I	EC_{50}	%I	EC_{50}	%I	EC_{50}	%I
Eszopiclone	240	115%	99	230%	102	235%	25	55%
(R)-Zopiclone	787	22%	-	-	-	-	-	-
Racemic zopiclone	97	129%	600	97%	117	64%	97	114%
(S)-DMZ	859	55%	305	75%	364	131%	82	84%
Zolpidem	69	149%	146	150%	298	-	277	22%

- = no response or not measurable. EC_{50} is the concentration in nM that resulted in 50% of maximum potentiation of GABA evoked Cl^- current. %I describes the increase relative to that observed for GABA at its EC_{10} for each receptor. Results reported in Sepracor Doc. No. 190-435.

Figure 11 **Comparison of Potency (EC_{50}) at GABA Alpha Subunits (nM)**

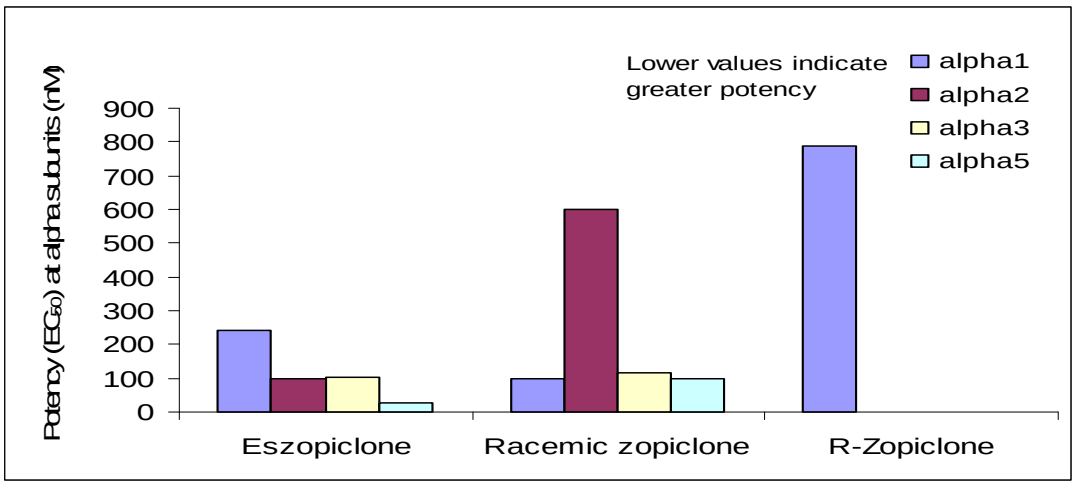
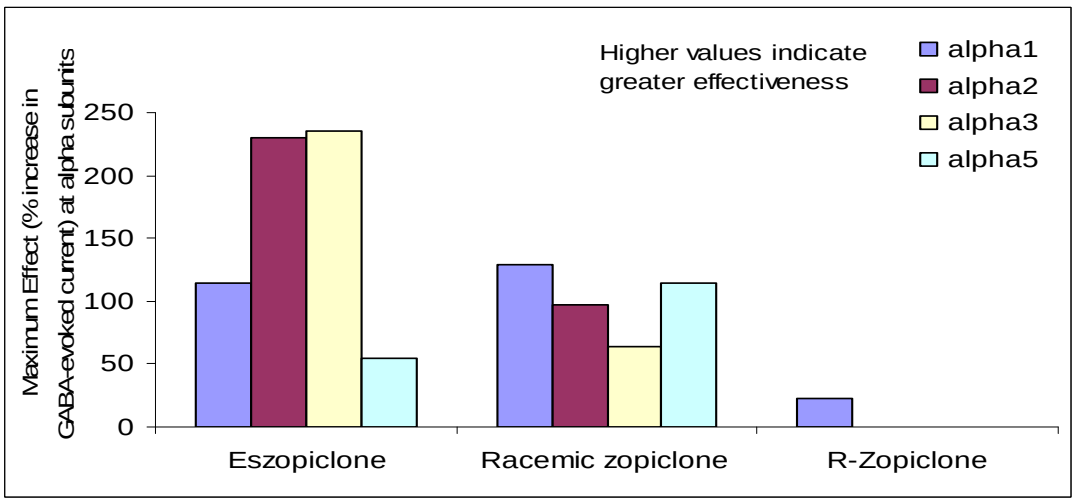


Figure 12 **Comparison of Effectiveness (% Cl^- Current Relative to that Evoked by GABA) at GABA Alpha Subunits.**



Based on the EC_{50} data, racemic zopiclone has its highest potency for α1 and α5 receptors with a potency at α1 that is similar to that of zolpidem (as shown in Table 4). In contrast, eszopiclone has its highest potency at α5, followed by α2 and α3 receptors, and is least potent at α1 (e.g. eszopiclone is

2.5 times less potent than racemic zopiclone). Based on the % maximal current data, racemic zopiclone has its maximal effectiveness at α1 and α5 receptors, whereas eszopiclone has its maximal effectiveness at α2 and α3 receptors.

A separate study (Sepracor Doc. No. 190-431A1) of eszopiclone and (R)-zopiclone evaluated the potentiation of GABA evoked currents in GABA receptors expressed in *Xenopus oocytes*. Racemic zopiclone was not included as a comparator in this study. Data from this study confirm the relative ratios for effectiveness (% current) of eszopiclone at α1 and α2 receptors, with %I at α2 (270%) greater than at α1 (170%). However, this study shows variability in the relative ratios for potency, with potency at α1 (30 nM) greater than at α2 (100 nM). Thus, both oocyte studies demonstrated that eszopiclone is highly efficacious at α2 subtypes and more than at α1 subtypes. (R)-Zopiclone had significant activity at the α1 subunit, though with much less potency than eszopiclone.

As noted above, both α1 and α5 subunits are known to be associated with effects on memory. For both eszopiclone and racemic zopiclone, the potency is greatest at α5 relative to the other receptor subunits. However, eszopiclone and racemic zopiclone differ with respect to the relative efficacy at the α5 subunit. The efficacy of eszopiclone at α5 is less than its efficacy at α1, α2 and α3; whereas, the efficacy of racemic zopiclone at α5 is similar to that at α1 and greater than the efficacy of zopiclone at the α2 and α3 receptors.

These data show distinct differences in the relative potencies and efficacies of eszopiclone and racemic zopiclone at the GABA alpha subunits. The following section discusses the clinical differences in risks and benefits noted in the scientific literature as well as comparative studies of eszopiclone and zopiclone, which provide the clinical relevance for the differences in receptor pharmacology observed in comparative studies and the known pharmacologic effects of the $GABA_A$ receptor alpha subunits.

CHMP position:

In the section below, the position of the applicant on differences in pharmacology between eszopiclone and zopiclone is presented.

The data in the following table confirm that the r-enantiomer shows almost insignificant affinities to the benzodiazepine binding sites, which in the CHMP view is the most important element

Table: Compilation of binding affinities (Ki values), potency (EC_{50} values) and efficacy (%I) values

	α1β2γ2			α2β2γ2			α3β2γ2			α5β2γ2		
	Ki	EC_{50}	%I	Ki	EC_{50}	%I	Ki	EC_{50}	%I	Ki	EC_{50}	%I
Eszopiclone	25	240	115	43	99	230	205	102	235	27	25	55
R-zopiclone	**>10000**	**787**	**22**	**>10000**	**---**	**---**	**>10000**	**>10000**	**?**	**>10000**	**>10000**	**?**
Racemic	45	97	129	68	600	97	487	117	64	256	97	114
S-DMZ	104	859	55	353	305	75	1070	364	131	608	82	84

--- no response; ? represents a curve that could not be finished because it had not reached a plateau even at the highest concentration of drug;
%I = % increase of GABA current; Ki [nM]; EC_{50} [nM]

It is therefore no surprise to the CHMP that in the original non-clinical overview of the submitted documentation was stated "*...sufficient comparative studies have been performed to indicate that results with zopiclone accurately predict results with eszopiclone....*" and "*... binding and receptor activation of zopiclone is attributed to the binding of eszopiclone, as (R)-zopiclone demonstrates minimal binding to the central benzodiazepine site....*". This was even strengthened by the statement that *" ... (R)-Zopiclone is not essential for the efficacy of eszopiclone ...,its effects are appropriately characterized as off-target activities. As the removal of (R)-zopiclone did not unmask any new risks of eszopiclone, the administration of eszopiclone alone represents a significantly enhanced delivery of the minimally essential drug to insomnia patients."*
Indeed, from the additional data presented by the applicant a certain effect of the R-enantiomer on the $GABA_A$ receptors has been shown. However, the magnitude of a possible clinical effect is still uncertain. So the CHMP was not convinced that the proposed binding differences will result in relevant distinct pharmacodynamic effects. If so, then they should be of clinical relevance on efficacy

and safety as well, however, as outlined earlier, from a clinical point of view there are more similarities than differences.

Detailed applicant's position:
In the section below, the position of the applicant on clinical impact of differential pharmacology is presented.

Clinical impact of differential pharmacology

Based on the known activity of the alpha subunits, one can predict that eszopiclone has the following properties when compared to zopiclone:

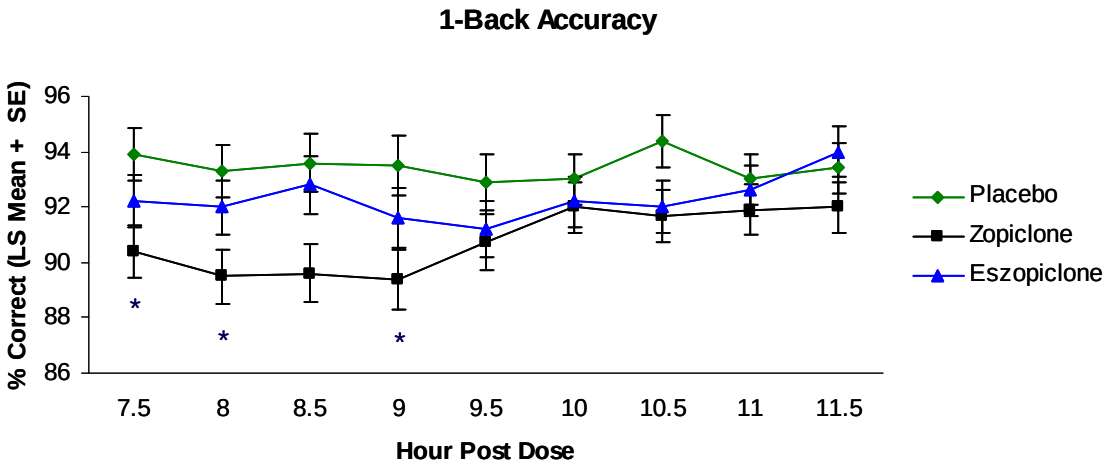
- Fewer detrimental effects on memory compared with zopiclone, related to the lower efficacy at the $\alpha 5$ and $\alpha 1$ subunits relative to the other subunits.
- Greater anxiolytic and antidepressive effects compared with zopiclone related to the relative modulation of $\alpha 2$ and $\alpha 3$ receptor subunits.
- Beneficial effects on comorbid pain related to the modulation of $\alpha 2$ and $\alpha 3$ compared with zopiclone.

These properties are discussed in further detail below.

- **Differences in effects on memory**

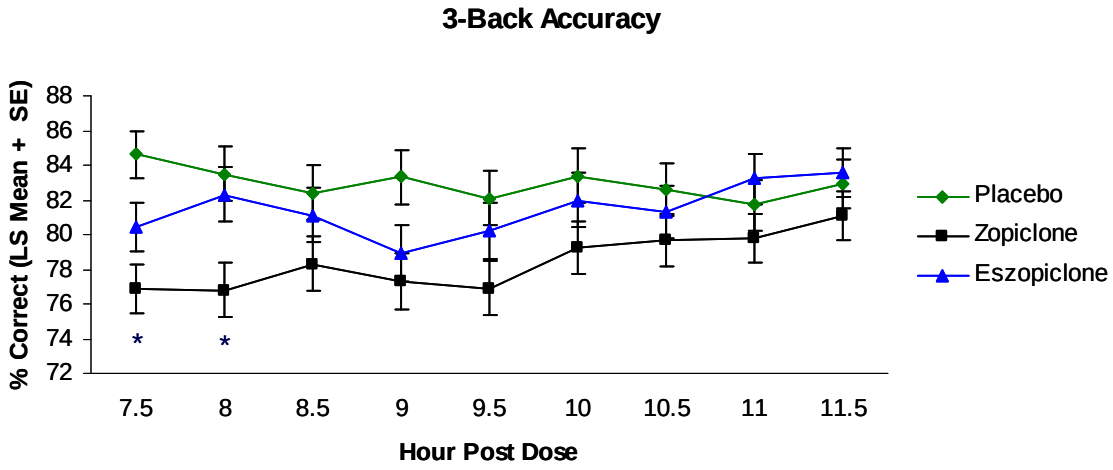
Differences in the effects of racemic zopiclone and eszopiclone on $\alpha 5$ and $\alpha 1$ subunits may contribute to the differences in observed effects on memory. In the recently completed double-blind cross-over study (ESZ111503) comparing placebo, eszopiclone 3 mg and zopiclone 7.5 mg following night-time administration in 91 healthy normal human subjects, eszopiclone was associated with less next-day impairment of memory compared with zopiclone. In this head-to-head study, subjects were administered cognitive tests at 7.5 hours through 11.5 hours post-dose at half hour intervals. Figures 13 and 14 display the number of correct responses on the N-back memory test for the 1-back and 3-back tests, respectively. Eszopiclone was not statistically significantly different from placebo in the number of correct responses on the N-back memory test at any timepoint for the 1-back test and was significantly different from placebo at only the 7.5 hour and 9 hour post-dose timepoints for the 3-back test. In contrast, racemic zopiclone was associated with significantly worse outcomes compared with placebo at all timepoints between 7.5 and 9 hours post dose on the 1-back test and at all timepoints between 7.5 and 11.5 hours, except the 10.5 and 11 hour timepoints, on the 3-back test. When comparing eszopiclone with zopiclone, statistically significant differences were noted at 7.5, 8, and 9 hours for the 1-back test and at 7.5 and 8 hours for the 3-back test. Thus, eszopiclone was consistently shown to have less memory impairment in the early next day hours (between 7.5 and 9 hours) post night-time dosing compared with racemic zopiclone in this head-to-head study.

Figure 13 – Mean percentage correct on the 1-back memory test



* p<0.05 eszopiclone vs zopiclone

Figure 14 – Mean percentage correct on the 3-back memory test



*p<0.001 eszopiclone vs zopiclone

CHMP position:

In the section below, the position of the CHMP on clinical impact of differential pharmacology and differences in effects on memory is presented.

Again the shown differences on memory tests might be more a consequence of the different dosages than a consequence of different enantiomeric properties.

Detailed applicant's position:

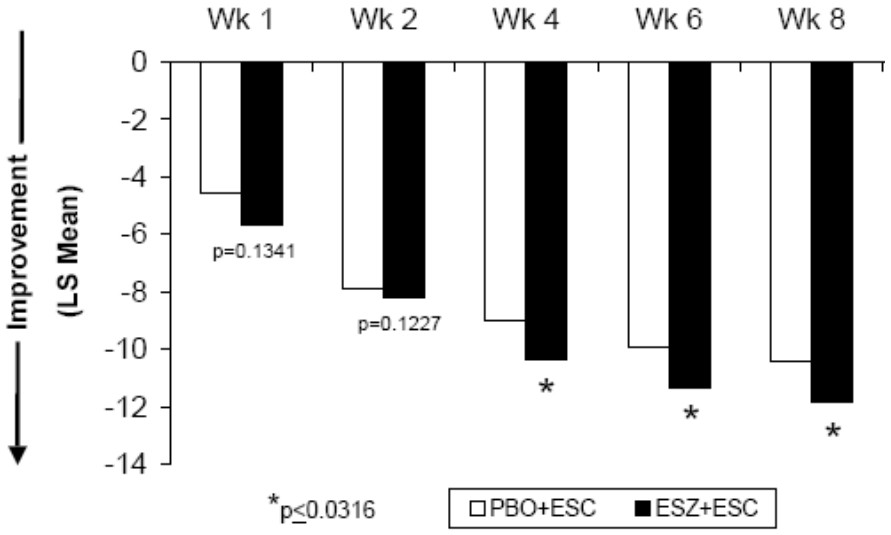
In the section below, the position of the applicant on differences in effects on anxiety, differences in effects on depression and differences in effects on pain is presented.

- **Differences in effects on anxiety**

The differences in pharmacology, particularly related to the α2 and α3 subunits, may explain the observation of anxiolytic effects associated with eszopiclone where none have been observed with racemic zopiclone. There is a growing body of clinical research demonstrating that eszopiclone has anxiolytic effects that are unrelated to its hypnotic effects. Studies 190-902 and 190-052 conducted in subjects with Generalised Anxiety Disorder (GAD) or Major Depressive Disorder (MDD) demonstrated significant reduction in anxiety in subjects receiving eszopiclone compared with

placebo. In each of these studies, all subjects received an SSRI with either eszopiclone 3 mg or placebo administered nightly over the course of 8 weeks. Figure 15 demonstrates the change from baseline in the Hamilton Anxiety Rating Scale (HAM-A) excluding the insomnia item in subjects with GAD in Study 190-902. Statistically significant differences were noted with eszopiclone relative to placebo by Weeks 4 through 8. Similar results were observed for the HAM-A total score including the insomnia item, indicating that the differences in the change in HAM-A scores were not modulated exclusively by the effect on sleep.

Figure 15 – HAM-A Total Score Excluding Insomnia Item (#4), LS Mean Change from Baseline (ITT Population, Study 190-902)

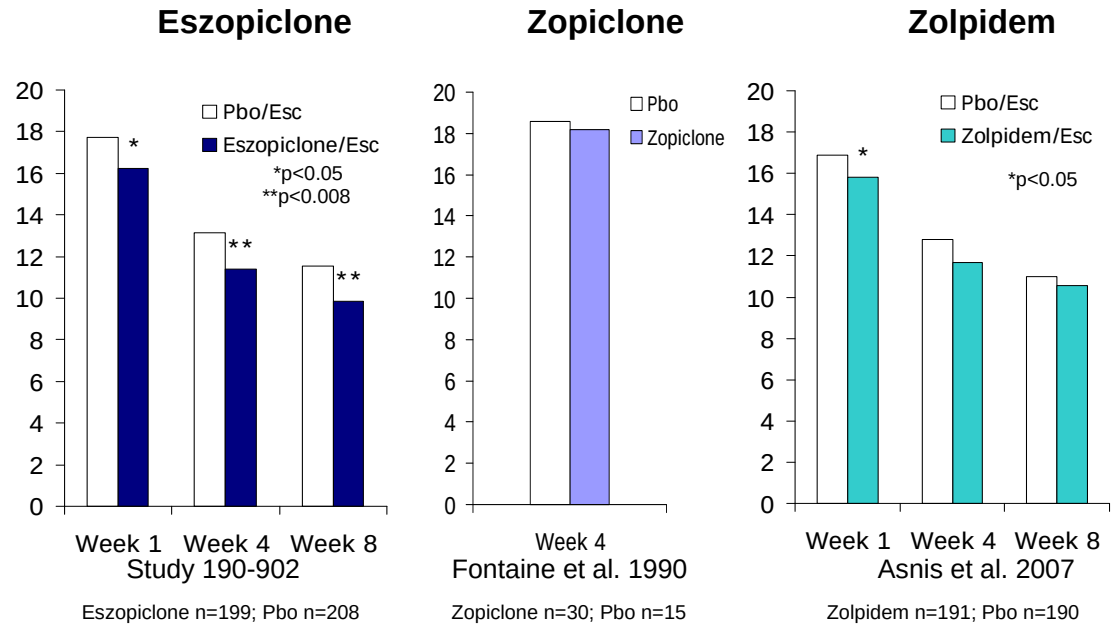


In Study 190-052, anxiety data were collected as part of the Hamilton Depression Rating Scale (HAM-D), where items #10 and #11 evaluate Anxiety Psychic and Anxiety Somatic. Eszopiclone demonstrated significant improvements on the Anxiety Psychic item over the course of the 8 week double-blind period compared with placebo (p=0.0307).

Such beneficial effects in subjects with anxiety have not been reported for the α1-selective hypnotic zolpidem, providing further evidence that differences in receptor pharmacology can predict clinically meaningful differences. Note, zolpidem, unlike eszopiclone, has only minimal effects at receptors containing α2 and α3 subunits. Asnis et al. (2007) recently reported results of a large study in which zolpidem or placebo was administered adjunctively with an SSRI in patients with GAD that was similar in design to the eszopiclone study 190-902. The results of this study are shown in Figure 16 along with the results from eszopiclone study 190-902. While an improvement in the HAM-A total score is demonstrated for the zolpidem group at week 1, there was no significant difference at Weeks 2-8. In contrast, the eszopiclone study demonstrated significant and sustained improvement in the total score at each week of the 8 week period, and at Weeks 4-8 when the insomnia item was removed from the total score.

Also shown in Figure 16 are the results of a zopiclone study in subjects with GAD. [Fontaine 1990] In this study, zopiclone 7.5 mg or placebo was administered as a monotherapy at night. Though the sample size is small, there appears to be no improvement in the HAM-A total score compared to placebo by week 4. The Applicant is not aware of any other placebo-controlled study of zopiclone in subjects with GAD.

Figure 16



Studies performed by Mizuki (1983) and Inanaga (1982) support the findings of a lack of anxiolytic effect associated with racemic zopiclone. They evaluated theta activity utilizing EEG as an indicator of anxiolytic effects in healthy male subjects administered placebo, diazepam 5 mg, zopiclone 5 mg and zopiclone 10 mg in a double-blind cross-over study. The EEG study demonstrated no effect of zopiclone 5 mg on EEG theta activity or as measured by the State Trait Anxiety Inventory (STAI) scale. Zopiclone 10 mg demonstrated a mild effect on these measures, but not as great as diazepam. The authors concluded that, while zopiclone is appropriate for use as a sedative/hypnotic, it demonstrated little anxiolytic potential in humans. It is important to note that the recommended dose of zopiclone for insomnia is 7.5 mg and that the low dose of zopiclone 5 mg contains 2.5 mg of the (S)-isomer.

In contrast, the Applicant evaluated daytime administration of eszopiclone 0.3, 0.6, 0.9 or 2.0 mg or placebo in healthy male subjects (Study 194-026)[2] utilising quantitative electroencephalography (qEEG), auditory P300 (evoked potential), and cognitive functioning from 30 minutes to 12 hours following daytime dosing. In this model, evaluation of EEG frequency bands can be used to distinguish anxiolytic activity (based on analysis of beta and theta EEG activity) from sedative activity (based on analysis of alpha and delta EEG activity). Based on qEEG analysis, all doses of eszopiclone administered in this study up to and including the 2.0 mg dose significantly increased beta EEG activity compared with placebo (the primary endpoint of the study) in a dose-dependent manner, indicating an anxiolytic effect. A dose-dependent decrease in theta power was also noted, which also indicates an anxiolytic effect. An increase in delta power and decrease in alpha power induced by the 2.0 mg dose indicated significant impairment of the subject's arousal level; doses below 2.0 mg did not exhibit significant effects on arousal or sedation. Taken together, results from qEEG analyses (beta, alpha, delta, and theta bands) and cognitive functioning analyses demonstrate that all doses of eszopiclone up to and including 2 mg are associated with anxiolytic effects.

In total, these data suggest that exposure to low levels of eszopiclone during the elimination phase the next day following nighttime administration may have an anxiolytic effect that contributed to the improvements observed on measures of anxiety in clinical studies. Conversely, the zopiclone data suggest that much higher doses of racemic zopiclone are necessary to have an anxiolytic effect and that this effect is not distinct from its sedative effects, possibly related to the interference of the (R)-isomer with respect to the pharmacological activity of the (S)-isomer at the $\alpha 2$ and $\alpha 3$ receptor

[2] Preliminary data were available in the response to the Day 120 List of Questions. A final study report is now available upon request.

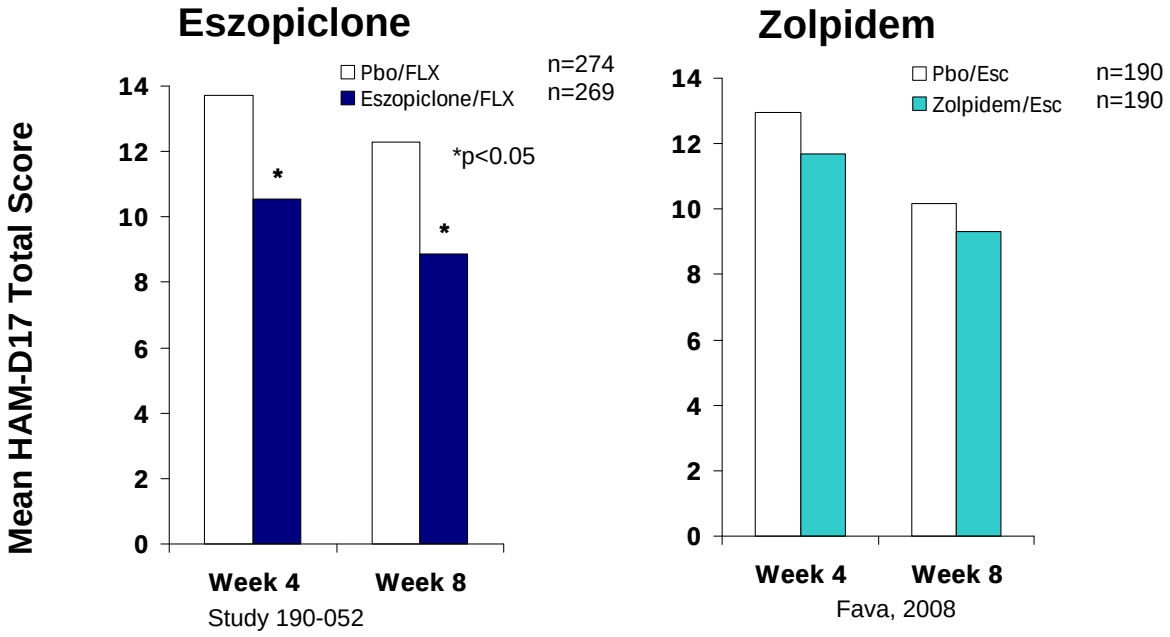
subunits. This is supported by animal studies where direct comparisons in rats demonstrated that racemic zopiclone and (R)-zopiclone exhibited anxiolytic activity only at doses that also impaired motor performance. In contrast, the single isomer eszopiclone demonstrated a separation between the anxiolytic and sedative activity such that anxiolysis was apparent at doses lower than those that disrupted motor performance. [Carlson 2001]

- **Differences in effects on depression**

The greater α3 subunit effects of eszopiclone are consistent with the differential effects of eszopiclone and racemic zopiclone on antidepressant outcomes. Recent studies suggest an association between major depression and the α3 subunit of the GABA receptor. [Henkel 2004, Fiorelli 2008]. These observations are consistent with data from clinical studies indicating that eszopiclone has greater effects on depression outcomes when co-administered with antidepressants than either zolpidem or racemic zopiclone, which have relatively less α3 activity.

The effect of eszopiclone on measures of depression has been evaluated in a number of clinical studies, including subjects with MDD (190-052), GAD (190-902), or women in the peri-menopausal transition (190-054). Significant improvements in underlying depressive symptoms have been consistently observed with eszopiclone in each of these studies as measured on a number of scales including the HAM-D and MADRS. The improvements in the antidepressant outcomes have been so significant that the Applicant is further evaluating the antidepressant effects in subjects with insomnia and MDD in an ongoing study in 11 countries throughout Europe (data not yet available). These benefits have been demonstrated to be separate from effects on sleep as the significant improvements remain, even when removing sleep items from the rating scales. Further substantiating the clinical effects of the differences in receptor pharmacology, a study of the α1-selective zolpidem utilizing a design similar to that of the eszopiclone Study 190-052 showed no effect of zolpidem on the HAM-D total score compared to placebo (Figure 17).

Figure 17



Pbo: Placebo; FLX: fluoxetine; Esc: Escitalopram.

Zopiclone has not been evaluated in any placebo-controlled study in depressed patients. However, in a double-blind placebo and active controlled 2-week crossover study of racemic zopiclone 7.5 mg in menopausal women age 40-60 years; racemic zopiclone demonstrated no effect on the Profile of Mood Scale (POMS). [Quadens 1983] As noted above, eszopiclone 3 mg was associated with significant improvements in mood in women with menopausal symptoms in study 190-054 as measured by the change from baseline MADRS score.

- **Differences in effects on pain**

Differences in GABA pharmacology related to the α2 and α3 subunits may explain differences observed in zopiclone's and eszopiclone's effects in subjects with chronic pain. Studies in genetically mutated knock-out mice demonstrated analgesic effects associated with GABA α2 and α3 subtypes in the spine. Agents that are selective for α2 and α3 subtypes have demonstrated analgesic effects, which may be related to both the diminished pain signals to the brain as well as a reduction in the associated emotional or anxiety aspects of pain. [Knabl 2008]

Eszopiclone was evaluated in a double-blind, placebo-controlled 4-week study of 153 subjects with insomnia and rheumatoid arthritis (190-055). In this study, eszopiclone 3 mg was associated with a statistically significant decrease in the number of tender joints, in overall pain, and in severity of pain as assessed by a number of scales ($p<0.05$).

Racemic zopiclone has been evaluated in a number of studies examining effects in patients with insomnia and chronic painful conditions including rheumatoid arthritis and fibromyalgia. Two studies were conducted in patients (n=49 and n=41) with insomnia comorbid with fibromyalgia and one study in 40 patients with insomnia comorbid with rheumatoid arthritis [Drewes 1991, Grönblad 1993, Drewes 1998]. All three studies demonstrated no improvements in measures of general pain, morning stiffness, tenderpoint sensitivity or other pain measures following 2 to 8 weeks of treatment with zopiclone 7.5 mg relative to placebo. However, one study showed that most zopiclone subjects had worsened tenderpoint sensitivity and global pain drawing scores at 8 weeks compared with placebo for which most placebo subjects showed improvements in these pain scores. [Gronblad 1993] Thus, improvements in sleep in subjects administered zopiclone were at the expense of the overall well-being of the patient due to worsening of the comorbid pain.

CHMP position:
In the section below, the position of the CHMP on differences in effects on anxiety, differences in effects on depression and differences in effects on pain is presented.

The comparison of the racemate zopiclone to other hypnotics in comorbid conditions with other psychiatric disorders is not helpful for the main question, whether there are clinically meaningful differences between eszopiclone and the racemate zopiclone or not. This could be only addressed by adequate planned direct head-to-head-studies regarding efficacy and safety between comparable dosages of eszopiclone and the racemate zopiclone. Moreover it will be very difficult methodologically to disentangle the improvement in these disorders from the hypnotic effects as sleep disturbances belong to the key symptoms of these disorders.

IV. Discussion and Scientific framework for concluding that eszopiclone is sufficiently different from zopiclone such that it is an NAS.

Detailed applicant's position:
In the section below, the position of the applicant to conclude that eszopiclone is sufficiently different from zopiclone such that it is an NAS is presented

Policies and guidelines in ICH regions have recognised since the early 1990s that the enantiomers of racemic drugs can be very different from each other and from the parent racemate. It is often the case that most or all of the desired therapeutic activity resides with one of the isomers (the eutomer), while the other isomer may be far less potent or in fact, active in an undesirable manner (and therefore a true distomer). Distomers can possess unwanted toxicities and/or can interfere with the therapeutic effect of the eutomer via a number of mechanisms (e.g., undesirable receptor interactions, other pharmacologic differences, effects on pharmacokinetics, effects on metabolism, etc). [Burke 2002] The potential advantages of a single enantiomer include: more selective pharmacodynamic profile, potential for an improved therapeutic index, less complex pharmacokinetic profile, and less complex relationship between plasma concentration and effect. [Burke, 2002, Hutt 2003] In the case of zopiclone, the (S)-isomer possesses the desired therapeutic activity as the eutomer, while the (R)-isomer does not make a positive contribution to therapeutic outcomes and is the distomer.

It is well understood that for enantiomers that exist in eutomer-distomer pairs, removal of the distomer can result in positive differences that are reliably and reproducibly detectable. When a distomer interferes to some degree with the desired therapeutic effect, its removal can permit the pre-existing dose of the eutomer to be demonstrably more effective than the parent racemate, can permit a lower dose of the eutomer to show efficacy comparable to the racemate, or can result in an opportunity for *concomitant* dose-lowering and efficacy improvements. It is also understood that these resultant differences do not necessarily preclude the continued medical use of the parent racemate; instead, development of the eutomer is desirable to the degree that the differences observed represent a meaningful opportunity for improvement in efficacy and/or safety. For this reason, development of single-isomer drugs, either *de novo* or from marketed racemates, is encouraged in the ICH regions.

There are a number of examples of isomers that differentiate from their respective racemic compounds. The initial use of racemic dopa for the treatment of Parkinson's disease was associated with adverse events of nausea, vomiting, anorexia, involuntary movements and granulocytopenia. The subsequent development of L-dopa resulted in a reduction in the effective dose and a reduction in the risk of adverse effects. Esomeprazole (Nexium®), a proton pump inhibitor indicated for the treatment of gastroesophageal reflux disease (GERD) is the S-enantiomer of omeprazole (Losec® or Prilosec®). Esomeprazole is associated with lower first pass metabolism, slower plasma clearance and increased systemic availability compared to the R-enantiomer. These variations allowed a modification of the dose to improve onset of effect while maintaining a similar tolerability profile. The S-enantiomer of ketamine produces an anesthetic effect, while the R-enantiomer can cause hallucinations. Other recent examples include escitalopram/citalopram (Cipralex or Lexapro / Cipramil or Celexa) and levocetirizine/cetirizine (Xyzal/Zyrtec). [Burke 2002, Hutt 2003] Thus the importance of developing a single enantiomer is well established

Table 5 summarises the overall findings as they relate to differences in the overall risk benefit profile of eszopiclone compared with racemic zopiclone. The data demonstrate that removal of the (R)-isomer permits a *lower* dose of the (S)-isomer to demonstrate *better* efficacy (particularly with respect to onset of action). Further, removal of the (R)-isomer permits the reduction in next day residual effects via reduction of the exposure to the eutomer and its active metabolite, resulting in an *improvement* in the safety profile. These are clinically relevant differences.

Table 5

	Differential findings	**Supportive evidence**
Recommended Dose	Administration as a single isomer allows for a reduced recommended eszopiclone dose of 3 mg that is at least as effective as zopiclone 7.5 mg.	• ESZ111503 head-to-head comparative study • Corroborated by published historical literature
Tmax	Eszopiclone Tmax of 1 hour is shorter than zopiclone Tmax of 1.5 hours	• Head-to-head comparative PK studies 190-010 and 190-001; • Corroborated by historical literature and label statements
Sleep onset	Latency to persistent sleep is faster with eszopiclone than racemic zopiclone.	• ESZ111503 head-to-head comparative study; • Comparison of studies of similar design: 190-045 and Lamphere et al. • Corroborated by historical literature
Residual effects	Eszopiclone showed a reduction in the magnitude of residual effects relative to zopiclone	• ESZ111503 head-to-head comparative study; • Comparison of studies of similar design: 190-024 and 190-025 (eszopiclone) with 190-027 (zopiclone) • Corroborated by historical literature and data from studies 190-024, 190-025, 190-027, 190-059 and 190-060

	Differential findings	Supportive evidence
Pharmacology	Eszopiclone is associated with greater relative effects at the α2 and α3 receptor subtypes compared with racemic zopiclone which has a greater relative effect at the α1 and α5 receptors.	• Comparative pharmacology study 190-435.
Anxiolysis, antidepressant and antinociceptive activity	Eszopiclone is associated with beneficial effects on anxiety, mood and pain whereas racemic zopiclone and α1-selective agents demonstrate no relevant therapeutic activity at comparable doses.	• Comparative animal studies – Carlson 2001 • Corroborated by historical zopiclone literature and data from studies 194-026, 190-902, 190-052, 190-054 and 190-055.

- **Discussion of Pharmacokinetic Differences**

There are a number of pharmacokinetic differences between eszopiclone and zopiclone. The absorption curve of eszopiclone is shifted to the left by thirty minutes with respect to the racemate with a corresponding Tmax of 1 hour. For drug elimination, the plasma concentrations of eszopiclone are approximately 20% lower at 8 hours post dose with eszopiclone than with racemate (on a ~ 1:2 mg dosing basis).

The data presented consistently show via studies of comparable design, employing objective polysomnographic (PSG) methods that eszopiclone provides robust sleep onset effects, ~10 minutes faster compared to racemic zopiclone, despite the lower recommended dose of 3 mg eszopiclone. These effects are reproducible as demonstrated by the actigraphy data from the head-to-head study (ESZ111503). Thus as anticipated, the differences seen in the faster Tmax of eszopiclone translate into significantly faster sleep promoting effects for eszopiclone compared with racemic zopiclone.

With regard to differences in safety, a body of literature, including studies of comparable design demonstrates no significant next day impairment following eszopiclone, whereas racemic zopiclone is associated with significant next day impairment observed in studies evaluating driving, and cognitive and psychomotor outcomes. The recently completed study (ESZ111503) that compared the residual effects of zopiclone to the single isomer eszopiclone further confirmed these observed effects, with eszopiclone differing significantly from zopiclone on an analysis of the primary psychomotor measure and secondary measures of memory impairment.

These data demonstrate that there are differences between eszopiclone and racemic zopiclone which are reliable and reproducible. The question remains then as to whether these reproducible differences are relevant and clinically meaningful?

To answer this, it is important first to understand the necessary attributes of a hypnotic agent. A desirable hypnotic agent should have a rapid onset of action (ensuring rapid sleep onset) and be able to maintain its level of sleep promotion through the night but have activity that drops off just before the patient starts their day (after approximately 7-8 hours) in order to minimise next day residual effects (Bogan 2008).

The pharmacokinetic properties of a sleep medication are particularly important in determining its onset of action and continued duration of action, which in turn affects a hypnotic agent's propensity to induce next-day sedation (residual effects). The capacity to exert a significant effect on sleep induction is dependent upon a rapid increase in plasma concentration (i.e. a short Tmax) following administration during which time the action of rapidly promoting sleep is desirable. Agents with a short Tmax, in the range of 30-60 minutes would be expected to have a therapeutic effect of promoting sleep more quickly than one with a longer Tmax.

In this regard, it has been determined that an improvement in mean or median sleep latency of approximately 10 minutes relative to placebo is a clinically meaningful measure of hypnotic efficacy. We note that a difference from placebo of approximately 10 minutes has been sufficient to support

approval with regards to claims of hypnotic efficacy. The EPARs for Circadin and Sonata discuss improvements relative to placebo in sleep latency of 9 to 11 minutes for Circadin and approximately 10 to 15 minutes for Sonata. Further, a recent meta-analysis of the effect of hypnotics on sleep onset yielded an average decrease from baseline of 11 minutes. [Youngstedt 2003] This would suggest that an improvement in sleep onset by approximately 10 minutes when comparing two active treatments, as was observed when comparing eszopiclone with racemic zopiclone, is indeed clinically relevant. This represents a 33% improvement over the observed 30min sleep latency for zoplicone.

Currently there is no hypnotic available in the EU that matches the ideal profile for sleep medication. Whilst the non-benzodiazepine hypnotics ("Z drugs") demonstrate advantages in safety over the benzodiazepines, a number of disadvantages are noted. Specifically, the duration of action of zaleplon is too short to confer sleep maintenance benefits due to its short half-life of 1 to 2 hours. (Refer to Table 4 in section 2.4.3.) Similarly, with a half-life of approximately 2 to 4 hours, zolpidem is also limited in its reliable maintenance of effect (an extended-release formulation has been developed in the US to partially address this shortcoming). Zopiclone possesses reliable sleep maintenance effects but the literature is now clear that this is at the cost of significant residual effects, which may be related to the higher dose required for efficacy with the racemic compound. In addition, having a longer Tmax than the other Z drugs, as well as a number of the older benzodiazepines, there is evidence to suggest sleep onset effects are delayed with racemic zopiclone, relative to agents with a shorter Tmax.

In a review comparing the pharmacokinetics and pharmacodynamics of zaleplon, zolpidem, and racemic zopiclone, Drover states (Drover, 2004):

> "Regardless of the pharmacodynamic profiles, pharmacokinetics are an important factor in describing the behavior of these drugs. Although one drug may have a specific intensity of pharmacodynamic response at a particular plasma concentration that is different from another drug at the same plasma concentration, the actual onset and duration are probably determined by pharmacokinetics."

The impact of the PK differences at the offset of action i.e., the other critical time point of sleep, 6-8 hrs after dosing when the patient is waking up and beginning their daily routine is also important. If the patient is still "sleepy" next morning this could lead to an impairment in driving ability, memory, attention, alertness and process speed. These effects have been strongly associated with the use of zopiclone at a dose of 7.5mg. In contrast there is no impairment in on the road driving tests with eszopiclone.

- **Discussion of Pharmacological Differences**

It is apparent that the observed pharmacological differences between eszopiclone and zopiclone regarding effects on the $GABA_A$ receptor alpha subunits lead to differences in the overall clinical risk/benefit profile of these two compounds. Differences in the relative activities at the alpha subunits are predictive of differences in effects on memory, anxiety, depression and pain, based on data noted in both the literature and recent clinical studies, (including head-to-head trials), where eszopiclone demonstrates less memory impairment and greater anxiolytic, antidepressant and antinociceptive effects than racemic zopiclone and zolpidem.

The head-to-head comparison of the next day effects of eszopiclone and racemic zopiclone demonstrates increased and longer lasting impairment of memory related to zopiclone compared with eszopiclone. These differences are consistent with the differential effects of these compounds at the $\alpha 1$ and $\alpha 5$ receptor subunits. This difference is an important indicator of residual effects on cognitive function. Decreased accuracy in recall can have a detrimental impact on daily functioning (e.g. ability to correctly complete complex tasks).

It has been estimated that 40% to 60% of patients with insomnia have a comorbid psychiatric condition, most often depression or anxiety. [Ohayon 2003] Because patients with anxiety constitute such a high portion of insomniacs, the potential for a hypnotic to benefit the comorbid anxiety is

clinically relevant to the overall well-being of the patient in this significant population. For example, when comparing temazepam to zopiclone, Fontaine et al. found the difference in effects on daytime anxiety to be relevant to the choice of hypnotic in patients with GAD. [Fontaine 1990] Similarly, when comparing eszopiclone and zopiclone, therapeutic benefits in the treatment of anxiety associated with eszopiclone would have a clinically relevant impact on the choice of hypnotic for use in patients with GAD.

While the therapeutic benefit of eszopiclone's anxiolytic effects is obvious for the patient suffering from an anxiety disorder, it is also relevant to the patient with primary insomnia. There is considerable evidence that excessive pre-sleep worry leads to difficulty in initiating sleep. Studies utilizing the Sleep Disturbance Questionnaire have shown that responses such as "my mind keeps turning things over" and "I am unable to empty my mind" are the most highly rated contributing causes of sleep disturbance. [Harvey and Greenall, 2003] Cognitive arousal is ten times more likely than somatic arousal to be cited as the main determinant of sleep disturbance. [Lichstein 1980] Additional studies of clock watching (periodic monitoring of the clock to see how long it is taking to fall asleep which fuels the worry of not getting to sleep) and catastrophic worry (dwelling on the worst possible outcomes of any situation in which there is a possibility for an unpleasant outcome; in this case the negative consequences of not being able to fall asleep) have been shown to be highly related to the prevalence of insomnia. [Tang 2007, Harvey 2003] Worrying in these situations does not rise to the syndromal diagnosis of GAD which is characterized by pathological worry, but nevertheless has an impact on the patient's ability to fall asleep.

Study 190-902 demonstrates that the night time administration of eszopiclone yields benefits in next day levels of anxiety in subjects with GAD. Study 194-026 demonstrates that daytime administration of eszopiclone results in anxiolytic effects measured by qEEG in healthy normal subjects within 30 minutes post dose. These effects have not been observed with zopiclone. Taken together with the faster rise in plasma concentration of the (S)-isomer, it is reasonable to conclude that the differences in anxiolytic activity may contribute to efficacy of eszopiclone in reducing sleep latency. Thus, the mechanism by which eszopiclone aids the induction of sleep may be related to its effects on $\alpha 2$ and $\alpha 3$ receptor subunits to reduce anxiety. This is a different characteristic than the predominantly $\alpha 1$ modulation associated with zopiclone.

Similar to the discussion of anxiety, the impact of eszopiclone on depression is relevant to both the depressed patient population as well as the primary insomnia population. Insomnia is one of the hallmark diagnostic criteria of major depressive disorder (MDD). Insomnia in depressed patients is associated with an increased risk of new major depressive episodes within a year and, more seriously, with an increased risk of suicidality. [Ford 1989, Agargun 1997, Fawcett 1991] Insomnia also may be a predictor for subsequent development of depression or a prodromal symptom accompanied by some depressive symptoms but yet to evolve into full blown depression. This link may lead clinicians to treat insomnia in an attempt to prevent the onset or recurrence of depression. [Fava 2004] Thus, eszopiclone's demonstrated differential effects compared with zopiclone with respect to the improvement of depressive symptoms in subjects with MDD suggest the potential for an additional benefit in the treatment of prodromal depressive symptoms in the broader primary insomnia population.

Finally, the differential effects of eszopiclone on pain are consistent with the greater relative activity of eszopiclone at the $\alpha 2$ and $\alpha 3$ receptors. This may be due to the direct association of these subunits with an antinociceptive effect as well as an indirect benefit from myorelaxation and anxiolysis. There has been a great deal of research regarding the relationship between chronic pain and insomnia. Pain can induce arousal in an otherwise healthy individual. Conversely, sleep disruption can lower the threshold for pain. [Tang 2007] In their review of insomnia co-occurring with chronic back pain, Tang et al. state that " a reciprocal link between longer term sleep problems and chronic pain would indicate the value of managing sleep disturbance occurring in the context of chronic pain. Such treatment should not only reduce the problems normally associated with insomnia, but also have a beneficial effect on the experience of pain and the restoration of normal functioning." Thus, the differences between the effects of eszopiclone and racemic zopiclone in subjects with insomnia and pain are relevant to the overall well being of the patient.

- **Determination of an isomer as a new active substance**

In considering the evaluation of an isomer as a new active substance, the current legislation and available guidance state that this determination rests on whether the isomer (i.e. eutomer) differs with respect to properties relating to safety and/or efficacy. For this assessment, one must consider whether the impact of removal of the distomer is clinically meaningful to some reasonable degree and whether the data utilised for making this determination are reproducible and reliable. There is no guidance with respect to the nature of the data necessary to meet the threshold for this determination. This is a legal matter as well as a clinical matter, and as such, the decision-making framework should not necessarily be the same as would be employed to make a drug approval decision. For example, a single strict statistical test applied to a comparative assessment of safety or efficacy would underestimate the combined benefit of concomitant improvements in safety and efficacy. This latter assessment of risk and benefit requires clinical judgment to be applied.

The Applicant has presented data from comparative studies that eszopiclone and zopiclone have differences in pharmacokinetics, pharmacodynamics and receptor pharmacology. The Applicant has further provided a discussion of the clinical relevance of these differences based on clinical judgment. For example, it is reasonable to conclude that a faster rise in the therapeutic plasma levels of the eutomer compared with the racemate would result in faster onset of hypnotic activity and correspondingly shorter sleep latency. It is also reasonable to conclude that a reduction in the total drug exposure by elimination of the distomer and reduction in the optimal dose of the eutomer would confer a reduction in residual next day effects. Finally, it is reasonable to conclude that differences in the activity at the GABA alpha subtypes will confer different pharmacological properties with respect to safety and efficacy. We recognise, however, that the CHMP was not fully comfortable with the dataset presented in the MAA and at the Oral Explanation and as such we have provided in this re-examination a discussion of available evidence corroborating the observations previously noted, supporting their reliability and reproducibility, and providing the context of these differences for the patient such that clinical judgment can be applied in the determination that eszopiclone is not the same as zopiclone.

Applicant's Conclusion

Whilst there have been substantial improvements in hypnotic agents over the past two decades, it is recognised that there are still clinical short-comings with respect to the available hypnotics. Highest of these concerns is the balance of efficacy with next day residual effects that impair memory function and the ability to operate automobiles. Eszopiclone has been demonstrated to have differences in pharmacokinetic and pharmacodynamic properties with regard to both efficacy (measured as sleep latency) and safety, in comparison to the racemate zopiclone.

In head to head comparative studies it has been clearly demonstrated, that eszopiclone has a substantially shorter Tmax, which results in a clinically relevant decrease in sleep latency. Again, in direct head to head comparative studies eszopiclone has been demonstrated to have substantially lower plasma levels at 7 – 9hours post dose, which generally results in fewer next day residual effects. Specifically, there is significantly reduced memory impairment compared to zopiclone.

These clinical findings are evident against a background of non-clinical data that predict that the increased effectiveness of eszopiclone at the $\alpha 2$ and $\alpha 3$ and a decreased effectiveness at the $\alpha 1$ and $\alpha 5$ GABA-A receptors would result in decreased memory effects and beneficial effects with respect to anxiety, depression, and pain. Clinical trial data have consistently demonstrated significant efficacy with respect to reductions in anxiety, depression and pain that are not apparent for racemic zopiclone.

In conclusion, eszopiclone should be classified as a new active substance, because it differs from zopiclone with respect to properties relevant to mechanism of action, efficacy and safety, in a manner that is clearly relevant from a clinical perspective.

CHMP position:

In the section below, the position of the CHMP on the above discussion where the applicant concludes that eszopiclone is sufficiently different from zopiclone such that it is an NAS is presented

The applicant summarized again in this part his line of arguments to justify that eszopiclone should be considered as a new active substance. However, as outlined in the specified parts of this report the CHMP is not in agreement. There are no head to head studies available, which allow the undoubted conclusion of an relevant and clinically meaningful difference of eszopiclone over the racemate of zopiclone. So in view of the CHMP the applicant has not shown sufficient evidence and CHMP maintains its initial opinion. The provided supportive data from study ESZ 111503 are hampered by major methodological shortcomings and are not considered as proof of clinical relevant and meaningful differences.

3.3. CHMP Overall conclusions from the Joined Assessment Report

The applicant argued that eszopiclone shows an improved clinical profile with faster sleep onset and lower next day residual effects based on pharmacokinetic and pharmacodynamic differences. Therefore eszopiclone should be considered as a new active substance.

The CHMP cannot agree with these arguments. : the reported pharmacokinetic differences are most probable an effect of the slightly different dosages, which are not directly comparable. In the pharmacodynamic profile eszopiclone and the racemate are not that different either, the S-enantiomer seems to be responsible for the pharmacodynamic hypnotic profile, whereas the R-enantiomer shows negligible effects on the GABA-receptor-complex of interest.
This is in line with the clinical profile of eszopiclone compared to the racemate, this seems to be more comparable than different. Prospectively planned, state of the art clinical trials to proof for differences in efficacy and safety (direct head to head comparison) have not been performed by the applicant. The study with supportive data (study ESZ111503) has major methodological short-comings for the questions to be addressed, the results could be considered at best preliminary and hypothesis-generating. Moreover, the final study report of this study could not be assessed in detail before the final discussion, which further hampers the interpretation of the results.

For the evaluation of the grounds for re-examination, the CHMP also consulted the Clinical Neurosciences Scientific Advisory group of Experts who met the 5th of February 2009.

3.4. The following questions were addressed by the CHMP to the Clinical Neurosciences Scientific Advisory Group

1. Binding characteristics
Does the R-zopiclone have a binding affinity to the GABA-A receptor subunits, which can influence the binding characteristics of S-zopiclone to this receptor and can these data (binding affinities, electrophysiological studies) predict or indicate differences in the pharmacodynamic activity of the racemate zopiclone versus S-zopiclone in patients?

2. Pharmacokinetic clinical data
If the described PK differences are caused due to absorption differences of S-zopiclone and racemic zopiclone and not due to the different pharmaceutical form, do you believe that they can lead to significant differences in the clinical efficacy of S-zopiclone and racemic zopiclone?

3. Clinical efficacy data
Do you consider the indirect clinical evidence, as presented by the applicant (effect on sleep parameters, memory, anxiety, depression and pain), as a proof of pharmacological activity of (R)-zopiclone, which can lead to relevant and clinically meaningful differences in the clinical efficacy or safety of S-zopiclone and racemic zopiclone?

The Applicant was also invited to discuss their position on these questions with the CNS SAG on 5th of February 2009.

The CNS SAG, following internal discussion and having listened and discussed the Applicant's presented arguments, reached conclusions in line with the conclusions from the CHMP:

Answer to Question. 1. Binding characteristics

Yes there may be an interaction between R-zopiclone and eszopiclone at the GABA receptor but this has not been unequivocally demonstrated by the submitted data. Available pharmacological results on eszopiclcone consist of various in *vitro/in vivo* data not immediately related to efficacy or safety effects. Binding receptor profile of eszopiclone and the racemate does show some differences but probably not at the benzodiazepine-site. Possibly these element do influence the binding characteristics of eszopiclone. The animal (anxiolysis) models presented (in rodents) are of limited applicability to the clinical setting. Therefore the removal of R-isomer could remove interactions but there is no solid conclusion on whether the pharmacological profile is influenced, and the available data can not be extrapolated to predict a clinical difference.

Answer to Question 2. Pharmacokinetic clinical data

The CNS SAG was not convinced that pharmacokinetic parameters are actually different between eszopiclone and the racemate given that these were administered as different pharmaceutical formulations. Probably there is a small residual difference (tmax 1.3h for Lunivia versus 1.6h for Imovane) with no substantial influence, and there is also uncertainty on the presentation of data (means vs medians).
When translated to the clinical studies there is no correct head to head comparison using identical doses. Recalculation with correct doses reduces size of effect to about 10%. In the previously performed 190-001 study the same effect on the PK profile was not shown.

Answer to Question 3. Clinical efficacy data

The SAG considered that the indirect clinical evidence presented on memory, depression and other neuropsychological parameters observed in the healthy volunteers is difficult to interpret in terms of whether they translate into any clinically meaningful differences for patients with insomnia. The clinical influence of the R- isomer remains unconvincing.

3.5. Questions addressed during the Oral Explanation on 16th February 2009

Following the SAG meeting, and during the February 2009 CHMP meeting the Applicant was invited to present at an Oral explanation their final position on the following questions:

1. The study ESZ111503 was considered by the Rapporteurs as a negative trial. Moreover, in this study several methodological deficiencies were identified. Therefore, even if the methodological issues identified by Rapporteurs are solved (different doses - 7.5 mg of zopiclone vs. 3 mg of eszopiclone, sensitivity of actigraphy for sleep onset, multiplicity issues etc.), this study has very limited value regarding the confirmation of clinically meaningful differences regarding eszopiclone and zopiclone. The applicant should comment.

Applicant's response:

The applicant has re-emphasized their previous interpretation of study ESZ111503.
In relation to the dose used (3 mg vs 7.5 mg), the applicant stated that the Tmax is not dose-dependent for eszopiclone and therefore the use of different doses should not be regarded as a methodological issue.

Regarding the validity of actigraphy used in the study ESZ111503, the applicant reiterated his position based on literature.

2. The SAG concluded that from the additional data presented by the applicant a certain effect of the R-enantiomer on the GABA-A receptors has been shown. However, the magnitude and clinical relevance of a possible effect is still uncertain. The applicant is asked to present any data that will show clinically meaningful effect of R-zopiclone that will have an impact on the comparison of zopiclone and eszopiclone.

Applicant's response:

The *in vitro* and *in-vivo* results of (R)-zopiclone are sufficient in their view to demonstrate that R-zopliclone has indeed some pharmacological activity (in particular CNS depressant-like activity) and that this activity interferes with the pharmacological activity of (S)-zopiclone in the racemic mixture.

3. The comparative PK study 190-010 raised doubts about pharmaceutical comparison of the preparations used in this study. The applicant is asked to clearly compare the pharmaceutical characteristics of formulations (disintegration times, dissolution times, composition) used in the PK study 190-010 and to demonstrate that these absorption differences are stereospecific rather that dependent on the formulation used.

Applicant's response:

They discussed again the results of the PK study 190-010 and concluded that the differences observed in the plasma concentration at 30 min cannot be attributed to the formulation. In fact the disintegration time, dissolution time, composition, all these are not different between the used tablets of Imovane and of Lunivia). The applicant concluded that the dissolution profile and PK profiles cannot be affected by the number of tablets (as the compared formulations behave identically), and that only the presence of (R)-zopiclone accounts for the observed PK differences.

4. The applicant is asked to compare all available data regarding zopiclone and eszopiclone (data on file, literature data) regarding clinically meaningful parameters (sleep parameters, development of tolerance and dependence, posology, duration of treatment, adverse events etc.) that will clearly show differences between those two compounds.

Applicant's response:

They presented a summary table of differences, that they attribute to (S)-zopiclone versus racemic zopiclone: shorter Tmax, lack of dose-dependency of Tmax , faster sleep onset, relative efficacy at the sub □-receptors, beneficial anxiolytic and antidepressant effects, reduced next day memory impairment and fewer residual effects.

Overall conclusions on grounds for re-examination:

The Applicant presented with the grounds for re-examination a detailed argumentation based on non-clinical, pharmacokinetic and preliminary clinical pharmacology data in healthy volunteers.

Following re-examination of the available data the CHMP considered that there is overall insufficient evidence to demonstrate a clinical influence of the (R)- isomer removal on the safety and efficacy properties of (S)-zopiclone in patients with insomnia. The pharmacological data provided by the Applicant based on the documented binding profile and on animal models cannot be extrapolated to predict clinical differences with respect to the racemate. The differences observed in the pharmacokinetic clinical data provided by the Applicant are not based on identical doses and recalculation with correct doses reduces the size of effect on Tmax to about 10%. Finally the newly

provided data on neuropsychological effects in healthy volunteers (from a study that failed on primary analysis) are difficult to interpret and their clinical meaningfulness for patients with insomnia remains to be established.

3.6. Overall conclusions of the re-examination procedure

Taking into consideration the initial data submitted, the additional data presented by the Applicant with the detailed grounds of re-examination on 23 December 2008, and after consultation of the CNS SAG, and further discussion at the CHMP meeting of February 2009, the CHMP confirmed that their initial opinion of October 2008 is still valid:

> The applicant failed to prove relevant and clinically meaningful differences between eszopiclone and the racemate zopiclone in an adequate planned clinical trial with direct head to head comparison. No relevant differences have been demonstrated in properties with regard to safety or efficacy.

Therefore eszopiclone is considered as a known active substance.

Recommendation

- Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of Lunivia in the treatment of insomnia, including difficulty falling asleep, nocturnal awakening or early awakening, in adults, usually for short term duration was favourable and therefore recommended the granting of the marketing authorisation.

- Based on the CHMP review of data on quality, safety and efficacy and taking into consideration the advice from the Clinical Neurosciences Scientific Advisory Group, the CHMP considered by consensus that no meaningful clinical difference could be established between eszopiclone and zopiclone regarding safety and efficacy. Therefore the final Opinion remains in line with the first assessment and did not recommend the granting of New Active Substance status to eszopiclone.