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Committee for Medicinal Products for Human Use (CHMP)

Nerventra

laquinimod

Procedure No. EMEA/H/C/002546

Applicant: Teva Pharma GmbH

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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List of abbreviations

9-HPT	9-Hole Peg Test
ACTH	Adrenocorticotropic Hormone
AE	Adverse Event
AhR	Aryl hydrocarbon receptor
ALT	Alanine transaminase/Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase/Aspartate Aminotransferase
AUC	Area Under Curve
AV	Atrioventricular
BCS	Biopharmaceutical Classification System
CALUX	Chemically-Activated Luciferase Expression
CDP	Confirmed Disability Progression
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CGR	Country and Geographical Region
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cmax	Maximum Plasma Concentration
Cmin	Minimum Plasma Concentration
CNS	Central Nervous System
CO	Completers (cohort)
CPRD	Clinical Practice Research DataLink
CQA	Critical Quality Attribute
CRP	C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CYPs	Cytochromes
DELAQ	N-deethylated metabolite
DLC	Dioxin-like compounds
DMSO	Dimethyl sulfoxide
DMT	Disease Modifying Therapy
DOE	Design of Experiments
DVT	Deep Venous Thrombosis
EAE	Experimental Autoimmune Encephalomyelitis
EC	European Commission
EC20	Effective concentration at 20%
ECG	Electrocardiogram
ED50	Effective dose at 50% (Median Effective Dose)
ED90	Effective dose at 90%
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions Health Survey

ER	Estrogen Receptor
ERA	Environmental Risk Assessment
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EV	Evaluable (cohort)
FMEA	Failure Mode Effect Analysis
GA	Glatiramer Acetate
GC	Gas Chromatography
GCP	Good Clinical Practices
GD	Gestation Day
Gd	Gadolinium
GdE	Gadolinium Enhancing
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GPRD	General Practice Research Database
HCT	Hematocrit
hERG	human ether-a-go-go-related gene
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HR	Hazard Ratio
I3C	Indol-3-Carbinol
ICH	International Conference On Harmonization
IFN	Interferon
Ig	Immunoglobulin
IHD	Ischaemic Heart Disease
IM or i.m	Intramuscular
IR	Infrared
ITT	Intention to Treat
IV or i.v	Intravenous
IVRS	Centralised Interactive Voice Response System
IWRS	Interactive Web Response System
KF	Karl Fisher
KLH	Keyhole Limpet Hemocyanin
Kow	Octanol/water partition coefficient
LAQ	Laquinimod
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LDPE	Low density polyethylene
LOAEL	Lowest Observed Adverse Effect Level
MCQME	methyl 5-chloro-4-hydroxy-1-methyl-2-oxo-1,2-dihydro-quinoline-3-carboxylate
MCV	Mean Cell Volume
MFIS	Modified Fatigue Impact Scale
MNAR	Missing Not At Random
MNBN	Micronucleated Binucleated (cell)

MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MTD	Maximum Tolerated Dose
Nb	Number
NFκB	Nuclear Factor kappa Light-Chain-Enhancer of Activated B
NK	Natural Killer (cell)
NMR	Nuclear magnetic resonance
NOAEL	No-Observed-Adverse-Effect-Level
NOEL	No-Observed-Effect-Level
NONMEM	Nonlinear Mixed Effects Modeling Methodology
NRU	Neutral Red Uptake
NTP	National Toxicology Program
p.o	Per os
PAR	Proven Acceptable Ranges
PASAT	Paced Auditory Serial Addition Test
PBMC	Peripheral Blood Mononuclear Cells
PBVC	Percent brain volume change
PD	Pharmacodynamic
PDCO	Paediatric Committee
PECsw	Predicted Environmental Concentration in the surface water
Ph Eur	European Pharmacopoeia
PHA	Phytohemagglutinin
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PND	Post Natal Day
PP	Per Protocol
PPMS	Primary Progressive Multiple Sclerosis
PRAC	Pharmacovigilance Risk Assessment Committee
PRL	Prolactin
QbD	Quality by Design
QTCB	QT Interval Corrected For Heart Rate Using the Bazett Formula
QTCF	QT Interval Corrected For Heart Rate Using the Fridericia Formula
QTCI	Individually Corrected QT Interval
QTPP	Quality Target Product Profile
RBC	Red Blood Cell
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Relapsing Multiple Sclerosis
RR	Rate Ratio
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SD	Sprague Dawley

SD	Standard Deviation
SEER	Surveillance Epidemiology and End Results
SF-36	Short Form 36 Health Survey
SIR	Standardized incidence ratio
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SMR	Standard Maintenance Diet
SOC	System Organ Class
SPMS	Secondary Progressive Multiple Sclerosis
SWP	Safety Working Party
T25FW	Timed -25- Foot-Walk
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TK	Toxicokinetic
Tmax	Time to maximum plasma concentration
TSE	Transmissible spongiform encephalopathy
UDS	Unscheduled DNA synthesis
UGT	UDP-glucuronosyltransferase
UKNEQAS	United Kingdom National External Quality Assessment Service
ULN	Upper Limit of Normal
USA	United States of America
UV	Ultraviolet
v.s	Versus
WBC	White Blood Cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma GmbH submitted on 26 June 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Nerventra, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 April 2011.

The applicant applied for the following indication: treatment of patients with relapsing remitting multiple sclerosis (RRMS).

The legal basis for this application refers to:

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

The application submitted is

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision, P/0027/2012, on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0027/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 June 2007. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pierre Demolis

Co-Rapporteur: Martina Weise

- The application was received by the EMA on 26 June 2012.
- The procedure started on 18 July 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 October 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 5 November 2012.
- During the meeting on 15 November 2012, 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 16 November 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 July 2013.
- During the PRAC meeting on 11 July 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 31 October 2013 and 4 November 2013.
- On 13 November 2013, the PRAC adopted an RMP Advice and assessment overview via written procedure.
- During the CHMP meeting on 21 November 2013, the CHMP agreed on a Second list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the Second CHMP List of Outstanding Issues on 29 November 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the Second List of Outstanding Issues to all CHMP members on 6 December 2013.
- During a meeting of a Safety Working Party (SWP) on 3 December 2013, experts were convened to address questions raised by the CHMP.
- On 12 December 2013, the PRAC adopted an RMP Advice and assessment overview via written procedure.

- During the CHMP meeting on 17 December 2013, outstanding issues were addressed by the applicant during an oral explanation.

- During the meeting on 23 January 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Nerventra.

1.3. Steps taken for the re-examination procedure

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

Rapporteur: Greg Markey

Co-Rapporteur: Arantxa Sancho-Lopez

PRAC Rapporteur: Julie Williams

PRAC Co-Rapporteur: Dolores Montero Corominas

- The applicant submitted written notice to the EMA on 4 February 2014 to request a re-examination of Nerventra CHMP opinion of 23 January 2014.

- During its meeting on 17-20 February 2014, the CHMP appointed Greg Markey as Rapporteur and Arantxa Sancho-Lopez as Co-Rapporteur.

- The applicant submitted the detailed grounds for the re-examination on 24 March 2014. The re-examination procedure started on 25 March 2014.

- The Rapporteur's Assessment Report was circulated to all CHMP members on 17 April 2014. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 16 April 2014.

- During a meeting of the Safety Working Party (SWP) on 30 April 2014, experts were convened to address questions raised by the CHMP.

- During a meeting of the Scientific Advisory Group (SAG) on 8 May 2014, experts were convened to consider the grounds for re-examination.

- During the PRAC meeting on 5-8 May 2014, the PRAC adopted a PRAC advice on the questions raised by the CHMP.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 13 May 2014.

- During the CHMP meeting on 19-22 May 2014, the detailed grounds for reexamination were addressed by the applicant during an oral explanation before the CHMP.

- During the meeting on 19-22 May 2014, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific Discussion

2.1. Introduction

Laquinimod (Nerventra) is an oral quinoline-3-carboxamide and is a derivative of a parent compound, roquinimex, a drug previously evaluated in clinical trials for Multiple Sclerosis (MS) treatment and that had been discontinued due to safety concerns (see 2.6). Laquinimod showed beneficial effects in animal models of experimental autoimmune encephalomyelitis (EAE) used in MS drug development. However, the mechanism of action of laquinimod is not fully elucidated because the molecular target is not known.

The following indication was initially applied for: treatment of patients with relapsing remitting multiple sclerosis (RRMS). The proposed posology was a single oral daily dose of 0.6 mg.

Multiple sclerosis is a chronic, progressive, autoimmune, debilitating neurodegenerative disorder with multifocal demyelination affecting the brain, optic nerves, and spinal cord and this process leads to neurological impairment and severe disability. It is one of the most common neurological diseases in young adults and the leading cause of non-traumatic disability in young and middle-aged adults. Typically, it begins in the second or third decade of life. In 2008, the global incidence was estimated at 2.5 individuals per 100 000 and the global prevalence was estimated at 30 individuals per 100 000, with women being at a two times higher likelihood to develop MS than men. Regionally, the estimated median prevalence of MS is greatest in Europe (80 per 100 000), followed by the Eastern Mediterranean (14.9 per 100 000), the Americas (8.3 per 100 000), the Western Pacific (5 per 100 000), Southeast Asia (2.8 per 100 000), and Africa (0.3 per 100 000).

The classification of MS into 4 distinct clinical categories was suggested by Lublin and Reingold shortly after the availability of the first disease-modifying treatments as a means to aid physicians in providing care. The following categories were included: relapsing-remitting (RR) MS, with clearly defined disease relapses (clinical attacks) with full recovery or with sequelae and residual deficit upon recovery, and with periods between relapses characterized by a lack of disease progression; secondary–progressive (SP) MS, with continuous neurological decline with or without superimposed relapses, that follows an initial period of RR disease; Primary–progressive (PP) MS, characterized by a slow worsening from onset, without superimposed relapses; and progressive–relapsing (PR) MS, indicating slow worsening from the onset, but with superimposed relapse events as well.

Relapsing forms of MS are the most frequent clinical presentation of the disease. Eighty-two (82) to 85 % of all patients present with relapsing-remitting MS (RRMS), which is characterised by unpredictable acute episodes of neurological dysfunction named relapses, followed by variable recovery and periods of clinical stability. Within ten years more than 50% of patients who presented with a RR form eventually develop sustained deterioration with or without superimposed relapses; this form is called the secondary progressive variety of MS (SPMS).

The term relapsing MS (RMS) applies to those patients either with a RRMS form or a SPMS form that are suffering relapses. Patients with RMS, in spite of suffering from different MS forms, constitute a common target for current treatments.

Available disease modifying therapies (DMT) for MS aim to prevent relapses and ultimately to diminish the accumulation of disability. Laquinimod is a novel orally administered therapy intended for the treatment of patients suffering from relapsing-remitting multiple sclerosis. Currently, three oral MS drugs received positive opinions by the CHMP for granting their initial marketing authorisations in the European Union (EU), fingolimod (Gilenya) and teriflunomide (Aubagio) which were authorised respectively in March 2011 and August 2013; and dimethyl fumarate (Tecfidera) which is awaiting Commission Decision. The other available MS drugs are parenteral formulations

and include first line interferons-beta therapies, glatiramer acetate, natalizumab (Tysabri) and Alemtuzumab (Lemtrada). Lemtrada was recently authorised in September 2013. Tecfidera, together with Aubagio were recommended an indication for treatment of adult patients with RRMS by the CHMP. Lemtrada is specifically indicated for adult patients with relapsing remitting multiple sclerosis with active disease defined by clinical or imaging features. Due to their safety profiles (e.g. risk of opportunistic infections and secondary malignancies), Gilenya and Tysabri were considered as second line options at the time of their initial marketing authorisations.

2.2. Quality aspects

2.2.1. Introduction

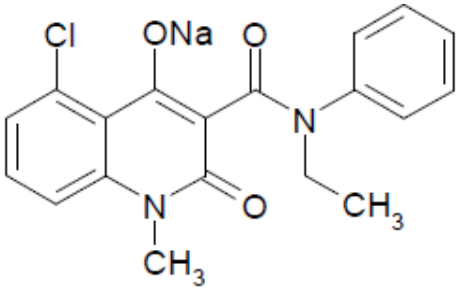
The finished product is presented as immediate release hard gelatin capsules containing 0.6 mg of laquinimod, as laquinimod sodium, as active substance.

Other ingredients are: mannitol, meglumine and sodium stearyl fumarate. The capsules shells are made of gelatin and titanium dioxide (E171); and the printing ink is composed of shellac, ethanol, iron oxide black (E172), propylene glycol (E1520), and ammonium hydroxide (E527).

The product is available in aluminum/aluminum blisters or high-density polyethylene bottles capped with child-resistant closure.

2.2.2. Active Substance

The chemical name of laquinimod sodium is sodium 5-chloro-3-(ethylphenylcarbamoyl)-1-methyl-2-oxo-1,2-dihydroquinolin-4-olate and has the following structure:



The structure of laquinimod sodium has been confirmed by elemental analysis (C/H/N/Cl) and spectroscopic analysis (UV, IR, ^{1}H-NMR and ^{13}C-NMR) and mass spectrometry.

Laquinimod is a white to off-white slightly hygroscopic crystalline powder.

It is a BCS Class I (highly soluble-highly permeable) compound. It is slightly soluble in DMF and ethanol; sparingly soluble in DMSO and methanol; and practically insoluble in acetone, acetonitrile and isopropanol.

Laquinimod has a non-chiral molecular structure.

Polymorph screening studies of laquinimod sodium identified several possible crystalline forms. It has been demonstrated that the proposed route of synthesis leads to crystalline form A, which is the most physically stable solid form.

The other forms , all convert to Form A under exposure to elevated temperatures.

Manufacture

Laquinimod sodium is synthesized in five main steps using commercially available well-defined starting materials with acceptable specifications. The main steps include preparation of laquinimod, preparation of crude laquinimod sodium and purification.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and design of experiment (DOE) studies. Based on these studies, proven acceptable ranges have been defined for the five steps of the manufacturing process of the active substance. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed proven acceptable ranges (PARs).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities, including potential genotoxic impurities, have been well discussed with regards to their origin and characterised, and they are controlled by appropriate limits. However, further information regarding the limit of detection of the analytical methods used to characterize two potential impurities has not been provided at the time of opinion. The applicant is recommended to provide this information post-approval. This is considered acceptable since the maximum daily dose of the product is very low (0.6 mg/day) and these impurities do not contain any structural alert of genotoxicity. In addition, these impurities were either not detected in stability studies carried under long term and accelerated conditions, or detected at levels below 0.05%.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Validation of the process has been performed on three consecutive commercial scale batches.

Specification

The active substance specification includes tests for description, identification (HPLC, IR, UV, sodium), assay (HPLC), impurities (HPLC), water content (KF), heavy metals (Ph. Eur.), sodium content (potentiometric titration), colour of solution (Ph. Eur.), free chloride (Ph. Eur.), residual solvents (GC) and microbial purity test (Ph. Eur.).

The exclusion of polymorphism and particle size distribution from the specification is justified since laquinimod sodium is completely dissolved during the first step of the drug product manufacturing process.

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines.

The proposed specifications are considered adequate. However, the applicant is recommended to tighten the specification limits for one of the solvents used in the manufacturing process of the active substance to bring them in line with the manufacturing capability, and further develop and revalidate its analytical method.

Batch analysis data six pilot scale and six commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on four production scale batches of active substance from the proposed manufacturer stored for 24 months (3 batches) or 12 months (one batch) under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The container closure of the batches used for the stability studies consisted in one low density polyethylene (LDPE) bag inserted into an aluminium bag, simulating the container closure proposed for storage and distribution (low density double polyethylene (LDPE) bag inserted in an aluminium bag).

The following parameters were tested: appearance, identification (HPLC), related substances (HPLC), water content (KF), assay (HPLC), and colour of solution. The analytical methods used were the same as for release and were stability indicating.

No significant changes or trends were observed in any of the parameters tested after storage at long term or accelerated conditions.

A photostability study performed in accordance with the ICH guideline Q1B was performed on one commercial scale batch, demonstrating that laquinimod sodium is photostable in the solid state.

Forced degradation studies were performed by treatment with heat, acidic, base or oxidizing conditions. The results from these studies showed that the drug substance is intrinsically stable in the powder form, with moderate degradation occurring for the drug in solution exposed to extreme conditions.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

A comprehensive overview on the history of laquinimod 0.6 mg hard gelatine capsules development has been provided. The first Phase I studies were performed with an aqueous oral solution of laquinimod free acid. For the Phase II studies, laquinimod tablets of 0.05 mg, 0.25 mg and 0.3 mg laquinimod (as the sodium salt) were developed. The proposed commercial is the capsule formulation, which was used successfully for both Phase III trials and for the open-label extension of Phase IIb.

Bioequivalence of the early clinical formulations (oral aqueous solution and tablets) and the proposed commercial formulation, which was used in the pivotal trials, was shown by bioequivalence studies.

The selected excipients for laquinimod 0.6 mg capsules are mannitol used as a filler, meglumine used as an alkalinizing agent to improve the stability of the formulation, and sodium stearyl fumarate used as a lubricant, all of which are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The pharmaceutical development of the finished product was based on the Quality by Design principles.

The quality target product profile (QTPP) was defined as immediate release oral dosage form for a once daily administration that meets compendial and other relevant quality standards, and is packaged protected from light and moisture in a bottle and a blister configuration. The formulation should be stable for 24 or 36 months at room temperature.

Based on the QTPP, a number of quality attributes of the drug product that could potentially affect the product quality were identified. In accordance with ICH Q6A, and taking scientific and prior knowledge into consideration when evaluating the impact of the quality attributes on the drug product safety and efficacy, several attributes were identified as Critical Quality Attributes (CQAs).

The manufacturing process has been developed through the use of risk assessment to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge as well as on the experience from formulation development. Based on the outcome of the FMEA, a series of Design of Experiments (DOEs) were performed in order to gain better and more insightful knowledge of the formulation and manufacturing process. The critical process parameters have been adequately identified.

The primary packaging is either aluminium/aluminium blisters or high density polyethylene bottles with child-resistant caps. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the supplier of the gelatine used in the manufacture is provided.

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

Manufacture of the product

The manufacture of laquinimod capsules is performed by two alternative manufacturers using a wet granulation procedure.

The manufacturing process consists of several steps: wet granulation, fluid bed drying, milling, capsule filling and packaging. Although the product is a very low dosage form, it has been demonstrated that a uniform distribution of the drug substance in the drug product is obtained and the manufacturing process can be considered to be a standard process.

Proven acceptable ranges have been defined for several steps of the medicinal product. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Process validation has been performed on four and three production scale batches at the two proposed manufacturing sites, respectively. The process validation data indicate that the manufacturing process is capable of consistently producing hard capsules of suitable quality which meet the release specifications.

Product specification

The finished product release specifications include appropriate tests for this dosage form and include: description, identification (HPLC, UV), dissolution (HPLC), uniformity of dosage units (HPLC), assay (HPLC), impurities/degradation products (HPLC), water content (KF), identification of color (Ph. Eur.) and microbial purity (Ph. Eur.). The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Batch analysis results are provided for 4 commercial scale batches from one manufacturer and 5 commercial scale batches from another manufacturer confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on eight commercial scale batches, manufactured at the two proposed manufacturing sites, stored under for up to 24 months long term conditions (25 ºC/60% RH), for up to 12 months under intermediate conditions (30 ºC/60% RH) and for up to 6 months under accelerated conditions (40 ºC/75% RH) according to the ICH guidelines were provided. The batches of Nerventra are representative to those proposed for marketing and were packed in the primary packagings proposed for marketing (HDPE bottles and Alu/Alu blisters).

Samples were tested for appearance, dissolution (HPLC), assay (HPLC), impurities/degradation products, water content (KF), microbial purity (Ph. Eur.). The analytical procedures used are stability indicating.

All stability results are within specification with exception of two out of specification assay results observed at accelerated storage conditions at 6 month time point, which led to the inclusion of the special storage condition “Do not store above 30 ºC”.

A photostability study was conducted according to ICH Q1B. The study showed that the drug product is not stable when unpackaged capsules are directly exposed to light. However, all the results on laquinimod capsules packaged in the proposed commercial packaging configurations were satisfactory and well within the specifications. Therefore, a statement to protect the capsules from exposure to direct light has been included in the product label.

In addition, an in-use stability study was performed as per Note for Guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99) on capsules packed ion HDPE bottles. As no significant changes were observed in any of the test parameters, no declaration of an in-use shelf life or additional storage conditions is required.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

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

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

The limits of detection of the analytical methods used to characterize two potential impurities of the active substance have not been provided. The specification limits of one of the solvents used in the synthesis of the active substance should be revised in the active substance specification based on the batch data results, and its analytical method should be revised and validated.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions proposed in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-To determine the limits of detection of the analytical methods used to characterize the two potential impurities.

-To tighten the specification limits for one of the solvents used in the manufacturing process of the active substance to bring them in line with the manufacturing capability, and further develop and revalidate its analytical method.

2.3. Non-clinical aspects

All main safety pharmacology and pivotal toxicology studies were performed according to Good Laboratory Practices (GLP), as stated by the applicant.

2.3.1. Introduction

The non-clinical documentation for laquinimod consisted of primary and secondary pharmacological studies, as well as safety pharmacology. Furthermore, pharmacokinetic data in various species were provided. The toxicological testing programme consisted of studies addressing general toxicity, genotoxicity, reproductive toxicity, carcinogenicity, local tolerance, immunotoxicity, phototoxicity and qualification of impurities.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The effect of laquinimod was evaluated in the acute, chronic-relapsing, and chronic progressive experimental autoimmune encephalomyelitis rodent model. In these studies, the effect of laquinimod on disease progression was assessed using clinical evaluation of ascending paralysis.

In mouse and rat models of acute EAE, laquinimod reduced disease severity and was more potent than the structurally-related compound roquinimex. The ED_{50} and ED_{90} of laquinimod determined in the murine acute EAE model were approximately 20-fold lower than that of roquinimex (≈ 0.2 mg/kg and 1 mg/kg vs. ≈ 5 mg/kg and 25 mg/kg, respectively). In chronic models of EAE, laquinimod caused reduction in the severity of the disease either in prophylactic or therapeutic settings. In addition, the prophylactic treatment regimen led to a decrease in the incidence of the disease at the highest dose tested (25 mg/kg). The minimal doses showing effect were 1 mg/kg and 5 mg/kg in the prophylactic and therapeutic settings, respectively. An additional pharmacokinetic/pharmacodynamic (PK/PD) study performed in a mouse model of chronic EAE suggested that the effect of laquinimod is minimum plasma concentration (C_{min})-driven. Further investigations in these models of chronic EAE showed that laquinimod-related reductions in demyelination of white matter in the spinal cord at ≥ 5 mg/kg/day in the prophylactic regimen and at 25 mg/kg/day in the therapeutic regimen. The data also provided support of myelin and axonal protecting activity of laquinimod in animal models of demyelinating disease (‘chronic EAE and cuprizone-induced demyelinating disease in mice). It should be noted that the minor metabolite DELAQ was a more potent inhibitor of disease development than laquinimod.

It was shown that treatment with laquinimod decreases inflammatory cell infiltration into the Central Nervous System (CNS) in different models of MS, as well as the secretion of pro-inflammatory cytokines. It was suggested that laquinimod is not acting as a general immunosuppressive/ immunotoxic agent, as there was no evidence of an effect of treatment on the primary (IgM) and secondary (IgG) humoral immune response against Keyhole Limpet Hemocyanin (KLH), on T- and B- cell numbers, and on cardiac allograft survival. In immunohistochemical acute EAE studies with mice and rats it was demonstrated that laquinimod significantly reduces the infiltration of leukocytes in the central nervous system and inhibited the inflammation of both $CD4^+$ T cells and macrophages into central nervous tissues. In another set of studies laquinimod’s

potency to modulate immune responses was investigated. A dose-dependent reduction of pro-inflammatory cytokines by antigen-specific T-cells was found. In addition, as the nuclear factor-κB (NF-κB) is an important transcription factors, which can activate inflammatory responses, the putative effects of laquinimod on NF-κB activation has been studied. Some data also suggested that laquinimod modulates signalling through NFκB pathway which is often associated with inflammatory diseases.

While acknowledging that the molecular target of laquinimod has not been identified, the applicant presented data on cellular effects or activities downstream this unidentified target to characterise the mechanism of action of laquinimod in MS. The potential of quinolone-3 carboxamide compounds to bind to protein S100A9 has been described by Björk *et al,* (2009) as a target of quinoline-3-carboxamide compounds underlying their immunomodulatory activity. Other data obtained with compounds of similar chemical structures suggest that laquinimod could bind to S100A9. The CHMP also noted that recent publications pointed out to a dual role of S100A9 in inflammation and cancer (Gebhardt et al 2006, Ghavami *et al.*, 2009, Goyette and Geczy 2011, Srikrishna *et al.,* 2012). In view of the claimed properties of laquinimod and the carcinogenicity findings (see 2.3.4), the CHMP requested further investigation of this protein and other proteins of S100 family as potential target for laquinimod. Additional experimental data were provided by the applicant showing that laquiminod was still active in animal models of EAE in S100A9 knockout mice (which lack also S100A8) suggesting that S100A9 was not the molecular target of efficacy of laquinimod in this model. A screening for the binding of laquinimod to S100A8 (which is the dimerization partner of S100A9 originally hypothesized as the target of laquinimod), using the technique of surface plasmon resonance was negative. The applicant committed to perform further testing of the binding of laquinimod to cells transfected with S100A8 cDNA to confirm the above results. Overall, the CHMP concluded that the mode of action of laquinimod remains unknown.

Secondary pharmacodynamic studies

Data on other inflammatory/autoimmune disease models (inflammatory bowel disease; rheumatoid arthritis; type I diabetes; Guillain-Barre Syndrome; systemic lupus erythematosus / lupus nephritis) were presented to further support the immunomodulatory properties of laquinimod. Overall, laquinimod showed dose-dependent activity in these inflammatory disease models in the oral dose range of 1-25 mg/kg when administered prophylactically or semi-prophylactically whereas reduced activity or no effect was detected when administered after disease onset.

Safety pharmacology programme

No potential effects of laquinimod on the CNS function (Irwin Test) and on gastrointestinal transit time were observed.

In vitro data using the hERG assay and in the Purkinje fiber assay (at concentrations approximately 30-fold and 1.4-fold the clinical maximum plasma concentration (Cmax), respectively and considering total plasma drug concentration) did not identify any concerns on the cardiovascular function. Although the GLP-compliant *in vivo* cardio-respiratory study was conducted in anaesthetized dogs by the intravenous route and may therefore be viewed as not fully clinically relevant, no effect of laquinimod on cardiovascular parameters was reported at up to 20 mg/kg. Since at this dose level, animals were 288- and 7.7-fold more exposed than humans based on Cmax and AUC, respectively, and in view of the *in vitro* data, the data seem sufficient to consider that there is no preclinical concern a drug-related arrhythmogenic potential.This is supported further by the negative outcome of the QT/QTc study (see 2.4.3).

At 20 mg/kg intravenous (i.v.), decreased peak expiratory and peak inspiratory flows were noted in anaesthetised dogs. These effects of laquinimod on the respiratory function were considered minor.

In male rats, there were some effects of laquinimod in urinary electrolyte concentrations (reduced sodium, potassium, chloride) and decreased urine volume at 90 mg/kg. At 30 mg/kg, reduced sodium and chloride concentration in urine were reported. No effect was seen at 10 mg/kg. Based on toxicokinetic data obtained in rats, there is considerable safety margin for this effect.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were carried out with laquinimod. This was considered acceptable based on available data from clinical studies and in view of the intended use as monotherapy in MS population.

2.3.3. Pharmacokinetics

The pharmacokinetics and toxicokinetic (TK) studies of laquinimod were performed in mice, rats, rabbits, dogs and monkeys. Several bioanalytical methods were developed and validated to characterize the disposition of total laquinimod in plasma including an HPLC assay using UV detection and LC-MS/MS methods with lower levels of sensitivity. Some of the studies were also conducted with its metabolites (DELAQ, DMLAQ and N-4'HLAQ). The metabolic profile of laquinimod and formation of protein adducts was also studied in mice, rats, rabbits, dogs and humans.

After oral administration, the absorption of laquinimod is relatively rapid in the mouse, rat, and dog (T_{max} within 2 hours) while it was slower in the rabbit (T_{max} within 4-8 hours). *In vitro* bi-directional permeability was tested, using Caco-2 model. High equal permeability was observed in both directions, suggesting that laquinimod is absorbed passively.

In these species, oral bioavailability was high (82-93%). The half life of laquinimod was found to be longer in humans (71 hours) than in the tested animal species (3 to 14 hours).

Exposure data measured following the first dose in toxicology studies showed that the kinetics is linear over the 2-160 mg/kg dose range in mice, over the 0.15-90 mg/kg dose range in rats, and over the 1-10 mg/kg dose range in dogs. In general, the kinetic remained linear after repeated administrations in toxicity studies performed in mice at up to 40 mg/kg. In rats, linearity was also observed at up to 10 mg/kg; at higher dose levels, the data suggested less than dose proportional increase in exposure. In some studies, the kinetics was time-dependent in mice and rats (decreased systemic exposure in relation to increased clearance). This was not clearly shown in dogs. A significant time-dependency on the kinetics of laquinimod at the proposed posology (0.6 mg/day) in man was also not suggested. Systemic exposure was also found to be 3-4-fold higher in female rats as compared male rats suggesting a gender related difference in this animal species.

Laquinimod is highly bound to mouse, rat, rabbit, dog and human plasma proteins (> 97%), with a free fraction of 1.8% in humans.

The volume of distribution in the different species was relatively low, 0.12 L/kg in rabbits, 0.17 L/kg in rats, 0.26 L/kg in dogs, and 0.45 L/kg in mice, suggesting that laquinimod is mainly distributed into the extracellular space. In dogs, the blood/plasma ratio was found to be about 0.6. These data further indicated that laquinimod does not substantially bind to, or enter, the blood cells but is rather distributed to plasma.

After dosing ^{14}C-labeled laquinimod in mice (i.v) and rats (p.o), drug related radioactivity distributed mainly to the liver and kidney cortex and was generally slowly cleared from tissues ($t_{1/2}$ ranging from 20 to 50 hours, and even up to 84 hours in kidney cortex). According to the

applicant, the slow clearance from tissues may be related to the formation of drug-protein adducts, that were specifically studied in the characterisation of the metabolic profile (see below). Brain penetration was also noted in both species with brain to blood ratios ranging from 0.04 to 0.08 and lower ratios at later time points. After i.v or p.o dosing in dogs, the level of radioactivity found in liver was more than 2-fold higher than levels found in blood; levels in lung and kidney were slightly lower and the levels in brain were about 7% of those in blood.

In murine EAE model (cerebellum of mice with compromised blood-brain-barrier), drug-related radioactivity was also shown to distribute into the CNS with brain: blood ratios up to 0.18.

In rats and rabbits, laquinimod-related radioactivity crosses the placenta and distributes homogenously within fetal tissues. In both species, the fetal radioactivity uptake is increased in the late gestational period.

Laquinimod was found to be primarily metabolised by CYP3A4 enzymes. *In vitro* and *in vivo* data suggested that the major metabolic pathway was quinoline hydroxylation at 2 positions (6-HLAQ and 8-HLAQ) followed by N-demethylation of the quinoline ring (DMLAQ), aniline hydroxylation (N-4'-HLAQ), and to a lesser extent N-deethylation at the aniline moiety (DELAQ) and dechlorination of the quinoline ring (DCLAQ). The liver extraction ratio is low. Both the parent compound and hydroxylated metabolites undergo also glucuronidation. *In vivo* data did not show significant inter-species differences in the qualitative and quantitative metabolic profile, and therefore the toxicity species are considered validated. In addition, no metabolite could be considered as major, since most were found to have circulating concentrations well below (<1% in most cases) that of the parent compound in all investigated species and humans. All human circulating and excreted metabolites have been observed and are well-represented in animal species. The metabolites (ABR-215818, ABR-215791, ABR-218287) and their conjugates are much more abundant in the excretaes than laquinimod. Their pharmacological activity was evaluated using the EAE mouse model. The results and metabolic patterns of laquinimod indicated that its metabolites, at circulating levels following clinical doses, did not contribute to the pharmacological activity of the drug.

Laquinimod is mainly eliminated by metabolism and therefore only low levels of unchanged laquinimod were recovered in excreta of animal species including humans. The main route of excretion was the feces in rats and dogs (50 to 70%) and the urine in rabbits and humans (50-60%). Laquinimod and/or its metabolites are also excreted in the milk of lactating rats.

In all animal species, laquinimod was shown to form tissue adducts. Data suggested that these adducts were the results of covalent binding of laquinimod drug material to lysine residues of plasma and liver microsome proteins after a reaction of N-deethylation (formation of DELAQ). In rats, such covalent binding was much higher in plasma than in the liver. In the plasma, 0.4-2% of the dose was covalently bound to proteins, and elimination of such adducts was low ($t_{1/2}$ = 7 days). The formation of adducts was also found to be dose-dependent in rats.

2.3.4. Toxicology

Single dose toxicity

Single-dose toxicity studies were conducted in rats and dogs. In rats, lethality was reported at 400 mg/kg. In dogs, laquinimod was not well tolerated at 60 mg/kg since it induced acute inflammatory reactions e.g. increased erythrocyte sedimentation rate (ESR) and fibrinogen in both sexes,

leukocytosis in females. At the No-Observed- Effect Levels (NOAELs), animal-to-human exposure ratios reached 200 and 100 in rats and dogs, respectively.

Repeat dose toxicity

The pivotal repeat-dose toxicity studies were conducted in rats and dogs for up to 26 weeks and to 52 weeks, respectively. Dose finding studies for carcinogenicity evaluation were also performed and used two mouse strains (CD-1; C57BL/6).

Toxicity studies in rats have identified the haematopoietic tissue (erythroid cell line), liver, thymus, and thyroid as target organs of laquinimod. In general, the findings occurred with dose-related incidence and/or severity and consisted mainly in pro-inflammatory effects and lymphoid atrophy. In the 26-week study, the effects noted from the low dose level of 1 mg/kg/day were decreased body weight and Red Blood Cell (RBC) parameters, hepatocyte vacuolation/hypertrophy/degeneration, inflammatory infiltrates in the liver, deposits of pigmented macrophages in the liver, liver fibrosis, bile duct hyperplasia in females, thymic atrophy, thyroiditis, and capsular fibrosis of the spleen. High toxicity was shown at the high-dose level (≥ 50-fold human exposure), with mortality associated with a marked anaemia, principally due to bone marrow and liver toxicity. In this dose-group, additional inflammatory findings in the pancreas and joints/skin, and proliferative lesions in lungs (broncho-alveolar hyperplasia) were observed. In line with finding in mice, laquinimod induced hyperplasia and hyperkeratosis of the squamous epithelium at the limiting ridge of the stomach. The incidence of this lesion was both dose and time-related. According to the applicant, this finding is related to the irritant effect of laquinimod deposited in the stomach after gavage. Findings reported in the thymus, spleen, thyroid and liver were not fully reversed after a 4-week treatment free period. A NOAEL could not be determined due to findings in the liver, thymus and thyroid. Total drug exposure at 1 mg/kg/day was about 11 (males) and 33 (females) fold higher than that at the intended clinical dose of 0.6 mg/day in humans based on Cmax, and 5 (males) and 18.3 (females) fold higher than humans based on AUC. Concerning thyroiditis, there is no safety margin to the mid dose exposure level in the 52-week dog study where thyroiditis was observed. In rats, thyroiditis was present down to the low dose group (1 mg/kg) in the 26-week study, and also in high dose males (1 mg/kg) in the carcinogenicity study.

In dogs, laquinimod was also shown to induce inflammatory reactions as shown by the occurrence of peritonitis, encephalitis, and myelitis in the 28-day study at ≥ 26-fold the human exposure. Furthermore, the interpretation of the 39-week study was complicated due to the occurrence of inflammatory episodes and arteritis in all groups, thus a 52-week study was conducted at the same dose levels. It showed that systemic inflammatory response occurred in two dogs at the high dose level (0.6 mg/kg/day) on isolated occasions with both clinical, haematological (leucocytes increase), and biochemical (fibrinogen and CRP increased levels) manifestations. One of these animals, and also two others in the mid- and high- dose groups showed minimal to marked thyroiditis, one case being associated with increased levels of anti-T3 and anti-thyroglobulin auto-antibodies. Based on these results, it is concluded that laquinimod induced inflammation in dogs. These studies also showed that haematopoietic tissue (erythroid cell line) and thymus (atrophy) are target organs of laquinimod.

Principal findings in the mouse were dose-related increase in liver weight, inflammatory foci of minimal to moderate intensity with single cell necrosis of the liver, gastritis and decreased thymus weight. The toxicity profile of laquinimod in mice is characterized mainly by liver toxicity (centrilobular hypertrophy, inflammation, degeneration) and inflammatory findings in various tissues. In the stomach, chronic gastritis and hyperkeratosis of the squamous epithelium at the

limiting ridge were reported after 13 weeks of treatment. Centrilobular hypertrophy/eosinophilia was observed in the liver of males and females in this study and is considered to be related to laquinimod's ability to induce enzymes involved in phase I and II metabolism. These findings were fully reversible on cessation of treatment. In CD-1 mice, a 31-38% decrease in CD161+ cells (including NK cells) in the immunotoxicity subset was observed and is in line with the decrease in NK cells observed in the specific immunotoxicity study conducted in rats. No NOAEL could be determined in these studies. At the identified Lowest Observed Adverse Effect Levels (LOAELs), animal-to-human exposure ratios ranged from 1.2 to 5.

The above mentioned toxicity findings are suggestive of an Aryl hydrocarbon receptor (AhR) agonist-like effect of laquinimod. This, together with the mechanistic data supportive of AhR activation (e.g. the metabolite DELAQ, although being present in minute levels, is a very potent agonist of this receptor) raise concerns on human safety.

In addition, in repeated dose studies, a myeloid-directed shift in the myeloid/erythroid ratio of bone marrow cells was observed in mice, rats and dogs; although the effects in rodents were not significant.. The bone marrow changes observed in laquinimod-treated dogs indicate a small myeloid shift that was observed at very high doses relative to the clinical exposure, and are most likely secondary to the effects of laquinimod on cytokines that regulate hematopoiesis.

Genotoxicity

Laquinimod was not mutagenic in the Ames assay and did not induce unscheduled repair of DNA in the unscheduled DNS synthesis (UDS) test. The genotoxicity test was positive in the mouse lymphoma TK assays with a long treatment of the cells without metabolic activation at high doses levels. *In vitro* test in V79 Chinese hamster cells and human peripheral lymphocytes revealed an increase of micronucleated cells. Using a pan-centromeric DNA probe, the mechanism of micronucleus induction in the *in vitro* study in human lymphocytes was suggested at the only one concentration that was analyzed (194.5 µg/mL) to be in favor of an aneugenic mechanism; however, these data cannot be used to rule out a clastogenic activity.

As aneuploidy is not considered to result from direct damage to DNA, it is generally accepted that a threshold for aneuploidy can be identified. The concentration of 65.61 µg/mL was identified by the applicant as the *in vitro* No Observed Effect Level (NOEL) using primary human lymphocytes. However, this was not endorsed by the CHMP since a statistically significant increase in micronuclei frequency was shown at the lowest concentration of 53.14 µg/mL. Therefore, no NOEL was identified *in vitro* for micronuclei induction. The CHMP was also concerned about the use of pan-centromeric probes to demonstrate a loss of chromosome as a good marker of aneugenicity. Actually, laquinimod has a clear clastogenic potential with a predominantly aneugenic mode of action. According to Kirsch-Volders *et al*. (2003) the increase of micronucleus frequency in the micronucleus assay demonstrates chromosome loss, but aneugens that induce chromosome loss induce also chromosome non-disjunction. As described by Kirsch-Volders *et al.* (2003), this determination should be performed using probes for at least 2 chromosomes in binucleated human lymphocytes.

In the acute (2-day) rat bone marrow assay, a statistically significant increase of micronucleus frequency was also reported vs. study controls at the highest dose levels, but vs. historical negative control data at 30 mg/kg/day. Therefore, the NOEL in this study was downgraded from 90 to 10 mg/kg/day. In the 28-day repeat-dose micronucleus study a statistically significant increase in bone marrow micronuclei compared to controls was seen at the highest dose tested (90

mg/kg/day). In the 28-day repeat-dose chromosome aberrations study, no indication of chromosome damage/breakage (clastogenicity) was detected at up to 90 mg/kg/day. This response is in favor of a non-clastogenic effect and of a pure aneugenic effect. Overall, the *in vivo* NOEL for genotoxicity identified by the applicant (30 mg/kg) was also not endorsed by the CHMP in view of the results of the 2-day *in vivo* micronucleus test. A new reading of the slides obtained in the 28-day micronucleus test was requested to increase the sensitivity of the observation, and the confidence in the result of the dose used to determine the threshold. However, the specimens of the original 28-day *in vivo* micronucleus rat study were found to be too old to allow a valid analysis and the applicant decided to repeat two of the studies performed for NOEL determination.

Based on the repeated studies, the *in vitro* data showed that laquinimod was both aneugenic and clastogenic. Laquinimod cannot be considered as a pure aneugen since no supporting mode of action is available, and because the threshold for chromosome loss is lower than that for non-disjunction (for aneugens, the threshold for non-disjunction is lower or equal to the threshold for chromosome loss).

The repeated acute *in vivo* micronuclei rat study demonstrated a NOEL between 60 and 90 mg/kg/day, consistent with the estimation of this value as 90 mg/kg/day in the original study. Overall, the results were consistent with those obtained previously in the original study. Therefore, the NOEL of 30 mg/kg/day obtained in the 28-day rat bone marrow micronucleus study was selected for determination of safety margin, which reached 100 based on AUC levels.

Although the exact genotoxic mode of action of laquinimod remains to be established, the threshold of genotoxic effect and the safety margin for this risk is considered acceptable at the present time. This however may require further reevaluation in the case of decrease in the safety margin (e.g. use of higher dose level in patients).

Carcinogenicity

Carcinogenicity was tested in a conventional 104 week study in rats, testing dose levels of 0.1, 0.3 and 1 mg/kg/day. Furthermore, a 26 weeks study in p53+/- mice, testing doses of 0, 1, 5, 15 and 40 mg/kg/day in male groups and 0, 2, 10, 30 and 80 mg/kg/day in female groups.

Laquinimod was shown to be carcinogenic in rats. Significant, dose-dependent increases of tumours were observed; namely neoplastic lesions in the uterus, in the thyroid in males and oral cavity squamous cell carcinoma in females. In addition to these findings, a range of proliferative lesions (hyperplasia) were observed in the kidney and urinary bladder at all dose levels. These were not associated with inflammatory processes.

An increased incidence of uterine adenocarcinomas was seen in high dosed females (1 mg/kg) and the margin to the NOAEL, No Observed Adverse Effect Level (0.3 mg/kg/day) was found to be low (5.8). The mechanism underlying these findings suggested by the applicant was a possible relation with a decrease in prolactinomas/prolactin (PRL) levels and age related changes in the regulation of prolactin secretion in rats. The applicant argued for an association between reduced body weight gain and lower prolactin levels. However, careful review of the available data did not support the claimed mechanism, and thus this hypothesis was not considered convincing by the CHMP. This aspect is further discussed below (see 2.3.6).

Thyroid gland was identified as a target organ for toxicity, both in rats and dogs. An increased incidence of thyroid follicular cell adenomas was noted in high dose rat males in the carcinogenicity study, which was suggested by the applicant to be a rat specific finding due to laquinimod's ability to increase the activity of two rat thyroxin UGTs that glucuronidate T3 and T4. The applicant

provided experimental evidence that follicular thyroid adenomas are species specific in the male rat. .

Increased incidence of oral cavity squamous cell carcinoma was noted in rats dosed at ≥ 0.3 mg/kg (both sexes). The applicant suggested that this effect may be related to a direct effect of laquinimod on the oral cavity tissue during repeated gavage procedures and not to a systemic effect of the drug as suggested by dose-related increased incidence and/or severity of non-neoplastic proliferative/ inflammatory findings in the oral and nasal cavities, lungs, larynx, and fore-stomach. It was also mentioned that such direct exposure was not relevant to humans as laquinimod is administered in a capsule, and that excretion in saliva in rats and humans is well below cytotoxic concentrations. However the CHMP was not convinced that an effect via systemic exposure can be excluded as an explanation for these findings. Additional studies with local application of laquinimod to the cheek pouch of hamsters and to the buccal mucosa of rats were conducted. Local inflammatory / proliferative / degenerative findings were observed in both species. In addition, in the hamster, discolouration of the incisor teeth was observed and associated with atrophy and disorganization of the ameloblastic cells at the base of the incisor teeth. In rat, despite inflammatory effect observed in treated and in non-treated animals, dental effects were also reported.

In the 26-week carcinogenicity study conducted in p53+/- mice, there was no significant treatment-related increased incidence of neoplastic lesions. A non-significant increase in skin sarcoma was reported at the high dose level. Similar findings were observed at lower dose levels and in the control group. This is considered as a common background tumour in this mouse strain, and all sarcomas identified in these studies were qualitatively comparable. The liver, heart (females), and skeletal muscles were considered to be target organs due to the presence of non-neoplastic inflammatory lesions. There was no safety margin for liver findings in both sexes, and skeletal muscle findings in females. The safety margin reached 4.3 and 8.6 times for cardiac (females) and skeletal muscle (males) findings, respectively. Mandibular lymph node hyperplasia was also observed at all dose levels. According to the applicant, mandibular lymph node hyperplasia was not considered as a generalized or systemic lymphoid reaction as no treatment related changes were noted in the morphology or lymphoid populations of the mesenteric lymph node, thymus and spleen. For the applicant, this finding is considered as a loco-regional response. No correlation was observed between incidence of local inflammation and mandibular lymph node hyperplasia in the treated animals.This finding was also not seen in other studies in mice, rats and dogs and may also be related to a response of mandibular lymph nodes following exposure to a variety of stimuli in the oropharyngeal region. However no firm conclusion could be drawn by the CHMP on this aspect.

Reproduction Toxicity

Laquinimod did not impair the fertility of male and female rats at doses inducing marked toxicity (mortality in males at 15 mg/kg, effects on body weight and consumption parameters at 1.5 mg/kg). An embryolethal effect was noted at the high dose level (15 mg/kg). The safety margin for this effect reached 12.

Conventional embryo-fetal toxicity studies in rats and rabbits showed that laquinimod is embryo-feto-toxic and abortive (rabbits) at maternotoxic high doses. In rats, maternal toxicity was shown from 6 mg/kg/day. Developmental toxicity was evidenced from the dose of 6 mg/kg/day by a decrease in fetal weights, and increased incidence of skeletal variations. At 18 mg/kg/day, this toxicity was increased as shown by embryo-feto-lethality and increased pelvic cavitation of the kidney. In rabbits, both maternal and fetal toxicities were noted from 0.5 mg/kg (mortality and

effects on body weights and food consumption in dams, abortions, embryo and fetal mortality, decreased fetal weight, increased skeletal variations). The NOAELs determined from these studies were 2 mg/kg/day in rats and 0.1 mg/kg/day in rabbits, yielding safety margins of 22 and 1.8, respectively.

Laquinimod is considered as teratogenic in female rats because it induced abnormalities of the urogenital tract occurring at non-maternotoxic dose levels (from 0.1 mg/kg/day). These abnormalities consisted of hypospadias (cleft phallus at macroscopic examination) which could be associated with hypertrophy/protrusion of the clitoris. A mechanistic study showed that the most sensitive period for the development of hypospadias in females exposed in utero was between gestation days (GD) 18 to 21, although this was also noted at lower frequency in offspring exposed on GD6-9, GD10-13 and GD14-17. Exposure before implantation or during lactation did not induce this type of malformation.

In the pre & postnatal study, hypospadias were also reported in F1 males on postnatal day 4 (PND4) of the pivotal study, but not confirmed on PND35 nor in the mechanistic study. Other findings consisted of dose-dependent delayed growth which persisted up to adult age in the high dose group, a clear dose-dependent delay in onset of puberty, and decreased fertility in spite of normal sperm parameters. In addition, the absolute weight of prostate and seminal vesicles were decreased at the high dose level (6mg/kg/day). In F1 females, in addition to the urogenital abnormalities, there were also treatment-related effects on growth, delayed vaginal opening at the high dose level only, prolonged estrous cycle length, decreased fertility at the mid and high dose levels. Treatment also had an impact on F2 generation as seen from decreased viability of F2 pups born from F1 females (high-dose group).

DELAQ, but not laquinimod, shows anti-estrogenic potential in the CALUX *in vitro* model system through the AhR-ER cross-talk pathway, and the EC_{20} of DELAQ (0.041 nM) was in the range of concentrations reached in patients following a single dose of laquinimod. Taken together, an endocrine-disrupting potential of laquinimod involving this pathway could not be excluded. Additional data were provided but they are not sufficient to exclude a mechanism involving the AhR-ER cross-talk pathway. According to the applicant, some differences in malformations were seen after exposure to laquinimod or TCDD and the applicant claims that there is no mechanistic relation between these two compounds. However, TCDD is known to cause also very species specific malformations, thus some variations in the malformation pattern between laquinimod and TCDD would be expected even though the common mechanistic factor is an activation of AhR. Also, dioxin like substances which are known to interact via the AhR, have been shown to differ in their malformation patterns. Considering the complexity of interaction between various substances and the AhR, a complete overlap in malformation pattern is unlikely. However, striking similarities were observed in the malformation patterns comparing the teratogenic effects of laquinimod and TCDD in rat, and a mechanism involving the AhR-ER cross-talk pathway could not be excluded.

In pregnant cynomolgus monkeys, a treatment-related increase in pre-natal losses was observed at the high dose level (8mg/kg/day), shown as slightly maternotoxic. At the low-dose level (1mg/kg/day), abortions were reported at an increased frequency vs. both study controls and spontaneous abortion rate in cynomolgus monkeys (17.8% according to Walker *et al.*, 2007). Therefore, there is some uncertainty regarding the determination of a NOAEL at 1 mg/kg/day. As a result of the increased abortions, number of infants examined post-natally was limited, particularly at the high dose level and the fact that no treatment-related malformations were observed in monkeys should be interpreted with caution. The CHMP considered that no definitive conclusions could be drawn regarding the teratogenic potential of laquinimod in cynomolgus monkeys.

Local Tolerance

In rabbits, studies were conducted after single and repeated administration to investigate dermal and ocular tolerance, respectively. Laquinimod was not shown to induce either skin or ocular irritation.

Other toxicity studies

In a 4-week immunotoxicity study in rats, CD161+ cells (including NK cells) were decreased, and this caused reduced cytotoxic NK activity in high dosed animals (4 mg/kg). Based on the data collected in the 26-week toxicology rat study on week 13 in males, the safety margin for this effect is 4 at the proposed therapeutic dose. Furthermore, no clinical evidence to support treatment effect on NK cell activity is available to date.

Laquinimod was positive in the 3T3 NRU phototoxicity test, but was shown to be devoid of phototoxic potential in a single-dose phototoxicity study performed in rats at up to 200 mg/kg. The limitation of this study (raised by the CHMP during the scientific advice) was that single doses were administered in comparison to the chronic administration schedule planned for humans. However, given the systemic exposure in the animals and also in view of the fact that, data do not demonstrate potential accumulation of laquinimod and/or its metabolites in eyes and skin tissues upon repeated dosing, laquinimod is not anticipated to be phototoxic in humans.

No evidence of a mutagenic potential or toxicity of the impurities was shown except for a weak mutagenic effect for one impurity. The specifications limits for the impurities were set at acceptable levels.

2.3.5. Ecotoxicity / environmental risk assessment

Table 1. Summary of main study results

Substance: laquinimod			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	pH-metric method	2.78 (neutral species) -0.51 (anionic species)	Potential PBT: No
pKa		4	
Bioaccumulation potential- log *D*	Liquid-Liquid Distribution Chromatography	2.56 (pH 2.5) <1 (pH 7.4)	
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	default: 0.003 refined*: 0.0003	µg/L	< 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Ready Biodegradability Test	OECD 301A	Not readily biodegradable	

Whilst, the potential endocrine disruption of DELAQ cannot be ruled out, this metabolite was not detected in human excreta and therefore the CHMP considered that no phase II was required to conclude on the ERA. On the basis of the presented data, laquinimod is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

In animal models of experimental autoimmune encephalomyelitis, it was shown that treatment with laquinimod decreases inflammatory cell infiltration into the Central Nervous System (CNS) in different models of MS, as well as the secretion of pro-inflammatory cytokines. Some data also suggested that laquinimod modulates signalling through NFκB pathway which is often associated with inflammatory diseases. There was no evidence of an effect of treatment on the primary and secondary humoral immune responses suggesting the absence of immunosuppressive/immunotoxic properties. However, the mechanism of action of laquinimod is not fully elucidated because the molecular target is not known. Data on other inflammatory/autoimmune disease models further supported the immunomodulatory properties of laquinimod.

The safety pharmacology studies suggested that laquinimod had a low or no potential to acutely affect the function of vital organ systems.

The pharmacokinetics properties of laquinimod were thoroughly evaluated in mice, rats, rabbits, and dogs and showed: relatively rapid oral absorption (slower in rabbits), main distribution into the plasma, crossing of the blood brain and placenta barriers, high protein binding. Laquinimod drug material is excreted both in urine and faeces and notably in milk. In all animal species, it was also found that laquinimod forms tissue adducts. Data suggested that these adducts were the results of covalent binding of laquinimod drug material to lysine residues of plasma and liver microsome proteins after a reaction of N-deethylation (formation of DELAQ). Covalently bound material was not found in human plasma after therapeutic dosing. However these clinical data were very limited (n=6 healthy volunteers, dosed once) and could not exclude this risk considering the chronic intended use of laquinimod and slow elimination of these adducts. Thus, the occurrence of drug hypersensitivity reactions could not be ruled out, and this safety concern is considered as a potential risk (see 2.6.10). In addition, laquinimod was found to be a potent inducer of CYP1A and this could be likely due to an interaction of laquinimod and metabolite DELAQ with the AhR transcription factor. CYP1A1 and 1A2 play critical roles in the metabolic activation of carcinogenic polycyclic aromatic hydrocarbons and heterocyclic aromatic amines/amides that lead to toxicity and cancer. A literature review was performed by the applicant suggesting that the role of CYP1A in the activation of procarcinogens to carcinogens is overestimated due to results obtained *in vitro*. However, CYP1A induction was reported *in vivo* in patients treated with laquinimod and no data were presented to exclude the potential carcinogenicity of laquinimod, in relation to CYP1A-mediated activation of PAHs and other carcinogens.

Laquinimod induced inflammatory reactions in various tissues in mice, rats, and dogs. In rodents, the liver was shown as a target organ. In rats and dogs, decreased RBC parameters, thymic atrophy and thyroiditis were also observed. The applicant indicated that thyroid toxicity as seen in dogs and rats is rather a species-specific effect, is not dose-dependent and occurs even in controls. However, the CHMP did not agree with the applicant, given the effects also noted in the lowest dose groups. No NOAEL could be determined in rodents, whereas it reached 0.2 mg/kg/day in dogs. The safety margins were low, *i.e.* <1.2 in mice, <5 in rats, and approximately 2 in dogs. The bone marrow changes observed in laquinimod-treated dogs indicated a small myeloid shift that was observed at very high doses relative to the clinical exposure, and are most likely secondary to the effects of laquinimod on cytokines that regulate hematopoiesis.

In genotoxicity testing, laquinimod was both aneugenic and probably clastogenic. Although the exact genotoxic mode of action of laquinimod remains to be established, the threshold of genotoxic effect and the safety margin for this risk is considered acceptable at the present time. This however may require further reevaluation in the case of decrease in the safety margin (e.g. use of higher dose level in patients).

There is currently a considerable level of uncertainty on the carcinogenic potential of laquinimod. The pharmacology of laquinimod is unclear thus making difficult the full appreciation of any pharmacology-driven proliferative or metaplastic processes. The mechanisms proposed by the applicant to explain the occurrence of the neoplastic lesions found in the oral cavity and uterus of rats in the carcinogenicity study were not convincing to exclude a relevance of the findings in animals with respect to human safety. For the oral cavity tumours, alternative explanations to a local effect, as claimed by the applicant, cannot currently be ruled out. For the uterine adenocarcinomas, the mechanism proposed by the applicant involving indirect, via reduced body weight, reductions of PRL, was not supported following careful review of the available data. This is further elaborated on below (see additional expert consultation).

On this basis, the CHMP requested, at their November 2013 Plenary meeting, the Safety Working Party (SWP) to address a number of questions related to these toxicological findings The SWP overall conclusions are presented below (see additional expert consultation). Further discussion from the applicant on this issue was also requested by the CHMP. A comparison was provided by the applicant between laquinimod, TCDD and DLCs with regard to major non-neoplastic toxicity, taking all repeat dose toxicity studies of laquinimod into consideration. These data showed that the histopathological findings did not show a complete overlap, however, from this analysis, the CHMP was of the opinion that it can be concluded that laquinimod shares a general pro-inflammatory, hyperplastic (forestomach, oral cavity and kidney), hepatic and thyroid toxicity profile with TCDD and DLCs. Considering the complexity and diversity of AhR-mediated toxic responses, complete overlap between laquinimod and TCDD is not to be expected. Moreover, striking similarities were observed in the malformation patterns comparing the teratogenic effects of laquinimod and TCDD in rat, and a mechanism involving the AhR-ER cross-talk pathway could not be excluded.

Laquinimod did not impair the fertility of male and female rats at doses inducing marked toxicity. However an embryo-feto-toxic and –lethal effect was observed and laquinimod was also found to be abortive in rabbits. The NOAELs determined from these studies were 2 mg/kg/day in rats and 0.1 mg/kg/day in rabbits, yielding safety margins of 22 and 1.8, respectively.

Laquinimod was teratogenic in rats at non-maternotoxic dose levels (above 0.1 mg/kg/day). These abnormalities consisted of hypospadias (cleft phallus at macroscopic examination) which could be associated with hypertrophy/protrusion of the clitoris. Exposure before implantation or during lactation did not induce this type of malformation. In F1 males, hypospadias were also reported and other findings consisted of dose-dependent delayed growth which persisted up to adult age in the high dose group, a clear dose-dependent delay in onset of puberty, and decreased fertility in spite of normal sperm parameters. In addition, the absolute weight of prostate and seminal vesicles were decreased at the high dose level. In F1 females, in addition to the urogenital abnormalities, there were also treatment-related effects on growth, delayed vaginal opening at the high dose level only, prolonged estrous cycle length, decreased fertility at the mid and high dose levels. Treatment also had an impact on F2 generation as seen from decreased viability of F2 pups born from F1 females (high-dose group). Most of the findings obtained in F1 animals were suggestive of a hormonal effect of laquinimod. An effect of laquinimod on the AhR-ER cross-talk pathway cannot be excluded as possible mechanism underlying its potential endocrine-disrupting effects.

No definitive conclusions could be drawn regarding the teratogenic potential of laquinimod in cynomolgus monkeys.

Additional expert consultation

On 3 December 2013, the SWP overall concluded by majority that:
- The mechanisms proposed by the applicant for uterine adenocarcinoma and, in particular, oral squamous cell carcinoma are not considered sufficiently substantiated by data. In contrast, there are pieces of evidence that speak against that these proposed mechanisms are plausible:

- The mechanistic hypothesis proposed by the applicant for the uterine adenocarcinoma is based on the observation that long-term decreased food consumption/body weight/body weight gain has been shown to influence the incidence of pituitary hyperplasia/adenoma (Greaves; Hargreaves & Harleman 2011). This, in turn, results in a relative reduction in circulating prolactin (relative hypoprolactinemia). In rats, but not humans, prolactin is a luteinizing hormone that stimulates ovarian production of progesterone and maintains progesterone dominance (Hargreaves & Harleman, 2011). Accordingly, a decrease in prolactin levels in rats leads to the opposite, i.e. estrogen dominance and associated risk for endometrial proliferation.

Although prolactin levels were not measured in the laquinimod rat carcinogenicity study, the applicant argues that a number of indirect findings and associations are highly suggestive of this rat-specific mechanism being at play. A statistically significant decrease in pituitary adenomas was observed for high dose females (1 mg/kg/day) compared to vehicle controls. At the high dose level, there was also an increased incidence of uterine adenocarcinoma (9% relative to controls). It was suggested that the decrease in the incidence of pituitary adenomas could be related to the uterine findings. As these adenomas typically produce prolactin, a higher incidence of pituitary adenomas in control females would produce higher prolactin levels in controls and fewer estrogen-related lesions in the uterus, such as adenocarcinomas, compared to high dose females.

It was further proposed that an inverse relationship between uterine and mammary tumours existed in the rat carcinogenicity study, i.e. fewer mammary tumours in the laquinimod-treated females as compared to controls. Since prolactin has a profound influence upon the promotion of mammary gland neoplasia in rodents, this would support the notion of a hypoprolactinemic mechanism [Hargreaves & Harleman, 2011].

It is agreed that there was an association between decreased body weight gain in female high-dose rats and a decreased incidence of pituitary adenomas in the same dose group. With regard to mammary tumours, the incidence of total mammary tumours was somewhat lower in laquinimod-treated females as compared to controls. However, there was no clear dose response relationship, mammary fibroadenoma were present in 4/7 high-dose females with uterine adenocarcinoma. Since prolactin is known to be the main driving force in the development of rat mammary tumours (Hargreaves & Harleman , 2011), the presence of mammary fibroadenoma in these rats argues against these rats being hypoprolactinemic. Clearly, there was no evidence of an inverse relationship between uterine and mammary tumours.

The most important argument put forward by the applicant to constitute the most plausible and direct experimental evidence for an inverse correlation between pituitary and uterine tumours – is the statement that none of the 7 high-dose females with uterine adenocarcinoma had prolactinoma. However, when taking a closer look at the histopathology and immunohistochemistry data this statement appears somewhat ambiguous. Of the 7 high-dose females with uterine adenocarcinoma no less than 4 had pituitary neoplasms (adenoma). In addition, 2 rats had pituitary hyperplasia ranging from minimal to moderate.

Immunohistochemistry (IHC) for the detection of prolactin was performed on all 4 tumours. The result is said to be negative for 3 tumours (animals N^{o} 514, 519, 539), and “not possible to judge” for 1 tumour (animal N^{o} 525). According to the study report [Study 8244655], the following grading system was used to evaluate the IHC results:

- The tumour is negative for prolactin. “1”: indicates a few of the tumour cells are positive for prolactin, “2”: Indicates many of the tumour cells are positive for prolactin, “3”: indicates the majority of the tumour cells are positive for prolactin

Although the tumors from animals No 525 and 539 were graded 1, they were in the final analysis judged to be “not possible to judge” and “negative”, respectively. Photographs of the IHC stainings in the report, especially Figure 13 showing a close-up of N^{o} 525, convey a different message. There are evidently several positively stained tumor cells, and it is not clear what the “not possible to judge” and “negative” diagnoses are based upon. For a third tumor judged negative (animal N^{o} 514) autolytic changes are present and there is no normal pituitary gland to compare the staining results with; thus the result cannot be considered conclusive.

Furthermore, it should be noted that 3 control animals also had uterine adenocarcinoma. These rats (N^{o} 324, 545 and 559) all had pituitary adenomas that were judged positive for prolactin (grade 3) for the two tumours that were investigated by IHC (N^{o} 545 and 559). Thus, there was no correlation between absence of prolactinoma and presence of uterine adenocarcinoma in these rats.

It is important to consider that there are rat strain differences with respect to the background incidence of uterine and mammary tumours, and to the response to decreased prolactin levels. All published articles regarding a relationship between uterine adenocarcinoma and decreased prolactin levels following reduced body weights and reduced number of pituitary tumors come from studies in Wistar rats (Harleman H *et al.*, 2012). In contrast, the carcinogenicity study with laquinimod was undertaken in Sprague-Dawley (SD) rats. In dietary restriction studies, both SD and Wistar rats have shown reduced number of pituitary and mammary tumours; however, only Wistar rats show an increase in uterine tumours (Keenan KP *et al.*, 1995; Harleman H *et al.,* 2012). The authors of a review on > 5000 Wistar rats and > 2000 SD rats from the RITA database state that there is an apparent specific sensitivity for this effect in the Wistar strain, which is not present in SD rats (Harleman H *et al.*, 2012). These data further question the mechanism proposed by the applicant.

In summary, since prolactin levels were not measured in the rat carcinogenicity study there is no direct evidence to show that the 7 high-dose females with uterine adenocarcinoma were hypoprolactinemic. Indirect evidence of hypoprolactinemia is not particularly convincing: 4 of these rats had mammary tumors (suggesting prolactin stimulation) and 4 had pituitary adenoma (3 animals had both types of tumours) with at least 2 pituitary tumors showing some degree of prolactin-positive IHC staining. Furthermore, a relationship between reduced body weight and uterine adenocarcinoma via reduced number of prolactinoma has not been found in SD rats.

Even assuming that the applicant’s hypothesis is correct, i.e. that these rats were hypoprolactinemic as a consequence of lower body weight gain and associated lower incidence of prolactinoma, it should be noted that an increase in uterine tumors has only been verified for compounds causing a direct effect on prolactin secretion, e.g. bromocriptine. Such an association has not been confirmed for relative hypoprolactinemia due to decreased incidence of pituitary neoplasia (Hargreaves & Harleman, 2011). Assuming that the applicant’s hypothesis is correct, i.e. that the occurrence of uterine adenocarcinomas in high-dosed animals is driven by a lower incidence in prolactinemia inducing in turn an “hypoprolactinemic state”, it is surprising that none of the 37 control females not presenting any prolactinoma was diagnosed with uterine adenocarcinoma (vs. 6/46 in the high dose group, according to the applicant’s hypothesis).

The applicant refers to the Biosure study (Roe *et al.*, 1995) where the feeding of a high fibre diet (LMA) to Wistar rats led to an increased incidence of uterine carcinomas. However, the authors of that study concluded that it could not be excluded that the effect might be due to a higher

exposure of the LMA-fed rats to dietary phyto-estrogens in some way associated with the fibre. Rats in the same study that were fed with a restricted standard maintenance diet (SMR) did not show an increase in uterus adenocarcinoma, although they had a lower incidence of pituitary tumors.

Furthermore, there is no strong regulatory acknowledgement of this mechanism. The examples provided by the applicant (fingolimod and ticagrelor) illustrate that regulatory bodies (FDA, CHMP) have come to different conclusions regarding the link between prolactin decrease and uterine tumors. It should be noted that the carcinogenicity studies with fingolimod as well as ticagrelor were conducted in Wistar rats.

In the absence of convincing data to support the applicant's hypothesis, alternative mechanisms have to be considered. AhR activity can modulate prolactin expression in the pituitary, which could theoretically result in similar hormonal disturbances as seen in true and relative hypoprolactinemia (Moran *et al.*, 2012). However, there are no findings (e.g. implantation failure, decreased fertility) suggestive of direct hypoprolactinemia in the repeat dose toxicity or reproductive toxicity studies with laquinimod.

On the other hand, TCDD and DLCs have been shown to induce a number of effects on female reproductive organs in rats, e.g. chronic inflammation in the ovary, acute and/or chronic inflammation of the uterus, cystic endometrial hyperplasia and uterine carcinoma (Yoshizawa K *et al.*, 2009b). These effects were possibly via anti-estrogenic mechanisms, endocrine disruption of the reproductive organs, or a local retinoid deficiency pathway resulting in abnormal epithelial differentiation.

In conclusion, for the majority, the applicant's proposed rat-specific mechanism is not considered sufficiently supported by data. Alternative mechanisms, e.g. mediated via the AhR, cannot be excluded.

- The applicant's proposed mechanism for oral squamous cell carcinoma observed in the laquinimod rat carcinogenicity study is as follows: during withdrawal of the gavage tube from the animal, reflux or leakage of residual dosing solution may lead to direct contact with high concentrations of drug in the oral cavity. Since laquinimod is cytotoxic to keratinocytes *in vitro* this high local concentration is likely to cause irritation, which in turn may progress to hyperplasia and carcinoma. If the above outlined hypothesis would be correct one would assume that many drugs would exert the same effect in rodent carcinogenicity studies; however, few if any therapeutic agents have been shown to cause oral cavity tumours in rodent bioassays [Greaves, 2007]. In contrast, a number of chemical carcinogens including TCDD and DLCs have been reported to induce squamous carcinomas in the oral cavity of rats.

TCDD and DLCs caused gingival hyperplasia as well as squamous cell carcinoma in Sprague-Dawley rats (Yoshizawa K *et al.*, 2005). These tumours occurred within the oral mucosa of the palate, located mainly lateral to the molar teeth. The gingival area in the vicinity of the molars was also the location of the proliferative oral findings in the laquinimod rat carcinogenicity study.

In mink, gingival hyperplasia characterized by cystic nests and infiltrative squamous epithelial cells in periodontal ligaments appeared during TCDD exposure (Haynes *et al.*, 2009). Similar histopathological lesions (periodontal/palatal cysts and gingival hyperplasia) were present in the laquinimod rat carcinogenicity study.

Although the exact mechanism whereby TCDD and DLCs induce oral squamous carcinoma is not known, one hypothesis relates to a disruption of retinoid homeostasis, leading to abnormal epithelial differentiation and a keratinized squamous phenotype (Lancillotti F *et al.*, 1992). From

this perspective it is of interest to note that laquinimod caused forestomach squamous hyperplasia, and squamous metaplasia in the urinary bladder and larynx.

Furthermore, dental lesions such as ameloblast degeneration and tooth developmental abnormalities have been reported in both animals and humans exposed to TCDD and DLCs (Yoshizawa K *et al.*, 2005). In view of the well-known dental toxicity of TCDD and DLCs it is interesting to note that distinct dental lesions were observed in the applicant's two local tolerance studies in hamsters and rats [Study 39926; Study 39924].

In these studies, laquinimod was directly applied to the oral mucosa for up to 13 weeks, at concentrations 5 and 20-fold higher than the top concentration of the dosing solution used in the rat carcinogenicity study. In the hamster study, laquinimod caused hyperplasia, hyperkeratosis and inflammation at the application site as well as in other sites of the oral cavity (oral mucosa, gingiva and palate). In addition, discolouration of the incisor teeth was observed and associated with atrophy and disorganization of the ameloblastic cells at the base of the incisor teeth. The results of the rat study were confounded by inflammatory changes in both control and drug-treated animals. However, there were clear treatment-related dental effects in the form of discolouration of the incisor teeth and degeneration/necrosis of the pulp.

It should be noted that AhR is detectable in molar teeth buds and palatal epithelial cells, in particular from the late embryonic stage in rodents and humans (Yoshisawa K *et al.*, 2005).

In conclusion, for the majority, the applicant's proposed mechanism for the oral squamous carcinomas is considered highly unlikely. Taking into account the similarities between oral/dental proliferative and degenerative lesions caused by TCDD/DLCs and laquinimod, a mechanism related to AhR activation cannot be excluded.

- Laquinimod has an overall toxicity profile (general toxicity, immune system effects, reproductive toxicity and carcinogenicity) that correlates well with what has been shown for AhR agonists such as e.g. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It is acknowledged that not all effects are completely overlapping; however, this is to be expected considering the complexity and diversity of AhR-mediated toxic responses. Thus, it cannot be excluded that the tumours were caused by the interaction of laquinimod or its metabolites with the AhR receptor. Such mechanism(s) can be of relevance for humans. Alternatively, although no obvious suggestion can be made, some other unidentified mechanism of unknown relevance to humans could be causing the tumours identified in the rat carcinogenicity study. The low exposure margins should then be considered.

- There are data showing that the human is less sensitive than animals for certain effects associated with activation of the AhR *(*Connor & Aylward Toxicol Environ Health B Crit Rev. 2006 Mar-Apr;9(2):147-71*)*. However, there are data showing that different AhR ligands affect the human and animal AhR differently, and some are more potent at the human receptor than the animal and vice versa (e.g. Moriguchi *et al.*, PNAS 2003, 5652–5657; Flaveny & Perdew; Mol Cell Pharmacol. 2009, 1(3): 119–123). Thus, it is not possible to in a general manner estimate that the human will be less sensitive AhR activation. It is thus not possible to conclude on larger margins of exposure than those established based on pharmacokinetic data.

Taken together, there are concerns related to carcinogenic risk associated with long-term human use of laquimimod.

- the SWP did not find it meaningful to recommend specific additional studies to be undertaken at this stage. There are several possible studies that could be considered to explore the interaction with laquinimod and its metabolites at the AhR. For instance, additional in vitro studies, in the same models as already used for testing of laquinimod and DELAQ, could be undertaken with other metabolites of laquinimod. The rationale for doing so, despite that other metabolites have been

observed in humans at very low levels only, would be the finding that DELAQ was very potent at the AhR (EC50 in the picomolar range), and that there are metabolites downstream of DELAQ with close structural similarity. Furthermore, there is a knock-out mouse available; and studies in AhR -/- mice could be used to dissect which effects of laquinimod are AhR dependent and which are AhR- independent.

- Regarding effects on the immune system, further exploration of the primary mechanism of action could be of interest. In addition, a reported reduction in IL-17 levels after laquinimod exposure *in vivo* (in the EAE model) confirmed in *in vitro* experiment on human PBMCs possibly indicates an direct or an indirect effect on Th17 differentiation or function and might be considered for further investigation.

- Further data on the effects of laquinimod on prolactin levels are not meaningful given the considerable evidence speaking against reduced prolactin as a plausible mechanism for the uterine adenocarcinoma in the rat carcinogenicity study.

- The toxicity profile shown in the general and reproductive toxicity studies, in addition to the tumours for which mechanistic explanations have not been possible to establish, and together with the available, although somewhat limited, mechanistic support for interaction with the AhR system, lead to serious concerns for human safety. Based on that, there are doubts that additional mechanistic data can help in excluding a human risk.

- The mechanisms proposed by the applicant for the uterine adenocarcinomas as well as the oral cavity tumours are not convincing; rather detailed review of available data speaks against these proposed mechanisms. Such interaction could be part of alternative mechanistic explanations for the development of these tumours. There are species differences between effects induced by AhR activation, and there is support that the human may be less sensitive for certain effects than animals. However, there are also data showing the opposite. Thus, it is not possible to conclude on a general increase in margins of exposure due to potential species differences. Alternatively, although no obvious suggestion can be made, some other unidentified mechanism of unknown relevance to humans could be causing the tumours identified in the rat carcinogenicity study. The low exposure margins should then be considered, and thus the tumours are of concern for human safety. Thus, the data at hand cannot be used to conclude a lack of human relevance of the tumours observed in the rat carcinogenicity study. In addition, no obvious risk minimisation activities could be proposed. Thus, there are concerns related to carcinogenic risk associated with long-term human use of laquinimod.

The applicant presented at an Oral Explanation held on 17 December 2013 the details of their rationale for considering AhR activation as a valid pharmacological target and their position regarding the potential risk of carcinogenicity and teratogenicity based on animal findings. No major changes to the applicant position regarding the potential risk of carcinogenicity and teratogenicity were noted by the CHMP. According to the applicant, AhR has been acknowledged as a viable pharmacological target for inflammatory diseases and cancer and the profile of laquinimod resembles to indole-3-carbinol, a compound found as nutrient in vegetables and used as food supplement.

Having considered the above SWP conclusions and the data submitted in the application, the CHMP concluded that:

the non-clinical aspects of laquinimod have not been adequately documented and do not meet the requirements to support this application for the following reasons:

- The overall toxicity profile (general toxicity, carcinogenicity and reproductive toxicity) of laquinimod correlates well with what has been shown for AhR agonists such as e.g. TCDD (dioxin).

This, in addition with the mechanistic data supportive of AhR activation, raised some serious concerns regarding the relevance of the findings in animals with respect to human safety.

- The mechanisms proposed by the applicant to explain the occurrence of neoplastic lesions found in the oral cavity and uterus of rats in the carcinogenicity study were not convincing to exclude a relevance of the findings in animals with respect to human safety.

- The mode of action of laquinimod has not been sufficiently investigated, and in particular, the identification of the molecular target remains unknown, contributing to the insufficient characterization of the safety profile of laquinimod.

Assessment of paediatric data on non-clinical aspects

During the evaluation, data on the juvenile toxicity study in rats were submitted at the CHMP request on the basis that the study was completed according to the PIP. The CHMP noted that preliminary data were reviewed by the PDCO in the context of a PIP modification procedure in January 2013. These data showed decreased femur width in males dosed with laquinimod. The effect seemed to be irreversible. Given the clinical relevance of the reduced femur width observed following exposure to laquinimod during maturation was unknown at that time, the PDCO agreed for further characterisation of this issue. Upon availability of the final results, findings and conclusions were requested to be discussed with the PDCO prior to initiating any paediatric studies. On this basis, no further assessment was considered necessary by the CHMP at the present time.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of laquinimod have not been adequately documented and do not meet the requirements to support this application for the following reasons:

- The overall toxicity profile (general toxicity, carcinogenicity and reproductive toxicity) of laquinimod correlates well with what has been shown for AhR agonists such as e.g. TCDD (dioxin). This, in addition with the mechanistic data supportive of AhR activation, raised some serious concerns regarding the relevance of the findings in animals with respect to human safety.

- The mechanisms proposed by the applicant to explain the occurrence of neoplastic lesions found in the oral cavity and uterus of rats in the carcinogenicity study were not convincing to exclude a relevance of the findings in animals with respect to human safety.

- The mode of action of laquinimod has not been sufficiently investigated, and in particular, the identification of the molecular target remains unknown, contributing to the insufficient characterization of the safety profile of laquinimod.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

The clinical development program to evaluate laquinimod in patients with MS includes both ongoing and completed studies:

- Phase I studies: thirteen studies in healthy volunteers were completed (one also included MS patients) and an ascending dose, sequential cohort study (MS-LAQ-101) is ongoing in RRMS patients.

- Phase II studies: one placebo-controlled (Study ID 01506203) and one open-label (study ID 03506207) in MS patients were completed. One study (LAQ/5062) and its extension study (LAQ/5063) were also completed. An extension of study LAQ/5063 is ongoing.

- Phase III studies, MS-LAQ-301 and MS-LAQ-302 studies were completed and extensions to both are currently ongoing.

Table 1. Summary of Clinical Studies Providing Efficacy Data

Study ID	No. of study centres, locations	Design	Study Posology	Study Objective	Subjects by arm entered/ completed	Duration	Gender M/F, Median Age	Diagnosis Inclusion criteria	Primary Endpoint
Phase II studies									
01506203	mc, 20 centers in UK, Russia, Sweden, and Netherlands	Phase II r,p, db,pc (n=209)	0.1mg LAQ/day 0.3mg LAQ/ day Placebo once/day	Efficacy and Safety in relapsing MS	0.1 mg: 68/65 0.3 mg: 74/69 placebo: 67/64	24 weeks treatment and 8 weeks follow-up	54 M 155 F, mean age 40.2 (19-62) years	RRMS (84%) SPMS (15.3%) based on Mc Donald criteria	cumulative number of active lesions between week 0 and 24
LAQ/5062	mn, mc, 51 centers in Italy, Germany, Spain, Czech Republic, Russia, Poland, UK, Hungary, and Israel	Phase IIb r, p, db, pc (n=306)	0.3mg LAQ/day 0.6mg LAQ/ day Placebo once/day	Efficacy, Tolerability and Safety in RRMS	0.3 mg: 98/92 0.6 mg: 106/100 placebo: 102/91	36 weeks double-blind phase	115 M 191F mean age 33.0 (18-51) years	RRMS based on Mc Donald criteria	cumulative number of GD-enhancing lesions on T1-weighted images, weeks 24,28,32 and 36
Phase III studies									
MS-LAQ-301 (ALLEGRO)	mc, USA, Canada, Israel and Europe 139 centers in 24 countries	Phase III r, p, db, pc (n=1106)	0.6 mg LAQ/day Placebo once/day	Efficacy, Tolera-bility and Safety in RRMS	0.6 mg: 550/437 Placebo: 556/427	24 months	347 M 759 F mean age 38.7 (18-56) years	RRMS based on revised Mc Donald criteria (2005)	Annualized Relapse Rate (ARR) secondary: -cumulative number of GD-enhancing lesions on T1-weighted images -cumulative number of new/enlarging T2 lesions -Time to confirmed EDSS progression -MSFC score at month 24
MS-LAQ-	mc, USA,	Phase III	0.6 mg	Efficacy,	0.6 mg:	24	421 M	RRMS	Number of

302 (BRAVO)	Israel, South Africa and Europe 155, 154, 153 centers in 15, 18 countries	r, p, ac, db for oral treatment arms (LAQ and Placebo) rb for inj. arm IFN-β 1a (Avonex) (n=1331)	LAQ/day Placebo once/day 30 mcg Avonex im once weekly	Tolera-bility and Safety in RRMS versus placebo and active c (Avonex)	434/353 Placebo: 450 /359 Avonex: 447/378	months	910 F mean age 37.6 (18-56) years	based on revised Mc Donald criteria (2005)	Annualized Relapse Rate (ARR) secondary: -brain atrophy -time to comfirmed EDSS progression -MSFC score at month 24
Open label extension studies									
LAQ/5063 Extension of LAQ/5062	mc	Phase IIb, r, p, db extension study.	0.3mg LAQ/day 0.6mg LAQ/ day	Efficacy, Tolera-bility and Safety in RRMS	257 RRMS patients	complet ed	103 M 154 F (18-51 years)	RRMS	
LAQ/5063 OL open label phase of LAQ/5063	mc	Phase IIb ol extension phase of study LAQ/5063	0.6mg LAQ/ day	Safety, Tolerabilit y and Efficacy in RRMS	209 RRMS patients	ongoing	83 M 126 F (19.8-52.5 years)	RRMS	
MS-LAQ-301 E	mc	phase III ol	0.6mg LAQ/ day	long-term Safety, Tolerabilit y and Efficacy	837 com-pleters of MS-LAQ-301	ongoing	270 M 567 F 20-58.2 years	RRMS	
MS-LAQ 302 E	mc	phase III ol	0.6mg LAQ/ day	long-term Safety, Tolerabilit y and Efficacy	1047 completers of MS-LAQ-302	ongoing	340 M 707 F 20.2-57.9 years	RRMS	

LAQ=laquinimod, r= randomized, p=parallel, db= double-blind, pc = placebo controlled, ol= open label, ac= active controlled, IFN-ß 1a = interferon-beta 1a, mc = multicenter, mn = multinational, rb = rater blinded, EDSS:Expanded Disability Status Scale

In addition, phase III studies in RRMS evaluating 1.2 mg dose are ongoing (CONCERTO) or planned (LIBRETTO) and one phase II study (ARPEGGIO) in PPMS is initiated by the applicant.

2.4.2. Pharmacokinetics

Pharmacokinetic (PK) data were derived from 14 Phase I clinical studies, involving a total of approximately 500 subjects as well as PK evaluation which was performed in four Phase II studies and one Phase III study in MS patients. In addition, a number of drug-drug interaction studies have been performed in healthy volunteers in order to investigate the potential effect of CYP3A4 modifiers and the effect of laquinimod on CYP1A2 and CYP3A4 substrates.

Concentrations of laquinimod were measured in the human plasma and urine using LC/MS/MS methods in the PK studies. Pharmacokinetic parameters were determined using non compartmental models. In addition, one population PK analysis using non linear mixed effects modeling methodology (NONMEM). The population PK analysis was conducted using sparse data from phase II and phase III studies together with the phase I studies.

Absorption

The absolute oral bioavailability of laquinimod has not been studied. Based on the human metabolism data, more than 90% of the drug was absorbed supporting a high level of absorption of laquinimod. The extent of absorption of laquinimod is not significantly modified by food intake absorption. The impact on food-intake on the rate of absorption is less clear. A 30 % decrease in Cmax was observed high fat meals resulted in a prolongation of T_{max} to approximately 5 hours. Laquinimod may be taken with or without food since the overall extent of absorption is not affected (AUC decrease by 10% only). The CHMP also noted that laquinimod was taken without regard to meals in phase III studies, thus supporting such recommendation.

All phase III clinical studies were conducted using the formulation intended to be marketed. In addition, bioequivalence was demonstrated between the earlier formulations used in phase I and II studies and the final formulation.

Distribution

The steady-state apparent volume of distribution of laquinimod is small (~10 L) and independent of dose, thus the drug is suggested to be poorly distributed to the peripheral tissues. Laquinimod is reversibly bound to human plasma proteins, primarily to serum albumin. Plasma protein binding of laquinimod is high in humans (>98%). After single dose administration of a dose of 14C-laquinimod to healthy volunteers, blood/ plasma partition of radioactivity was 0.6, hence laquinimod was mainly distributed to plasma with minimal distribution to red blood cells.

Elimination

Laquinimod is very slowly eliminated primarily by metabolization as only a marginal fraction of the unchanged parent drug is recovered in the excretae (1.57% in faeces and 1.88% in urine). The plasma elimination half-life is approximately 80 hours. From the available data, laquinimod is primarily but slowly eliminated by oxidative metabolism. No major metabolite was identified in plasma and consequently accumulation of metabolites in humans was not tested. The main route of excretion was via the urine with 50.8±2.2 per cent of the dose recovered. Faecal excretion accounted for 28.1±3.4 per cent resulting in a total recovery of 78.9±4.3 (mean±SEM, n=6) per cent.

Dose proportionality and time dependencies

Laquinimod PK appeared to evolve proportionally to the dose after single and repeated doses ranging from 0.05 up to 2.4 mg/day in healthy volunteers and also in patients. No time dependency was observed. Upon once daily repeated dosing, laquinimod reaches steady state concentrations within approximately 14 days of dosing, accumulates in plasma approximately 5-6 fold, and fluctuation during the 24 hours dosing interval is low (about 30%).
The intra-individual and inter-individual variability were relatively small, respectively less than 16% and 20%, respectively.

Special populations

Specific phases I studies evaluating renal and hepatic functions were conducted. Other age and gender related data were derived from the population PK analysis. The effects of race and weight could not be evaluated in the population PK analysis because Caucasians were accounted from 90% of the population and the underweighted and obese patients were not adequately studied. Additional analyses were therefore performed to evaluate the effects of race and weight using

Bayesian estimation of the clearance and volume of distribution in the different race and weight subgroups.

A specific study was conducted in subjects with moderate renal impairment after 0.6 mg oral single dose. Exposure to laquinimod in moderate renal impaired subjects was found to be approximately 40% (1.4 fold) higher comparatively to healthy volunteers. No difference was observed for the maximum plasma concentration, Cmax. The influence of severe renal impairment on the pharmacokinetics of laquinimod has not been studied.

A specific study was conducted in subjects with mild/moderate hepatic impairment after 0.6 mg oral single dose. The AUC for laquinimod was approximately 1.3 and 2.3 fold higher in subjects with mild/moderated hepatic impairment. No difference was observed for the maximum plasma concentration, Cmax. The influence of severe hepatic impairment on the pharmacokinetics of laquinimod has not been studied.

No data are available in the paediatric population as the clinical studies included in the PIP had been deferred at the time of initial submission. The elderly population was also not studied and there was a limited exposure to patients aged 55 years or above.

In the population pharmacokinetic analysis, laquinimod clearance was higher (about 8%) in males compared to females and its volume of distribution of the central compartment was approximately 21% higher in males compared to females of similar weight. These differences were not considered of clinical relevance. No effect of age was observed.

Bayesian estimation of clearance and volume of distribution did not reveal any significant differences across race and weight (obese, underweighted and normal patients) subgroups.

Pharmacokinetic interaction studies

In vitro studies with human hepatocytes demonstrated a little or no inhibitory effect of laquinimod on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1. At 25 µM, the activity of CYP2C8 and CYP3A4/5 were inhibited by laquinimod, up to 4 and 11%, respectively. At 10 µM, a moderate effect on CYP2C9 activity was observed at a concentration of 10 µM, i.e. a 32% decrease.

Potential for induction effect of laquinimod was also studied in vitro evaluating a number of CYP450 enzymes. No induction effect was observed on CYP3A4, however a potent induction of CYP1A2 activity was noted. CYP2B6 activity was also found to increase 2 to 4-fold over the tested concentration range (0.1, 1 and 10 µM) whereas no clear change was seen in CYP2C8, CYP2C9 or CYP2C19 activity. The activity of CYP3A4/5 showed a 2-4- fold decrease at 1-10 µM associated with low change in the levels of CYP3A4 mRNA. In vivo data suggested a potent induction effect of laquinimod in rats with a level of hepatic CYP1A1 increases of 20-, 130- and 600-fold following doses of 0.1, 1, and 10 mg/kg/day for 4 days, respectively. Hepatic CYP1A2 content increased 4, 9, and 10-fold at the corresponding doses. In the same studies no relevant change in the level of CYP3A2 (the rat analogue to the human CYP3A4) or CYP2B1/2 was detected.

The induction effect on CYP1A1 and CYP1A2 activities and inhibitory effect on CYP3A4 activity was further investigated in an additional study, evaluating both laquinimod and DELAQ metabolite. In this study, laquinimod or DELAQ caused increases in CYP1A2 activity and CYP1A1 and CYP1A2 mRNA levels and a decrease in CYP3A4/5 activity and, in the case of DELAQ, a decrease in CYP3A4 mRNA levels was also noted. Laquinimod was found to be a more potent inducer of CYP1A2 activity than DELAQ but had no relevant effect on CYP3A4 mRNA levels. According to the applicant, the CYP induction potential of laquinimod is likely related to its interaction with the AhR transcription factor, as shown in dioxin responsive CALUX bioassay and in human MCF7 cells.

Laquinimod was also shown to cause a concentration-dependent induction of two uridine diphosphate glucuronosyltransferase enzymes, UGT1A1/6 and UGT2B2, when examined in primary cultures of male rat hepatocytes. Laquinimod at 1, 10 and 100 µM caused up to 6.9-fold and 2.4-fold concentration dependent increase in UGT1A1/6 and UGT2B2 activities, respectively.

When the inhibitory effect of laquinimod (10 µM) on transport of substrate by P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3 was investigated, no decrease in the transport of probe substrates for these transporters was observed.

The potential interactions were studied in humans for the following drugs: rifampin (CYPA3A4 inducer),cimetidine (weak CYP3A4 inhibitor), fluconazole (moderate CYP3A4 inhibitor) and ketoconazole (strong CYP3A4 inhibitor). In addition, the effect of laquinimod on the PK of midazolam, a CYP3A4 substrate, and caffeine, a CYP1A2 substrate, was evaluated in healthy volunteers.

After receiving ketoconazole, at 400 mg once daily for 28 days or fluconazole, at 200 mg once daily for 21 days, systemic exposure (AUC) of laquinimod increased approximately 3.1-fold with ketoconazole and 2.5-fold with fluconazole. No effect was observed on Cmax in both situations. After receiving cimetidine, at 1600 mg once daily for 21 days, systemic exposure (AUC and Cmax) of laquinimod was found not to be affected. Systemic laquinimod exposure was decreased approximately 5-fold with no effect on Cmax, after receiving rifampicin, at a dose of 600 mg once daily for 21 days.

After receiving caffeine or midazolam with repeated doses of laquinimod (0.6 mg), the AUC and Cmax of caffeine were decreased approximately 5-fold and 2-fold, respectively, the AUC of midazolam was increased approximately 1.5-fold, while its Cmax was not affected.

Considering the teratogenic properties of laquinimod, an additional vivo interaction study investigating the potentially inducing effect of laquinimod on oral contraceptives was recommended by the CHMP to be performed. Results were recommended by the CHMP to be available within a reasonable timeframe.

2.4.3. Pharmacodynamics

Limited data were provided regarding the pharmacodynamic effects of laquinimod in humans.

Mechanism of action

The mechanism of action of laquinimod is not fully elucidated because the molecular target is not known. Data on various types of experimental autoimmune encephalomyelitis models, as well as in cuprizone induced demyelination and on other inflammatory/autoimmune disease models were presented to support the immunomodulatory properties of laquinimod and therapeutic effect in MS population.

Primary and Secondary pharmacology

Pharmacodynamic effects of laquinimod on heart (QT/QTc study) and lymphocytes counts have been specifically investigated in healthy volunteers and RRMS patients (phase III sub-study), respectively.

Cardiac effects

The presented QT/QTC study was well conducted and is considered valid. Laquinimod (up to 1.2 mg daily during 14 days) did not show an effect on the cardiac ventricular repolarization. The mean QTcI was not increased in a clinically meaningful manner during the study. The largest time

matched QTcI against placebo was in the 3 ms range for 0.6 mg and in the 4 ms range around Cmax for the 1.2 mg. The upper limit of the confidence interval always remained within the 10 ms limit, defined by the ICH E14 guideline. One volunteer only experienced a QTcI prolongation >60 ms. Moxifloxacin increases the QTcI in the 10 ms range, as expected, confirming the sensitivity of the assay. Analysis of QTcB and QTcF yields comparable results.

Immunological tests

Immune analyses in a subgroup of patients enrolled in phase III ALLEGRO study were performed to identify possible immune parameters that may be specifically modified in patients receiving laquinimod. Blood samples were collected prior to commencement of therapy, and again after 1, 3, 6, 12 and 24 consecutive months of laquinimod or placebo therapy. Main objectives were to examine 148 patients with regard to: 1) Immune cell type distribution analysis and 2) Immune cell proliferation in response to mitogen and recall antigen. Measures collected over time in the laquinimod treated group were compared to baseline data, and to data obtained from the placebo control cohort. No changes from baseline were observed in the composition of Peripheral Blood Mononuclear Cell (PBMC): i.e. none of the major populations of PBMC showed any changes over time of between groups. Similarly, there were no changes in the preponderance of any of the sub-populations thus far assessed. After simultaneous evaluation of the proliferative response of PBMC in the presence of PHA or tetanus toxoid, there were no changes from baseline in the proliferative response of PBMC from patients receiving laquinimod therapy, and no differences between the laquinimod treated and placebo control cohorts. According to the applicant, these data demonstrate that patients receiving laquinimod therapy had no apparent changes in their peripheral blood repertoire and retain their capacity to respond accordingly to immunological stimuli. However the CHMP was concerned that the presented results of this study were not adequately substantiating the applicant claim. Details of the CHMP position are presented in 1.7.4.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic profile (absorption, distribution, metabolism and elimination) of laquinimod has been studied in healthy volunteers and multiple sclerosis patients and is considered sufficiently characterised in the intended patient population.

As laquinimod was almost completely metabolised, the CHMP considered that genetic polymorphism could be an important intrinsic factor. The potential impact of genetic polymorphism was thoroughly discussed by the applicant, in particular of the isoenzyme CYP3A4 and the CHMP agreed that the potential for genetic polymorphism could be considered low.

Bioequivalence was demonstrated between the earlier formulations used in phase I and II studies and the final formulation.

No dosage adjustment is required for patients with moderate renal impairment. In the absence of data in subjects with severe renal impairment, the use of laquinimod should be avoided in this population.

Although data in subjects with mild/moderate hepatic impairment did not suggest a very significant increase in the systemic exposure of laquinimod (1.3 to 2.3 fold higher, respectively), the CHMP recommended strengthening the warning, initially proposed by the applicant, as to reflect that the use of laquinimod should be avoided in this population as well as in severe hepatic impaired subjects due to the known and extensive hepatic metabolism.

No data are available in the paediatric population as the clinical studies included in the PIP had been deferred at the time of initial submission. The elderly population was also not studied and there was a limited exposure to patients aged 55 years or above.

Population pharmacokinetic analyses did not reveal any significant effect of gender nor age. Bayesian estimation of clearance and volume of distribution did not reveal any significant differences across race and weight (obese, underweighted and normal patients) subgroups.

The extent of exposure of laquinimod depends mainly on the CYP3A4 activity. Inhibition of the CYP3A4 increases the plasma levels of laquinimod depending on the potency of the inhibitor and a reverse effect is observed when CYP3A4 is induced. Laquinimod itself is a strong inducer of CYP1A2. Consequently, a number of recommendations related to concomitant use with CYP3A4 modifiers and CYP1A2 substrates should be considered as follows: 1) The concomitant prolonged (> 1 month) use of moderate or strong CYP3A4 inhibitors and laquinimod should be avoided, 2) Concomitant use of strong CYP3A4 inducers with laquinimod is not recommended and 3) Dosage adjustment should be made in case of concomitant administration with CYP1A2 substrates with a narrow therapeutic index.

Laquinimod showed a weak effect on CYP3A4 substrates and is not expected to significantly impair their pharmacokinetic profiles. No dosage adjustment is required.

Considering the teratogenic properties of laquinimod, an additional vivo interaction study investigating the potentially inducing effect of laquinimod on oral contraceptives was recommended by the CHMP to be performed. Results were recommended by the CHMP to be available within a reasonable timeframe.

Laquinimod (up to 1.2 mg daily during 14 days) did not show an effect on the cardiac ventricular repolarization.

The applicant presented data to demonstrate that patients receiving laquinimod therapy had no apparent changes in their peripheral blood repertoire and retain their capacity to respond accordingly to immunological stimuli. Although, there were no statistically nor clinically significant differences in the composition or proliferative response of patient's Peripheral blood mononuclear cells PBMCs in the laquinimod-treated group as compared to the baseline data, and to data obtained from the placebo group, the CHMP questioned the relevance of the selected markers for the analysed cell subsets (e,g. CD83+ for dendritic cells, CD57+ for NK-T cells). In its analysis, the CHMP was concerned about the lack of clear presentation of the data and recommended the applicant to provide relevant longitudinal information on the variations of lymphocytes subsets such as the absolute values and percentages (obtained by a bead-based standardized flow cytometry procedure performed on whole blood and carried out by a single lab registered to a recognized quality control such UKNEQAS). Overall, these issues remained to be addressed. The applicant claim was therefore not endorsed by the CHMP.

Overall, limited data were provided regarding the pharmacodynamic effects of laquinimod in humans. Given the mechanism of action has not been sufficiently investigated and the molecular target remains unknown, the CHMP considered that no conclusion could be drawn on the clinical pharmacology of laquinimod.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of laquinimod in human studies has not been adequately documented and does not meet the requirements to support this application for the following reasons:

- Whilst the pharmacokinetic profile has been sufficiently characterised, there is a lack of relevant data on the pharmacodynamic effects of laquinimod in humans reinforcing the uncertainties raised on its mechanism of action and potential risks.

2.5. Clinical efficacy

The applicant applied for the following indication: treatment of patients with relapsing remitting multiple sclerosis (RRMS).
The clinical development program comprises the following clinical studies:
- a phase II, 24-week, double- blind, randomised, placebo- controlled, parallel-group, study **(01506203)** evaluating the efficacy and safety of laquinimod 0.1 mg and 0.3 mg versus placebo in patients with relapsing multiple sclerosis (RMS) patients;

- a phase II, 36 week, double-blind, randomised, placebo-controlled, parallel-group study (**LAQ/5062**) evaluating the efficacy and safety of laquinimod 0.3 and 0.6 mg versus placebo in RRMS patients. LAQ/5062 had an extension study (**LAQ/5063**) that has been completed and has been then subject to another extension study, which is currently ongoing.

- a phase III, 24-month, double-blind, randomised, placebo-controlled, parallel-group study **(LAQ-301),** evaluating the efficacy and safety of 0.6 mg laquinimod administered once daily versus placebo in RRMS patients. LAQ-301 (also called '**ALLEGRO'**) has an ongoing extension study **(LAQ-301E).**

- a phase III, 24-month, randomised,parallel-group study **(LAQ-302),** evaluating the efficacy and safety of 0.6 mg laquinimod administered once daily versus placebo in a double-blind design and versus interferon β-1a (Avonex) administered i.m. once weekly in a rater-blinded design in RRMS patients. LAQ-302 (also called '**BRAVO'**) has an ongoing extension study (**LAQ-302E**).

2.5.1. Dose response studies

In study 01506203, 2 doses were tested (0.1 mg and 0.3mg). A total of 209 patients were randomised (n=67 for placebo group, n=68 for 0.1 mg laquinimod group and n=74 for 0.3 mg group). The population study was representative of the MS population (RRMS, SPMS), with 74.2 % of women and 98.6% of Caucasian patients. Around 15.3% were SPMS patients. The mean age was around 40, the mean duration of the disease was 5.82 years and patients had at least one documented clinical or subclinical (defined as a gadolinium-enhanced lesion on MRI examination or a new T2 lesion demonstrated on two consecutive Magnetic Resonance Imaging or MRI examinations) exacerbation in the last year or two documented exacerbations in the last two years (one of which could be subclinical) or the presence of one gadolinium-enhanced lesion on the Week -4 MRI scan and had had at least nine T2 lesions on the Week -4 MRI scan or at least three T2 lesions and at least one gadolinium-enhanced lesion on a T1 weighted scan at Week -4.
In the primary analysis using Per Protocol (PP) population, the mean cumulative number of active lesions was reduced by 44% in the 0.3mg laquinimod group compared with placebo (5.24 vs 9.44) and there was a reduction in the geometric mean for the cumulative number of active lesions at Week 24 in the laquinimod 0.3 mg group (2.264) as compared to placebo group (3.164); this difference was of borderline significance (p=0.0498). At 0.1 mg, this difference was not statistically significant (p=0.2615). The CHMP also noted that there was an imbalance at baseline regarding the number of active lesions (higher in the placebo group) which could introduce a bias in favour of the laquinimod groups. The analysis using Intention To Treat (ITT) population showed a non-statistically significant difference between laquinimod (both 0.1 mg and 0.3 mg dose) and placebo groups (p=0.202 at 0.1 mg and p=0.172 at 0.3 mg). No statistically significant differences were observed in any clinical parameters (e.g. number of relapses, time to first relapse or severity of

relapse) between treatment groups over the treatment period. Taking into account the lack of effect of the 0.1 mg dose and the inconclusive results for the 0.3 mg dose, study LAQ/5062 was conducted using higher dose of laquinimod.

In study LAQ/5062, only one higher dose was tested (0.6 mg) together with the 0.3 mg dose, that was previously investigated and only RRMS patients were included. In addition, the primary endpoint was changed to measure the cumulative number of active lesions between week 0 to week 14, as opposed to week 24. The number of randomized patients was 98 in the laquinimod 0.3 mg group, 106 in the laquinimod 0.6 mg group and 102 in the placebo group. The population studied was representative of the RRMS population with 62.4% of it being women and 99.0% of it being Caucasian patients. The mean age was around 33 years; the mean duration of disease was short (3.7 years). Patients had 1.46 relapses in the previous one year and had a baseline EDSS of 2.3. A statistically significant treatment effect (p=0.0048) of laquinimod 0.6 mg was observed as compared to placebo, with a reduction of 40% in the cumulative number of Gd-enhancing lesions at weeks 24, 28, 32 and 36 (primary endpoint). Results on a number of secondary MRI parameters (e.g. cumulative number of new T2 lesions, mean number of new hypointense lesions on T1) were positive and consistent with the primary efficacy analysis for the 0.6 mg dose. On the other hand, no significant effect on the primary endpoint was observed with the 0.3 mg dose with a reduction of 8% as compared to placebo (p=0.6740) and no significant effects were observed on the other analysed MRI endpoints. Regarding the proportion of relapse-free subjects, and clinical endpoints related to relapses and EDSS there was no effect of any of the laquinimod treatments compared to placebo. The mean number of relapses was decreased in the Laquinimod 0.6 mg group (0.40) as compared to placebo (0.54); however this result was not statistically significant (p=0.2079). In the laquinimod 0.3 mg group there was no difference in the number of relapses (0.56) compared to placebo.

2.5.2. Main studies

2.5.2.1. Study LAQ-301 – ALLEGRO

This was a randomised, double-blind, parallel-group, placebo-controlled study evaluating the efficacy and safety of laquinimod administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis. Treatment duration was 24 months with a possibility of extension to 36 months.

The study was conducted in a number of European countries and also in non-EU regions (e.g. the US, Canada, Israel, Russia, Ukraine, Turkey, Georgia, Serbia).

2.5.2.1.1. Methods

Study Participants

Main inclusion criteria

Males or females aged 18 to 55 years inclusive, with a diagnosis of MS as defined by 2005 revised McDonald criteria, with a relapsing-remitting course with at least one documented relapse during the previous year or two documented relapses during the previous 2 years, prior to screening or one documented relapse between 12 and 24 months prior to screening with at least one documented T1-Gadolinium enhancing (GdE) lesion in an MRI performed within 12 months prior to

screening, with an Expanded Disability Status Scale score of 0 to 5.5 inclusive and with a disease duration of at least 6 months prior to screening.

Main exclusion criteria

Patients who met any of the following criteria were excluded: subjects with progressive forms of MS; an onset of relapse, unstable neurological condition or any treatment with corticosteroids [iv, intramuscular or i.m, and/or per os or ACTH between Month -1 (screening) and 0 (baseline); use of immunosuppressive including mitoxantrone or cytotoxic agents within 6 months prior to the screening visit ; previous use of either of the following: natalizumab, cladribine, laquinimod; previous treatment with glatiramer acetate, Interferon-β (either 1a or 1b) or IVIG within 2 months prior to screening visit; systemic chronic corticosteroid treatment (30 or more consecutive days) within 2 months prior to screening visit; previous total body irradiation or total lymphoid irradiation; previous stem cell treatment, autologous bone marrow transplantation or allogenic bone marrow transplantation; a known history of tuberculosis; acute infection within two weeks prior to baseline visit; major trauma or surgery within two weeks prior to baseline; use of inhibitors of CYP3A4 within 2 weeks prior to baseline visit (1 month for fluoxetine) , use of amiodarone within 2 years prior to screening visit; pregnancy or breastfeeding; a ≥3x Upper Limit of Normal (ULN) serum elevation of either ALT (Alanine Transaminase) or AST (Aspartate Transaminase) at screening; serum direct bilirubin which is ≥2x ULN at screening; a QTc interval which is ≥ 450 msec (according to machine output), obtained from two ECG recordings at screening visit, or the mean value calculated from 3 baseline ECG recordings; subjects with a clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation, as determined by medical history, physical exams, ECG, abnormal laboratory tests or chest X-ray, those included a cardiovascular or pulmonary disorder that could not be well-controlled by standard treatment permitted by the study protocol, a gastrointestinal disorder that could affect the absorption of laquinimod, renal or metabolic diseases, any form of acute or chronic liver disease, known human immunodeficiency virus (HIV) positive status, a family history of long-QT syndrome, an history of drug and/or alcohol abuse, major psychiatric disorder.

Treatments

Laquinimod was given for 24 months at an oral dose of 0.6 mg (capsules). Patients were randomized to one of the two treatment groups in a 1:1 ratio. They received fixed once-a-day doses of study medication with no adjustment permitted.

Objectives

The **primary objective** was to evaluate the efficacy of a daily dose of laquinimod 0.6 mg compared to placebo, as measured by the number of confirmed relapses during the 24-month double blind study period.

The **secondary objectives** were as follows: 1) to compare the cumulative number of enhancing lesions on T1-weighted images taken on Months 12 and 24 (termination/early discontinuation visit after Month 12) between the laquinimod 0.6 mg and the placebo groups; 2) to compare the cumulative number of new/enlarging T2 lesions on scans taken on Months 12 and 24 (termination/early discontinuation visit after Month 12) between the laquinimod 0.6 mg and the placebo groups; 3) to compare the accumulation of physical disability as measured by the time from randomization to confirmed progression of EDSS during the 24-Month double blind study period, between laquinimod 0.6 mg and the placebo groups and 4) to compare the disability as assessed by the Multiple Sclerosis Functional Composite (MSFC) score at Month 24 (termination/early discontinuation visit) between the laquinimod 0.6 mg and the placebo groups.

Outcomes/endpoints

Primary outcome measure

The total number of confirmed relapses observed during the double-blind treatment period as a mechanism for estimating the treatment effect on the annualized relapse rate. The primary analysis was aimed at the comparison of the annualized relapse rate between the 0.6 mg laquinimod arm and the placebo arm.

Secondary outcome measures

- *MRI variables:* cumulative number of Gd-enhancing lesions on T1-weighted images taken on Months 12 and 24 (termination/early discontinuation visit after Month 12); cumulative number of new/enlarging (hyperintense) T2 lesions on scans taken on Months 12 and 24 (termination/early discontinuation visit after Month 12).

- *Disability progression related variables:* accumulation of physical disability measured at the time of confirmed progression of EDSS (progression was defined as at least 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or at least 0.5 point increase if baseline EDSS was 5.5 or higher, confirmed 3 months later; progression could not be confirmed during an MS relapse); MSFC score at Month 24 (termination/early discontinuation visit after Month 12).

Other outcome measures

Other outcomes measures considered as exploratory were: time to the first confirmed relapse during the study period; rate of confirmed relapses during the study period, requiring hospitalization and/or IV steroids; proportion of relapse free subjects; total volume of T2 lesions at Month 12; total volume of T2 lesions at Month 24 (termination/early discontinuation visit after Month 12); total volume of hypointense lesions on GdE T1 scans at Month 12; total volume of hypointense lesions on GdE T1 scans at Month 24 (termination/early discontinuation visit after Month 12); brain atrophy as defined by the percentage change in normalized brain volume from baseline to Months 12 and 24 (termination/early discontinuation visit after Month 12); MSFC z-score at months 6, 12, and 18; cumulative number of new hypointense lesions on enhanced T1 scans at Months 12 and 24 (termination/early discontinuation visit after Month 12); Modified Fatigue Impact Scale (MFIS) score at Month 24 (termination/early discontinuation visit after Month 12); EuroQoL (EQ5D) score at Month 24 (termination/early discontinuation visit after Month 12), Short-Form general health survey (SF-36) change from baseline to Month 24 (termination/early discontinuation visit after Month 12); binocular low-contrast visual acuity assessment, using 100%, 2.5% and 1.25% contrast charts.

Sample size

The sample size considerations for the study are based on the following assumptions: 1) an individual patient's number of confirmed relapses during a one year period reflects a Poisson process with an individual rate of λi, and this individual patient rates λi is exponentially distributed with mean $1/\theta$, where θ is the population's annualized relapse rate (this approach models the total number of confirmed relapses as an Over Dispersed Poisson distribution), 2) the expected annualized relapse rate in an untreated patient population is $\theta=0.65$ relapses per year; 3) in the placebo treatment group, the expected annualized relapse rate is $\theta=0.6$ relapses per year, due to a placebo effect and 4) treatment with laquinimod will reduce the patient population annualized relapse rate by 25% or more when compared to the placebo group. That is, the expected annualized relapse rate of the laquinimod treated population is $\theta=0.45$ relapses per year or less. Following simulation using the Quasi- Likelihood (over-dispersed) Poisson Regression, it was found

that a total of 830 subjects (415 per treatment group) will provide approximately 90% power to detect a statistically significant difference in the total number of confirmed relapses between the treatment group and the placebo group, as described above. To correct for anticipated withdrawal rate of 20% over 24 months, the sample was adjusted and rounded to a total of 1000 patients (500 subjects per treatment group).

The study was also powered to show a statistically significant effect on the time to confirmed progression of EDSS under the following assumptions: 1) EDSS progression rate of untreated subjects is 30% over two years, 2) expected effect of treatment with laquinimod is 25% reduction of the untreated population progression rate, i.e. progression rate of laquinimod treated subjects will be 22% or less over two years. This assumption reflects a relative risk of 0.75 and 3) Progression rate is constant over time in both treatment groups. Using SAS PROC POWER a sample size of 500 subjects per arm was calculated to provide the long-rank test a power of 82.7% detect a 25% reduction in progression rate of subjects treated with laquinimod with respect to subjects in the placebo group.

The study protocol allowed for possible extension of the double blind placebo controlled phase duration to 30 months, depending on the results of a blinded variance analysis of the population disability progression rate and power reassessment. The reassessment was performed on July 2009. The results of this assessment, according to the pre-defined decision rule, led to the decision to end the study as planned, at the end of 24 months of treatment and not to extend it to 30 months.

Randomisation

After meeting eligibility criteria, at the baseline visit, subjects were assigned to one of two possible treatment groups by the Centralised Interactive Voice/Web Response Systems (IVRS/IWRS) according to the randomization scheme that employed a 1:1 assignment ratio. The randomization scheme used blocks stratified by center. Each subject was allocated a unique number in sequential chronological order per site. This number replaced the screening number. The randomization list and the seed used to generate were kept sealed in a fire-protected safe.

Blinding (masking)

The investigators, the sponsor and any personnel involved in subjects' assessment, monitoring, analysis and data management (excluding the designated Clinical Supplies Unit's personnel), were blinded to the subject assignment.

Statistical methods

Level of Significance

The overall significance level for this study is 5% using two-tailed tests and/or two-sided confidence intervals with 95% confidence level. In order to protect the study from type-I error inflation, the secondary endpoints were interpreted inferentially only if a statistically significant treatment effect was detected in the primary analysis. The study's overall type-I error was further controlled in the analysis of the secondary endpoints by applying the following gate-keeping procedure: the first two MRI-based secondary endpoint were analyzed simultaneously with an overall type-I error of 5%, using the Hochberg's step-up modification to Bonferroni's method to the two p-values obtained from the analyses of these two endpoints; the third secondary endpoint, accumulation of physical disability measured by the time to confirmed progression of EDSS was to be interpreted inferentially only if at least one of the 2 endpoints analyzed in the first step of the secondary analysis was significant under Hochberg's procedure, the fourth secondary endpoint, disability as assessed by MSFC was to be interpreted inferentially only if the accumulation of physical disability endpoint analyzed in the second step of the secondary analysis was significant.

Primary Endpoint

The principal statistical analysis of the annualized relapse rate during study was performed on the ITT cohort and was based on the outcome of a contrast (laquinimod 0.6 mg vs. placebo) derived from a baseline-adjusted, quasi-likelihood (over-dispersed) Poisson regression. Subject's number of relapses during the double blind placebo controlled phase served as the response variable. An offset based on the log of subject's exposure in years was employed to adjust for variability of treatment exposure. In addition to the treatment group, the model included the covariates: baseline EDSS score, log of prior 2-year number of relapses+1 and country or geographical region (CGR). The robustness of the results obtained by the principal analysis was explored by applying the principal model (Poisson regression) on completers (CO) and evaluable (EV) analysis sets. Additional models, negative binomial and ANCOVA (with and without covariates) and the Wilcoxon rank-sum test were applied to the ITT analysis set.

Secondary Endpoints

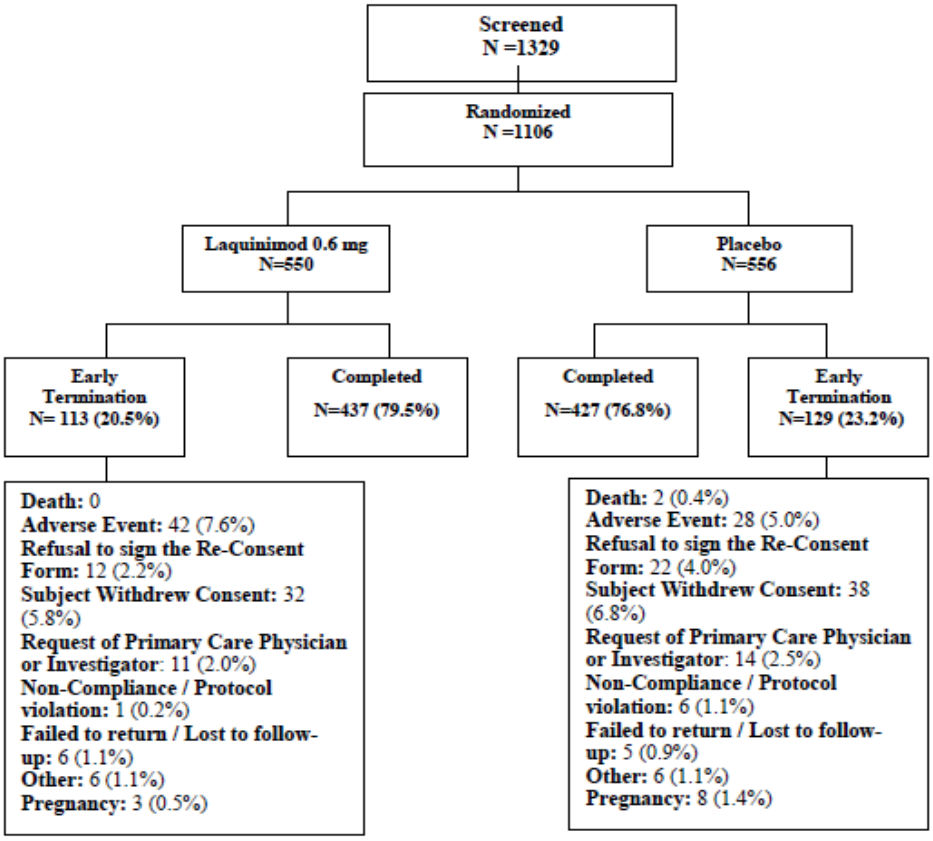
Analyses of the two MRI endpoints, the cumulative number of Gd-enhancing lesions on T1-weighted and the cumulative number of New/Enlarging T2 lesions were employing the negative binomial regression model. An offset based on the log of relative exposure in the study (actual exposure (years)/2 years) was employed to adjust for early termination's lack of exposure. In addition to the treatment group, the model included the number of T1 Gd-enhancing lesions at baseline and CGR as covariate, for both endpoints and in addition the baseline T2 volume for the new/enlarging T2 count endpoint. The third endpoint, time to EDSS progression confirmed after 3 months, was analyzed based on Cox Proportional Hazard model. The inference was based on the 95% confidence limit for the hazards ratio of the treatment. The model also included baseline EDSS, log of the (prior 2-year number of relapses +1) and country/geographical region (CGR) as covariates. The fourth endpoint, disability as assessed by the MSFC score at Month 24 (termination/early discontinuation visit after Month 12), was analyzed based on Analysis of Covariance, with baseline MSFC, baseline EDSS, log of the (prior 2-year number of relapses +1) and CGR as covariates.

2.5.2.1.2. Results

Participant flow

This is presented in Figure 1.

Figure 1



Recruitment

The study period was from 13 November 2007 to 8 November 2010.

Conduct of the study

The original protocol was amended 4 times and these changes mainly aimed at 1) cancelling some of the exclusion criteria (especially patients with a history of vascular thrombosis and patients with a carrier state of factor V Leiden mutation), 2) further emphasizing the issue of contraception and intensifying the measures to detect pregnancies earlier, 3) maximizing the chances of success to demonstrate the effect in these measures, without reducing the chance to show an effect on either EDSS or MSFC scores and 4) changing the safety monitoring procedures regarding liver safety.

A total of 176 subjects (15% of the subjects on laquinimod 0.6 mg and 17% on placebo) had at least one major protocol violation. The most frequent violations were related to use of disallowed medications.

Baseline data

These are summarised in Tables 2 and 3.

Table 2. Baseline characteristics (randomized population)

	Placebo	Laquinimod 0.6 mg/day	Total
Number of patients	556	550	1156
(%females/males)	66.2/33.8	71.1/28.9	68.6/31.4
Age (mean±SD)	38.5 ± 9.1	38.9 ± 9.2	38.7 ± 9.1
Race(%Caucasian)	96.0	97.1	96.6
BMI (mean ±SD)	25.3 ± 5.5	25.1 ± 5.5	25.2 ± 5.5
Time from first symptoms (years)			
(mean±SD)	8.6 ± 6.7	8.7 ± 6.9	8.6 ± 6.8
Previous use of MS medications N			
(%)	221 (39.7)	210 (38.2)	431 (39)
Relapses in the one year prior to			
screening (Mean ±SD)	1.3 ± 0.7	1.2 ± 0.7	1.2 ± 0.7
Relapses in the 2 years prior to			
screening (Mean±SD)	1.9 ±1.0	1.9 ±1.0	1.9 ±1.0
Baseline EDSS (converted) Mean			
±SD	2.6 ±1.3	2.6 ±1.3	2.6 ±1.3
Nb Gd enh.T1lesions	N=556	N=547	
Mean ± SD	2.0 ± 5.7	1.7 ± 3.9	
Median	0	0	
Min, max	0 - 84	0 - 30	
Vol hypointenseT1 lesions cm^3	N=556	N=547	
Mean (SD)	2.7 ± 3.7	2.8 ± 4.2	
Median	1.3	1.3	
Min, max	0 - 26.0	0 - 34.9	
T1 enhancing lesions vol cm^3	N=556	N=547	
Mean (SD)	0.2 ± 0.6	0.2 ± 1.0	
Median	0	0	
Min, max	0 - 8.2	0 - 22.6	
Tot vol T2 lesions cm^3	N=556	N=547	
Mean (SD)	9.7 ± 10.5	9.8 ± 10.4	
Median	6.8	6.3	
Min, max	0 - 77.5	0 - 82.1	
Normalized brain vol (cm^3)	N=555	N=546	
Mean (SD)	1584.7 ± 92.1	1578.9 ± 94.3	
Median	1590	1578	
Min, max	1299 - 1824	1312-1823	

Table 3. Previous therapy taken by patients

MS-LAQ-301 (ALLEGRO)			Placebo (N=556, Subject Years=953.3)		Laquinimod 0.6 mg (N=550, Subject Years=965.6)	
			No. of Subjects	% of Subjects	No. of Subjects	% of Subjects
Therapeutic Subgroup	Chemical Subgroup	Preferred Term/Generic				
ALL	ALL	ALL	221	39.7	210	38.2
Antineoplastic Agents	ALL	ALL	14	2.5	17	3.1
	Anthracyclines And Related Substances	ALL	11	2.0	17	3.1
		Mitoxantrone	11	2.0	17	3.1
		Mitoxantrone Hydrochloride	.	.	1	0.2
	Monoclonal Antibodies	ALL	3	0.5	.	.
		Monoclonal Antibodies	1	0.2	.	.
		Rituximab	2	0.4	.	.
Immune Sera And Immunoglobulins	ALL	ALL	4	0.7	5	0.9
	Immunoglobulins	ALL	2	0.4	.	.
		Immunoglobulins	2	0.4	.	.
	Immunoglobulins, Normal Human	ALL	3	0.5	5	0.9
		Gammonativ	1	0.2	.	.
		Immunoglobulin	1	0.2	5	0.9
		Immunoglobulin Human Normal	2	0.4	1	0.2
Immunostimulants	ALL	ALL	212	38.1	206	37.5
	Interferons	ALL	177	31.8	179	32.5
		Betaseron	2	0.4	4	0.7
		Interferon	3	0.5	.	.
		Interferon Alfa	.	.	1	0.2
		Interferon Beta	.	.	3	0.5
		Interferon Beta-1a	123	22.1	132	24.0
		Interferon Beta-1b	80	14.4	72	13.1
	Other Immunostimulants	ALL	89	16.0	84	15.3
		Glatiramer Acetate	89	16.0	84	15.3
Immunosuppressants	ALL	ALL	21	3.8	13	2.4
	Other Immunosuppressants	ALL	19	3.4	12	2.2
		Azathioprine	7	1.3	6	1.1
		Azathiprine	17	3.1	10	1.8
		Immunosuppresants	.	.	1	0.2
		Methotrexate	1	0.2	.	.
	Selective Immunosuppressants	ALL	3	0.5	1	0.2
		Mycophenolate Mofetil	3	0.5	1	0.2

The table presents data combined from the Medication Log and the field of 'previous use of disease modifying therapies' in the MS History form

Numbers analysed

In total, 100% of randomized patients were included in the ITT population.

The completers analysis set included 864 subjects who completed the 24 months of double-blind treatment; 437 (79.5%) on laquinimod 0.6 mg and 427 (76.8%). All completers were included in the principal analysis of the primary analysis endpoint.

The evaluable (EV analysis set) included all subjects in the CO analysis set who complied with major protocol guidelines. A total of 752 subjects were included in this analysis set; 382 subjects on laquinimod 0.6 mg, and 370 subjects on placebo All subjects in this analysis set were included in the principal analysis of the primary endpoint analysis. All subjects who had protocol violations are excluded from the primary endpoint analysis of this analysis set.

Outcomes and estimation

Primary outcome measure

Results are summarised in Table 4.

Table 4. Total number of confirmed relapses observed during the double-blind treatment period (24 months)

Analysis Set	Model	Covariates	Mean Annualized Relapse Rate	Treatment Effect	P-value
Principal Analysis					
ITT	Principal Model: Analysis of Annualized Relapse Rate - Poisson Regression	1) EDSS at Baseline 2) Log of prior 2-year number of relapses+1 3) CGR	Laq 0.6 =0.304 Placebo =0.395	Risk Ratio= 0.770	0.0024
Sensitivity Analysis					
ITT	*Unadjusted* Analysis of Annualized Relapse Rate - Poisson Regression	No Covariates	Laq 0.6 =0.307 Placebo=0.392	Risk Ratio= 0.781	0.0057
	Analysis of Annualized Relapse Rate – Negative Binomial Regression	1) EDSS at Baseline 2) Log of prior 2-year number of relapses+1 3) CGR	Laq 0.6 =0.307 Placebo=0.406	Risk Ratio= 0.756	0.0018
	Unadjusted Analysis of Annualized Relapse Rate – Negative Binomial Regression	No Covariates	Laq 0.6 =0.313 Placebo=0.409	Risk Ratio= 0.765	0.0045
	Analysis of Number of Relapses– ANCOVA	1) EDSS at Baseline 2 Log of prior 2-year number of relapses+1 3) CGR 4) Exposure (Years)	Laq 0.6 =0.603 Placebo=0.738	Means Difference= -0.135	0.0097
	Unadjusted Analysis of Number of Relapses– ANCOVA	Exposure (Years)	Laq 0.6 =0.538 Placebo=0.673	Means Difference= -0.135	0.0130
	Wilcoxon Rank Sum Test	NA	NA	NA	0.0018
Completers	Principal Model: Analysis of Annualized Relapse Rate - Poisson Regression	1) EDSS at Baseline 2) Log of prior 2-year number of relapses+1 3) CGR	Laq 0.6 =0.238 Placebo =0.294	Risk Ratio= 0.810	0.0314
Evaluable	Principal Model: Analysis of Annualized Relapse Rate - Poisson Regression	1) EDSS at Baseline 2) Log of prior 2-year number of relapses+1 3) CGR	Laq 0.6 =0.210 Placebo=0.269	Risk Ratio= 0.782	0.0218

Secondary outcome measures

These are presented in Figures 2-4 and Tables 5-6.

Cumulative number of enhancing lesions/ number of New or Enlarging Lesions at Months 12 and 24 at months 12 and 24 (Termination/Early Discontinuation Visit After Month 12) – Figures 2 and 3

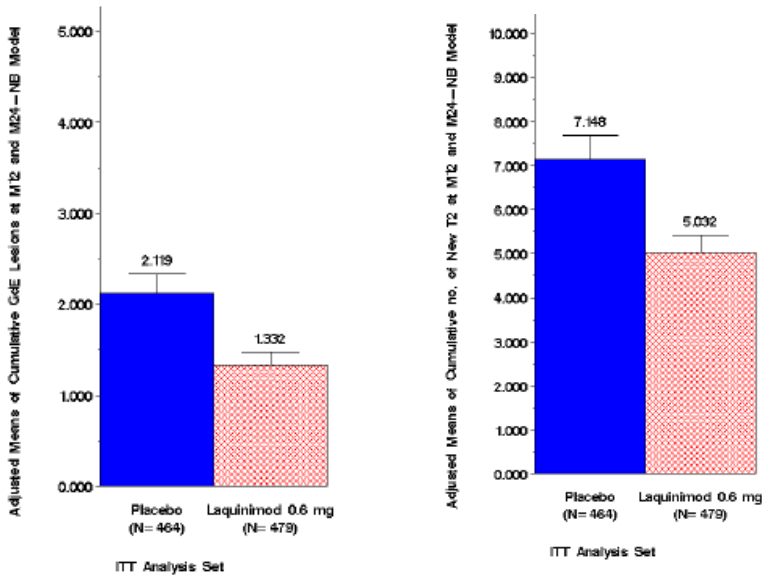


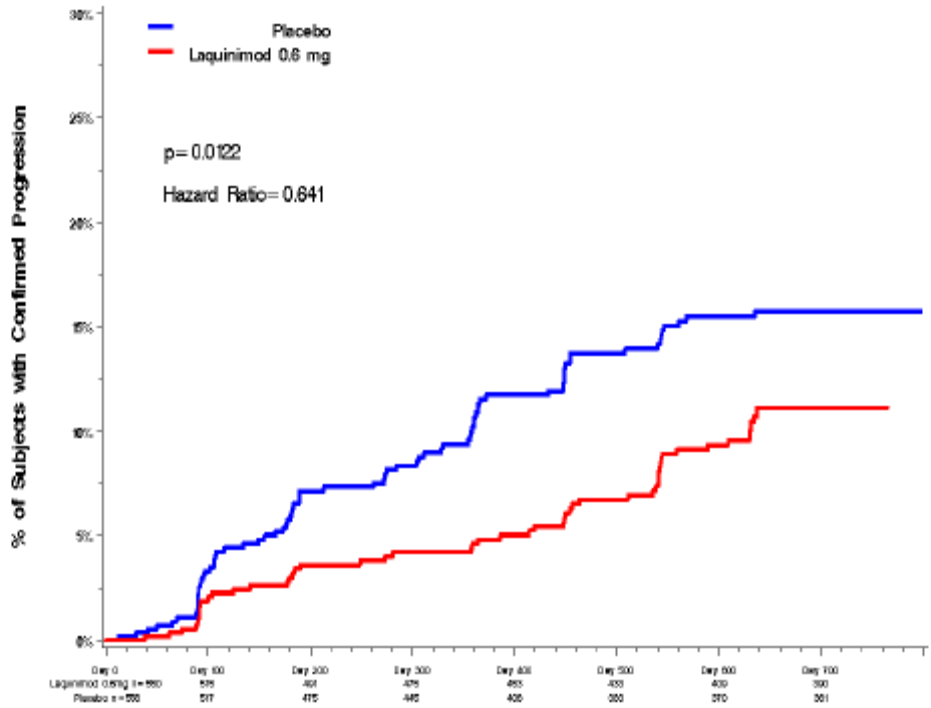
Table 5. Rate Ratio and 95% CI for Cumulative number of enhancing lesions/ number of New or Enlarging Lesions at Months 12 and 24 at months 12 and 24

Cumulative number of enhancing lesions at months 12 and 24 (Termination/Early Discontinuation Visit After Month 12)			**Cumulative Number of New or Enlarging Lesions at Months 12 and 24 (Termination/Early Discontinuation Visit After Month 12)**	
Comparison	**Laquinimod 0.6 mg vs placebo**		**Comparison**	**Laquinimod 0.6 mg vs placebo**
Rate ratio	**0.629**		**Rate ratio**	**0.704**
SE	0.081		SE	0.067
Lower confidence limit	0.488		Lower confidence limit	0.584
Upper confidence limit	0.809		Upper confidence limit	0.849
P-value	**0.0003**		**P-value**	**0.0002**

Table 6. Disability progression - Time to 3-month confirmed disability progression at Month 24

Comparison	**Laquinimod 0.6 mg (N=550)**	**Placebo (N=556)**
Proportion of patients free of progression	90.2%	86%
Hazard ratio (95% CI)	0.641 (0.452, 0.908)	-
p- value vs placebo	0.0122	-

Figure 4. Time to 3-month confirmed disability progression at Month 24



No effect of laquinimod on disability assessed by the MSFC at Month 24 was demonstrated as compared to placebo. The mean difference was 0.019 (p =0.5893).

Other outcome measures

An effect of treatment with laquinimod 0.6 mg over placebo was shown for the relapse-related endpoints of time to first relapse, proportion of relapse-free subjects (64.5% in laquinimod group and 54.7% in placebo group) and rate of severe confirmed relapse.

Laquinimod 0.6 mg reduced brain atrophy over placebo at Months 12 and Month 24.

Regarding the cumulative number of new/enlarging hypointense lesions, the results showed rate ratio of 0.733 (95% CI: 0.593,0.905; p=0.0039), reflecting a reduction of 27% in the mean rate of developing New/enlarging hypointense T1 with laquinimod 0.6 mg as compared to placebo.

There was no difference between laquinimod and placebo at Months 12 or 24 measurements, neither for the T2 lesions volume nor for the hypointense lesions volume.

Regarding MSFC at months 6, 12 or 18, there was no difference between the treatment groups similarly to the results of MSFC at Month 24 (secondary endpoint).

2.5.2.2. Study LAQ-302 – BRAVO

This was a randomised, parallel-group study evaluating the efficacy and safety of laquinimod administered orally once daily versus placebo in a double-blind design and versus interferon beta-1a (Avonex) in a rater-blinded design.

The study was conducted in a number of European countries and also in non-EU regions (e.g. the US, Israel, Russia, Ukraine, Georgia, Macedonia and South Africa).

2.5.2.2.1. Methods

Study Participants

Main inclusion criteria

The inclusion criteria were the same as for those for the LAQ-301 study except that the disease duration was not limited to at least 6 months (from the first symptom) prior to screening.

Main exclusion criteria

The exclusion criteria were the same as for those for the LAQ-301 study except that subjects were excluded in case of previous use of interferons, regardless of the timepoint of treatment. The following exclusion criteria were also added: thyroid disease, and history of seizure disorder.

Treatments

Subjects were administered either of the following: one capsule of laquinimod 0.6 mg taken orally; one matching placebo capsule taken orally ; an injection of Avonex 30 mcg given IM once weekly. In case of oral capsules, subjects were allowed to omit study drugs up to 3 consecutive days during the study. In the event of a delay of up to 5 days in the administration of the once-weekly Avonex treatment, the subject was administered the injection immediately and continued with the former treatment scheduling. In the event of a delay of 6 to 7 days in administration of the once-weekly Avonex treatment, one treatment was skipped.

Objectives

The **primary objective** was to evaluate the efficacy of 0.6 mg daily dose of laquinimod in subjects with RRMS, as measured by the number of confirmed relapses during the treatment period.

The **secondary objectives** were as follows: 1) to evaluate the effect of 0.6 mg daily dose of laquinimod on the development of brain atrophy as defined by the per cent brain volume change from baseline at the end of the treatment period; 2) to evaluate the effect of 0.6 mg daily dose of laquinimod on the accumulation of physical disability as measured by the time to confirmed progression of EDSS during the treatment period (a confirmed progression of EDSS is defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5, confirmed 3 months later; progression cannot be confirmed during a relapse) and 3) to evaluate the effect of 0.6 mg daily dose of laquinimod on the accumulation of disability, as assessed by the MSFC score at the end of the treatment period.

Outcomes/endpoints

Primary outcome measure

The total number of confirmed relapses during the treatment period as a mechanism for estimating the treatment effect on the annualized relapse rate.

Secondary outcome measures

These included: brain atrophy, measured as the percent brain volume change from baseline to end of the treatment period; time to confirmed progression of EDSS sustained for 3 months during the treatment period (progression was defined as a 1.0 point increase if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5); the MSFC score at the end of the treatment period.

Other outcome measures

Other outcomes measures considered as exploratory were: cumulative number of enhancing lesions on T1-weighted images taken at Months 12 and 24 (termination/early discontinuation visit, if occurred after month 12); number of enhancing lesions on a T1-weighted image taken at Month 12, the number of enhancing lesions on a T1-weighted image taken at Month 24 (termination/early discontinuation visit, if occurred after Month 12); cumulative number of new or enlarging hypointense lesions on enhanced T1 scans taken at months 12 and 24 (termination/early discontinuation, if occurred after Month 12);number of new or enlarging hypointense lesions on an enhanced T1 scan taken at Month 12; number of new or enlarging hypointense lesions on enhanced T1 scans taken at Month 24 (termination/early discontinuation, if occurred after Month 12); cumulative number of new or enlarging T2 lesions on scans taken at months 12 and 24 (termination/early discontinuation, if occurred after Month 12); number of new or enlarging T2 lesions on a scan taken at Month 12; number of new or enlarging T2 lesions on a scan taken at Month 24 (termination/early discontinuation, if occurred after Month 12); volume of T2 lesions at Month 24 (termination/early discontinuation, if occurred after Month 12); volume of T2 lesions at Month 12; volume of hypointense lesions on enhanced T1 scans at Month 24 (termination/early discontinuation visit, if occurred after Month 12); volume of hypointense lesions on enhanced T1 scans at Month 12; brain atrophy as defined by the per cent brain volume change from baseline to Month 12 and Month 12 to Month 24 (termination/early discontinuation visit, if occurred after Month 12); Modified Fatigue Impact Scale change from baseline to Month 24 (termination/early discontinuation visit, if occurred after Month 12); time to the first confirmed relapse during the study period; proportion of relapse-free subjects; rate of confirmed relapses during the study period requiring hospitalization and/or IV steroids; the EuroQoL (EQ-5D) change from baseline to Month 24 (termination/early discontinuation visit if occurred after Month 12); the Short-Form general health survey change from baseline to Month 24 (termination/early discontinuation visit if occurred after Month 12), change from baseline to Month 24 (termination/early discontinuation visit) in binocular visual acuity, as assessed by the number of letters read correctly from 2 meters distance on 1.25%, 2.5% and 100% contrast Sloan letter/Tumbling E charts.

Sample size

Using the same assumptions as in study LAQ-301, it was found that a total of 666 subjects (333 subjects per arm) will provide approximately 80% power to detect a statistically significant reduction of 25% in the total number of confirmed relapses between the placebo group and the laquinimod group. This sample size also enabled 92% power to detect a statistically significant reduction of 30% in the total number of confirmed relapses between the laquinimod 0.6 mg treatment group and the placebo group. To correct for anticipated withdrawal rate of 20% over 24 months, the sample was adjusted and rounded to 400 subjects per arm. The size of the Avonex reference arm was set to be equal to the other study arms. Since the Avonex arm is included in the study for reference only, there was no need to adjust for multiplicity when comparing the laquinimod and Avonex arms to the placebo arm.

Randomisation

The study had a screening period of up to 1 month, during which the subject was assigned a screening number through the IVRS/IWRS. At the baseline visit, subjects were assigned by the IVRS to one of three possible treatment groups in a 1:1:1 ratio, according to the randomization scheme. Each subject was allocated a unique number. This number replaced the screening number.

Blinding (masking)

For oral treatment (laquinimod or placebo capsules), the investigators, the sponsor and any personnel involved in subjects' assessment, monitoring, analysis and data management (excluding the designated Clinical Supplies Unit's personnel), were blinded to the subject assignment. For the injectable treatment (Avonex), the administration was not provided in a blinded manner. A subject assigned to injectable treatment was unblinded, as well as the site personnel involved in dispensing the drug. The Examining Neurologist/ Physician was blinded to the treatment assignment and was not present during the study drug dispensing process.
In order to maintain reliable evaluation and reduce the potential for bias the following actions were undertaken regardless of the treatment assignment: the Examining Neurologist/Physician was the only one to evaluate the subject neurologically; the Examining Neurologist/Physician had no access to the subject's file, including previous neurostatus forms and AEs; a decision as per treatment of a relapse was under the sole responsibility of the Treating Neurologist/Physician; the subject was neurologically assessed by the Examining Neurologist/Physician. It was verified that the subject, regardless of treatment assignment, was clothed in a manner that the arms (down to the elbows) and thighs (down to the knees) were fully covered. In addition, the subject was instructed not to discuss his/her well-being and AEs or the treatment route/assignment (oral or injectable) with the Examining Neurologist/Physician. These activities were under the responsibility of the Treating Neurologist/Physician/Study Coordinator and were recorded in the source documents.

Statistical methods

Level of Significance

The overall significance level for this study is 5% using two-tailed tests and/or two-sided confidence intervals with 95% confidence level. In order to protect the study from type-I error inflation, secondary endpoints were interpreted inferentially only if a statistically significant treatment effect was detected in the primary analysis. The study's overall type-I error was further controlled in the analysis of the secondary endpoints by employing the hierarchical approach (i.e. each secondary endpoint was analyzed only in case the preceding endpoint had a p-value less or equal to 0.05 for laquinimod 0.6 mg over placebo comparison).

Primary Endpoint

Same statistical methods as in study LAQ-301 for the comparison of laquinimod 0.6 mg versus placebo were applied for the primary endpoint. A post-hoc exploratory comparison of laquinimod 0.6 mg versus Avonex was also conducted using the same model.
A sensitivity analysis was also performed to address the issue of missing values, in order to estimate the amount of treatment effect preserved under the Missing Not At Random (MNAR) assumption.

Secondary Endpoints

Same statistical methods as in study LAQ-301 for the comparison of laquinimod 0.6 mg versus placebo were applied for the time to EDSS progression confirmed after 3 months and MSFC score at Month 24. Brain atrophy, as defined by the per cent volume change from baseline to termination/early discontinuation visit after Month 12, was based on the outcome of a contrast (laquinimod 0.6 mg vs placebo) derived from a baseline-adjusted analysis of covariance (ANCOVA). In addition to treatment group, the model also included as covariates the number of enhancing lesions on T1-weighted images taken at baseline and CGR.

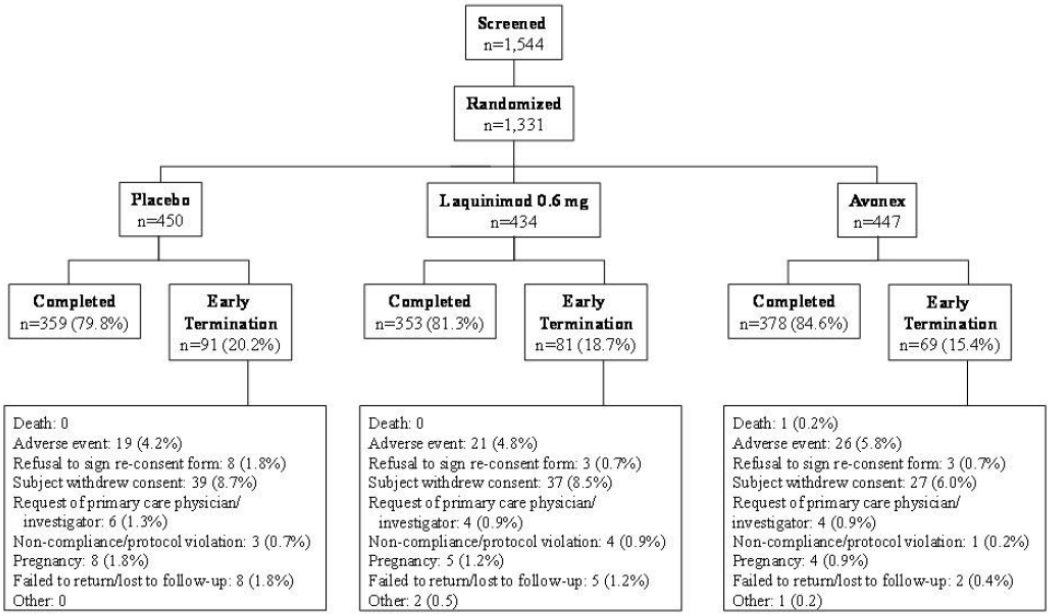
Within the same models, additional exploratory contrasts were constructed to assess the treatment effect of Avonex vs placebo for all the secondary endpoints.

2.5.2.2.2. Results

Participant flow

This is presented in Figure 5.

Figure 5



Recruitment

The study period was from 24 April 2008 to 10 June 2011.

Conduct of the study

The original protocol was amended 4 times and these changes mainly aimed at 1) modifying the inclusion and exclusion criteria and the safety monitoring of inflammatory conditions 2) further emphasizing the issue of contraception and intensifying the measures to detect pregnancies earlier, 3) changing the safety monitoring procedures regarding liver safety; 4) changing the hierarchy order of the secondary endpoints.

A total of 146 subjects had at least one major protocol violation: 51 (12%) on laquinimod 0.6 mg, 51 (11%) on placebo and 44 (9.8%) on Avonex .The most frequent violations were related to use of disallowed medications.

Baseline data

These are summarised in Tables 7 and 8.

Table 7. Baseline characteristics (randomized population)

	Placebo	Laquinimod 0.6 mg/day	Avonex	Total
Number of patients (%females/males)	321 71.3/28.7	282 65/35	307 68.7/31.3	910 68.4/31.6
Age (mean±SD)	37.5 ± 9.5	37.0 ± 9.3	38.2 ± 9.5	37.6 ± 9.5
Race(%Caucasian)	98.4	98.2	98.4	98.3
BMI (mean ±SD)	24.4 ± 4.6	24.1 ± 4.5	24.6 ± 5.0	24.4 ± 4.7
Time from first symptoms (years) (mean±SD)	6.9 ± 6.6	6.6 ± 6.0	7.0 ± 5.9	
Previous use of MS medications N (%)	27 (6)	30 (6.9)	42 (9.4)	
Relapses in the one year prior to screening (Mean ±SD)	1.3 ± 0.6	1.3 ± 0.6	1.3 ± 0.6	
Relapses in the 2 years prior to screening (Mean±SD)	1.9 ±0.9	1.9 ±1.0	1.9 ±0.9	
Baseline EDSS (converted) Mean ±SD	2.7 ±1.2	2.7 ±1.3	2.6 ±1.2	
Nb Gd enh.T1lesions Mean ± SD	N=449 1.5 ± 5.7	N=434 1.8 ± 5.2	N=443 1.8 ± 6.7	
Proportion of subjects with number of Gd enh T1 lesions ≥ 1 (%)	N=150 33.4	N=172 39.6	N=169 38.1	
Vol hypointenseT1 lesions cm^3 Mean (SD)	N=449 2.8 ± 4.2	N=434 3.5 ± 4.9	N=440 3.0 ± 5.0	
Tot vol T2 lesions cm^3 Mean (SD)	N=449 7.9 ± 8.9	N=434 9.6 ± 10.3	N=440 8.6 ± 10.4	
Normalized brain vol (cm^3) Mean (SD)	N=449 1586.3 ± 93.3	N=432 1581.5 ± 95.5	N=441 1586.2 ± 84.4	

Table 8. Previous therapy taken by patients

MS-LAQ-302 (BRAVO)			Placebo (N=450, Subject Years=785.6)		Laquinimod 0.6 mg (N=434, Subject Years=766.7)		Avonex® (N=447, Subject Years=803.2)	
			No. of Subjects	% of Subjects	No. of Subjects	% of Subjects	No. of Subjects	% of Subjects
Therapeutic Subgroup	Chemical Subgroup	Preferred Term/Generic						
ALL	ALL	ALL	27	6.0	30	6.9	42	9.4
Antineoplastic Agents	ALL	ALL	.	.	.	.	1	0.2
	Anthracyclines And Related Substances	ALL	.	.	.	.	1	0.2
		Mitoxantrone Hydrochloride	.	.	.	.	1	0.2
Immune Sera And Immunoglobulins	ALL	ALL	1	0.2	1	0.2	3	0.7
	Immunoglobulins, Normal Human	ALL	1	0.2	1	0.2	2	0.4
		Immunoglobulin	1	0.2	.	.	.	.
		Immunoglobulin Human Normal	.	.	1	0.2	2	0.4
	Specific Immunoglobulins	ALL	.	.	.	.	1	0.2
		Immunoglobulin G Human	.	.	.	.	1	0.2
Immunostimulants	ALL	ALL	23	5.1	26	6.0	35	7.8
	Interferons	ALL	20	4.4	25	5.8	33	7.4
		Glatiramer Acetate	18	4.0	21	4.8	30	6.7
		Interferon	2	0.4	4	0.9	3	0.7
	Interleukins	ALL	3	0.7	.	.	1	0.2
		Interleukins	3	0.7	.	.	1	0.2
	Other Immunostimulants	ALL	3	0.7	3	0.7	11	2.5
		Glatiramer Acetate	3	0.7	2	0.5	10	2.2
		Meglumine Acridonacetate	.	.	1	0.2	1	0.2
Immunosuppressants	ALL	ALL	3	0.7	3	0.7	3	0.7
	Other Immunosuppressants	ALL	3	0.7	3	0.7	3	0.7
		Azathioprine	3	0.7	3	0.7	3	0.7

Numbers analysed

In total, 100% of randomized patients were included in the ITT population.

The completers' analysis set included 1,090 subjects who completed 24 months of double-blind treatment: 353 (81.3%) on laquinimod 0.6 mg, 359 (79.8%) on placebo and 378 (84.6%) on Avonex. All completers were included in the principal analysis of the primary endpoint applied to the CO set. All subjects who terminated the study prematurely were excluded from the primary endpoint analysis of the CO analysis set.

The evaluable (EV analysis set) included 990 subjects from the CO analysis set who complied with major protocol guidelines: 321 (74.0%) to laquinimod 0.6 mg, 327 (72.7%) to placebo and 342 (76.5%) to Avonex. All subjects in this analysis set are included in the principal analysis of the primary endpoint applied to the EV set. All subjects with major protocol violations or early termination from the study were excluded from the primary endpoint analysis of the EV set.

Outcomes and estimation

Primary outcome measure

Results are summarised in Table 9 and Figure 6.

Table 9.Total Number of confirmed relapses observed during the double-blind treatment period (24 months)

Analysis Set	Analysis Model	Covariates	Adjusted Mean Values	Treatment Effect**	P-value
		Principal Analysis			
ITT	**Annualized RR: Negative Binomial (Primary Model)**	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR	Placebo = 0.344 Laq = 0.283 Avonex® = 0.255	Risk Ratio Laq = 0.823 Avonex® = 0.741	 0.0746 0.0067
		Sensitivity Analysis			
ITT	**Annualized RR: Negative Binomial (Unadjusted)**	Treatment only	Placebo = 0.367 Laq = 0.304 Avonex® = 0.272	Risk Ratio Laq = 0.827 Avonex® = 0.740	 0.0968 0.0089
	Annualized RR: Negative Binomial (Corrected Analysis, Additional Covariates*)	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR 4) Baseline T2 volume 5) ≥1 T1 GdE lesions at baseline	Placebo = 0.371 Laq = 0.292 Avonex® = 0.265	Risk Ratio Laq = 0.787 Avonex® = 0.714	 0.0264 0.0021
	Annualized RR: Poisson Regression	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR	Placebo = 0.330 Laq = 0.277 Avonex® = 0.250	Risk Ratio Laq = 0.839 Avonex® = 0.757	 0.0744 0.0054
	Annualized RR: Poisson Regression (Unadjusted)	Treatment only	Placebo = 0.354 Laq = 0.299 Avonex® = 0.268	Risk Ratio Laq = 0.844 Avonex® = 0.756	 0.0947 0.0069
	Annualized RR: Poisson Regression (Corrected Analysis, Additional Covariates*)	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR 4) Baseline T2 volume 5) ≥1 T1 GdE lesions at baseline	Placebo = 0.357 Laq = 0.284 Avonex® = 0.262	Risk Ratio Laq = 0.796 Avonex® = 0.733	 0.0192 0.0018
	No. of Relapses: ANCOVA	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR 4) Exposure (years)	Placebo = 0.628 Laq = 0.541 Avonex® = 0.497	Adj. Mean Diff. Laq = -0.087 Avonex® = -0.131	 0.1328 0.0231
	No. of Relapses: ANCOVA	Treatment and exposure only	Placebo = 0.620 Laq = 0.528	Adj. Mean Diff. Laq = -0.092	 0.1239

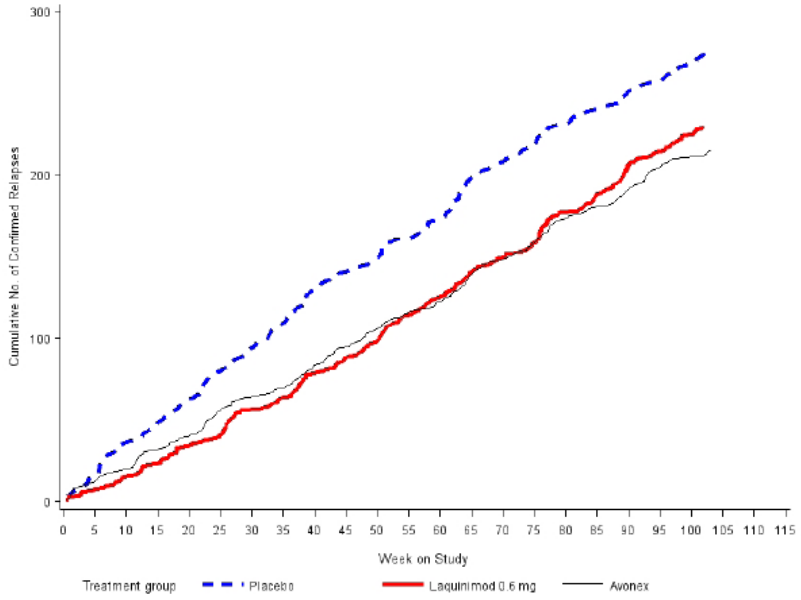
Analysis Set	Analysis Model	Covariates	Adjusted Mean Values	Treatment Effect**	P-value
ITT (cont'd)	(Unadjusted)		Avonex® = 0.478	Avonex® = -0.142	0.0171
	No. of Relapses: ANCOVA (Additional Covariates*)	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR 4) Exposure (years) 5) Baseline T2 volume 6) ≥1 T1 GdE lesions at baseline	Placebo = 0.694 Laq = 0.579 Avonex® = 0.549	Adj. Mean Diff. Laq = -0.115 Avonex® = -0.145	 0.0454 0.0111
	Wilcoxon Rank Sums Test[ccc]	NA	NA	NA	0.1381 0.0120
CO	Annualized RR: Negative Binomial (Primary Model)	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR	Placebo = 0.258 Laq = 0.229 Avonex® = 0.210	Risk Ratio Laq = 0.887 Avonex® = 0.816	0.3114 0.0875
	Annualized RR: Negative Binomial (Corrected Analysis, Additional Covariates*)	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR 4) Baseline T2 volume 5) ≥1 T1 GdE lesions at baseline	Placebo = 0.277 Laq = 0.236 Avonex® = 0.220	Risk Ratio Laq = 0.851 Avonex® = 0.795	0.1670 0.0513
EV	Annualized RR: Negative Binomial (Primary Model)	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR	Placebo = 0.251 Laq = 0.209 Avonex® = 0.177	Risk Ratio Laq = 0.833 Avonex® = 0.708	0.1497 0.0079
	Annualized RR: Negative Binomial (Corrected Analysis, Additional Covariates*)	1) EDSS at BL 2) Log of prior 2-year number of relapses+1 3) CGR 4) Baseline T2 volume 5) ≥1 T1 GdE lesions at baseline	Placebo = 0.269 Laq 0.6 = 0.216 Avonex® = 0.189	Risk Ratio Laq = 0.804 Avonex® = 0.701	0.0822 0.0058

Abbreviations: RR, relapse rate; Laq, laquinimod 0.6 mg; BL, baseline; EDSS, Expanded Disability Status Scale; CGR, country/geographical region; GdE, gadolinium-enhancing

* Model was corrected by adding MRI baseline covariates (baseline T2 lesions volume and indicator for subjects with T1 Gd-enhancing lesions ≥1 at baseline)

** Treatment effects were calculated based on the outcome of a contrast (either laquinimod 0.6 mg vs placebo or Avonex® vs placebo)

Figure 6. Cumulative number of confirmed relapses



Secondary outcome measures

These are presented in Table 10.

Table 10.Secondary Efficacy Results (brain atrophy at Month 24, time to confirmed progression of EDSS sustained for 3 months, MSFC score at Month 24)

Analysis Results	Laquinimod 0.6 mg vs Placebo		Avonex® vs Placebo	
	Original Analysis	Corrected Analysis*	Original Analysis	Corrected Analysis*
Brain Atrophy at Month 24 (Termination/Early Discontinuation Visit After Month 12)				
Adjusted Mean Difference [95% CI]	**0.284 [0.139; 0.429]** Reflecting a 27.6% reduction	**0.313 [0.168; 0.459]** Reflecting a 27.5% reduction	**-0.107 [-0.249; 0.035]** Reflecting a 10.4% increase	**-0.108 [-0.250; 0.035]** Reflecting a 9.5% increase
P-Value	**0.0001**	**<0.0001**	**0.1392**	**0.1380**
Time to Confirmed Progression of EDSS				
Hazard Ratio [95% CI]	**0.687 [0.462; 1.020]** Reflecting a 31.3% reduction	**0.665 [0.447; 0.989]** Reflecting a 33.5% reduction	**0.742 [0.507; 1.088]** Reflecting a 25.8% reduction	**0.713 [0.484; 1.051]** Reflecting a 28.7% reduction
P-Value	**0.0628**	**0.0440**	**0.1269**	**0.0878**
Disability as Assessed by MSFC				
Adjusted Mean Difference [95% CI]	**0.104 [-0.038; 0.247]** Reflecting a 77.0% reduction	**0.115 [-0.028; 0.258]** Reflecting a 77.2% reduction	**0.089 [-0.050; 0.229]** Reflecting a 65.9% reduction	**0.095 [-0.045; 0.235]** Reflecting a 63.8% reduction
P-Value	**0.1505**	**0.1152**	**0.2083**	**0.1852**

* Analysis was performed *post-hoc* using original model corrected for the two additional MRI covariates (T2 lesions volume and indicator for subjects with number of T1 Gd-enhancing lesions ≥1 at baseline)

Other outcome measures

As compared to placebo, laquinimod 0.6 mg had no effect on time to first confirmed relapse (HR= 0.835, 95% CI: 0.67, 1.040), the proportion of relapse-free subjects (65.7% in laquinimod group versus 61.3% in placebo group) and rate of severe relapses requiring hospitalization and/or administration of steroids (RR= 0.835, 95% CI: 0.668, 1.045, p=0.1152). In contrast, an effect of Avonex over placebo was observed for all three relapse-related endpoints. In Avonex group, 68.9% of patients were relapse free.

A favourable effect of laquinimod 0.6 mg over placebo was observed for the reduction of enhancing T1 lesions at Month 24 (RR= 0.611, 95% CI: 0.439, 0.852, p=0.0037) but not at Month 12 (RR= 0.884, 95% CI: 0.658, 1.186, p=0.4099). There was a reduction in the mean rate of development of cumulative number of T1 Gd-enhancing lesions on laquinimod 0.6 mg over placebo but this was not statistically significant (RR= 0.785, 95% CI: 0.604, 1.019, p=0.0691). Avonex showed a reduction versus placebo in the number of enhancing T1 lesions at both Month 12 and Month 24 measurements (respectively, RR= 0.410, 95% CI: 0.299, 0.562, p<0.0001 and RR=0.336, 95% CI: 0.237, 0.474, p<0.0001) as well as for the cumulative lesion counts for Months 12 and 24 and this was statistically significant (RR= 0.385, 95% CI: 0.239, 0.505, p<0.0001).

An effect of laquinimod 0.6 mg versus placebo was seen for reduction of new/newly T2 lesions at Month 12 (RR= 0.813, 95% CI: 0.664, 0.996, p=0.0462). As compared to placebo, Avonex reduced the new T2 lesions at Months 12 and 24 (RR= 0.491, 95% CI: 0.400, 0.602, p<0.001).

No differences between laquinimod 0.6 mg and placebo were observed for T2 lesions volume, either at Month 12 or Month 24 (respectively mean ratio= 0.996, 95% CI: 0.925, 1.071, p=0.9053 and mean ratio= 1.005, 95% CI: 0.930, 1.085, p=0.9019). A statistically significant effect for Avonex over placebo was seen for both endpoints (respectively p=0.0019 and p=0.0104). No differences between laquinimod 0.6 mg and placebo were observed for T1 hypointense lesions volume, either at Month 12 or Month 24; there was no difference between the Avonex and placebo groups for either endpoint.

Laquinimod 0.6 mg demonstrated a reduction in brain atrophy over placebo from baseline to Month 12 (adjusted mean difference=0.221, 95% CI: 0.125, 0.317, p<0.001) , whereas no appreciable difference between the two groups was shown between Months 12 to 24(adjusted mean difference=0.033, 95% CI: -0.062, 0.127, p=0.4972). No treatment effects on reduction in brain atrophy were seen for Avonex over placebo for either measurement period (Month 12: adjusted mean difference=-0.134, 95% CI: -0.229,-0.040, p=0.0053 and Month 24: adjusted mean difference=0.018 , 95% CI: -0.074, 0.111, p=0.6975, respectively).

No difference between laquinimod 0.6 mg and placebo were observed for change from baseline to Month 24 in any of the following exploratory endpoints related to health status and quality of life: subject-reported fatigue (assessed by MFIS score); any of the EQ-5D dimensions or subjects' subjective overall health assessment scores; general health status assessed by SF-36 (both physical and mental component summary scores); and binocular visual acuity. Similarly, no appreciable differences could be demonstrated between Avonex and placebo for these endpoints, with the exception of subjects' subjective overall health assessment scores, for which there was a lesser decline from baseline in health status at Month 24 for subjects on Avonex compared to those on placebo.

2.5.2.3. Ancillary analyses

During the evaluation, additional efficacy subgroup analyses were requested by the CHMP based on the following criteria: prior use of MS treatment, severity of relapses at baseline. No efficacy analysis based on the severity of relapses at baseline was provided by the applicant as the data were not collected in the clinical studies. At baseline, as per inclusion, patients were stable and free of relapses for at least 60 days. The applicant presented an analysis based on ALLEGRO study only due to the design of the other pivotal study BRAVO which excluded all patients with prior use of interferons and the small sample size for patients previously treated with glatiramer acetate (4% vs 4.8 in placebo and laquinimod groups, respectively. Data are presented in Tables 11 and 12.

Table 11. ALLEGRO: summary of treatment effects (laquinimod 0.6 mg vs placebo) by prior interferon use

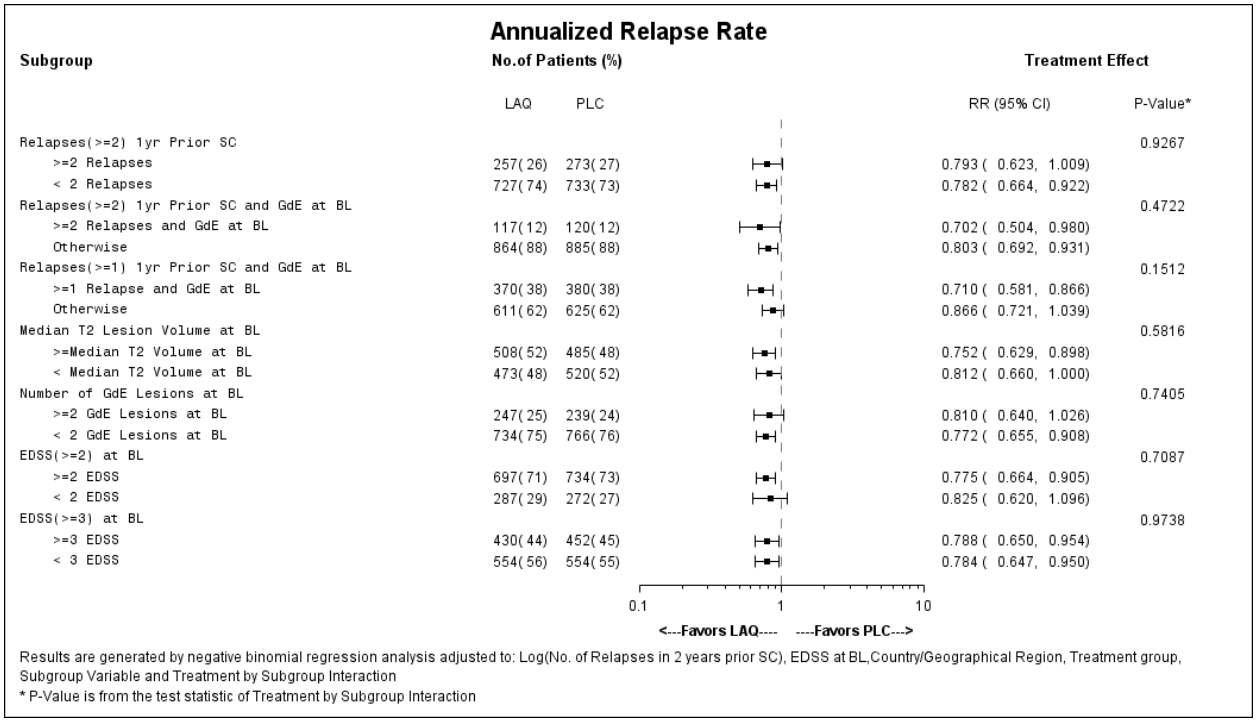
		Prior use of interferon=No LAQ 0.6 mg, n=371 (67.5%) Placebo, n=379 (68.2%)	Prior use of interferon=Yes LAQ 0.6 mg, n=179 (32.5%) Placebo, n=177 (31.8%)
Annualized Relapse Rate	Risk Ratio	0.735 [0.596; 0.905]	0.865 [0.647; 1.156]
	Laquinimod Effect	27%	13%
	p-value	p=0.0038	p=0.3257
Brain Atrophy Defined by PBVC	Adj. Mean Diff.	0.466 [0.269; 0.663]	0.209 [-0.092; 0.509]
	Laquinimod Effect	34.6%	17.4%
	p-value	p<0.0001	p=0.1731
Time to Confirmed EDSS Progression (3m)	Hazard Ratio	0.506 [0.324; 0.791]	0.965 [0.542; 1.717]
	Laquinimod Effect	49.4%	3.5%
	p-value	p=0.0028	p=0.9029
Time to Confirmed EDSS Progression (6m)	Hazard Ratio	0.418 [0.239; 0.731]	0.713 [0.364; 1.400]
	Laquinimod Effect	58.2%	28.7%
	p-value	p=0.0022	p=0.3260
Cumulative GdE T1 Lesions at Months 12 and 24	Rate Ratio	0.643 [0.472; 0.876]	0.589 [0.378; 0.918]
	Laquinimod Effect	35.7%	41.1%
	p-value	p=0.0052	p=0.0193
Cumulative New/Enlarging T2 Lesions at Months 12 and 24	Rate Ratio	0.697 [0.556; 0.875]	0.719 [0.515; 1.004]
	Laquinimod Effect	30.3%	28.1%
	p-value	p=0.0018	p=0.0525

Table 12. ALLEGRO: summary of treatment effects (laquinimod 0.6 mg vs placebo) by prior glatiramer acetate (GA) use

		Prior use of GA=No LAQ 0.6 mg, n=466 (84.7%) Placebo, n=467 (84.0%)	Prior use of GA=Yes LAQ 0.6 mg, n=84 (15.3%) Placebo, n=89 (16.0%)
Annualized Relapse Rate	Risk Ratio	0.734 [0.608; 0.886]	0.987 [0.672; 1.449]
	Laquinimod Effect	27%	1%
	p-value	p=0.0013	p=0.9470
Brain Atrophy Defined by PBVC	Adj. Mean Diff.	0.436 [0.266; 0.607]	0.405 [-0.003; 0.812]
	Laquinimod Effect	32.8%	31.3%
	p-value	p<0.0001	p=0.0516
Time to Confirmed EDSS Progression (3m)	Hazard Ratio	0.631 [0.427; 0.930]	0.690 [0.314; 1.518]
	Laquinimod Effect	36.9%	31.0%
	p-value	p=0.0201	p=0.3561
Time to Confirmed EDSS Progression (6m)	Hazard Ratio	0.497 [0.311; 0.795]	0.612 [0.221; 1.696]
	Laquinimod Effect	50.3%	38.8%
	p-value	p=0.0036	p=0.3452
Cumulative GdE T1 Lesions at Months 12 and 24	Rate Ratio	0.617 [0.471; 0.809]	0.645 [0.329; 1.262]
	Laquinimod Effect	38.3%	35.5%
	p-value	p=0.0005	p=0.2002
Cumulative New/Enlarging T2 Lesions at Months 12 and 24	Rate Ratio	0.699 [0.570; 0.855]	0.740 [0.452; 1.211]
	Laquinimod Effect	30.1%	26.0%
	p-value	p=0.0005	p=0.2309

In addition, at the CHMP request, the applicant presented additional efficacy analysis in patients with high disease activity (see Figures 7-9). Indirect efficacy comparison with other MS treatments (interferons and glatiramer acetate) was also performed and is presented in Figures 10 and 11.

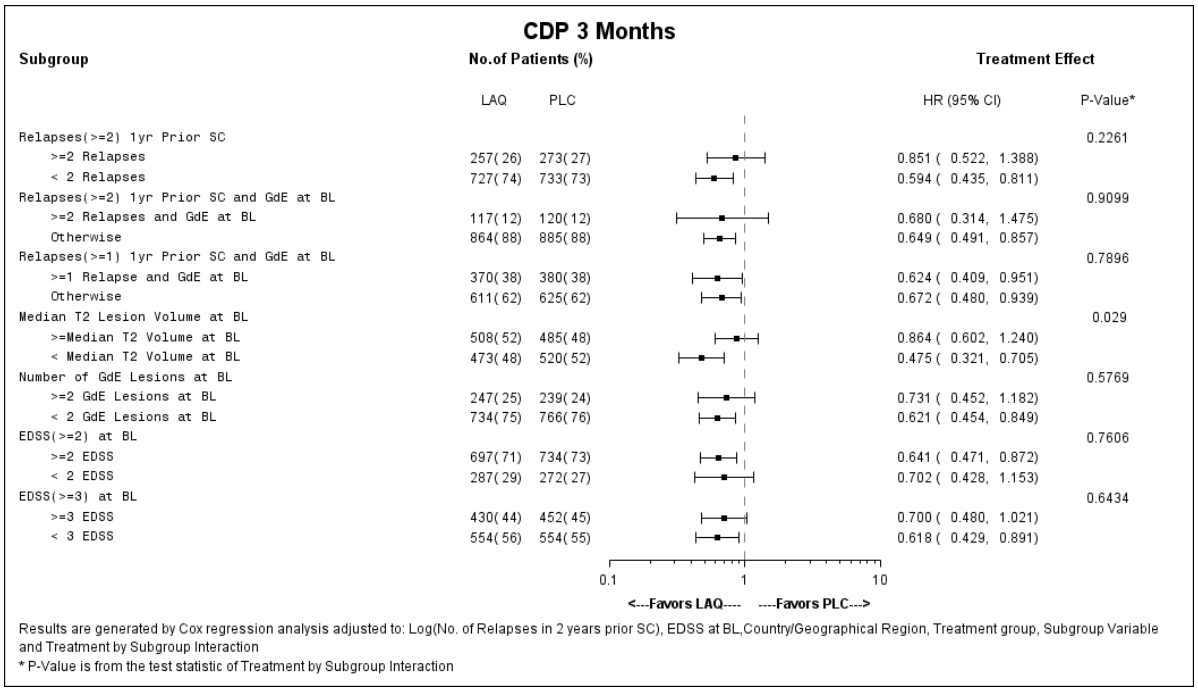
Figure 7: Efficacy results on ARR



Results are generated by negative binomial regression analysis adjusted to: Log(No. of Relapses in 2 years prior SC), EDSS at BL,Country/Geographical Region, Treatment group, Subgroup Variable and Treatment by Subgroup Interaction

* P-Value is from the test statistic of Treatment by Subgroup Interaction

Figure 8: Efficacy results on 3 month confirmed disease progression (CDP)



Results are generated by Cox regression analysis adjusted to: Log(No. of Relapses in 2 years prior SC), EDSS at BL,Country/Geographical Region, Treatment group, Subgroup Variable and Treatment by Subgroup Interaction

* P-Value is from the test statistic of Treatment by Subgroup Interaction

Figure 9: Efficacy results on 6 month confirmed disease progression (CDP)

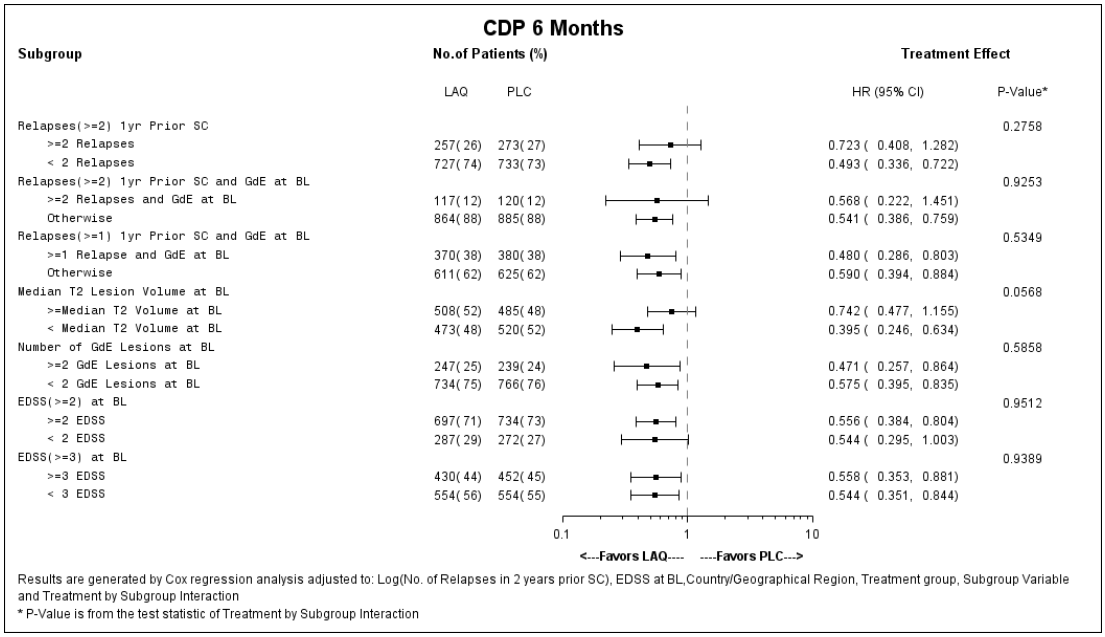


Figure 10: ARR (Point Estimates, 95% CI)

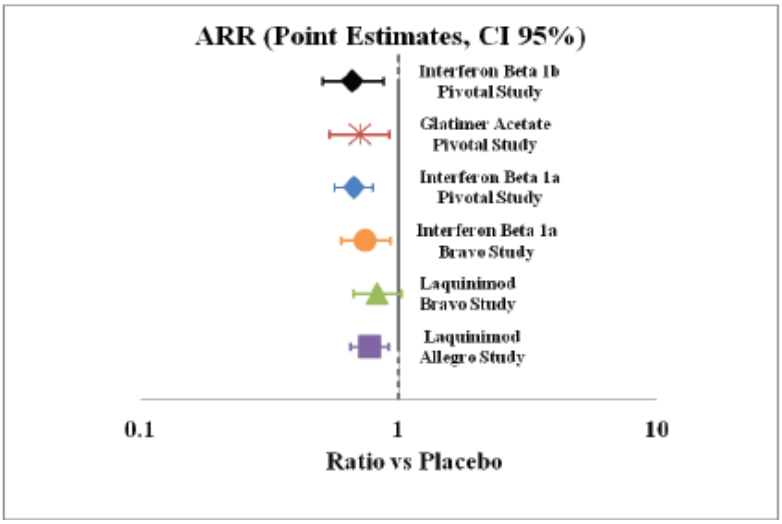
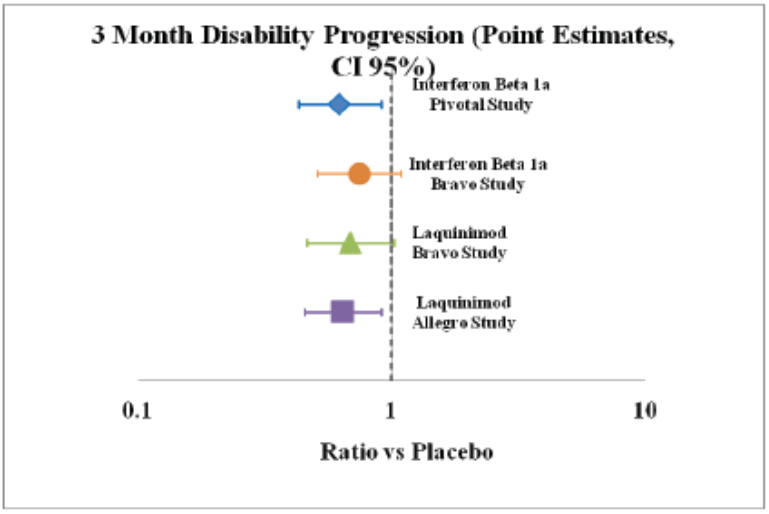


Figure 11: 3-Month Disability Progression (Point Estimates, 95% CI)



Furthermore, additional data were presented to support the efficacy profile of laquinimod in the subsets of RRMS population that would benefit from laquinimod according to the applicant. These included efficacy data in the following patient groups: patients who completed 2 years of Avonex treatment then switched to laquinimod (Figure 12), patients with baseline EDSS scores ≥4 (Table 13), patients who were relapse-free throughout the studies (Tables 14 and 15), patients in the 25% quartile of the MSFC z-score (i.e. patients in the bottom quartile of the MSFC change, Table 16, Figure 13), treatment naïve patients per baseline characteristics (Figure 14).

Figure 12: Annualised relapse rate in BRAVO for the original Avonex arm over 4 years (switch to laquinimod occurred in the beginning of year 3)

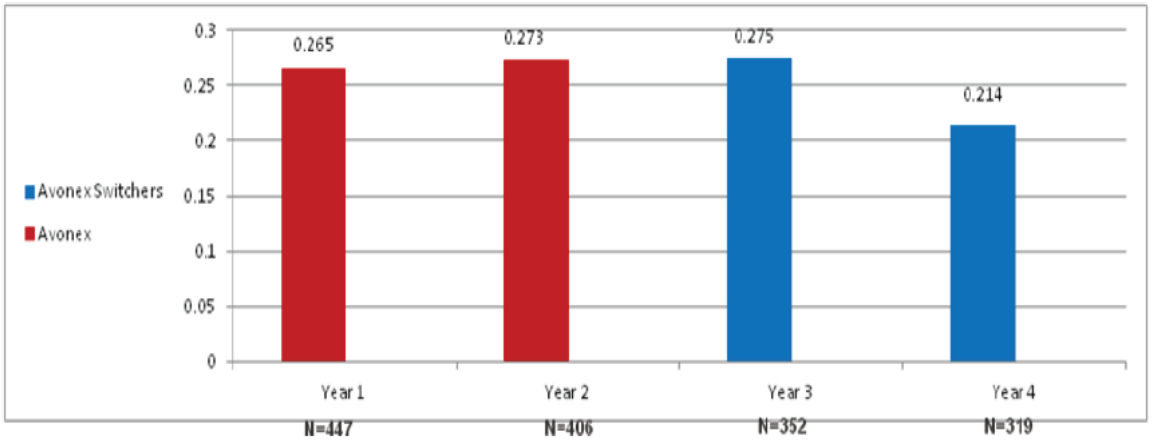


Table 13: subgroup analysis of pooled data: summary of treatment effects (laquinimod 0.6 mg vs placebo) by EDSS baseline score

		EDSS <4 LAQ 0.6 mg, n=769 (78.2%) Placebo, n=814 (80.9%)	EDSS ≥4 LAQ 0.6 mg, n=215 (21.8%) Placebo, n=192 (19.1%)
Annualized Relapse Rate	Risk Ratio	0.804 [0.688; 0.941]	0.747 [0.567; 0.984]
	Laquinimod Effect	19.6%	25.3%
	p-value	p=0.0064	p=0.0382
Brain Atrophy As Defined By PBVC	Adj. Mean Diff.	0.342 [0.223; 0.462]	0.423 [0.184; 0.661]
	Laquinimod Effect	29.6%	31.0%
	p-value	p<0.0001	p=0.0005
Time To Confirmed EDSS Progression (3m)	Hazard Ratio	0.647 [0.479; 0.875]	0.654 [0.383; 1.117]
	Laquinimod Effect	35.3%	34.6%
	p-value	p=0.0047	p=0.1201
Disability As Assessed By MSFC Z-Score At Month 24	Adj. Mean Diff.	0.007 [-0.084; 0.099]	0.311 [0.128; 0.494]
	p-value	p=0.8747	p=0.0009
Cumulative GdE T_1 Lesions At Months 1_2 and 24	Rate Ratio	0.688 [0.563; 0.840]	0.801 [0.537; 1.193]
	Laquinimod Effect	31.2%	19.9%
	p-value	p=0.0002	p=0.2749
Cumulative New/Enlarging T_2 Lesions At Months 12 and 24	Rate Ratio	0.77 [0.661; 0.898]	0.778 [0.571; 1.058]
	Laquinimod Effect	23%	22.2%
	p-value	p=0.0009	p=0.1098

Table 14: ITT Analysis Set – EDSS Data

ISE		Treatment Group			
		Placebo		Laquinimod 0.6 mg	
		N	%	N	%
Relapsing Subject Indicator	Confirmed Progression				
Relapse-Free	Did not progress	536	92.4	609	95.2
	Progressed	44	7.6	31	4.8
	All	580	100.0	640	100.0
Relapsing	Confirmed Progression				
	Did not progress	332	77.9	279	81.1
	Progressed	94	22.1	65	18.9
	All	426	100.0	344	100.0

ISE - Double Blind ITT

Table 15: Statistical Analysis of Time to Confirmed Progression by Relapse-Free – Additional Covariates

SAS PHREG - Cox Model (Hazard Ratio and 95% confidence intervals)

Comparison	Hazard Ratio	Lower Confidence Limit	Upper Confidence Limit	P-value
Laquinimod 0.6 mg vs. Placebo Relapse-Free	0.611	0.385	0.969	0.0362
Laquinimod 0.6 mg vs. Placebo Relapsing	0.733	0.531	1.011	0.0581

Table 16: Proportions of Patients by MSFC's Quartile vs. the Risk for EDSS Confirmed Progression Per Treatment Group

	Treatment Group											
	Placebo				Laquinimod 0.6 mg				All			
	Did not progress		Progressed		Did not progress		Progressed		Did not progress		Progressed	
	N	%	N	%	N	%	N	%	N	%	N	%
MSFC Quartile												
MSFC Q25%	159	73.61	57	26.39	162	81.82	36	18.18	321	77.54	93	22.46
MSFC Q50%	202	90.58	21	9.42	172	89.58	20	10.42	374	90.12	41	9.88
MSFC Q75%	183	88.41	24	11.59	190	91.79	17	8.21	373	90.10	41	9.90
MSFC Q100%	165	87.30	24	12.70	212	93.81	14	6.19	377	90.84	38	9.16

Figure 13: Proportions of Patients by MSFC's Quartile vs. the Risk for EDSS Confirmed Progression Per Treatment Group

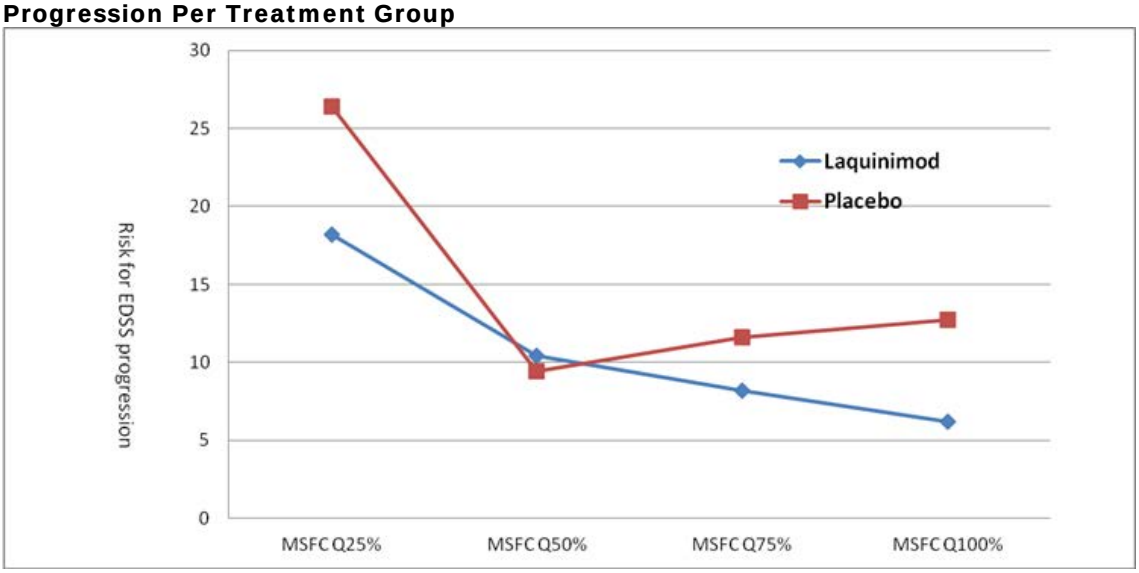
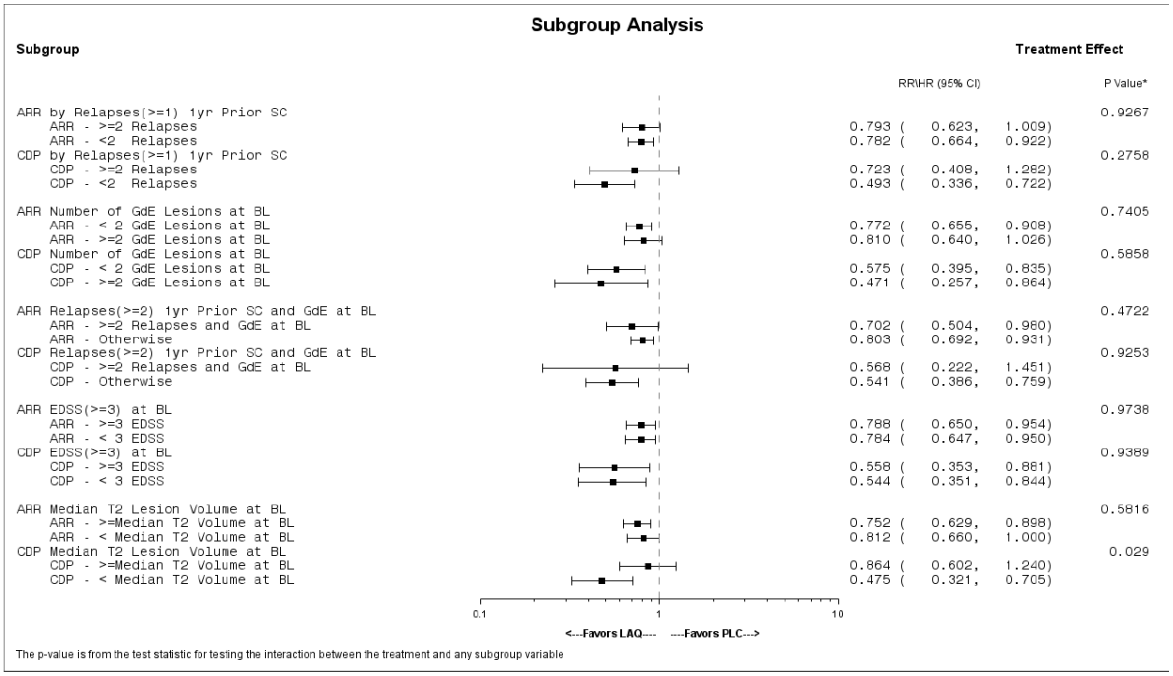
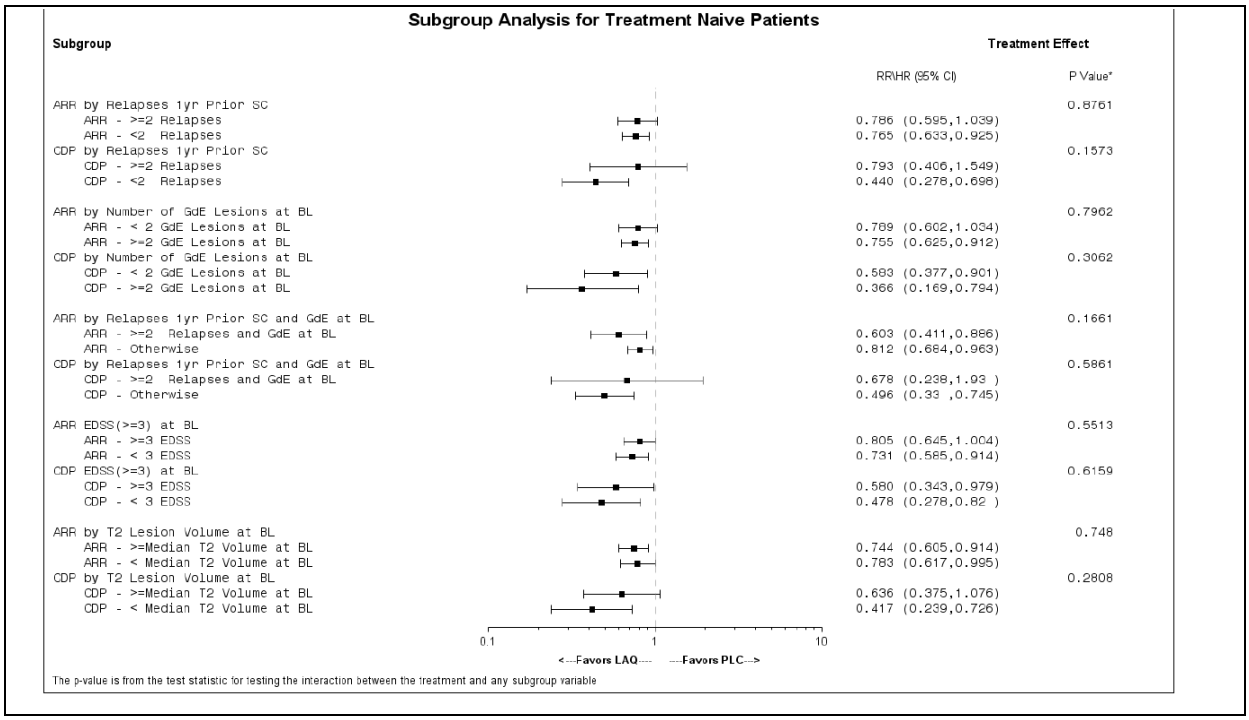


Figure 14: Subgroup analysis dichotomized by baseline parameters of disease activity for ARR and CDP





According to the applicant, reduction in time to 3, 6, 9 and 12 month confirmed disability Progression has been observed with laquinimod with a large magnitude, higher than predicted by the corresponding effect on relapse reduction. Based on laquinimod effect on ARR, 5% reduction in 3 month confirmed disability progression was predicted. However, 36% was observed. See Figures 15 and 16.

Figure 15. Laquinimod 3,6,9,12 month CDP effect versus placebo

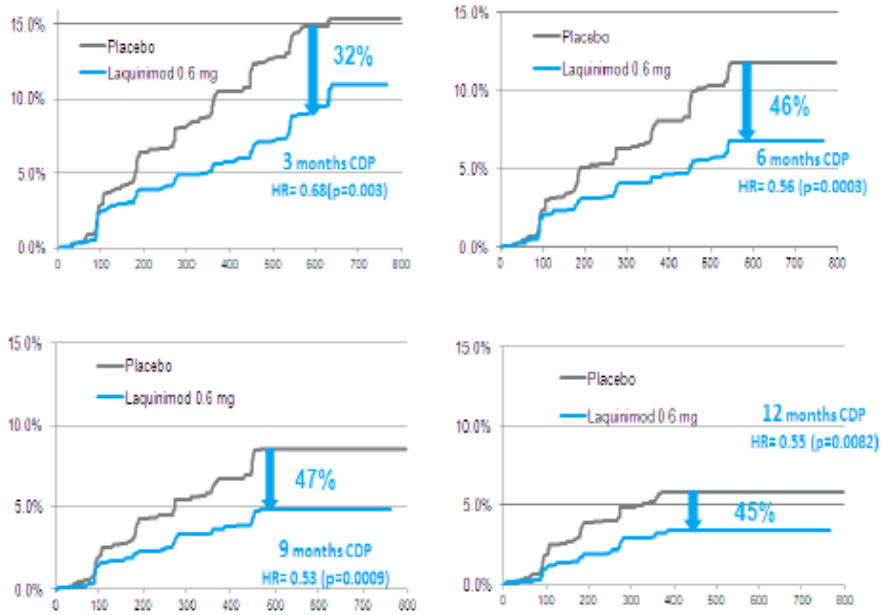
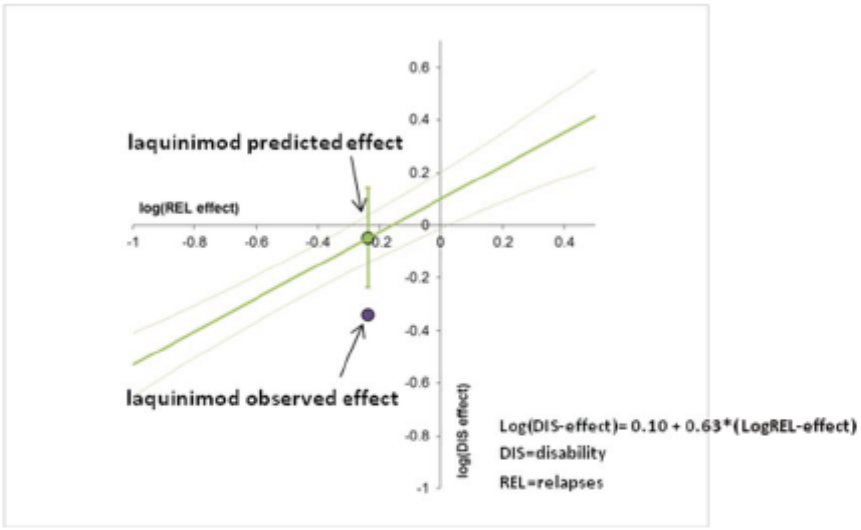


Figure 16. Effect on 3 month confirmed disability in the Sormani Equation relating effect on relapses to the effect on disability progression



The green regression line depicts the relationship between ARR and CDP and its 95% confidence bounds based on all available clinical RRMS trial data. The green dot signifies the point estimate of the predicted CDP effect of laquinimod by this Sormani equation; the black dot is the actual effect observed for laquinimod, well outside the 95%CI. The ARR effect of laquinimod is not predictive of its more pronounced CDP effect.

Summary of main study(ies)

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

Table 17.Summary of efficacy for trial Laq-301 (ALLEGRO)

Title: A multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate the safety, tolerability and efficacy of daily oral administration of laquinimod 0.6 mg in subjects with relapsing remitting multiple sclerosis (RRMS)			
Study identifier	Laq-301 (ALLEGRO)		
Design	Multicentre,Randomized, double-blind, parallel-group, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months not applicable ongoing
Hypothesis			
Treatments groups	Laquinimod		0.6 mg p.o. daily (capsule) N=550 (ITT)
	Placebo		capsule N=556 (ITT)
Endpoints and definitions	Co-primary endpoint	Relapse rate	A relapse was defined as the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities, lasting at least 48 hours and immediately precede by an improved neurological state of at least 30 days from onset of previous relapse.
	Secondary endpoint	Cumulative Nb of GdE T1lesions	Sum of T1 enhancing lesions at M12 and number of T1 enhancing lesions at M24
		Cumulative Nb of new or enlarging T2 lesions	Sum of new T2 lesions count at M12 and new T2 lesions count at M24
		Time to confirmed EDSS progression	A confirmed progression of EDSS is defined as at least 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0 or at least 0.5 point increase if baseline EDSS was 5.5 or higher, confirmed 3 months later.

Results and Analysis

Analysis description	**Primary and secondary Endpoint Analysis**		
Analysis population and time point description	ITT set (all randomized patients from baseline to last day in the study) Time point : 24 months		
Descriptive statistics and estimate variability	Treatment group	Laquinimod	Placebo
	Number of subject	550	556
	Relapse rate (Annualized relapse rate)	0.304	0.395
	SE	0.022	0.027
	Cumulative Nb of GdE T1lesions	1.332	2.119
	SE	0.142	0.218

	Cumulative Nb of new or enlarging T2 lesions	5.032	7.148
	SE	0.400	0.536
	EDSS (3 months)	2.8 (N=551)	2.7 (N=543)
	SD	1.5	1.5
Effect estimate per comparison	Annualized relapse rate	Comparison groups	Laquinimod vs placebo
		Rate Ratio	0.770
		95% CI	0.650;0.911
		Risk reduction	23%
		P value	0.0024
	Cumulative Nb of GdE T1lesions	Comparison groups	Laquinimod vs placebo
		Rate Ratio	0.629
		95% CI	0.488 ; 0.809
		Risk reduction	37.1%
		P value	0.0003
	Cumulative Nb of new or enlarging T2 lesions	Comparison groups	Laquinimod vs placebo
		Rate Ratio	0.704
		95% CI	0.584 ; 0.849
		Risk reduction	29.6%
		P value	0.0002
	Time to confirmed EDSS progression (3 months)	Comparison group	Laquinimod vs placebo
		Hazard Ratio	0.641
		95% CI	0.452;0.908
		Risk reduction	35.9%
		P value	0.0122

Table 18. Summary of efficacy for Laq-302 (BRAVO)

Title: A multinational, multicenter, randomized, parallel-group study performed in subjects with relapsing-remitting multiple sclerosis (RRMS) to assess the efficacy, safety and tolerability of laquinimod over placebo in a double-blind design and of a reference arm of interferon β-1a (Avonex) in a rater blinded design.			
Study identifier	Laq-302 (BRAVO)		
Design	Multicentre, Randomized, parallel-group, placebo-controlled in a double-blind design, with a reference arm in a rater blinded design		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months not applicable ongoing
Hypothesis			
Treatments groups	Laquinimod		0.6 mg p.o. daily (capsule) N=434 (ITT)
	Placebo		One capsule matching placebo p.o daily N=450 (ITT)
	Avonex		30 mcg i.m. once weekly N=447 (ITT)
Endpoints and definitions	Co-primary endpoint	Relapse rate	A relapse was defined as the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities, lasting at least 48 hours and immediately precede by an improved neurological state of at least 30 days from onset of previous relapse.
	Secondary endpoint	Brain atrophy	Percent brain volume change (PBVC) in normalized brain volume from baseline to month 24
		Disability measured by Time to confirmed progression of EDSS	A confirmed progression of EDSS is defined as at least 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0 or at least 0.5 point increase if baseline EDSS was 5.5 or higher, confirmed 3 months later
		Disability as assessed by MSFC score	.A 3 dimensional clinical measure which includes cognitive function in addition to leg function/ambulation and arm/hand function.

Results and Analysis

Analysis description	**Primary and secondary Endpoint Analysis**			
Analysis population and time point description	ITT set (all randomized patients from baseline to last day in the study) Time point : 24 months			
Descriptive statistics and estimate variability	Treatment group	Laquinimod	Placebo	Avonex
	Number of subject	434	450	447
	Relapse rate (Annualized relapse rate)	0.283	0.344	0.255
	SE	0.025	0.029	0.023
	Brain atrophy (PBVC)	-0.746	-1.030	-1.137

	SE	0.058	0.057	0.056
	EDSS (3months)	2.7 (N=428)	2.9 (N=447)	2.7 (N=438)
	SE	1.4	1.4	1.3
	Disability as assessed by MSFC score	-0.030	-0.135	-0.045
	SE	0.057	0.056	0.055
Effect estimate per comparison	Annualized relapse rate	Comparison groups	Laquinimod vs placebo	Avonex vs placebo
		Rate Ratio	0.823	0.741
		95% CI	0.664;1.020	0.596; 0.920
		Risk reduction	17.7%	25.9%
		P value	0.0746	0.0067
	Brain atrophy (PBVC)	Comparison groups	Laquinimod vs placebo	Avonex vs placebo
		Adjusted mean difference	0.284	-0.107
		95% CI	0.139 ; 0.429	-0.249 ; 0.035
		Risk reduction	27.6%	-10%
		P value	0.0001	0.14
	Disability measured by Time to confirmed progression of EDSS (3 months)	Comparison groups	Laquinimod vs placebo	Avonex vs placebo
		Hazard Ratio	0.687	0.742
		95% CI	0.462 ; 1.020	0.507 ; 1.088
		Risk reduction	31.3%	25.8%
		P value	0.0628	0.1269
	Disability as assessed by MSFC score	Comparison group	Laquinimod vs placebo	Avonex vs placebo
		Adjusted mean difference	0.104	0.089
		95% CI	-0.038;0.247	-0.050; 0.229
		P value	0.1505	0.2083

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

Naïve pooling of the raw data from the two pivotal studies (ALLEGRO and BRAVO) has been used to provide combined efficacy estimates for laquinimod and to evaluate whether the overall positive efficacy results are also evident in pre-specified subgroups of patients. The analysis was pre-planned. The population for the pooled analysis was the ITT analysis set. The results on ARR and EDSS score were numerically similar in these studies although these results did not reach the statistical significance in the BRAVO study. Taking into account these findings, it is not unexpected that the data pooled analysis led to statistically significant results for ARR (RR= 0.786, 95% CI: 0.686, 0.900, p=0.0005). However the effect of laquinimod 0.6 mg was modest with a reduction in the risk of occurrence of relapses of 21.4% as compared to placebo. The analysis of pooled data for time to confirmed EDSS progression yielded a hazard ratio of 0.658 (95% CI 0.506, 0.854, p=0.0017) reflecting a reduction of 34.2% in the risk for confirmed EDSS (3 months) progression as compared to placebo. The magnitude of the effect of laquinimod 0.6 mg over placebo on brain atrophy was statistically significant and consistent between the two studies ALLEGRO and BRAVO

(respectively reduction of brain atrophy of 32.8% and 27.6%). Results of the pooled data showed a slowing of brain atrophy at Month 24 in patients treated with laquinimod 0.6 mg as compared to placebo leading to a 29.7% reduction in brain atrophy ($p<0.0001$).

In the ALLEGRO study, laquinimod 0.6 mg showed a statistically significant effect over placebo for both MRI endpoints (cumulative number of GdE T1 lesions and cumulative number of New or Enlarging T2 lesions); in BRAVO the results were numerically similar but did not reach statistical significance. The analysis of pooled data for these MRI endpoints showed a statistically significant effect of laquinimod 0.6 mg.

At the CHMP request, a meta-analysis using the two pivotal studies ALLEGRO and BRAVO, and the phase IIb study LAQ/5062 was conducted. The results showed an effect of laquinimod on ARR with an overall Risk Ratio [95% CI] of 0.79 [0.69, 0.89] suggesting a 21% reduction for laquinimod versus placebo ($p=0.0002$). This result was consistent with the results of the pre-planned pooled analysis, previously described. Moreover, a treatment effect on GdE T1 lesions was observed with a rate ratio of 0.68 suggesting a reduction of 32% as compared to placebo. This effect was statistically significant ($p<0.00001$). The effect on new T2 lesions was also statistically significant with a reduction of 27% versus placebo (RR= 0.73, $p<0.00001$). Regarding brain atrophy, the effect of laquinimod was statistically significant as compared to placebo (difference of 0.31 in % brain volume change, $p<0.00001$). Regarding the disability progression, there was a 32% reduction in the risk for 3-month confirmed disease progression (HR= 0.68, 95% CI: 0.52, 0.87, $p=0.003$). This result was also consistent with the results of the pre-planned pooled analysis, described previously.

In addition, the CHMP also requested a meta-analysis including ALLEGRO and BRAVO studies on the 6 month sustained disability progression. In this post-hoc analysis, an effect of laquinimod 0.6 mg was observed with a 44% reduction in the risk for 6 month confirmed disability progression (HR= 0.56, 95% CI: 0.41, 0.76, $p=0.003$). This result was in line with previously reported data showing reduction in 6 months confirmed disability progression in the 2 individual studies (48% in ALLEGRO and 39% in BRAVO, respectively).

In subgroup analyses (according to gender, geographic region, age, EDSS baseline score, disease activity at baseline), results were consistently in favour of laquinimod 0.6 mg efficacy to reduce the relapse rate in all subgroups. Some unexpected statistical interactions between treatments and gender on EDSS score and cumulative New/Enlarging T2 lesions were observed.

2.5.2.5. Clinical studies in special populations

No trials have been performed in any special MS patient populations.

2.5.2.6. Supportive studies

Data from 3 extension studies were initially submitted (studies LAQ/5063, LAQ-301 and LAQ-302). At the CHMP request, the applicant also provided data from the ongoing open label study of LAQ/5063 which is a completed double blind active extension study. The cut-off date for all ongoing studies was November 2012.

After completing the 36 week, placebo-controlled, phase II study (LAQ/5062), 91% of patients (257 patients) enrolled in a 36 week, randomized, double-blind active extension study (LAQ/5063). Patients in each of the treatment arms continued their original dosing regimen, while placebo – treated patients were randomized to either laquinimod 0.3 mg or 0.6 mg daily for a further 36 weeks duration. MRI scans were performed prior to and after 36 weeks in the extension. Most patients continued directly into the extension after the original study ended. Treatment with

Laquinimod 0.6 mg resulted in a higher proportion of lesion-free subjects at the end of LAQ/5062 (50% vs 46.5%). This trend was sustained for the subjects who continued on laquinimod 0.6 mg (46.7% at both baseline and termination). Similar trend was maintained in the subjects who continued on laquinimod 0.3 mg. In its open label study, as of November 2012, 209 patients were included and 123 were followed-up for more than 5 years. Although the efficacy findings are considered exploratory in this open label design, the CHMP noted that the ARR and EDSS score remain low suggesting a maintenance of the effect since the mean duration of exposure to laquinimod 0.6 mg (core and extension and open label study) was 49.9 months.

Study LAQ-301E was an extension to the 24-month, Phase III study ALLEGRO. All patients who completed the 24-month core period could continue in the extension phase. Patients who were treated with laquinimod 0.6 mg in the core study continued on the same dose of study medication in the extension study. Patients who received placebo in the core study switched to laquinimod 0.6 mg in the extension study. Of the 864 patients who completed the core study, 839 entered in the extension phase. A total of 775 patients completed the year 4 visit, 127 patients discontinued the extension phase, 712 patients are still in the ongoing trial. At the end of the core study, the ARR was 0.305 in the 0.6 mg laquinimod treated group and 0.391 in the placebo group. At Month 48, cumulative ARR for the laquinimod 0.6 mg/laquinimod 0.6 mg was 0.262 compared 0.326 for the placebo/laquinimod 0.6 mg group. The results indicate that patients who started laquinimod earlier show less relapses than those who started later. At Month 48, mean EDSS for the total population was 2.6 ±2.5 and then remained stable. At the end of the core study there was a progression of EDSS sustained for 6 months in 6% of patients on laquinimod as compared to 10.8% of patients of the placebo group. At Month 48, 18% of patients in placebo/laquinimod 0.6mg group had confirmed disease progression as compared to 13.8% in the laquinimod 0.6 mg/laquinimod 0.6 mg group. Patients who started earlier laquinimod treatment had less disability progression than those started later. No conclusions on long term effect on the MRI parameters could be drawn due to small number of patients who consented to continue with MRI follow-up during the extension study (166 in total).

Study LAQ-302E was an extension to the 24-month Phase III study LAQ-302 (BRAVO). All patients who completed the 24-month core period on study treatment could continue in the extension phase. Patients who were randomized to laquinimod 0.6 mg continued to the same dose in the extension study and patients randomized to placebo or Avonex in the core study switched to laquinimod 0.6 mg. One thousand and ninety (1,090) patients completed the core study and 1,047 entered the extension phase. Taking into account the small number of patients who have completed the Month 48 (only 17), the available results should be interpreted with caution. At the end of the core study, ARR was 0.297 in the laquinimod group and 0.354 in the placebo group. At Month 48, the cumulative ARR for the laquinimod/laquinimod group was 0.280 as compared to 0.325 for the Placebo/laquinimod group. For patients treated with Avonex in the core study, cumulative ARR was also lower at the end of 2 years (0.269) compared to subjects treated with placebo. After switching from Avonex to laquinimod, there was no worsening in ARR and the difference achieved with Avonex during the core study was maintained under laquinimod. At Month 48, the cumulative ARR for the Avonex/laquinimod group was 0.269. Regarding disability progression, the too small number of patients at Month 48 does not allow to have interpretable results. Results at Month 36 (813 patients) showed that 87% of patients did not experience confirmed 6-month disability progression.

Overall, the supportive studies suggested maintenance of the effect of laquinimod during long-term treatment regarding ARR and disability progression.

Data after discontinuation of treatment at the end of study LAQ5062 and its extension LAQ5063 were available to evaluate the possible rebound effect. In study LAQ/5062, patients were treated

with either laquinimod 0.3 mg, laquinimod 0.6 mg or placebo for 36 weeks and were originally planned to immediately continue to an active extension of the study. However, a possible effect of laquinimod withdrawal on MRI activity (Gd-enhanced T1 lesions and new T2 lesions) could be examined in some patients due to the fact that, for some logistical reasons (according to the applicant), they had to wait without treatment before enrolling in the extension study. Of the 257 patients who enrolled in the extension study, 86 had a gap of at least 15 days (30 in 0.6 mg group, 29 in 0.3 mg group and 27 in placebo group); 77 of them (26 in 0.6 mg group, 26 in 0.3 mg group and 25 in placebo group) had a MRI scan before or shortly after the beginning of the extension study, providing data on rebound effect. However, only 30 patients treated with 0.6 mg had a gap of at least 15 days between the end of study LAQ/5062 and the beginning of treatment in study LAQ/5063. Patients of the three groups (0.6 mg, 0.3 mg and placebo) were classified as suspected or not suspected of having a post-withdrawal effect according to the 95th percentile of their individual Poisson distribution for the number of Gd-enhancing lesions. The individual means of the Poisson distribution were estimated using three different calculations: 1) all MRI scans during study LAQ/5062, 2) LAQ/5062 Post-baseline MRI scans, 3) LAQ/5062 pre-treatment MRI scans. Irrespective of the calculation used, the percentage of patients suspected of having a rebound effect was systematically higher in the laquinimod 0.6 mg group than in the laquinimod 0.3 mg and placebo groups. The percentages were similar in the laquinimod 0.3 mg and placebo groups. However, the CHMP noted that the difference between laquinimod 0.6 mg and placebo was derived from a difference of only a few cases between the two groups. There was no correlation between the lesion difference (difference between the post-withdrawal number of gadolinium (Gd)-enhancing T1 lesions and the mean number at pre-treatment) and the gap length. Therefore, these data were considered not conclusive of a rebound effect based on the number of Gd-enhancing T1 lesions. No statistically significant difference between the three groups was observed regarding the number and volume of new T2 lesions and no obvious difference between the three groups was seen regarding the number of relapses. Taking into account the long terminal half-life of laquinimod (approximatively 80 hours), the duration of action of laquinimod and the kinetics of MRI activity in MS, it seems uncertain that the duration of discontinuation of laquinimod treatment is long enough to ascertain a potential rebound effect.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme consisted of 2 phase II placebo controlled studies (study 01506203 and LAQ/5062) and 2 phase III studies, one placebo controlled study (LAQ-301, also called ALLEGRO) and one placebo and active controlled (study LAQ-302, also called BRAVO). However the latter study including the active comparator (interferon-beta 1a: Avonex) was not designed for a comparison of treatment effects between laquinimod and Avonex. In addition, data from extension studies were provided with a cut-off date of November 2012 since some of them were still ongoing.

The duration of the phase II and III studies (6-9 months and 2 years, respectively) were considered adequate by the CHMP.

All studies were multicentre and multinational and included patients with relapsing-remitting MS. Phase II study 010506203 also included SPMS patients (15.3%) and used triple Gd dose which restricts the comparability of results with the other three studies. Diagnosis of MS was based on the McDonald criteria. Inclusion and exclusion criteria for the pivotal studies (ALLEGRO and BRAVO) were closely similar to the exception that the duration of the disease in BRAVO study was not limited to at least 6 months and all subjects with previous use of interferons were excluded

from the study. These criteria may have contributed to the longer MS disease duration observed in subjects enrolled into ALLEGRO study. The time from first MS symptom was at least 8.6 years in ALLEGRO study and 6.6 years in BRAVO study. Time from MS diagnosis was ≥5.0 years in ALLEGRO study and ≥3.0 years in BRAVO study. Furthermore, a number of exclusion criteria were added to these studies (thyroid disease, history of seizure disorder).

In each individual study there were inter-group differences with respect to baseline MRI disease activity. In BRAVO, the proportion of subjects with GdE T1 lesions ≥1 at baseline was higher in the laquinimod 0.6 mg group than in the placebo group (39.6% vs. 33.4%; p =0.0548) ; mean (±SD) T2 lesions volume was also higher in the laquinimod 0.6 mg group compared to placebo (9.6 [±10.3] vs. 7.9 [±8.9]; p=0.009). The CHMP also noted that these baseline imbalances were also present in the Avonex group, the mean volume of T2 lesions was 10.4% and proportion of subjects with T1 Gd-enhancing lesions≥1 at baseline was 38.1%. In ALLEGRO, mean (±SD) T2 lesion volume was comparable for both treatment groups (9.8 [±10.4] and 9.7 [±10.5] for laquinimod 0.6 mg and placebo, respectively), but the proportion of subjects with GdE T1 lesions ≥1 at baseline was higher for placebo as compared to the laquinimod 0.6 mg group (45.7% vs. 40.4%, respectively, p= 0.0766) suggesting that subjects on placebo had higher disease activity at baseline.

The population of the two pivotal studies was representative of the MS population (68.5% of patients were women); 97.4% were Caucasian and the mean age was 38.1. The mean duration of the disease was 8.6 years in LAQ-301 study and 6.8 years in LAQ-302 study. In the two studies the mean number of relapses in the last year and in the last two years was similar (respectively 1.2 and 1.9). The mean EDSS score was similar (2.6) in the two studies. In the LAQ-301, more than 60% of patients were naïve of previous MS therapy and in study LAQ-302, there were more than 90% naïve patients.

Relevant efficacy endpoints were selected and were in accordance with the guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis or MS Guideline (CPMP/EWP/561/98, Rev.1). The primary efficacy endpoint was the total number of confirmed relapses during the treatment period as a mechanism for estimating the treatment effect on annual relapse rate in both studies. Furthermore, the CHMP noted that both studies included in addition to disability progression endpoints, different MRI endpoints related to clinical activity, and for some to long term clinical outcome (cumulative numbers of Gd enhancing lesions, new/enlarging T2 lesions for ALLEGRO, brain atrophy measure for BRAVO) as secondary efficacy endpoints. Relapse evaluation was performed in all scheduled as well as unscheduled visits as deemed necessary by the investigator/coordinator. Neurological examination was conducted at each visit. MRI scans (T1 and T2) were performed at baseline, after 12 months, after 24 months (termination) or at early discontinuation visit. Either two separate neurologists or two physicians assessed the subjects. An Examining Neurologist/Physician assessed the subject's neurological status, unaware of subject's well-being and a Treating Neurologist/Physician decided whether a subject experienced a relapse and prescribed steroids or other concomitant medications as needed. In order to maintain reliable evaluation and reduce the potential for bias, the examining neurologist/physician was the only one to evaluate the subject neurologically and the examining neurologist/Physician had no access to the subject's file, including previous neurostatus forms and adverse events (AEs).

A confirmed progression of EDSS was defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5, confirmed 3 months later. Hence, the six-month sustained disability progression endpoint, as recommended in the MS GL (CPMP/EWP/561/98, Rev.1) was evaluated as a post-hoc analysis.

The statistical methods used for analysis of the primary, secondary and exploratory endpoints and the data analysis sets are generally considered to be appropriate. Methods were similar in the

ALLEGRO and the BRAVO studies, but there were differences for the type I error adjustment for the secondary endpoints and the hierarchy of the endpoints. In addition, according to the hierarchical approach taken for the statistical analysis, it is important to note that testing of the secondary endpoints does not ensure preservation of the overall type-I error in case the primary endpoint does not meet statistical significance , such as in the case of the BRAVO study. According to the applicant, the borderline p value observed for the primary endpoint in the BRAVO study is partly due to the lack of power in addition to the observed imbalances across group (described further below). From the CHMP viewpoint, no pre-specified blinded sample size reassessment was included in the study protocol, which might have addressed this issue. This study focused more on brain atrophy and EDSS based disease progression to confirm the applicant's claim on neuroprotective properties of the active substance.

For the model based analyses of the primary endpoints pre-tests for the adequacy of the models were performed. The predefined set of sensitivity analyses is considered appropriate. The sensitivity analyses demonstrate that the results of the primary analyses can be considered robust.

Efficacy data and additional analyses

Dosing rationale

Although the CHMP supported the choice of 0.6 mg dose for the phase III studies based on the overall findings observed in preclinical and clinical dose ranging studies, the CHMP considered that the optimal dose had not been defined because 0.6 mg dose was the sole dose tested in the phase III studies. According to the applicant, preliminary findings from ascending dose evaluation in healthy volunteers and MS patients (study 99506202) identified 1.2 mg dose of laquinimod as not being the optimal dose due to the applied stopping criteria, although these were based on pre-defined, laboratory-related threshold stopping criteria (increased CRP and fibrinogen levels) rather than clinical criteria. At the present time, the applicant however considered this study as a failed maximum tolerated dose (MTD) study and planned to investigate higher dose (1.2 mg) in RRMS patients as well as in other patient populations. In the absence of data using higher doses than 0.6 mg, the CHMP concluded that the dose response effect of laquinimod has not been sufficiently evaluated to determine the optimal dose in the intended population.

Effect on relapses

In ALLEGRO study, a statistically significant effect of laquinimod 0.6 mg compared to placebo was demonstrated for the annualised relapse rate (p=0.0024). Whilst this result was consistent with other efficacy endpoints related to relapses and supported by sensitivity analyses, the reduction in ARR for laquinimod over placebo was modest, 23% over 24 months (RR= 0.770, 95% CI: 0.650, 0.911). In BRAVO study including an active comparator (Avonex), laquinimod 0.6 mg dose failed to show a statistically significant effect as compared to placebo on the ARR (RR=0.823, 95% CI: 0.664, 1.020, p=0.0746) reflecting a reduction of ARR of 17.7%. In contrast, the comparison of the Avonex treatment arm with placebo yielded a risk ratio of 0.741 (95% CI: 0.596; 0.920, p=0.0067), demonstrating a 25.9% reduction in the annualized relapse rate.

Whereas BRAVO study was not designed for a direct comparison between laquinimod and Avonex, the applicant conducted a post-hoc exploratory comparison of the ARR of laquinimod 0.6mg and Avonex to further analyse the relative efficacy of laquinimod on ARR. This analysis yielded a risk ratio of 1.102 (with a difference of 0.03 relapses a year) seemingly rejecting the apparent superiority of Avonex over laquinimod (95%CI – 0.883-1.376, p=0.3887) However the CHMP did not consider such analysis as sufficient to conclude on the relative efficacy of laquinimod versus

Avonex and relied upon the pre-specified sensitivity analyses that were consistent with the primary analysis.

Due to the imbalances observed at baseline for mean T2 lesions volume and proportion of subjects with GdE T1 lesions ≥1 across treatment groups, additional post-hoc analyses were performed using these MRI parameters as covariates in a corrected model. Such corrected analysis resulted in an increase in magnitude of effect of laquinimod 0.6 mg compared to placebo on ARR (RR=0.787, 95% CI: 0.637, 0.972, p=0.0264) of statistical significance. However this corrected result was still suggesting a modest reduction in ARR of 21.3% in patients treated with laquinimod 0.6 mg in BRAVO study. Importantly, whilst these baseline imbalances were also present in the Avonex group, treatment effect of Avonex over placebo was statistically significant (p=0.0067) in the primary model due to an observed larger treatment effect size of 25.9% reduction in the ARR (RR= 0.741, 95% CI: 0.596, 0.920). Numerically, the results on ARR were in favour of Avonex as compared to laquinimod. In addition, laquinimod failed to show statistical significance over placebo on the time to first relapse (HR: 0.813, 95% CI:0.653, 1.014); p=0.0659), questioning the sensitivity of the results observed for the ARR, after the baseline corrected analysis.

An additional post-hoc analysis employing propensity score also revealed the overall bias introduced in the predefined primary analysis. The results of this analysis showed that when the primary analysis model was adjusted for the continuous propensity score, laquinimod 0.6 mg reduced the risk for relapses by 23.1% compared to placebo (risk ratio=0.769, nominal p-value=0.026). Similarly, when the primary analysis model was adjusted for the categorical propensity score, laquinimod 0.6 mg reduced the risk for relapses by 22.4% compared to placebo (risk ratio=0.776, nominal p value= 0.0315).

In a meta-analysis including the 2 pivotal studies and the phase II study LAQ/5062, an effect of laquinimod on ARR was demonstrated suggesting a 21% reduction for laquinimod versus placebo (RR=0.79, 95% CI : 0.69,0.89, p=0.0002). This result was consistent with the initially submitted pooled analysis of the two pivotal studies (reduction of 21.4% in ARR, p=0.0005) and is considered modest.

Effect on disability progression

ALLEGRO study showed also that laquinimod delayed the time to 3-month confirmed disability progression, with a statistically significant reduction of 36% over placebo (HR= 0.641; 95% CI: 0.452, 0.908; p=0.0122). BRAVO study failed to demonstrate such effect with a lower risk reduction of 31.3% over placebo (HR=0.687, 95% CI: 0.462, 1,020; p=0.0628). However, the CHMP noted that results on disability progression were numerically in favour of laquinimod as compared to Avonex, although the 95% CIs for each of the outcomes were overlapping. In addition, results from the pooled analysis using both pivotal studies, demonstrated a 34% reduction in the risk for 3-month confirmed disease progression (HR = 0.66, p=0.002). When adding the data from the phase II study LAQ/5062 in this pooled analysis, the effect on disability remain with a reduction of around 32% in the risk of disability progression confirmed at 3 months, although the CHMP noted that study LAQ/5062 on its own failed to show an effect on disability (HR= 1.12, 95%CI: 0.33, 3.74). A 44% reduction of disability progression confirmed at 6-months was also observed based on post-hoc analysis of pooled data provided by the applicant from both pivotal studies, data from study LAQ/5062 was not included in this analysis due to its short duration.

In both studies, results on MSFC score were not consistent with the EDSS score as there was no difference between treatment groups at month 24 on this disability progression related endpoint.

In the corrected analysis, results on disability progression were comparable across pivotal studies.

Effect on MRI parameters

In ALLEGRO study, there was a statistically significant effect of laquinimod on mean adjusted number of T1 Gd-enhancing lesions (RR=0.629,95% CI: 0.488, 0.809, p=0.0003) showing a reduction of 37% in the mean rate of developing T1 Gd-enhancing lesions on laquinimod 0.6 mg compared to placebo. A statistically significant treatment effect of laquinimod 0.6 mg over placebo was also shown on the cumulative number of New/Enlarging T2 lesions (RR=0.704,95% CI: 0.584, 0.849, p=0.0002) indicating a reduction of 30% in the mean rate of developing New/Enlarging T2 lesions on laquinimod 0.6 mg compared to placebo.

In BRAVO study, statistically significant effects of laquinimod over placebo were demonstrated on brain atrophy from baseline to month 24 (adjusted mean difference=0.284, 95%CI: 0.139, 0.429; p=0.0001).A favourable effect of laquinimod 0.6 mg over placebo was observed for the reduction of enhancing T1 lesions at Month 24 (RR= 0.611, 95% CI: 0.439, 0.852, p=0.0037) but not at Month 12 (RR= 0.884, 95% CI: 0.658, 1.186, p=0.4099). There was a reduction in the mean rate of development of cumulative number of T1 Gd-enhancing lesions on laquinimod 0.6 mg over placebo but this was not statistically significant (RR= 0.785, 95% CI: 0.604, 1.019, p=0.0691). In contrast, Avonex showed a reduction versus placebo in the number of enhancing T1 lesions at both Month 12 and Month 24 measurements (respectively, RR= 0.410, 95% CI: 0.299, 0.562, p<0.0001 and RR=0.336, 95% CI: 0.237, 0.474, p<0.0001) as well as for the cumulative lesion counts for Months 12 and 24 and this was statistically significant (RR= 0.385, 95% CI: 0.239, 0.505, p<0.0001). An effect of laquinimod 0.6 mg versus placebo was seen for reduction of new/newly enlarging T2 lesions at Month 12 (RR= 0.813, 95% CI: 0.664, 0.996, p=0.0462). As compared to placebo, Avonex reduced the new T2 lesions at Months 12 and 24 (RR= 0.491, 95% CI: 0.400, 0.602, p<0.001). No differences between laquinimod 0.6 mg and placebo were observed for T2 lesions volume, either at Month 12 or Month 24 (respectively mean ratio= 0.996, 95% CI: 0.925, 1.071, p=0.9053 and mean ratio= 1.005, 95% CI: 0.930, 1.085, p=0.9019). A statistically significant effect for Avonex over placebo was seen for both endpoints (respectively p=0.0019 and p=0.0104). No differences between laquinimod 0.6 mg and placebo were observed for T1 hypointense lesions volume, either at Month 12 or Month 24; there was no difference between the Avonex and placebo groups for either endpoint.

Laquinimod 0.6 mg demonstrated a reduction in brain atrophy over placebo from baseline to Month 12 (adjusted mean difference=0.221, 95% CI: 0.125, 0.317, p<0.001), whereas no appreciable difference between the two groups was shown between Months 12 to 24 (adjusted mean difference=0.033, 95% CI: -0.062, 0.127, p=0.4972). No treatment effects on reduction in brain atrophy were seen for Avonex over placebo for either measurement period (Month 12: adjusted mean difference=-0.134, 95% CI: -0.229,-0.040, p=0.0053 and Month 24: adjusted mean difference=0.018 , 95% CI: -0.074, 0.111, p=0.6975, respectively).

In the corrected analysis performed due to the imbalances observed at baseline for mean T2 lesions volume and proportion of subjects with GdE T1 lesions ≥1 across treatment groups, results on brain atrophy were comparable across pivotal studies.

In the meta-analysis using the two pivotal studies ALLEGRO and BRAVO, and the phase IIb study LAQ/5062, a treatment effect on GdE T1 lesions was observed with a rate ratio of 0.68 suggesting a reduction of 32% as compared to placebo. This effect was statistically significant (p<0.00001). The effect on new T2 lesions was also statistically significant with a reduction of 27% versus placebo (Rate Ratio of 0.73, p<0.00001). Regarding brain atrophy, the effect of laquinimod was statistically significant as compared to placebo (difference of 0.31 in % brain volume change, p<0.00001).

Indirect comparison with other MS treatments

An indirect comparison between the point estimates of ARR with laquinimod and interferon beta and glatiramer show that, although the 95% CI are overlapping, the effect of laquinimod is modest (see Figure 10). The CHMP considered that other drugs (i.e. Tysabri, Gilenya) have shown substantially larger effects. According to the applicant, the magnitude on the disability effect is only matched by potent immunosuppressive DMTs, mediated by their effect on relapses. However, the presented data on the effect on 3-month disability progression suggested a similar effect as compared to Avonex (see Figure 11).

Long-term efficacy and withdrawal after discontinuation

Data from 3 extension studies were initially submitted (studies LAQ/5063, LAQ-301 and LAQ-302). At the CHMP request, the applicant also provided data from the ongoing open label study of LAQ/5063 which is a completed double blind active extension study. The cut-off date for all ongoing studies was November 2012.

Although the efficacy findings are considered exploratory in study LAQ/5063 (open label), the CHMP noted that the ARR and EDSS score remain low suggesting a maintenance of the effect since the mean duration of exposure to laquinimod 0.6 mg (core and extension and open label study) was 49.9 months.

In study LAQ-301E, results indicate that patients who started laquinimod earlier show less relapses than those who started later. At Month 48, mean EDSS for the total population was 2.6 ±2.5 and then remained stable. At the end of the core study there was a progression of EDSS sustained for 6 months in 6% of patients on laquinimod as compared to 10.8% of patients of the placebo group. At Month 48, 18% of patients in placebo/laquinimod 0.6mg group had confirmed disease progression as compared to 13.8% in the laquinimod 0.6 mg/laquinimod 0.6 mg group. Patients who started earlier laquinimod treatment had less disability progression than those started later. No conclusions on long term effect on the MRI parameters could be drawn due to small number of patients who consented to continue with MRI follow-up during the extension study (166 in total).

In study LAQ-302E, a small number of patients completed the Month 48 (only 17), and available results should be interpreted with caution. At the end of the core study, ARR was 0.297 in the laquinimod group and 0.354 in the placebo group. At Month 48, the cumulative ARR for the laquinimod/laquinimod group was 0.280 as compared to 0.325 for the Placebo/laquinimod group. For patients treated with Avonex in the core study, cumulative ARR was also lower at the end of 2 years (0.269) compared to subjects treated with placebo. After switching from Avonex to laquinimod, there was no worsening in ARR and the difference achieved with Avonex during the core study was maintained under laquinimod. At Month 48, the cumulative ARR for the Avonex/laquinimod group was 0.269. Regarding disability progression, the too small number of patients at Month 48 does not allow to have results. Results at Month 36 (813 patients) showed that 87% of patients did not experience confirmed 6-month disability progression.

Overall, the supportive studies suggested maintenance of the effect of laquinimod during long term treatment regarding ARR and disability progression.

In study LAQ5062 and its extension LAQ5063, irrespective of the calculation method used, the percentage of patients suspected of having a rebound effect was systematically higher in the laquinimod 0.6 mg group than in the laquinimod 0.3 mg and placebo groups. The percentages were similar in the laquinimod 0.3 mg and placebo groups. However, the CHMP noted that the difference between laquinimod 0.6 mg and placebo was derived from a difference of only a few cases between the two groups. There was no correlation between the lesion difference (difference between the post-withdrawal number of Gd-enhancing T1 lesions and the mean number at pre-treatment) and

the gap length. Therefore, these data were considered not conclusive of a rebound effect based on the number of Gd-enhancing T1 lesions. No statistically significant difference between the three groups was observed regarding the number and volume of new T2 lesions and no obvious difference between the three groups was seen regarding the number of relapses. Taking into account the long terminal half-life of laquinimod (approximatively 80 hours), the duration of action of laquinimod and the kinetics of MRI activity in MS, it seems uncertain that the duration of discontinuation of laquinimod treatment is long enough to ascertain a potential rebound effect.

Limited data after discontinuation of laquinimod treatment are not suggestive of a potential rebound effect, however, it cannot be excluded and remain a potential risk.

Patients previously treated, with high disease activity

Because the BRAVO study excluded all patients with prior use of interferons and the sample size for patients previously treated with glatiramer acetate is small, data in patients previously treated were analysed based ALLEGRO study only. In this study, the effect of laquinimod 0.6 mg was two-fold smaller in the subgroup with prior use of interferon than in the subgroup without prior use of interferon for ARR (13% vs 27%), brain atrophy (17.4% vs 34.6%) and time to confirmed EDSS progression-6 month (28.7% vs 58.2%). In patients previously treated with interferons, the effect of treatment for time to confirmed EDSS progression-3 month was much weaker than in patients without prior use of interferon ((3.5% vs 49.4%). The effect of laquinimod was considered as similar for cumulative Gd T1 lesions and new/enlarging T2 lesions in the two subgroups of patients (respectively 41.1% vs 35.7% and 28.1% vs 30.3%).In patients with prior glatiramer acetate use, there was no effect of laquinimod on ARR as compared to placebo, however the sample size is small (n=84 for laquinimod and n=89 for placebo) to conclude on this efficacy finding. For all other endpoints (disability progression and MRI parameters) an effect of laquinimod over placebo was observed but not statistically significant and the treatment effect was similar in both patients with and without prior use of GA.

In pooled data using the pivotal studies, there was a consistent effect of laquinimod over placebo on relapses and disability progression across the subgroups of patients with more or less active disease.

Overall discussion on the patient population

The applicant' s proposal for a broad indication in RRMS patients was maintained at an Oral Explanation held on 17 December 2013. Considering the overall efficacy results, a number of subsets of the RRMS population that would benefit from laquinimod were identified by the applicant as follows: patients with RRMS who are treatment-naïve and have positive predictive markers for lower disease activity (based on relapse rate prior to treatment initiation and MRI markers of inflammatory activity); patients with RRMS who have been mostly stable on injectable therapies (interferon-beta, GA) and who are seeking non-injectable therapies; and RRMS patients who have shown disease progression largely independent of relapses. These subsets have been mainly identified according to the applicant's claim that laquinimod has a more pronounced effect on the degenerative process of the disease than on its anti-inflammatory properties. This claim is supported by the efficacy data showing a more pronounced effect of laquinimod on disability progression at 3 and 6 months in patients with a lower T2 burden of disease (52% versus 14% as suggested by the HR of 0.475 and 0.864 and 60% versus 26% as suggested by the HR of 0.395 and 0.742 after 3 and 6 months, respectively) and in patients with a lower pre-trial relapse rate (< 2 in the year prior to screening) whereas the degree of baseline EDSS does not modify disease progression. Other supportive efficacy analyses were presented to support these subsets of RRMS patient population (see 1.8.2.3). The CHMP was however of the opinion that these subgroup analyses were of exploratory nature and that it was not appropriate to consider data on specific

subsets of RRMS population to support a broad indication in the RRMS population, as proposed by the applicant.

Having considered the above and the overall efficacy data, the CHMP remained concerned that the efficacy of laquinimod at the proposed 0.6 mg dose, was modest on the relapse rate in the proposed broad RRMS population, notwithstanding the more encouraging effect on disability progression. The unknown mechanism of action and the rather modest effect on relapses questions the suitability of laquinimod as treatment for the broad population with relapsing remitting multiple sclerosis (RRMS) patients.

2.5.4. Conclusions on the clinical efficacy

The CHMP concluded the following:

- Only modest efficacy of laquinimod on relapse rate in adult patients with relapsing remitting multiple sclerosis at the proposed 0.6mg dose has been shown, notwithstanding the more encouraging effect on the disability progression.

2.6. Clinical safety

The safety database presented in this dossier included the following cohorts: 1) phase III studies (ALLEGRO and BRAVO), 2) all placebo-controlled studies (99506202, 01506203, LAQ/5062, ALLEGRO, BRAVO, and MS-LAQ-101), 3) all MS studies (99506202, 01506203, 03506207, LAQ/5062, LAQ/5063, LAQ/5063OL, ALLEGRO, MS-LAQ-301E, BRAVO, MS-LAQ-302E, and MS-LAQ-101) and 4) MS studies with patients exposed to laquinimod 0.6 mg for at least one year (LAQ/5062, LAQ/5063, LAQ/5063OL, ALLEGRO, MS-LAQ- 301E, BRAVO and MS-LAQ-302E).

In addition to these data, safety experience in non-MS studies ie, patients with Crohn's disease (CD-LAQ-201) and systemic lupus erythematosus (SLE, studies LN-LAQ-201 and LA-LAQ-202) was provided. During the evaluation, the applicant also provided another cohort "cohort 5" with a cut-off date of November 2012 to provide further long term safety data with laquinimod.

2.6.1. Patient exposure

As of March 2012, 2,632 subjects with MS were exposed to laquinimod for a total duration of approximately 4,920 subject-years and 321 volunteers (healthy volunteers and special populations) received various doses of laquinimod in several Phase I studies for a total duration of 6.4 subject-years. A total of 1,456 MS patients were exposed to laquinimod 0.6 mg for at least one year and the mean exposure to study drug was 2.6± 1.2 years in cohort 4. A total of 2,346 subjects (89.1%) were exposed to the proposed therapeutic daily dose of 0.6 mg.

As of November 2012, a total of 1,009 MS patients who participated in clinical were included in cohort 5 and were exposed to laquinimod 0.6 mg for 3683.0 subject-years. Mean exposure to study drug was 3.7 ± 1.0 years. In total, 74.3% (750) of subjects in this long-term cohort were exposed for more than 3 years and 19.2% of subjects (194 subjects) were exposed for more than 4 years.

To date, the maximal duration of exposure to laquinimod was observed in open label extension study LAQ5063OL and is approximately 7 years.

2.6.2. Adverse events

The AE profile for cohort 1 is considered representative of the safety profile of laquinimod and included the 2 pivotal studies, ALLEGRO and BRAVO.

In cohort 1, the incidence of adverse events was the highest in the system organ class (SOC) of Infections and Infestations and comparable between two groups, laquinimod and placebo (48.7% vs 47%). The incidence of AEs was higher in the group laquinimod for SOC Musculoskeletal and Connective Tissue Disorders (30.4% vs 25.4%), SOC Investigations (27% vs 20.8%), SOC gastrointestinal or GI disorders (26.9%vs 22.6%), SOC Metabolism disorders (5.3% vs 2.9%), Neoplasm (4.6% vs 2.7%) compared to placebo. The common AEs are summarised in Table 19.

Table 19: Cohort #1: Common* Adverse Events by Descending Order of Incidence in the Laquinimod 0.6 mg Group

Cohort #1: Placebo-Controlled Pivotal Studies in MS Patients Treated with Laquinimod 0.6 mg	Placebo (N=1005)			Laquinimod 0.6 mg (N=983)		
Preferred Term	No. of Reports	No. of Subjects	% of Subjects	No. of Reports	No. of Subjects	% of Subjects
Headache	278	152	15.1	319	179	**18.2**
Nasopharyngitis	240	153	15.2	225	141	14.3
Back Pain	121	82	8.2	179	134	**13.6**
Upper Respiratory Tract Infection	105	84	8.4	102	76	7.7
Arthralgia	73	60	6.0	89	71	**7.2**
Influenza	83	73	7.3	69	60	6.1
Alanine Aminotransferase Increased	28	27	2.7	72	58	**5.9**
Urinary Tract Infection	61	42	4.2	75	56	**5.7**
Diarrhoea	55	48	4.8	60	54	5.5
Depression	49	47	4.7	55	53	5.4
Insomnia	62	49	4.9	61	53	5.4
Cough	35	31	3.1	57	51	**5.2**
Nausea	51	44	4.4	57	50	5.1
Abdominal Pain	26	26	2.6	54	49	**5.0**
Pain In Extremity	68	58	5.8	58	47	4.8

* Common AEs: AEs reported by 5% or more of any treatment group.

A comparison of AE in ALLEGRO and BRAVO studies is presented in Table 20. When the incidence of common AEs is compared between ALLEGRO and BRAVO studies, the adverse events that are higher in the laquinimod groups in both studies are abdominal pain, ALT increased, back pain, arthralgia and headache.

Table 20: Comparison of AEs in Studies ALLEGRO and BRAVO by SOC

	ALLEGRO (N=1106, Subject Years=1933.2)		BRAVO (N=1324, Subject Years=2365.4)		
	Placebo (N=556, Subject Years=959.3)	Laquinimod 0.6 mg (N=550, Subject Years=973.9)	Placebo (N=449, Subject Years=790.2)	Laquinimod 0.6 mg (N=433, Subject Years=768.7)	Avonex® (N=442, Subject Years=806.5)
	% of Subjects	% of Subjects	% of Subjects	% of Subjects	% of Subjects
System Organ Class					
-ALL	81.5	87.3	69.7	74.8	82.4
Blood And Lymphatic System Disorders	5	7.3	4	5.3	5.7

Cardiac Disorders[a]	4.3	4.4	2.4	2.1	3.8
Ear And Labyrinth Disorders	5	6.2	3.3	3.2	3.2
Eye Disorders[a]	6.3	8.5	4.5	2.5	2.9
Gastrointestinal Disorders	26.6	32	17.6	20.3	11.3
General Disorders And Administration Site Conditions	20.7	19.8	12.5	13.2	62.4
Infections And Infestations	54.9	56.5	37.2	38.8	30.5
Injury, Poisoning And Procedural Complications[a]	14	13.3	8.9	2.3	4.8
Investigations	21.9	28.7	19.4	24.9	20.4
Metabolism And Nutrition Disorders	4.3	6.2	1.1	4.2	1.8
Musculoskeletal And Connective Tissue Disorders	29.9	36.9	19.8	22.2	14.5
Nervous System Disorders	34.2	36.2	23.4	21	21.5
Psychiatric Disorders	17.6	18.4	10.7	12.5	12
Renal And Urinary Disorders	5	7.3	5.1	4.8	2.3
Reproductive System And Breast Disorders	9.2	11.8	5.6	7.6	2.5
Respiratory, Thoracic And Mediastinal Disorders	17.4	15.5	6.9	8.5	6.1
Skin And Subcutaneous Tissue Disorders[a]	9.9	14.9	10	6.5	6.1
Surgical And Medical Procedures[a]	9.4	9.1	2.9	4.2	3.4
Vascular Disorders[a]	4.9	6	4.9	2.5	5.7
Hepatobiliary Disorders	2.9	3.3	2	1.8	2.3
Immune System Disorders[a]	2.3	1.8	1.3	0.9	0.5
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	3.8	5.8	1.3	3	2
Congenital, Familial And Genetic Disorders	0.5	.	0.9	0.2	0.2
Endocrine Disorders	1.3	0.7	1.1	1.6	3.4
Social Circumstances[a]	0.2	0.9	0.4	0.2	0.2
Pregnancy, Puerperium And Perinatal Conditions	.	0.2	0.2	0.5	0.7

a SOC with incidence of AEs higher in laquinimod than placebo and difference between laquinimod groups of the individual studies ≥2 fold.

In the non-MS studies, headache was the most common AE. In study CD-LAQ-201, AEs were more frequent in the high-dose laquinimod 2mg group. Headache was dose-dependent AE as the incidence was the highest in the laquinimod 2mg group compared to less dosed groups. GI disorders (vomiting, diarrhoea, abdominal pain) were very frequent. Unexpectedly, back pain occurred in less patients in 2mg group (3.4%) compared to 10.3%, 10% and 13.8% in other groups (0.5mg, 1mg and 1.5mg); however, the number of patients by group was limited (n=29).

In healthy volunteers, headache and nasopharyngitis were the most common AEs, especially in the high dose group (2.4mg). One subject experienced asymptomatic tachycardia 6 hours after first 1.2mg dose. Even if the event was considered unlikely related to study drug, drug imputability cannot be excluded. Laboratory markers of inflammation (CRP, ESR, fibrinogen) have been found to be increased in 6 healthy volunteers. These elevations in ESR, CRP and fibrinogen were characterised to be large notably during laquinimod exposure at 2.4 mg/day and were reversible after stopping study drug.

2.6.3. Serious adverse event / deaths / other significant events

Deaths

A total of 13 deaths were reported during the clinical development programme with 9 deaths in the laquinimod groups. These are presented in table 21.

Table 21. Deaths in all MS studies

Age (years)	Gender	Treatment group	Preferred term
44	M	laquinimod	Sepsis
33	M	placebo	Accident
50	M	placebo	Suicide
39	M	Avonex	Cardiopulmonary failure
46	F	laquinimod	Subdural haematoma, ataxia
29	M	laquinimod	Acute coronary syndrome, diabetic ketoacidosis
29	M	laquinimod	Completed suicide, depression
45	F	laquinimod	Acute leukaemia, disseminated intravascular coagulation, cerebral haemorrha
34	F	laquinimod	Rectal cancer, large intestine perforation, colonic obstruction, infectious peritonitis, cardiopulmonary failure
47	F	laquinimod	Cardiac failure acute, cardiovascular insufficiency, respiratory failure
39	M	laquinimod	Myocardial infarction
47	M	laquinimod	Ulcerated gastric adenocarcinoma, acute gastroenteritis, clostridium difficile
38	F	placebo	Pneumonia bacterial, coma, pulmonary edema

Overall, among 9 deaths that occurred with laquinimod treatment, one death (completed suicide) was considered as possibly related to study drug by the investigator. It seems that long placebo period with 4 confirmed MS relapses could have led to severe depression and finally to suicide. Also the death accompanied by acute leukaemia, anemia, thrombocytopenia should be considered potentially drug-related, as laquinimod can cause hematotoxicity. Two sudden deaths were reported due to cardiovascular insufficiency (within 5 hours after taking laquinimod) and myocardial infarction (5 months of treatment with laquinimod). The available information for these 2 cases is insufficient to conclude on the causality of laquinimod. Indeed, in both cases, no autopsy was performed, and no ECG was done during the event. Confounding factors for ischaemic heart disease included overweight for both cases. In addition, in one case the subject was a former smoking. In one case, ECG was previously assessed during clinical trial as abnormal (no further information was provided) by investigator but the abnormality was considered not clinically significant. The death occurred 3 weeks after starting the drug treatment and 5 hours after taking laquinimod.

No deaths were initially reported in the non-MS studies. During the evaluation, one additional death due to pneumonia occurred in a SLE study.

Serious Adverse Events

The number of SAEs was similar in cohort 1 between the laquinimod and the placebo group: 9.4% vs 8.9%. However, the number of appendicitis was significantly higher in the laquinimod group: 6 cases vs 1 case in the placebo group. Serious cases of peritonitis occurred also but the exact number was not presented in cohort 1; the incidence of cellulitis serious AEs was higher for laquinimod than for placebo however, these cases had confounding factors suggesting no evidence

for an increased risk of cellulitis in subject treated with laquinimod (see Table 22). In cohort 3, in all MS patients ever exposed to laquinimod, 12 appendicitis and 6 infectious peritonitis were noted.

Table 22: Cohort #1: SAEs Reported by at Least Two Subjects in any Group by Preferred Term in Descending Order of Incidence in the Laquinimod 0.6 mg Group

Cohort #1: Placebo-Controlled Pivotal Studies in MS Patients Treated with Laquinimod 0.6 mg	Placebo (N=1005)		Laquinimod 0.6 mg (N=983)	
	No. of Subjects	% of Subjects	No. of Subjects	% of Subjects
Preferred Term				
Appendicitis	1	0.1	6	0.6
Multiple Sclerosis Relapse	7	0.7	5	0.5
Cellulitis	.	.	3	0.3
Hysterectomy	6	0.6	3	0.3
Anaemia	.	.	2	0.2
Diarrhoea	.	.	2	0.2
Pyrexia	.	.	2	0.2
Oedema Peripheral	.	.	2	0.2
Hypokalaemia	.	.	2	0.2
Osteoarthritis	.	.	2	0.2
Cervicobrachial Syndrome	.	.	2	0.2
Headache	1	0.1	2	0.2
Abortion Threatened	.	.	2	0.2
Depression	1	0.1	2	0.2
Cervical Dysplasia	.	.	2	0.2
Appendicectomy	.	.	2	0.2
Spinal Fusion Surgery	.	.	2	0.2
Gastritis	3	0.3	1	0.1
Abdominal Pain	2	0.2	1	0.1
Cholelithiasis	3	0.3	1	0.1
Pneumonia	3	0.3	1	0.1
Migraine	2	0.2	1	0.1
Nephrolithiasis	2	0.2	1	0.1
Renal Colic	2	0.2	1	0.1
Rehabilitation Therapy	3	0.3	1	0.1
Liver Disorder	2	0.2	.	.
Hepatic Enzyme Increased	2	0.2	.	.
Intervertebral Disc Protrusion	2	0.2	.	.
Depression Suicidal	1	0.1	.	.
Endometrial Hyperplasia	2	0.2	.	.
Dyspnoea	2	0.2	.	.
Cholecystectomy	2	0.2	.	.

No severe cases have been retrieved with worrying neurological AEs, rapid deterioration of neurological conditions following infection or atypical MS exacerbation after laquinimod initiation.

Furthermore, two SAEs were reported in the laquinimod 2.4 mg group: severe constipation, and pleuritis with pleural effusion in 61 year-old male with traumatic fracture of rib on the same side. Pleural effusion persisted 6 months later. The applicant did not exclude a relationship with study drug.

Malignant Tumours

Overall, malignant tumors have been reported in 26 patients (0.6%) treated with laquinimod in all clinical studies; 6 breast carcinomas including one metastatic breast cancer (3 in cohort 1, all in

ALLEGRO and no case in BRAVO; 1 additional case of breast cancer in study LAQ/5062 have been reported in laquinimod group. One breast cancer was reported in placebo group). Data on the frequency and incidence of malignant tumours are presented in Table 23.

Table 23: Cohort #3: Frequency and Incidence of Malignant Tumours (SMQ) and Preferred Term

All MS Patients Ever Exposed to Laquinimod in Clinical Studies		Laquinimod (N=2632, Subject Years=4994.2)			
		No. of Reports	No. of Subjects	% of Subjects	Event Rate per 100 Subject Years
SMQ (3)	Preferred Term	29	26	1.0	0.6
-ALL	-ALL				
Malignant tumours (SMQ)	-ALL	29	26	1.0	0.6
	Acute Leukaemia	1	1	0.0	0.0
	Basal Cell Carcinoma	5	4	0.2	0.1
	Breast Cancer	4	4	0.2	0.1
	Breast Cancer Metastatic	1	1	0.0	0.0
	Breast Cancer Stage II	1	1	0.0	0.0
	Chronic Lymphocytic Leukaemia	1	1	0.0	0.0
	Colon Cancer	1	1	0.0	0.0
	Gastric Cancer	1	1	0.0	0.0
	Glioblastoma	1	1	0.0	0.0
	Keratoacanthoma	2	2	0.1	0.0
	Lung Neoplasm Malignant	1	1	0.0	0.0
	Lymphoma	1	1	0.0	0.0
	Malignant Melanoma	1	1	0.0	0.0
	Metastases To Lung	1	1	0.0	0.0
	Metastatic Neoplasm	1	1	0.0	0.0
	Oesophageal Adenocarcinoma	1	1	0.0	0.0
	Rectal Cancer	1	1	0.0	0.0
	Renal Cancer	1	1	0.0	0.0
	Squamous Cell Carcinoma	1	1	0.0	0.0
	Squamous Cell Carcinoma Of Skin	1	1	0.0	0.0
	Thyroid Cancer	1	1	0.0	0.0

In cohort 1, 10 (1%) patients in the laquinimod group vs 6 (0.6%) patients with placebo experienced a malignant tumour [p=0.2944, 95% CI (-0.37, 1.21)]. In addition to 3 cases of breast cancer, sporadic cases of glioblastoma (1), lung neoplasm malignant (1), lymphoma (1), oesophageal adenocarcinoma (1), squamous cell carcinoma (1), thyroid cancer (1) were reported.

One case of thyroid cancer has been reported in BRAVO study in a 32.5 year-old female after 189 days of laquinimod treatment. The AE was considered as moderate and not related to study drug; the subject recovered. One case of thyroid cancer occurred in Avonex group.

Concerning skin malignancy, 2 cases (basal cell carcinoma, squamous cell carcinoma) occurred in cohort 1 compared to one case (basal cell carcinoma) in the placebo group. In total, in cohort 3 (all patients treated with laquinimod), 7 subjects suffered from skin malignancies: basal cell carcinoma (4), malignant melanoma (1) and squamous cell carcinoma (2).

Comparison of malignancies incidences with Surveillance Epidemiology and End Results SEER (age-adjusted SIR=1.4; 95% CI [0.90-2.08]) and CPRD (age-adjusted SIR=1.397; 95% CI [0.97-1.95] for general population; age-adjusted SIR=1.088; 95% CI [0.75-1.52] for MS population) databases did not demonstrate an increase in malignant tumors with laquinimod therapy. For breast cancer, incidence comparison did not demonstrate an increased risk with laquinimod therapy when compared to SEER and General Practice Research Databases (GPRD). According to the applicant, malignant tumours are not considered to constitute a safety signal of concern at the present time. However, from the CHMP viewpoint, the number of events to date and duration of

follow-up is too limited to definitively exclude a relationship. In addition, based on available pre-clinical data, there remain relevant uncertainties on the potential risk for malignancies.These uncertainties currently represent an important concern with long term use of laquinimod (see 1.6.6).

Liver Safety

The events of ALT and AST increased were more important in the laquinimod group for >1 and ≤ 5 x ULN elevation (see Table 24).

Table 24: Cohort # 1: Shift from Normal at Baseline to Highest Value for ALT and AST at any Time during Study

Test Name	Category of Abnormality	Placebo (N=1005)	Laquinimod 0.6 mg (N=983)
AST (IU/l)	Patients with Normal Test at Baseline	977	950
	>1 and ≤3 x ULN	83 (8.5%)	**159 (16.7%)**
	> 3 and ≤5 x ULN	6 (0.6%)	**9 (0.9%)**
	> 5 and ≤8 x ULN	4 (0.4%)	1 (0.1%)
	> 8 x ULN	2 (0.2%)	0 (0.0%)
ALT (IU/l)	Patients with Normal Test at Baseline	930	888
	>1 and ≤3 x ULN	165 (17.7%)	**262 (29.5%)**
	> 3 and ≤5 x ULN	5 (0.5%)	**30 (3.4%)**
	> 5 and ≤8 x ULN	6 (0.6%)	5 (0.6%)
	> 8 x ULN	7 (0.8%)	5 (0.6%)

The following protocols are included: MS-LAQ-301 (ALLEGRO) and MS-LAQ-302 (BRAVO)

Five patients terminated early due to AEs of elevations in liver enzymes. No Hy's law cases or liver failure have been reported. None of ALT/AST increases were accompanied by bilirubin elevation >2x ULN. In both treatment groups, the vast majority of subjects had a baseline bilirubin grade 0 ([93.2%] placebo; [92.9%] laquinimod). Of subjects with normal bilirubin values at baseline, the majority during the course of the study still had normal values, less in the placebo group (93.5% vs. 98.9%, placebo vs. laquinimod). During the course of the study no patient in both of the treatment groups had a bilirubin increase grade 4. Grade 3 increase of bilirubin occurred in one patient in the laquinimod group (at baseline this patient already had a bilirubin grade 2 increase) and none in the placebo group.

Analysis using common toxicity criteria or CTCAE (common terminology criteria for AEs) suggested that laquinimod treatment was associated with elevations from normal to Grade 1 for AST, ALT, GGT and normal to grade 1 and 2 (up to 5xULN) for ALT and gamma glutamyl transferase (GGT). Shifts to grade 3 and 4 were uncommon and reported with a similar incidence in the placebo and laquinimod groups, apart from GGT increase grade 3 which was slightly more frequent in the laquinimod group.

Mostly mild, asymptomatic liver enzyme elevations (AST, ALT and GGT) were reported and generally occurred within 6 months after initiation of treatment. Overall in the pivotal placebo-controlled trials, 4.7% of laquinimod treated subjects reached relevantly significant [> 3xULN] levels of ALT. ALT increase was the event that was more notable for male than for female (11.6% vs 3.3%) in the laquinimod 0.6 mg group. Laquinimod-treated subjects with elevated liver parameters while on study-drug returned to baseline under continued treatment within a mean of up to 4 months, partially similar to placebo patients. ALT elevations persisted for a longer period compared to AST elevations: In the laquinimod-group AST >1 and ≤3x ULN maximally persisted for 209 days and AST >3 and ≤5x ULN maximally persisted for 122 days. Whereas ALT >1 and ≤3x ULN maximally persisted for 448 days, ALT >3 and ≤5x ULN for 149 days and ALT >5 and

≤8x ULN maximally persisted for 204 days. In 74% of subjects who had elevated levels of ALT on laquinimod, ALT decreased to within the normal range while on laquinimod.

The incidence of drug-related hepatic disorders was similar between laquinimod and Avonex groups (9.9% vs 8.4%). The incidence of post-baseline shift changes from low/normal to high AST/ALT/GGT levels was comparable between laquinimod and Avonex groups.

In cohort 1, more drug-related hepatic disorders were reported among laquinimod-treated subjects (11.2% vs 6.4%) compared to placebo. Analysis of liver- related AEs did not reveal any signal in addition to the laboratory findings.

Back/Neck Pain

Data are presented in Tables 25 and 26.

Table 25: Cohort #1: Incidence of Grouped Term Back/Neck Pain

	Placebo (N=1005)		**Laquinimod 0.6 mg (N=983)**		**Difference**	**p-value 95% CI Laquinimod 0.6 vs Placebo**
	No. of Subjects	% of Subjects	No. of Subjects	% of Subjects		
Drug related back/neck pain	92	9.2	144	14.6	5.4%	0.0002 [0.0265, 0.0833]

Table 26: Cohort #1: Grouped Term Back/Neck Pain by Outcome

Outcomes	**Placebo** Subjects with back/neck pain=92	**Laquinimod 0.6 mg** Subjects with back/neck pain =144
Not recovered n (%)	27 (29.3%)	47 (32.6%)
Recovered n (%)	68 (73.9%)	105 (72.9%)
Sequelae n (%)	3 (3.3%)	1 (0.7%)

More subjects experienced back/neck pain in the laquinimod group compared to placebo: 114 (14.6%) vs 92 (9.2%). Among 144 subjects with back/neck pain, 44 (32.6%) subjects did not recover in cohort 1 compared to 29.3% in placebo group. Similar number of events was severe in both groups: 4.9% vs 5.4%. One subject had sequelae in laquinimod group and 3 subjects in placebo group. In patients reporting back pain a slightly higher percentage (4.4% vs. 2.2%) had both elevated CRP and fibrinogen at the same time.

In addition, a higher frequency of back and neck pain was reported in the laquinimod group in the first months of treatment. After 3 months of laquinimod treatment, use of anti-inflammatory and anti-rheumatic medications was similar in the laquinimod and placebo groups. However some peaks in the use of these drugs occur again at 9 and 15 months of treatment by laquinimod that seems to be correlated to increases in musculoskeletal AEs in the laquinimod group between 9 and 18 months of treatment, whereas a decrease was observed between 6 and 9 months.

When compared to Avonex group, the incidence of back/neck pain was significantly higher in the laquinimod group: 10.2% (44 subjects) vs 3.4% (15 subjects).

In cohort 1, three serious AEs of back pain have been reported in the laquinimod group and none in the placebo group. All subjects recovered, 2 with symptomatic treatment and one with invasive fixing treatment at L5-S1. In addition, in cohort 5, back pain continued to be commonly reported with laquinimod (8.9 reports/100 subjects/year), supporting an effect not limited to the first weeks of treatment.

Infections

Data are presented in Table 27.

Table 27: Cohort #1: AEs with SOC Infections and Infestations Reported by at Least 1% of Subjects in Any Group by Preferred Term and Descending Order of Incidence in the Laquinimod 0.6 mg Group

Cohort #1: Placebo-Controlled Pivotal Studies in MS Patients Treated with Laquinimod 0.6 mg	Placebo (N=1005)			Laquinimod 0.6 mg (N=983)		
Preferred Term	**No. of Reports**	**No. of Subjects**	**% of Subjects**	**No. of Reports**	**No. of Subjects**	**% of Subjects**
Nasopharyngitis	240	153	15.2	225	141	14.3
Upper Respiratory Tract Infection	105	84	8.4	102	76	7.7
Influenza	83	73	7.3	69	60	6.1
Urinary Tract Infection	61	42	4.2	75	56	5.7
Sinusitis	50	36	3.6	53	42	4.3
Bronchitis	39	32	3.2	39	34	3.5
Cystitis	21	18	1.8	28	25	2.5
Rhinitis	26	20	2	24	20	2
Gastroenteritis	10	10	1	19	17	1.7
Pharyngitis	43	35	3.5	20	17	1.7
Oral Herpes	32	22	2.2	18	17	1.7
Respiratory Tract Infection	19	14	1.4	19	16	1.6
Respiratory Tract Infection Viral	14	11	1.1	17	14	1.4
Viral Infection	23	20	2	19	14	1.4
Tonsillitis	16	15	1.5	15	13	1.3
Tooth Abscess	13	12	1.2	13	12	1.2
Gastroenteritis Viral	10	9	0.9	9	9	0.9
Ear Infection	11	11	1.1	9	8	0.8
Acute Tonsillitis	14	13	1.3	8	8	0.8
Pneumonia	13	11	1.1	6	6	0.6
Vulvovaginal Mycotic Infection	13	10	1	6	4	0.4

Overall, the incidence of infections was similar between the laquinimod and the placebo treatment groups (48.7% vs 47%). Although the incidence of severe infections was low (1.1 reports/100 subject years), severe cases of appendicitis, infectious peritonitis, cellulitis, pneumonia have been observed. One death was reported due to pneumonia and sepsis in cohort 1. One additional death due to pneumonia occurred in SLE study.

With regards to opportunistic infections, 4 cases of tuberculosis occurred during the laquinimod clinical trials.

Red Blood Cells Parameters

Data are presented in Table 28.

Table 28: Cohort #1: Incidence of Post Baseline Shifts to Abnormally Low Red Blood Cells

Placebo-Controlled Pivotal Studies in MS Patients Treated with Laquinimod 0.6 mg	Placebo (N=1005)		Laquinimod 0.6 mg (N=983)	
	All*	**Change From High / Normal to Low**	**All***	**Change From High / Normal to Low**
	N	**%**	**N**	**%**
HgB	1000	25.1	974	36.6
HCT	999	8.11	973	16.2
RBC	1000	12.1	974	25.6
MCV	999	3.7	973	3.2
MCH	1000	8.9	973	5.0

MCHC	999	31.2	973	31.8

Cases of haemoglobin decrease occurred more frequently in laquinimod group (in 36.6% of subjects) compared to placebo (25%). In cohort 1, 2 cases of anaemia have been observed in the laquinimod group and none with placebo.

One female patient received a blood transfusion; she had an AE of menorrhagia and underwent a radical hysterectomy 2.5 months later. All other patients returned to normal of their low red blood cell levels without a blood transfusion.

Photosensitivity

In cohort 1, one report of photodermatosis and 3 reports of photosensitivity reaction have been reported compared to 1 report (photodermatosis) with placebo, 0.3% vs 0.1%. Overall, 11 reports of photosensitivity have been reported with laquinimod in all clinical studies. Most of the events were of mild severity and related to sun exposure, with a variable drug exposure prior to adverse event onset (ranging from 19 days to 30 months). All cases resolved with no interruption in laquinimod treatment. Five of the cases resolved spontaneously, 3 subjects required topical steroids and 2 subjects were treated with oral antihistamines.

Incidence of photosensitivity in cohort 3 is presented in Table 29.

Table 29: Cohort #3: Incidence of Photosensitivity Adverse Events

All MS Patients Ever Exposed to Laquinimod in Clinical Studies		Laquinimod (N=2632, Subject Years=4994.2)			
		No. of Reports	No. of Subjects	% of Subjects	Event Rate per 100 Subject Years
Category	**Preferred Term**				
Photosensitivity	-ALL	11	9	0.3	0.2
	Photodermatosis	1	1	0.0	0.0
	Photosensitivity Allergic Reaction	4	3	0.1	0.1
	Photosensitivity Reaction	6	5	0.2	0.1

Oral Cavity Disorder

One case of oral leukoplakia was reported occurred in a patient with a predisposing factor (smoking). The event regressed spontaneously within less than two months under continued laquinimod therapy.

2.6.4. Laboratory, ECG findings, Vital signs

Haematological parameters

Data are presented in Table 30.

Table 30: Cohort #1: Incidence* of Post Baseline Shift to Abnormal Haematology Values

Cohort #1: Placebo-Controlled Pivotal Studies in MS Patients Treated with Laquinimod 0.6 mg	Placebo (N=1005)			Laquinimod 0.6 mg (N=983)		
	All[a]	Change From High / Normal to Low	Change From Low / Normal to High	All[a]	Change From High / Normal to Low	Change From Low / Normal to High
	N	%	%	N	%	%
WBC	996	8.23	14.76	967	3.62	**27.4**

Neutrophils	994	5.63	21.03	963	3.32	**30.63**
Lymphocytes	994	9.46	2.52	963	4.57	6.02
Monocytes	994	6.74	10.66	963	5.5	**22.95**
HgB	1000	25.1	0.9	974	**36.55**	0.31
HCT	999	8.11	26.03	973	16.24	14.18
RBC	1000	12.1	11.5	974	**25.56**	5.03
MCV	999	3.7	46.05	973	3.19	50.77
Platelet	995	4.62	2.01	965	**12.02**	2.69

a Subjects with a measurement at baseline and at least one measurement after baseline
* Incidence :percent out of subjects who had a test baseline and at least one post baseline test, only for tests with at least a 1% higher incidence of shifts in the laquinimod 0.6 mg group; HCT: hematocrite, MCV:Mean Cell Volume, WBC: White Blood Cells

Significantly more subjects experienced a change in WBC from low/normal to high level (including increase of subpopulations, e.g. neutrophils) in the laquinimod group (27.5%) compared to placebo (14.6%) or Avonex (11.2%). In the pivotal studies shift in WBC was generally mild and is not considered clinically significant (no grade 3 leucocytosis occurred). Nevertheless in the BRAVO extension study after exposure to laquinimod for more than 700 days there was one death by anemia, thrombocytopenia and acute leucemia.

In addition, haemoglobin level decreased in clearly more subjects in the laquinimod group (36.55%) compared to placebo (25.1%) or Avonex (31.2%). However, only one patient suffering from anemia required transfusion due to menorrhagia.

Platelets also shifted to low level in more patients in the laquinimod group (12%) than in placebo group (4.6%), but was not considered clinically significant apart from the fatal case described above.

Haematological toxicity was relevant with laquinimod when compared to placebo, with mostly mild increase in leucocyte levels and decrease in red blood cells and platelets. Two cases of anaemia and one case of leukemia in the laquinimod group were considered as serious.

Chemistry, metabolic parameters

Data are presented in Table 31.

Table 31: Cohort #1: Incidence* of Post Baseline Shift to Abnormal Biochemistry Values at Any Time during Study

Cohort #1: Placebo- Controlled Pivotal Studies in MS Patients Treated with Laquinimod 0.6 mg	Placebo (N=1005)			Laquinimod 0.6 mg (N=983)		
	All[a]	Change From High / Normal to Low	Change From Low / Normal to High	All[a]	Change From High / Normal to Low	Change From Low / Normal to High
	N	%	%	N	%	%
Sodium	999	1.1	28.8	973	2.7	27.1
Potassium	999	4	18.7	974	2.3	21.7
Calcium	999	66.7	5	974	68.8	3.8
Creatinine	999	27.9	1.1	974	42.5	0.6
CPK	1000	17.1	14.5	974	13.4	17.2
ALP	999	5.1	1.8	974	2.8	3.7
AST	999	0	9.5	974	0	**17.4**
ALT	999	2.9	18.3	974	2.5	**31.1**
GGT	999	3	10.2	974	1.3	**18**
Total Protein	999	7.3	10.8	974	8.7	9.3
Fibrinogen	985	4.7	28.4	966	3.7	**39.9**
P-Amylase	997	2.9	7.9	975	1.3	14.4

a Subjects with measurement at baseline and at least one post baseline measurement
*Incidence:percent out of subjects who had a test at baseline and at least one post-baseline test, only tests with an incidence higher in the laquinimod group by at least 1%

During escalating-dose phase I studies (using higher doses than 0.6 mg of laquinimod), laboratory markers of inflammation (CRP, ESR, fibrinogen) have been increased in healthy volunteers. In addition, a clear increase of fibrinogen above normal values was observed in phase II study (0350627). Some results have been provided on CRP in ALLEGRO study showing CRP increase in 7.3% of subjects compared to 5.8% in the placebo group. Fibrinogen, other marker of inflammation changed from normal to high level in 40% of patients in laquinimod group in Cohort 1 while it changed in clearly less patients in placebo group (28.4%).

In the pivotal studies, mean CRP elevations (and also percentage of potentially clinically significant CRP) were similar in the laquinimod and placebo group. Nevertheless until month 15 the proportion of patients with elevations in both CRP and fibrinogen was slightly higher (by approximately 1-2%) in the laquinimod group compared to placebo. At month 2 this difference was statistically significant (approximately 4.1% vs. 2.3%) and this was considered clinically relevant. Long-term data up to 4 years are available and revealed that at month 48, the percentage of patients with potentially clinically significant CRP elevation increased to 5.4% in the laquinimod group. In the pivotal studies, the incidence of fibrinogen level considered potentially clinically significant (> 6g/l), was higher in the laquinimod group compared to placebo (5.5% vs. 2.6%). Maximal fibrinogen did not exceed the >2.5xULN and was 9.0 g/l in the laquinimod group and 8.4 g/l in the placebo group at any time until month 24. Overall, mean duration of elevated fibrinogen or CRP tended to be longer in the laquinimod group compared to placebo.

In 72% of the potentially clinical significant CRP elevations there was an intercurrent AE in the laquinimod group compared to 91% in the placebo-group. There were also some patients with CRP increase and at the same time without a concurrent AE in both placebo and laquinimod groups. There were also patients with AEs in both groups that could not explain the long duration of CRP-increase (e.g. a patient on laquinimod with nasopharyngitis and duration of CRP-increase for 170 days). Laquinimod was also associated with a higher incidence of elevated fibrinogen levels, but according to the presented analyses, these elevations were accompanied by clinical findings in 33% for laquinimod group and 46% for placebo group.

Slightly more patients with back/neck pain in the laquinimod group (n=4) as compared to the placebo group (n=2) had both increased CRP and fibrinogen, nevertheless these were small numbers of patients. Regarding appendicitis, for at least 4 subjects in the laquinimod group who had appendicitis and for whom laboratory data were available during the visits of the appendicitis event, concurrent elevations in CRP and fibrinogen were observed (with no record of elevated CRP or fibrinogen prior to the appendicitis report). As suggested by the applicant these elevations are expected, as CRP and fibrinogen are acute phase reactants and appendicitis is an inflammatory process, thus association cannot be excluded between the events, contrary to applicant conclusion.

Changes that concerned ALT and AST levels occurred also in higher frequency in the laquinimod group compared to placebo (31% and 17.4% vs 18.3% and 9.5%). In cohort 4, shifts to abnormally high fibrinogen and cholesterol as well as shifts to abnormally low calcium and creatinine in a considerable number of patients (more than 40%) have been reported during long-term treatment.

Electrocardiogram (ECG)

One thorough QT study was performed by the applicant, as requested, comparing two doses of laquinimod (0.6 mg and 1.2 mg) to placebo and moxifloxacin. One hundred and eighteen subjects (59%) reported one adverse event, mainly headache, all of mild to moderate intensity. It seems that no signal of laquinimod effect on heart rate has been detected in this study; nevertheless, it is

to be noted that T wave changes occurred in 5 subjects in the laquinimod groups (3 in 1.2 mg and 2 in 0.6 mg group) compared to 2 changes in the placebo group. The clinical relevance is unknown.

The number of subjects with abnormal ECG was comparable between placebo (0.5%) and laquinimod groups (0.3%; 3 subjects: one experiencing sinus bradycardia at M3, normal at M6, and 2 subjects with first degree atrioventricular (AV) block and PR prolongation).

Vital signs

No signal emerged from the review of vital signs such as blood pressure, heart rate and weight in cohort 1.

2.6.5. Safety in special populations

No trials have been performed in any special multiple sclerosis patient populations. Patients with significant cardiovascular, pulmonary, gastrointestinal, psychiatric, neurologic (other than MS), renal impairment, hepatic conditions as well as HIV patients were excluded from the pivotal trials.

Data for patients with renal, hepatic impairment and other special populations (paediatric, elderly) are discussed under clinical pharmacology (see 2.4.4).

In MS studies, females of child bearing potential were required to practice effective contraception. Nonetheless, 74 pregnancies have been reported in the laquinimod development programme, of which 43 were reported in subjects exposed to laquinimod (38 female patients treated and 5 male subjects reporting pregnancies of partners) as of 1 September 2013. Nineteen pregnancies were reported in the placebo group and 12 in the Avonex group. Of these 38 pregnancies in laquinimod-treated female patients, the outcome is unknown in 3 cases (ongoing pregnancies or no information), 6 resulted in spontaneous abortions, 16 normal newborns, 2 obstetric or perinatal complications (one case of premature baby and intrauterine infection, one case low birth weight and neonatal asphyxia), 1 case of microcephaly (later corrected to borderline head circumference) and 10 induced abortions. Concerning the 10 induced abortions reported, reason of induced abortion is unknown in 1/3 of cases (3 cases) and for the 7 remaining cases, regarding the gestational age at abortion (< week 9), the applicant assumed that abortions were the result of personal choice and not of evidence of fetal defects.

Subgroup analyses were performed to evaluate the safety profile of laquinimod according to demographic characteristics. In general the AE profile in MS did not depend on gender or age, except for ALT increase. Whilst two third of female and one third of male were enrolled in MS studies, the incidence of common AEs was higher in laquinimod groups for both, males and females. However the ALT increase was a more notable event for male than for female (11.6% vs 3.3%). There was no signal of drug abuse potential or overdose with laquinimod.

2.6.6. Safety related to drug-drug interactions and other interactions

No additional data were presented other than those presented in the clinical pharmacology studies.

2.6.7. Discontinuation due to adverse events

In the pivotal studies, the overall incidence of AEs leading to early termination was higher in the laquinimod 0.6 mg group than the placebo group (6.4% vs. 4.7%). The most frequent AEs leading to early termination with a higher incidence in the laquinimod group than the placebo group included abdominal pain (overall 2.0% vs. 0.1%), AEs of elevated liver enzymes (overall increased ALT and GGT, increased transaminases and abnormal liver function test : 2.0% vs. 1.6%),

headache (0.5% vs 0%) and diarrhoea (0.4% vs 0%). These findings were confirmed by the other analysed safety populations.

In the long-term analysis AEs leading to early termination with a calculated event rate >0 were: pyrexia, pulmonary tuberculosis, asthma, nail discolouration, and thrombocytopenia, and increased ALT, GGT and aspartate aminotransferase (0.1 reports/100 subjects years).

2.6.8. Post marketing experience

No post-marketing data are available.

2.6.9. Additional analyses

The applicant analysed the AE profile of laquinimod in relation to the safety data of roquinimex, a pharmaceutical compound, structurally related to laquinimod. Serious toxicities (including myocardial infarction, pericarditis and pleuritis, venous thrombotic events) occurred during Phase III trials with roquinimex and led to early termination of these trials. The mechanism by which roquinimex caused these events was not identified, but these were assessed by the applicant as possible manifestations of a systemic inflammatory response, an assessment which was also supported quite extensively by roquinimex non-clinical findings.

Pericarditis and pleuritis

In roquinimex trial, pericarditis was reported in 19 subjects (2%) and pleuritis was observed in 8 subjects (0.8%).With regards to laquinimod cohorts, one case of pleuritis with pleural effusion was reported in healthy 61 year-old male with traumatic fracture of rib on the same side. A relationship with the study drug was not excluded by the applicant. Two cases of pericarditis were reported in laquinimod group. In one case the diagnosis of pericarditis was questionable, and in the second case causality for laquinimod is doubtful.

Myocardial infarction

Although low, the incidence of ischemic heart disease was higher in the laquinimod group compared to placebo (0.6% vs 0.1%) in the pivotal studies. Overall, 20 reports in 15 subjects (0.6%) reported ischemic heart disease including 2 subjects that were diagnosed with myocardial infarction in the laquinimod group. Two out of 9 deaths in the laquinimod group were due to cardiovascular failure (sudden death within 5 hours post treatment) and myocardial infarction (after 5 months of treatment), respectively. Even if the applicant considers that ischaemic heart disease (IHD) does not constitute a safety signal for laquinimod, the relationship could not be completely excluded.

Ten definite cases of myocardial infarction were reported in laquinimod group including 9 cases where cardiovascular risk factors including obesity, hypertension, hypercholesterolemia, diabetes, smoking, family history of IHD, and evidence of IHD were reported. Indirect comparison to the Clinical Practice Reasearch Datalink (CPRD) database found no signal of increased incidence of MI with laquinimod exposure over time, however such analysis is of limited relevance due to its methodology.

Venous Thrombotic Events

Whilst venous thrombotic events were identified as safety concern for roquinimex, a single case of Budd Chiari syndrome in a 44 year-old female with factor V Leiden mutation occurred with laquinimod.

The applicant performed a literature search to retrieve the incidence rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) and compare them to the incidence rates of these

events found in the laquinimod development program. A recent study conducted by Christensen *et al.* reported that the incidence rates of DVT and PE in the MS population were 2 per 1,000 person-years (95% CI: 1.41– 2.76) and 0.94 per 1,000 person-years (95% CI: 0.56–1.49), respectively. In the laquinimod development program, the incidence rates of DVT and PE among patients exposed to laquinimod were 0.67/ 1000 subject years and 0.17/1000 subject years, respectively. Thus, these results indicate that the incidence rates of DVT and PE among patients exposed to laquinimod were lower than the rates reported in MS patients. Available data to date did not suggest an increased rate of any thrombotic events.

2.6.10. Discussion on clinical safety

The safety profile of laquinimod has been characterised with data from a total of 2,632 MS patients that were exposed to different doses of laquinimod, with the majority of the patients (more than 2,300) having taken the intended dose of 0.6 mg. In the pivotal studies (cohort 1), 983 patients in the laquinimod 0.6 mg group had total mean exposure of 1.8 years, that was comparable to placebo. In addition, 442 patients were included in active comparator arm (Avonex) with similar mean exposure. These exposure data were considered adequate and the CHMP considered cohort 1 as representative of the AE profile of laquinimod in the intended MS population.

In the pivotal studies, the incidence of adverse events was the highest in the system organ class of Infections and Infestations and comparable between two groups, laquinimod and placebo (48.7% vs 47%). The incidence of AEs was higher in the group laquinimod for SOC Musculoskeletal and Connective Tissue Disorders (30.4% vs 25.4%), SOC Investigations (27% vs 20.8%), SOC gastrointestinal disorders (26.9% vs 22.6%), SOC Metabolism disorders (5.3% vs 2.9%), Neoplasm (4.6% vs 2.7%) compared to placebo.

Although the incidence of severe infections was low (1.1 reports/100 subject years), numerically some serious infections have been observed more frequently in the laquinimod group compared to placebo in the pivotal studies: appendicitis (6 vs. 1) and cellulitis (3 vs. 0). Appendicitis was partially accompanied by peritonitis, mainly due to delayed time to surgery. Non-SAE urinary tract infections were slightly increased in the laquinimod group compared to placebo.

The number of SAEs was similar in cohort 1 between the laquinimod and the placebo group: 9.4% vs 8.9%. However, the number of appendicitis, as previously described, was significantly higher in the laquinimod. In cohort 3, in all MS patients ever exposed to laquinimod, 12 appendicitis and 6 infectious peritonitis were noted. Based on animal findings, a pro-inflammatory mechanism underlying these events cannot be excluded.

The safety profile indicated liver enzyme elevations, inflammatory markers increased (e.g. CRP, fibrinogen), back and neck pain, haematological changes, appendicitis as important identified risks, in addition to the interaction with CYP3A4 inhibitors/inducers that was observed in clinical pharmacology.

Laquinimod treatment was associated with elevations from normal to Grade 1 for AST, ALT, GGT and normal to grade 1 and 2 (up to 5x ULN) for ALT and GGT. Shifts to grade 3 and 4 were uncommon and reported with a similar incidence in the placebo and laquinimod groups, apart from GGT increase grade 3 which was slightly more frequent in the laquinimod group. Severe hepatic AEs were reported in a slightly higher frequency in the laquinimod group (1%) compared to placebo (0.5%), however these were related to only liver enzyme elevations with no specific clinical pattern. Liver-related serious AEs were uncommon, and reported with similar incidence and types in the laquinimod and placebo groups. In addition no case of 'hepatitis' was reported with laquinimod (versus one case in placebo group); increased blood bilirubin was reported by more subjects in the placebo group (0.6%) than in the laquinimod 0.6 mg group (0.1%); no Hy's law or

liver failure cases were reported throughout the laquinimod clinical development program. Overall, the effect of laquinimod on the liver appeared to be limited to liver enzyme elevations, but the mechanism underlying these events is unknown. Mostly mild, asymptomatic liver enzyme elevations (AST, ALT and GGT) were reported that generally occurred within 6 months after initiation of treatment Overall in the pivotal trials, 4.7% of laquinimod treated subjects reached clinically significant [> 3x ULN] levels of ALT. This was more notable for male than for female in laquinimod treated subjects. In 74% of subjects who had elevated levels of ALT on laquinimod, ALT decreased to within the normal range while on laquinimod.

The higher incidence of AEs in laquinimod group for SOC Musculoskeletal and Connective Tissue Disorders as compared to placebo group was associated with a higher frequency of back and neck pain in the laquinimod group in the first months of treatment. After 3 months of laquinimod treatment, use of anti-inflammatory and anti-rheumatic medications was similar in the laquinimod and placebo groups. However some peaks in the use of these drugs occurred again at 9 and 15 months of treatment by laquinimod that seems to be correlated to increases in musculoskeletal AEs in the laquinimod group between 9 and 18 months of treatment, whereas a decrease was observed between 6 and 9 months. Thus, the applicant's claim that the higher incidence of musculoskeletal AEs reported in the laquinimod group appeared to be limited to the first 3 months of treatment after which the incidence declines and becomes similar to the placebo group, was not agreed by the CHMP. In addition, in cohort 5, back pain continued to be commonly reported with laquinimod (8.9 reports/100 subjects/year), supporting an effect not limited to the first weeks of treatment.

Inflammatory markers (CRP, ESR, fibrinogen) were increased in healthy volunteers in phase I studies. In pivotal studies, fibrinogen (40% vs. 28%) and WBC levels (27% vs. 15%) clearly increased to values above ULN in a higher percentage of patients with laquinimod in comparison with placebo. Increase of fibrinogen was apparent from month 1. The increase in WBC was generally mild and was not considered clinically significant (no grade 3 leucocytosis occurred). Nevertheless in the extension study MS-LAQ-302E there was one death due to acute leukemia with disseminated intravascular coagulation and cerebral haemorrhage, accompanied by anemia and thrombocytopenia. In contrast, mean CRP elevations (and also percentage of potentially clinically siginificant CRP) were similar in the laquinimod and placebo group in cohort 1. Nevertheless until month 15 the proportion of patients with elevations in both CRP and fibrinogen was slightly higher (by approximately 1-2%) in the laquinimod group compared to placebo. At month 2 this difference was statistically significant (approximately 4.1% vs. 2.3%) and this was considered clinically relevant. Long-term data up to 4 years are available and revealed that, at month 48, the percentage of patients with potentially clinically significant CRP elevation increased to 5.4% in the laquinimod group. In the pivotal studies, the incidence of fibrinogen level considered potentially clinically significant (> 6g/l), was higher in the laquinimod group compared to placebo (5.5% vs. 2.6%). Maximal fibrinogen did not exceed the >2.5x ULN and was 9.0 g/l in the laquinimod group and 8.4 g/l in the placebo group at any time until month 24. Overall, mean duration of elevated fibrinogen or CRP tended to be longer in the laquinimod group compared to placebo. The CHMP acknowledged that the inflammatory markers (including also WBC count) are not specific and that their measurement is supportive in the context of inflammatory diseases. The interpretation of markers in the context of MS as underlying inflammatory disease or in the case of relapse is therefore much more complicated. Based on the presented data, a CRP increase by laquinimod could be specific (e.g. infections) but also unspecific/not identified and could be sign of an undetected inflammatory process. In case of a pro-inflammatory process, some uncertainties remain with regard to possible deterioration of MS and long-term carcinogenic effect. Whereas, no evidence of increased risk for malignancy has been found based on the available clinical data of laquinimod at the present time, long term data are limited to ascertain the level of this risk. Since an increase in pro-inflammatory markers has been observed in animal studies (dogs) and

considering the available clinical findings, the CHMP considered that increased CRP is a safety concern for laquinimod and further data are required to better understand this identified risk and adverse events related to a possible pro-inflammatory mechanism of laquinimod.

Haematological toxicity was relevant with laquinimod when compared to placebo, with mostly increase in leucocyte levels and decrease in red blood cells and platelets. Two cases of anaemia and one case of leukemia in the laquinimod group were considered as serious.

Although low, the incidence of ischemic heart disease was higher in the laquinimod group compared to placebo (0.6% vs 0.1%) in the pivotal studies. Overall, 20 reports in 15 subjects (0.6%) reported ischemic heart disease including 2 subjects that were diagnosed with myocardial infarction in the laquinimod group. Two out of 9 deaths in the laquinimod group were due to cardiovascular failure (sudden death within 5 hours post treatment) and myocardial infarction (after 5 months of treatment), respectively. Patients with significant cardiovascular conditions were excluded from the pivotal trials. On this basis and considering the safety data from roquinimex, a structurally related product, the CHMP considers cardiotoxicity as a potential risk for laquinimod.

Malignant tumours have been reported in 26 patients (0.6%) treated with laquinimod in all clinical studies; 6 breast carcinomas including one metastatic breast cancer (3 in cohort 1, all in ALLEGRO and no case in BRAVO; 1 additional case of breast cancer in study LAQ/5062 has been reported in laquinimod group. One breast cancer was reported in placebo group). In cohort 1, 10 (1%) patients in the laquinimod group vs 6 (0.6%) patients with placebo experienced a malignant tumour [p=0.2944, 95% CI (-0.37, 1.21)]. In addition to 3 cases of breast cancer, sporadic cases of glioblastoma (1), lung neoplasm malignant (1), lymphoma (1), oesophageal adenocarcinoma (1), squamous cell carcinoma (1), thyroid cancer (1) were reported. One case of thyroid cancer has been reported in BRAVO study in a 32.5 year-old female after 189 days of laquinimod treatment. The AE was considered as moderate and not related to study drug; the subject recovered. One case of thyroid cancer occurred in Avonex group. Concerning skin malignancy, 2 cases (basal cell carcinoma, squamous cell carcinoma) occurred in cohort 1 compared to one case (basal cell carcinoma) in the placebo group. In total, in cohort 3 (all patients treated with laquinimod), 7 subjects suffered from skin malignancies: basal cell carcinoma (4), malignant melanoma (1) and squamous cell carcinoma (2). Comparison of malignancies incidences with SEER (age-adjusted SIR=1.4; 95% CI [0.90-2.08])and CPRD (age-adjusted SIR=1.397; 95% CI [0.97-1.95] for general population ; age-adjusted SIR=1.088; 95% CI [0.75-1.52] for MS population) databases did not demonstrate an increase in malignant tumors with laquinimod therapy. For breast cancer, incidence comparison did not demonstrate an increased risk with laquinimod therapy when compared to SEER and GPRD databases. According to the applicant, malignant tumours are not considered to constitute a safety signal of concern at the present time. However, from the CHMP viewpoint, the number of events to date and duration of follow-up is too limited to definitively exclude a relationship and further long term data are required to ascertain the level of this potential risk. In addition, based on available pre-clinical data, there remain relevant uncertainties on the potential risk for malignancies. These uncertainties currently represent an important concern with long term use of laquinimod (see 2.3.6).

In MS studies, females of childbearing potential were required to practice effective contraception. Nonetheless, 74 pregnancies have been reported in the laquinimod development programme, of which 43 were reported in subjects exposed to laquinimod (38 female patients treated and 5 male subjects reporting pregnancies of partners) as of 1 September 2013. The CHMP is of the opinion that a pregnancy rate of 2 % of the exposed women in the 2 pivotal studies in MS (ALLEGRO and BRAVO) and their extensions, despite all the measures to avoid pregnancy is of concern. The applicant explained this high rate of pregnancies by the considerable fraction of the population included in clinical trials which consisted of females of childbearing potential and the possible

demographic/cultural attitudes based on the fact that most of the pregnancies were reported in Russia, Ukraine, Poland and Bulgaria. The lack of data on these unexpected pregnancies (e.g. lack of reason for induced abortions in one third of the cases) did not allow a proper evaluation of the level of this risk by the CHMP. The potentially delayed effects of laquinimod seen in preclinical studies (notably on puberty and fertility), which would not be noticeable at birth are of important concern for the CHMP, especially considering the intended use in MS patients (mostly females of child bearing potential) and the absence of an *in vivo* interaction study investigating the potential effect of laquinimod on the pharmacokinetics of oral contraceptives.

Due to the potential of formation of adducts seen in preclinical studies, the CHMP considered that drug hypersensitivity reactions should be considered as a potential risk for laquinimod, given its intended chronic use.

2.6.11. Conclusions on the clinical safety

The CHMP concluded the following:

Laquinimod is associated with a number of important identified risks (e.g. liver enzyme elevations, and haematological changes which were mostly mild, inflammatory markers increased (e.g. fibrinogen, CRP), back and neck pain, appendicitis) and potential safety concerns (carcinogenicity, teratogenicity, cardiotoxicity, hypersensitivity). While the currently available clinical data did not show evidence of an increased risk of malignancies, immunosuppression or infections, there remain significant uncertainties on the mechanism of action of laquinimod, in particular with regards to immunomodulator or immunosuppressant potential, and on the risks associated with long-term use (i.e. cancer, infections, inflammation), contributing to the insufficient characterization of the safety profile of laquinimod in the intended patient population.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 2.2, the PRAC considered by consensus that the risk management system for Laquinimod (Nerventra) in the treatment of relapsing remitting multiple sclerosis (RRMS) is not acceptable in the current format since the documented proposals for pharmacovigilance activities and risk minimisation measures are not sufficiently robust and should be revised.

The PRAC commented that serious concerns remain on possible risk minimization given the safety profile of laquinimod, notably regarding carcinogenicity for which there are no obvious risk minimisation measures and regarding potential endocrine disrupting effects, for which the effectiveness of the pregnancy preventive measures is questionable because of the high frequency

of pregnancy experienced in the context of the clinical development programme and in reason of the delayed effect after in utero exposure.

Specifically:

- the PRAC, was of the opinion that the proposed post-authorisation PhV development plan is insufficient to identify and characterise the risks of the product.

- the PRAC was informed of the conclusions of the discussion of the Safety Working Party on the meeting of 3 December 2013 and expressed very serious concerns on the laquinimod safety profile, in particular because of the potential long term effects and of the potential delayed effects with respect to the following hazards:

- Carcinogenicity
- Delayed effect (endocrine disrupting potential effect – need of a long follow up for infants exposed in utero)
- Important information missing (primary mechanism and DDI study with oral contraceptives)

It should be taken into account that there are no obvious risk minimisation measures for the carcinogenic risk. Furthermore the experience with the clinical development programme of laquinimod has shown poor control of pregnancy in the target population. In such a context the effectiveness of pregnancy prevention measures for the teratogenic and long-term endocrine disrupting risks is doubtful.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 32: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Liver enzyme elevations Back and neck pain* Appendicitis* Fibrinogen increased* CRP increased* Haematological changes: • WBC increased • Haemoglobin decreased/Anaemia • Platelets decreased Interactions of laquinimod with: • CYP3A4 strong or moderate Inhibitors • CYP3A4 strong inducers • CYP1A2 substrates
Important potential risks	Teratogenicity (urogenital malformations) Carcinogenicity Hypersensitivity Cardiotoxicity (MI, acute coronary syndrome)
Missing information	• Paediatric patients (below 18) • Elderly patients • Pregnancy • Breastfeeding

Summary of safety concerns	
	• Patients with renal impairment • Patients with liver impairment • Long-term safety

* Wording about a possible role for inflammation has been added as “potential mechanism” for these risks

- **Pharmacovigilance plans**

Table 33: Ongoing and planned studies in the PhV development plan

Activity/Study title(type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started	Date for submission of interim or final reports (planned or actual)
PASS, A long term, prospective, observational study [category 1]	To collect long term safety data, and to further characterise identified and potential safety concerns	Liver enzyme elevations, back and neck pain, appendicitis; Drug-drug interactions; teratogenicity; Missing information on paediatric,elderly, pregnancy, breastfeeding, patient with renal or hepatic impairment, long term safety	Planned	Final study report: Within 12 months from end of data collection.
Pregnancy registry [category 1]	A pregnancy registry to characterise and assess pregnancy outcomes in clinical practice should a pregnancy occur, to be incorporated into the company’s safety database.	Potential risk: teratogenicity; missing information: pregnancy	Planned	Periodic overview in PSUR/PBRER; Final study report: Within 12 months from end of data collection
DDI study [category 1]	A randomized, double-blind, placebo-controlled, crossover study to assess the effect of Laquinimod 0.6 mg on the PK and PD of oral contraceptives (EE+LNG) in healthy young female volunteers		Planned	Final study report: Within 6 months after CHMP opinion

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

- **Risk minimisation measures**

Table 34: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Liver enzyme elevations	Labeling information (SmPC section 4.4 and 4.8, Package Leaflet)	None
Back and neck pain	Labeling information (SmPC section 4.8, Package Leaflet)	None
Appendicitis	Labeling information (SmPC section 4.8, Package Leaflet)	None
Fibrinogen and CRP increase	Labeling information (SmPC section 4.8, Package Leaflet)	None
Haematological changes (anaemia, increase white blood cells, decreased platelets)	Labeling information (SmPC section 4.8, Package Leaflet)	None
Interaction with; CYP3A4 Strong or moderate inhibitors CYP3A4 strong Inducers CYP1A2 Substrates	Labeling information (SmPC sections 4.4 and 4.5, Package Leaflet)	None
Teratogenicity (urogenital malformations)	Labeling information (SmPC sections 4.3, 4.6, and 5.3, Package Leaflet)	Need to use effective contraception and avoid pregnancy will be communicated as follows: ☐ DHPC ☐ Educational materials ☐ Other material provided to patients or HCPs ☐ By field representatives ☐ By medical activities
Carcinogenicity	Labeling information (SmPC section 5.3)	None
Hypersensitivity	In the absence of a specific safety signal relating to hypersensitivityno risk minimisation activities are proposed at this time	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardiotoxicity (MI, acute coronary syndrome)	In the absence of a specific safetysignal relating to cardiotoxicity no risk minimisation activities are proposed at this time	None
Paediatric patients	Labeling information (SmPC section 4.2, Package Leaflet)	None
Elderly patients	Labeling information (SmPC section 4.2, Package Leaflet)	None
Pregnancy	Labeling information (SmPC sections 4.3, 4.6, and 5.3, Package Leaflet)	Need to use effective contraception and avoid pregnancy will be communicated as follows: ☐ DHPC ☐ Educational materials ☐ Other material provided to patients or HCPs ☐ By field representatives ☐ By medical activities
Breastfeeding	Labeling information (SmPC sections 4.6 and 5.3, Package Leaflet)	None
Patients with renal impairment	Labeling information (SmPC sections 4.2, 4.4, and 5.2, Package Leaflet)	None
Patients with liver impairment	Labeling information (SmPC sections 4.2, 4.4, and 5.2, Package Leaflet)	None
Long term safety	Labeling information (SmPC section 4.8, Package Leaflet)	None

The applicant presented the details of their proposed Risk Management at the Oral Explanation held on 17 December 2013. No major changes to the pharmacovigilance plan and risk minimisation measures were noted by the CHMP.

The CHMP, having considered the latest PRAC advice and the data submitted in the application is of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level.

2.9. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

Laquinimod is a novel orally administered therapy, intended for the treatment of patients suffering from relapsing-remitting multiple sclerosis. Laquinimod is claimed to fulfil an unmet medical need for an oral agent by acting as an immumodulator with CNS protective activity that is at least as effective as the currently available first-line treatments. The exact mechanism of action of laquinimod is unknown but it has shown beneficial effects in various types of experimental autoimmune encephalomyelitis models as well as in cuprizone induced demyelination, all accepted animal models of multiple sclerosis.

Prevention and/or modification of relapse features as well as prevention or delay of the accumulation of disability are meaningful goals in the treatment of relapsing multiple sclerosis.

Two large phase 3 pivotal studies (ALLEGRO, BRAVO) over two years were conducted. Both used relapse rate as a primary outcome measure. Time to confirmed EDSS progression was a key secondary endpoint.

In ALLEGRO study, a statistically significant effect of laquinimod 0.6 mg compared to placebo was demonstrated for the annualised relapse rate (p=0.0024). Whilst this result was consistent with other efficacy endpoints related to relapses and supported by sensitivity analyses, the reduction in ARR for laquinimod over placebo was modest, 23% over 24 months (RR= 0.770, 95% CI: 0.650, 0.911). In BRAVO study including an active comparator (Avonex), laquinimod 0.6 mg dose failed to show a statistically significant effect as compared to placebo on the ARR (RR=0.823, 95% CI: 0.664, 1.020, p=0.0746) reflecting a reduction of ARR of 17.7%. In contrast, comparison of the Avonex treatment arm with placebo yielded a risk ratio of 0.741 (95% CI: 0.596; 0.920, p=0.0067), demonstrating a 25.9% reduction in the annualized relapse rate. The pre-specified sensitivity analyses were consistent with the primary analysis.

Due to the imbalances observed at baseline for mean T2 lesions volume and proportion of subjects with GdE T1 lesions ≥1 across treatment groups, additional post-hoc analyses were performed using these MRI parameters as covariates in a corrected model. Such corrected analysis resulted in an increase in magnitude of effect of laquinimod 0.6 mg compared to placebo on ARR (RR=0.787, 95% CI: 0.637, 0.972) of statistically significance (p=0.0264) however this corrected result was still suggesting a modest reduction in ARR of 21.3% in patients treated with laquinimod 0.6 mg in BRAVO study. Importantly, whilst these baseline imbalances were also present in the Avonex group, treatment effect of Avonex over placebo was statistically significant (p=0.0067) in the primary model due to an observed larger treatment effect size of 25.9% reduction in the ARR (RR= 0.741, 95% CI: 0.596, 0.920). Numerically, the results on ARR were in favour of Avonex as compared to laquinimod. In addition, laquinimod failed to show statistical significance over placebo on the time to first relapse (HR=0.813, 95% CI: 0.653, 1.014); p=0.0659), questioning the sensitivity of the results observed for the ARR, after the baseline corrected analysis.

In a meta-analysis including the 2 pivotal studies and the phase II study LAQ/5062, an effect of laquinimod on ARR was demonstrated suggesting a 21% reduction for laquinimod versus placebo (RR=0.79, 95% CI : 0.69,0.89, p=0.0002). This result was consistent with the initially submitted pooled analysis of the two pivotal studies (reduction of 21.4% in ARR, p=0.0005) and is considered modest.

ALLEGRO study showed that laquinimod delayed the time to 3-month confirmed disability progression, with a statistically significant reduction of 36% over placebo (HR= 0.641; 95% CI: 0.452, 0.908; p=0.0122). BRAVO study failed to demonstrate such effect with a lower risk reduction of 31.3% over placebo (HR=0.687, 95% CI: 0.462, 1,020; p=0.0628). However, the CHMP noted that results on disability progression were numerically in favour of laquinimod as compared to Avonex, although the 95% CIs for each of the outcomes were overlapping. In addition, results from the pooled analysis using both pivotal studies, demonstrated a 34% reduction in the risk for 3-month confirmed disease progression (HR = 0.66, p=0.002). When adding the data from the phase II study LAQ/5062 in this pooled analysis, the effect on disability remain with a reduction of around 32% in the risk of disability progression confirmed at 3 months, although the CHMP noted that study LAQ/5062 on its own failed to show an effect on disability (HR= 1.12, 95% CI: 0.33, 3.74). A 44% reduction of disability progression confirmed at 6-months was also observed based on post-hoc analysis of pooled data provided by the applicant from both pivotal studies, data from study LAQ/5062 was not included in this analysis due to its short duration.

Different MRI endpoints related to clinical activity and for some to long term clinical outcome (cumulative numbers of Gd enhancing lesions, new/enlarging T2 lesions for ALLEGRO, brain atrophy measure for BRAVO) were also used as secondary efficacy endpoints.

In ALLEGRO study, there was a statistically significant effect of laquinimod as compared to placebo on mean adjusted number of T1 Gd-enhancing lesions (RR=0.629,95% CI: 0.488, 0.809, p=0.0003) showing a reduction of 37% in the mean rate of developing T1 Gd-enhancing lesions on laquinimod 0.6 mg compared to placebo. A statistically significant treatment effect of laquinimod 0.6 mg over placebo was also shown on the cumulative number of New/Enlarging T2 lesions (RR=0.704,95% CI: 0.584, 0.849, p=0.0002) indicating a reduction of 30% in the mean rate of developing New/Enlarging T2 lesions on laquinimod 0.6 mg compared to placebo.

In the meta-analysis using the two pivotal studies ALLEGRO and BRAVO, and the phase IIb study LAQ/5062, a treatment effect on GdE T1 lesions was observed with a rate ratio of 0.68 suggesting a reduction of 32% as compared to placebo. This effect was statistically significant (p<0.00001). The effect on new T2 lesions was also statistically significant with a reduction of 27% versus placebo (Rate Ratio of 0.73, p<0.00001). Regarding brain atrophy, the effect of laquinimod was statistically significant as compared to placebo (difference of 0.31 in % brain volume change, p<0.00001).

The supportive studies suggested maintenance of the effect of laquinimod during long term treatment regarding ARR and disability progression.

Uncertainty in the knowledge about the beneficial effects.

Limited data were provided regarding the pharmacodynamic effects of laquinimod in humans. Given the mechanism of action has not been sufficiently investigated and the molecular target remains unknown, no conclusion could be drawn on the clinical pharmacology of laquinimod.

The optimal dose had not been defined because 0.6 mg dose was the sole dose tested in the phase III studies. In the absence of data using higher doses than 0.6 mg, the CHMP concluded that the

dose reponse effect of laquinimod has not been sufficiently evaluated to determine the optimal dose in the intended population.

Limited data after discontinuation of laquinimod treatment are available to evaluate the potential risk of rebound effect.

The mechanism of action of laquinimod is unknown and the rather modest effect on relapses questions the suitability of laquinimod as treatment for the broad population with relapsing remitting multiple sclerosis (RRMS) patients.

Risks

Unfavourable effects

Liver enzyme elevations, inflammatory markers increased (e.g. CRP, fibrinogen), back and neck pain, haematological changes, appendicitis, interaction with CYP3A4 inhibitors/inducers have been identified as important risks.

The effect of laquinimod on the liver appeared to be limited to liver enzyme elevations, but the mechanism underlying these events is unknown. Mostly mild, asymptomatic liver enzyme elevations (AST, ALT and GGT) were reported that generally occur within 6 months after initiation of treatment. Overall in the pivotal trials, 4.7% of laquinimod treated subjects reached relevantly significant [> 3xULN] levels of ALT. This was more notable for male than for female in laquinimod treated subjects. In 74% of subjects who had elevated levels of ALT on laquinimod, ALT decreased to within the normal range while on laquinimod.

Inflammatory markers (CRP, ESR, fibrinogen) were increased in healthy volunteers in phase I studies. In pivotal studies, fibrinogen (40% vs. 28%) and WBC levels (27% vs. 15%) clearly increased to values above ULN in a higher percentage of patients with laquinimod in comparison with placebo. Increase of fibrinogen was apparent from month 1. In the pivotal studies, until month 15, the proportion of patients with elevations in both CRP and fibrinogen was slightly higher (by approximately 1-2%) in the laquinimod group compared to placebo. At month 2 this difference was statistically significant (approximately 4.1% vs. 2.3%) and was considered clinically relevant. Long-term data up to 4 years are available and revealed that, at month 48, the percentage of patients with potentially clinically significant CRP elevation increased to 5.4% in the laquinimod group. In the pivotal studies, the incidence of fibrinogen level considered potentially clinically significant (> 6g/l), was higher in the laquinimod group compared to placebo (5.5% vs. 2.6%). Maximal fibrinogen did not exceed the >2.5x ULN; maximal fibrinogen was 9.0 g/l in the laquinimod group and 8.4 g/l in the placebo group at any time until month 24. Overall, mean duration of elevated fibrinogen or CRP tended to be longer in the laquinimod group compared to placebo.

Haematological toxicity was relevant with laquinimod when compared to placebo, with mostly mild increases in leucocyte levels and decreases in red blood cells and platelets. Two cases of anaemia and one case of acute leukemia in the laquinimod group were considered as serious.

Uncertainty in the knowledge about the unfavourable effects

There is currently a considerable level of uncertainty on the carcinogenic potential of laquinimod. The pharmacology of laquinimod is unclear thus making difficult the full appreciation of any pharmacology-driven proliferative or metaplastic processes. Based on pre-clinical data, a potential carcinogenicity relative to oral cavity and uterus could not be ruled out. There is a lack of mechanistic data to exclude these potential risks in humans. A comparison between laquinimod,

TCDD and DLCs with regard to major non-neoplastic toxicity, taking all repeat dose toxicity studies of laquinimod into consideration, showed that, although the histopathological findings did not show a complete overlap, it can be concluded that laquinimod shares a general pro-inflammatory, hyperplastic (forestomach, oral cavity and kidney), hepatic and thyroid toxicity profile with TCDD and DLCs. Laquinimod shared also the dioxins class effect of being a potent inducer of CYP1A2. Considering complexity and diversity of AhR-mediated toxic responses, complete overlap between laquinimod and TCDD is not expected. Moreover, striking similarities were observed in the malformation patterns (see below) comparing the teratogenic effects of laquinimod and TCDD in rat, and a mechanism involving the AhR-ER cross-talk pathway could not be excluded. Significant uncertainties also remain with regards to the unknown immunomodulator or immunosuppressant potential, and the potential risks associated with long-term use (i.e. cancer, infections, inflammation), also contributing to the insufficient characterization of the safety profile of laquinimod in the intended patient population, although the currently available clinical data did not show evidence of an increased risk of malignancies, immunosuppression or infections.

Malignant tumours have been reported in 26 patients (0.6%) treated with laquinimod in all clinical studies; 6 breast carcinomas including one metastatic breast cancer (3 in cohort 1, all in ALLEGRO and no case in BRAVO; 1 additional case of breast cancer in study LAQ/5062 have been reported in laquinimod group. One breast cancer was reported in placebo group). In cohort 1, 10 (1%) patients in the laquinimod group vs 6 (0.6%) patients with placebo experienced a malignant tumour (p=0.2944, 95% CI: -0.37, 1.21). In addition to 3 cases of breast cancer, sporadic cases of glioblastoma (1), lung neoplasm malignant (1), lymphoma (1), oesophageal adenocarcinoma (1), squamous cell carcinoma (1), thyroid cancer (1) were reported. One case of thyroid cancer has been reported in BRAVO study in patient treated with laquinimod. One case of thyroid cancer occurred in Avonex group. Concerning skin malignancy, 2 cases (basal cell carcinoma, squamous cell carcinoma) occurred in cohort 1 compared to one case (basal cell carcinoma) in the placebo group. In total, in cohort 3 (all patients treated with laquinimod), 7 subjects suffered from skin malignancies: basal cell carcinoma (4), malignant melanoma (1) and squamous cell carcinoma (2). Overall incidences of malignancies comparison with SEER Database did not demonstrate an increase in malignant tumours with laquinimod therapy. However, the number of events to date and duration of follow-up is too limited to definitively exclude a relationship and further long term data are required to ascertain the level of this potential risk. In addition, based on available pre-clinical data, there remain relevant uncertainties on the potential risk for malignancies .These uncertainties currently represent an important concern with long term use of laquinimod.

Laquinimod was teratogenic in rats, causing hypospadias in females. The most sensitive days for induction of these malformations were days 18-21 of gestation in rats, while exposure before implantation or during lactation did not induce this type of malformation. In F1 males, hypospadias were also reported and other findings consisted of dose-dependent delayed growth which persisted up to adult age in the high dose group, a clear dose-dependent delay in onset of puberty, and decreased fertility in spite of normal sperm parameters. In addition, the absolute weight of prostate and seminal vesicles were decreased at the high dose level. In F1 females, in addition to the urogenital abnormalities, there were also treatment-related effects on growth, delayed vaginal opening at the high dose level only, prolonged estrous cycle length, decreased fertility at the mid and high dose levels. Treatment also had an impact on F2 generation as seen from decreased viability of F2 pups born from F1 females (high-dose group). Most of the findings obtained in F1 animals were suggestive of a hormonal effect of laquinimod. An effect of laquinimod on the AhR-ER cross-talk pathway cannot be excluded as possible mechanism underlying its potential endocrine-disrupting effects. No definitive conclusions could be drawn regarding the teratogenic potential of laquinimod in cynomolgus monkeys. In clinical MS studies, females of child bearing potential were required to practice effective contraception. Nonetheless, 74 pregnancies have been reported in the

laquinimod development programme, of which 43 were reported in subjects exposed to laquinimod (38 female patients treated and 5 male subjects reporting pregnancies of partners) as of 1 September 2013. The potentially delayed effects of laquinimod seen in preclinical studies (notably on puberty and fertility), which would not be noticeable at birth are of important concern for the CHMP, especially considering the intended use in MS patients (mostly females of child bearing potential) and the absence of an *in vivo* interaction study investigating the potential effect of laquinimod on the pharmacokinetics of oral contraceptives.

Although low, the incidence of ischemic heart disease was higher in the laquinimod group compared to placebo (0.6% vs 0.1%) in the pivotal studies. Overall, 20 reports in 15 subjects (0.6%) reported ischemic heart disease including 2 subjects that were diagnosed with myocardial infarction in the laquinimod group. Two out of 9 deaths in the laquinimod group were due to cardiovascular failure (sudden death within 5 hours post treatment) and myocardial infarction (after 5 months of treatment), respectively. Patients with significant cardiovascular conditions were excluded from the pivotal trials. On this basis and considering the safety data from roquinimex, a structurally related product, cardiotoxicity was considered as a potential risk for laquinimod.

Due to the potential of formation of tissue adducts seen in preclinical studies, drug hypersensitivity reactions should be considered as a potential risk for laquinimod, given its intended chronic use.

Benefit-risk balance

Importance of favourable and unfavourable effects

Laquinimod is a novel substance, which is proposed as orally administered treatment of relapsing remitting multiple sclerosis. Currently, a number of MS drugs are available in the EU as oral or parenteral formulations and are indicated either as first line or second line therapies. The exact mechanism of action of laquinimod is unknown and the molecular therapeutic target has not been identified. This lack of knowledge raised serious concerns over the pharmacology of laquinimod, especially given its overall unfavourable toxicity profile (general toxicity, carcinogenicity and reproductive toxicity). Furthermore, the toxicity profile correlates well with what has been shown for AhR agonists such as TCDD (dioxin). The main risks in humans for laquinimod included liver enzyme elevations, inflammatory markers increased (e.g. CRP, fibrinogen), back and neck pain, haematological changes, appendicitis as well as potential risks of carcinogenicity and teratogenicity based on findings in animal studies. There are no obvious risk minimisation measures for the potential carcinogenic risk. The experience with the clinical development programme of laquinimod has shown poor control of pregnancy in the target population. In such a context, the effectiveness of preventive measures for potential teratogenic and long-term endocrine disrupting effects is doubtful. Overall, the proposed risk minimisation measures were considered not able to reduce these risks to an acceptable level. Whilst an effect on disability progression was shown, the effect on relapses was modest at the proposed 0.6 mg dose in the broad adult RRMS population, not outweighing the safety concerns.

Benefit-risk balance

Having considered the efficacy of laquinimod was modest on relapse rate in the adult RRMS population at the proposed dose, notwithstanding the more encouraging effect on disability progression, the CHMP concluded that the benefit-risk balance for Nerventra was negative based on the unknown mechanism of action, the unfavourable overall toxicity profile (general toxicity, carcinogenicity and reproductive toxicity) seen in animal studies with potential human risks that cannot be currently excluded, and the absence of obvious risk minimisation measures to ensure

its safe long term use, for the following indication:

"Nerventra is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) (please refer to section 5.1 for important information on the populations for which efficacy has been established)".

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Nerventra in the treatment of adult patients with relapsing remitting multiple sclerosis, the CHMP considers by consensus that:

the safety and efficacy of the above mentioned medicinal product are not sufficiently demonstrated,

and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The overall toxicity profile (general toxicity, carcinogenicity and reproductive toxicity) seen in animal studies is unfavourable and a potential carcinogenic risk with long term use in humans cannot currently be excluded, especially considering that the mechanism of action of laquinimod has not been sufficiently investigated and is unknown;

- The modest efficacy of laquinimod on relapse rate in adult patients with relapsing remitting multiple sclerosis (RRMS) at the proposed 0.6mg dose does not outweigh the safety concerns, notwithstanding the more encouraging effect on disability progression;

- The absence of obvious measures to address the potential carcinogenic risk and potential endocrine disrupting effects and consequently to ensure the safe long term use of laquinimod in the RRMS population is of concern. There is also evidence of limited effectiveness of the pregnancy preventive measures in clinical studies to address the potential risk of teratogenicity and delayed effects.

Thus, the CHMP concluded that the benefit-risk balance of laquinimod was negative at the proposed dose of 0.6 mg in the treatment of adult patients with relapsing remitting multiple sclerosis.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet and risk management plan cannot be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

5. Re-examination of the CHMP opinion of 23 January 2014

Following the CHMP conclusion that the application for marketing authorisation of Nerventra (laquinimod) was not approvable because of the unfavourable toxicity profile seen in animal studies and the potential carcinogenic risk with long term use in humans that cannot currently be excluded, especially considering that the mechanism of action is unknown; the modest efficacy of laquinimod on relapse rate at the proposed dose and in the intended population and the absence of

obvious measures to address the potential carcinogenic risk and potential endocrine disrupting effects, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the applicant

The applicant presented in writing and at an oral explanation.

A summary of the applicant's detailed grounds for the re-examination of the grounds for refusal is presented below.

Ground for refusal #1: The overall toxicity profile (general toxicity, carcinogenicity and reproductive toxicity) seen in animal studies is unfavourable and a potential carcinogenic risk with long term use in humans cannot currently be excluded, especially considering that the mechanism of action of laquinimod has not been sufficiently investigated and is unknown.

Applicant responses: grounds for appeal- non clinical considerations

A major concern of the CHMP, as indicated in the SWP report, arises from the association of "laquinimod with an overall toxicity profile (general toxicity, immune system effects, reproductive toxicity and carcinogenicity) that correlates well with what has been shown for AhR agonists such as e.g. TCDD." and that "it cannot be excluded that the tumours were caused by the interaction of laquinimod or its metabolites with the AhR receptor. Such mechanism(s) can be of relevance for humans".

Taking into consideration the above, the applicant provided the following arguments:

- Laquinimod is an AhR activator and as such there are some similarities to other AhR-activating compounds, which include drugs and dietary compounds. In the CHMP negative opinion, it was concluded that laquinimod and AhR-activating compounds share molecular effects (CYP1A induction) and some toxicities, and therefore laquinimod may be associated with the toxicities of TCDD and DLC. Based on further analyses (including literature, published data and expert opinions) conducted in order to understand the mechanisms involved, the applicant argued that it is clear that laquinimod is very different from TCDD/DLCs, and does not result in the same toxic effects as this class of compounds. There is a greater similarity between laquinimod and the dietary AhR activator indol-3- carbinol (I3C), a component of broccoli and other cruciferous vegetables.

Laquinimod and TCDD are both potent inducers of CYP1A1/2. However, CYP1A induction is a dissociated event from dioxin-like toxicity, even if both activities are mediated by AhR activation. The applicant view is that CYP1A induction is considered a biomarker of AhR activation, but not an indicator of AhR toxicity.

Laquinimod and DLCs differ in critical attributes of mode of AhR activation, gene expression, and pharmacological responses. The major differences between laquinimod and TCDD/DLCs include:

- Structural and physicochemical differences: TCDD (like all other DLCs) is a highly lipophilic, non-ionized, planar molecule that distributes extensively into adipose tissue. Laquinimod is a non-planar molecule, ionized at physiologically relevant pH with relatively high aqueous solubility. These differences may explain the different AhR activation characteristics noted for the two compounds.

- No sensitivity of laquinimod to a TCDD/DLC antagonist: laquinimod transiently activates AhR by a mechanism other than the canonical direct binding to the TCDD/DLCs binding site.

- The pharmacokinetic properties of laquinimod are fundamentally different from those of TCDD, with the most notable difference being the biological persistence of TCDD. In humans, the elimination half-life of TCDD is 8 to 10 years, compared with an 80-hour half-life of laquinimod.

- Laquinimod and TCDD induce distinct sets of hepatic genes with very little overlap. Laquinimod induces only a small subset of TCDD responsive genes, most of which encode enzymes involved in xenobiotic metabolism that are not mediators of TCDD toxicity. Furthermore, gene expression analysis of samples from the ALLEGRO study showed that laquinimod does not induce TCDD/DLC-responsive genes in peripheral blood mononuclear cells (PBMCs) from treated patients.

- Laquinimod lacks the hallmark toxicities characteristic of TCDD and related compounds in animals and humans, namely wasting syndrome, immune suppression, porphyria, progressive liver toxicity and chloracne.

- The laquinimod tumourigenic profile in rodents is different from that of TCDD and DLCs.

Laquinimod exhibits a toxicity response in animals that is substantially different from and much more benign than that caused by TCDD and DLCs in terms of both non-neoplastic and neoplastic endpoints. Laquinimod in rats does not induce tumours in lung, liver or pancreas. In contrast, the incidence of these tumours with TCDD is very high. See Tables 34 and 35:

Table 34. Comparison of Incidence of Pivotal Non-Neoplastic Lesions Induced by TCDD, I3C and Laquinimod in 2-Year Studies – Female SD Rats

Organ and lesion	**TCDD**	**I3C**	**LAQUINIMOD** (Study 1028/119)
High Dose (mg/kg)	0.0001	300	1
CYP 1A fold induction (liver)	70	81	130
Liver – Toxic hepatopathy	**+++**	**+/-**	**+/-**
Liver – Oval cell hyperplasia	**+++**	**-**	**-**
Bile duct hyperplasia	**+++**	**-**	**-**
Lungs –metaplasia	**+++**	**-**	**-**
Adrenal cortex – Atrophy, vacuolation, degeneration	**++**	**+**	**-**
Pancreas – lesions	**+++**	**+**	**-**
Heart – cardiomyopathy	**+++**	**++**	**-**
Thyroid gland – lesions	**+**	**++**	**+**
Thymus atrophy	42/42 (**average severity 3.9**) compared to 36/51in control (**average severity 2.6**)[i)]	38/50 (**average severity 2.3**) compared to 38/47 in control (**average severity 2.2**) [i)]	39/58 (**average severity 2.5**) compared to 31/59 in control (**average severity 2.2**)[ii)]
Oral mucosa –hyperplasia	**+**	**+**	**+**
Forestomach –hyperplasia/ hyperkeratosis	**+**	**+**	**++**
Uterus –cystic hyperplasia, metaplasia	**-**	**++**	**-**
Nose –epithelium hyperplasia	**-**	**+**	**-**
Larynx - metaplasia	**-**	**-**	**+/-**
Kidney – nephropathy	**-**	**+++**	**-**
Kidney - hyperplasia	**++**	**++**	**+**
Urinary bladder - hyperplasia, metaplasia	**-**	**-**	**+/-**

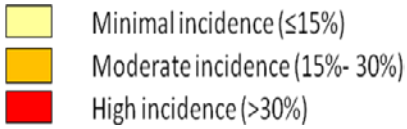
[i)] Severity scale: 1-minimal 2-mild 3-moderate 4-marked
[ii)] Severity scale: 1-minimal 2-slight 3-moderate 4-moderately severe

Minimal incidence (<33%)
Moderate incidence (33%- 66%)
High incidence (>66%)

Table 35. Comparison of Incidence (%) of Pivotal Neoplastic Lesions Induced by TCDD, I3C and Laquinimod in 2-Year Studies – Female SD Rats

Neoplasm	TCDD	I3C	LAQUINIMOD- (Study 1028/119)
High Dose (mg/kg)	0.0001	300	1
CYP 1A fold induction (liver)	70	81	130
Cholangiocarcinoma	47	-	-
Hepatocellular adenoma	24.5	-	-
Hepatocholangioma	4	-	-
Lung – Cystic keratinizing epithelioma	17	2	-
Oral Mucosa – Gingival squamous cell carcinoma	19	4	3.3
Uterus-adenoma/carcinomas	-[i)]	8	11
Pancreas- acinar adenoma/carcinoma	6	-	-

[i)] Equivocal results are reported for TCDD. In one study, there was a reduced incidence and in a second study, there was an increase but not in the highest dose tested.



The applicant claimed that experts in the field clearly dissociate laquinimod from TCDD and conclude that it does not fulfil the toxicity equivalence criteria set by the WHO for DLCs. According to the criteria of the World Health Organization (WHO), laquinimod and its minor metabolite DELAQ cannot be classified as DLCs, and laquinimod is not expected to have a similar toxicity risk as DLCs.

According to the applicant, there is a clear distinction between DLCs and non-DLCs that activate AhR in as much as there is no evidence that any non-DLC, the class of compounds to which laquinimod belongs, can elicit the spectrum of effects characteristic of TCDD toxicity.

Therefore, it is the applicant's view that risk assessment for laquinimod should be done independent of DLCs, based on the safety signals identified in the development program of laquinimod.

With regard to rat carcinogenicity findings, the applicant indicated that the hallmarks of TCDD carcinogenicity in rats, namely liver and lung tumours, were not seen with laquinimod. The uterine tumours are not considered characteristic of the carcinogenicity profile of DLCs. Thus, only the oral tumours can be considered similar between laquinimod and DLCs. Notably, this type of tumour was also demonstrated in rats for the dietary AhR activator, I3C, a component of broccoli and other cruciferous vegetables.

Laquinimod induced a low incidence of tumours in the oral cavity and in the uterus of female rats and thyroid tumours in male rats.The applicant maintains that the carcinogenicity findings are species-specific and do not imply an elevated carcinogenicity risk in humans.

The uterine adenocarcinomas seen with laquinimod likely involve mechanisms specific to aged female rats. An involvement of the AhR pathway activation for the oral mucosa squamous cell tumours in rats is plausible. The mode of administration and the high local concentration are likely to separate this mechanism from the human condition. It should be noted that in humans, no significant increase in oral tumours is associated with exposure to TCDD. Furthermore, gene expression data indicate that rats are a more sensitive species to laquinimod than humans.

With regard to the CHMP concern of laquinimod's endocrine disruption potential, the applicant argued that laquinimod is distinctly different from endocrine disruptors like diethylstilbestrol (DES) as neither laquinimod nor its trace metabolite, DELAQ, bind or activate the oestrogen receptor. Even though DELAQ displayed indirect anti-estrogenic effects in an in vitro assay, it did so at concentrations higher than those in the plasma of laquinimod-treated patients. In any case, anti-estrogenic effects would be expected to protect against, rather than cause uterine tumours.

Regarding the CHMP concern related to developmental and reproductive toxicity, the applicant acknowledged that AhR involvement in these findings remains a possibility in view of an AhR role in developmental processes in animals. The applicant pointed out the species specificity of the noted malformations and presents epidemiological data indicating that the risk of birth defects is not increased in populations exposed to TCDD. This notwithstanding, to mitigate the potential human teratogenic risk, the applicant committed to implement a rigorous pregnancy prevention programme in clinical trials and in the post-marketing program to prevent exposure to laquinimod during pregnancy.

To address the CHMP concerns regarding lack of understanding of laquinimod pharmacological mode of action and the possible involvement of AhR, the applicant has summarised (i) studies that have been performed to further explore the mechanism underlying the immunomodulatory and neuroprotective properties of laquinimod and (ii) demonstrate that key elements in laquinimod mode of action are different from other AhR activators and that laquinimod elicits only a subset of AhR-mediated biological responses. The applicant argued that the pharmacological mode of action of laquinimod was extensively investigated and concluded that laquinimod and other AhR activators (including TCDD/DLCs) share a number of biological effects on the immune system. However, there are marked differences in the cellular mechanisms involved: whilst laquinimod targets Antigen Presenting Cells (APCs) which lead to T-cell modulation, with no direct effect on T-cells, high affinity AhR ligands such as TCDD/DLCs target both T-cells and APCs. Although it is plausible that AhR may be involved in the biological/pharmacological mode of action of laquinimod, there is currently no molecular proof for this hypothesis. The applicant committed to continue the investigations on the mode of action of laquinimod, as well as to investigate the mechanisms involved in the adverse signals seen in animals to further elucidate possible human relevance.

The applicant concluded that the overall properties and toxicity profile of laquinimod are markedly different from those of DLCs. Laquinimod cannot be considered a DLC and risk assessment of laquinimod should be independent of this group of chemicals. The carcinogenicity findings are species-specific and do not imply an elevated carcinogenicity risk in humans. In terms of the teratogenicity findings, the applicant proposes a comprehensive pregnancy prevention programme that incorporates all measures suggested by the CHMP.

Ground for refusal #2: The modest efficacy of laquinimod on relapse rate in adult patients with relapsing remitting multiple sclerosis (RRMS) at the proposed 0.6mg dose does not outweigh the safety concerns, notwithstanding the more encouraging effect on disability progression

Applicant responses: risk and benefit statement

The applicant was of the view that laquinimod has demonstrated efficacy on relapse-based outcomes in line with other standard therapies for RRMS. The effects of laquinimod on disability progression are large, consistent, maintained over increasingly rigorous confirmation time intervals and demonstrated across the spectrum of baseline EDSS.

A published analysis using mediation modelling showed that the disability effect was substantially mediated by the effect on relapses in the first year for fingolimod, the proportion of treatment effect (PTE) was 60% (Sormani 2013), a similar analysis was performed on the pooled ALLEGRO

and BRAVO laquinimod data set, the relapse contribution to the effect on disability was only 11%. In other words, while, the processes which contribute to fingolimod's disability reduction overlap substantially with those which lead to its relapse suppression, most of laquinimod's disability reduction is likely explained by other mechanisms. On this basis, the applicant argued that laquinimod likely has a direct effect on CNS processes related to disability progression outside of relapses.

The applicant noted that the clinical profile corresponds to non-clinical findings related to diffuse changes in the normal appearing brain tissue, chronic white matter changes and grey matter. Further corroboration of the effect on brain tissue loss come from an ALLEGRO MRI ancillary study showing a decrease in whole brain atrophy, regional thalamic atrophy, preservation of MTR in whole brain as well as in normal appearing white matter (NAWM), and reduction in the evolution of permanent T1 hypointense lesions.

Such a mechanism may offer an alternative treatment approach in RRMS patients and may be of specific value for MS patients in whom the impact of relapses and relapse frequency are expected to be clinically less significant and the reduction of CDP via an alternate pathway is sought.

The applicant therefore proposed that laquinimod will be indicated for patients with RRMS who have demonstrated disease worsening and have reached an EDSS above 3. A summary of the baseline characteristics and post hoc analyses of this subgroup of RRMS population is presented below. See Tables 36 and 37.

Table 36. Baseline characteristics

Pooled ALLEGRO and BRAVO	EDSS≤3.0 (N=1335)	EDSS>3.0 (N=655)
Age (Years) Mean ± SD	36.5± 9.1	41.3± 8.7
Weight (kg) Mean ± SD	71.0± 15.9	70.4± 15.7
BMI (kg/m^2) Mean ± SD	24.8± 5.2	24.8± 5.0
Female Gender N (%)	910 (68.2%)	452 (69.0%)
Previous MS Treatment N (%)	325 (24.3%)	163 (24.9%)
EDSS at Baseline Mean ± SD	1.9± 0.7	4.1± 0.7
Time from MS Diagnosis (Years) Mean ± SD	3.7± 4.6	5.2± 5.3
Time from First Symptom (Years) Mean ± SD	6.9± 6.1	9.7± 7.2
# of Relapses in 1y Prior to Screening Mean ± SD	1.2± 0.7	1.3± 0.7
# of Relapses in 2y Prior to Screening Mean ± SD	1.8± 0.9	2.0± 1.0
# of GdE-T1 Lesions Mean ± SD	1.5± 4.2	2.2± 6.7
Volume of T2 Lesions (cm^3) Mean ± SD	7.8± 8.7	12.3± 12.0
Baseline Brain Volume Mean ± SD	1601± 90.0	1547± 90.8
GdE lesions>0 at Baseline N (%)	538 (40.3%)	259 (39.5%)

Table 37: Results of Key Clinical Outcomes by EDSS at Baseline

		EDSS ≤3.0 LAQ 0.6 mg, n=656 (66.7%) Placebo, n=679 (67.5%)	EDSS >3.0 LAQ 0.6 mg, n=328 (33.3%) Placebo, n=327 (32.5%)
Annualized Relapse Rate	Risk Ratio [CI]	0.798 [0.672; 0.948]	0.751 [0.601; 0.939]
	laquinimod Effect	20%	25%
	p-value	0.0103	0.0119
Time To 3-month CDP	Hazard Ratio [CI]	0.692 [0.501; 0.956]	0.595 [0.381; 0.931]
	laquinimod Effect	31%	40%
	p-value	0.0256	0.0229
Time To 6-month CDP	Hazard Ratio [CI]	0.600 [0.410; 0.879]	0.468 [0.266; 0.823]
	laquinimod Effect	40%	53%
	p-value	0.0088	0.0083
Disability As Assessed By MSFC Z-Score At Month 24	Adj. Mean Diff. [CI]	-0.016 [-0.116;0.085]	0.245 [0.101; 0.389]
	p-value	0.7614	0.0009
Brain Atrophy As Defined By PBVC	Adj. Mean Diff. [CI]	0.338 [0.208; 0.469]	0.393 [0.208; 0.578]
	p-value	<.0001	<.0001
Cumulative GdE T1 Lesions At Months 12 and 24	Rate Ratio	0.662 [0.533; 0.822]	0.829 [0.607; 1.133]
	laquinimod Effect [CI]	34%	17%
	p-value	0.0002	0.2390
Cumulative New/Enlarging T2 Lesions At Months 12 and 24	Rate Ratio [CI]	0.772 [0.653; 0.912]	0.753 [0.592; 0.959]
	laquinimod Effect	23%	25%
	p-value	0.0024	0.0214

For the proposed population, the importance of reducing further disability progression is heightened, as the next steps in their progression have clinically significant functional and especially ambulation impact. These patients are older, have longer disease duration, largely will have received prior DMTs in the member states and developed moderate disability and brain tissue loss in spite of treatment with available DMTs. The point estimates of the efficacy profile in this

group include a 25% reduction in relapse rate, a 53% reduction in 6 months CDP, as well as reduced brain atrophy. Overall, while the above table shows no differential treatment effects on key clinical and MRI endpoints between these two EDSS subgroups, the MSFC is an exception. In the EDSS>3 subgroup, a significant MSFC effect of laquinimod (mean z-score difference of 0.25; p=0.0009) is noted. The interaction for this MSFC treatment effect by subgroup is statistically significant (p= 0.0037). As shown in Table 38, there was a significant treatment benefit on the T25FW, which appears to drive the MSFC effect in the EDSS>3 subgroup. A treatment effect on the T25FW is also evident in the individual studies (ALLEGRO and BRAVO). There was no significant PASAT or 9HPT difference between laquinimod and placebo treated subjects in either subgroup, although the directions of change were consistent with a laquinimod effect.

Table 38: ALLEGRO and BRAVO Efficacy Results: MSFC Components by EDSS at Baseline

		EDSS ≤3.0 LAQ 0.6 mg, n=656 (66.7%) Placebo, n=679 (67.5%)	EDSS >3.0 LAQ 0.6 mg, n=328 (33.3%) Placebo, n=327 (32.5%)
PASAT Change from Baseline to Month 24	Adj. Mean Diff. [CI]	0.302 [-0.467; 1.071]	0.586 [-0.515; 1.687]
	p-value	0.4411	0.2967
9HPT Change from Baseline to Month 24	Adj. Mean Diff. [CI]	-1.108 [-3.041; 0.681]	-1.590 [-4.257; 1.077]
	p-value	0.2137	0.2425
T25FW Change from Baseline to Month 24	Adj. Mean Diff. [CI]	0.055 [-1.250; 1.359]	-2.79 [-4.664; -0.917]
	p-value	0.9342	0.0035

* Adj Mean Diff: adjusted mean difference

According to the applicant, these patients experienced a significant 59% effect on the T25FW, denoting an important benefit to motor activity and substantiation of the profound CDP effect.

The identified clinical and laboratory risks with laquinimod are generally mild and do not pose a concern in this specific population in the applicant's opinion. The potential risks of human teratogenicity and potential carcinogenicity, which may be associated with long term treatment, are expected by the applicant to be mitigated in the newly identified targeted subpopulation through considerably lower pregnancy rates expected in this population and overall shorter potential exposure during the RRMS phase, as these patients start treatment later in the disease. According to the applicant, this is specifically pertinent as laquinimod has no mutagenic or clastogenic potential.

While the precise molecular target of laquinimod remains unknown, key elements in the laquinimod mode of action are different from other AhR activators and laquinimod elicits only a subset of AhR-mediated biological responses. Laquinimod is clearly characterized as a non-DLC AhR pathway activator with substantial differentiation from TCDD and other DLCs on organ toxicology, carcinogenicity in target organs, and gene expression profiling. Transcriptome analyses only demonstrate minimal overlap, predominantly in CYP1 genes.

Regarding the potential carcinogenicity risk, the applicant maintains that the carcinogenicity findings from rodent studies are species-specific and do not imply an elevated carcinogenicity risk in humans.

Warnings are proposed to be implemented in the SmPC. According to the applicant, additional measures to determine whether the hypothetical carcinogenicity poses a risk to humans, include an adequately powered PASS aligned with EMA expectations.

Regarding the potential teratogenicity risk, the mechanism underlying the findings in rat offspring is unknown and AhR involvement in the teratogenic findings in rats remains a possibility in view of its role in developmental processes in many experimental animals. Laquinimod is contraindicated during pregnancy. The applicant has adopted a comprehensive pregnancy prevention program for ongoing clinical trials and the postmarketing setting.

Taking into consideration laquinimod's modest effect on relapses, its larger effect on disability progression and the potential risks, the applicant considered that the benefit and risk balance in the targeted population of patients that reached an EDSS greater than 3 is positive.

Ground #3: The absence of obvious measures to address the potential carcinogenic risk and potential endocrine disrupting effects and consequently to ensure the safe long-term use of laquinimod in the RRMS population is of concern. There is also evidence of limited effectiveness of the pregnancy preventive measures in clinical studies to address the potential risk of teratogenicity and delayed effects.

Applicant responses: measures to address the potential risks

The applicant acknowledges that a potential long term carcinogenic risk to humans cannot be excluded, because an increase in the incidence of oral mucosa cancers and uterine adenocarcinomas was observed in rats treated with laquinimod. However, it is the applicant's contention that the carcinogenicity findings from rodent studies are species-specific and do not imply an elevated carcinogenicity risk in humans. The uterine adenocarcinomas are not considered characteristic of the carcinogenicity profile of DLCs, and likely involve mechanisms specific to aged female rats. An involvement of the AhR pathway activation for the oral mucosa squamous cell tumours in rats is plausible. The mode of administration and the high local concentration that occur with rodents does not occur during the treatment of humans and thus, this mechanism is not relevant to any risk associated with administration of laquinimod to humans. Furthermore, the absence of a signal for an increased risk of cancer from the extensive clinical trial program, the fact that laquinimod activates the AhR pathway in a non-DLC manner, as well as the significant uncertainty regarding an observable human cancer risk even for DLCs in exposed individuals, mitigates the concern of this potential long-term risk. Furthermore, for the populations of RRMS patients with EDSS greater than 3, exposure will be substantially reduced. The absence of obvious clinical or laboratory measures to address potential carcinogenicity is inherent in this type of risk, which is in line with similar issues with other products demonstrating animal carcinogenicity. The applicant proposed to implement similar measures to those that have been proposed for other products with a potential or identified cancer risk, including a PASS to further characterise the risk. This PASS will be aligned with all CHMP recommendations. Further changes to labelling, including an additional warning related to the potential carcinogenic risk were suggested.

The applicant also agreed that the human relevance of potential teratogenicity and long term effects cannot be excluded for laquinimod, and that a comprehensive pregnancy prevention program should be in place. The mechanism underlying the findings in rat offspring is unknown and AhR involvement in these findings remains a possibility in view of its role in developmental processes in many experimental animals. An anti-estrogenic effect on the fetus (through ER-AhR cross talk) cannot be excluded, but the "endocrine disrupting" effect of the compounds listed by the CHMP (ethinyl estradiol, 17β-estradiol, diethylstilbestrol, tamoxifen and testosterone) and the clinical consequences of exposure to these compounds are not relevant for laquinimod. In regards to the concern about an AhR-related effect in humans, lack of malformations in subjects who were

exposed to TCDD, in the Seveso cohort, is somewhat reassuring. The applicant is committed to prevent foetal exposure to laquinimod, and is implementing all components of the pregnancy prevention program in the clinical studies. For the proposed indicated population as a whole, the attributable risk of potential teratogenicity in this older, more disabled population is substantially reduced due to the significant drop in expected pregnancy rates.

5.2. Additional expert consultation

Following a request from the applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the applicant's response.

In addition, during the re-examination, the CHMP requested, at their April 2014 Plenary meeting, the Safety Working Party (SWP) and the PRAC to address a number of questions related to the applicant's detailed grounds for the re-examination.

Report from the SWP

The CHMP questions to be addressed by the SWP were as follows:

1) Given the new arguments developed by the applicant in the grounds for the re-examination, in particular that laquinimod would be a non-toxic AhR activator, different from TCDD or DLCs (e.g. transient effects, different gene activation pattern), does SWP consider that its previous position on the safety of laquiminod should be amended?

2) Considering the non-clinical findings of teratogenicity in rats and the presence of laquinimod in the semen measured in the monkey study, what is the SWP position regarding a risk of male-transmitted malformations in human?"

The SWP discussion and main conclusions are summarised below:

- Laquinimod has similarities and dissimilarities with TCDD and I3C as AhR activators.

o It is dissimilar in having a shorter duration (TCDD effect is very persistent), but the intended daily administration weakens this aspect.

o Humans are less sensitive to TCDD (10 x lower affinity to the human AhR than the rat AhR), but it is not proven that this is true for AhR-mediated effects of laquinimod or DELAQ (human metabolite). Data do exist mainly for liver cells, and not for other tissues, whereas these differences might be essential

o Gene expression data show only a very small overlap between laquinimod and TCDD. However, these data are only present for hepatic cells. Data on other gene expression was not documented and therefore was not further discussed.

o There is a major point of discussion regarding the comparison of the toxicity profile of laquinimod and TCDD/DLCs. The company has emphasized that there are differences in target organs and effects, as well as in the degrees of severity and incidences. SWP members indicate that the company still is selective in discussing the similarity and dissimilarity of the toxicity profiles. Especially the general pro-inflammatory, hyperplastic and hepatic profile is shared with TCDD.

- Regarding carcinogenicity, particularly uterine and oral cavity tumors observed in rats, most of SWP members were not convinced by the new argumentation of the company.

o With respect to the uterine tumors, the lack of prolactin measurement, and inconsistencies in the explanation by the company are a stumbling block to accept the hypothesis of the company.

o With respect to oral cavity tumours it is stated that the NTP report on I3C is not yet available. The similarity between laquinimod and I3C can therefore not be assessed. In addition, tumour incidence is difficult to compare between studies conducted at different laboratories. There

were no increased inflammatory changes in the oral cavity caused by laquinimod, which would be expected following local irritation. Regardless the mode of action, if the local exposure of the oral tissues is causing the lesions there is a sufficient safety margin, but when it is a tissue specific response to systemic exposure the exposure margin at the NOAEL is less than two. The human relevance of the laquinimod-induction of oral cavity tumors if caused by Ah Receptor stimulation cannot be assessed as the activation by laquinimod of the human Ah receptor is unknown and thus far only subject to speculation.

Regarding question 1, the SWP supported by majority that the general toxicity remains an issue, especially because the underlying mechanism of action is unknown. The SWP supported the conclusion that laquinimod is a multi-site carcinogen as well as a teratogenic product in rats and the underlying mechanism of action for these toxic effects remains unknown regardless the mechanism of toxicity. Therefore, its relevance to humans cannot be excluded.

Taken together, it was concluded that there is no new evidence that justify an amendment of the previous SWP position on the safety of laquiminod.

The SWP considers that further mechanistic studies may be helpful to understand better the safety of laquiminod in humans, although doubts that additional mechanistic data can help in excluding a human risk remain. Reference was made to the SWP position made during the initial evaluation.

Regarding question 2, the company has made a calculation of the potential the exposure of women, based on the concentration of laquinimod measured in semen in animals and concluded that this exposure via semen is negligible.The SWP agreed by consensus with the company that the potential exposure of women via semen is negligible. Therefore the use of a condom during sexual intercourse for males treated with laquinimod is not deemed necessary.

PRAC advice

The CHMP questions to be addressed by the PRAC were as follows:

The views of PRAC are sought on:

- the acceptability and feasibility of the proposed additional risk minimisation measures for pregnancy prevention (as submitted in the re-examination package).
- the acceptability and feasibility of the submitted PASS and registry protocols (to adequately address/characterise the potential risks of carcinogenicity and teratogenicity/endocrine-disrupting effects- as submitted in the re-examination package)

The PRAC discussion and main conclusions are summarised below:

Proposed additional risk minimisation measures for pregnancy prevention.

The RMP (version 2.2) submitted by the applicant during the initial submission proposed routine pharmacovigilance activities with a PASS and pregnancy registry as additional measures to manage the safety concerns of pregnancy and teratogenicity. The routine risk minimisation measures included a contraindication in pregnancy, effective contraception in women of child-bearing potential, pregnancy testing before initiation of laquinimod or if pregnancy suspected, and counselling on all elements of the laquinimod pregnancy prevention programme and potential teratogenicity for females of child-bearing potential. The potential risk of teratogenicity was summarised in sections 4.3, 4.6 and 5.3 of the SmPC and also in the Package Leaflet. Educational materials for healthcare providers (including a prescription guide and counselling verification guide) and a direct healthcare professional letter at launch were also proposed to address the teratogenic risk and long-term effects on puberty and fertility in children after in utero exposure (infant follow-

up to 18 years). The effectiveness of these proposed activities was to be measured by the frequency of pregnancies on laquinimod.

Additional activities proposed by the applicant in this re-examination submission include regular pregnancy testing during laquinimod therapy, male contraceptive measures if their partner is female and of childbearing potential (and provision of counselling materials for them) and section 4.6 of the SmPC was updated to include 'relevance of these findings to humans cannot be excluded'.

The effectiveness of the pregnancy prevention programme is doubtful because of the high frequency of pregnancy experienced in the context of the clinical development programme, the population to be exposed and the long term nature of treatment.

The PRAC commented that no information had been presented by the applicant that provided reassurance about adherence to the pregnancy prevention programme. Therefore, it was recommended that a continuation form that confirms the ongoing acceptance of the conditions associated with laquinimod treatment should be completed and signed by the neurologist and women of child bearing potential at regular appropriate intervals.

The PRAC noted the consensus position of the SWP that there was negligible risk of exposure to laquinimod through semen. However, a concern was raised that the amount in human semen is unknown and no observed adverse effect level can be determined and on that basis a risk to the foetus cannot totally be excluded. Overall by a majority, the PRAC supported the views of the SWP and the PRAC Rapporteurs that contraceptive measures for males treated with laquinimod was no longer considered necessary.

Proposed additional Pharmacovigilance (PhV) activities for teratogenicity (i.e Pregnancy Registry)

There are serious questions on the feasibility of long-term follow up through the pregnancy registry due to inadequate reassurance from the information in the re-examination submission. Even with a proposed restricted use, these concerns still remain.

Proposed additional risk minimisation measures for carcinogenicity.

In addition, the PRAC maintains their position that there are no obvious risk minimisation measures to address the potential risk of carcinogenicity which is perceived as a general risk without any specific target tissue identified. Screening for early or pre-cancerous lesions, avoiding genetic or environmental risk factors and counselling are not appropriate or feasible.

Proposed additional PhV activities for carcinogenicity (i.e PASS)

The RMP (version 2.2) submitted by the applicant during the initial application proposed routine pharmacovigilance and a PASS for the carcinogenicity safety concern..The applicant also now additionally proposes in the re-examination submission that long term extension studies and changes in SmPC labelling will also be implemented to address the potential carcinogenicity of laquinimod. Given the absence of any new data relating to the safety concern of carcinogenicity, numerous issues with the PASS synopsis and lack of any detailed PASS protocol, the PRAC has serious doubts that the proposed study will serve to clarify the uncertainty regarding the long-term risk of laquinimod and also provide the necessary information to improve risk characterization and identification.

General discussion on impact of proposed new indication on RMP

The PRAC noted that in their response to the grounds for refusal the applicant has proposed a restricted indication of adult patients with relapsing remitting MS (RRMS), who have demonstrated

disease worsening and have reached an EDSS above 3, however, it is unclear the extent to which the applicant proposes to revise the content of the RMP. Furthermore no major changes have been proposed regarding the details of the additional risk minimisation measures (information related to prescription guide, counselling verification form and DHPC).

General discussion on adequacy of additional risk minimisation measures and PhV activities

The PRAC also noted that no major updates have been proposed in relation to the draft synopses for the PASS and pregnancy registry. On this basis, the PRAC maintains its initial position that the documented proposals for PV activities and risk minimisation measures are not sufficiently robust and consequently considered that the feasibility of the studies cannot be established at the present time. A detailed list of deficiencies is annexed in the PRAC advice.

Overall, pending the SAG consultation, the PRAC maintains their serious concerns over the safety profile of laquinimod and therefore concluded that the proposed risk minimisation activities would not be able to reduce the risks to an acceptable level.

In summary, the PRAC concluded that this submission provided with the grounds for re-examination is deficient in a number of areas. Based on the submission of the grounds for re-examination, the PRAC considers that

i) with regards to carcinogenicity there are no obvious risk minimisation measures to address the potential risk given that this appears to be a general risk for which no specific target tissue or clear mechanism has been identified.

ii) there remain important concerns about the effectiveness and feasibility of the proposed additional risk minimisation measures for pregnancy prevention

iii) the submitted PASS and registry protocol synopses are not approvable since there is no reassurance that they will allow for adequate and timely further characterisation of the important risks and any emerging safety signals.

Report from the SAG

The CHMP questions to be addressed by the SAG were as follows:

1. The non-clinical SAG experts are invited to discuss the safety concerns related to the findings seen in animals (general toxicity, carcinogenicity and reproductive toxicity, presence of laquinimod in monkey semen and potential teratogenicity) and their relevance for humans in the context of a long-term use of laquinimod.

2. Bearing in mind the grounds for negative opinion and re-examination, the potential safety concerns and the newly proposed indication for laquinimod in the "treatment of RRMS patients who have demonstrated disease worsening and have reached an EDSS above 3", the experts are asked to discuss:

a) whether a clearly defined target population within the broad RRMS could be identified, in whom the benefit/risk balance of laquinimod would be considered positive.

b) whether the population as defined by the applicant represents a valid clinical entity (i.e. whether the chosen cut-off of EDSS above three is based on clinical reasoning)

c) whether the robustness of the presented data on relapses and disability is considered sufficient, bearing in mind that the effect seen on disability seems to be mainly driven by ambulation (and not in other dimensions of Multiple Sclerosis), and that no patient with EDSS > 5.5 was included in the Phase III studies.

3. The views of the SAG are sought on the acceptability/feasibility of the proposed additional risk minimisation measures for pregnancy prevention (as submitted in the re-examination package).

The main SAG conclusions were the following:

- The SAG experts agreed that laquinimod, while activating AhR seems different from dioxin-like compounds. However, differences with I3C-like compounds are difficult to ascertain. The non-clinical experts suggested that applicant should present changes in global gene expression, preferentially in the form of heat maps. This would allow a direct comparison of gene expression patterns produced by laquinimod, TCDD and I3C and help to decide whether laquinimod is different with respect to its activity on AhR. It was agreed that laquiminod is clearly a multi-carcinogenic compound in animals as indicated in the SWP report. Considering the overall carcinogenicity findings and the probable non-genotoxic mechanism of carcinogenicity this is not considered however as a major concern in humans. Concerns still remain due to the difficulty to predict the relevance to humans because of the lack of mechanistic understanding of the animal findings. These risks could be acceptable in the context of clear clinical benefits.

Laquinimod is a clear teratogenic compound and would need a strict pregnancy control. However the practical feasibility will have to be appropriately addressed.

The SAG agreed that there was no concern about exposure of female partners through the quantities of laquinimod in semen which are negligible.

- The SAG considered that according to the available data there was no sub-group of patients that stood out on the basis of the observed efficacy. The drug did not seem to perform differently according to baseline EDSS or other characteristics of the RRMS population.

The SAG also made the comment that the studied dose may not be the most appropriate one.

- SAG and the patient representatives were not convinced that the proposed population (patients with EDSS>3) represented a clearly defined, real-life entity that could be considered a valid therapeutic target group. It includes a very heterogenous group of patients according to clinical features and to future evolution. Additionally, the vast majority of these patients would already be on treatment with other compounds. Available data indicate that efficacy could be lower (as much as by two fold) in this category of patients as compared to previously untreated patients.

The SAG made the observation that a more appropriate target population would have been the PPMS or SPMS population, in order to validate a mechanism of action more active on neurodegeneration and less dependent on inflammation. In a second step, patients who are in the transitional window from RRMS to SPMS could be a relevant population.

- In both the phase III randomised clinical trials presented, the effect size of the medication on the primary outcome measure (relapses) was modest. The observed effect size on disability, although meaningful, should only be considered as exploratory as the trials had methodological shortcomings, the most prominent one being the fact that in both pivotal studies disability was only a pre-specified secondary end point. Additionally, in the BRAVO study the statistical significance of the difference of the effect on disability vs placebo was borderline and the overall data on disability were at least in part based on a post-hoc meta-analysis of the two studies.

Because of the methodological shortcomings described above, the SAG considered that the data were not robust from a methodological point of view for the whole RRMS population included.

- The SAG's position was that the proposed measures were certainly wide and useful, however uncertainties remain regarding their feasibility and implementation in clinical practice, rendering their effectiveness doubtful.

Additional information provided by the applicant

The applicant submitted written documents for the Oral Explanation held on Monday 19 May 2014, which included revised SmPC and RMP.

Of note, the limited MS population as proposed as revised indication within the re-examination package was finally not pursued by the applicant in their latest SmPC proposal; a decision reportedly made in view of the Neurology SAG meeting outcome and latest available assessment on the grounds for re-examination.

Therefore, the revised SmPC and RMP were submitted to support the following indication:
"Nerventra is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) (see section 5.1)."

5.3. Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the Scientific Advisory Group, the SWP and the PRAC.

CHMP position on Ground for refusal #1

The CHMP maintains its view that the mechanism of action of laquinimod had not been sufficiently investigated and is unknown. This contributes to the insufficient characterisation of the safety profile, considering that laquinimod is a multi- site carcinogenic and teratogenic compound in animals. The CHMP was still of the opinion that a potential carcinogenic risk with long term use in humans cannot be currently excluded. Although the animal findings may not be seen as a major concern because of a probable non-genotoxic mechanism of carcinogenicity, such concerns remain due to the difficulty to predict the relevance of toxicity to humans because of the lack of mechanistic understanding of the animal findings, as indicated by the SAG and the SWP. The indirect evidence provided by the applicant to explain the mechanisms underlying the carcinogenic finding (oral cavity tumors and uterine adenocarcinoma) was also not particularly convincing and further mechanistic data would be necessary to exclude these safety concerns.

Although the CHMP acknowledged the SAG view that laquinimod while activating AhR seems different from dioxin-like compounds, the CHMP did not consider the comparison of the toxicity profile of laquinimod, TCDD and I3C as sufficient evidence to support the conclusions that laquinimod is a non-toxic AhR agonist. As indicated by the SWP, the comparison of the toxicity profile of laquinimod, TCDD/DLCs, as presented by the applicant, was considered selective. The CHMP considered more appropriate a comparison using the overall toxicity data for laquinimod, as presented in the previous SWP report during the initial evaluation. Laquinimod shares a general pro-inflammatory, hyperplastic (forestomach, oral cavity and kidney), hepatic and thyroid toxicity profile with TCDD and DLCs. It should be noted that inflammatory adverse reactions have been observed in clinical trials with laquinimod, based on the occurrence of peritonitis, appendicitis and increased fibrinogen and CRP levels. Other adverse events in clinical trials include liver enzyme elevations, haematological changes and higher frequency of back and neck pain. In line with these concerns, the CHMP also noted that the incidence of appendicitis was significantly increased in workers exposed to TCDD following a 1953 chemical reactor incident, thus questioning the comparative data, as presented by the applicant. Presentation of all the results of gene expression

studied by the applicant, preferentially in the form of heat maps, would have allowed a direct comparison of gene expression patterns produced by laquinimod, TCDD and I3C and could be helpful to understand the mechanism of action and toxicity of laquiminod which remain unknown, although the CHMP overall agreed that laquinimod toxicity profile should be evaluated on its own.In addition, as commented by the SAG, differences with I3C-like compounds are difficult to ascertain. No conclusions could be drawn on the data presented to support the similarity between I3C and laquinimod in the absence of submission of the referred National Toxicology Program (NTP) report on I3C.

Furthermore, there are potential endocrine disruptive effects, in particular in view of the teratogenicity findings in rats. These effects could be related to AhR activation following treatment with laquinimod, but cannot be further evaluated due to insufficient investigation on the mechanism of action of laquinimod.

Taking into consideration the uncertainties related to the mechanism of action, the CHMP remains concerned on the overall toxicity profile of laquinimod seen in animal studies, in particular the potential for carcinogenicity and teratogenicity.

The CHMP noted the SAG conclusions regarding the teratogenicity and carcinogenicity findings, notably that the carcinogenic risk could be acceptable in the context of a clear clinical benefit and that a strict pregnancy control would be required since laquinimod is a clear teratogenic compound. As sufficient benefits were not considered to be shown in the main clinical studies submitted for this application, the CHMP considered that the safety concerns remained unbalanced at the present time.

CHMP position on Ground for refusal #2

During the re-examination, the applicant proposed to restrict the indication to “adult patients with worsening relapsing remitting MS and at least moderate neurological disability (such as EDSS over 3). Nerventra is not indicated for patients with primary or secondary progressive MS”. In line with the SAG conclusions, the CHMP was of the opinion that such RRMS population was not a clearly defined target population. The CHMP further noted that the applicant proposal was based on a clinical reference, yet to be published. The applicant based their proposal on post-hoc analyses on this particular subset of patients, which can be considered as a subgroup within the global population included in the clinical studies. As such, the subgroup analyses need to be interpreted with caution and their validity needs to be ensured, as recommended by the “Guideline on the investigation of subgroups in confirmatory clinical trials” (EMA/CHMP/539146/2013). Given that the mechanism of action of laquinimod remains undetermined, it is uncertain whether a differential effect might be expected based on the EDSS value at baseline.

The Phase III programme for Nerventra included RRMS patients with EDSS of 0 to 5.5 hence no data is available in patients with more severe disability; the median EDSS score at baseline was 2.5. Patients are fully ambulatory up to a score of 4.5 with ability to walk 500 meters with a score of 4.0 when the walking distance is reduced to 100 meters for a score of 5.5 (but with disability severe enough to preclude full daily activities; Kurtze JF, 1983). It has been reported that from scores of 3.0 the EDSS is weighted heavily toward ambulatory disability and is less sensitive to other dimensions of MS such as arm and cognitive function (Polman CH et al., 2010); also the EDSS is less responsive to changes in more severely ill patients. Disability in MS comprises a number of functional systems and includes symptoms other than impaired ambulation such as fatigue, pain, cognitive impairment, bowel and bladder disturbances and the benefits in all of these symptoms remain unclear.

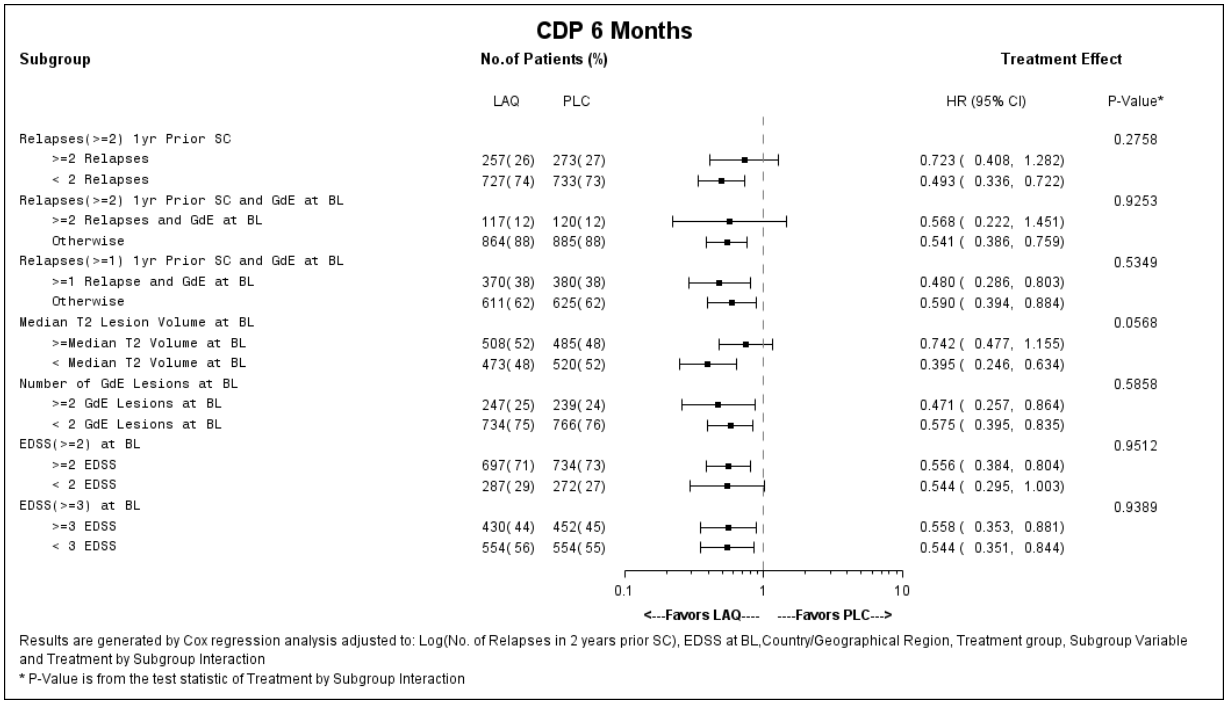
The treatment effect was slightly better in patients with EDSS above 3.0 as opposed to EDSS 3.0 and below, whether for ARR (25 % vs. 20 %), time to 3-month CDP (40 % vs. 31 %), time to 6-

month CDP (53 % vs. 40 %) and MSFC z-score. However little difference is seen for brain atrophy or T2 lesions and the effect on Gd-enhanced T1 lesions is halved. The lesser effect on Gd-T1 enhanced lesions was observed in patients with more disability, which might be of concern in the long term therapy.

Data provided are indeed indicative of a rather consistent effect throughout the spectrum of EDSS from 0 to 5.5. Laquinimod did not seem to perform differently according to baseline EDSS or other characteristics of the RRMS population as also noted by the SAG.

Subgroup analyses of 6-month CDP showed little numerical difference whether a cut-off point of 2 or 3 was chosen for the EDSS score. See Table 39.

Table 39. Subgroup Analysis of CDP (6 months)



Results are generated by Cox regression analysis adjusted to: Log(No. of Relapses in 2 years prior SC), EDSS at BL,Country/Geographical Region, Treatment group, Subgroup Variable and Treatment by Subgroup Interaction

* P-Value is from the test statistic of Treatment by Subgroup Interaction

The CHMP agreed that the main difference seemed to lay in the improvement of the MSFC z-score where a statistically significant difference is seen from a baseline EDSS score of 3.5. The MSFC is a 3-part quantitative instrument that measures arm, leg, and cognitive function with the 9-Hole Peg Test (9HPT, arm/hand dexterity), the Timed 25-Foot Walk (T25FW, leg function), and the Paced Auditory Serial Addition Test (3-second version, PASAT3; cognition). In the overall population the results on the MSFC score at month 24 did not show a statistically significant difference between laquinimod and placebo (p=0.5893); this was deemed inconsistent with the effect seen for the EDSS score and brain atrophy.

The improvement of the MSFC z-score for patients with EDSS > 3 was 0.245. However there is no accepted clinically meaningful change for MSFC z-score (Polman JC et al., 2010). This effect seems to be mainly due to an improvement in T25FW and very little difference is seen for PASAT and 9HPT. Baseline T25FW was 8.29 +/- 6.81 seconds in patients with EDSS >3.0. After 24 months the T25FW was 4.732 seconds longer in the placebo group but only 1.941 seconds longer in the laquinimod 0.6mg group. However no responder data (increase of 20 % or greater in the T25FW) have been submitted which would have been useful to assess the clinical relevance. Nevertheless the main contribution to improvement of CDP with laquinimod 0.6 mg was seen for the Pyramidal (37%), cerebellar (33%) and ambulation Functional System Scores (41%) of the EDSS score. Also

the improvement in ambulation was independent of a disability progression during the Phase III studies.

The exact mechanism for the effect on T25FW is unknown and the fact that no parallel improvement (e.g on vision, quality of life) was discussed, makes it difficult to put these changes into context or to make assumptions in the long term therapy, especially when only a modest effect was seen on relapses and MRI T1 and T2 lesions. Also the T25FW is a short test and the results are not confirmed by other ambulatory tests such as longer walking test or the Multiple Sclerosis Walking Scale. Altogether the absence of similar positive results in dimensions other than ambulation for patients with a baseline EDSS > 3 adds to the argument that such population was not a properly defined and clinical justified subgroup of the RRMS population. In addition, based on the natural history of this disease, once a certain degree of disability has been reached in RRMS, some patients would enter into a phase where disease progression seems to be less dependent of the early inflammation/relapses, which otherwise tend to decrease/disappear over time, and more dependent of the degenerative component of the disease. This is the so call “secondary progressive multiple sclerosis” form. However, this is highly variable within patients and does not occur at a given point in time, but rather is a continuous transitional process. There is not agreed definition to identify patients who will progress into a SPMS and the degree of accumulated disability measured by the EDSS on its own is not considered enough to properly define those patients. In fact, from a clinical point of view, a clear “cut-off” point in the EDSS cannot be established and the 3-point score appears rather arbitrary. To identify patients on the “verge” of progressive disability might not be feasible.

The CHMP recognised the fact that patients transitioning into a progressive form might likely benefit from therapies targeting the degenerative component of the disease, but so far laquinimod has not demonstrated that it has such an effect on patients with true progressive MS forms, as clearly required in the guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis or MS Guideline (CPMP/EWP/561/98, Rev.1).

Patients with “disease worsening and an EDSS>3”, is not an agreed definition for patients whose disease progresses independently of relapses and does not define a homogeneous subset of patients. In fact, RRMS patients with an EDSS>3 might well have progressed and continue progressing in close relation to relapses. Given that in the EU, RRMS patients with an EDSS>3 will universally be on treatment, in case of lack of response to a DMT (“disease worsening”) a number of therapeutic alternatives exist with a well defined benefit-risk ratio in RRMS, being thus candidates to any of the available treatment options. Furthermore, data from the previous procedure indicated that the effect of laquinimod on ARR, brain atrophy and disability progression was not statistically significant as compared to placebo for patients previously treated with IFNs (only the effect on MRI parameters was statistically significant). In fact, the effect of laquinimod 0.6 mg was 2-fold smaller than in the subgroup without prior use of interferon for ARR (13% vs 27%), brain atrophy (17.4% vs 34.6%) and time to confirmed EDSS progression-6 month (28.7% vs 58.2%). In the small subgroup of patients with prior GA use (n=84), there was no effect of laquinimod on ARR as compared to placebo (n=89). For all other endpoints (disability progression and MRI parameters), an effect of laquinimod over placebo was observed but not statistically significant. These findings question the adequacy of laquinimod treatment in a subgroup of RRMS patients with disease worsening despite treatment.

In addition no extrapolation can be made to patients with more severe disability with regards to ambulation as no patient with EDSS 6 and above was included in the main clinical studies submitted for the present application.

The proposed mode of action relates to pre-clinical findings of neuroprotective effects and anti-inflammatory effects. In that respect the CHMP noted that an increase of white blood cells has been

reported together with increased C-reactive protein following treatment with laquinimod questioning such claim. Back and neck pain and appendicitis have been clearly identified as clinical risks. Increased liver enzymes, fibrinogen levels, erythrocyte sedimentation rate and CRP have been noted and proposed to be included in sections 4.4 and 4.8 of the SmPC. With regards to increased inflammatory markers, fibrinogen and CRP have been studied in detail in relation to cardiovascular events and mortality. In the clinical studies, a shift from normal to elevated fibrinogen occurred in more laquinimod-treated patients compared to placebo (42.9% vs. 33.8%), whereas the change from normal to high CRP was similar in the laquinimod and placebo group (16.5 vs. 17.8%). The majority of the patients had no change in their baseline CRP condition (80.4% vs. 79.4%).

During the Oral Explanation held on 19 May 2014, the applicant did not pursue the proposed restricted indication "adult patients with worsening relapsing remitting MS and at least moderate neurological disability (such as EDSS over 3). Nerventra is not indicated for patients with primary or secondary progressive MS". The applicant proposed to revert back to the broad indication in RRMS patients as initially applied for. Based on the latest available assessment and the SAG conclusions, the applicant maintained their position regarding the suitability of laquinimod as treatment for the broad population with relapsing remitting multiple sclerosis (RRMS), as according to the applicant, the SAG assessed that the non-clinical risk does not pose a major concern to humans. The applicant remained also committed to considering a restrictive labelling indication to mitigate the raised potential safety concern, including e.g. a second line indication.

Having considered the above and the overall efficacy data, the CHMP remained concerned that the efficacy of laquinimod at the proposed 0.6 mg dose, was modest on the relapse rate in the proposed broad RRMS population. A more encouraging effect was seen on disability progression but this requires confirmation. The unknown mechanism of action and the rather modest effect on relapses questions the suitability of laquinimod as treatment for the broad population with relapsing remitting multiple sclerosis (RRMS) patients.

CHMP position on Ground for refusal #3

The CHMP maintains its view that the potential carcinogenic risk and potential endocrine disrupting effects cannot be currently excluded and that there are no obvious measures to address these concerns. As commented by the PRAC and SAG during the re-examination procedure, the uncertainties on the effectiveness of the pregnancy preventive measures in clinical practice to address the potential risk of teratogenicity, do not alleviate the concerns. Overall, these potential risks were considered by the CHMP to outweigh the modest benefit on relapses shown with the proposed 0.6 mg dose of laquinimod in the intended RRMS population, notwithstanding the more encouraging effect on disability progression.

As sufficient benefits were not considered to be shown in the main clinical studies submitted for this application, the CHMP was of the opinion that the proposed risk minimisation activities do not alleviate the concerns raised by the non-clinical findings and therefore were not able to reduce the risks to an acceptable level at the present time.

5.4. Updated Benefit-Risk Balance

Benefits

Beneficial effects

Laquinimod is a novel orally administered therapy, intended for the treatment of patients suffering from relapsing-remitting multiple sclerosis. Laquinimod is claimed to fulfil an unmet medical need for an oral agent by acting as an immumodulator with CNS protective activity that is at least as effective as the currently available first-line treatments. The exact mechanism of action of laquinimod is unknown but it has shown beneficial effects in various types of experimental autoimmune encephalomyelitis models as well as in cuprizone induced demyelination, all accepted animal models of multiple sclerosis.

Prevention and/or modification of relapse features as well as prevention or delay of the accumulation of disability are meaningful goals in the treatment of relapsing multiple sclerosis.

Two large phase 3 pivotal studies (ALLEGRO, BRAVO) over two years were conducted. Both used relapse rate as a primary outcome measure. Time to confirmed EDSS progression was a key secondary endpoint.

In ALLEGRO study, a statistically significant effect of laquinimod 0.6 mg compared to placebo was demonstrated for the annualised relapse rate (p=0.0024). Whilst this result was consistent with other efficacy endpoints related to relapses and supported by sensitivity analyses, the reduction in ARR for laquinimod over placebo was modest, 23% over 24 months (RR= 0.770, 95% CI: 0.650, 0.911). In BRAVO study including an active comparator (Avonex), laquinimod 0.6 mg dose failed to show a statistically significant effect as compared to placebo on the ARR (RR=0.823, 95% CI: 0.664, 1.020, p=0.0746) reflecting a reduction of ARR of 17.7%. In contrast, comparison of the Avonex treatment arm with placebo yielded a risk ratio of 0.741 (95% CI: 0.596; 0.920, p=0.0067), demonstrating a 25.9% reduction in the annualized relapse rate. The pre-specified sensitivity analyses were consistent with the primary analysis.

Due to the imbalances observed at baseline for mean T2 lesions volume and proportion of subjects with GdE T1 lesions ≥1 across treatment groups, additional post-hoc analyses were performed using these MRI parameters as covariates in a corrected model. Such corrected analysis resulted in an increase in magnitude of effect of laquinimod 0.6 mg compared to placebo on ARR (RR=0.787,

95% CI: 0.637, 0.972) of statistically significance (p=0.0264) however this corrected result was still suggesting a modest reduction in ARR of 21.3% in patients treated with laquinimod 0.6 mg in BRAVO study. Importantly, whilst these baseline imbalances were also present in the Avonex group, treatment effect of Avonex over placebo was statistically significant (p=0.0067) in the primary model due to an observed larger treatment effect size of 25.9% reduction in the ARR (RR= 0.741, 95% CI: 0.596, 0.920). Numerically, the results on ARR were in favour of Avonex as compared to laquinimod. In addition, laquinimod failed to show statistical significance over placebo on the time to first relapse (HR=0.813, 95% CI: 0.653, 1.014); p=0.0659), questioning the sensitivity of the results observed for the ARR, after the baseline corrected analysis.

In a meta-analysis including the 2 pivotal studies and the phase II study LAQ/5062, an effect of laquinimod on ARR was demonstrated suggesting a 21% reduction for laquinimod versus placebo (RR=0.79, 95% CI : 0.69,0.89, p=0.0002). This result was consistent with the initially submitted pooled analysis of the two pivotal studies (reduction of 21.4% in ARR, p=0.0005) and is considered modest.

ALLEGRO study showed that laquinimod delayed the time to 3-month confirmed disability progression, with a statistically significant reduction of 36% over placebo (HR= 0.641; 95% CI: 0.452, 0.908; p=0.0122). BRAVO study failed to demonstrate such effect with a lower risk reduction of 31.3% over placebo (HR=0.687, 95% CI: 0.462, 1,020; p=0.0628). However, the CHMP noted that results on disability progression were numerically in favour of laquinimod as compared to Avonex, although the 95% CIs for each of the outcomes were overlapping. In addition, results from the pooled analysis using both pivotal studies, demonstrated a 34% reduction in the risk for 3-month confirmed disease progression (HR = 0.66, p=0.002). When adding the data from the phase II study LAQ/5062 in this pooled analysis, the effect on disability remain with a reduction of around 32% in the risk of disability progression confirmed at 3 months, although the CHMP noted that study LAQ/5062 on its own failed to show an effect on disability (HR= 1.12, 95% CI: 0.33, 3.74). A 44% reduction of disability progression confirmed at 6-months was also observed based on post-hoc analysis of pooled data provided by the applicant from both pivotal studies, data from study LAQ/5062 was not included in this analysis due to its short duration. It is noted that given the mild status of the studied population, this 44% risk reduction for 6 month confirmed disability progression (CDP) translated just into a 4% difference over the placebo in the absolute reduction for the incidence of CDP.

Different MRI endpoints related to clinical activity and for some to long term clinical outcome (cumulative numbers of Gd enhancing lesions, new/enlarging T2 lesions for ALLEGRO, brain atrophy measure for BRAVO) were also used as secondary efficacy endpoints.

In ALLEGRO study, there was a statistically significant effect of laquinimod as compared to placebo on mean adjusted number of T1 Gd-enhancing lesions (RR=0.629,95% CI: 0.488, 0.809, p=0.0003) showing a reduction of 37% in the mean rate of developing T1 Gd-enhancing lesions on laquinimod 0.6 mg compared to placebo. A statistically significant treatment effect of laquinimod 0.6 mg over placebo was also shown on the cumulative number of New/Enlarging T2 lesions (RR=0.704,95% CI: 0.584, 0.849, p=0.0002) indicating a reduction of 30% in the mean rate of developing New/Enlarging T2 lesions on laquinimod 0.6 mg compared to placebo.

In the meta-analysis using the two pivotal studies ALLEGRO and BRAVO, and the phase IIb study LAQ/5062, a treatment effect on GdE T1 lesions was observed with a rate ratio of 0.68 suggesting a reduction of 32% as compared to placebo. This effect was statistically significant (p<0.00001). The effect on new T2 lesions was also statistically significant with a reduction of 27% versus placebo (Rate Ratio of 0.73, p<0.00001). Regarding brain atrophy, the effect of laquinimod was statistically significant as compared to placebo (difference of 0.31 in % brain volume change, p<0.00001).

The supportive studies suggested maintenance of the effect of laquinimod during long term treatment regarding ARR and disability progression.

Uncertainty in the knowledge about the beneficial effects.

Limited data were provided regarding the pharmacodynamic effects of laquinimod in humansIt is hypothesised that the disability reduction is likely explained by mechanisms unrelated to the suppression of acute inflammation and that are different to other DMTs, possibly taking place within the central nervous system and acting directly on the degenerative process . However, since the mechanism of action has not been sufficiently investigated and the molecular target remains unknown, no conclusion could be drawn on the clinical pharmacology of laquinimod.

The optimal dose had not been defined because 0.6 mg dose was the sole dose tested in the phase III studies. In the absence of data using higher doses than 0.6 mg, the CHMP concluded that the dose reponse effect of laquinimod has not been sufficiently evaluated to determine the optimal dose in the intended population.

Limited data after discontinuation of laquinimod treatment are available to evaluate the potential risk of rebound effect.

The mechanism of action of laquinimod is unknown and the rather modest effect on relapses questions the suitability of laquinimod as treatment for the broad population with relapsing remitting multiple sclerosis (RRMS) patients.

Risks

Unfavourable effects

Liver enzyme elevations, inflammatory markers increased (e.g. CRP, fibrinogen), back and neck pain, haematological changes, appendicitis, interaction with CYP3A4 inhibitors/inducers have been identified as important risks.

The effect of laquinimod on the liver appeared to be limited to liver enzyme elevations, but the mechanism underlying these events is unknown. Mostly mild, asymptomatic liver enzyme elevations (AST, ALT and GGT) were reported that generally occur within 6 months after initiation of treatment. Overall in the pivotal trials, 4.7% of laquinimod treated subjects reached relevantly significant [> 3xULN] levels of ALT. This was more notable for male than for female in laquinimod treated subjects. In 74% of subjects who had elevated levels of ALT on laquinimod, ALT decreased to within the normal range while on laquinimod.

Inflammatory markers (CRP, ESR, fibrinogen) were increased in healthy volunteers in phase I studies. In pivotal studies, fibrinogen (40% vs. 28%) and WBC levels (27% vs. 15%) clearly increased to values above ULN in a higher percentage of patients with laquinimod in comparison with placebo. Increase of fibrinogen was apparent from month 1. In the pivotal studies, until month 15, the proportion of patients with elevations in both CRP and fibrinogen was slightly higher (by approximately 1-2%) in the laquinimod group compared to placebo. At month 2 this difference was statistically significant (approximately 4.1% vs. 2.3%) and was considered clinically relevant. Long-term data up to 4 years are available and revealed that, at month 48, the percentage of patients with potentially clinically significant CRP elevation increased to 5.4% in the laquinimod group. In the pivotal studies, the incidence of fibrinogen level considered potentially clinically significant (> 6g/l), was higher in the laquinimod group compared to placebo (5.5% vs. 2.6%).

Maximal fibrinogen did not exceed the >2.5x ULN; maximal fibrinogen was 9.0 g/l in the laquinimod group and 8.4 g/l in the placebo group at any time until month 24. Overall, mean duration of elevated fibrinogen or CRP tended to be longer in the laquinimod group compared to placebo.

Haematological toxicity was relevant with laquinimod when compared to placebo, with mostly mild increases in leucocyte levels and decreases in red blood cells and platelets. Two cases of anaemia and one case of acute leukemia in the laquinimod group were considered as serious.

Uncertainty in the knowledge about the unfavourable effects

There is currently a considerable level of uncertainty on the carcinogenic potential of laquinimod. The pharmacology of laquinimod is unclear thus making difficult the full appreciation of any pharmacology-driven proliferative or metaplastic processes. Based on pre-clinical data, a potential carcinogenicity relative to oral cavity and uterus could not be ruled out. There is a lack of mechanistic data to exclude these potential risks in humans. At the present time, there is also insufficient evidence to conclude that laquinimod can be considered as a non-toxic AhR agonist. Significant uncertainties also remain with regards to the unknown immunomodulator or immunosuppressant potential, and the potential risks associated with long-term use (i.e. cancer, infections, inflammation), also contributing to the insufficient characterization of the safety profile of laquinimod in the intended patient population, although the currently available clinical data did not show evidence of an increased risk of malignancies, immunosuppression or infections.

Malignant tumours have been reported in 26 patients (0.6%) treated with laquinimod in all clinical studies; 6 breast carcinomas including one metastatic breast cancer (3 in cohort 1, all in ALLEGRO and no case in BRAVO; 1 additional case of breast cancer in study LAQ/5062 have been reported in laquinimod group. One breast cancer was reported in placebo group). In cohort 1, 10 (1%) patients in the laquinimod group vs 6 (0.6%) patients with placebo experienced a malignant tumour (p=0.2944, 95% CI: -0.37, 1.21). In addition to 3 cases of breast cancer, sporadic cases of glioblastoma (1), lung neoplasm malignant (1), lymphoma (1), oesophageal adenocarcinoma (1), squamous cell carcinoma (1), thyroid cancer (1) were reported. One case of thyroid cancer has been reported in BRAVO study in patient treated with laquinimod. One case of thyroid cancer occurred in Avonex group. Concerning skin malignancy, 2 cases (basal cell carcinoma, squamous cell carcinoma) occurred in cohort 1 compared to one case (basal cell carcinoma) in the placebo group. In total, in cohort 3 (all patients treated with laquinimod), 7 subjects suffered from skin malignancies: basal cell carcinoma (4), malignant melanoma (1) and squamous cell carcinoma (2). Overall incidences of malignancies comparison with SEER Database did not demonstrate an increase in malignant tumours with laquinimod therapy. However, the number of events to date and duration of follow-up is too limited to definitively exclude a relationship and further long term data are required to ascertain the level of this potential risk. In addition, based on available pre-clinical data, there remain relevant uncertainties on the potential risk for malignancies .These uncertainties currently represent an important concern with long term use of laquinimod.

Laquinimod was teratogenic in rats, causing hypospadias in females. The most sensitive days for induction of these malformations were days 18-21 of gestation in rats, while exposure before implantation or during lactation did not induce this type of malformation. In F1 males, hypospadias were also reported and other findings consisted of dose-dependent delayed growth which persisted up to adult age in the high dose group, a clear dose-dependent delay in onset of puberty, and decreased fertility in spite of normal sperm parameters. In addition, the absolute weight of prostate and seminal vesicles were decreased at the high dose level. In F1 females, in addition to the urogenital abnormalities, there were also treatment-related effects on growth, delayed vaginal opening at the high dose level only, prolonged estrous cycle length, decreased fertility at the mid and high dose levels. Treatment also had an impact on F2 generation as seen from decreased

viability of F2 pups born from F1 females (high-dose group). Most of the findings obtained in F1 animals were suggestive of a hormonal effect of laquinimod. An effect of laquinimod on the AhR-ER cross-talk pathway cannot be excluded as possible mechanism underlying its potential endocrine-disrupting effects. These effects could be related to AhR activation following treatment with laquinimod but cannot be further evaluated due to insufficient investigation on the mechanim of action of laquinimod. No definitive conclusions could be drawn regarding the teratogenic potential of laquinimod in cynomolgus monkeys. In clinical MS studies, females of child bearing potential were required to practice effective contraception. Nonetheless, 74 pregnancies have been reported in the laquinimod development programme, of which 43 were reported in subjects exposed to laquinimod (38 female patients treated and 5 male subjects reporting pregnancies of partners) as of 1 September 2013. The potentially delayed effects of laquinimod seen in preclinical studies (notably on puberty and fertility), which would not be noticeable at birth are of important concern for the CHMP, especially considering the intended use in MS patients (mostly females of child bearing potential) and the absence of an *in vivo* interaction study investigating the potential effect of laquinimod on the pharmacokinetics of oral contraceptives.

Although low, the incidence of ischemic heart disease was higher in the laquinimod group compared to placebo (0.6% vs 0.1%) in the pivotal studies. Overall, 20 reports in 15 subjects (0.6%) reported ischemic heart disease including 2 subjects that were diagnosed with myocardial infarction in the laquinimod group. Two out of 9 deaths in the laquinimod group were due to cardiovascular failure (sudden death within 5 hours post treatment) and myocardial infarction (after 5 months of treatment), respectively. Patients with significant cardiovascular conditions were excluded from the pivotal trials. On this basis and considering the safety data from roquinimex, a structurally related product, cardiotoxicity was considered as a potential risk for laquinimod.

Due to the potential of formation of tissue adducts seen in preclinical studies, drug hypersensitivity reactions should be considered as a potential risk for laquinimod, given its intended chronic use.

Benefit-risk balance

Importance of favourable and unfavourable effects

Laquinimod is a novel substance, which is proposed as orally administered treatment of relapsing remitting multiple sclerosis. Currently, a number of MS drugs are available in the EU as oral or parenteral formulations and are indicated either as first line or second line therapies. The exact mechanism of action of laquinimod is unknown and the molecular therapeutic target has not been identified. This lack of knowledge raised serious concerns over the pharmacology of laquinimod, particularly considering the potential for carcinogenicity and teratogenicity seen in animal studies and possibly related to AhR activation. According to the SAG conclusions, the carcinogenic risk could be acceptable in the context of a clear clinical benefit and that a strict pregnancy control would be required since laquinimod is a clear teratogenic compound. As sufficient benefits were not considered to be shown in the main clinical studies submitted for this application, the CHMP considered that the safety concerns remained unbalanced at the present time for the RRMS population.The main risks in humans for laquinimod included liver enzyme elevations, inflammatory markers increased (e.g. CRP, fibrinogen), back and neck pain, haematological changes, appendicitis as well as potential risks of carcinogenicity and teratogenicity based on findings in animal studies. There are no obvious risk minimisation measures for the potential carcinogenic risk and potential endocrine disrupting effect.These potential risks were considered to outweigh the modest benefits on relapses shown with the proposed 0.6 mg dose of laquinimod in the intended RRMS population. In line with the PRAC and SAG conclusions, the CHMP was of the view that laquinimod is a clear teratogenic compound and uncertainties remain regarding the

feasibility and implementation of the proposed pregnancy prevention programme in clinical practice.

In this context, the modest efficacy of laquinimod on relapse rate in adult patients with relapsing remitting multiple sclerosis (RRMS) at the proposed 0.6mg dose is not considered sufficient to outweigh the safety concerns.

Benefit-risk balance

The demonstrated efficacy of laquinimod on relapse rate in adult patients with relapsing remitting multiple sclerosis (RRMS) at the proposed 0.6mg dose is considered modest. A more encouraging effect was seen on disability progression but this requires confirmation. The toxicity profile (in particular carcinogenicity but also reproductive toxicity) seen in animal studies is of concern, given the difficulty in predicting the relevance to humans in the absence of mechanistic understanding of the animal findings.There are concerns regarding the adequacy of the pregnancy prevention measures to minimise the potential risk of teratogenicity in clinical practice. There is a lack of available measures to minimise a potential carcinogenic risk. The proposed risk management measures therefore do not alleviate the concerns raised by the non-clinical findings. In this context, the modest efficacy of laquinimod on relapse rate in adult patients with relapsing remitting multiple sclerosis (RRMS) at the proposed 0.6mg dose is not considered sufficient to outweigh the safety concerns.

Therefore, the CHMP concluded that the benefit/risk balance for Nerventra was negative for the following indication:

“Nerventra is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) (see section 5.1)”.

5.5. Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by consensus that:

the safety and efficacy of the above mentioned medicinal product are not sufficiently demonstrated,

and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product:

The CHMP considers that:

- The demonstrated efficacy of laquinimod on relapse rate in adult patients with relapsing remitting multiple sclerosis (RRMS) at the proposed 0.6mg dose is considered modest. A more encouraging effect was seen on disability progression but this requires confirmation.

The toxicity profile (in particular reproductive toxicity but also carcinogenicity) seen in animal studies is of concern, given the difficulty in predicting the relevance to humans in the absence of mechanistic understanding of the animal findings. There are concerns regarding the adequacy of the pregnancy prevention measures to minimise the potential risk of teratogenicity in clinical practice. There is a lack of available measures to minimise a potential carcinogenic risk. The proposed risk management measures therefore do not alleviate the concerns raised by the non-clinical findings.

In this context, the modest efficacy shown for laquinimod in RRMS is not considered sufficient to outweigh the safety concerns. The benefit-risk balance in the studied RRMS population is therefore considered negative at the present time.

Thus, the CHMP concluded that the benefit-risk balance of laquinimod was negative at the proposed dose of 0.6 mg in the treatment of adult patients with relapsing remitting multiple sclerosis.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet and risk management plan cannot be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.