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Assessment report

Gilenya

International nonproprietary name: Fingolimod

Procedure No. EMEA/H/C/2202

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novartis Europharm Ltd submitted on 22 December 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Gilenya, 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 28 July 2008.

The applicant applied for the following indication: disease-modifying therapy in adults for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/125/2008 for the following condition:

- Multiple sclerosis

on the agreement of a paediatric investigation plan (PIP) and on the granting of a deferral.

The PIP is not yet completed.

Information relating to Orphan Market Exclusivity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advices from the CHMP on 27/05/2005, 15/11/2007, 24/07/2008, The Scientific Advices pertained to the 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: Philippe Lechat

Co-Rapporteur: Tomas Salmonson

- The application was received by the EMA on 22 December 2009.
- The procedure started on 21 January 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 April 2010.
- During the meeting on 20 May 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 May 2010.
- The applicant submitted responses to the CHMP consolidated List of Questions on 20 August 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 01 October 2010.
- During the CHMP meeting on 21 October 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted responses to the CHMP List of Outstanding Issues on 10 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 December 2010.
- The applicant submitted responses to the Rapporteur's Joint Assessment Report on the applicant's responses to the List of Outstanding Issues on 3 January 2011.
- During a meeting of Scientific Advisory Group (SAG) on 12 January 2011, experts were convened to address questions raised by the CHMP.
- The Rapporteurs circulated updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 14 January 2011.
- During the meeting on 17-20 January 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Gilenya on 20 January 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 January 2011.

2. Scientific discussion

2.1. Introduction

Fingolimod[1] (Gilenya) is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate, binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptors 1, 3, and 4 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptors 1, 3, and 5 located on neural cells in the central nervous system. By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. This redistribution is claimed to reduce the infiltration of pathogenic lymphocyte cells into the central nervous system, where they would be involved in nerve inflammation and nervous tissue damage.

The following indication is initially applied for: disease-modifying therapy in adults for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

The recommended dose of Gilenya is one 0.5 mg capsule taken orally once daily.

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative disorder of the central nervous system (CNS), characterized by inflammation, demyelination, oligodendrocyte and neuronal loss. MS represents the leading cause of non-traumatic neurologic disability in young and middle-aged adults and has a major physical, psychological, social and financial impact on patients and their families, friends and institutions responsible for health care. MS affects an estimated 2.5 million individuals worldwide. The prevalence varies considerably, from regions with low prevalence (< 5 cases per 100 000 people) across much of central Asia, to areas with high prevalence (greater than 30 cases per 100 000 people) across the USA, Canada, Australia and large parts of Europe and northern Asia.

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 re lapses, 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 MS is the most frequent clinical presentation of the disease. The majority of patients are females (2:1 female to male ratio) diagnosed between the ages of 20 and 40. At diagnosis, approximately 85% of patients have relapsing remitting MS (RRMS), characterized by recurrent acute exacerbations (relapses) of neurological dysfunction followed by recovery. A significant proportion (42 - 57%) of relapses may result in incomplete recovery of function and leave permanent disability and impairment. After 6 - 10 years, 30 - 40% of patients with RRMS have progressed to secondary progressive MS (SPMS), in which a less inflammatory and more neurodegenerative course of the disease take over. SPMS presents with steady progression in disability with or without superimposed relapses.

[1] Also called FTY720 through the report

Currently, no oral medication is approved for the treatment of relapsing multiple sclerosis. All available disease modifying therapies for multiple sclerosis are administered subcutaneously, intramuscularly or intravenously.

2.2. Quality aspects

2.2.1. Introduction

Composition

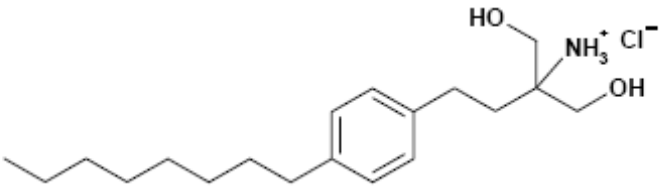
Gilenia is presented as immediate-release hard gelatin capsules containing 0.56 mg of fingolimod hydrochloride as the active substance corresponding to 0.5 mg of fingolimod base. Other ingredients include mannitol and magnesium stearate.
The proposed formulation is a white to almost white powder filled in a hard gelatin capsule (size 3) with white opaque body, bright yellow opaque cap, radial imprint with black ink "FTY 0.5 mg" on the cap and two radial bands imprinted on the body with yellow ink. The capsules are packed in PVC/PVDC blister packs.

2.2.2. Active Substance

Fingolimod is a sphingosine-1-phosphate receptor modulator. In the body, fingolimod is metabolized by sphingosine kinase to the active metabolite fingolimod phosphate.

Fingolimod hydrochloride has not been previously authorised in a medicinal product registered in EU and therefore is considered to be a new chemical entity (NCE). Neither fingolimod nor the hydrochloride salt is described in Ph. Eur. and/ or USP.

The chemical name of fingolimod hydrochloride is 2-Amino-2-(2-(4-octylphenyl)ethyl)propan-1,3-diol hydrochloride and its molecular structure is presented in the figure below.



It is a white to practically white powder. The salt form of fingolimod is freely soluble in water and pH 1.0 buffer, very slightly soluble in pH 4.0 buffer and practically insoluble in pH 6.8 buffer. This solubility profile can be seen as normal for a salt of a primary amine of relatively low molecular mass.

Fingolimod is not a chiral molecule and therefore does not show any specific rotation. However, fingolimod hydrochloride exhibits polymorphism. The active substance used for Gilenia is the polymorphic form I which is stable under the storage conditions specified in the SmPC and is routinely controlled in the specifications.

Manufacture

The manufacturing process of fingolimod hydrochloride consists of multi-step chemical synthesis and uses simple molecules as starting materials.

The levels of the specified impurities are supported by the results of toxicological studies and the solvents used in the synthesis have been shown to be efficiently removed during the purification and drying operations. Appropriate specifications have been set.

Batch analysis results from 30 batches demonstrate that the route of synthesis is capable of reproducibly producing an active substance of the intended quality.

The bulk drug substance fingolimod hydrochloride is primarily packed either in sealed triple laminated foil bags (polyethylene / aluminium / polyethylene terephthalate) or in quadruple laminated foil bags (polyethylene / polyethylene terephthalate / aluminium / polyethylene terephthalate).

The polyethylene material in contact with the active substance meets the requirements of monograph "Polyolefines" in the current Ph.Eur.3.1.3. The laminate packaging material complies with the requirements of the EU Directive 2002/72/EC including later amendments.

Specification

The active substance specification includes tests for appearance, particle size (laser diffraction) identification (IR,X-ray diffraction), assay (HPLC), related impurities (HPLC,), residual solvents (GC), loss on drying (Ph. Eur), heavy metals (ICP-OES) and microbial enumeration (plate count).

An adequate justification has been provided for the choice of specification limits and analytical test methods. The acceptance criteria regarding related substances are either in line with toxicological batches results or with ICH Q3A, the residual solvents limits are in line with Q3C (R3) and the metal catalysts limits are in line with the EU Note for Guidance EMEA/CHMP/SWP/4446/2000.

Batch analysis results for over than 30 batches manufactured according to the intended for commercial manufacture route of synthesis comply with the set specifications.

Stability

Stability studies have been performed with three batches manufactured with the synthetic route intended for commercial production and packaged in either triple laminated foils or amber glass bottles with PP screw caps used for accelerated testing, shipping of small samples and reference. Samples have been stored in accordance to ICH Guidelines for up to 60 months at 25 ^{o}C/60% RH, 30 ^{o}C/65% RH and for 6 months at 40 ^{o}C/75% RH, 20 ^{o}C and 5 ^{o}C.

The parameters tested included appearance by visual examination, identification by IR and X-ray diffraction, related substances by HPLC, loss on drying, clarity and colour of the solution and assay by HPLC. The analytical methods used were validated and stability indicating. In all cases the results met the predefined specifications.

Photostability studies were conducted in one batch showing no discolouration or degradation. Results from stress tests showed no evidence of degradation.

The results of the stability studies show that the active substance is very stable and a re-test period of 5 years was granted when stored either in sealed triple laminated foil bags (polyethylene / aluminium / polyethylene terephthalate) or in quadruple laminated foil bags (polyethylene / polyethylene terephthalate / aluminium / polyethylene terephthalate).

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The active substance is a micronised hydrochloride salt of fingolimod. The free base and ten different salts were evaluated for stability, solubility and morphic properties during development and the hydrochloric salt was chosen due to superior solubility and stability properties in a standard excipient mixture.
The excipients were chosen based on compatibility studies and experience from development of similar formulations. The compatibility studies showed that the active substance interacts with several excipients. Mannitol was chosen as a filler due to the optimum degradation profile. It was also considered that the probability of producing a stable product was higher when developing a capsule as compared to a tablet. Therefore a hard capsule formulation was developed
A standard direct blending was chosen for the manufacture of the capsule fill. In order to ensure content uniformity the active substance is micronised.

Adventitious agents

The gelatin in the capsules is of animal origin and meets the requirements of Ph. Eur. TSE issues for gelatin were addressed by submission of TSE CEPs.

Manufacture of the product

The manufacturing process is a standard process for these kind of formulations.
All critical process parameters have been identified and controlled by appropriate in process controls. The validation report from three production scale batches demonstrates that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification (TLC and HPLC), assay (HPLC), degradation products (HPLC), Dissolution, uniformity of dosage units (content uniformity by HPLC) and microbial enumeration (plate count method)
All tests included in the specification have been satisfactorily described and validated.
Batch analysis data from 3 stability and 3 process validation batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

Stability of the product

Stability studies were carried out on 3 production scale batches of tablets according to the ICH requirements. Samples were stored at 25°C/60 % RH and 30°C/75 % RH for up to 24 months and in 40°C/75 % RH for 6 months.
The parameters tested included appearance, dissolution (HPLC), assay and related substances (HPLC) and microbial limit tests using stability indicating analytical methods.
In all cases the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Gilenia is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.
The active substance is well characterised and documented. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard

process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Risk-benefit balance of the product. The applicant gave a Letter of Undertaking and committed to resolve this as Follow Up Measure after the opinion, within an agreed timeframe. There are no unresolved quality issues, which could have a negative impact on the Benefit Risk balance of the product.

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

Fingolimod (FTY720) has been evaluated in a series of *in vitro* and *in vivo* pharmacological tests used to characterise its effects on biological targets and selectivity, and on lymphocytes and neural cells/astrocytes. In vitro studies primarily investigated receptor binding and cellular activity on lymphocytes and neural cells. In vivo studies mainly included evaluation of the down modulation of S1P1 lymphocyte receptor induced by fingolimod and its effects on experimental autoimmune encephalomyelitis (EAE) disease model using different species (rats, mice). In vivo secondary pharmacodynamic studies were also performed to investigate effects of fingolimod on inflammation, immune and contractile responses.

Some of the studies were conducted with its enantiomers (AML629, AML627) and its active moiety, fingolimod phosphate (FTY720-P).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Fingolimod (FTY720) is claimed to be a novel synthetic Sphingosine 1-phosphate (S1P) receptor modulator indicated as disease-modifying therapy in patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

Mechanistic studies demonstrated that FTY720 is phosphorylated by sphingosine kinase in a variety of cell types and organ cultures. The phosphorylated form (FTY720-P) is claimed to be the active moiety of the drug. In receptor binding assays, FTY720 did not bind to the human receptors S1P1-S1P5, but FTY720-P had good affinity to S1P1, S1P3, S1P4 and S1P5 receptors.

Knock-out studies using conditional S1P receptor-deficient mice have suggested S1P1 as the key receptor responsible for the therapeutic effects of FTY720 in an EAE model. Furthermore, in vivo studies with FTY720 demonstrated a reduction in blood lymphocyte count, which correlated to a down-modulation of S1P1 in lymphocytes which further slowed down the S1P-S1P1 dependent egress kinetics of CD4 and CD8 T-cells and B-cells from lymph nodes.

T-cells seemed to require S1P1 activation to be able to emigrate from the thymus and T- and B-cells seem to depend on this receptor to egress from peripheral lymph organs. Down-modulation of S1P1 reduces the recirculation of lymphocytes from lymph nodes into blood and CNS. Also, PK/PD studies in rats showed a clear correlation between blood concentrations of FTY720-P and the degree of depletion of peripheral blood lymphocytes.

FTY720 is suggested to mimic a conditional S1P1-deficiency in neuronal cells which is correlated to reduced glial fibrillary acidic protein staining and reduced astrogliosis. This may reduce the pro-inflammatory activities of S1P and reduce negative effects on gap junctions in astrocytes.

Fingolimod was studied in EAE disease model systems in Wistar rats, Lewis rats, SJL/J mice and in a new DA rat model developed and validated by the applicant. FTY720 was tested in both prophylactic and therapeutic settings.

In Lewis rats EAE model, a dose of 0.1 mg/kg completely prevented the onset of disease symptoms for a 2-week treatment period and protected against a rebound for at least 1 month. In Lewis rats immunized with Myelin Basic Protein (MBP), therapeutic treatment with FTY720 significantly inhibited the progression of EAE and the disease-associated histological changes in the spinal cords.

In SJL/J mice, the development of proteolipid protein-induced EAE was almost completely prevented and the infiltration of CD4+ T cells into spinal cords was suppressed. Therapeutic treatment of EAE-diseased SJL/J mice inhibited disease scores and demyelination, and the numbers of CD4+ T cells in spinal cords were reduced. The therapeutic effects in SJL mice further correlated to a normalization of mRNAs encoding myelin proteins and inflammatory mediators. Similar therapeutic effects of FTY720 were observed in myelin oligodendrocyte glycoprotein (MOG)-induced EAE in C57BL/6 mice.

In DA rats with severe-protracted EAE, FTY720 inhibited established disease (ED50 $\leq$ 0.1 mg/kg) and the protective effect after discontinuation of FTY720 lasted for up to 2.5 months.

Secondary pharmacodynamic studies

A number of off-targets related to safety pharmacology were identified for FTY720 in a radioligand binding assay comprising GPCRs, transporters, ion channels and enzymes. Ki values were between 1-10 µM (well above human Cmax) with the exception of the histamine H2 receptor, where the affinity was slightly higher, with a Ki of 0.50 µM (172 ng/mL).

In an in vivo murine model of allergen-induced inflammation, reduction of fluid MRI signals, related to plasma leakage and mucus secretion was mainly explained by the action on endothelial barrier integrity through S1P1 receptors.

In non-human primates (NHP) in vivo and in vitro models vaccinated with tetanus toxoid (TTx), FTY720 inhibited the induction of primary TTx-specific IgG responses, presumably by inhibiting the migration of T and B cells from other sites to the antigen-draining lymph nodes.

In an in vitro study (dose range of 1 nM – 10 µM), none of FTY720, FTY720-P or S1P triggered contractile responses in muscle-nerve preparation of the guinea pig (Dunkin-Hartley) ileum and trachea suggesting no facilitation of acetylcholine or histamine release.

Safety pharmacology programme

Cardiovascular system

No in vitro effects were observed on platelet aggregation, cardiac action potential in sheep or rabbit purkinje fibres, QT interval prolongation or QRS in isolated pig hearts. An increased sinus frequency and a slight QT shortening (3%) were observed by both FTY720 and FTY720-P in isolated pig hearts.

In isolated rabbit nodes, FTY720-P slightly but significantly decreased the spontaneously beating rate in sino-atrial (SA) node in two different studies by -8 and -12 % versus baseline and on atrio-ventricular (AV) node with a decrease in the spontaneously beating rate of -9 % versus baseline at 1000 nM.

Conduction velocity, amplitude and duration were not significantly modified. FTY720 inhibited hERG tail current from 200 ng/mL by 25.2 % in HEK293 cells and the active (S)-enantiomer of FTY720-P (AML629) inhibited hERG channel activity from 100 ng/mL by 18.1%, which is well above the human Cmax,ss at the therapeutic dose of 0.5 mg/day (3.4 ng/mL).

In wistar rats, an increased diastolic and systolic blood pressure was observed at an oral dose of 1 and 10 mg/kg of FTY720 and decreased heart rate and sinus arrhythmia were observed at 10 mg/kg.

In guinea pigs, an intravenous dose from 0.01 mg/kg caused sinus arrhythmia and 0.1 and 1 mg/kg decreased heart rate and blood pressure. The QT interval was prolonged as heart rate was decreased but there were no QTc prolongation observed.

Oral administration in conscious dogs caused a dose-dependent decrease in blood pressure at 0.3 and 1 mg/kg. No clear effect on heart rate was observed. In another oral dog study, doses from 5 mg/kg showed a decrease in heart rate (minimal effects in individual animals at 1 mg/kg) and an increase in blood pressure from 2.5 mg/kg.

In monkeys dosed at 10 mg/kg orally, there was an increased systolic and diastolic blood pressure 4-72 hours after administration with maximum increase after 6 hr (133.3 and 135.8% respectively) and a decreased heart rate 8-12 hr after administration by approximately 22%, compared to baseline, and an increased ECG T-wave potential in 2/4 animals that peaked 2, 6 and 8 hr post dose.

Intravenous administration of the active (S)-enantiomer of FTY720-P (AML629) in rats showed a marked and transient sinus bradycardia with concomitant sinus arrhythmia and sinoatrial and/or atrioventricuar blocks and decreased heart rate at 0.1 mg/kg. There was a trend towards reversibility of these effects.

In guinea pigs administered intravenously with 0.01 mg/kg AML629, a decreased heart rate and blood pressure, prolonged PR and QT interval but no QTc prolongation was observed. At 0.1 mg/kg also sinus arrhythmia and ECG changes were noted.

Respiratory system

No significant effects on respiratory minute rate, respiratory minute volume and respiratory tidal volume were observed in anaesthetised dogs administered intraduodenally with 1 mg/kg FTY720. Also, no effects were noted on respiratory rate, blood pH, blood gas tension or haemoglobin oxygen saturation in monkeys administered orally with 0.1, 1 or 10 mg/kg of FTY720. Intravenous administration of AML629 to rats at 0.1, 0.2, 0.5 mg/kg induced dyspnea. In addition, a decreased respiratory minute volume was observed at 0.003 mg/kg and a tendency to decreased respiratory minute volume and respiratory minute rate at 0.001 and 0.1 mg/kg, however not statistically significant.

CNS system

FTY720 showed some decrease in motor coordination in mice and mild depressive activity in the central nervous system in rats at 10 mg/kg. In rats a prolonged narcotic sleep time was observed on Phenobarbital-induced narcotic sleep at 1-week treatments from 10 mg/kg for 4 days and 4 mg/kg for

3 days. This is considered as high dose effects. In a variety of other tests on central nervous effects FTY720 did not show relevant effects.

Other systems
FTY720 resulted in transient decreases in renal function (dogs) and urine output (rats) at 10 mg/kg.

No effects were observed on gastrointestinal functions in rats and mice, on the plasma level of corticosterone in rats and on the smooth muscle contraction of the isolated guinea pig ileum. There was a slight effect on the contraction of the gastrocnemius muscle in rabbits following intraduodenal treatment.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were carried out with fingolimod. The available supportive data were based on clinical studies and were considered sufficient to characterize the drug interaction profile of fingolimod.

2.3.3. Pharmacokinetics

The pharmacokinetics and metabolism of fingolimod were investigated using five animal species: mouse, rat, rabbit, dog and monkey.

The absorption of fingolimod was slow and almost complete after oral administration in most species (≥ 49%). Cmax was reached at 4-12 hours following a single oral administration. FTY720-P in the blood was present almost exclusively (≥ 94%) in the form of the (S)-enantiomer (AML629). The absolute oral bioavailability was high with > 50% of the dose in mice, rats, dogs, and monkeys.

FTY720 and AML629 were highly bound to plasma proteins of the mouse, rat, dog, monkey (>99%).

After i.v. or p.o. dosing of [14C]-FTY720, drug-related radioactivity was extensively distributed to most organs and tissues of mice, rats and dogs. The tissue distribution was consistent with the large steady-state volume of distribution (Vss) of FTY720 observed in the mouse (17.3 L/kg), rat (21 L/kg), and dog (7.6 L/kg).

FTY720 and FTY720-P crossed the blood-brain barriers of several species (mice, rats, dogs and monkeys). FTY720-P was found in the cerebral cortex and spinal cord of the rat almost exclusively in form of the (S)-enantiomer (AML629). FTY720 and its metabolites crossed the placental barrier of pregnant rats and rabbits. FTY720 and its metabolites excreted into the milk of lactating rats.

In pregnant rats [14C]-fingolimod-related radioactivity penetrated readily into the placenta and fetuses after a single oral dose of 0.45 mg/kg [14C]-fingolimod on gestational days 13 and 18. In pregnant rabbits [14C]-fingolimod-related radioactivity penetrated the placental barrier after a single oral dose of 5 mg/kg [14C]- fingolimod at gestational day 17, reaching radioactivity concentrations in fetuses about 4-fold lower than in the dam. FTY720-related radioactivity slowly passed into the milk after a single oral dose of 7.5 mg/kg of [14C]-fingolimod in rats, reaching maximum radioactivity concentrations (3.91 µmol/L; 1.2 µg-eq/mL) 24 hours post-dose. The radioactivity in milk consisted mainly of fingolimod and fingolimod-P (exclusively the (S)-enantiomer) and reached 2- to 3-fold higher concentrations in milk than in the blood of the dam.

In rats, the highest radioactivity concentrations after multiple oral dosing of 2.5 mg/kg were observed in the glandular stomach, liver, oesphagus, kidney, pituitary gland, spleen and adrenal followed by brain tissue, spinal cord and choroids plexus. Fingolimod-related radioactivity disappeared slowly from blood and most tissues, with apparent terminal half-lives of about 30-60 hours. The elimination of

radioactivity was slower from brain tissue (t1/2 ~140 h), eyes and white fat (t1/2 ~160 h), nerves (t1/2 ~200 h), epididymis (t1/2 ~320 h), and testis (t1/2 ~460 h).

In an in vitro study with human liver microsomes, M12 (8-hydroxyoctyl metabolite) was identified as the major metabolite of fingolimod. The biotransformation of fingolimod occurred by three primary pathways for most of the drug-related material in blood and/or excreta across all studied species (including human): reversible phosphorylation of fingolimod to fingolimod-P (the pharmacologically active (S)-enantiomer AML629); CYP-dependent (mainly CYP4F2) hydroxylation at the octyl side chain to metabolite M12, followed by further oxidation to M1, M2, M3 and M4 and formation of ceramide analogs of FTY720 (M27-M30).

Mainly CYP2D6, CYP2E1, CYP3A4, CYP4F2, CYP4F3B and CYP4F12 were shown to catalyze the biotransformation of FTY720 to M12, M15-M20 with measurable turn-over, of which CYP4F2 contributed predominantly. All metabolites found in vivo in human blood were also detected in at least one animal species (mouse, rat, rabbit, dog or monkey) with rat and monkey showing the most similar metabolite pattern.

After repeated dosing of 7.5 mg/kg [14C]-fingolimod for 14 days to male rats, fingolimod was more abundant than fingolimod-P in the cerebral cortex, whereas fingolimod-P was more abundant than fingolimod in the spinal cord. The ceramide analogue metabolites M28 and M30 were present in traces. Other unidentified radiolabeled components were detected in small amounts (<2% of radioactivity).

Balance of excretion in urine and feces was almost complete (generally > 90% of the p.o. dose) after 7 days in mice and rats, and after 10 days in dogs. In monkeys, the balance of excretion in urine and feces was incomplete (72%, after p.o.) due to loss of excreta during sample collection. In bile duct-cannulated rats, 43, 17, and 24% of the radioactive dose was recovered in the urine, bile, and feces within 72 hours post-dose, respectively.

2.3.4. Toxicology

Single dose toxicity

Acute toxicity studies were performed in mice, rats and dogs using oral and/or intravenous routes. The estimated lethal dose in 50% of animals (LD50) for acute intravenous toxicity of FTY720 in mice was 25<LD50<50 mg/kg for males and >50 mg/kg for females. The LD50-estimation for acute intravenous toxicity of FTY720 in rats was >50 mg/kg for males and 21 mg/kg for females. In acute oral toxicity study in dogs, no considerable clinical signs or mortality were observed mainly due to dose limiting effect (as expressed by vomiting) of the test compound at 2000 mg/kg. No effect on peripheral blood pressure after oral single dose of 1 mg/kg in dogs was observed. The main finding was lymphopenia which was seen without recovery from days 1 to 8 post-administration and correlated with atrophic changes in lymph nodes.

Repeat dose toxicity

Repeat dose studies were performed in mice, rats, monkeys and dogs using the oral route.

In mice, the "no observed adverse effect level" (NOAEL) after 4 weeks of dosing was set at 0.3 mg/kg/day.

In rats, a decrease in lymphocytes in peripheral blood was seen at all dose levels and correlated histopathologically with dose-related atrophic changes of lymphatic organs and immunohistochemically

with a decreased number of circulating (intrasinusoidal/intravascular) CD3-positive T-lymphocytes in the liver in a 13 week study. Additionally, interstitial collagenization was seen in the lungs at all FTY720 treated groups and smooth muscle hypertrophy in bronchiolo-alveolar junctions at 5 mg/kg/day. Effects on lymphoid organs and decreased lymphocyte counts were noted for all treated groups in a 26 week study. Effects in the lungs and kidneys were observed and were associated with the pharmacological action of fingolimod in a 27 week study.

In dogs, a dose-limiting effect (as expressed by vomiting), an increase in AST, and a decrease in body weight were seen at 30 mg/kg/day in a 2 week study. A decrease in lymphocyte counts and atrophy of lymph nodes were seen at dose equal or greater than 0.01 mg/kg/day in a 4 week study, the NOAEL of FTY720 was set at 0.001 mg/kg/day. In a 26-week study, a decrease in total cholesterol, an increase in lung weights, alveolar macrophage infiltration of the lungs and vascular wall thickening of the heart were noted at 1 mg/kg/day in a 26 week study, the NOAEL was set at 0.01 mg/kg/day.

In cynomolgus monkeys, an increased incidence of insufficient pulmonary collapse was observed in compound treated animals and generally correlated with increased lung weights and histologic evidence of smooth muscle hypertrophy and/or increased collagen in a 43 week study at doses of 0.5 or 3 mg/kg/day. Pulmonary smooth muscle hypertrophy/increased collagen was reduced after recovery periods of 13 and 26 weeks, indicating partial reversibility. In a longer 52-week study, main findings included a generally dosage-related effect on body weight, water consumption and lung weight, the latter being associated with hypertrophy of the smooth muscle at the bronchiolo-alveolar junction and hyper-distension of the alveoli at all dose levels. Hyperplasia of smooth muscle cells with an associated increase in the amount of collagen in the walls of the respiratory bronchioles and alveolar ducts and the entrances to the alveolar sacs, together with aggregates of alveolar macrophages were also observed in a number of animals.

Genotoxicity

The mutagenicity and clastogenicity of fingolimod was evaluated in vitro in an Ames test, DNA repair tests, and in a gene mutation assay in mouse lymphoma cells. Rat and mouse micronucleus tests were also performed. All of these studies had negative results.

Carcinogenicity

The oncogenic potential of fingolimod was assessed in mice and rats following oral administration.

In 104 week studies following oral administration of FTY720, an increased incidence in malignant lymphomas at 0.25 and 2.5 mg/kg/day was observed in mice. No tumorigenic potential up to the highest dose level of 2.5 mg/kg/day were noted in rats.

In mice, dose dependent increased incidences of hemangiosarcoma in the liver ≥ 0.25 mg/kg/day in males, increased incidences of hemangiosarcoma for the total body at 2.5 mg/kg in males and increased incidences of hemangioma for the total body in females at 2.5 mg/kg/day were also observed.

Reproduction Toxicity

The effect of fingolimod on fertility and early embryonic development was assessed in male and female rats and in female rabbits.

In a 4-week repeat-dose toxicity study in dogs, all males showed hyperspermatogenesis in tubuli of testes and hypospermia in epidymis at 30 mg/kg. In male rats, atrophy of prostate and seminal vesicle at 10 mg/kg (n=2), decreased prostate weight and secretion were observed in a dose related manner from 0.5 mg/kg. Howewer, fingolimod had no effect on sperm count/motility or on fertility in

male and female rats up to the highest dose tested (10 mg/kg), representing an approximate 150-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

In rabbits, maternal toxicity and high embryo-fetal mortality at doses equal or greater than 10 mg/kg/day were observed. In another study, a significant increase in embryo-fetal mortality in rabbits at doses equal or greater than 1.5 mg/kg and a decrease in the number of viable fetuses as well as fetal growth retardation were noted at 5 mg/kg/day, in the absence of severe maternal toxicity.

In pre- and postnatal development study in pregnant and lactating rats, FTY720 administered at doses of 0.05, 0.15 or 0.5 mg/kg/day resulted in maternal effects at 0.5 mg/kg/day which included slightly decreased food consumption and body weight parameters and, decreased F1 pup survival in the early postpartum period at all doses. The most common foetal visceral malformations included persistent truncus arteriosus and ventricular septum defect. Treatment-related effects in neonatal/ juvenile animals were comparable to those seen in adult rats at that dose levels, with the exception of the absence of smooth muscle hypertrophy in the lungs of the juvenile rats.

Toxicokinetic data

Toxicokinetic data on FTY720, FTY720-P, and a number of metabolites were collected from pharmacokinetic or toxicology studies previously described.

Exposure of all animals to FTY720, FTY720-P, and metabolites M2, M3, M29 and M30 was shown in the mice, rats, rabbits, dogs and monkeys.

Across all studied species, systemic exposure to FTY720 (Cmax and AUC) increased approximately proportional with the dose. Steady-state blood concentrations of FTY720 were reached generally after 1-2 weeks of daily treatment. There was no apparent gender difference in exposure to FTY720, in all studied species. Brain/blood concentration ratios were different between species and dependent on dose and treatment period. In monkeys at 0.5 to 10 mg/kg, respectively, the brain-to-blood ratios were approximately 117- or 346-fold at the end of a 13- and 39-week treatment period.

Local Tolerance

Following intravenous administration, local irritation at the injection site was observed in dogs and rats in studies investigating doses up to 5mg/kg. Other findings not related to local tolelance were similar to the previously described oral toxicity studies.

Other toxicity studies

FTY720 did not induce anti-FTY720 IgE antibody production in mice. In addition, FTY720 did not induce the production of antibodies specific to FTY720 or anaphylactic reactions in guinea pigs.

FTY720 and its active moiety FTY720 did not absord light at ≥ 290 nm. No specific photoxicity study has been performed. Fingolimod-related radioactivity was reversibly taken up to melanin-containing structures of the eye in pigmented rats.

FTY720 did not induce anti-FTY720 IgE antibody production in mice. In addition, FTY720 did not induce the production of antibodies specific to FTY720 or anaphylactic reactions in guinea pigs.

In immunotoxicity studies, T cell-dependent antibody generation specific to Sheep Red Blood Cell (SRBC) was still possible at FTY720 doses of 0.3, 1.5 or 7.5 mg/kg/day. FTY720 at 7.5 mg/kg/day, by dietary administration to rats, resulted in a reduction of cortical proliferating cells (undifferentiated T-cells and thymocytes). An increase of CD3 positive (differentiated T-lymphocytes) medullary cells, with no proliferation, was also observed. In monkeys, FTY720 inhibited the induction of primary TTx-specific IgG responses, presumably by inhibiting the migration of T and B cells from other sites to the antigen-draining lymph nodes (LN).

Transcriptomic studies were performed on rat and monkey lungs to elucidate the mechanism of action of the lung toxicity (hypertrophy/hyperplasia), in addition of other in vitro and in vivo studies. The results of these studies showed that important modifications of the gene expression profiles, generally an increased expression of many categories of transcripts.

No evidence of a mutagenic or clastogenic/ aneugenic potential on impurities was shown.

2.3.5. Ecotoxicity/environmental risk assessment

An ERA according to CHMP guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, June 2006) was submitted. The physiochemical properties of fingolimod are: Molecular mass: 343.94; solubility in water>200g/l; Log Kow (pH 6): 3.6, Log D (pH7): 2.6. Based on a daily dose of 1.25 mg fingolimod, the predicted environmental concentration in surface water was $PEC_{SURFACE\ WATER}$ was 0.00625 µg/L (< 0.01 µg/L). No Phase II studies were performed. However, the Log D determination was questioned by the CHMP prior to any conclusion on the persistent, bioaccumulative and toxic (BPT) properties of fingolimod. Following clarifications on the method used and LogD determination, the CHMP considered that a risk for the environment due to the intended use of fingolimod in patients with multiple sclerosis is not expected.

2.3.6. Discussion on non-clinical aspects

In mechanistic and receptor binding studies, fingolimod has shown to be phosphorylated to fingolimod-P, claimed to be the active moiety. Fingolimod P has a good affinity to S1P1, S1P3,S1P4 and S1P5 receptors. By acting as a functional antagonist of S1P receptors in its phosphorylated form, fingolimod has further demonstrated in vivo a reduction in blood lymphocyte count, which correlated to a down-modulation of S1P1 in lymphocytes which further slowed down the S1P-S1P1 dependent egress kinetics of CD4 and CD8 T-cells and B-cells from lymph nodes. This mechanism is claimed to reduce the recirculation of lymphocytes from lymph nodes into blood and CNS. In vivo studies also indicated that fingolimod may also act via interaction with S1P receptors on neural cells.

Several EAE disease model systems were used in both prophylactic and therapeutic settings. Fingolimod showed beneficial effects in these models by either preventing the onset of disease symptoms, protecting against a rebound effect or inhibiting the progression of EAE and disease-associated histological changes. A number of other secondary pharmacodynamic effects (e.g immune and contractile responses) were also observed.

The safety pharmacology identified several cardiac effects (e.g decrease heart rate, increased blood pressure, ECG changes, arrhythmia, sinoatrial and atrioventricular blocks) observed in different species. Respiratory effects (e.g dyspnea) were also reported in rats.

The results of the pharmacokinetic studies in animals showed: slow oral absorption, extensive tissue distribution (crossed the blood brain and placenta barriers), high protein binding and slow elimination. Fingolimod drug related material is excreted both in urine and faeces and notably in milk.

The majority of the findings in the repeated dose toxicity studies were related to the pharmacological activity of fingolimod. Main target organs were the lymphoid system (lymphopenia and lymphoid atrophy), lungs (increased weight, smooth muscle hypertrophy at the bronchio-alveolar junction), and heart (negative chronotropic effect, increase in blood pressure, perivascular changes and myocardial degeneration) in several species; blood vessels (vasculopathy) in rats only.

An initial increase in vascular permeability in concert with activation, differentiation and/or transmigration of phagocytes in the lungs and arterial wall leading to an increased secretion of soluble

markers was suggested to contribute to the smooth muscle hypertrophy. Increased permeability and vasculopathy were also seen in several other organs.

In the 2 year carcinogenicity studies conducted in mice and rats, different results were observed. An increased incidence in malignant lymphomas at 0.25 and 2.5 mg/kg/day was observed in mice representing an approximate 6-fold margin based on the human systemic exposure (AUC) at a daily dose of 0.5 mg. No tumorigenic potential up to the highest dose level of 2.5 mg/kg/day were noted in rats representing an approximate 50-fold margin based on human systemic exposure (AUC) at the 0.5 mg dose. FTY720 is not a classical immunosuppressive drug and consequently the mechanism behind the increased incidence of lymphomas, and the clinical relevance of immunosuppression remain unclear. This issue is discussed under the clinical aspects.

Taking into account the above non clinical findings, the long term effects of fingolimod on T cells and their egression to the peripheral circulation should be further addressed by the applicant and this is discussed under the clinical aspects.

There was no evidence of genotoxicity in a standard package of tests.

In a 4-week repeat-dose toxicity study in dogs, all males showed hyperspermatogenesis in tubuli of testes and hypospermia in epidymis at 30 mg/kg. In male rats, atrophy of prostate and seminal vesicle at 10 mg/kg (n=2), decreased prostate weight and secretion were observed in a dose related manner from 0.5 mg/kg. Howewer, fingolimod had no effect on sperm count/motility or on fertility in male and female rats up to the highest dose tested (10 mg/kg), representing an approximate 150-fold margin based on human systemic exposure (AUC) at a daily dose of 0.5 mg.

In rabbits, maternal toxicity and high embryo-fetal mortality at doses equal or greater than 10 mg/kg/day were observed. In another study, a significant increase in embryo-fetal mortality in rabbits at doses equal or greater than 1.5 mg/kg and a decrease in the number of viable fetuses as well as fetal growth retardation were noted at 5 mg/kg/day, in the absence of severe maternal toxicity. There were some limitations in this study (e.g decreased number of viable foetuses) and the CHMP concluded that the teratogenic potential could not be fully assessed in rabbits.

Fingolimod was teratogenic in rats when given at doses of 0.1 mg/kg or higher. The most common foetal visceral malformations included persistent truncus arteriosus and ventricular septum defect.

Regarding the reduction of survival in F1 pups, in utero effects may have likely induced peri-natal deaths even though no cardiac abnormalities were found in the examined pups. Immature metabolism could also have contributed to the high mortality rate in F1 pups. However, the CHMP concluded that the reduction of the survival of F1 pups at all doses in the pre and postnatal development study has not been fully elucidated. Furthermore, fingolimod was excreted in milk of treated animals during lactation at concentrations 2-3-fold higher than that found in maternal plasma. Fingolimod and its metabolites crossed the placental barrier in pregnant rabbits.

Appropriate recommendations concerning pregnancy, lactation and breastfeeding are included in the SmPC.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical aspects of fingolimod have been adequately documented and meet the requirements to support this application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Summary of Placebo- and Active-controlled Studies

Table 1

Study No.	Study objective, population	Patients randomized	Treatment duration	Dosage	Primary efficacy endpoint
Phase III					
[D2301] (placebo-controlled)	FTY720 pivotal Efficacy and safety in patients with RRMS	1250 (planned) 1272 (actual)	24 months	FTY720 1.25 mg orally o.d. FTY720 0.5 mg orally o.d. Placebo	ARR up to 24 months
[D2302] (active-controlled)	FTY720 pivotal Efficacy and safety in patients with RRMS	1275 (planned) 1292 (actual)	12 months	FTY720 1.25 mg orally o.d. FTY720 0.5 mg orally o.d IFN β-1a 30 µg i.m. once/week	ARR up to 12 months
Phase II					
[D2201] (placebo-controlled)	FTY720 efficacy and safety in patients with relapsing MS (RRMS and SPMS)	240 (planned) 281 (actual)	6 months	FTY720 1.25 mg orally o.d. FTY720 5.0 mg orally o.d. Placebo	Total number of post-baseline MRI Gd-enhancing lesions over 6 months

Abbreviations: ARR = annualized relapse rate, IFN = interferon, i.m. = intramuscularly, MRI = magnetic resonance imaging, o.d. = once a day, RRMS = relapsing remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.

Summary of Studies Providing Long-term Data

Table 2

Study No.	Study objective, population	Patients	Treatment duration	Dosage	Efficacy variables
[D2201] [D2201E1] (Extension to study D2201)	FTY720 long-term efficacy and safety in patients with relapsing MS	281 (ITT population)* 250 (Extension population) †	Ongoing 60 months interim data (6 months core study and 54 months in extension)	FTY720 initially 1.25 mg or 5.0 mg orally o.d.; between Months 15 and 24, 5.0 mg patients switched to open-label 1.25 mg orally o.d.	MRI, relapses and disability (EDSS)

Abbreviations: EDSS = expanded disability status scale, ITT = intent-to-treat, o.d. = once a day.
* ITT population = all patients who received at least one dose of study drug (including placebo) and at least 1 valid post-baseline MRI scan. † Extension population = all patients who received at least one dose of extension study drug.

Summary of Ongoing Clinical Studies in Multiple Sclerosis

Table 3

Study design and purpose	Planned /actual number of patients	Treatment duration	Treatment/dose	Type of control/blinding
FTY720D2309 Efficacy and safety of FTY720 in patients with relapsing-remitting MS	1080 planned 1089 actual	24 months	FTY720 0.5 mg/day FTY720 1.25 mg/day Placebo orally	Placebo-controlled; double-blind
FTY720D2301E1 Long-term efficacy and safety of FTY720 in patients with relapsing-remitting MS	Not specified*	Open-ended	FTY720 0.5 mg/day FTY720 1.25 mg/day orally	Dose-blinded (FTY720 patients continued on their original dose; placebo patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)
FTY720D2302E1 Long-term efficacy and safety of FTY720 in patients with relapsing-remitting MS	Not specified* 1030 actual	Open-ended	FTY720 0.5 mg/day FTY720 1.25 mg/day orally	Dose-blinded (FTY720 patients continued on their original dose; interferon patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)
FTY720D2309E1 Long-term efficacy and safety of FTY720 in patients with relapsing-remitting MS	Not specified*	Open-ended	FTY720 0.5 mg/day FTY720 1.25 mg/day orally	Dose-blinded (FTY720 patients continued on their original dose; placebo patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)

Study design and purpose	Planned /actual number of patients	Treatment duration	Treatment/dose	Type of control/blinding
FTY720D2201E1 Long-term safety and effect on efficacy parameters of FTY720 in patients with relapsing MS	Not specified* 250 actual	Open-ended	FTY720 1.25 mg/day orally. Initially included the FTY720 5.0 mg dose.	Open-label. Initially dose-blinded (FTY720 patients continued on their original dose; placebo patients were re-randomized to FTY720 1.25 mg or 5.0 mg). When patients were 15-24 months in study (9-18 months in extension), the FTY720 5.0 mg dose was discontinued and patients switched to 1.25 mg
FTY720D1201 Efficacy and safety of FTY720 in patients with relapsing MS in Japan	165 planned	6 months	FTY720 0.5 mg/day FTY720 1.25 mg/day Placebo orally	Placebo-controlled; double-blind
FTY720D1201E1 Long-term efficacy and safety of FTY720 in patients with relapsing MS in Japan	Not specified*	At least 12 months	FTY720 0.5 mg/day FTY7201.25 mg/day orally	Dose-blinded (FTY720 patients continue on their original dose; placebo patients re-randomized to FTY720 either 0.5 mg or 1.25 mg)
FTY720D2306 Efficacy and safety of FTY720 in patients with primary progressive MS	650 planned	Up to 4-5 years**	FTY720 1.25 mg/day Placebo orally	Placebo-controlled; double-blind

*There was no specific sample size for the extension studies. Generally, patients could enter the extensions if they completed the respective core study.
**The double-blind phase continues until the last randomized patient completes 36 months (unless discontinued earlier). All E1 extensions will continue until drug is available on the market.

2.4.2. Pharmacokinetics

Pharmacokinetic (PK) data were derived from 14 phase I clinical pharmacology studies including a total number of 372 volunteers: 253 healthy volunteers, 88 renal transplant patients, 22 hepatic impaired patients and 9 renal impaired patients. In addition, 2 studies have been performed in order to investigate the potential for drug-drug interaction and included 14 psoriasis patients (cyclosporine) and 22 healthy volunteers (ketoconazole). The pharmacokinetic/pharmacodynamic profile of fingolimod was also investigated in a study including 112 healthy volunteers.

Concentrations of fingolimod and its analysed metabolites (e.g fingolimod-phosphate) were measured in whole blood using LC-MS/MS methods in the PK studies. Pharmacokinetic parameters were determined using non compartmental models. In addition, population PK analyses using nonlinear

mixed effects modeling methodology (NONMEM) and exposure-response relationship modelling were also performed.

Absorption

Fingolimod was extensively (≥ 85%) and rapidly absorbed upon oral administration as it could be detected 0.5 to 1 h after administration. However, the absorption was slow (tmax of 12-16 hours). The absolute oral bioavailability appeared to be high (93%, 95%CI: 79-111%).

The extent of absorption of fingolimod is not significantly modified by food intake absorption. The impact of food-intake on the rate of absorption is less clear. A 34% decrease in Cmax was observed with the active metabolite fingolimod-phosphate and was considered marginal in comparison to average blood concentration at steady state. The SmPC recommends that Gilenya may be taken without regard to meals.

All phase II and III clinical studies were conducted using the formulation intended to be marketed.

Distribution

The volume of distribution estimated after administration of 1 mg fingolimod by IV route is 1200 ± 260 l, indicating an extensive distribution of fingolimod to body tissues. At blood level, a high distribution into red blood cells was evidenced with a fraction of 86% for fingolimod. Fingolimod-P showed much less uptake by blood cells with a fraction in blood cells (<17%). At plasma level, Fingolimod and fingolimod-P are extensively bound to plasma proteins with an unbound fraction of 0.15% in the concentration range 0.1- 100 ng/mL. The level of binding was similar in healthy volunteer and in patients with hepatic and severe renal impairment.

Elimination

Apparent Fingolimod blood clearance is low, 6.3±2.3 L/h, and the average apparent terminal half-life is long, 6-9 days. Blood levels of fingolimod-P decline in parallel with fingolimod in the terminal phase yielding similar half-lives for both.

After an oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites. Fingolimod and fingolimod-P are not excreted intact in urine but are the major components in the feces with amounts representing less than 2.5% of the dose each. As expected from high protein binding and high volume of distribution, hemodialysis results in only a minor, 14% decrease in fingolimod blood concentration. After 34 days, the recovery of the administered dose is 89%.

Dose proportionality and time dependencies

Fingolimod and fingolimod-P PK appeared to evolve proportionally to the dose for a wide range of doses including the therapeutic dose range of interest i.e. 1.25 mg - 0.5 mg and lower doses.

The intra-individual and inter-individual variability (respectively 15% and 30% approximately) was in general relatively low in healthy volunteers. The inter-subjects variability was higher in patients (approximately 50-65 %).

Special populations

Specific phases I studies evaluating renal and hepatic functions, paediatric population and effect of race were conducted. Other data related to age, gender were derived from population PK analyses. Exposure- response relationship modelling in patients with RRMS was also performed.

A specific study was conducted in subjects with stable severe renal impairment after 1.25 mg oral single dose. Exposure to fingolimod and fingolimod-P was slightly enhanced in severe renal impaired patient comparatively to healthy volunteers (increase of Cmax and AUC by 32 and 43 % for fingolimod and 25 and 14% for fingolimod-P). A 14-fold increase of exposure to M3 inactive metabolite was also observed.

Specific studies were conducted in subjects with hepatic impairment after oral single dose, at 1 mg dose for subjects with mild/moderate impairment and 5 mg dose for subjects with severe impairment. For fingolimod, AUC was increased by 12%, 44% and 103% for subjects with mild, moderate and severe hepatic impairment, respectively. The apparent elimination half-life was unchanged in mild hepatic impairment but was prolonged by 49-50% in moderate and severe hepatic impairment. For fingolimod-P, AUC was increased by 29% in subjects with severe hepatic impairment. There were no data on exposure to fingolimod-P in subjects with mild/moderate hepatic impairment. Recovery of the inactive metabolite M2 in urine over the first 4 days post-dose was not affected by mild hepatic impairment but was reduced by an average of 70% and 53% in moderate and severe hepatic impairment, respectively. M3 urine recovery was reduced on average by 47%, 68% and 65% in mild, moderate and severe hepatic impairment, respectively.

A specific study was conducted in Caucasian and Japanese subjects to evaluate the effect of race. There were no significant differences observed between Caucasian and Japanese after single 1.25, 2.5 or 5 mg dose and multiple 5 mg dose. Additional population PK analyses in renal transplant and MS patients revealed no significant influence of ethnicity on pre-dose blood concentrations for fingolimod.

There are limited data available in adolescent population that included 7 children above 11 years of age with renal transplant. No conclusions could be drawn regarding the pharmacokinetic profile in this population.

Population pharmacokinetic analyses did not reveal any significant effect of gender nor age. No conclusions could be drawn regarding the pharmacokinetic profile in the elderly population.

Exposure- response relationship modelling in patients with RRMS showed that 0.5 mg dose was as beneficial as 1.25 mg dose.

Pharmacokinetic interaction studies

In vitro studies suggested that the oxidative metabolism of FTY720 is mediated predominantly by CYP4F2 with additional contribution of CYP3A4 and several other enzymes. Lack of specific identified CYP4F inducer or inhibitor in the submitted clinical studies did not allow drawing definite conclusion on CYP4F interaction. In addition, the metabolism of FTY720 was inhibited in vitro by ketoconazole, and slight inhibitions were observed with troleandomycin (TAO), being a well-known mechanism-based inhibitor for CYP3A4. The inducing properties of fingolimod seemed to be low. In vitro studies indicated that fingolimod was not an inducing agent for isoenzymes/transporters regulated via PXR, CAR and the Ah-receptor pathways.

The potential interactions were studied in humans for the following drugs: ketoconazole (CYP3A4/CYP4F2 inhibitor) and cyclosporine (CYP3A4/MDR1 inhibitor).

In the study with ketoconazole, the AUCt and AUC of both FTY720 and FTY720-P were increased by approximately 70% in co-administration with ketoconazole, as compared to FTY720 administered alone. In the study with cyclosporine, there was no influence of ciclosporine on the Cmax or AUCt of fingolimod; however the total AUC indicated a slight increase in co-administration with cyclosporine, although not statistically significant. Also, fingolimod did not appear to be a substrate of the protein P-glycoprotein transporter (P-gp).

Considering the teratogenic properties of fingolimod and the lack of in vivo interaction study investigating the inducing effect of fingolimod on oral contraceptives, an additional study evaluating the interaction between fingolimod, ethinyl estradiol and levonorgestrel was performed at the CHMP request. Following this co-administration, no changes were observed neither in the oral contraceptives exposure nor in fingolimod and fingolimod P.

2.4.3. Pharmacodynamics

Mechanism of action

After oral dosing, fingolimod is phosphorylated in vivo by sphingosine kinase to form the active moiety fingolimod-phosphate (fingolimod-P). GTPγS binding assays revealed that FTY720-P can bind to four of the five known S1P receptors in vitro, namely S1P1, S1P3, S1P4, and S1P5 but not S1P2.

Depending on the cell type, the concentration, and the time following administration, fingolimod-P may act as an "agonist" or "functional antagonist" at S1P receptors. The key claimed pharmacodynamic effect of fingolimod relevant for MS is a dose-dependent reduction of the peripheral lymphocyte count mediated by down-modulation of the S1P1 receptor on lymphocytes.

Under normal circumstances, lymphocytes exit from lymph nodes via S1P1 receptor signaling along a sphingosine 1-phosphate gradient. Both T- and B-cells require this receptor for emigration from peripheral lymphoid organs and T-cells selectively require S1P1 activation for emigration from the thymus.

Fingolimod-P is claimed to act as a functional antagonist of the S1P1 receptor on lymphocytes, inducing its uncoupling/internalization. The internalization of S1P1 renders these cells unresponsive to S1P, depriving them of the obligatory signal to egress from lymphoid organs and recirculate to peripheral inflammatory tissues. Thus, fingolimod-P is claimed to cause a re-distribution, rather than depletion, of lymphocytes. This reduces infiltration of pathogenic lymphocyte cells into the CNS where they would be involved in inflammation and nervous tissue damage. Other principal pharmacodynamic effects of fingolimod include effects on the heart (decreased heart rate, AV conduction block) and lung (increased airway resistance).

Primary and Secondary pharmacology

Pharmacodynamic effects of fingolimod on lymphocytes count, heart and lungs have been investigated in healthy volunteers, patients with renal transplant, psoriasis, moderate asthma, renal or hepatic impairment. Some of these studies were previously discussed in relation to the pharmacokinetic profile of fingolimod.

Lymphocyte count

Single doses of fingolimod ≥ 0.5 mg resulted in a dose dependent decrease in lymphocyte count up to 27% of baseline at 3.5 mg. This decrease occured rapidly, within 3-4 hours of the oral dose. With single doses from 5 to 40 mg, there is a dose-dependent decrease in lymphocyte count between 74% and 90% from baseline. With multiple dosing (28 days) of fingolimod from 0.125 mg to 5 mg there was a dose dependent decrease in lymphocyte count. Even at the lowest dose of fingolimod tested, 0.125 mg, a decrease in lymphocyte count can be detected within several days after the start of treatment. For fingolimod 0.5 mg, lymphocytes counts developed an average decrease of approximately 60% from the baseline and the recovery was not full at day 56 (one month later) with lymphocytes count achieving 80% of the baseline. At doses ≥ 1 mg/day, reductions around 70% to 80% were observed. A full recovery was observed at day 56 for 0.125 mg and 0.25 mg.

In a specific study in healthy volunteers, the capacity to mount a primary IgG and IgM response to a novel T-cell dependent antigen (Keyhole limpet hemocyanin or KLH) was reduced by approximately 45% and 88%, respectively, in the fingolimod 0.5 mg treatment group as compared to placebo group. Similar findings were observed in relation to immune response to Pneumococcal vaccine (PPV-23), with a reduction by approximately 50% and 30%, respectively. Placebo and fingolimod 0.5 mg groups had similar capacity to mount a > 4 fold increase in IgG antibody level to PPV-23 immunization, 54% and 41%, respectively. There were lower > 4 fold responder rates for both KLH IgG (57%) and PPV-23 IgG (10%) in the fingolimod 1.25 mg group compared to either placebo or fingolimod 0.5 treatment groups. Anti-tetanus toxoid IgG levels did not change over the course of the study on placebo or fingolimod treatment. Skin delayed type hypersensitivity was decreased in subjects receiving fingolimod treatment compared to placebo treatment. While the fingolimod 0.5 mg treatment group had a DTH response similar to placebo, the fingolimod 1.25 mg treatment group manifested a clearly lower capacity to mount a DTH.

The use of short course of corticosteroids therapy for relapses was not associated with an increased risk of infection in MS clinical studies. However, no further investigation of pharmacodynamic interaction with other MS treatment modalities was performed.

Cardiac effects

Single doses of fingolimod 0.5 and 1.25 mg have a mean negative chronotropic effect especially on the first day of treatment. This effect began to attenuate after 14 days of dosing. With continued chronic dosing, the negative chronotropic effect of fingolimod disappeared. With multiple dose administration of fingolimod 0.5, 1.25 or 5 mg, the negative chronotropic effect occurred especially on the first day of dosing. The transient acute decrease in heart rate after the first dose of fingolimod and the subsequent recovery was similar in Asian and Caucasian subjects after both single dose and multiple doses.

Fingolimod acts synergistically with atenolol inducing severe bradycardia in healthy volunteers representing 15% additional reduction of heart rate. An intense bradycardia was present during the first 8 hours, and recurred at night time, when vagal activation was maximal.

When fingolimod was used with diltiazem, there was no additional effect on heart rate over 12 hours compared with fingolimod treatment alone.

Atropine did not relevantly antagonize nor prevent fingolimod induced bradycardia in healthy volunteers.

Fingolimod induced bradycardia and shift the dose response of isoproterenol to the right in healthy volunteers, acting similarly to beta-blocker agents.A titration regimen (0.125 – 1.25 mg) over the first week reduced the initial bradycardia induced by fingolimod.

In addition to bradycardia, treatment with fingolimod is associated with an increased incidence of AV block. The incidence rate of 2nd degree atrioventricular block with fingolimod doses ≤1.25 mg (7%) was approximately twice the incidence rate measured in placebo-treated subjects (3%). The duration of the blocks were longer as well with fingolimod. In most subjects receiving fingolimod, the 2nd degree atrioventricular blocks occurred within 6-8 hours of receiving the Day 1 dose, when the maximal negative chronotropic effect was observed. The AV blocks were typically asymptomatic and did not require treatment. No second degree Mobitz type II or wide complex 3rd degree heart blocks were observed. However, one subject received a supratherapeutic, single fingolimod dose of 15 mg on day 1 and developed within several hours, a 2:1 and transient complete heart block (CHB), narrow QRS and rate of approximately 45 bpm.

In a specific study in healthy volunteers, fingolimod treatment at 1.25 and 2.5 mg doses, using an escalating dosing schedule, resulted in a significant, mild prolongation of QTcI on Day 7, and the upper bound of the 90% CI was ≤13.0 ms.

Pulmonary effects

Fingolimod treatment with single or multiple doses of 0.5 and 1.25 mg for two weeks was not associated with a detectable increase in airway resistance as measured by FEV1 and forced expiratory flow rate (FEF) 25-75. However, single fingolimod doses ≥5 mg (10-fold the recommended dose) were associated with a dose-dependent increase in airway resistance.

Fingolimod treatment with multiple doses of 0.5, 1.25, or 5 mg was not associated with impaired oxygenation or oxygen desaturation with exercise or an increase in airway responsiveness to methacholine.

Subjects on fingolimod treatment had a normal bronchodilator response to inhaled beta-agonists.

In a specific study in patients with moderate asthma, effect on pulmonary function was observed at doses higher than 0.5 mg.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic profile (absorption, distribution, metabolism and elimination) of fingolimod has been studied in multiple sclerosis patients. PK comparisons between healthy volunteers subjects were carried out using fingolimod and fingolimod-P predose concentrations for the multiple sclerosis patients from phase II/III studies (D2201, D2301 and D2302).

Bioequivalence was demonstrated between the clinical service formulation of 1.25 and 25 mg used in phase II and the final market image used in phase III of the renal transplant studies.

No dosage adjustment is required for patient with renal impairment. A 14-fold increase of exposure to M3 was observed in severe renal impaired subjects but was not considered clinically relevant since this metabolite was pharmacologically inactive.

Hepatic impaired subjects were not sufficiently investigated to allow valid dosing recommendation of use in this population. There were no data on exposure to fingolimod-P in subjects with mild/moderate hepatic impairment. The exposure to fingolimod-P was increased by 29% in subjects with severe hepatic impairment. Considering fingolimod is mainly eliminated via metabolism, a contraindication in severe hepatic impairment and a warning in mild to moderate to moderate hepatic impairment have been reflected in the SmPC.

Population pharmacokinetic analyses did not reveal any significant effect of gender nor age. However from these data, no conclusions could be drawn regarding the pharmacokinetic profile in the elderly population. Due to the lack of sufficient information in this population, the CHMP accepted the proposed recommendation that Gilenya should be used with caution in patients aged 65 years and over.

There are limited data available in adolescent population that included 7 children above 11 years of age with renal transplant. The comparison of these data to that of adult healthy volunteers is of limited relevance and no conclusions could be drawn regarding the pharmacokinetic profile in this population. This information has been reflected in the SmPC.

There were no significant PK differences between Caucasian and Japanese subjects. Additional population PK analyses in renal transplant and MS patients revealed no significant influence of ethnicity on pre-dose blood concentrations for fingolimod. The CHMP considered that the SmPC adequately reflects this information.

Co-administration of fingolimod with ketoconazole resulted in an 1.7-fold increase in fingolimod and fingolimod-P exposure (AUC). As further investigations on the role of CYP4F2/CYP3A4 are required, a cautionary statement concerning potential interactions with CYP3A4 inhibitors (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin) has been reflected in the SmPC.

Co-administration of fingolimod with ciclosporin did not elicit any clinically relevant change in the ciclosporin or fingolimod exposure.

When fingolimod is used with atenolol, there was an additional 15% reduction of heart rate at fingolimod treatment initiation, an effect not seen with diltiazem. A cautionary statement concerning treatment initiation with patients receiving beta blockers or other substances that may decrease heart rate (class Ia and III antiarrhythmics, calcium channel blockers like verapamil or diltiazem, digoxin, anticholinesteratic agents or pilocarpine) has been reflected in the SmPC.

Exposure- response relationship modelling in patients with RRMS showed that 0.5 mg dose was as beneficial as 1.25 mg dose.

A dose-dependent decrease in lymphocyte count was observed. At doses equal or greater than 1 mg/ day, reductions around 70-80% were observed. A full recovery at day 56 was reported for doses of 0.125 and 0.25 mg. Additionnally, decrease in immune responses were observed using different antigens. A contraindication of co-administration with anti-neoplastic, immunosuppressive or immune-modulating therapies has been reflected in the SmPC together with a cautionary statement concerning switching patients from long-acting therapies with immune effects. In addition, the SmPC reflects that during and for up to two months after treatment with Gilenya, vaccination may be less effective and the use of live attenuated vaccines may carry a risk of infections and should therefore be avoided. On the basis of the available data to date, the CHMP recommended to further investigate the risk of immunodepression by monitoring the balance between Th1 effectors and T-regulators in a post-authorisation study.

When co-administered with inhaled beta-agonist, no pharmacodynamic interaction was reported with the bronchodilator response. This has been reflected in the SmPC together with the findings related to effects on airway resistance and oxygenation.

Considering the teratogenic properties of fingolimod, an additional study evaluating the interaction between fingolimod, ethinyl estradiol and levonorgestrel was performed at the CHMP request. Following this co-administration, no changes were observed neither in the oral contraceptives exposure nor in fingolimod and fingolimod P.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of fingolimod in human studies has been adequately documented and meet the requirements to support this application. Further investigations role on the metabolism (role of CYP4F2/CYP3A4) and risk of immunodepression were requested by the CHMP.

2.5. Clinical efficacy

The following indication is initially applied for: disease-modifying therapy in adults for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability.

The clinical development program comprises the following clinical studies:

- a phase II, 6 month, double-blind, randomised, placebo-controlled, parallel-group, study (**D2201**) evaluating efficacy and safety of fingolimod versus placebo in patients with relapsing multiple sclerosis. D2201 has an ongoing extension study (**D2201E1)**.

- a phase III, 24-month, double-blind, randomised, placebo-controlled, parallel-group study (**D2301**) evaluating efficacy and safety of fingolimod 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis;

- a phase III, 12-month double-blind, randomised, active-controlled, parallel-group study (**D2302**) evaluating the efficacy and safety of 0.5 mg and 1.25 mg fingolimod administered orally once daily versus interferon β-1a (Avonex®) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis;

Another study (**D2309**) is currently ongoing. This study is a 24-month double-blind, randomised, placebo-controlled, parallel-group evaluating the efficacy and safety of 0.5 and 1.25 mg of fingolimod administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis.

2.5.1. Dose response study

One dose ranging study (D2201) using 5mg and 1.25 mg was performed including a total number of randomised patients of 187 patients (n=94 for fingolimod groups, n=93 for placebo group). The population studied was representative of the MS population (RRMS, SPMS) with 70% of women and 98.2% of Caucasian patients. The mean age was around 38, the mean duration of disease was 8.8 years and patients had two relapses in the previous two years.

A significant improvement in MRI measures and relapses-related clinical endpoints was observed in fingolimod treated patients with relapsing MS. The total cumulative numbers of lesions per patient on post-baseline, monthly gadolinium-enhanced, T1 lesions were lower in both fingolimod groups than in placebo group. These results were highly statistically significant ($p<0.001$ for the 1.25 mg dose and $p=0.006$ for the 5 mg dose). There was no statistically significant difference between the two fingolimod treatment groups. The analysis using the ITT population leads to similar results and statistical significance to that seen with the evaluable population.

There was a statistically significant reduction in the number of post-baseline T1 weighted lesions in both fingolimod dose groups (1.25 mg and 5 mg) in the RRMS population. There was no reduction in both fingolimod groups as compared to placebo in the small SPMS population. However, this group was small (7 and 10 patients in the fingolimod 1.25 mg and 5 mg groups respectively and 7 patients in the placebo group); moreover in this sub-group, a reduction in the number of post-baseline T1 weighted lesions was observed.

At 6 months, the proportion of patients who were free of Gadolinium-enhanced lesions was greater in both fingolimod groups (1.25 mg and 5 mg) than in the placebo group (77% and 82% respectively versus 47%). The number of relapse free patients was significantly increased in both fingolimod groups (p=0.007 and p=0.008 for fingolimod 1.25 mg versus placebo and fingolimod 5 mg versus placebo comparisons respectively). The time to first relapse was increased in the two fingolimod groups versus placebo (p=0.007 for the 1.25 mg fingolimod group and p=0.012 for the 5 mg fingolimod group versus placebo). The annualized relapse rate was reduced in the fingolimod 1.25 mg group (0.35; p=0.009) and in the 5 mg fingolimod group (0.36; p=0.014) compared to placebo (0.77).

At 6 months, no significant differences between fingolimod groups and placebo were observed in the change from baseline for Expanded Disability Status Scale (EDSS) and MSFC z score.

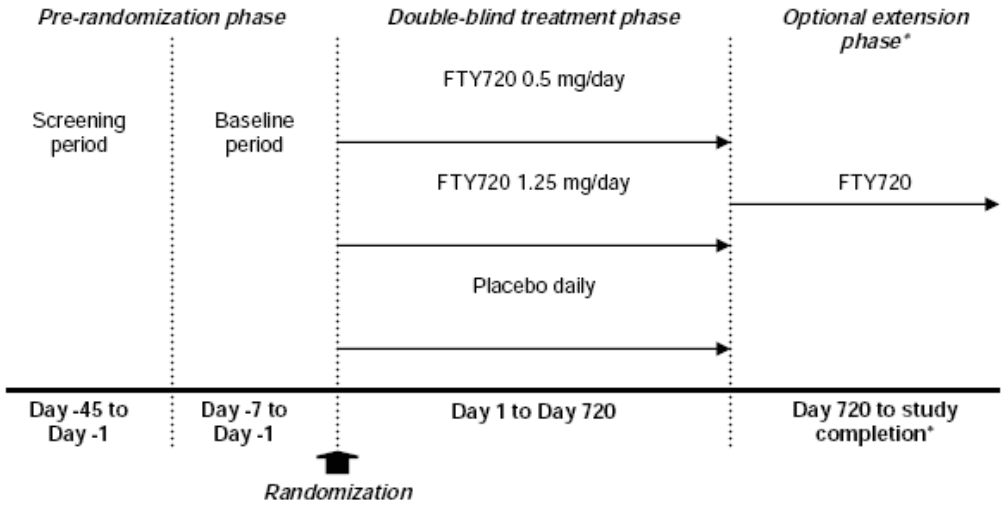
A dose response effect between 1.25 mg and 5 mg was not clearly observed. The 5 mg dose was no longer tested in phase III as it showed no efficacy benefit over the 1.25 mg dose and was associated with a less favourable safety profile.

2.5.2. Main studies

2.5.2.1. Study D2301

This was a 24 month double-blind, randomised, placebo-controlled, parallel-group study evaluating the efficacy and safety of fingolimod 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing -remitting multiple sclerosis (see Figure 1).

Figure 1



The study was conducted in a number of European countries and also in non-EU regions (e.g Switzerland, Canada, Australia, South Africa, Russia, Turkey, Israel).

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 the revised McDonald criteria (2005), 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 randomization, with an Expanded Disability Status Scale (EDSS) score of 0 to 5.5 inclusive and neurologically stable with no evidence of relapse or corticosteroid treatment within 30 days prior to randomisation.

Main exclusion criteria

Patients who met any of the following criteria were excluded: manifestation of MS other than RRMS; known or 'new' diagnosis of diabetes mellitus; diagnosis of macular edema during the pre-randomization phase; patients who had been treated with systemic corticosteroids or adrenocorticotropic hormones (ACTH) within 1 month prior to randomization, immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomization, immunoglobulins and/or monoclonal antibodies (including natalizumab) within 6 months prior to randomization, IFN-β or glatiramer acetate within 3 months prior to randomization, or cladribine, cyclophosphamide, or mitoxantrone at any time; any cardiovascular disease (especially myocardial infarction within the 6 months prior to enrolment, history of angina pectoris, cardiac failure at time of screening, history of cardiac arrest, symptomatic bradycardia, sick sinus syndrome or sino-atrial heart block, or positive tilt test from workup for vasovagal syncope, resting pulse rate < 55 bpm prior to randomization, history or presence of a second degree AV block or a third degree AV block or an increased QTc interval > 440 ms on screening ECG, arrhythmia, hypertension uncontrolled by medication); any pulmonary disease (especially severe respiratory disease or pulmonary fibrosis, tuberculosis, abnormal pulmonary function tests, asthma); white blood cell (WBC) count < 3,500/mm3 (< 3.5 x 109/ L); lymphocyte count < 800/mm3 (< 0.8 x 109/ L).

Treatments

Fingolimod was given for 24 months at an oral dose of 1.25 mg and 0.5 mg (capsules). Patients were randomised to one of the three treatment groups in a 1:1:1 ratio. They received fixed one-a-day doses of study medication with no adjustment permitted.

Objectives

The **primary objectives** were to compare two doses of fingolimod (1.25 mg and 0.5 mg) with placebo and to demonstrate that at least 1.25 mg fingolimod is superior to placebo in terms of annualized relapse rate (ARR) in patients treated for up to 24 months. This was measured by the number of confirmed relapses per year over 24 months.

The **key secondary objective** was to evaluate the effect of fingolimod 1.25 mg and 0.5 mg relative to placebo on disability progression as measured by the time to 3-month confirmed disability progression in patients treated for up to 24 months. This was measured using the Expanded Disability Status Scale (EDSS).

Other secondary objectives were to evaluate the safety and tolerability of fingolimod (1.25 and 0.5 mg) compared to placebo in patients with RRMS treated up to 24 months and to determine the effects of fingolimod (1.25 mg and 0.5 mg) compared to placebo on a number of endpoints mainly related to relapses, disability progression and inflammatory disease activity.

Outcomes/endpoints

Primary outcome measure

Aggregate annualized relapse rate (ARR) at 24 months.

Secondary outcome measures

The key secondary endpoint was the 3-month confirmed disability progression up to 24 months (

Other secondary endpoints included:

- *MRI variables:* number of new and newly enlarged T2 lesions*,* proportion of patients free of new/newly enlarged T2 lesions*,* proportion of patients free of Gd-enhancing T1 lesions, number of Gd-enhancing T1 lesions*,* volume of Gd-enhancing T1 lesions*,* proportion of patients free of new inflammatory activity (no Gd-enhancing T1 lesions and no new/ newly enlarged T2 lesions)*,* change and percent change from baseline in volume of T2 lesions*,* change and percent change from baseline in volume of T1 hypointense lesions*,* percent change from baseline in brain volume (atrophy).

- *Relapses variables:* time to first relapse, time to second relapse, frequency of corticosteroid use to treat relapses, frequency of hospitalizations due to relapses, proportion of relapse free patients.

- *Additional endpoints:* severity of relapses*,* impact on daily activities*,* recovery status*,* duration of relapse.

- *Disability progression-related variables:* time to 6-month confirmed disability progression as, change from baseline on EDSS and the MSFC z-score to the end of the study.

Sample size

The power calculations for the primary endpoint are based on the Wilcoxon/Mann-Whitney rank sum test to compare the 1.25 mg vs. placebo using the hierarchical method to adjust for multiplicity. Assuming that the annualized relapse rate at 24 months is 0.7 for placebo and 0.42 for fingolimod1.25 mg arm, the relative reduction is 40%. Based on data from the Phase II study FTYD2201, its extension phase and other historical data for other MS treatment studies, the common standard deviation is assumed to be 1.06. With these assumptions, 416 patients per arm would provide 95% power at the two-sided significance level of 0.05. A simulation study confirmed that the sample size of 416 per arm would provide an adequate power for the primary efficacy analysis.

The sample size and power calculations were assuming an absolute difference of 12% in the proportion of progressing patients at 24 months (30% of patients progressing in the placebo arm and 18% in the fingolimod arms). The sample size required for each treatment group was 312 using a 0.05 level of two-sided log-rank test for equality of survival curves with a power of 93%, assuming there were no drop-outs before month 24. It was planned to randomise a total of 1250 patients, i.e., approximately 416 patients per arm, to allow for a drop-out rate of approximately 25% at 24 months.

Randomisation

At Visit 2, all patients who fulfill all the inclusion/exclusion criteria will be given the lowest available number on the randomization list. This number assigns them to one of the treatment arms. The investigator or designated study personnel will enter the randomization number on the respective Case Report Form. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

Blinding (masking)

Study medication assignments were blinded for the entire double-blind treatment phase and remained blinded until the database lock and data analysis for the double-blind treatment phase had been completed. Unblinding only occurred in the case of patient emergencies and at the conclusion of the double-blind phase. Emergency unblinding was only to be done when necessary in order to treat the patient.

Statistical methods

Only confirmed relapses were considered for the primary analysis and were defined as "relapse accompanied by an increase of at least half a step (0.5) on the EDSS or an increase of 1 point on two different functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS)". The primary null hypotheses to be tested were: 1) there is no difference in the ARRs between patients treated with fingolimod 1.25 mg and placebo, and 2) there is no difference in the ARRs between patients treated with fingolimod 0.5 mg and placebo.

Efficacy analyses were performed on the ITT population, all randomized patients who had received at least one dose of treatment. Per-protocol population (PP) was only used for the supportive analyses of the primary and key secondary efficacy endpoints.

The test of the hypotheses (p-value) was performed based on a negative binomial regression model adjusting for treatment group, country, baseline number of relapses in the previous 2 years, and baseline EDSS as covariates, in the intent-to-treat (ITT) population. Two types of supportive analyses were provided for the primary endpoint: 1) negative binomial regression model using the per-protocol population and 2) rank analysis of covariance (ANCOVA) on patient-level ARR using ITT population. Both models used the same covariates as the primary efficacy analysis.

The key secondary endpoint was compared by means of the log-rank test. Cox regression with covariates of treatment, country, baseline EDSS and age was performed as well. Proportions of disability free patients at 12 and 24 months were obtained using the Kaplan–Meier method.

To control the overall type-I error rate of the study, the testing of fingolimod comparisons vs. placebo was performed in a hierarchical order as follows: fingolimod 1.25 mg (ARR); fingolimod 0.5 mg (ARR); fingolimod 1.25 mg (3-month disability progression) and fingolimod 0.5 mg (3-month disability progression). Each testing was performed at a significant level of 0.05 for these four comparisons. However, the lower-rank testing was performed only when every high-rank testing was statistically significant.

ARR for all relapses (confirmed and unconfirmed) was analyzed similarly to the primary efficacy variable. For time to first relapse and time to second relapse, log-rank test and Cox regression with the same covariates as in the primary analysis were used. The proportion of relapse-free patients was

obtained from the Kaplan–Meier method. Fisher's exact test and Wilcoxon rank sum test were used for testing treatment differences for relapse characteristics.

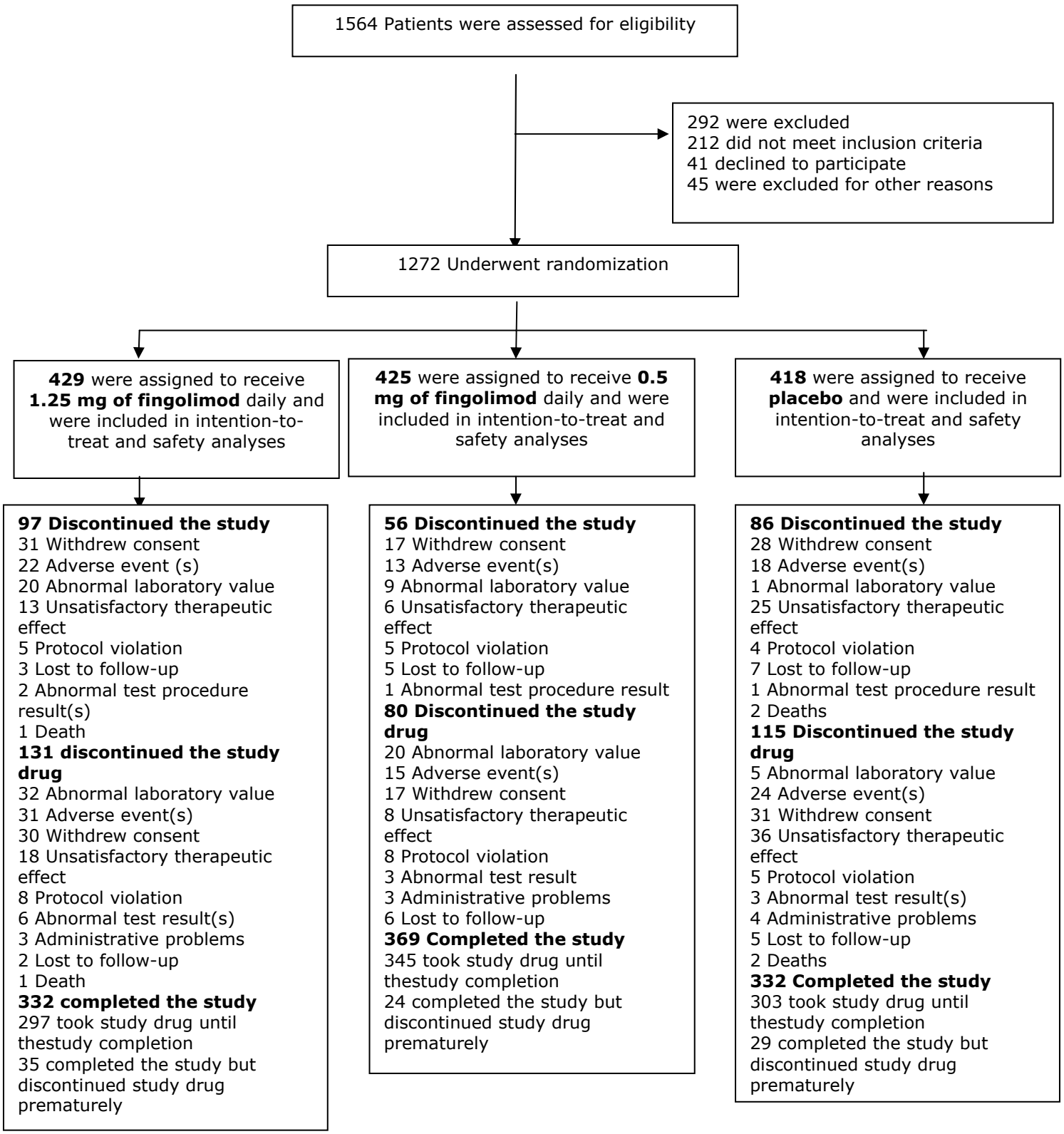
For other efficacy disability-related and EDSS, log-rank test and Cox regression with the same covariates as in the key secondary analysis were used. The proportion of disability progression-free patients was obtained from the Kaplan–Meier method. Change from baseline to the end of study for EDSS, and change from baseline to the end of study for the MSFC z-score and subscales were analyzed using rank ANCOVA with covariates of treatment, country, the corresponding baseline value, and age.

For the proportion type of MRI endpoints, the treatment comparisons were performed using the logistic regression model adjusting for treatment, country, and the corresponding baseline value (when available). The number of new/newly enlarged T2 lesions was analyzed using negative binomial model adjusted for treatment and country. For the other MRI endpoints (number and total volume of Gd-enhanced T1 lesions, change and percent change from baseline in total volume of T2 lesions, change and percent change from baseline in total volume of T1 hypointense lesions, percent change from baseline in brain volume), rank ANCOVA with covariates treatment, country, and corresponding baseline values (when available) were used for treatment comparisons.

Results

Participant flow

Figure 2



Among the 292 patients who were assessed for eligibility but were not enrolled, some were excluded for more than one reason. For one patient receiving 1.25 mg of fingolimod faily who completed the study while receiving the study drug, the status was incorrectly recorded by the investigator as having discontinued the study while still receiving the study drug. Patients who discontinued the study drug include those who discontinued the study; the correct status is shown here.

Recruitment

Study period was from 26 January 2006 to 30 July 2009.

Conduct of the study

Out of the 10 protocol amendments, 4 were related to study design and evaluation. These included changes in the eligibility criteria (revised McDonald criteria), sample size (increased) and statistical plan analysis (use of the negative binomial regression according to CHMP scientific advice).

Overall, 3.6% of patients had protocol deviations which excluded them from the PP population.The proportion of patients was 4.4% in the fingolimod 1.25 mg group, 3.3% in the fingolimod 0.5 mg group and 3.6% in the placebo group.

Baseline data

These are summarised in Tables 4 and 5.

Table 4 baseline characteristics

	Fingolimod 1.25 mg	Fingolimod 0.5 mg	Placebo	Total
Number of patients	429	425	418	1272
(%females/males)	68.8/31.2	69.6/30.4	71.3/28.7	69.9/30.1
Age (median)	38.0	36.0	37.0	37.0
(min, max)	17-55	18-55	18-55	17-55
Race (%white)	95.1	95.5	95.5	95.4
Weight (kg)				
median	68.00	70.00	69.00	69.00
(min, max)	40.1-154.3	40.0-128.8	40.0-118.0	40.0-154.3
Duration of MS since first symptoms	8.4 (6.86)	8.0 (6.60)	8.1 (6.35)	8.2 (6.60)
(mean, SD,	6.9	6.6	7.0	6.7
median years;	0-37	0-35	0-32	0-37
min, max)				
Relapses in the last year				
Mean SD	1.5 (0.81)	1.5 (0.76)	1.4 (0.73)	1.5 (0.77)
Median	1.0 (0-6)	1.0 (0-5)	1.0 (0-6)	1.0 (0-6)
(min, max)				
Relapses in the last 2 years		(n=424)		(n=1271)
Mean SD	2.1 (1.25)	2.1 (1.13)	2.2 (1.19)	2.1 (1.19)
(Median	2.0	2.0	2.0	2.0
(min, max)	1-10	1-11	1-10	1-11
Median baseline EDSS				
Mean SD	2.41 (1.36)	2.30 (1.29)	2.49 (1.29)	2.40 (1.32)
Mediane	2.00	2.00	2.00	2.00
(min, max)	0.0-5.5	0.0-5.5	0.0-5.5	0.0-5.5
MSFC z-score	n=424	n=422	n=413	n/a
Mean SD	-0.02 (0.75)	0.06 (0.60)	-0.04 (0.76)	n/a
Median	0.13	0.13	0.09	n/a
min-max	-5.9-1.3	-2.9-1.6	-6.4-1.9	n/a

% patients free Gd enhanced T1 lesions N (%)	n=424 257 (60.6)	n=424 263 (62.0)	n=416 262 (63.0)	n=1264 782 (61.9)
Nb Gd enhanced T1 lesions Mean (SD) Median Min, max	n=424 1.8 (4.66) 0.0 0-50	n=424 1.6 (5.57) 0.0 0-84	n=416 1.3 (2.93) 0.0 0-26	n=1264 1.6 (4.53) 0.0 0-84
Vol Gd-enhanced T1 lesions mm ^{3} Mean (SD) Median Min, max	n=424 197.14 (603.74) 0.00 0.0-6852.7	n=424 169.87 (601.42) 0.00 0.0-6849.8	n=416 162.33 (421.21) 0.00 0.0-2970.0	n=1264 176.54 (549.31) 0.00 0.0-6852.7
Total volume T2 lesions mm ^{3} Mean (SD) Median Min, max	n=425 6828.70 (8490.54) 3556.50 0.0-47734.1	n=424 6127.71 (7622.97) 3303.35 0.0-47147.6	n=416 6162.40 (7084.84) 3416.25 0.0-37147.8	n=1265 6374.63 (7759.71) 3453.30 0.0-47734.1
Total volume T1 hypointense lesions mm ^{3} Mean (SD) Median Min, max	n=424 2113.52 (3219.65) 859.55 0.0-25885.9	n=424 1897.62 (2854.6) 814.05 0.0-22377.8	n=416 1962.00 (3131.13) 811.15 0.0-20955.9	n=1264 1991.23 (3070.76) 826.90 0.0-25885.9
Normalized brain Volume (cc) Mean (SD) Median Min, max	n=423 1510.51 (85.94) 1514.69 1217.1-1763.8	n=424 1520.84 (83.16) 1528.50 1143.7-1733.7	n=414 1512.16 (85.49) 1514.84 1229.8-1722.6	n=1261 1514.53 (84.92) 1520.22 1143.7-1763.8

Table 5. Previous MS therapy taken by patients

	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)	Total N=1272 n (%)
Treatment-naïve patients*	259 (60.4)	244 (57.4)	249 (59.6)	752 (59.1)
Previously treated patients	170 (39.6)	181 (42.6)	169 (40.4)	520 (40.9)
Any Interferon beta	125 (29.1)	127 (29.9)	115 (27.5)	367 (28.9)
Interferon beta 1a i.m.	50 (11.7)	65 (15.3)	60 (14.4)	175 (13.8)
Interferon beta 1a s.c.	53 (12.4)	56 (13.2)	49 (11.7)	158 (12.4)
Interferon beta 1b s.c.	44 (10.3)	41 (9.6)	44 (10.5)	129 (10.1)
Glatiramer acetate	52 (12.1)	42 (9.9)	44 (10.5)	138 (10.8)
Natalizumab	1 (0.2)	4 (0.9)	2 (0.5)	7 (0.6)
Other MS medications	43 (10.0)	46 (10.8)	52 (12.4)	141 (11.1)

* Treatment-naïve patients are defined as those not receiving any of the approved 5 MS disease-modifying drugs listed above or any other MS medications.

Numbers analysed

In total, 100% of randomized patients were included in the ITT and Safety populations.

Table 6

Population	FTY720 1.25mg n (%)	FTY720 0.5mg n (%)	Placebo n (%)	Total n (%)
Randomized population	429 (100)	425 (100)	418 (100)	1272 (100)
Intent-to-treat (ITT) population	429 (100)	425 (100)	418 (100)	1272 (100)
Per-protocol (PP) population	408 (95.1)	405 (95.3)	397 (95.0)	1210 (95.1)
Safety population	429 (100)	425 (100)	418 (100)	1272 (100)
Follow-up population	114 (26.6)	74 (17.4)	94 (22.5)	282 (22.2)

A total of 17 (1.3%) patients were excluded from the PP population due to treatment code unblinding (not necessarily protocol deviations): 4 (0.9%) in the fingolimod 1.25 mg group, 6 (1.4%) in the fingolimod 0.5 mg group and 7 (1.7%) in the placebo group.

Outcomes and estimation

Primary outcome measure

Results are summarised in Table 7.

Table 7. Aggregate ARR up to Month 24 (confirmed relapses only) (ITT population)

	FTY720 1.25mg N=429	FTY720 0.5mg N=425	Placebo N=418
Aggregate ARR estimate	0.16	0.18	0.40
(95% CI)	(0.13,0.19)	(0.15,0.22)	(0.34,0.47)
Treatment comparison of FTY720 vs. placebo			
ARR ratio	0.40	0.46	---
P-value	<0.001*	<0.001*	---

Aggregate ARR related to group-level annualized relapse rate.
Aggregate ARR estimate (95% CI), ARR ratio, and p-value are calculated using negative binomial regression adjusted by treatment, country, number of relapses in the previous 2 years, and baseline EDSS.
Log (time of study) is the offset variable.
*Indicates two-sided statistical significance at 0.05 level.

Results of the two supportive analyses (confirmed relapses for PP population and patient level ARR for ITT population) were consistent and confirm results in ITT population.

Secondary outcome measures

Results of the key secondary endpoints are summarised in Figure 3 and Table 8.

Figure 3. Time to 3-month confirmed disability progression at Month 24 (ITT population)

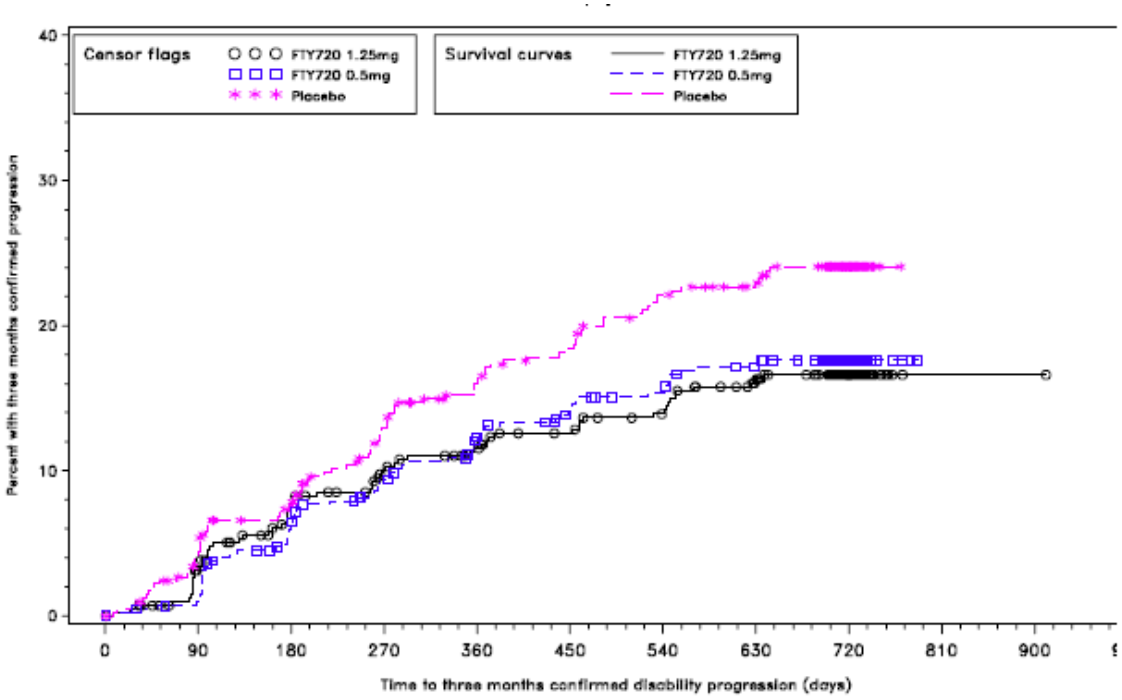


Table 8. Proportion of patients free of disability progression at Month 24 (ITT population)

	FTY720 1.25 mg N = 429	FTY720 0.5 mg N = 425	Placebo N = 418
P-value vs. placebo (log-rank test)	0.012*	0.026*	---
Hazard ratio (95% CI)	0.68 (0.50, 0.93)	0.70 (0.52, 0.96)	0.99 (0.71, 1.38)
P-value vs. placebo	0.017*	0.024*	---
Proportion of patients free of progression by Kaplan-Meier estimate at 720 days (95% CI)	83.4 (79.72, 87.06)	82.3 (78.63, 86.05)	75.9 (71.69, 80.20)

Abbreviation: CI = Confidence interval
P value for proportion of patients free of progression was calculated using log-rank test. P-value for hazard ratio was calculated using Cox's proportional hazards model adjusted for treatment, country, baseline EDSS and age.
* Indicates two-sided statistical significance at 0.05 level.

In the two fingolimod groups, the time to a first relapse was increased as compared to placebo ($p<0.001$). The risk reduction in relapses over 2 years was 62% for the fingolimod 1.25 mg group and 52% for the fingolimod 0.5 mg group compared to placebo.

The percentage of patients who did not have confirmed relapse during the study was highest in the fingolimod treatment groups (75.5% and 71.1%, for 1.25 mg and 0.5 mg, respectively) compared to the placebo group (47.8%). The percentage of patients who had 2 or more relapses was highest in the placebo group (21.5%) compared with the fingolimod 1.25 mg and 0.5 mg treatment groups (7.0% and 8.2%, respectively).

Overall there was no substantial difference between the two fingolimod doses in the percentages of patients who had no relapse, or at least 1 or 2 confirmed relapses. These findings were consistent when taking all relapses (both confirmed and unconfirmed) into consideration. The total steroid dose and number of hospitalizations due to relapses are lower in the treated groups as compared to placebo.

The proportion of patients free of 3-month confirmed disability progression was greater in the two fingolimod groups (83.4% in the fingolimod 1.25 mg group, 82.3% in the fingolimod 0.5 mg group versus 75.9% in the placebo group). The reduction of progression of disability was small, which is expected taking into account that less than 24% of progression in the placebo group).

The proportion of patients free of 6-month confirmed progression was higher in the fingolimod groups compared to placebo (88.5% for 1.25 mg, 87.5% for 0.5 mg and 81% for placebo).Regarding disability progression that was confirmed at 6 month, the risk was also reduced with fingolimod over the 24-month study period. The hazard ratio were 0.60 [95% CI: 0.41, 0.86, p=0.004] aand 0.63 [95% CI: 0.44, 0.90, p=0.011] for 1.25 mg and 0.5 mg doses, respectively.

Patients in either fingolimod group had significantly fewer new or enlarged lesions on T2 lesions at 6, 12 and 24 months (p<0.001 for all comparisons). The proportion of patients free of new /newly enlarged T2 lesions at 24 months compared to baseline was more important in patients in the fingolimod groups (51.9% and 50.5% at 1.25 mg and 0.5 mg) than in the placebo group (21.2%).

Patients in both fingolimod groups had significantly fewer Gadolinium-enhancing lesions than in the placebo group at 6, 12 and 24 months (p<0.001 for all comparisons).At these time points, the proportion of patients free of Gadolinium-enhancing T1 lesions was greater in the fingolimod groups compared to placebo. At 24 month, this proportion was 89.8% at 1.25 mg and 89.7% at 0.5 mg and 65.1% in the placebo group.

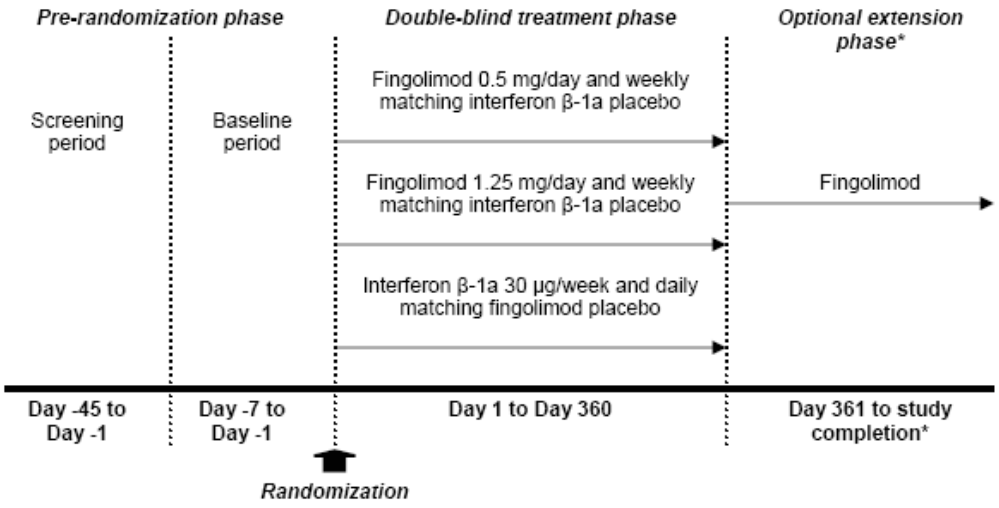
The median volume of lesions on T2 decreased between baseline and month 24 with both doses of fingolimod but increased with placebo.

Reduction in brain volume was smaller and statistically significant in the fingolimod groups (- 0.885 at 1.25 mg and – 0.843 at 0.5 mg) as compared to placebo group (-1.306) over the 24 month study period.

2.5.2.2. Study D2302

This was a 12 month double-blind, randomised, active-controlled, parallel-group study evaluating the efficacy and safety of fingolimod 1.25 mg and 0.5 mg administered orally once daily versus interferon beta-1a (Avonex) administered i.m. once weekly in patients with relapsing -remitting multiple sclerosis with an optional extension phase (see Figure 4).

Figure 4



The study was conducted in a number of European countries and also in non EU regions (e.g Switzerland, Australia, Brazil, Canada, Argentina, Egypt, Korea and the United States).

2.5.2.2.1. Methods

Study Participants

Main inclusion criteria

The inclusion criteria were the same as for those for the D2301 study except that patients on treatment with interferon beta-1a i.m. or glatiramer acetate could be randomised without a wash-period.

Main exclusion criteria

The exclusion criteria were the same as for those for the D2301 study except the following exclusion criteria were added: history of epileptic seizures within 3 months of randomization, episode of severe depression within 3 months of randomization and relevant history of suicide attempt or patients who, in the opinion of the investigator, were at risk of suicide attempt.

Treatments

Randomised patients were assigned in a ratio of 1:1:1 in a double-dummy design to receive: Fingolimod 0.5 mg orally once daily plus once-weekly i.m. interferon beta-1a matching placebo Fingolimod 1.25 mg orally once daily plus once-weekly i.m. interferon beta-1a matching placebo.

Objectives

The **primary objective** was to compare two doses of fingolimod (1.25 mg and 0.5 mg) with interferon beta-1a i.m. to demonstrate that at least 1.25 mg fingolimod is superior to interferon beta-1a i.m. in terms of annualized relapse rate (ARR) in patients treated for up to 12 months. This was measured by the number of confirmed relapses per year over 12 months.

The **key secondary objectives** were to demonstrate superiority of fingolimod 1.25 mg and 0.5 mg over interferon beta-1a i.m. in patients with RRMS treated for up to 12 months on the following endpoints: time to 3-month confirmed disability progression and number of new/ newly enlarged T2 lesions.

Other secondary objectives were to evaluate the safety and tolerability of fingolimod 1.25 mg and 0.5 mg compared to interferon beta-1a i.m. in patients with RRMS treated for up to 12 months and to determine the effects of fingolimod (1.25 mg and 0.5 mg) compared to interferon beta-1a i.m on a number of endpoints mainly related to relapses and inflammatory disease activity.

Outcomes/endpoints

Primary outcome measure

Aggregate annualized relapse rate (ARR) at 24 months

Secondary outcome measures

The two key secondary variables were the 3-month confirmed disability progression and the number of new/newly enlarged T2 lesions at 12 months.

Other secondary endpoints included:

- *MRI variables:* proportion of patients free of Gd-enhanced T1 lesions, proportion of patients free of new or newly enlarged T2 lesions at 12 months, number of Gd-enhanced T1 lesions, volume of Gd enhanced T1 lesions, proportion of patients free of new inflammatory activity (Gd-enhanced lesions and new/ newly enlarged T2 lesions), change and % change from baseline in volume of T2 lesions at 12 months, change and % change from baseline in volume of T1 hypointense lesions at 12 months, normalized brain volume at baseline and percent brain volume change from baseline at 12 months

- *Relapses variables:* proportion of relapse-free patients

- *Disability progression-related variables:* proportion of patients with 3-month confirmed disability progression, time to confirmed disability progression sustained until last observation, time to severe disability (EDSS score ≥6.0), EDSS score, MSFC z-score, MSFC subscales.

Sample size

The sample size calculation used the Wilcoxon/Mann-Whitney rank sum test to compare the fingolimod 1.25 mg group with the interferon beta-1a i.m. group. The ARRs for interferon beta-1a i.m. and fingolimod 1.25 mg group were assumed to be 0.55 and 0.33, respectively (relative reduction 40%). The common standard deviation (SD) was assumed to be 0.9. With these assumptions, 368 patients per group would provide 90% power at the two-sided significance level of 0.05. Based on drop-out rate from study D2201, 57 patients (15.5%) were added to each group. Therefore, a total sample size of 1275 was required (425 patients per group).

The mean (SD) for the number of new or newly enlarged T2 lesions at Month 12 for the interferon beta-1a i.m. group was chosen as 2.4 (4.1). It was assumed that the fingolimod 1.25 mg group would have an effect size of 25% on the number of new or newly enlarged T2 lesions at 12 Month vs. interferon beta-1a i.m. (i.e. the mean is 1.375 or 25% of 2.4). With the sample size of 368 patients completing the 12-month study, the power to detect a treatment difference for the fingolimod 1.25 mg group vs. the interferon beta-1a i.m. group was 90% using a conservative Wilcoxon rank-sum test at a two-sided 0.05 significance level.

It was also assumed that 15% of patients in the interferon beta-1a i.m. group would have 3-month confirmed disability progression. With 425 randomized patients and 57 dropout patients in each group (exponentially distributed), assuming the 12-month progression rate for the fingolimod group was 12% (a relative reduction of 20% from interferon beta-1a i.m.), the power for detecting a treatment difference was 22% using a log-rank test at a two-sided 0.05 significance level.

Randomisation

At the Visit 3, all eligible patients will be assigned a randomization number by the IVRS that assigns them to one of the treatment arms. The investigator or designated study personnel will call the IVRS and confirm that the patient fulfills all the inclusion/exclusion criteria. The IVRS will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient (The randomization number is not communicated to the caller). A randomization list will be produced by the IVRS provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different

treatment arms, which in turn are linked to medication numbers. A separate medication randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to medication packs containing each of the study drugs.

Blinding (masking)

Study medication assignments were blinded for the entire double-blind treatment phase and remained blinded until the data base lock and data analysis for the double-blind treatment phase had been completed. In order to maintain the blind, patients were instructed to cover injection sites (e.g. with a plaster or appropriate clothing to completely cover the injection sites) before all scheduled visits and relapse-related neurologic examinations and not to discuss AEs (e.g. injection site reactions or flu-like symptoms) with the independent evaluating physician. Unblinding only occurred in the case of patient emergencies and at the conclusion of the double-blind phase.

Statistical methods

Only confirmed relapses were considered for the primary analysis. The primary null hypotheses to be tested were: 1) there is no difference in the ARRs between patients treated with the fingolimod 1.25 mg and interferon beta-1a i.m., and 2) there is no difference in the ARRs between patients treated with the FTY720 0.5 mg and interferon beta-1a i.m. The test of the hypotheses (p-value) was performed based on a negative binomial regression model adjusting for treatment group, country, baseline number of relapses in the previous 2 years, and baseline EDSS as covariates, in the intent-to-treat (ITT) population.

Two types of supportive analyses were provided for the primary endpoint: 1) Per-protocol analysis was done with the negative binomial regression model adjusting for treatment group, country, baseline number of relapses in the previous 2 years and baseline EDSS as covariates for the primary efficacy variable. 2) Rank Analysis of Covariance (ANCOVA) using treatment group, country, baseline number of relapses in the previous 2 years, and baseline EDSS as covariates was used with the ARR as the response variable.

The number of new or newly enlarged T2 lesions at Month 12, in treatment groups (fingolimod versus interferon beta-1a i.m) was compared using a negative binomial model adjusting for treatment group, country, baseline number of relapses in the previous 2 years, and baseline EDSS.

The time to 3- month confirmed disability progression up to 12 months was analyzed using the Kaplan–Meier method and compared by means of the log-rank test. Cox regression with the same covariates as in the primary analyses was performed as well.

To control the overall type-I error rate of the study, the testing of FTY720 comparisons vs. interferon beta-1a i.m. was performed in a hierarchical order as follows: fingolimod 1.25 mg (ARR);fingolimod 0.5 mg (ARR); fingolimod 1.25 mg (number of new and newly enlarged T2 lesions at 12 months), fingolimod 0.5 mg (number of new and newly enlarged T2 lesions at 12 months), fingolimod 1.25 mg,(3 month disability progression) and fingolimod 0.5 mg (3 month disability progression). Each testing was performed at a significant level of 0.05 for these six comparisons. However, the lower-rank testing was performed only when every high-rank testing was statistically significant.

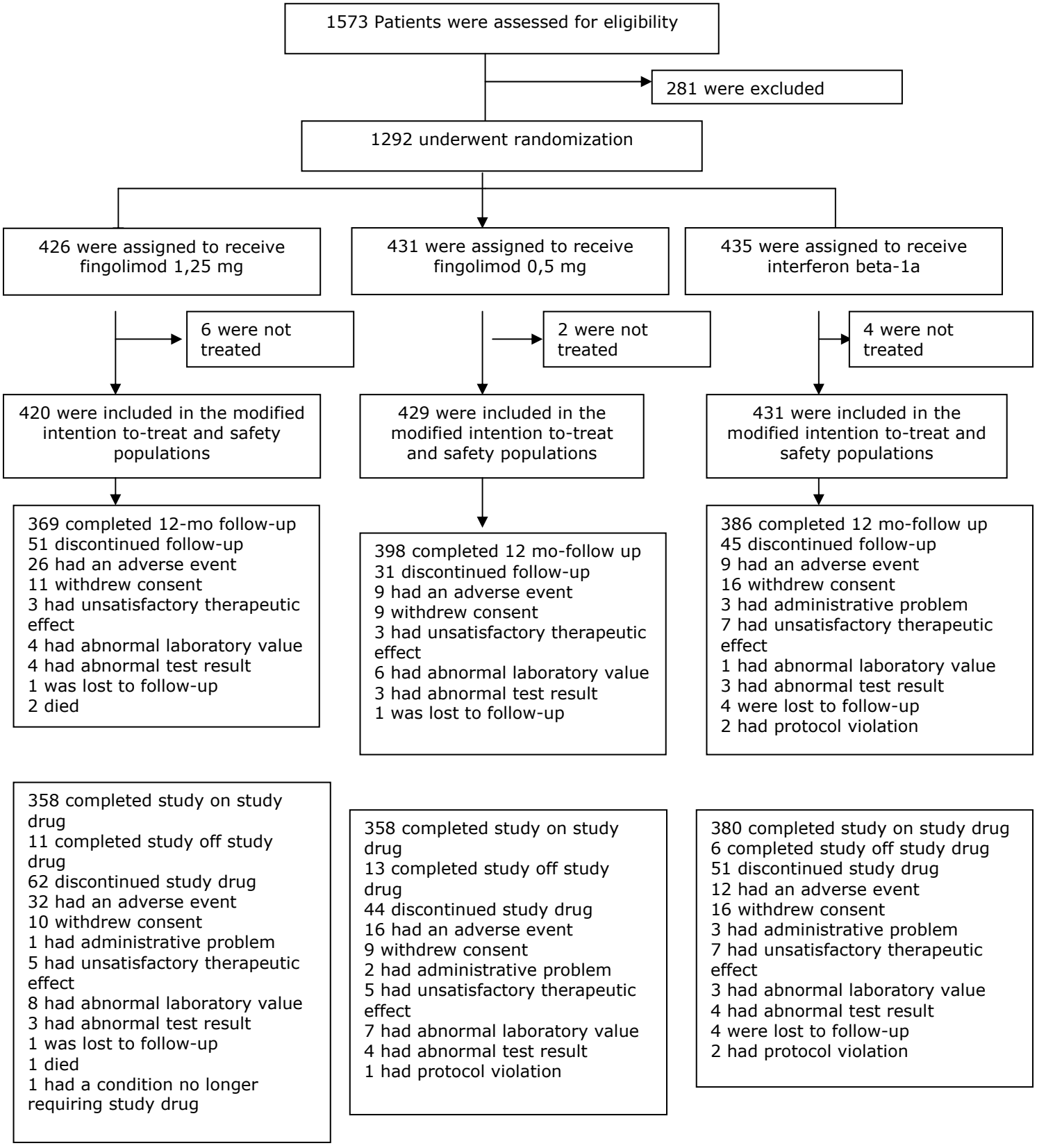
Other efficacy relapse variables were analyzed similarly to the primary efficacy variable. Log-rank test and Cox regression with the same covariates as in the primary analyses were used for the time to event variables. The proportion of relapse-free patients was compared between treatment groups with logistic regression adjusting for country, baseline relapse rate in the previous 2 years and baseline EDSS.

For other efficacy disability-related and EDSS variables, both the naïve estimate of the proportions, regardless of when a patient dropped out and the Kaplan-Meier estimates at 12 months were used. Wilcoxon rank sum test as well as ANCOVA on ranks were performed to compare the EDSS and MSFC z-scores at 12 months as well as the change from baseline between the treatment groups.

For the proportion type of MRI endpoints, the treatment comparisons were performed using the logistic regression model adjusting for treatment, country, and the corresponding baseline number of lesions (when available). For the other MRI endpoints, summary statistics of actual values and changes from baseline were presented. Wilcoxon rank sum test and rank ANCOVA with covariates treatment, country, and corresponding baseline values (when available) were used for treatment comparisons.

Results
Participant flow

Figure 5



Recruitment

Study period was from 30 May 2006 to 11 November 2008.

Conduct of the study

Out of the 10 protocol amendments, 5 were related to study design and evaluation. These included change in the eligibility criteria (stricter requirements for monitoring and prevention of pregnancies), statistical plan analysis (use of the negative binomial regression according to CHMP scientific advice).

Overall, 3.7% of patients had protocol deviations which excluded them from the PP population.The proportion of patients was 5.8% in the fingolimod 1.25 mg group, 3.0% in the fingolimod 0.5 mg group and 2.9% in the interferon beta-1a group.

Baseline data

These are summarised in Tables 9 and 10.

Table 9. baseline characteristics

	Fingolimod 1.25 mg	Fingolimod 0.5 mg	Interferon beta-1a i.m.	Total
Number of patients	426	431	435	1292
(%females/males)	68.8/31.2	65.4/34.6	67.8/32.2	67.3/32.7
Age (median)	36.0	37.0	36.0	36.0
(min, max)	18-54	18-55	18-55	18-55
Race (%white)	94.8	93.7	93.8	94.1
Weight (kg)				
median	69.00	69.00	69.00	69.00
(min, max)	42.0-130	37.0-126.5	43.0-139.7	37.0-139.7
Duration of MS since first	n =420	n =429	n =431	n =1280
symptoms	7.3 (5.96)	7.5 (6.20)	7.4 (6.33)	7.4 (6.16)
(mean, SD,	6.0	5.8	5.8	5.9
median years;	0-33	0-34	0-40*	0-40*
min, max)				
Relapses in the last year	n=425	v=431	n =435	n =1291
Mean SD	1.5 (0.87)	1.5 (1.19)	1.5 (0.79)	1.5 (0.97)
Median	1.0 (0-7)	1.0 (0-20*)	1.0 (0-6)	1.0 (0-20*)
(min, max)				
Relapses in the last 2 years	n =425	n =431)	n =434	n =1290)
Mean SD	2.2 (1.19)	2.24 (2.20)	2.3 (1.22)	2.2 (1.61)
(Median	2.0	2.0	2.0	2.0
(min, max)	1-8	1-40*	1-12	1-40
Median baseline EDSS	n =420	n =429	n =431	n =1280
Mean SD	2.21 (1.311)	2.30 (1.326)	2.19 (1.261)	2.21 (1.299)
Mediane	2.00	2.00	2.00	2.00
(min, max)	0.0-5.5	0.0-5.5	0.0-5.5	0.0-5.5
MSFC z-score	n=416	n=424	n=423	N=1263
Mean SD	-0.006 (0.7272)	0.007 (0.6327)	0.005 (0.6159)	0.002 (0.6595)
Median	0.106	0.159	0.128	0.124
min-max	-5.35-2.04	-5.23-1.19	-2.81-2.51	-5.35-2.51

% patients free Gd enh T1lesions N (%)	n=412 270 (65.5)	n=427 288 (67.4)	n=425 268 (63.1)	n=1264 826 (65.3)
Nb Gd enh.T1lesions	n=412	n=427	n=425	n=1264
Mean (SD)	1.5 (4.77)	1.0 (2.81)	1.1 (2.80)	1.2 (3.57)
Median	0.0	0.0	0.0	0.0
Min, max	0-66	0-29	0-36	0-66
Vol Gd-enh T1 lesions mm^3	n=412	n=427	n=425	n=1264
Mean (SD)	147.5 (667.21)	93.9 (288.05)	100.7 (263.55)	113.7 (443.54)
Median	0.00	0.00	0.00	0.00
Min, max	0-11507	0-3250	0-2609	0-11507
Total Vol T2 lesions mm^3	n=413	n=418	n=425	n=1266
Mean (SD)	5085.4 (5962.05)	5169.6 (6641.97)	4923.6 (5710.90)	5059.5 (6116.41)
Median	3095.9	2381.8	2901.1	2786.6
Min, max	0-38870	0-46280	0-38712	0-46280
Tot vol T1 hypointense lesions mm^3	n=413	n=428	n=425	n=1266
Mean (SD)	1386.7 (2298.52)	1620.4 (3107.07)	1404.2 (2357.82)	1471.6 (2618.03)
Median	454.9	444.9	420.6	439.2
Min, max	0-20399	0-30610	0-19561	0-30610
Normalized brain vol (cc)	n=409	n=421	n=420	n=1250
Mean (SD)	1526.2 (76.37)	1524.1 (83.88)	1526.7 (77.93)	1525.7 (79.42)
Median	1527.8	1526.2	1533.3	1529.5
Min, max	1300-1794	1185-1862	1231-1762	1185-1862

n = number of patients with an evaluable MRI scan at baseline

Table 10. Previous MS therapy taken by patients

	FTY720 1.25mg (N=426) n (%)	FTY720 0.5mg (N=431) n (%)	Interferon beta-1a i.m. (N=435) n (%)	Total (N=1292) n (%)
Treatment-naïve patients*	177 (41.5)	193 (44.8)	190 (43.7)	560 (43.3)
Previously treated patients	249 (58.5)	238 (55.2)	245 (56.3)	732 (56.7)
Any interferon beta	209 (49.1)	219 (50.8)	207 (47.6)	635 (49.1)
Interferon beta 1a i.m.	118 (27.7)	119 (27.6)	118 (27.1)	355 (27.5)
Interferon beta 1a s.c.	79 (18.5)	89 (20.6)	72 (16.6)	240 (18.6)
Interferon beta 1b s.c.	57 (13.4)	59 (13.7)	69 (15.9)	185 (14.3)
Glatiramer acetate	67 (15.7)	57 (13.2)	67 (15.4)	191 (14.8)
Natalizumab	3 (0.7)	4 (0.9)	1 (0.2)	8 (0.6)

* Treatment-naïve patients are defined as those not receiving any of the approved 5 MS disease-modifying drugs listed above.

Numbers analysed

In total, 99% of randomized patients were included in the ITT. The ITT and Safety populations were identical. The PP population included all ITT patients who did not have any major protocol deviations and 96% of randomized patients were included in this population. Overall, 12 (0.9%) patients were excluded from both the ITT and Safety populations because they were randomized in error and did not receive study drug (see Table 11).

Table 11

Population	FTY720 1.25mg n (%)	FTY720 0.5mg n (%)	Interferon beta-1a i.m. n (%)	Total n (%)
Randomized population	426 (100.0)	431 (100.0)	435 (100.0)	1292 (100.0)
Intent-to-treat (ITT) population	420 (98.6)	429 (99.5)	431 (99.1)	1280 (99.1)
Per-protocol (PP) population	406 (95.3)	418 (97.0)	422 (97.0)	1246 (96.4)
Safety population	420 (98.6)	429 (99.5)	431 (99.1)	1280 (99.1)
Follow-up population	91 (21.4)	74 (17.2)	89 (20.5)	254 (19.7)

Outcomes and estimation

Primary outcome measure

Results are summarised in Table 12.

Table 12. Aggregate ARR up to Month 24 (confirmed relapses only) (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
Number of relapses	105	89	179
Time on study (days)	147663	155100	151844
Aggregate ARR	0.26	0.21	0.43
ARR estimate	0.203	0.161	0.331
(95% CI)	(0.157,0.264)	(0.122,0.212)	(0.262,0.417)
ARR ratio for treatment comparison of FTY720 vs. Interferon beta-1a i.m.	0.617	0.484	–
P-value for treatment comparison of FTY720 vs. interferon beta-1a i.m.	<0.001*	<0.001*	–

ARR estimate (95% CI), ARR ratio, p-value are calculated using negative binomial regression adjusted by treatment, country, number of relapses in the previous 2 years, and baseline EDSS.
Log(time of study) is the offset variable.
*Indicates two-sided statistical significance at 0.05 level.

Secondary outcome measures

Results of the key secondary endpoints are summarised in Table 13, Figure 6 and Table 14.

Table 13

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
As Intended per Protocol			
n**	350	372	361
Mean (SD)#	1.5 (2.73)	1.7 (3.92)	2.6 (5.81)
Median	1.0	0.0	1.0
Range	0 – 26	0 - 38	0 - 63
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	<0.001*	0.004	–
As analyzed by MRI Central reader			
n**	350	372	361
Mean (SD)	1.4 (2.51)	1.5 (3.520)	2.1 (4.89)
Median	1.0	0.0	1.0
Range	0 - 22	0 - 32	0 - 60
P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)	0.017*	0.041	–
~~n**~~	~~356~~	~~380~~	~~365~~
~~Mean (SD)~~	~~1.4 (2.51)~~	~~1.5 (3.50)~~	~~2.1 (4.86)~~
~~Median~~	~~1.0~~	~~0.0~~	~~1.0~~
~~Range~~	~~0 - 22~~	~~0 - 32~~	~~0 - 60~~
~~P-value for treatment comparison of FTY720 vs. Interferon beta-1a i.m. (negative binomial regression with covariates)~~	~~0.017*~~	~~0.053~~	~~–~~

n=the number of patients with evaluable MRI at baseline and Month 12
P-value is calculated using a negative binomial model adjusting for treatment, country, baseline number of relapses in the previous 2 years, and baseline EDSS.
* Indicates two-sided statistical significance at 0.05 level.
** Eighteen patients were excluded from analysis because the Month 12 T2 MRI was not compared to the Screening MRI.
# Calculated by adding the number of new or newly enlarged T2 lesions and the number of Gd-enhanced T1 lesions (both as recorded in the database) observed on the Month 12 MRI.

Figure 6. Time to 3-month confirmed disability progression at Month 12 (ITT population)

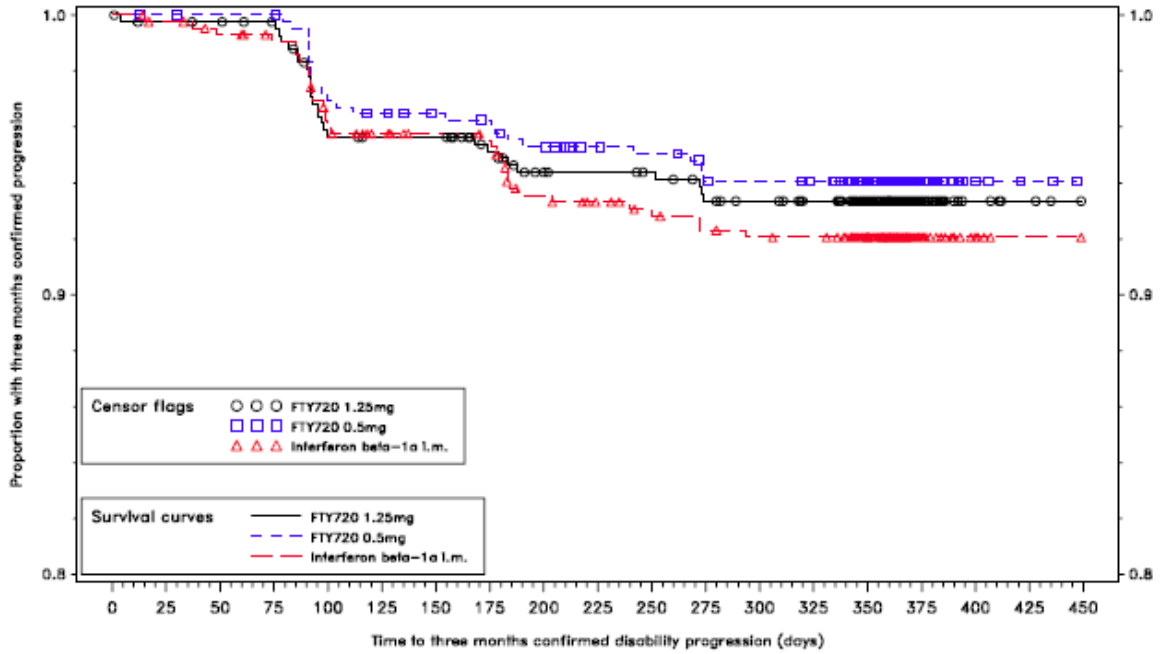


Table 14. Proportion of patients free of disability progression at Month 12 (ITT population)

	FTY720 1.25mg N=420	FTY720 0.5mg N=429	Interferon beta-1a i.m. N=431
Kaplan–Meier estimate (SE) of % free of disability progression at Month 12 (360 days)	93.3 (1.24)	94.1 (1.15)	92.1 (1.33)
95% CI	(90.92, 95.77)	(91.82, 96.33)	(89.45, 94.66)
Treatment comparison of FTY720 vs. interferon beta-1a i.m.			
Difference of Kaplan–Meier estimates (95% CI)	1.30 (-2.26,4.86)	2.03 (-1.42,5.47)	–
P-value (Log-rank test)	0.498	0.247	–

SE=standard error
P-value from Log-rank test is used to compare the survival distributions between treatment groups.
* Indicates two-sided statistical significance at 0.05 level.

Results of the two supportive analyses (confirmed relapses for PP population and patient level ARR for ITT population) were consistent and confirm results in ITT population.

There was no difference in the magnitude of the treatment effect regardless age, sex, previous treatment or treatment naïve or EDSS at baseline.

The time to first confirmed relapse was prolonged in both fingolimod treatment groups compared to interferon beta-1a i.m.

The proportion of patients who were relapse-free at 12 months was higher in the fingolimod treatment groups (79.8% for fingolimod 1.25 mg and 82.6% for fingolimod 0.5 mg treatment groups) compared to the interferon beta-1a i.m. group (69.3%) and this difference is statistically significant.The proportion of patients who did not have a confirmed relapse during the study was statistically significantly higher in the fingolimod treatment groups compared to the interferon beta-1a i.m. group.There was no statistically significant difference between the fingolimod treatment groups (p=0.413).

There were less relapses in the two fingolimod treatment groups than in the interferon beta-1a i.m. group.

There was no statistically significant difference in the proportion of patients with 3-month confirmed disability progression as measured by EDSS among the three treatment groups for the ITT population.

There was a significant improvement in the mean MSFC z-score and MSFC subscale (PASAT-3) at month 12 in both fingolimod groups compared to the baseline as compared to interferon beta-1a.

At 12 months, the proportion of patients free of Gadolinium-enhanced T1 lesions was significantly reduced in both fingolimod groups (90.1% at 0.5 mg and 91.2% at 1.25 mg) compared to interferon beta-1a group (80.8%). The mean number and mean volume of Gd-enhanced T1 lesions at Month 12 were also statistically significantly lower in the FTY720 treatment groups compared to the interferon beta-1a i.m. group ($p<0.001$). No significant change for the 0.5 mg dose was observed in the total volume of T1 hypointense lesions as compared to interferon beta-1a. There was a statistically significant lower reduction in brain volume in both fingolimod groups (-0.297 at 1.25 mg and -0.307 at 0.5 mg) compared to interferon beta-1a group (-0.400).

At 12 months, mean changes from baseline on PRIMUS-QoL and UFIS, EQ-5D utility scores were not statistically significantly different among the three treatment groups. For all three treatment groups, changes from baseline in EQ-5D Visual Analog Scale score at Month 12 were small (0.6 to 1.9) and not statistically significantly different.

At 6 months, mean change from baseline scores on UFIS score for the fingolimod 0.5 mg group (-1.01) was statistically significantly lower compared to interferon beta-1a i.m. (0.84; $p=0.042$); the mean change from baseline in the fingolimod 1.25 mg group (0.21) was also lower compared to interferon beta-1a i.m., but the difference was not statistically significant ($p=0.232$).

2.5.2.3. Ancillary analyses

Additional post-hoc analyses on primary and key secondary endpoints for studies D2301 and D2302 were performed taking into account previous treatment with MS drugs (interferons, glatiramer acetate), duration and discontinuation of prior MS treatment due to lack of efficacy or AEs.

Study D230

Figure 7 Forest plot of ARR in study D2301 comparing FTY720 0.5 mg vs. placebo, previous MS treatment (ITT population)

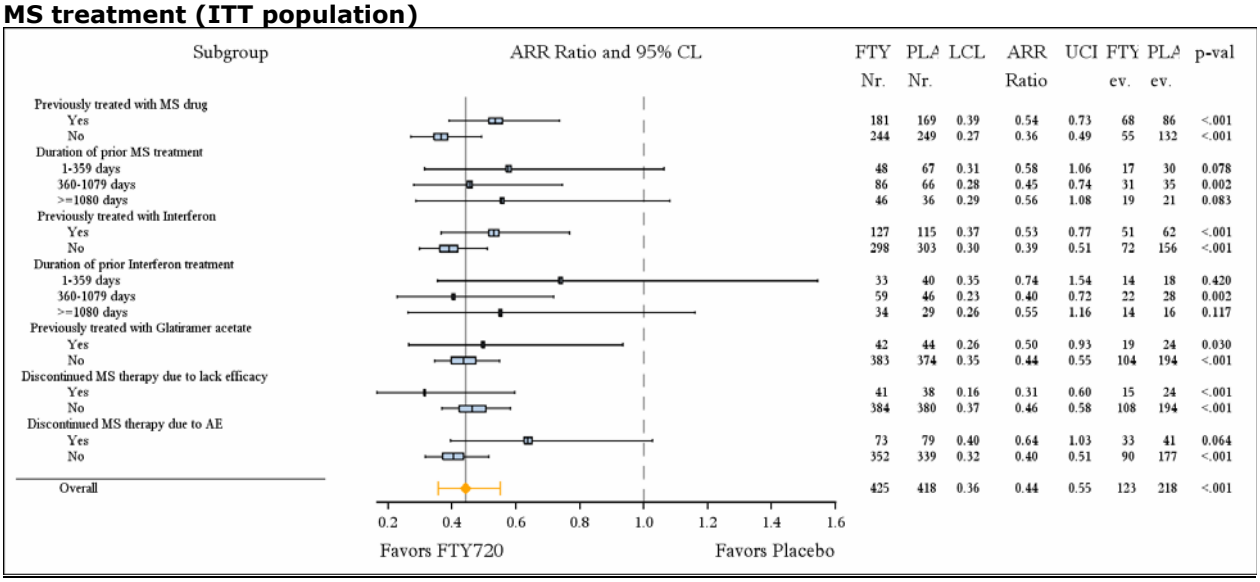
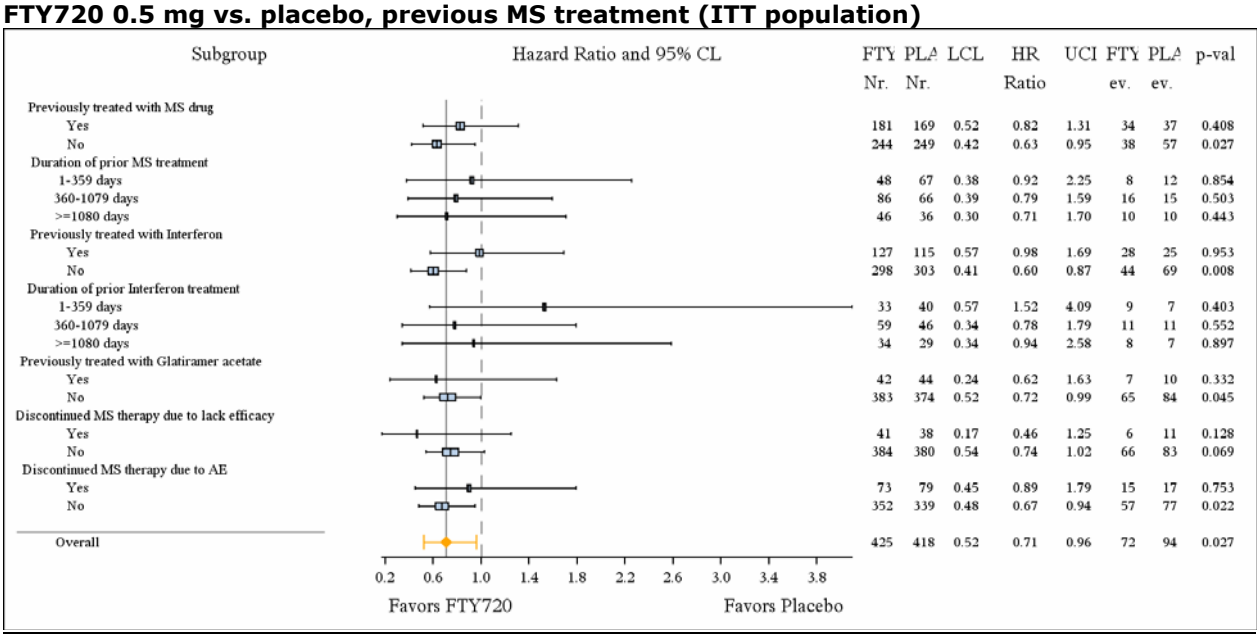


Figure 8 Forest plot of 3-month confirmed disability progression in study D2301 comparing FTY720 0.5 mg vs. placebo, previous MS treatment (ITT population)



Study D2302

Figure 9 Forest plot of ARR in study D2302 comparing FTY720 0.5 mg vs. interferon beta-1a i.m., previous MS treatment (ITT population)

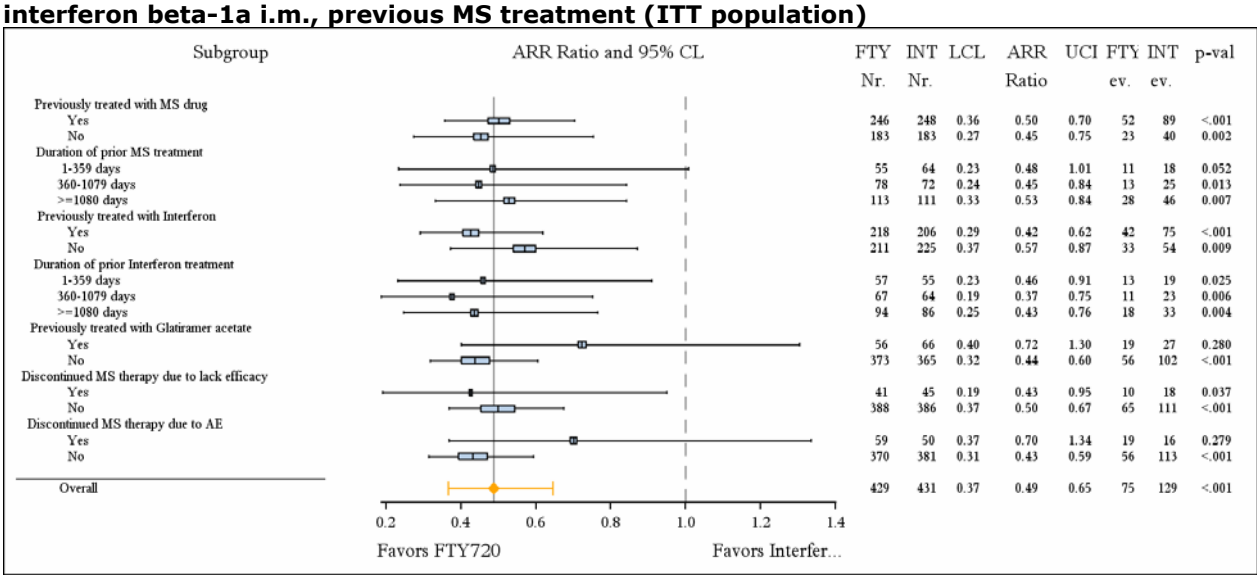


Figure 10 Forest plot of disability progression in study 2302 comparing FTY 0.5mg dose with Interferon for pre-defined subgroups (prior treatment) Intent-to-treat population

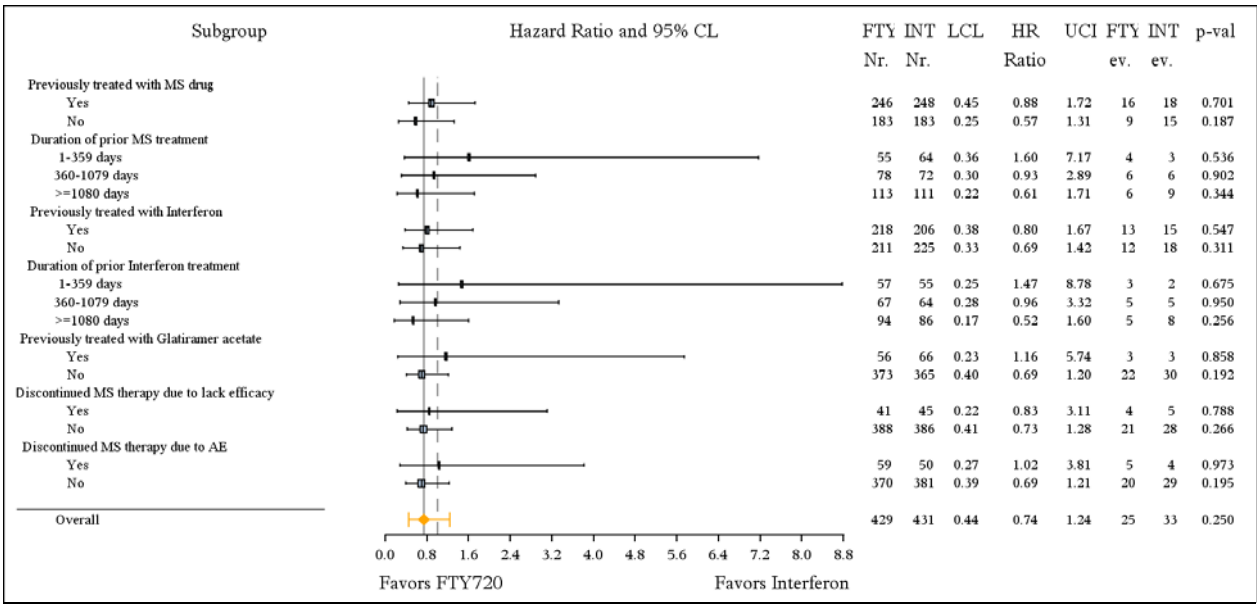
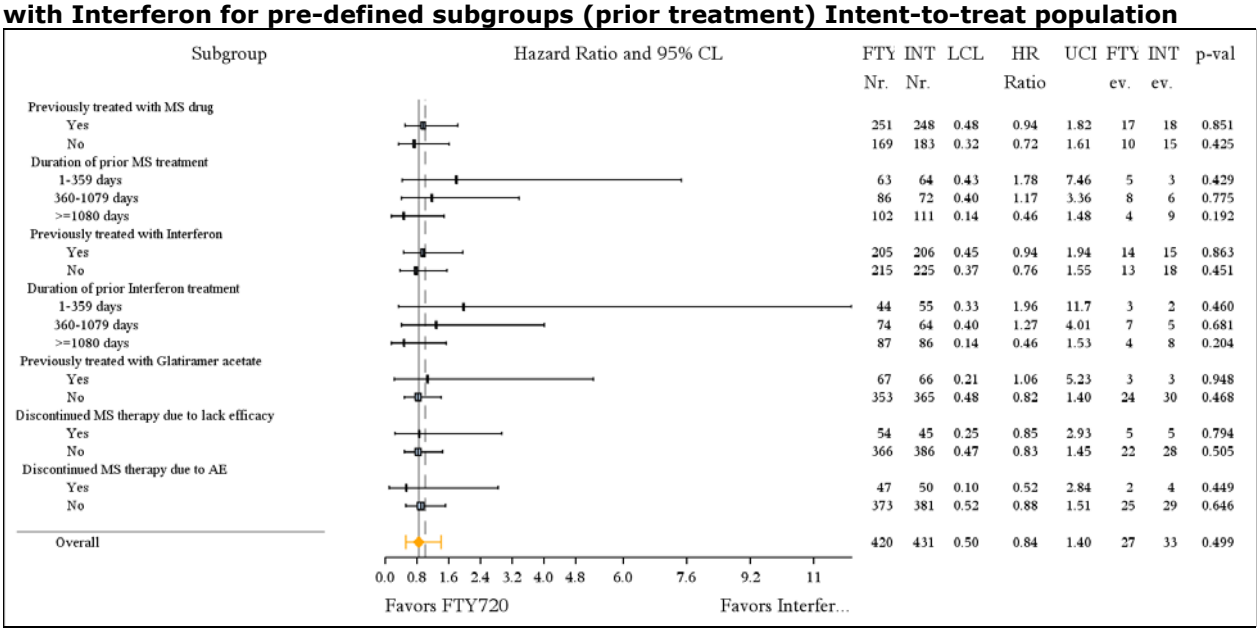


Figure 11 Forest plot of disability progression in study 2302 comparing FTY 1.25mg dose with Interferon for pre-defined subgroups (prior treatment) Intent-to-treat population



A multivariate analysis aiming at identifying potential interacting factors with treatment efficacy was conducted. In both studies, a decrease in relapse rates and a reduction of the effect of fingolimod was observed with increasing age. Nonetheless, no reduction of the effects of fingolimod with increasing age is observed on EDSS score nor on new/newly enlarged T2 lesions in study 2301, thus no additional information concerning elderly population in the SmPC is required at this point time.

Additional post-hoc analyses on primary and secondary endpoints for studies D2301 and D2302 were also performed for different subgroups of patients, as defined by the applicant during the evaluation. At CHMP request, the subgroup analysis related to high disease activity (as defined by patients with 2 or more relapses in the prior year and 1 more Gd-enhancing lesions at baseline) was also presented. Results are provided in the following tables. For the subgroup analyses, a simpler model was used that included only treatment and subgroup and a treatment*subgroup interaction. The overall mean of ARR ratio for fingolimod 0.5 mg dose versus placebo was therefore 0.44 in this model.

Study D2301

Table 15. Other, additional subgroup analyses (at D120)

Analysis description	**Other, additional subgroup analyses (at D120)**			
Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #1 defined as: **Recently treated with clinical activity**: patients who had been on treatment with an approved disease-modifying MS drug for at least 6 months (sufficient duration to evaluate efficacy), were still on treatment in the year before starting study drug, and had at least 1 relapse during the last year. The relapse may or may not have occurred while on the MS disease-modifying therapy.			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
	Number of subjects	61	72	66
	Number of patients with confirmed relapses	19	24	36
	Number of patients with 3 months-confirmed disability progression	13	12	18
Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 1.25 mg versus Placebo**	
		Negative binomial regression – rate ratio	0.52	
		CI	(0.31,0.88)	
		P-value	0.016	
		Comparison groups	**FTY720 0.5 mg versus Placebo**	
		Negative binomial regression – rate ratio	0.47	
		CI	(0.28,0.78)	
		P-value	0.004	
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 1.25 mg versus Placebo**	
		Cox Proportional Hazard Ratio	0.73	
		CI	(0.36,1.48)	
		P-value(Hazard Ratio)	0.381	
		Comparison groups	**FTY720 0.5 mg versus Placebo**	
		Cox Proportional Hazard Ratio	0.56	
		CI	(0.27,1.16)	
		P-value(Hazard Ratio)	0.121	

Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #2 defined as : **Non-responders**: patients who were on treatment with an approved disease-modifying MS drug for at least 6 months and had at least one relapse in the last year prior to starting study drug while on treatment with the same MS drug. This is a subgroup of the patients in #1 above (relapse has occurred while on treatment)			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
	Number of subjects	21	25	24
	Number of patients with confirmed relapses	8	8	19
	Number of patients with 3 month-confirmed disability progression	7	6	6

Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Negative binomial regression – rate ratio	0.26
		CI	(0.12,0.59)
		P-value	0.001
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.26
		CI	(0.12-0.56)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Cox Proportional Hazard Ratio	1.28
		CI	(0.43,3.82)
		P-value(Hazard Ratio)	0.653
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.89
		CI	(0.29,2.75)
		P-value(Hazard Ratio)	0.834

Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #3 defined as: **Recently treated with clinical and MRI activity**: -Patients who had been on treatment with an approved disease-modifying MS drug for at least 6 months (sufficient duration to evaluate efficacy), were still on treatment in the year before starting study drug, and had at least 1 relapse during the last year. The relapse may or may not have occurred while on the MS disease-modifying therapy **and;** - At least one Gd-enhancing lesion on baseline MRI. This is a subgroup of the patients in #1 above (group 1 and at least one Gd-enhancing lesion on baseline MRI)			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
	Number of subjects	30	35	35
	Number of patients with confirmed relapses	8	14	17
	Number of patients with 3 month-confirmed disability progression	6	8	10

Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Negative binomial regression – rate ratio	0.45
		CI	(0.20,1.01)
		P-value	0.052
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.57
		CI	(0.28-1.16)
		P-value	0.122
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.69
		CI	(0.25,1.89)
		P-value(Hazard Ratio)	0.466
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.73
		CI	(0.29,1.84)
		P-value(Hazard Ratio)	0.499

Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #4 defined as : **Active or non-responders with MRI activity:** combining two types of patients, active patients at baseline independent of whether the patients were treatment naive or not (defined as patients who had 2 or more relapses in the prior year plus at least one Gd-enhancing lesion at baseline) and non-responders with MRI activity at baseline (defined as Group #2 but also with at least one Gd-enhancing lesion at baseline).			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
	Number of subjects	72	84	71
	Number of patients with confirmed relapses	27	31	54
	Number of patients with 3 month-confirmed disability progression	14	15	15

Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Negative binomial regression – rate ratio	0.33
		CI	(0.21,0.51)
		P-value	<0.001
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.36
		CI	(0.24,0.54)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.91
		95%CI	(0.44,1.89)
		P-value(Hazard Ratio)	0.805
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.80
		95%CI	(0.39,1.63)
		P-value(Hazard Ratio)	0.534

Table 16. Other, additional subgroup analyses (at D180)

Analysis description	**Other, additional subgroup analyses: Highly disease potential need of highly effective therapy(at D180)**		
Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #1 defined as: Patients with 2 or more relapses in the prior year		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Placebo
	Number of subjects	160	155
	Number of patients with confirmed relapses	50	101
	Number of patients with 3 months-confirmed disability progression	26	35
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.37
		CI	(0.27,0.51)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.67
		CI	(0.40,1.11)
		P-value(Hazard Ratio)	0.116

Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #2 defined as: Patients with 2 or more relapses in the prior year and 1 or more Gd enhancing lesions at baseline		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Placebo
	Number of subjects	77	63
	Number of patients with confirmed relapses	29	47
	Number of patients with 3 month-confirmed disability progression	13	13
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.37
		CI	(0.24,0.57)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.78
		CI	(0.36,1.68)
		P-value(Hazard Ratio)	0.521

Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #3 defined as: Patients with 1 relapse in the prior year and 1 or more Gd enhancing lesions at baseline		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Placebo
	Number of subjects	158	152
	Number of patients with confirmed relapses	54	97
	Number of patients with 3 month-confirmed disability progression	26	36
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.41
		CI	(0.30,0.56)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.64
		CI	(0.38,1.06)
		P-value(Hazard Ratio)	0.081

Analysis population and time point description	Intent to treat at 24 months Subgroup of patients #4 defined as: Patients with 1 relapse in the prior year and EDSS 2.5 or higher		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Placebo
	Number of subjects	191	197
	Number of patients with confirmed relapses	69	120
	Number of patients with 3 month-confirmed disability progression	28	51
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.52
		CI	(0.39,0.70)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.50
		CI	(0.32,0.80)
		P-value(Hazard Ratio)	0.003

Study D2302

Table 17. Other, additional subgroup analyses (at D120)

Analysis description	**Other, additional subgroup analyses (at D120)**			
Analysis population and time point description	Intent to treat at 12 months Subgroup of patients #1 defined as: **Recently treated with clinical activity:** patients who had been on treatment with an approved disease-modifying MS drug for at least 6 months (sufficient duration to evaluate efficacy), were still on treatment in the year before starting study drug, and had at least 1 relapse during the last year. The relapse may or may not have occurred while on the MS disease-modifying therapy.			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Interferon beta-1a 30µg
	Number of subjects	180	178	177
	Number of patients with confirmed relapses	45	36	66
Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 1.25 mg versus Interferon beta-1a 30µg**	
		Negative binomial regression – rate ratio	0.66	
		CI	(0.46,0.96)	
		P-value	0.032	
		Comparison groups	**FTY720 0.5 mg versus Interferon beta-1a 30µg**	
		Negative binomial regression – rate ratio	0.45	
		CI	(0.30,0.68)	
		P-value	<0.001	

Analysis population and time point description	Intent to treat at 12 months Subgroup of patients #2 defined as : **Non-responders**: patients who were on treatment with an approved disease-modifying MS drug for at least 6 months and had at least one relapse in the last year prior to starting study drug while on treatment with the same MS drug. This is a subgroup of the patients in #1 above (relapse has occurred while on treatment)			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Interferon beta-1a 30µg
	Number of subjects	44	53	62
	Number of patients with confirmed relapses	13	13	31
Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**		**FTY720 1.25 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio		0.68
		CI		(0.36,1.27)
		P-value		0.228
		Comparison groups		**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio		0.39
		CI		(0.20-0.76)
		P-value		0.006

<table>
<tr><td>Analysis population and time point description</td><td colspan="4">Intent to treat at 12 months

Subgroup of patients #3 defined as:

Recently treated with clinical and MRI activity:
-Patients who had been on treatment with an approved disease-modifying MS drug for at least 6 months (sufficient duration to evaluate efficacy), were still on treatment in the year before starting study drug, and had at least 1 relapse during the last year. The relapse may or may not have occurred while on the MS disease-modifying therapy and;
- At least one Gd-enhancing lesion on baseline MRI.
This is a subgroup of the patients in #1 above (group 1 and at least one Gd-enhancing lesion on baseline MRI)</td></tr>
<tr><td rowspan="3">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>FTY720 1.25 mg</td><td>FTY720 0.5 mg</td><td>Interferon beta-1a 30µg</td></tr>
<tr><td>Number of subjects</td><td>90</td><td>90</td><td>97</td></tr>
<tr><td>Number of patients with confirmed relapses</td><td>22</td><td>19</td><td>43</td></tr>
<tr><td rowspan="8">Effect estimate per comparison</td><td rowspan="8">Primary endpoint: Aggregate ARR</td><td colspan="2">Comparison groups</td><td colspan="2">FTY720 1.25 mg versus Interferon beta-1a 30µg</td></tr>
<tr><td colspan="2">Negative binomial regression – rate ratio</td><td colspan="2">0.70</td></tr>
<tr><td colspan="2">CI</td><td colspan="2">(0.42,1.16)</td></tr>
<tr><td colspan="2">P-value</td><td colspan="2">0.163</td></tr>
<tr><td colspan="2">Comparison groups</td><td colspan="2">FTY720 0.5 mg versus Interferon beta-1a 30µg</td></tr>
<tr><td colspan="2">Negative binomial regression – rate ratio</td><td colspan="2">0.44</td></tr>
<tr><td colspan="2">CI</td><td colspan="2">(0.25-0.77)</td></tr>
<tr><td colspan="2">P-value</td><td colspan="2">0.004</td></tr>
</table>

Analysis population and time point description	Intent to treat at 12 months Subgroup of patients #4 defined as : **Active or non-responders with MRI activity:** combining two types of patients, active patients at baseline independent of whether the patients were treatment naive or not (defined as patients who had 2 or more relapses in the prior year plus at least one Gd-enhancing lesion at baseline) and non-responders with MRI activity at baseline (defined as Group #2 but also with at least one Gd-enhancing lesion at baseline).			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
	Number of subjects	74	74	80
	Number of patients with confirmed relapses	17	18	33
Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**		**FTY720 1.25 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio		0.62
		CI		(0.35,1.09)
		P-value		<0.096
		Comparison groups		**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio		0.48
		CI		(0.27,0.87)
		P-value		0.015

Table 18. Other, additional subgroup analyses (at D180)

Analysis description	**Other, additional subgroup analyses: Highly disease potential need of highly effective therapy(at D180)**		
Analysis population and time point description	Intent to treat at 12 months Subgroup of patients #1 defined as: Patients with 2 or more relapses in the prior year		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Interferon beta-1a 30µg
	Number of subjects	168	157
	Number of patients with confirmed relapses	33	56
	Number of patients with 3 month-confirmed disability progression	10	11
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio	0.43
		CI	(0.29,0.65)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Cox Proportional Hazard Ratio	0.83
		CI	(0.35,1.96)
		P-value(Hazard Ratio)	0.674

Analysis population and time point description	Intent to treat at 12 months Subgroup of patients #2 defined as: Patients with 2 or more relapses in the prior year and 1 or more Gd enhancing lesions at baseline		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Interferon beta-1a 30µg
	Number of subjects	56	65
	Number of patients with confirmed relapses	12	23
	Number of patients with 3 months-confirmed disability progression	4	5
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio	0.48
		CI	(0.24,0.94)
		P-value	0.033
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Cox Proportional Hazard Ratio	0.95
		CI	(0.25,3.53)
		P-value(Hazard Ratio)	0.935

Analysis population and time point description	Intent to treat at 12 months Subgroup of patients #3 defined as: Patients with 1 relapse in the prior year and 1 or more Gd enhancing lesions at baseline		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Interferon beta-1a 30µg
	Number of subjects	138	153
	Number of patients with confirmed relapses	27	58
	Number of patients with 3 month-confirmed disability progression	10	12
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio	0.43
		CI	(0.27,0.67)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Cox Proportional Hazard Ratio	0.92
		CI	(0.40,2.13)
		P-value(Hazard Ratio)	0.848

Analysis population and time point description	Intent to treat at 12 months Subgroup of patients #4 defined as: Patients with 1 relapse in the prior year and EDSS 2.5 or higher		
Descriptive statistics and estimate variability	Treatment group	FTY720 0.5 mg	Interferon beta-1a 30µg
	Number of subjects	164	172
	Number of patients with confirmed relapses	33	63
	Number of patients with 3 month-confirmed disability progression	7	13
	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio	0.47
		CI	(0.31,0.72)
		P-value	<0.001
	Key Secondary endpoint: Time to 3 month-confirmed disability progression	**Comparison groups**	**FTY720 0.5 mg versus Interferon beta-1a 30µg**
		Cox Proportional Hazard Ratio	0.54
		CI	(0.21,1.34)
		P-value(Hazard Ratio)	0.183

2.5.2.4. Summary of main studies

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

Table 19 Summary of efficacy for trial D2301

Title: A 24-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of FTY720 1.25 mg and 0.5 mg administered orally once daily versus placebo in patients with relapsing-remitting multiple sclerosis			
Study identifier	Protocol no. CFTY720D2301; EUDRACT no. 2005-000365-19		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		720 days 45 days Optional - until FTY720 is commercially available or development is stopped (under a separate protocol no FTY720D2301E1)
Hypothesis	Superiority		
Treatments groups	FTY720 1.25 mg		1.25mg capsule/day, 429 randomised
	FTY720 0.5 mg		0.5 mg capsule /day, 425 randomised
	Placebo		Matching placebo capsule/day, 418 randomised
Endpoints and definitions	Primary endpoint	Aggregate annualized relapse rate (ARR)	Number of confirmed relapses per year over 24 months. A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS (Kurtzke's Expanded Disability Status Scale) or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS).
	Key Secondary endpoint	Time to 3 months confirmed disability progression	Time to 3-month confirmed disability progression (as measured by at least a 1-point increase in EDSS, or 0.5 for those with baseline EDSS of 5.5) up to 24 months. A 3-month confirmed disability progression required that the onset EDSS, the 3-month confirmatory EDSS (in the absence of relapse), and all EDSS scores in between met the disability progression criteria.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat at 24 months			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Placebo
	Number of subjects	429	425	418
	Aggregate ARR (Negative binomial regression)	0.16	0.18	0.40
	95%CI	(0.13,0.19)	(0.15,0.22)	(0.34,0.47)

	Proportion of patients free of 3-month confirmed disability progression (Kaplan Meier)	83.4	82.3	75.9
	95%CI	(79.7,87.1)	(78.6,86.1)	(71.7,80.2)

Effect estimate per comparison	Primary endpoint: Aggregate ARR	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Negative binomial regression – rate ratio	0.40
		P-value	<0.001
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Negative binomial regression – rate ratio	0.46
		95%CI	(0.36,0.55)
		P-value	<0.001
	Key Secondary endpoint: Time to 3-month confirmed disability progression	**Comparison groups**	**FTY720 1.25 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.68
		95%CI	(0.50,0.93)
		P-value(Hazard Ratio) P-value (Log rank test)	0.017 0.012
		Comparison groups	**FTY720 0.5 mg versus Placebo**
		Cox Proportional Hazard Ratio	0.70
		95%CI	(0.52,0.96)
		P-value(Hazard Ratio) P-value (Log rank test)	0.024 0.026

Table 20 Summary of efficacy for trial D2302

Title: A 12-month double-blind, randomized, multicenter, active-controlled, parallel-group study comparing the efficacy and safety of 0.5 mg and 1.25 mg fingolimod (FTY720) administered orally once daily versus interferon β-1a (Avonex®) administered i.m. once weekly in patients with relapsing-remitting multiple sclerosis with optional Extension Phase			
Study identifier	Protocol no. CFTY720D2302; EudraCT no. 2006-000704-17		
Design	A 12-month, randomized, multicenter, double-blind, double-dummy, active controlled, parallel-group study in approximately 1275 patients with RRMS with ann optional Extension Phase. Patients were randomized to receive FTY720 0.5 mg/d orally (p.o.), FTY720 1.25 mg/d p.o., or interferon beta-1a 30 µg/week intramuscularly (i.m.) in a double dummy design.		
	Duration of main phase:		360 days
	Duration of Run-in phase:		45 days
	Duration of Extension phase:		Optional - until FTY720 is commercially available or development is stopped.
Hypothesis	Superiority		
Treatments groups	FTY720 1.25 mg		1.25mg capsule/day and weekly matching interferon beta-1a placebo , 426 randomised
	FTY720 0.5 mg		0.5 mg capsule /day and weekly matching interferon beta-1a placebo, 431 randomised
	Interferon beta-1a 30µg		30µg i.m/week and matching FTY720 placebo daily, 435 randomised
Endpoints and definitions	Primary endpoint	Aggregate annualized relapse rate (ARR)	Number of confirmed relapses per year over 24 months. A relapse was confirmed when it was accompanied by an increase of at least half a step (0.5) on the EDSS (Kurtzke's Expanded Disability Status Scale) or an increase of 1 point on two different Functional Systems (FS) of the EDSS or 2 points on one of the FS (excluding Bowel/Bladder or Cerebral FS).
	Key Secondary endpoint	Number of new or newly enlarged T2 lesions	Effect on inflammatory disease activity as measured by the number of new or newly enlarged T2 lesions at 12 months
	Key Secondary endpoint	Time to 3-month confirmed disability progression	Time to 3-month confirmed disability progression (as measured by at least a 1-point increase in EDSS, or 0.5 for those with baseline EDSS of 5.5) up to 24 months. A 3-month confirmed disability progression required that the onset EDSS, the 3-month confirmatory EDSS (in the absence of relapse), and all EDSS scores in between met the disability progression criteria.

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat at 12 months			
Descriptive statistics and estimate variability	Treatment group	FTY720 1.25 mg	FTY720 0.5 mg	Interferon beta-1a 30µg
	Number of subjects	420	429	431
	Aggregate ARR (Negative binomial regression)	0.203	0.161	0.331
	95%CI	(0.157,0.264)	(0.122,0.212)	(0.262,0.417)

	Proportion of patients free of 3-month confirmed disability progression (Kaplan Meier)	93.3	94.1	92.1
	95%CI	(90.92, 95.77)	(91.82, 96.33)	(89.45, 94.66)
	Number of new or newly enlarged T2 lesions (mean, standard deviation)	1.4 (2.51)	1.5 (3.5)	2.1(4.86)
	Range Number of patients with evaluable MRI at 12 months	0 – 22 356	0-32 380	0-60 365

Effect estimate per comparison	Primary endpoint: aggregate annualized relapse rate (ARR)	**Comparison groups**	**FTY720 1.25mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio	0.62
		P-value	<0.001
		Comparison groups	**FTY720 0.5mg versus Interferon beta-1a 30µg**
		Negative binomial regression – rate ratio	0.48
		P-value	<0.001
	Key Secondary endpoint: Time to 3-month confirmed disability progression	**Comparison groups**	**FTY720 1.25mg versus Interferon beta-1a 30µg**
		Cox Proportional Hazard Ratio	0.85
		95%CI	(-2.26,4.86)
		P-value(Hazard Ratio) P-value (Log rank test)	0.54 0.50
		Comparison groups	**FTY720 0.5mg versus Interferon beta-1a 30µg**
		Cox Proportional Hazard Ratio	0.71
		95%CI	(0.42, 1.21)
		P-value(Hazard Ratio) P-value (Log rank test)	0.21 0.25
	Key Secondary endpoint: Number of new or newly enlarged T2 lesions	**Comparison groups**	**FTY720 1.25mg versus Interferon beta-1a 30µg**
		P-value	0.017
		Comparison groups	**FTY720 0.5mg versus Interferon beta-1a 30µg**
		P-value	0.053

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

Data from studies D2301 and D2302 were pooled for analyses of the primary efficacy endpoint, the ARR, specifically for subgroups (Gd lesions at baseline: equal to 0, ≥1, number of relapses in two years prior to study entry: ≤2, ≥3, treatment naïve patients, previously treated patients). Otherwise no pooling of data across studies was performed. Results were consistent with those of the two studies (D2301 and D2302). Each individual study was strongly demonstrative, and the submitted pooled analysis did not add significant knowledge as compared to both studies being considered separately (see Tables 21 and 22).

Table 21 Aggregate ARR by age, gender and treatment (pooled ITT population)

		FTY720 1.25 mg N = 849	FTY720 0.5 mg N = 854	Placebo N = 418	Interferon N = 431
All patients	n	849	854	418	431
	ARR	0.21	0.21	0.47	0.43
	Rate ratio / p-value:				
	FTY720 1.25 mg vs. control			0.47 / < 0.001	0.49 / < 0.001
	FTY720 0.5 mg vs. control			0.47 / < 0.001	0.49 < 0.001
Age (years)					
≤ 40	n	537	547	262	297
	ARR	0.21	0.18	0.54	0.46
	Rate ratio / p-value:				
	FTY720 1.25 mg vs. control			0.39 / < 0.001	0.46 / < 0.001
	FTY720 0.5 mg vs. control			0.33 / < 0.001	0.39 / < 0.001
> 40	n	312	307	156	134
	ARR	0.21	0.26	0.36	0.36
	Rate ratio / p-value:				
	FTY720 1.25 mg vs. control			0.58 / 0.001	0.58 / 0.085
	FTY720 0.5 mg vs. control			0.72 / 0.024	0.72 / 0.330
Gender					
Male	n	266	277	120	139
	ARR	0.24	0.19	0.54	0.34
	Rate ratio / p-value:				
	FTY720 1.25 mg vs. control			0.44 / < 0.001	0.71 / 0.355
	FTY720 0.5 mg vs. control			0.35 / < 0.001	0.56 / 0.063
Female	n	583	577	298	292
	ARR	0.20	0.22	0.44	0.47
	Rate ratio / p-value:				
	FTY720 1.25 mg vs. control			0.45 / < 0.001	0.43 / < 0.001
	FTY720 0.5 mg vs. control			0.50 / < 0.001	0.47 / < 0.001

p-value was to compare the treatment difference by subgroup based on a negative binomial regression model adjusted for study. No other covariates were included in the model.

	FTY720 1.25 mg N = 849	FTY720 0.5 mg N = 854	Placebo N = 418	Interferon N = 431
All patients - n	849	854	418	431
ARR	0.21	0.21	0.47	0.43
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.45 / < 0.001	0.49 / < 0.001
FTY720 0.5 mg vs. control			0.45 / < 0.001	0.49 < 0.001
Gd-enhancing lesions at baseline:				
No lesion - n	527	551	262	268
ARR	0.19	0.18	0.36	0.35
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.53 / < 0.001	0.54 / 0.020
FTY720 0.5 mg vs. control			0.50 / < 0.001	0.51 0.005
≥1 lesion(s) - n	309	300	154	157
ARR	0.25	0.26	0.66	0.54
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.38 / < 0.001	0.46 / < 0.001
FTY720 0.5 mg vs. control			0.39 / < 0.001	0.48 / < 0.001
Number of relapses in the two years prior to study entry:				
≤ 2 relapses - n	619	621	301	295
ARR	0.17	0.18	0.42	0.35
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.40 / < 0.001	0.49 / < 0.001
FTY720 0.5 mg vs. control			0.43 / < 0.001	0.51 / < 0.001
≥ 3 relapses - n	230	232	117	135
ARR	0.32	0.30	0.59	0.61
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.54 / < 0.001	0.52 / 0.024
FTY720 0.5 mg vs. control			0.51 / < 0.001	0.49 / 0.006

P-value was to compare the treatment difference by subgroup based on a negative binomial regression model adjusted for study. Rate ratios in this table do not feature in ISE source table, but were manually calculated

Table 22 Aggregate ARR by baseline disease characteristics and treatment (Pooled ITT population)

	FTY720 1.25 mg N = 849	FTY720 0.5 mg N = 854	Placebo N = 418	Interferon N = 431
All patients - n	849	854	418	431
ARR	0.21	0.21	0.47	0.43
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.45 / < 0.001	0.49 / < 0.001
FTY720 0.5 mg vs. control			0.45 / < 0.001	0.49 < 0.001
Treatment-naïve* - n	428	427	249	183
ARR	0.17	0.16	0.45	0.31
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.38 < 0.001	0.55 / 0.004
FTY720 0.5 mg vs. control			0.36 < 0.001	0.52 / < 0.001
Previously treated - n	421	427	169	248
ARR	0.26	0.27	0.50	0.52
Rate ratio / p-value: FTY720 1.25 mg vs. control			0.52 / < 0.001	0.50 < 0.001
FTY720 0.5 mg vs. control			0.54 < 0.001	0.52 < 0.001

* Treatment naïve patients were defined as those not receiving any MS treatment drugs, approved for the treatment of relapsing MS or not, according to MS history CRFs.
P-value was to compare the treatment difference by subgroup based on a negative binomial regression model adjusted for study.

Additionally, data from the Phase II extension study (D2201E1) and Phase III D2301 and D2302 studies were pooled to evaluate the efficacy after withdrawal and possible rebound effect. This analysis included all patients from studies D2301, D2302, and D2201E1 who received a cumulative dose of at least 3 months and had any follow-up data beyond 14 days after study drug discontinuation. Results are presented below.

Table 23
ARR while on treatment and after stopping treatment (Follow –up population)

	FTY720 5.0 mg - 1.25 mg N = 44	FTY720 1.25 mg N = 213	FTY720 0.5 mg N = 164	All FTY720 treated N = 421	Placebo N = 110	IFN β-1a i.m. N = 71
On treatment						
(From Day 1 to last dose date + 14 days)						
n	44	213	164	421	110	71
Number of relapses	16	87	51	154	114	25
ARR	0.15	0.31	0.26	0.26	0.81	0.42
Proportion (%) of patients relapse-free	77.3	75.1	74.4	75.1	36.4	73.2
After stopping treatment						
(from last dose date + 15 days to last follow-up/last available assessment date)						
n	44	213	164	421	110	71
Number of relapses	7	21	13	41	13	2
ARR	0.31	0.21	0.18	0.21	0.22	0.10
Proportion (%) of patients relapse-free						
Day 15-90 off drug	90.9	94.4	97.6	95.2	97.3	97.2
>90 days off drug)	91.4	94.1	90.4	92.5	86.8	100

Table 24. Gd-enhancing lesions at baseline, last treatment and follow-up visit (with MRI data)

	FTY720 5 mg-1.25 mg N = 44	FTY720 1.25 mg N = 213	FTY720 0.5 mg N = 164	All FTY720 treated N = 421	Placebo N = 110	Interferon N = 71
Baseline						
Number of lesions						
n	26	95	67	188	51	9
Mean (SD)	2.3 (3.45)	1.9 (4.07)	2.3 (10.39)	2.1 (6.93)	1.1 (2.33)	1.3 (2.29)
Median	0.5	0.0	0.0	0.0	0.0	0.0
Range	0 – 14	0 – 26	0 – 84	0 - 84	0 – 14	0 - 7
Volume of lesions						
n	26	94	67	187	51	9
Mean (SD)	202 (288)	208 (598)	191 (862)	201 (674)	190 (501)	135 (230)
Median	15.7	0.0	0.0	0.0	0.0	0.0
Range	0-1036	0-4232	0-6850	0-6850	0-2060	0-658
Proportion of patients free of lesions						
n	26	95	67	188	51	9
n (%)	13(50.0)	51(53.7)	41 (61.2)	105 (55.9)	30 (58.8)	5 (55.6)
Last on-treatment						
Number of lesions						
n	26	95	67	188	51	9
Mean (SD)	0.8 (2.76)	0.3 (1.23)	0.4 (1.59)	0.4 (1.64)	1.2 (2.15)	1.3 (3.64)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0 - 14	0-10	0 - 11	0 - 14	0 – 9	0 - 11
Volume of lesions						
n	26	94	67	187	51	9
Mean (SD)	58 (187)	63 (220)	99 (502)	75 (344)	155 (358)	102 (298)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0-939	0-1456	0-3943	0-3943	0-2155	0-896
Proportion of patients free of lesions						
n	26	95	67	188	51	9
n (%)	21 (80.8)	82 (86.3)	58 (86.6)	161 (85.6)	31 (60.8)	7 (77.8)
Last Available Follow-up Scan (beyond Day 14 after discontinuation)						
Number of lesions						
n	26	95	67	188	51	9
Mean (SD)	3.0 (5.14)	2.7 (7.64)	1.1 (2.12)	2.2 (5.92)	0.5 (1.12)	0.7 (1.41)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0-18	0-63	0-11	0-63	0-6	0-4
Volume of lesions						
n	26	94	67	187	51	9
Mean (SD)	435 (892)	378 (901)	127 (295)	296 (749)	94 (223)	122 (244)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0-3302	0-5488	0-1657	0-5488	0-953	0-604
Proportion of patients free of lesions						
n	26	95	67	188	51	9
n (%)	14 (53.8)	56 (58.9)	47 (70.1)	117 (62.2)	36 (70.6)	7 (77.8)

Table 25

Follow-up Scan done between Day 15 and Day 90 after discontinuation						
Number of lesions						
n	18	49	34	101	27	6
Mean (SD)	3.0 (5.43)	2.6 (9.26)	1.2 (2.8)	2.2 (7.02)	1.3 (1.84)	0.7 (1.63)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0 - 18	0 - 63	0 - 12	0 - 63	0-6	0-4
Volume of lesions						
n	18	48	34	100	27	6
Mean (SD)	419 (912)	298 (952)	162 (526)	274 (821)	100 (162)	83 (203)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0-3302	0-5488	0-2979	0-5488	0-595	0-498
Proportion of patients free of lesions						
n	18	49	34	101	27	6
n (%)	10 (55.6)	34 (69.4)	24 (70.6)	68 (67.3)	14 (51.9)	5 (83.3)
Follow-up Scan done beyond Day 90 after discontinuation						
Number of lesions						
N	13	65	45	123	42	3
Mean (SD)	2.4 (3.91)	2.5 (5.06)	1.2 (2.36)	2.0 (4.16)	0.3 (0.60)	0.7 (1.15)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0 - 11	0 - 22	0 - 11	0 - 22	0-2	0-2
Volume of lesions						
N	13	65	45	123	42	3
Mean (SD)	322 (726)	404 (838)	151 (345)	303 (691)	80 (225)	201 (349)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0-2647	0-3651	0-1657	0-3651	0-953	0-604
Proportion of patients free of lesions						
N	13	65	45	123	42	3
n (%)	7 (53.8)	36 (55.4)	32 (71.1)	75 (61.0)	32 (76.2)	2 (66.7)

Last on-treatment: latest MRI up to 14 days after study drug discontinuation
Gd-enhancing lesion data obtained less than 30 days after the steroid used to treat MS relapses was excluded.
Source: [Appendix 2- FTY720D Ad Com Table 6-1 and Table 6-2], [Appendix 2-Table 106-1.2]

2.5.2.6. Clinical studies in special populations

No trials have been performed in any special multiple sclerosis patient populations.

2.5.2.7. Supportive studies

D2201E1 is an ongoing extension study of the phase II D2201. All patients who completed the Month 6 visit were eligible to enter the extension study. The objectives were to evaluate long-term effects of fingolimod on efficacy related outcomes and collect long-term safety and tolerability data.

The extension consisted of two phases: a double-blind treatment phase and an open-label treatment phase (lasting until the drug becomes available on the market in the specific country or until drug development discontinuation).

During the blinded phase, all patients received four capsules per dose administration, i.e. patients on fingolimod 1.25 mg received 1 x fingolimod 1.25 mg capsule plus 3 x matching placebo capsules, patients on fingolimod 5.0 mg received 4 x fingolimod 1.25 mg capsules. After switching all patients to fingolimod 1.25 mg, all patients received one capsule per day.

Patients who were randomized to fingolimod 1.25 mg or 5.0 mg qd in the core study kept the same randomization number as in the core study and continued on the same dose of fingolimod during the first 6 months of the extension. Patients who were randomized to placebo in the core study were re-randomized in a 1:1 ratio to either fingolimod 1.25 mg or 5.0 mg qd during the initial double-blind phase of the extension. After all patients had completed the Month 12 visit (6 months core plus 6

months extension), treatment with fingolimod 5.0 mg was discontinued and all patients were offered open-label treatment with fingolimod 1.25 mg.

Results from the interim analysis at month 60 was submitted as part of the present application and are presented below.

Table 26 Patients free of Gd-enhanced T1 weighted lesions by visit (ITT population, 60 month analysis)

	Placebo/ FTY720** N=93	FTY720 1.25 mg N=94	FTY720 5.0 mg/ 1.25 mg N=94	All N=281
Visit	N* n (%)	N* n (%)	N* n (%)	N* n (%)
Baseline	93 46 (49.5)	92 48 (52.2)	93 45 (48.4)	278 139 (50.0)
Month 6	83 39 (47.0)	90 69 (76.7)	87 68 (78.2)	260 176 (67.7)
Month 12	72 57 (79.2)	77 64 (83.1)	71 63 (88.7)	220 184 (83.6)
Month 24	64 55 (85.9)	63 51 (81.0)	61 53 (86.9)	188 159 (84.6)
Month 36	58 52 (89.7)	56 49 (87.5)	56 50 (89.3)	170 151 (88.8)
Month 48	51 49 (96.1)	53 52 (98.1)	46 43 (93.5)	150 144 (96.0)
Month 60	45 41 (91.1)	48 44 (91.7)	43 40 (93.0)	136 125 (91.9)

A patient was defined as free of lesions if there were zero lesions.
** Patients were on placebo up to Month 6.
N* = number of patients with information recorded at visit. n = patients free of Gd-enhanced lesions. % = (n/N*)x100

Table 27 Patients free of new T2-weighted lesions by visit (ITT population, 60 month analysis)

	Placebo/ FTY720** N=93	FTY720 1.25 mg N=94	FTY720 5.0 mg/ 1.25 mg N=94	All N=281
Visit	N* n (%)	N* n (%)	N* n (%)	N* n (%)
Month 1-6	81 19 (23.5)	85 43 (50.6)	78 32 (41.0)	244 94 (38.5)
Month 12	71 45 (63.4)	79 54 (68.4)	71 51 (71.8)	221 150 (67.9)
Month 24	64 45 (70.3)	66 46 (69.7)	61 44 (72.1)	191 135 (70.7)
Month 36	59 45 (76.3)	57 40 (70.2)	56 44 (78.6)	172 129 (75.0)
Month 48	52 46 (88.5)	53 42 (79.2)	46 36 (78.3)	151 124 (82.1)
Month 60	45 40 (88.9)	49 43 (87.8)	42 35 (83.3)	136 118 (86.8)

1. A patient is defined as free of lesions if there were zero lesions.
2. N* = Number of patients with T2 information recorded at scan. n = Number of patients free of new T2-weighted lesions. % = (n/N*)x100
3. New T2 lesions at a specific visit are assessed relative to the previous visit scan. Exception: New T2 lesions at Month 24 were assessed relative to the Month 12 scan.
4. Month 1-6 refers to the sum of all new T2-weighted lesions at Month 1 to Month 6 (the sum is missing if one of the assessments is missing). A patient is free of new T2-weighted lesions at Month 1-6, if the sum is zero.

Table 28 Number of patients free from any inflammatory activity

	Placebo/ FTY720** N=93	FTY720 1.25 mg N=94	FTY720 5.0 mg/ 1.25 mg N=94	All N=281
Visit	N* n (%)	N* n (%)	N* n (%)	N* n (%)
Month 1	90 38 (42.2)	90 45 (50.0)	83 32 (38.6)	263 115 (43.7)
Month 6	80 38 (47.5)	87 67 (77.0)	83 67 (80.7)	250 172 (68.8)
Month 12	70 40 (57.1)	77 52 (67.5)	70 51 (72.9)	217 143 (65.9)
Month 24	64 44 (68.8)	63 44 (69.8)	61 44 (72.1)	188 132 (70.2)
Month 36	58 44 (75.9)	55 36 (65.5)	56 44 (78.6)	169 124 (73.4)
Month 48	51 45 (88.2)	52 41 (78.8)	46 36 (78.3)	149 122 (81.9)
Month 60	45 40 (88.9)	48 42 (87.5)	42 35 (83.3)	135 117 (86.7)

At Month 6, the percent of patients free from any inflammatory activity (i.e. had no new T2-weighted and no Gd-enhanced T1-weighted lesions) in the FTY720 groups was 77.0 to 80.7% and in the placebo/FTY720 group was 47.5%. At Month 60, 86.7% of all patients were free of any inflammatory activity.

Table 29 Aggregated annualized relapse rates from core baseline to month 60 (confirmed relapses) (ITT population)

Statistics	Placebo/ FTY720* N=93	FTY720 1.25 mg N=94	FTY720 5.0 mg/ 1.25 mg N=94	All N=281
Number of relapses	74	56	58	188
Time in study (days)	117772	121771	111796	351339
Annualized rate	0.23	0.17	0.19	0.20

Aggregated annualized relapse rate was calculated for each treatment arm as (total number of relapses per treatment arm / total time at risk per treatment arm (days)) x 365.25. Relapses that occurred after permanent treatment discontinuation were not included in the analysis.
* Patients were on placebo up to Month 6

Figure 12 Time to first relapse (confirmed relapse only) Kaplan-Meier plot of time from core baseline to first confirmed relapse (ITT population, 60-month analysis)

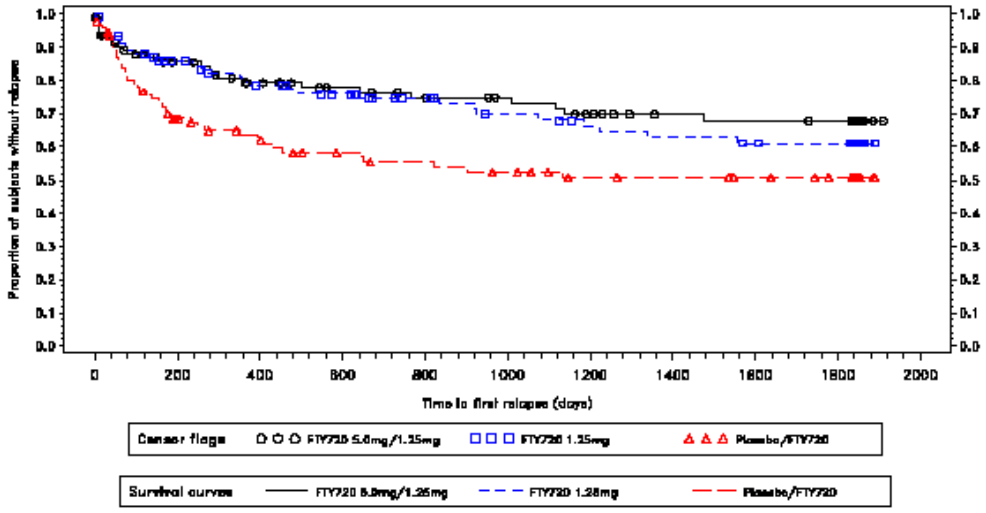


Table 28 Kaplan-Meier estimate of the proportion of patients relapse free at Month 60 (confirmed relapses only) (ITT population, 60-month analysis)

Treatment group	Number with event (relapse)	KM estimate† (SE)	95% CI
Placebo/FTY720*	41	0.51 (0.056)	(0.399, 0.619)
FTY720 1.25 mg	30	0.61 (0.058)	(0.496, 0.724)
FTY720 5.0 mg/1.25 mg	25	0.68 (0.055)	(0.570, 0.786)

† Kaplan-Meier estimate is the proportion of patients free of event at Month 60 (Core Day 1800). The confidence intervals (CIs) are Kaplan-Meier estimates. Only confirmed relapses (as indicated on the MS Relapses eCRF) were considered. Relapses that occurred after permanent treatment discontinuation were not included in the analysis.
*Patients were on placebo up to Month 6

2.5.3. Discussion on clinical efficacy

With respect to the phase II study, the design followed the guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis (CPMP/EWP/561/98 Rev.1). However, only 2 doses were tested (5 mg and 1.25 mg) in multiple sclerosis patients and no clear dose-response effect was observed, questioning if the minimum effective dose was achieved. Exposure- response

relationship modelling in patients with RRMS showed that 0.5 mg dose was as beneficial as 1.25 mg dose. Considering that no additional beneficial effects were observed over 1.25 mg dose, 0.5 mg ($1/10^{th}$ of 5 mg) was selected as an additional dose to be evaluated for the phase III studies.

With respect to the phase III studies, 2 pivotal studies were conducted: a single 2-year placebo controlled study (D2301) and a 1-year active-controlled study with no placebo arm (D2302). The minimum duration of 2 years, as recommended in the above-referred guideline was therefore fulfilled in study D2301. Addditionally, the primary (ARR) and secondary endpoints (time to 3 month-confirmed disability progression) were considered in line the recommendations from the above-referred guideline.

In study 2301, the population was representative of the MS population with a large majority of women (70%) and Caucasian subjects (95.5%) included in the trial. The mean duration of the disease was 8.2 years. The mean of relapses in the last year was 1.5 and in the last two years 2.1, and the mean EDSS score was 2.40. Slightly more than half of all patients were treatment naïve (approximatively 57-60% across the groups). Among those who had been previously treated, interferon beta had been most often commonly used MS drugs (70.6%).

At 24 months treatment, the aggregate ARR was statistically significantly lower with fingolimod at all doses tested (0.5 mg : 0.18, 95% CI: 0.15, 0.22; 1.25 mg: 0.16, 95% CI: 0.13, 0.19) versus placebo (0.40, 95% CI: 0.34, 0.47), representing relative reductions of 54% and 60%, respectively, in the annualized relapse rate (ARR ratio: 0.40 and 0.46 for 1.25 mg and 0.5 mg, respectively). However, there was no statistically significant difference between the two doses in the ARR (p=0.226).

At 24 months, the time to 3 month- confirmed disability progression, was statistically longer with all doses tested than with placebo. Fingolimod reduced the risk of disability progression, confirmed at 3 months, over the 24-month study period (0.5 mg: HR= 0.68, 95% CI: 0.50, 0.93, p=0.017; 1.25 mg: 0.5 mg: HR= 0.70, 95% CI: 0.52, 0.96, p=0.024) as compared to placebo. However, there was no difference between the two doses using the ITT population (p=0.743).

The proportion of patients free of progression was greater in the two fingolimod groups : 83.4% in the for 1.25 mg, 82.3% for 0.5 mg versus 75.9% for the placebo group. All additional secondary efficacy parameters concerning relapses and MRI were supportive of the results on the primary endpoint.

In study D2302, the population was also was representative of the MS population with a large majority of women (67%) and Caucasian subjects (94.1%) included in the trial. The mean duration of the disease was 7.4 years. The mean of relapses in the last year was 1.5 and in the last two years 2.2 and the mean EDSS score was 2.21. The percentages of treatment naïve patients and previously treated patients were respectively 43.3% and 56.7%. Patients who were previously treated with at least one MS therapy could be considered in failure according to the study protocol. Approximately 47.6 % of patients randomized to receive interferon beta-1a i.m. were already been receiving a form of interferon beta within the 3 months prior to the start of study drug treatment and 27% were already been receiving interferon beta-1a.

At 12 months, the aggregate ARR was statistically significantly lower with fingolimod at all doses tested (0.5 mg : 0.16, 95% CI: , 0.122, 0.212, p<0.001 ; 1.25 mg: 0.20, 95% CI: 0.157,0.264, p<0.001) versus interferon beta-1a (0.33, 95% CI: 0.262, 0.417), representing relative reductions of 52% and 38%, respectively, in the annualized relapse rate (ARR ratio: 0.62 and 0.48 for 1.25 mg and 0.5 mg, respectively).

At 12 months, both fingolimod treatment groups had a lower mean number of new or newly enlarged T2 lesions compared to the interferon beta-1a i.m. group, which reached statistical significance for both the fingolimod 1.25 mg group (p<0.001) and the fingolimod 0.5 mg group (p=0.004). However,

there was no difference between the two fingolimod treatment groups and the interferon beta-1a i.m. group in the time to 3-month confirmed disability progression as based on Kaplan-Meier estimates (0.5 mg: difference=2.03, 95% CI: -1.42, 5.47, p=0.247, 1.25 mg: difference=1.30, 95% CI: -2.26, 4.86, p=0.498) .

The proportion of patients who were relapse-free at month 12 was higher in the fingolimod treatment groups (79.8% for fingolimod 1.25 mg and 82.6% for fingolimod 0.5 mg treatment groups) compared to the interferon beta-1a i.m. group (69.3%) and this difference was statistically significant (p<0.001 All additional secondary efficacy parameters concerning relapses and MRI were supportive of the results on the primary endpoint.

Having considered these data, the CHMP was of the opinion that study D2301 had an adequate duration and methodology used. Efficacy results were considered consistent and robust for both tested doses as compared to placebo on both primary and key secondary endpoints as well as a number of other secondary endpoints related to relapses and MRI. The effect on disease progression as measured by EDSS was reassuring even if modest considering the relatively low active population of RRMS patients included in the trial. In addition, efficacy was also confirmed in the more severe group at baseline (2-3 relapses in the last two years). In study D2302, there was no difference between the two fingolimod treatment groups and the interferon beta-1a i.m. group in the time to 3-month confirmed disability progression, however this might be expected taking into account the shorter duration of the study as compared to study D2301 (one year) and again the low active population of RRMS patients included in the trial. Nonetheless, both fingolimod groups had a lower mean number of new or newly enlarged T2 lesions compared to the interferon beta-1a i.m. group, the other key secondary endpoint. Overall, efficacy results from study D2302 were also considered consistent and robust for both tested doses as compared to placebo on primary endpoint as well as a number of other secondary endpoints related to relapses and MRI.

Regarding efficacy after withdrawal and possible rebound effect, there was no tendency for increase in ARR in the fingolimod groups at 90 days after study drug discontinuation, except for those patients who switched from 5 mg dose to 1.25 mg dose which can be expected. After study drug discontinuation in the placebo group, there was a decrease in the disease activity as measured by number of patients free of Gadolinium enhancing lesions (58% at baseline, 52% between day 15 and day 90 after discontinuation and 76.2% beyond 3 months). In the fingolimod group, the decrease in the disease activity was smaller. (56% of patients free of lesions at baseline, 67% between day 15 and day 90 after discontinuation and 61% beyond 3 months).The effect of fingolimod as based on MRI data was observed only during the treatment (85% of patients free of lesions at the last MRI on treatment and 61% beyond 3 months after discontinuation). However, there was no obvious evidence of rebound effect based on MRI data.

Considering the heterogeneous safety profile of fingolimod (see 3.6 clinical safety), the benefit risk of fingolimod was considered negative by the CHMP in the indication initially applied for: *"Disease-modifying therapy in adults for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay the progression of disability"*. Subsequently, post-hoc analyses in highly active subgroups of relapsing-remitting multiple sclerosis were performed by the applicant to evaluate the benefit-risk in a restricted population. Results of these subgroups analyses were consistent with those obtained in the overall population. In light of these results and the subgroups of patients defined and proposed by the applicant , the CHMP agreed to convene a SAG meeting to discuss the place of fingolimod in the multiple sclerosis therapy.

Additional expert consultation

At the SAG Neurology meeting held on 12 January 2011, the applicant proposed indication under discussion was as follows:

"Gilenya is indicated as disease-modifying therapy to reduce the frequency of relapses and to delay the progression of disability in adult patients with relapsing-remitting multiple sclerosis (MS):

- *who have an inadequate response to an alternative MS therapy (at least 1 relapse while on an alternative therapy of at least 6 months duration)*

or

- *who stop an alternative MS therapy due to drug hypersensitivity or unacceptable adverse reactions such as persistent flu-like symptoms, laboratory abnormalities or injection site and infusion reactions or in those who decide to limit cumulative exposure to an alternative MS therapy*

or

- *who have active relapsing-remitting MS (at least 1 relapse in the prior year) and who have either gadolinium-enhancing lesion(s) or have accumulated MS-related neurological impairment (i.e. Expanded Disability Status Score (EDSS) ≥2.5)."*

The applicant clarified during the meeting that the proposed definition of inadequate response ("at least 1 relapse while on an alternative therapy of at least 6 months duration") meant "at least 1 relapse after alternative therapy of at least 6 months duration".

The main SAG conclusions were as follows:

- In general, fingolimod is an efficacious drug and potentially a valuable addition to the existing disease-modifying treatments in MS. However, there was concern about the safety profile of fingolimod such that fingolimod cannot be recommended for first line treatment.

- The efficacy of fingolimod in the treatment of multiple sclerosis could be regarded as broadly similar to that of natalizumab. However, the efficacy and safety of fingolimod in relation to drugs other than Avonex used for treatment of MS could only be assessed by head-to head comparisons.

- The group recognised that the oral route of administration of fingolimod is advantageous.

- The group considered fingolimod as a potential therapeutic option for patients with clinically aggressive disease (high disease activity) causing disabling relapses or accumulating disability at a stage before they have serious impairment. The group did not a priori see any reason to apply different indications for second line therapy drugs in MS.

The difference in the nature and severity of the risk profile of fingolimod and natalizumab can not be used to differentiate these two drugs. There was no specific safety evaluation of fingolimod in a high disease activity group.

- In general, the group recommended that the indication should be in line with that for natalizumab.

- With regard to inadequate response, 6 months treatment duration was considered too short and at least 1 year would be more appropriate. The group was concerned that the criterion of only 1 relapse may be too sensitive because of early relapses after initiating first-line treatment due to a delayed onset of action of the first-line treatment.

- Concerning the proposed indication for "high disease activity", a significant increase in lesion load has not been well defined, and the MRI criteria may need to be revisited.

- Intolerance to alternative MS therapy should include also Copaxone being tried. There are subjective issues involved in the reporting of intolerance including the attractiveness of an oral treatment. It is not consistent with the approved natalizumab indication to include intolerance to alternate MS therapy as a separate indication. No evidence has been presented for the second part of the indication, i.e.

intolerance to alternative MS therapy. The group can not comment further on this issue in the absence of data.

Furthermore, the SAG recommended to convene an expert group to draft criteria for defining subpopulations eligible for second line treatment of multiple sclerosis.

Following the SAG recommendations and having considered consistent treatment effects in highly active subgroups was demonstrated (see 3.5.2.3), the CHMP recommended to align the indication to the already authorised indication in the EU as second line treatment of multiple sclerosis, as follows:

"GILENYA is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

Patients with high disease activity despite treatment with a beta-interferon.
These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion.
A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year,
or
patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI."

The applicant accepted the wording of the indication as recommended by the CHMP, in line with already authorised indication in the EU as second line treatment of multiple sclerosis. In addition, the CHMP recommended that the treatment should be initiated and supervised by a physician experienced in multiple sclerosis.

Further long term data will be generated from ongoing studies and will be submitted by the applicant to monitor the benefit-risk balance of the product.

2.5.4. Conclusions on the clinical efficacy

The CHMP concluded that the efficacy in reducing the number of relapses was demonstrated in patients with relapsing-remitting multiple sclerosis with high disease activity in the proposed dosing regimen for Gilenya (fingolimod).

2.6. Clinical safety

2.6.1. Patient exposure

Studies submitted to support the safety of fingolimod included the following in patients with relapsing-remitting MS: Two pivotal Phase III studies applying the doses 0.5 mg and 1.25 mg daily (D2301 (placebo-controlled) and D2302 (active-controlled)) for 24 months and 12 months, respectively, and one pivotal 6-month, placebo-controlled Phase II study (study D2201) applying the doses 5.0 mg and 1.25 mg daily, supported by interim safety data from ongoing open-label extensions to two of the studies (D2302E1 and D2201E1) and a total of 29 Phase I clinical pharmacology studies.

A number of additional clinical studies in MS patients are ongoing for which reports of deaths and SAEs are included and AEs leading to study drug discontinuation are also summarized. These are 3 double-blind, placebo-controlled studies (D2309; D1201; D2306), the long-term extensions to two of these

(D2309E1; D1201E1), and 3 ongoing long-term extensions of studies for which the core studies are complete (D2301E1; D2302E1; D2201E1).

Pooling of Phase II and III safety studies

The data from three completed, double-blind, controlled MS studies and interim data from two long-term extension studies in MS patients were pooled into 5 datasets using appropriate cut-offs to accommodate differences between studies in duration of treatment, doses, and comparators and are shown in the table below. Pivotal studies included only patients between 18 - 60 years.

Summary of pooled treatment groups

Table 30

Analysis datasets, number of patients	Studies (cut-off)	Treatment regimens	Pooled treatment groups
Group A (12-month treatment) N = 2552	D2301 (up to Month 12 visit)	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 1.25 mg FTY720 0.5 mg Placebo Interferon beta-1a i.m.
	D2302	FTY720 1.25 mg FTY720 0.5 mg Interferon beta-1a i.m.	
Group B (24-month treatment) N = 1272	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 1.25 mg FTY720 0.5 mg Placebo
Group C (6-month treatment) N = 2833	D2301 (up to Month 6 visit)	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg FTY720 1.25 mg FTY720 0.5 mg Placebo Interferon beta-1a i.m.
	D2302 (up to Month 6 visit)	FTY720 1.25 mg FTY720 0.5 mg Interferon beta-1a i.m.	
	D2201	FTY720 5 mg FTY720 1.25 mg Placebo	
Group D (all patients from randomized, double-blind, controlled studies regardless of differences in treatment duration or comparators) N = 2833	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg FTY720 1.25 mg FTY720 0.5 mg Placebo Interferon beta-1a i.m.
	D2302	FTY720 1.25 mg FTY720 0.5 mg Interferon beta-1a i.m.	
	D2201	FTY720 5 mg FTY720 1.25 mg Placebo	
Group E (all FTY720-treated population) N = 2615	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg–1.25 mg* FTY720 1.25 mg FTY720 0.5 mg
	D2302, D2302E1 (up to 01-Jun-2009 or Month 24, whichever came first)	FTY720 1.25 mg FTY720 0.5 mg Interferon–FTY720 0.5 mg Interferon–FTY720 1.25 mg	
	D2201, D2201E1 (up to the Month 60 visit)	FTY720 5 mg–1.25 mg* FTY720 1.25 mg Placebo–FTY720 1.25 mg Placebo–FTY720 5 mg–1.25 mg	
Group E follow-up population N = 538	D2301	FTY720 1.25 mg FTY720 0.5 mg Placebo	FTY720 5 mg–1.25 mg* FTY720 1.25 mg FTY720 0.5 mg
	D2302	FTY720 1.25 mg FTY720 0.5 mg Interferon–FTY720 0.5 mg Interferon–FTY720 1.25 mg	
	D2201E1 (up to the Month 60 visit)	FTY720 5 mg–1.25 mg* FTY720 1.25 mg	

		Placebo–FTY720 1.25 mg Placebo–FTY720 5 mg–1.25 mg	

Note: FTY720 5 mg–1.25 mg indicates the treatment regimen of FTY720 5 mg switched to FTY720 1.25 mg during D2201E1. Interferon–FTY720 1.25 mg and 0,5 mg Interferon–FTY720 0.5 mg indicate the treatment regimen of interferon during D2302 core study switched to FTY720 1.25 mg or 0.5 mg, respectively, in D2302E1. Likewise, Placebo–FTY720 1.25 mg indicates the treatment regimen of placebo during D2201 switched to FTY720 1.25 mg in D2201E1. Placebo–FTY720 5 mg–1.25 mg indicates the treatment regimen of placebo in D2201 initially switched to FTY720 5 mg in D2201E1 and then switched to FTY720 1.25 mg during D2201E1.
*The Group E FTY720 5 mg–1.25 mg pooled treatment group includes all patients who took either FTY720 5 mg only or FTY720 5 mg and were switched to FTY720 1.25 mg.

A summary of the overall number of patients exposed and the duration of exposure for all fingolimod treated patients presented in Table 31.

Table 31 Duration of exposure to study drug after randomization in Group E (all FTY720-treated patients safety population)

Duration of Exposure (days)	FTY720 5 mg-1.25 mg (N=137)	FTY720 1.25 mg (N=1302)	FTY720 0.5 mg (N=1176)	Total (N=2615)
≥ 1	137 (100)	1302 (100)	1176 (100)	2615 (100)
≥ 7	135 (98.5)	1285 (98.7)	1173 (99.7)	2593 (99.2)
≥ 14	134 (97.8)	1279 (98.2)	1168 (99.3)	2581 (98.7)
≥ 30	131 (95.6)	1259 (96.7)	1163 (98.9)	2553 (97.6)
≥ 60	128 (93.4)	1222 (93.9)	1141 (97.0)	2491 (95.3)
≥ 90	126 (92.0)	1170 (89.9)	1100 (93.5)	2396 (91.6)
≥ 180	118 (86.1)	1087 (83.5)	1025 (87.2)	2230 (85.3)
≥ 360	108 (78.8)	884 (67.9)	851 (72.4)	1843 (70.5)
≥ 540	101 (73.7)	724 (55.6)	697 (59.3)	1522 (58.2)
≥ 720	96 (70.1)	561 (43.1)	567 (48.2)	1224 (46.8)
≥ 900*	91 (66.4)	204 (15.7)	141 (12.0)	436 (16.7)
≥ 1080	85 (62.0)	114 (8.8)	29 (2.5)	228 (8.7)
≥ 1260	77 (56.2)	79 (6.1)	1 (0.1)	157 (6.0)
≥ 1440	70 (51.1)	79 (6.1)	0 (0.0)	149 (5.7)
≥ 1620	66 (48.2)	76 (5.8)	0 (0.0)	142 (5.4)
≥ 1800	62 (45.3)	73 (5.6)	0 (0.0)	135 (5.2)
≥ 1980	45 (32.8)	47 (3.6)	0 (0.0)	92 (3.5)
≥ 2160	5 (3.6)	9 (0.7)	0 (0.0)	14 (0.5)
n	137	1302	1176	2615
Mean	1296.7	622.3	583.3	640.1
SD	780.45	459.01	295.43	447.20
Median	1542.0	675.0	715.5	711.0
Minimum	1	1	2	1
Maximum	2240	2246	1266	2246
Patient years	486.4	2218.3	1878.0	4582.6

Note: This table is an update from the [FTY720D-ISS Table 110].

The duration of exposure is the total actual days patients took the study medication until cut-off date. * Patient PID D2201-0061-00012 in the FTY720 5-1.25 mg group has updated dosing data since the full submission which has introduced a period where he did not receive any study medication; hence, this has

reduced his duration of FTY720 exposure from 993 days as reported in the ISS to 957 days in this ISS Update. - Patients are counted by each level of the duration of exposure cumulatively. - Patient years is defined as the sum of the number of days on study drug for all patients in each dose group divided by 365.25.

- FTY720 5 mg-1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg.

Across the 3 completed controlled clinical studies in MS, a total of 2833 patients were treated, 1891 with fingolimod, 511 with placebo, and 431 with IFN β-1a. Considering the extension phases, a total of 2615 patients received fingolimod at doses of 5 mg, 1.25 mg, or 0.5 mg, accumulating more than 4582.6 patient-years of exposure to fingolimod.

In all clinical trials in MS as of 30 November 2010, the applicant estimated that approximately 4,600 patients had received at least one dose of fingolimod, approximately 10,000 patient-years.

Clinical trials from the program studying FTY720 in renal transplantation provide multiple-dose safety data for FTY720 from approximately 1600 patients, of whom about 1500 received FTY720 (2.5 or 5.0 mg/day) in combination with Neoral and corticosteroids.

2.6.2. Adverse events

The AE profile for Group B, a 24-month treatment in 1272 MS patients, is considered representative of the FTY720 safety profile and included 2 fingolimod doses and placebo groups (see Table 32).

Table 32 Number (%) of patients with AEs by preferred term (>=5% patients in any treatment group) in Group B (24-month treatment)

Preferred term	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Any preferred term	404 (94.2)	401 (94.4)	387 (92.6)
Headache	114 (26.6)	107 (25.2)	96 (23.0)
Nasopharyngitis	112 (26.1)	115 (27.1)	115 (27.5)
Upper respiratory tract infection	62 (14.5)	73 (17.2)	73 (17.5)
Alanine aminotransferase increased	50 (11.7)	43 (10.1)	16 (3.8)
Fatigue	47 (11.0)	48 (11.3)	45 (10.8)
Back pain	45 (10.5)	50 (11.8)	29 (6.9)
Diarrhoea	40 (9.3)	50 (11.8)	31 (7.4)
Influenza	40 (9.3)	55 (12.9)	41 (9.8)
Bronchitis	39 (9.1)	34 (8.0)	15 (3.6)
Nausea	38 (8.9)	38 (8.9)	36 (8.6)
Cough	37 (8.6)	43 (10.1)	34 (8.1)
Gamma-glutamyltransferase increased	32 (7.5)	22 (5.2)	4 (1.0)
Dizziness	30 (7.0)	31 (7.3)	23 (5.5)
Arthralgia	27 (6.3)	30 (7.1)	33 (7.9)
Hypertension	27 (6.3)	26 (6.1)	16 (3.8)
Sinusitis	27 (6.3)	28 (6.6)	19 (4.5)
Depression	26 (6.1)	33 (7.8)	28 (6.7)
Hypercholesterolaemia	26 (6.1)	24 (5.6)	26 (6.2)
Pharyngitis	25 (5.8)	27 (6.4)	24 (5.7)
Pain in extremity	24 (5.6)	28 (6.6)	28 (6.7)
Dyspnoea	23 (5.4)	30 (7.1)	19 (4.5)
Hepatic enzyme increased	22 (5.1)	14 (3.3)	1 (0.2)
Urinary tract infection	21 (4.9)	34 (8.0)	47 (11.2)
Oropharyngeal pain	17 (4.0)	29 (6.8)	29 (6.9)
Paraesthesia	17 (4.0)	23 (5.4)	18 (4.3)
Insomnia	16 (3.7)	21 (4.9)	25 (6.0)

Preferred term	FTY720 1.25mg N=429 n (%)	FTY720 0.5mg N=425 n (%)	Placebo N=418 n (%)
Weight increased	14 (3.3)	14 (3.3)	22 (5.3)

Preferred terms are sorted in descending frequency for the FTY720 1.25 mg group.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
A patient with multiple occurrences of an AE under one treatment group is counted only once in the AE preferred term for that treatment group.
This table contains AEs whose missing start dates were imputed as part of the analyses performed for the D2301 CSR, contrary to the convention used for the other pooled analyses in this submission (Source: [D2301 PT-Table 14.3.1-1.1]

AEs which occurred at a clinically relevantly higher incidence in both FTY720 groups compared with placebo included the following preferred terms: headache, elevations in liver enzymes, back pain, diarrhea, bronchitis, dizziness, sinusitis, dyspnea, and hypertension. For the two of the most common AEs (nasopharyngitis, and upper respiratory tract infection) there were no noteworthy differences among dose groups.

In the pooled analysis of clinical pharmacology studies, FTY720 treatment had a higher number of subjects than placebo with (placebo vs. FTY720, respectively): lymphopenia (0% vs. 1.7%), bradycardia (0% vs. 4.2%), palpitations (0.5% vs. 1.9%), abdominal pain (0.3% vs. 1.9%), diarrhea (0.7% vs. 3.3%), dry mouth (0.5% vs. 1.1%), nausea (1.3% vs. 5.1%), vomiting (0.7% vs. 2.3%), chest discomfort (1.0% vs. 4.7%), fatigue (0.7% vs. 3.0%), peripheral edema (0% vs. 1.4%), pyrexia (0% vs. 1.4%), nasopharyngitis (1.1% vs. 3.8%), decreased lymphocyte count (0% vs. 2.5%), back pain (0.8% vs. 1.9%), myalgia (0.2% vs. 1.3%), dizziness (3.1% vs. 7.0%), headache (9.2% vs. 15.4%), cough (0.3% vs. 3.4%), dyspnea (0.5% vs. 1.8%), epistaxis (0.5% vs. 1.1%), nasal congestion (0.2% vs. 1.7%), oropharnygeal pain (1.3% vs. 4.0%).

2.6.3. Serious adverse event/deaths/other significant events

Deaths

A total of 84 deaths were reported in the clinical development program including 12 patients in the MS and ongoing studies (cut off date: 30 September 2009) and 72 in the renal transplantation completed studies. Deaths in MS studies are summarised in Table 33.

Table 33 Deaths in all MS studies, completed and ongoing as of 30 September 2009

Age (years)	Gender	Treatment group	Timing relative to last dose	Cause Preferred term (completed studies) or investigator term (ongoing studies)
55	F	FTY720 5 mg	Died 3 years after last dose Cancer diagnosed 5 months after stopping study drug.	Ovarian adenocarcinoma
53	M	FTY720 1.25 mg	Died Day 539 of the study (last dose on Day 539)	Depression, suicide
29	F	FTY720 1.25 mg	Died Day 320 of study (last dose on Day 317)	Herpes zoster disseminated
23	M	FTY720 1.25 mg	Died Day 407 of study (last dose on Day 339)	Herpes simplex encephalitis

Age (years)	Gender	Treatment group	Timing relative to last dose	Cause Preferred term (completed studies) or investigator term (ongoing studies)
42	M	FTY720 1.25 mg	Died 187 days after last dose	Aspiration pneumonia, acute disseminated encephalomyelitis, lower respiratory tract infection
53	F	FTY720 1.25 mg	Died 305 days after last dose	Breast cancer metastatic
35	F	FTY720 1.25 mg	Died on extension Day 638	Road traffic accident
52	M	Placebo	Died on Day 657 of the study (6 days after last dose)	Pulmonary embolism
37	F	Placebo	Died on Day 365 of the study (58 days after last dose)	Road traffic accident
46	M	FTY720 1.25 mg	Died 103 days after commencing study medication	Rapidly deteriorating MS
35	F	–	Died in the screening period, (prior to receiving any study drug)	Sudden death at home
54	M	–	Died in the screening period, (prior to receiving any study drug)	Suicide

In completed studies, there were eight deaths in MS patients exposed to FTY720 – seven in patients who had been randomized to FTY720 1.25mg and one on FTY720 5 mg. No deaths have been reported in patients receiving the FTY720 0.5 mg dose.

Three of the deaths occurred while the patients were on therapy or had recently discontinued (Depression/suicide, herpes zoster disseminated, herpes simplex encephalitis). One additional patient of interest presented with symptoms consistent with a chest infection approximately 11 months after commencing FTY720 1.25 mg. Study medication was permanently discontinued. Three days later, the patient developed neurological symptoms, which led to a diagnosis of acute disseminated encephalomyelitis by the investigator. However, CSF analysis was negative for JC virus. The patient's neurological condition continued to worsen and approximately 6 months after discontinuing study drug, the patient developed an aspiration pneumonia due to progressive neurological decline and subsequently died.

In ongoing studies (cut off date: 30 September 2009), there were 5 deaths reported: 1 patient in the FTY720 5 mg group, 2 patients in the FTY720 1.25 mg group, and 2 patients who died prior to receiving the first dose of study medication. The 3 patients from the FTY720 treatment groups died of ovarian cancer (FTY720 5 mg group), rapidly deteriorating primary progressive MS (FTY720 1.25 mg group) and road traffic accident (FTY720 1.25 mg group).

From 1 October 2009 through 29 January 2010**,** 2 additional deaths were reported concerning 1 patient in the FTY720 0.5 mg dose group and another patient whose study drug is still and blinded (see Table 34).

Table 34

Age (years)	Gender	Treatment group	Timing relative to last dose	Cause Preferred term (completed studies) or investigator term (ongoing studies)
42	M	FTY720 0.5 mg	Died 1 year after last dose Possible malignancy diagnosed 6 months after stopping study drug	Cause not determined-autopsy revealed diffuse large B-cell lymphoma in the brain (Epstein-Barr virus-associated), lymphoproliferative disorder in the lungs, kidneys, and thyroid gland, and lymphoma (later on qualified as lymphangioma) in the jejunum Also developed aspiration pneumonia, herpes zoster
55	F	Blinded	Died on Day 269 of the study (last dose on Day 269)	Aortic dissection (investigator did not suspect a relationship between the event and study medication)

Serious adverse events (SAE)

A total of 1962 patients (of whom 190 remain blinded in the MS studies) experienced SAE in the clinical development program including 12 patients in all completed studies, 615 patients in the MS and ongoing studies (cut off date: 30 September 2009) and 1335 in the renal transplantation completed studies.

The SAE profile for all fingolimod treated patients is presented in Table 35. Additionally, The SAE profile for Group B, a 24-month treatment in 1272 MS patients, is considered representative of the FTY720 SAE profile and is presented in Table 36.

Table 35 Number (%) of patients with SAEs (at least 2 patients in any treatment group) by primary SOC and preferred term in Group E (all FTY720-treated safety population)

Primary system organ class Preferred term	FTY720 5 mg-1.25 mg (N=137) n (%)	FTY720 1.25 mg (N=1302) n (%)	FTY720 0.5 mg (N=1176) n (%)
Any primary system organ class	**38 (27.7)**	**170 (13.1)**	**111 (9.4)**
Blood and lymphatic system disorders	**1 (0.7)**	**7 (0.5)**	**3 (0.3)**
Lymphopenia	0 (0.0)	5 (0.4)	0 (0.0)
Cardiac disorders	**4 (2.9)**	**34 (2.6)**	**11 (0.9)**
Bradycardia	3 (2.2)	16 (1.2)	6 (0.5)
Atrioventricular block second degree	0 (0.0)	7 (0.5)	1 (0.1)
Atrioventricular block first degree	0 (0.0)	4 (0.3)	1 (0.1)
Palpitations	1 (0.7)	4 (0.3)	0 (0.0)
Angina pectoris	0 (0.0)	2 (0.2)	1 (0.1)
Sinus bradycardia	0 (0.0)	2 (0.2)	1 (0.1)
Supraventricular extrasystoles	0 (0.0)	2 (0.2)	0 (0.0)
Ear and labyrinth disorders	**0 (0.0)**	**3 (0.2)**	**1 (0.1)**
Vertigo	0 (0.0)	3 (0.2)	0 (0.0)
Eye disorders	**1 (0.7)**	**12 (0.9)**	**3 (0.3)**
Macular oedema	1 (0.7)	9 (0.7)	2 (0.2)
Gastrointestinal disorders	**3 (2.2)**	**13 (1.0)**	**5 (0.4)**
Constipation	0 (0.0)	2 (0.2)	0 (0.0)
General disorders and administration site conditions	**2 (1.5)**	**8 (0.6)**	**6 (0.5)**
Chest pain	2 (1.5)	1 (0.1)	2 (0.2)
Non-cardiac chest pain	0 (0.0)	1 (0.1)	2 (0.2)
Hepatobiliary disorders	**0 (0.0)**	**7 (0.5)**	**5 (0.4)**
Biliary colic	0 (0.0)	2 (0.2)	2 (0.2)
Cholelithiasis	0 (0.0)	3 (0.2)	2 (0.2)
Infections and infestations	**5 (3.6)**	**33 (2.5)**	**18 (1.5)**
Appendicitis	1 (0.7)	3 (0.2)	1 (0.1)
Herpes zoster	1 (0.7)	3 (0.2)	0 (0.0)
Herpes zoster ophthalmic	0 (0.0)	2 (0.2)	1 (0.1)
Pneumonia	0 (0.0)	2 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	**6 (4.4)**	**4 (0.3)**	**11 (0.9)**
Investigations	**0 (0.0)**	**10 (0.8)**	**6 (0.5)**
Alanine aminotransferase increased	0 (0.0)	2 (0.2)	1 (0.1)
Hepatic enzyme increased	0 (0.0)	2 (0.2)	1 (0.1)
Liver function test abnormal	0 (0.0)	2 (0.2)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**9 (0.7)**	**7 (0.6)**
Back pain	0 (0.0)	1 (0.1)	2 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**8 (5.8)**	**17 (1.3)**	**22 (1.9)**

Basal cell carcinoma	1 (0.7)	5 (0.4)	7 (0.6)
Malignant melanoma	0 (0.0)	4 (0.3)	2 (0.2)
Breast cancer	1 (0.7)	3 (0.2)	2 (0.2)
Uterine leiomyoma	0 (0.0)	0 (0.0)	5 (0.4)
Nervous system disorders	**6 (4.4)**	**27 (2.1)**	**15 (1.3)**
Multiple sclerosis relapse	2 (1.5)	4 (0.3)	4 (0.3)
Cerebral ischaemia	0 (0.0)	2 (0.2)	0 (0.0)
Epilepsy	1 (0.7)	2 (0.2)	1 (0.1)
Grand mal convulsion	0 (0.0)	2 (0.2)	0 (0.0)
Headache	0 (0.0)	2 (0.2)	0 (0.0)
Paraparesis	0 (0.0)	2 (0.2)	0 (0.0)
Presyncope	0 (0.0)	2 (0.2)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	**1 (0.7)**	**2 (0.2)**	**0 (0.0)**
Abortion spontaneous	0 (0.0)	2 (0.2)	0 (0.0)
Psychiatric disorders	**1 (0.7)**	**9 (0.7)**	**2 (0.2)**
Depression	0 (0.0)	5 (0.4)	0 (0.0)
Anxiety	0 (0.0)	2 (0.2)	1 (0.1)
Renal and urinary disorders	**0 (0.0)**	**2 (0.2)**	**2 (0.2)**
Nephrolithiasis	0 (0.0)	1 (0.1)	2 (0.2)
Reproductive system and breast disorders	**1 (0.7)**	**3 (0.2)**	**5 (0.4)**
Cervical dysplasia	0 (0.0)	2 (0.2)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**4 (2.9)**	**10 (0.8)**	**5 (0.4)**
Dyspnoea	1 (0.7)	4 (0.3)	0 (0.0)
Pleurisy	0 (0.0)	2 (0.2)	0 (0.0)

Note: This table is an update from the [FTY720D-ISS-Table 2-36].

Primary SOCs are presented alphabetically; preferred terms are sorted within primary SOC in descending frequency for the FTY720 1.25 mg group. A patient with multiple SAEs within a primary SOC is counted only once in the total row. A patient with multiple occurrences of an AE under 1 dose group is counted only once in the AE preferred term for that dose group.

The FTY720 5 mg-1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg switched to 1.25 mg. Source: ISS Update PT-Table 4.5-12

Table 36 Number (%) of patients with SAEs (at least 2 patients in any treatment group) by primary SOC and preferred term in Group B (24-month treatment)

Primary system organ class Preferred term	FTY720 1.25 mg N=429 n (%)	FTY720 0.5 mg N=425 n (%)	Placebo N=418 n (%)
Any serious adverse event	**51 (11.9)**	**43 (10.1)**	**56 (13.4)**
Infections and infestations	11 (2.6)	7 (1.6)	8 (1.9)
Urinary tract infection	0	2 (0.5)	0
Nervous system disorders	11 (2.6)	10 (2.4)	4 (1.0)
Multiple sclerosis relapse	3 (0.7)	2 (0.5)	1 (0.2)
Epilepsy	2 (0.5)	0	0
Headache	2 (0.5)	0	0
Multiple sclerosis	0	2 (0.5)	0
Cardiac disorders	7 (1.6)	7 (1.6)	4 (1.0)
Bradycardia	3 (0.7)	4 (0.9)	1 (0.2)
Myocardial infarction	0	0	2 (0.5)
Eye disorders	6 (1.4)	1 (0.2)	1 (0.2)
Macular oedema	3 (0.7)	0	0
Investigations	6 (1.4)	3 (0.7)	1 (0.2)
Liver function test abnormal	2 (0.5)	0	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (1.2)	5 (1.2)	11 (2.6)
Basal cell carcinoma	1 (0.2)	4 (0.9)	2 (0.5)
Breast cancer	1 (0.2)	0	3 (0.7)
Gastrointestinal disorders	4 (0.9)	4 (0.9)	4 (1.0)
Musculoskeletal and connective tissue disorders	3 (0.7)	2 (0.5)	4 (1.0)
Back pain	0	2 (0.5)	1 (0.2)
Intervertebral disc protrusion	0	0	2 (0.5)
Respiratory, thoracic and mediastinal disorders	3 (0.7)	2 (0.5)	3 (0.7)
Blood and lymphatic system disorders	2 (0.5)	1 (0.2)	0
Lymphopenia	2 (0.5)	0	0
General disorders and administration site conditions	2 (0.5)	5 (1.2)	2 (0.5)
Chest pain	0	2 (0.5)	0
Non-cardiac chest pain	0	2 (0.5)	2 (0.5)
Psychiatric disorders	2 (0.5)	1 (0.2)	3 (0.7)
Depression	2 (0.5)	0	1 (0.2)
Reproductive system and breast disorders	2 (0.5)	1 (0.2)	2 (0.5)
Hepatobiliary disorders	1 (0.2)	2 (0.5)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)	3 (0.7)	6 (1.4)
Renal and urinary disorders	1 (0.2)	1 (0.2)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	0	0	4 (1.0)
Abortion	0	0	3 (0.7)
Vascular disorders	0	1 (0.2)	2 (0.5)

The overall proportion of patients with SAEs was higher in the FTY720 5 mg-1.25 mg group and 1.25 mg group compared to the 0.5 mg group. Of note, one subject in the FTY720 1.25 mg group experienced a complete AV block that was accompanied by loss of consciousness about 3 hours after the first dose of study medication on extension Day 1. The patient recovered without any intervention.

In the pooled datasets of Groups A, B, C, D and E, consistent with the mechanism of action, more SAE were reported in the FTY720 groups as compared to placebo mainly for the following events: lymphopenia, bradycardia and AV block (1st and 2nd degree), liver function abnormalities, macular edema and dyspnoea.

In clinical pharmacology studies, one 2nd degree AV block, one dyspnoea and one hepatic enzyme increase were reported as SAEs.

In an ongoing study CFTY720D2306, an atypical MRI lesion was reported as SAE according to the Investigator's Brochure. The patient remains clinically stable compared to baseline.

Infections

In group A, the rate of infections overall was not increased in patients treated with fingolimod 1.25 mg or 0.5 mg for up to 12 months as compared to the control groups, with a relative risk of infection compared to placebo of 0.94 (95% CI:0.85-1.04) for fingolimod 1.25 mg and 0.93 (095% CI:0.84-1.03) for fingolimod 0.5 mg . In group B, similar findings were seen up to 24 months compared to placebo. However, a dose-dependent increased risk of lower respiratory tract infections (mainly bronchitis, few cases of pneumonia) was noted with fingolimod: 6.8%, 5.7% and 4.5% in Group A and 11.4%, 9.6% and 6.0% in Group B for fingolimod 1.25 mg, 0.5 mg and placebo respectively.

In group B, a risk of infection with lower circulating lymphocytes count has been observed with progressive higher infection rate respectively of 63.7% when lymphocytes count is > 0.7x109/L to 82.6% when lymphocytes count is below 0.2 x109/L. The proportion of patients with infections related AEs was greater in females than in males in all treatment groups: 71.9 versus 61.2% for fingolimod 1.25 mg; 76.0 versus 61.2 % for fingolimod 0.5 mg and 74.2 versus 66.7 % for the placebo.

Analyses of the relationship of nadir blood lymphocyte counts and occurrence of infections in Group A showed that the proportion of patients with infections in the group with the lowest lymphocyte counts (< 0.2×109/L) was increased (61.6%) compared to those with higher cell counts on fingolimod (45.0-56.6%).

Additionally, a total of 3 cases of disseminated herpes infection were reported in patients treated with fingolimod 1.25 mg. In these cases, 2 deaths were reported. The third patient had disseminated herpes zoster with pulmonary involvement and made a complete recovery after treatment with aciclovir therapy.

Malignancies

Incidence of malignant neoplasm in all fingolimod treated patients (group E) is presented in Table 37.

Table 37 Number (%) of patients with malignant neoplasms in Group E (FTY720-treated safety population)

Preferred term	FTY720 5 mg-1.25 mg N=137 n (%)	FTY720 1.25 mg N=1302 n (%)	FTY720 0.5 mg N=1176 n (%)	Total N=2615 n (%)
Basal cell carcinoma	4 (2.9)	5 (0.4)	9 (0.8)	18 (0.7)
Malignant melanoma	0 (0.0)	4 (0.3)	2 (0.2)	6 (0.2)
Breast cancer	1 (0.7)	3 (0.2)	2 (0.2)	6 (0.2)
Malignant melanoma in situ	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)
Squamous cell carcinoma of skin	0 (0.0)	1 (0.1)	1 (0.1)	2 (0.1)
Breast cancer in situ	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Ovarian cancer metastatic	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.0)
Squamous cell carcinoma	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.0)
Cervix carcinoma	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.0)
Ovarian epithelial cancer	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.0)
Thyroid cancer	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.0)

Note: This table is an update from the [FTY720D-ISS-Table 2-83].
The FTY720 5 mg–1.25 mg group includes patients who received either FTY720 5 mg alone or FTY720 5 mg initially and were later switched to 1.25 mg.
Source: ISS Update PT-Table 4.5-1

There have been a total of 3 reported cases of lymphoma in the fingolimod MS clinical development program and a causal relationship between those cases and treatment by fingolimod can not be excluded. Of note, one of the lymphoma cases was an EBV associated B-cell lymphoma. This case is particularly worrisome. EBV infection is known to induce malignancies and EBV induced cancers incidence is higher in immunodepressed patients. In the second case, fingolimod could have acted as a booster, transforming a pre-cancerous lesion to lymphoma, 1 year after initiation. In the last case, lymphoma occurred 13 months after treatment initiation. With a population more than 4,000 patients exposed to fingolimod (approximately 10,000 patient-years, the estimated incidence of lymphoma with fingolimod is 3 in 10,000 patient years (95%CI: 0.6-8.8 per 10,000 patient years). In contrast, no lymphoma has been reported in the placebo arm nor in the interferon arm.

Cardiac events

Effects on heart

In group B, bradycardia (including sinus bradycardia and bradyarrhythmia) was reported as an AE in 16 patients in the FTY720 1.25mg and 0.5mg groups, and 3 patients in placebo group. Out of the 16 patients in the FTY720 groups, 13 of them had bradycardia AEs during the day 1 first dose administration period. No patients in the placebo group had bradycardia reported as an AE during the first-dose monitoring. Bradycardia has been reported in 0.6% of patients in fingolimod 0.5 mg arm versus 0% in placebo group.

In group B, greater proportion of patients with first degree AV block was reported in the FTY720 1.25 mg group than in the FTY720 0.5 mg and placebo groups. First degree AV block was reported as an AE in 5 patients in the FTY720 1.25 mg group (1.2%), 2 patients in the FTY720 0.5 mg group (0.5%), and 2 patients in the placebo group (0.5%). Out of the 7 patients in the FTY720 groups, 3 of them had first

degree AV during day 1 first dose administration, 2 in the FTY720 1.25 mg group (including one SAE) and one in the FTY720 0.5 mg group.

Two cases of second degree AV block were reported as SAE in the FTY720 1.25 mg and placebo groups, respectively. In the FTY720 1.25 mg group the event occurred on Day 1 of treatment and resulted in discontinuation of study drug. There were no AE reports of second degree AV block in the FTY720 0.5 mg group.

A dose-dependent reduction in sitting pulse and heart rate on ECGs was observed following initiation of FTY720 treatment. In all groups, the decreases in sitting pulse peaked at 4-5 hours after the first dose administration but returned to baseline values by Month 1. There were no relevant differences between FTY720, placebo and interferon groups in mean sitting pulse or heart rate over long term treatment period.

Dose dependent increases in QTc interval was also observed at 6 hours after the first FTY720 dose. When adjusted using Fridericia' s formula, there was no evidence of QTc prolongation >60 ms from pre-dose or any QTc interval >500 ms (males) or <520 ms (females) within the first 6 hours of the first or second dose administration, except for one patient in the FTY720 0.5 mg group who had a Fridericia-corrected QTc increase of >60 ms at more than 6 hours after the first dose.

Effect on blood pressure

In group B, hypertension was reported in 6.3% in the 1.25 mg group and 6.1% in the fingolimod 0.5 mg group compared to 3.8% with the placebo group. These increases were of 1mmHg on average in mean arterial pressure, generally manifesting 2 months after treatment initiation and persisting with continued treatment.

In group B, a higher percentage of patients in both FTY720 groups reported at least one notably high or notable increase in systolic or diastolic BP compared to the placebo group. In contrast, there were higher percentages of patients with notably low measurements or notable decreases from baseline in the placebo group compared to the FTY720 groups.

In group E, changes in blood pressure appeared to be reversible and returned to baseline values within 3 months after study drug discontinuation.

Macular edema

In group B, macular edema was reported as SAE in the FTY20 1.25 mg group (n=3, 0.7%) only. Macular oedema has been reported in 0.4% of patients in fingolimod 0.5 mg arm versus 0.1% in placebo group.

Up to 29 January 2010, 12 cases of macular edema were reported as SAE, of which 8 have been confirmed, 1 in the fingolimod 0.5mg and 7 in the fingolimod 1.25mg groups, respectively. The 8 confirmed macular edema cases were reported in both male (n=4) and female patients (n=4), were unilateral (n=6) or occurred in both eyes (n=2). Six of these cases were detected within the first 4 to 16 weeks of treatment. The remaining 2 cases were detected 10 and 12 months respectively after commencing treatment with fingolimod 1.25 mg. The reported seriousness assessment for these cases included medical significant events (4 cases), disability (1 case), medically significant and disability (1 case) and hospitalisation (2 cases).

The majority of cases occurred within the first 3-4 months of therapy. Some patients presented with blurred vision or decreased visual acuity, but others were asymptomatic and diagnosed on routine ophthalmological examination. Generally, reported macular oedema improved or resolved spontaneously after discontinuation of fingolimod.

Respiratory events

In group B, cough and dyspnea were the most frequently reported respiratory AEs in the FTY720 1.25 mg and 0.5 mg groups. The proportions of patients with cough and dyspnea were higher for the FTY720 groups compared to placebo. There was no evidence of dose-dependence and the proportions of patients experiencing these two AEs were similar between the FTY720 1.25 mg and placebo treatment group with 8.6% versus 8.1% and 5.4% versus 4.5 %, respectively for cough and dyspnea.

Most dyspnea events occurred in the first six months of treatment, and resolved without concomitant treatment. Dyspnea resulted in discontinuation of study drug for one patient (0.2%) in each of the FTY720 treatment groups and for 2 patients (0.5%) in the placebo group. One SAE of dyspnea was reported in the FTY720 0.5 mg group.

Neurological disorders

Six cases of severe neurological adverse events of interest were reported during clinical trials with fingolimod: 2 cases of PRES (Posterior reversible Encephalopathy Syndrome), one fatal case suggestive of acute disseminated encephalomyelitis (ADEM), one MS relapse, one fatal case of severe neurological degenerescence, one acute inflammatory neurological event possibly related to ADEM.

2.6.4. Laboratory findings

Safety analysis from group B is presented below. Electrolyte levels were not analysed in the MS studies, data are derived from a clinical pharmacoly study (D2113) and the renal transplant studies.

Hematology parameters

At 2 weeks post-baseline, the mean lymphocyte count in the FTY720 1.25 mg group was reduced by approximately 74%, and in the FTY720 0.5 mg group was reduced by approximately 70%. Lymphocyte. At 24 months, these were reduced by approximately 77% in the FTY720 1.25 mg group and 74% in the FTY720 0.5 mg group. In the placebo group, no relevant changes in mean lymphocyte counts were seen. There was a trend towards greater mean reductions from baseline in lymphocyte counts for females compared to males in both FTY720 1.25 mg and 0.5 mg groups. At Month24, mean lymphocyte count in females was reduced by approximately 78% (vs. 71% in males) for FTY720 1.25 mg and by approximately 75% (vs. 72% in males) for FTY720 0.5 mg.

At 2 weeks post-baseline, mean neutrophil counts were reduced from baseline by approximately 22% in the FTY720 1.25 mg group and by approximately 17% in the FTY720 0.5 mg group. At 24 months, these were reduced by approximately 29% in the FTY720 1.25 mg group and 20% in the FTY720 0.5 mg group. In the placebo group, there were no relevant changes in mean neutrophil counts.

At 2 weeks post-baseline, mean total WBC counts were reduced from baseline by approximately 35% in the FTY720 1.25 mg group and by approximately 31% in the FTY720 0.5 mg group at 2 weeks. At 24 months, mean total WBC counts were reduced from baseline by approximately 41% in the FTY720 1.25 mg group and 35% in the FTY720 0.5 mg group. There were no meaningful changes over time in mean total WBC counts in the placebo group.

At 2 weeks post-baseline, mean platelet counts were relatively reduced by approximately 6% in the FTY720 1.25 mg group and approximately 4% in the FTY720 0.5 mg group. At 3 months, platelet counts in both these treatment groups, had returned to levels similar those at baseline with approximately 96% and 98% of baseline in the 1.25 mg and 0.5 mg groups, respectively. In the placebo group, no relevant change for mean platelet count was seen.

Chemistry parameters

Mean ALT, AST and GGT values for the FTY720 1.25 mg and 0.5 mg groups were increased from baseline in both FTY720 groups. At 24 months, mean increases from baseline in ALT, AST and GGT values in the 1.25 mg and 0.5 mg groups were: 13.30 and 13.52 U/L (ALT); 4.77 and 5.34 U/L (AST); 36.12 and 31.80 U/L (GGT), respectively. There were no meaningful changes over the treatment period for placebo group. Changes from baseline in ALT, AST and GGT values in the 1.25 mg and 0.5 mg groups were greater for males than females, irrespective of the dose.

Mean alkaline phosphatase (ALP) slightly increased from baseline in both FTY720 groups. At 24 months, mean increases from baseline in ALP values in the 1.25 mg 0.5 mg groups were 4.41 and 2.65 versus 0.09 mmol/l in the placebo group.

Mean total cholesterol, HDL and LDL cholesterol slightly increased from baseline in both FTY720 groups. At 24 months, mean increases from baseline in total cholesterol, HDL and LDL cholesterol values in the 1.25 mg 0.5 mg groups were: 0.411 and 0.355 (total cholesterol), 0.147 and 0.1315 (HDL cholesterol), 0.207 and 0.170 mmol/l (LDL cholesterol), respectively, versus 0.086 mmol/l (total cholesterol), 0.09 mmol/l (HDL cholesterol) and 0.002 mmol/l (LDL cholesterol) in the placebo group.

Mean levels of triglycerides increased from baseline in both FTY720 groups. At 24 months, mean increases from baseline in triglycerides values in the 1.25 mg and 0.5 mg groups were 0.137 and 0.125 mmol/l, respectively and versus -0.011 mmol/l in the placebo group.

Mean changes in glucose values increased from baseline in both FTY720 groups. At 24 months, mean changes from baseline were 0.245 mmol/L and 0.123 mmol/L for FTY720 1.25 mg and 0.5 mg groups, and versus -0.025 mmol/l in the placebo group.

No clinically relevant changes were observed in electrolyte levels.

In all safety groups, no differences in proportions of patients with proteinuria were seen.

Safety in special populations

No trials have been performed in any special multiple sclerosis patient populations. Patients with diabetes mellitus (uncontrolled diabetes in D2201), significant cardiovascular or pulmonary disease, renal impairment and hepatic conditions were excluded in the pivotal studies.Recommendations for patients with renal, hepatic impairment and other special population (paediatric, elderly) are discussed under clinical pharmacology aspects (see 3.4.4.)

In MS clinical studies, females of childbearing potential were required to have a negative pregnancy test prior to entering the treatment period and to use 2 effective forms of contraception until 3 months after treatment discontinuation. Nonetheless, a total of 30 out of 52 pregnancies were reported in fingolimod-treated patients in the clinical studies including a total of 2380 female patients as of 29 January 2010. Thirteen successful deliveries with 12 normal newborns and 1 case report of congenital shortening of the right leg with congenital posteromedial bowing of the tibia were observed. Limited information was available on abortions, however, one abortion was reported tostudie be due to Fallot's tetralogy (fetal abnormality) in a female patient on fingolimod 1.25 mg.

Subgroups analyses were performed on differences in the rate of AEs by gender, age, and previous treatment status. A higher percentage of naive patients had high ALT values and high AST compared to pre-treated patients in the safety population group A (12 months treatment). A higher percentage of pre-treated patients presented lymphocytes count < 0.2 x 10^9 /L was also observed compared to naive patients in fingolimod 1.25 and 0.5 mg arms in group A and group E suggesting potential need for a therapeutic window after administration of other immunossupressive agent and before fingolimod initiation. Due to the half life of the fingolimod (6-9 days), a warning to ensure that a 6 week interval

period of wash-out is done after treatment has been included before initiation of natalizumab or other immunosuppressants.

Drug interactions and other interactions

No specific investigation has been conducted in multiple sclerosis patient populations.

Considering the risk of additive immune system effects; co-administration of anti-neoplastic, immunosuppressive or immune-modulating therapies is not recommended.

Discontinuation due to adverse events

Discontinuations from study drug due to AEs and abnormal laboratory values, when taken together, were notably more frequent on FTY720 1.25 mg (14.7%) and slightly more frequent on FTY720 0.5 mg (8.2%) compared with placebo (6.9%), these were possibly related to the dose response that could be observed for a number of AEs: macular edema, bradycardia and AV blocks, lymphopenia, infections and to some extent elevations in liver enzymes. About 16% patients exposed to fingolimod 0.5mg required a more extensive monitoring than 6 hours.

Discontinuation due to lack of efficacy were 4.2, 1.9 and 8.6%, for the FTY720 1.25 mg, FTY720 0.5 mg and placebo groups, respectively.

Post marketing experience

Not applicable

2.6.5. Discussion on clinical safety

The safety profile of fingolimod has been characterized with data from 2615 MS patients, comprising 4582.6 patient-years of exposure. Of these patients, >1700 were exposed to daily doses of 0.5 mg and 1.25 mg in the two completed pivotal Phase III studies, including 94 exposed to a higher dose of 5.0 mg in the MS Phase II study. However, patients with diabetes mellitus (uncontrolled diabetes in D2201), significant cardiovascular or pulmonary disease, renal impairment and hepatic conditions were excluded in the pivotal studies. Very limited safety information has been received from pregnancy.

In MS clinical studies, the overall incidence of adverse events and serious adverse events was similar for fingolimod and matched controls (placebo, interferon beta-1a). However, specific events associated with the biologic effects of fingolimod were reported on the cardiac, ocular, immune, hepatic, and pulmonary systems.

About 90% of patients experienced one or more AEs in all groups. The system organ class (SOC) with the highest proportion of patients with AEs was infections and infestations. The incidence of infection and infestation SAEs were comparable between the different groups during the 12 month-treatment and appeared to be increased during the 24 month-treatment. Additionally, a total of 3 cases of disseminated herpes infection were reported in patients treated with fingolimod 1.25 mg. In these cases, 2 deaths were reported. The third patient had disseminated herpes zoster with pulmonary involvement and made a complete recovery after treatment with aciclovir therapy.

Among cases of malignancies reported in the fingolimod groups, there have been a total of 3 cases of lymphoma in the MS clinical development program and a causal relationship between those cases and treatment by fingolimod can not be excluded. Of note, one of the lymphoma cases was an EBV associated B-cell lymphoma. This case is particularly worrisome. EBV infection is known to induce malignancies and EBV induced cancers incidence is higher in immunodepressed patients. In the second

case, fingolimod could have acted as a booster, transforming a pre-cancerous lesion to lymphoma, 1 year after initiation. In the last case, lymphoma occurred 13 months after treatment initiation. With a population more than 4,000 patients exposed to fingolimod (approximately 10,000 patient-years, the estimated incidence of lymphoma with fingolimod is 3 in 10,000 patient years (95%CI: 0.6-8.8 per 10,000 patient years). In contrast, no lymphoma has been reported in the placebo arm nor in the interferon arm.

Other specific AEs that were reported more commonly in MS patients treated with fingolimod than in placebo-treated patients included: reductions in white blood cell counts (lymphocytes and total WBC), bradycardia on treatment initiation (Day 1), elevations of liver enzymes (in particular increases in ALT and GGT), macular edema, hypertension and dyspnea. In addition, a number of cases of severe neurological adverse events were reported including 2 cases of PRES (Posterior reversible Encephalopathy Syndrome) and one fatal case suggestive of acute disseminated encephalomyelitis (ADEM).

In preclinical studies, fingolimod has shown a teratogenic potential. A total of 30 out of 52 pregnancies were reported in fingolimod-treated patients in the clinical studies including a total of 2380 female patients as of 29 January 2010. Thirteen successful deliveries with 12 normal newborns and 1 case report of congenital shortening of the right leg with congenital posteromedial bowing of the tibia were observed. Limited information was available on abortions, however, one abortion was reported to be due to Fallot's tetralogy (fetal abnormality) in a female patient on fingolimod 1.25 mg. Considering the population fingolimod is intended to be used for, this finding is considered as an important identified risk. A pregnancy exposure registry to prospectively collect outcome data on the babies born to women treated with fingolimod is part of the risk management plan.

Discontinuations from study drug due to AEs and abnormal laboratory values, when taken together, were notably more frequent on FTY720 1.25 mg (14.7%) and slightly more frequent on FTY720 0.5 mg (8.2%) compared with placebo (6.9%), these were possibly related to the dose response that could be observed for a number of AEs : macular edema, bradycardia and AV blocks, lymphopenia, infections and to some extent elevations in liver enzymes. About 16% patients exposed to fingolimod 0.5mg required a more extensive monitoring than 6 hours. Dose-dependent toxicity were also observed for hypertension, leukopenia.

In general, the AE profile of fingolimod in MS patients did not depend on gender or age. However, there was a trend towards greater mean reductions from baseline in lymphocyte counts for females compared to males in both FTY720 1.25 mg and 0.5 mg groups. In addition, changes from baseline in ALT, AST and GGT values in the 1.25 mg and 0.5 mg groups were greater for males than females, irrespective of the dose. Differences have also been observed regarding haematological parameters and hepatic enzymes in non-naive patients compared with naive patients**.** A higher percentage of naive patients had high ALT values and high AST compared to pre-treated patients in the safety population group A (12 months treatment). A higher percentage of pre-treated patients presented lymphocytes count $< 0.2 \times 10^9$ /L was also observed compared to naive patients in fingolimod 1.25 and 0.5 mg arms in group A and group E.

Overall, the CHMP considered that fingolimod exhibits a heterogeneous and complex safety profile. Safety concerns of fingolimod include bradycardia, AV- blocks, leukopenia, risk of increased frequency and seriousness of infections, occurrence of lymphoma related to its immunosuppressant effect, as well as neurological manifestations including Posterior reversible Encephalopathy Syndrome (PRES), which could be due to the drug itself or the immune suppression. A risk of liver toxicity and strong signals of teratogenicity are also part of this unfavourable safety profile. Thus, the CHMP was of the opinion that the benefit risk balance in the initial indication applied for *"Disease-modifying therapy in adults for the treatment of patients with relapsing multiple sclerosis to reduce the frequency of relapses and to delay*

the progression of disability" was negative. Subsequently, post-hoc subgroup analyses were performed by the applicant to evaluate the benefit-risk in a restricted population and a SAG was convened to discuss the place of fingolimod in the multiple sclerosis therapy. Having considered the efficacy results of highly active subgroups of patients with relapse remitting multiple sclerosis and the SAG recommendations, the CHMP concluded that the indication should be restricted in line with the already authorised indication in the EU as second line treatment of multiple sclerosis (see 3.5.3). A number of measures have been proposed to ensure safe and effective use of the product in the risk management plan and were considered appropriate by the CHMP for this restricted indication.

Hypertension, liver enzyme elevation, macular edema, infections have been considered as important identified risks requiring additional pharmacovigilance activities. A 5 year post-approval safety (PASS) study will be conducted by the applicant to monitor these risks and potential long term complications. Other important identified risks such as bradyarrthythmia (including conduction defects) occurring first post dose, reductions in white blood cell counts and bronchoconstriction were considered manageable through routine pharmacovigilance and adequate labelling. Incidence of the risk of bradyarrhythmia (including conduction defects) and risk factors will be further characterised via a specific safety study.

Skin cancer, other malignant neoplasms, thromboembolic events have been considered as important potential risks requiring additional pharmacovigilance activities. These risks will also be monitored in the 5 year post-approval safety conducted by the applicant. In addition, further investigation on malignant neoplasms will be performed in a long term observational study (D2339E1), similar to the PASS study. Other important potential risks such as QT interval prolongation, PRES and ADEM like events, reactivation of chronic viral infections, decreased renal function and potential interactions with ketoconazole and atenolol will be monitored via routine pharmacovigilance and are reflected in the Labelling.

Details of these measures including additional pharmacovigilance activities such as post-authorisation safety studies and risk minimization activities are presented in section 3.7.

In addition, further long term data will be generated from ongoing studies and will be submitted by the applicant to monitor the benefit-risk balance of the product.

2.6.6. Conclusions on the clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Appropriate measures including additional pharmacovigilance activities and risk minimization activities (see 3.7) have been put in place to ensure safe and effective use of the product in the recommended indication.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

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

Table 38 Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risks		
Bradyarrhythmia (including conduction defects) occurring post-first dose	Routine pharmacovigilance, including cumulative review in PSUR . 4-month, open-label, multi-center study to explore tolerability and safety and health outcomes of FTY720 in patients with relapsing forms of MS (Study D2316)	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: SmPC Sections 4.4 and 4.8 state that initiation of fingolimod treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays. Observe all patients for a period of 6 hours for signs and symptoms of bradycardia. Should post-dose bradyarrhythmia-related symptoms occur, initiate appropriate management and continue observation until the symptoms have resolved. Fingolimod has not been studied in patients with sitting heart rate less than 55 bpm and in patients receiving concurrent therapy with beta blockers or in those with a history of syncope. At treatment initiation in patients receiving beta blockers, or other substances which may decrease heart rate, such as verapamil, digoxin, anticholinesteratic agents or pilocarpine, caution should be exercised because of the additive effects on heart rate (see also section 4.5). Should post-dose, bradyarrhythmia-related symptoms occur, appropriate management should be initiated as necessary and the patient should be observed until the symptoms have resolved. SmPC also states that fingolimod has not been studied in patients with 2nd-degree or higher AV blocks, sick-sinus-syndrome, ischemic cardiac disease, or congestive heart failure. Use of fingolimod in such patients should be based on overall benefit-risk assessment and careful observation during initiation of therapy is recommended due to potential for serious rhythm disturbances. Before initiation of treatment in these patients, advice from a cardiologist is recommended. Fingolimod has not been studied in patients with arrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medicinal products. Class Ia and Class III

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		antiarrhythmic medicinal products have been associated with cases of torsades de pointes in patients with bradycardia. Since initiation of fingolimod treatment results in decreased heart rate, fingolimod should not be co-administered with these medicinal products. SmPC also states that if fingolimod therapy is discontinued for more than 2 weeks, the effects on heart rate and atrio-ventricular conduction may recur on reintroduction of fingolimod treatment and the same precautions should apply. <u>Additional risk minimization activity:</u> Educational material for physicians and patiens. A physician's checklist prior to prescribing and a patient reminder card will describe this transient pharmacodynamic effect and will highlight that during initiation of Gilenya therapy, all patients should be observed for a period of 6 hours for signs and symptoms of bradycardia.
Hypertension	Routine pharmacovigilance, including cumulative review in PSUR. Post-approval 5-year safety study to monitor for potential long-term complications.	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: Blood pressure should be regularly monitored during treatment with Gilenya. Patients with hypertension uncontrolled by medication were excluded from participation in premarketing clinical trials and special care is indicated if patients with uncontrolled hypertension are treated with Gilenya. In MS clinical trials, patients treated with fingolimod 0.5 mg had an average increase of approximately 2 mmHg in systolic pressure, and approximately 1 mmHg in diastolic pressure, first detected approximately 2 months after treatment initiation, and persisting with continued treatment. In the two-year placebo-controlled study, hypertension was reported as an adverse event in 6.1% of patients on fingolimod 0.5 mg and in 3.8% of patients on placebo.
Liver transaminase elevation	Routine pharmacovigilance, including cumulative review in PSUR. Post-approval 5-year safety study to monitor for clinically significant liver injury.	Risk addressed in SmPC sections 4.2, 4.4 and 4.8 and derived local labels: SmPC states that during clinical trials, elevations 3-fold the upper limit of normal (ULN) or greater in liver transaminases occurred in 8%

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		of patients treated with fingolimod 0.5 mg compared to 2% of placebo patients. Elevations 5-fold the ULN occurred in 2% of patients on fingolimod and 1% of patients on placebo. In clinical trials, fingolimod was discontinued if the elevation exceeded 5 times the ULN. Recurrence of liver transaminase elevations occurred with rechallenge in some patients, supporting a relationship to fingolimod. The majority of elevations occurred within 3-4 months. Serum transaminase levels returned to normal within approximately 2 months after discontinuation of fingolimod. Gilenya has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and must not be used in these patients (see section 4.3). Due to the immunosuppressive properties of fingolimod, initiation of treatment should be delayed in patients with active viral hepatitis until resolution. Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with Gilenya. In the absence of clinical symptoms, liver transaminases levels should be monitored at months 1, 3 and 6 on therapy and periodically thereafter. If liver transaminases riseabove 5 times the ULN, more frequent monitoring should be instituted, including serum bilirubin and alkaline phosphatase (ALP) measurement. With repeated confirmation of liver transaminases above 5 times the ULN, treatment with Gilenya should be interrupted and only re-commenced once liver transaminases values have normalized. Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes checked and Gilenya should be discontinued if significant liver injury is confirmed (for example liver transaminase levels greater than 5-fold the ULN and/or serum bilirubin elevations). Resumption of therapy will be dependent on whether or not another cause of liver injury is determined and on the benefits to patient of resuming therapy versus the risks of

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		recurrence of liver dysfunction. Although there are no data to establish that patients with pre-existing liver disease are at increased risk of developing elevated liver function tests when taking Gilenya, caution in the use of Gilenya should be exercised in patients with a history of significant liver disease. Additional risk minimization activity: Educational material for physicians and patiens. A physician's checklist prior to prescribing and a patient reminder card will inform on the need for liver function tests prior to initiation and during Gilenya therapy.
Macular edema	Routine pharmacovigilance, including cumulative review in PSUR. 4-month, open-label, multi-center study to explore tolerability and safety and health outcomes of FTY720 in patients with relapsing forms of MS (Study D2316) Post-approval 5-year safety study to monitor for this and other potential long-term complications.	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: Macular edema with or without visual symptoms has been reported in 0.4% of patients treated with fingolimod 0.5 mg, occurring predominantly in the first 3-4 months of therapy (see section 4.8). An ophthalmological evaluation is therefore recommended at 3-4 months after treatment initiation. If patients report visual disturbances at any time while on therapy, evaluation of the fundus, including the macula, should be carried out. Patients with history of uveitis and patients with diabetes mellitus are at increased risk of macular edema. Gilenya has not been studied in multiple sclerosis patients with concomitant diabetes mellitus. It is recommended that multiple sclerosis patients with diabetes mellitus or a history of uveitis undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy. Continuation of Gilenya in patients with macular edema has not been evaluated. It is recommended that Gilenya be discontinued if a patient develops macular edema. A decision on whether or not Gilenya therapy should be re-initiated after resolution of macular edema needs to take into account the potential benefits and risks for the individual patient. Additional risk minimization activity:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		Educational material for physicians and patiens. A physician's checklist prior to prescribing and a patient reminder card will inform on the risk of macular edema. Through this activity physicians and patients will be made aware of potential vision deterioration on fingolimod and the need for regular vision checks.
Infections	Routine pharmacovigilance, including cumulative review in PSUR. Post-approval 5-year safety study to monitor for infections and other potential complications.	Risk addressed in SmPC sections 4.4 and 4.8 and derived local labels: SmPC state that the immune system effects of fingolimod therapy may increase the risk of infections. The SmPC will also state that two fatal herpetic infections occurred in patients on the 1.25 mg dose. As could be considered for any immune modulating drug, before initiating fingolimod therapy, patients without a history of chickenpox or without vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV. VZV vaccination of antibody negative patients should be considered prior to commencing treatment with fingolimod, following which initiation of treatment with fingolimod should be postponed for 1 month to allow full effect of vaccination to occur. SmPC recommendation to avoid the administration of live or live attenuated vaccines while patients are taking fingolimod and for 2 months after discontinuation. SmPC states that before initiating treatment with fingolimod, a recent complete blood count (CBC) (i.e. within 6 months) should be available. Assessments of CBC are also recommended periodically during treatment, and in case of signs of infections. Absolute lymphocyte count <0.2 $x10^9$/L, if confirmed, should lead to treatment interruption, until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count <0.2 $x10^9$/L. <u>Additional risk minimization activity</u>: Educational material for physicians and patiens. A physician's checklist prior to prescribing and a patient reminder card will inform on the risk of increased infection with fingolimod, and the need to

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
		immediately report signs and symptoms of infections to the prescriber.
Leucopenia and lymphopenia	Routine pharmacovigilance, including cumulative review in PSUR.	Risk addressed in SmPC Section 4.4, 5.1 and CDS Section 6 and derived local labels: SmPC Section 4.4 and CDS Section 6 state that a core pharmacodynamic effect of Gilenya is a dose-dependent reduction of the peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. Further information relating to this risk is provided under infections above.
Reproductive toxicity	Routine pharmacovigilance, including cumulative review in PSUR. Establish a Fingolimod Pregnancy Exposure Registry to prospectively collect outcome data on the babies born to women treated with fingolimod and compare it to reference data from general surveillance systems. With the establishment of a Fingolimod Pregnancy Exposure Registry, Novartis seeks to obtain comprehensive data on the outcome of any pregnancies that occur during the use of fingolimod.	Risk addressed in SmPC section 4.6 and derived local labels: SmPC recommendation for females of child-bearing potential to practice effective contraception during treatment with fingolimod and for 2 months post-drug discontinuation to cover the period of elimination of the drug. SmPC also states that it should be confirmed that a woman is not pregnant at the time of initiation of treatment. If a woman becomes pregnant while taking Gilenya, discontinuation of Gilenya is recommended. <u>Additional risk minimization activity</u>: Educational material for physicians and patiens. A physician's checklist prior to prescribing and a patient reminder card will outline the known teratogenic risks with fingolimod and explain the importance of avoiding pregnancy, confirmed by a negative pregnancy test, when undergoing treatment with fingolimod.
Bronchoconstriction	Routine pharmacovigilance, including cumulative review in PSUR.	SmPC section 4.4 states that minor dose-dependent reductions in values for forced expiratory volume (FEV_1) and diffusion capacity for carbon monoxide (D_LCO) were observed with Gilenya treatment starting at Month 1 and remaining stable thereafter. Fingolimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease. Physicians are properly informed of this risk.
Important potential risks		
Skin cancer	Routine pharmacovigilance, including cumulative review in	Risk is not presented in the SmPC.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	PSUR. Post-approval 5-year safety study to monitor for skin cancers and other potential long-term complications.	
Other malignant neoplasms	Routine pharmacovigilance, including cumulative review in PSUR. Post-approval 5-year safety study to monitor for malignant neoplasms and other potential long-term complications. Long-term observational study in patients who participated in the fingolimod clinical development program (Study D2399E1).	SmPC section 5.3 states that fingolimod increased the risk of developing lymphomas in animal studies. SmPC section 4.8 states that three cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma including one fatal EBV positive B-cell lymphoma) have been reported in a population of more than 4,000 patients (approximately 10,000 patient-years) exposed to fingolimod at, or above, the recommended dose of 0.5 mg, during the clinical program in multiple sclerosis. This incidence of 3 in 10,000 patient years (95% CI: 0.6-8.8 per 10,000 patient years) compares to a background incidence of 1.9 in 10,000 patient years in the general population. Physicians are properly informed of this risk.
Posterior Reversible Encephalopathy Syndrome (PRES) and acute disseminated encephalomyelitis-like (ADEM-like) events	Routine pharmacovigilance, including cumulative review in PSUR.	SmPC section 4.8 states that rare events involving the nervous system which occurred in patients treated with fingolimod at higher doses (1.25 or 5.0 mg) including posterior reversible encephalopathy syndrome. Neurological atypical disorders have also been reported, such as ADEM-like events. Physicians are properly informed of this risk.
Thromboembolic events	Routine pharmacovigilance, including cumulative review in PSUR. Post-approval 5-year safety study to monitor for these and other potential complications.	SmPC section 4.8 includes information on the small number of cases with possible thromboembolic events (including cerebrovascular and peripheral vascular events) observed in the fingolimod clinical trial program.
QT interval prolongation	Routine pharmacovigilance, including cumulative review in PSUR.	SmPC Sections 4.4 and 5.1 include results of the thorough QT study which showed a prolongation of mean corrected QT interval, with the upper limit of the 90% CI ≤13.0 msec on fingolimod treatment.
Convulsions	Routine pharmacovigilance, including cumulative review in PSUR.	Risk is not presented in the SmPC.
Progressive multifocal leukoencephalopathy (PML)	Routine pharmacovigilance, including cumulative review in PSUR.	Risk is not presented in the SmPC.
Reactivation of chronic viral	Routine pharmacovigilance,	Risk is addressed in SmPC Section

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
infections	including cumulative review in PSUR.	4.4, 4.8 and CDS Section 6 and derived local labels. See section on Infections above.
Off-label use	Routine pharmacovigilance, including cumulative review in PSUR.	Risk is not presented in the SmPC.
Pulmonary edema	Routine pharmacovigilance, including cumulative review in PSUR.	Risk is not presented in the SmPC.
Decreased renal function	Routine pharmacovigilance, including cumulative review in PSUR.	According to SmPC section 4.2, fingolimod has not been studied in patients with renal impairment in the MS pivotal studies. Based on clinical pharmacology studies, no dose adjustments are needed in patients with mild to severe renal impairment.
Potential interactions with Ketoconazole	Routine pharmacovigilance, including review in PSUR.	According to SmPC section 4.5, co-administration of fingolimod with ketoconazole resulted in a 1.7-fold increase in fingolimod and fingolimod phosphate exposure (AUC). Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).
Potential interactions with Atenolol	Routine pharmacovigilance, including review in PSUR.	According to SmPC section 4.5, when fingolimod is used with atenolol, there is an additional 15% reduction of heart rate at fingolimod treatment initiation. At treatment initiation in patients receiving beta blockers, or other substances which may decrease heart rate, caution should be exercised because of the additive effects on heart rate. The potential risks and benefits of initiating fingolimod treatment in patients already on a substance which lowers the heart rate should be considered.
Important missing information		
Elderly patients	Routine pharmacovigilance, including cumulative review in PSUR.	According to SmPC Section 4.2, fingolimod should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.
Pediatric patients	Routine pharmacovigilance, including cumulative review in PSUR. [Study D2311]: EMEA pediatric investigation plan (EMEA-000087-PIP01-07): Open-label, randomized, multicenter, multiple dose, active controlled (interferon beta-1a), parallel group 2-year trial to evaluate pharmacokinetics, safety and efficacy of fingolimod using blinded MRI assessment in patients with MS from 10 to less	The safety and efficacy of fingolimod in children aged 0 to 18 years have not yet been established. Currently available data are described in section 5.2 of SmPC but no recommendation on a posology can be made.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	than 18 years of age followed by a long-term extension.	
Pregnant and lactating women	Routine pharmacovigilance, including review in PSUR. Establish a Fingolimod Pregnancy Exposure Registry to prospectively collect outcome data on the babies born to women treated with fingolimod.	According to SmPC Section 4.6, before initiation of fingolimod treatment, women of childbearing potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception during treatment with fingolimod. Since it takes approximately two months to eliminate fingolimod from the body on stopping treatment (see section 4.4), the potential risk to the fetus may persist and contraception should be continued during that period. It should be confirmed that a woman is not pregnant at the time of initiation of treatment. While on treatment, women should not become pregnant and active contraception is recommended. If a woman becomes pregnant while taking Gilenya, discontinuation of Gilenya is recommended. Fingolimod is excreted in milk of treated animals during lactation. Because of the potential for serious adverse drug reactions in nursing infants from fingolimod, women receiving fingolimod should not breast feed.
Patients with diabetes mellitus	Routine pharmacovigilance, including cumulative review in PSUR.	Recommendation in the SmPC Section 4.4 that patients with diabetes mellitus undergo an ophthalmologic evaluation prior to initiating fingolimod therapy and have follow-up evaluations while receiving fingolimod therapy. According to the SmPC section 4.2, fingolimod has not been studied in MS patients with concomitant diabetes mellitus. It should be used with caution in patients with diabetes mellitus due to a potential increased risk of macular edema.
Patients with cardiovascular conditions	Routine pharmacovigilance, including review in PSUR. Post-approval 5 year safety study which includes patients with cardiovascular conditions.	Recommendation in the SmPC Section 4.4 that patients with 2nd-degree or higher AV blocks, sick-sinus-syndrome, ischemic cardiac disease, or congestive heart failure the use of fingolimod be based on overall benefit-risk assessment and that they undergo careful observation during initiation of therapy due to potential for serious rhythm disturbances. Before initiation of treatment in these patients, advice from a cardiologist is recommended.
Long-term risk of cardiovascular morbidity/mortality	Routine pharmacovigilance, including review in PSUR. Post-approval 5 year safety study	Risk is not presented in the SmPC

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
	to monitor for cardiovascular morbidity/mortality.	
Long-term risk of malignant neoplasms	Routine pharmacovigilance, including review in PSUR. Post-approval 5 year safety study monitoring malignant neoplasms. Long-term observational study in patients who participated in the fingolimod clinical development program (Study D2399E1)	According to SmPC Section 4.8, cases of lymphoma (cutaneous T-cell lymphoproliferative disorders or diffuse B-cell lymphoma) have been reported in MS patients receiving fingolimod at, or above, the recommended dose of 0.5 mg. Based on the small numbers of cases and short duration of exposure, the relationship to Gilenya remains uncertain.

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

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where GILENYA is marketed, at launch and after launch all physicians who intend to prescribe GILENYA are provided with a physician information pack containing the following elements:

- The Summary of Product Characteristics
- Physician's checklist prior to prescribing GILENYA
- Information about the Fingolimod Pregnancy Exposure Registry
- Patient reminder card

The physician's checklist shall contain the following key messages:

- The need to monitor patient heart rate after the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago) for signs and symptoms of bradycardia during at least 6 hours.
- GILENYA should not be co-administered to patients receiving Class IA or Class III anti-arrhythmic medicines.
- Caution when using GILENYA in patients with a cardiac disease or those taking medicines concomitantly known to decrease heart rate.
- GILENYA reduces peripheral blood lymphocyte counts. There is the need to check prior to initiation and to monitor during treatment with GILENYA the patient's peripheral lymphocyte count (CBC).
- GILENYA may increase the risk of infections. There is the need to delay treatment initiation in patients with severe active infection until resolution. Suspension of treatment during serious infections should be considered. Concomitant treatment with immunosuppressants or immune modulating medicines should be avoided.
- The need to instruct patients to immediately report signs and symptoms of infections to their prescriber during and up to two months after treatment with GILENYA.

- Specific recommendations regarding vaccination for patients initiating or currently on GILENYA treatment.
- The need for a full ophthalmologic assessment 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular edema.
- The need for ophthalmologic assessment prior to initiation and during treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.
- The teratogenic risk of GILENYA: the importance of avoiding pregnancy when undergoing treatment with GILENYA and the need to confirm a negative pregnancy test result prior to treatment initiation.
- The need to advise women of child-bearing potential on the serious risk to a fetus and to practice effective contraception during and for at least two months following discontinuation of treatment with GILENYA.
- The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3 and 6 during GILENYA therapy and periodically thereafter.
- The need to provide patients with the patient reminder card.

The patient reminder card shall contain the following key messages:

- The need to monitor patient heart rate after the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago) for signs and symptoms of bradycardia during at least 6 hours.
- The need to immediately report signs and symptoms of infections to the prescriber during and up to two months after treatment with GILENYA.
- The need to immediately report signs of visual impairment to the prescriber during and up to two months after treatment with GILENYA.
- Women with childbearing potential must ensure effective contraception during and for at least two months following discontinuation of treatment with GILENYA. Any (intended or unintended) pregnancy during and two months following discontinuation of treatment with GILENYA must immediately be reported to the prescriber: where available contact details for teratogenic information services should be provided.
- The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3 and 6 during GILENYA therapy and periodically thereafter.

User consultation

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

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

Fingolimod is a structural analogue to endogenous sphingosine, phosphorylated to the active moiety FTY720-P which down-modulates S1P1 receptors on lymphocytes and slows down the S1P-S1P1-dependent egress kinetics of CD4 and CD8 T cells and B cells from lymph nodes. This reduces the recirculation of lymphocytes from lymph nodes into blood and CNS. In vivo effects were demonstrated in several EAE disease models.

Multiple sclerosis is a chronic, inflammatory, demyelinating disease of the central nervous system and is the one of the most common causes of neurological disability in young adults. In humans, fingolimod leads to a dose-dependent decrease in peripheral blood lymphocyte count. This may potentially reduce the infiltration of pathogenic lymphocyte cells into the CNS where they would be involved in inflammation and nervous tissue damage.

Currently, no oral medication is approved for the treatment of relapsing multiple sclerosis. All available disease modifying therapies for multiple sclerosis are administered subcutaneously, intramuscularly or intravenously. The drug product has the advantage that it can be administered orally without regard to food intake. The proposed dose is 0.5 mg daily.

Study D2301 was a 2 year, double-blind, placebo controlled randomized study in patients 17 to 55 years, with RRMS and an EDSS score of 0 to 5.5 who had had at least one relapse in the previous year or at least two relapses in the previous two years. Overall, this pivotal phase III study of adequate duration and methodology, showed consistent and robust efficacy of fingolimod (1.25 and 0.5 mg) both on the primary efficacy criteria (aggregate annualized relapse rate ARR) and all secondary clinical and MRIs efficacy criteria as compared to placebo. The results on primary efficacy parameter (ITT population) showed statistically significantly lower aggregate ARR at all doses tested (0.5 mg : 0.18, 95% CI: 0.15, 0.22; 1.25 mg: 0.16, 95% CI: 0.13, 0.19) versus placebo (0.40, 95% CI: 0.34, 0.47),representing relative reduction of 54% and 60%, respectively in the annualized relapse rate (ARR ratio: 0.40 and 0.46 for 1.25 mg and 0.5 mg, respectively). Results on the key secondary endpoint, time to disability progression confirmed at 3 months, was also statistically longer with all doses tested than with placebo. Fingolimod reduced the risk of disability progression, confirmed at 3 months, over the 24-month study period (0.5 mg: HR= 0.68, 95% CI: 0.50, 0.93, p=0.017; 1.25 mg: 0.5 mg: HR= 0.70, 95% CI: 0.52, 0.96, p=0.024) as compared to placebo. Both doses showed consistent efficacy on primary and key secondary endpoints. The results did not seem to evidence clinical difference of relevance in the efficacy results for the two doses, and the choice of 0.5 mg dose choice was considered appropriate.

Study D2302 was a one year duration, phase III, double-blind, double dummy, 2 doses of fingolimod (1.5 mg and 0.5mg, once a day) active controlled randomized study of one year duration, in patients 18 to 55 years with RRMS and an EDSS score 0 to 5.5 who had had at least one relapse in the previous year or at least two relapses in the previous two years. Overall, this well design active controlled study showed superior efficacy of both doses (1.5 mg and 0.5 mg) of fingolimod as compared to Avonex on primary efficacy criteria (ARR). For the ITT population the aggregate ARR was statistically significantly lower with fingolimod at all doses tested (0.5 mg : 0.16, 95% CI: , 0.122, 0.212, p<0.001 ; 1.25 mg: 0.20, 95% CI: 0.157,0.264, p<0.001) versus interferon beta-1a (0.33, 95% CI: 0.262, 0.417), representing relative reductions of 52% and 38%, respectively, in the annualized relapse rate (ARR ratio: 0.62 and 0.48 for 1.25 mg and 0.5 mg, respectively). Regarding key secondary endpoints, both fingolimod treatment groups had a lower mean number of new or newly enlarged T2 lesions compared to the interferon beta-1a i.m. group, which reached statistical significance for both the fingolimod 1.25 mg group (p<0.001) and the fingolimod 0.5 mg group (p=0.004).

There was no obvious evidence of rebound effect based on MRI data.

Additional post-hoc subgroup analyses in highly active patients with RRMS were performed by the applicant to evaluate the benefit-risk in a restricted population. Results of these subgroups analyses were consistent with those obtained in the overall population.

- Uncertainty in the knowledge about the beneficial effects.

Regarding key secondary endpoints, there was no difference between the two fingolimod treatment groups and the interferon beta-1a i.m. group in the time to 3-month confirmed disability progression as based on Kaplan-Meier estimates (0.5 mg: difference=2.03, 95% CI: -1.42, 5.47, p=0.247, 1.25 mg: difference=1.30, 95% CI: -2.26, 4.86, p=0.498) . This may be explained by the shorter duration of the trial D2302 (one year) and low active population included. However, efficacy on the 2 year placebo controlled study (D2301) is supportive on this aspect.

Relapsing MS including both RRMS and SPMS that still experienced relapses was not studied.

The elderly population was not studied.

There is a lack of information concerning disease activity (frequency and severity of relapses) after discontinuation of fingolimod.

Risks

- Unfavourable effects

Safety concerns associated with the biologic effects of fingolimod were reported on the cardiac, ocular, immune, hepatic, and pulmonary systems. These were also observed in the non clinical studies.

Infection is an important identified unfavourable effect. The incidence of infection and infestation serious adverse events appeared to be increased during the 24 month-treatment. A total of 3 cases of disseminated herpes infection were reported in patients treated with fingolimod 1.25 mg. In these cases, 2 deaths were reported. The third patient had disseminated herpes zoster with pulmonary involvement and made a complete recovery after treatment with aciclovir therapy.

Among the cases for malignancies reported in the fingolimod groups , a total of 3 cases of lymphoma in MS clinical development program were identified and a causal relationship between those cases and treatment by fingolimod can not be excluded. With a population more than 4,000 patients exposed to fingolimod (approximately 10,000 patient-years, the estimated incidence of lymphoma with fingolimod is 3 in 10,000 patient years (95%CI: 0.6-8.8 per 10,000 patient years). In contrast, no lymphoma has been reported in the placebo arm nor in the interferon arm.

Other unfavourable effects that were reported more commonly in MS patients treated with fingolimod than in placebo-treated patients included: reductions in white blood cell counts (lymphocytes and total WBC), bradycardia on treatment initiation (Day 1), elevations of liver enzymes (in particular increases in ALT and GGT), macular edema, hypertension and dyspnea. In addition, a number of cases of severe neurological adverse events were reported including 2 cases of PRES (Posterior reversible Encephalopathy Syndrome) and one fatal case suggestive of acute disseminated encephalomyelitis (ADEM).

In preclinical studies, fingolimod has shown a teratogenic potential. A total of 30 out of 52 pregnancies were reported in fingolimod-treated patients in the clinical studies including a total of 2380 female patients as of 29 January 2010. Thirteen successful deliveries with 12 normal newborns and 1 case report of congenital shortening of the right leg with congenital posteromedial bowing of the tibia were observed. Limited information was available on abortions, however, one abortion was reported to be due to Fallot's tetralogy (fetal abnormality) in a female patient on fingolimod 1.25 mg. Considering the

the population fingolimod is intended to be used for, this finding is considered as an important unfavourable effect.

- Uncertainty in the knowledge about the unfavourable effects.

Considering the heterogeneous safety profile, further long term data are required and a post-approval 5 year safety study will be conducted as part of the risk management plan to further investigate a number of risks and potential complications such as hypertension, liver enzyme elevation, macular edema, infections, thromboembolic events, skin cancer and other malignant neoplasms.

Additional data are required to further document the potential risk of malignancies and this will be additionally monitor in a long term observational study which is part of the risk management plan.

PRES syndromes and other neurological atypical manifestations (ADEM) were reported, the relationship with fingolimod cannot be excluded and this concern has been identified as an important potential risk.

Given the effect of teratogenicity seen in rats and the embryo/fetotoxic effect in rabbits, an effective contraception is recommended during treatment and 2 months after treatment discontinuation. A pregnancy exposure registry to prospectively collect outcome data on the babies born to women treated with fingolimod is an additional pharmacovigilance activity set up as part of the risk management plan.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The effects demonstrated versus placebo as well as the active comparator Avonex were considered clinically relevant in the overall population. Oral administration was considered to be of particular benefit given that the currently available therapies are using the parenteral route. A number of important safety concerns have been identified related to the mechanism of action that is first in the class. The safety of fingolimod is characterised by a heterogeneous profile which required to recommend a restricted use in multiple sclerosis population as well as a number of measures to ensure safe and effective use of the product. Consistent treatment effects were observed in highly active group of RRMS patients as compared to the overall population and therefore this restricted population was recommended for the indication..

- Benefit-risk balance

Having considered the benefits of this first oral treatment for multiple sclerosis over the potential and identified risks, the CHMP concluded that the benefit risk balance for Gilenya is positive for the following indication:

"GILENYA is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

Patients with high disease activity despite treatment with a beta-interferon.
These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion.
A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year,
or
patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more

disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI."

Risk management plan

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

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- the following additional risk minimisation activities were required:

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where GILENYA is marketed, at launch and after launch all physicians who intend to prescribe GILENYA are provided with a physician information pack containing the following elements:

- The Summary of Product Characteristics
- Physician's checklist prior to prescribing GILENYA
- Information about the Fingolimod Pregnancy Exposure Registry
- Patient reminder card

The physician's checklist shall contain the following key messages:

- The need to monitor patient heart rate after the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago) for signs and symptoms of bradycardia during at least 6 hours.
- GILENYA should not be co-administered to patients receiving Class IA or Class III anti-arrhythmic medicines.
- Caution when using GILENYA in patients with a cardiac disease or those taking medicines concomitantly known to decrease heart rate.
- GILENYA reduces peripheral blood lymphocyte counts. There is the need to check prior to initiation and to monitor during treatment with GILENYA the patient's peripheral lymphocyte count (CBC).
- GILENYA may increase the risk of infections. There is the need to delay treatment initiation in patients with severe active infection until resolution. Suspension of treatment during serious infections should be considered. Concomitant treatment with immunosuppressants or immune modulating medicines should be avoided.
- The need to instruct patients to immediately report signs and symptoms of infections to their prescriber during and up to two months after treatment with GILENYA.
- Specific recommendations regarding vaccination for patients initiating or currently on GILENYA treatment.
- The need for a full ophthalmologic assessment 3-4 months after starting GILENYA therapy for the early detection of visual impairment due to drug-induced macular edema.
- The need for ophthalmologic assessment prior to initiation and during treatment with GILENYA in patients with diabetes mellitus or with a history of uveitis.

- The teratogenic risk of GILENYA: the importance of avoiding pregnancy when undergoing treatment with GILENYA and the need to confirm a negative pregnancy test result prior to treatment initiation.
- The need to advise women of child-bearing potential on the serious risk to a fetus and to practice effective contraception during and for at least two months following discontinuation of treatment with GILENYA.
- The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3 and 6 during GILENYA therapy and periodically thereafter.
- The need to provide patients with the patient reminder card.

The patient reminder card shall contain the following key messages:

- The need to monitor patient heart rate after the first dose of GILENYA (or when the last dose of GILENYA has been administered more than two weeks ago) for signs and symptoms of bradycardia during at least 6 hours.
- The need to immediately report signs and symptoms of infections to the prescriber during and up to two months after treatment with GILENYA.
- The need to immediately report signs of visual impairment to the prescriber during and up to two months after treatment with GILENYA.
- Women with childbearing potential must ensure effective contraception during and for at least two months following discontinuation of treatment with GILENYA. Any (intended or unintended) pregnancy during and two months following discontinuation of treatment with GILENYA must immediately be reported to the prescriber: where available contact details for teratogenic information services should be provided.
- The need for a liver function test prior to treatment initiation and for liver function monitoring at months 1, 3 and 6 during GILENYA therapy and periodically thereafter.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Gilenya as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups:

- Patients with high disease activity despite treatment with a beta-interferon.
These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadolinium-enhancing lesion.
A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year,

or

- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

was favourable and therefore recommended the granting of the marketing authorisation.