EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/529295/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

AUBAGIO

International non-proprietary name: TERIFLUNOMIDE

Procedure No. EMEA/H/C/002514/0000

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

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List of abbreviations

4-TFMA: 4-trifluoro-methylaniline
A782068: 2-cyano-3-hydroxy-pent -2-enoic acid-(4'-trifluoromethylphenyl)-amide
A813226: 2-cyano-ethanoic acid-(4'-trifluoromethyl-phenyl)-amide
AE: adverse event
AESI: adverse events of special interest
ALT: alanine aminotransferase
ARR: annualised relapse rate
AST: aspartate aminotransferase
BCRP: breast cancer resistant protein
BCS: Biopharmaceutics Classification System
BfArM: Federal Institute for Drugs and Medical Devices
BOD: burden of disease
BP: blood pressure
CHMP: Committee for Medicinal Products for Human Use
CI: confidence interval
CIS: clinically isolated syndrome
CMV: cytomegalovirus
CT: computed tomography
CTD: common technical document
CYP: cytochrome P450
DMT: disease-modifying therapies
EAE: experimental autoimmune encephalomyelitis
EDSS: expanded disability status scale
EMA: European Medicines Agency
EQ-5D: EuroQoL
FIS: Fatigue Impact Scale
FS: functional score
GA: glatiramer acetate
Gd: gadolinium
HLT: high level term
IC50: half maximum inhibitory concentration
IFN: interferon
IgG: immunoglobin G
IgM: immunoglobin M
ILD: interstitial lung disease
IV: intravenous
IVIVC: in vitro/in vivo correlation
LS: least-squares
MAA: Marketing Authorisation Application
MEB: Medicines Evaluation Board
MedDRA: Medical Dictionary for Regulatory Activities
MRI: magnetic resonance imaging
MS: multiple sclerosis
MSFC: multiple sclerosis functional composite

NCT: nerve-conduction test
NOAEL: no-observable-adverse-effect level
OAT: organic anion transporter
OATP: organic anion transporting polypeptide
PCSA: potentially clinically significant abnormality
PDCO: Paediatric Development Committee
PFT: pulmonary function testing
PIP: paediatric investigation plan
PML: progressive multifocal leukoencephalopathy
PPMS: primary progressive multiple sclerosis
PRMS: progressive-relapsing multiple sclerosis
PT: preferred term
QD: once a day
QOL: quality of life
RA: rheumatoid arthritis
RBC: red blood cell
RRMS: relapsing-remitting multiple sclerosis
SAE: serious adverse event
SAWP: Scientific Advice Working Party
SD: standard deviation
SF-36: Short Form (36) Health Survey
SMQ: standardised MedDRA query
SOC: system organ class
SPMS: secondary progressive multiple sclerosis
TEAE: treatment-emergent adverse event
TSQM: Treatment Satisfaction Questionnaire for Medication
ULN: upper limit of normal
WBC: white blood cell
WPAI: work productivity and activities impairment

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sanofi-Aventis submitted on 1 February 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for AUBAGIO, 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 17 February 2011.

The applicant applied for the following indication: treatment of adult patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of relapses and to delay the accumulation of physical 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/or 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/209/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/209/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Applicant's request for consideration

New active Substance status

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 18 November 2001 and 22 July 2010. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: USA, Brazil and Australia.

1.2. Manufacturers

Manufacturer responsible for batch release

Sanofi Winthrop Industrie
56 route de Choisy au Bac, COMPIEGNE, 60205, France

1.3. Steps taken for the assessment of the product

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

Rapporteur: Martina Weise

Co-Rapporteur: Barbara van Zwieten-Boot

- The application was received by the EMA on 1 February 2012.
- The procedure started on 22 February 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 May 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2012.
- During the meeting on 18-21 June 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 June 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 12 September 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 October 2012.
- During the CHMP meeting on 12-15 November 2012, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and/or in an oral explanation by the applicant.
- During the CHMP meeting on 10-13 December 2012, the CHMP agreed on a List of Questions to SAG Neurology.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 January 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 8 February 2013.

- During a meeting of the SAG Neurology on 14 February 2013 experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 18-21 February 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP and a 2nd List of Outstanding issues was adopted.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 28 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 19 March 2013 (Annex 10).
- During the meeting on 18-21 March 2013, 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 AUBAGIO.

1.4. Steps taken for the re-examination procedure

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

Rapporteur: Bengt Ljungberg

Co-Rapporteur: Arantxa Sancho Lopez

- The applicant submitted written notice to the EMA on 2 April 2013 to request a re-examination of Aubagio CHMP opinion of 21 March 2013.
- During its meeting on 22-25 April 2013, the CHMP appointed Bengt Ljungberg as Rapporteur and Arantxa Sancho Lopez as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 29 April 2013. The re-examination procedure started on 30 April 2013.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 27 May 2013. The Co-Rapporteur's Assessment Report was circulated to all CHMP members on 27 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 12 June 2013.
- During the CHMP meeting on 25 June 2013, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 27 June 2013, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that teriflunomide is qualified as a new active substance as claimed by the applicant.

2. Scientific discussion

2.1. Introduction

Multiple sclerosis is a chronic, progressive, autoimmune, debilitating neurodegenerative disorder

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

Multiple sclerosis is an immune-mediated disease involving both cellular and humoral components of the immune system. The generally accepted view of the immunopathogenesis of MS in humans implicates non-anergic myelin-specific auto-reactive T-cells activated in the peripheral immune system via interplay between environmental triggers and genetic susceptibility. After activation, T-cells acquire the potential to cross the blood-brain barrier resulting in central nervous system lesions, which can be assessed by various magnetic resonance imaging (MRI) techniques.

Clinically, MS presents with neurologic deficits with differing localisations presenting at different times. Diagnosis is made by clinical features and supportive MRI with the evaluation of volumetric abnormalities. Clinical onset most frequently accompanies an acute or sub-acute episode of neurological disturbance, known as a clinically isolated syndrome (CIS). Patients with defined MS can be classified into four essential groups depending on the nature of the disease course: relapsing-remitting (RRMS), secondary progressive (SPMS), progressive-relapsing (PRMS) or primary progressive (PPMS). Relapses may occur in RRMS, PRMS or SPMS, and the term “relapsing MS” is used to encompass all forms involving relapses. Relapsing forms of MS are the most frequent clinical presentation of the disease.

Teriflunomide is the predominant active metabolite of leflunomide (Arava), which has been marketed as a disease-modifying therapy for rheumatoid arthritis in the United States since September 1998, in Europe since 1999, and for the treatment of active RA in adults in Canada since April 2000.

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence teriflunomide reduces the proliferation of dividing cells that need de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

2.2. Quality aspects

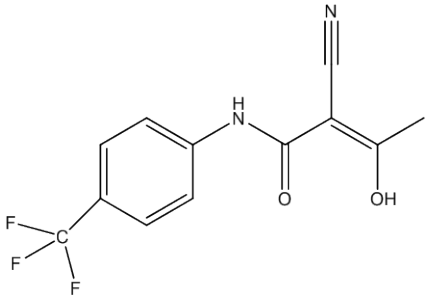
2.2.1. Introduction

The finished product is presented as immediate release film-coated tablets containing 14 mg of teriflunomide as active substance. The composition is described in section 6.1. of the SmPC.

The medicinal product is packed in aluminium-aluminium blisters inserted in wallets and packed in cartons.

2.2.2. Active Substance

The chemical name of teriflunomide is (Z)-2-Cyano-3-hydroxy-but-2-enoic acid-(4-trifluoromethylphenyl) amide with molecular formula $C_{12}H_9F_3N_2O_2$ and relative molecular mass 270.2 g/mol. Its structural formula is shown below:



Teriflunomide appears as a white to almost white, odourless, non-hygroscopic powder. It is a biopharmaceutical classification system (BCS) Class 2 compound, which is practically insoluble in water; sparingly soluble in acetone; and slightly soluble in ethanol, acetonitrile and methylene chloride.

Teriflunomide contains no asymmetric centres, therefore no enantiomers are possible.

The presence of polymorphs of teriflunomide has been evaluated using DSC and X-ray powder diffraction and recrystallization from different solvents and only one polymorphic form has been observed. In addition, single crystal X-ray diffraction analysis studies have demonstrated that teriflunomide in the solid state (crystalline phase) is only the Z-isomer.

The structure of teriflunomide has been elucidated by elemental analysis (C, H and N), spectroscopic analyses (IR, UV, ^{1}H-NMR, ^{13}C-NMR,^{15}N-NMR, ^{19}F-NMR and mass spectrometry) and single X-ray diffraction analysis. All data are consistent with the proposed structure.

Manufacture

At the time of CHMP opinion the active substance teriflunomide used for Aubagio is manufactured at two manufacturing sites in accordance with the current Good Manufacturing Practices. QP declarations issued by the Qualified Person have been provided.

Teriflunomide is synthesized in three main steps starting from 4-(Trifluoromethyl) aniline, cyanoacetic acid and acetic anhydride. Teriflunomide is then crystallized and jet-milled.

Detailed information on the manufacturing process, control of critical reaction temperatures and reaction times has been provided by the applicant. The specifications and control methods for starting materials, reagents and intermediate products have been presented. Potential impurities arising from the starting materials, reagents, the route of synthesis or potential degradation products have been adequately discussed.

The packaging of teriflunomide drug substance consists of double low-density polyethylene (LDPE) bags placed inside fibre drums or cardboard boxes. The LDPE bags used as primary packaging are of food grade quality and comply with Ph. Eur. and European Directive 2002/72/EC.

Specification

As no Eur. Ph. monograph exists for teriflunomide, in-house specifications have been set for the active substance, in accordance with the principles of the relevant ICH guidelines.

The active substance specification includes appropriate tests for appearance (visual), identification (HPLC, IR), assay (HPLC), impurities (HPLC), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), residual solvents (GC), water content (KF) and microbial contamination (Ph. Eur).

The control tests and specifications of the drug substance have been adequately justified. The influence of the particle size distribution on bioavailability and content uniformity has been studied. Data have been provided to demonstrate that jet-milling used as final manufacturing step of the drug substance ensures adequate and reproducible particles sizes and therefore, it is acceptable to omit particle size distribution from the drug substance specification.

The analytical methods used to test the drug substance have been properly described and validated in accordance with the ICH guidelines.

Batch analysis data have been provided on six pilot scale batches and fourteen production scale batches. All results are within the proposed specification limits and consistent from batch to batch.

Stability

Stability studies have been carried out on three production scale batches of the active substance stored in LDPE bags representative of the primary packaging intended for commercial use.

The parameters tested during stabilities studies were appearance, identification (XRPD), assay, related substances, water content, microbial contamination, particle size and relative humidity (water activity).

Long term studies for up to 24 months at 25°C±2°C/60%±5% RH**,** and accelerated studies for up to 6 months at 40°C±2°C/75%±5% RH have shown no significant degradation and all the results remained within the specification.

In addition, forced degradation studies on teriflunomide drug substance in solid state and in solution have been performed by treatment with heat, humidity, oxidizing, acidic or alkaline conditions. The data obtained in stress studies show that teriflunomide in solid state is very stable, while in solution under neutral, acid or oxidative conditions degradation is observed.

A photostability study following ICH Q1B guideline has been performed on three production scale batches showing that teriflunomide is not sensitive to light.

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

2.2.3. Finished Medicinal Product

The proposed drug product is a pale blue to pastel blue, pentagonal immediate release film-coated tablet containing 14 mg of active substance.

Pharmaceutical Development

Since teriflunomide is intended for long-term treatment of multiple sclerosis in adult patient population, which is a chronic disease, the aim of the pharmaceutical development was to develop easy to swallow immediate-release film-coated tablet formulation containing teriflunomide as active substance.

The development of the formulation has been adequately described. Initial investigations were focused on the selection of the appropriate dosage strength.

The development studies of the tablet focused on physicochemical properties of the drug substance, which were identified as potentially having a higher impact on drug product performance. These properties were particle size, water content, stability and purity.

Particle size was initially identified as potentially impacting dissolution and thus bioavailability because teriflunomide is a BCS Class 2 active substance (high permeability, low solubility). To investigate whether particle size had an impact on bioavailability, a bioequivalence study with formulations manufactured with milled versus unmilled, sieved drug was performed. This study demonstrated that the particle size of the drug substance (within the range studied) does not have an impact on bioavailability. In addition, it was demonstrated that particle size has no impact on content uniformity. Nonetheless, as described in section 2.2.2., teriflunomide particle size is controlled on the last jet-milling step of the manufacturing process of the active substance.

The non-hygroscopic nature of teriflunomide and the use of the aluminium blister ensured that the risk of hydrolytic formation of degradation products and the risk of microbial growth would be minimal.

With regards to stability and purity, batch analysis results have been submitted demonstrating that these parameters remain within the approved specification during the re-test period.

The choice of excipients has been justified based on results obtained from drug substance/excipient compatibility studies. No incompatibility issues were identified between teriflunomide and the excipients selected.

Most of the formulations used in clinical studies have essentially the same composition and were manufactured with similar manufacturing process as of the 14 mg commercial product.

However, during formulation development one major change was performed. Colloidal anhydrous silica was removed from the tablet core formulation, as it was shown that it had an effect on the stability of teriflunomide within the drug product, promoting the formation of one of the degradation products. In addition, the film-coating thickness was slightly increased. Since colloidal anhydrous silica may affect the dissolution, and thus absorption and efficacy, a bioequivalence study was conducted. This study demonstrated the bioequivalence of the formulations, and therefore the new formulation was introduced into the on-going phase II clinical program.

Other clinical batches differed in colorant composition and had different shape and embossment. Although, these were small differences not likely to affect dissolution, comparative dissolution studies supported their equivalence to the commercial formulation.

The excipients used in the formulation are well known and commonly used in the pharmaceutical industry. All excipients comply with the requirements of the current Ph. Eur. monographs except for the colorant indigo carmin aluminium lake (E132) which complies with EU Directive 2008/128/EC.

Adventitious agents

A declaration has been submitted to confirm that magnesium stearate is of vegetable origin.

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

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

Manufacture of the product

The manufacturing process for teriflunomide commercial film-coated tablets is a standard wet granulation process involving conventional mixing, fluid–bed granulation, drying, sieving, mixing and lubrication, tableting and film-coating. A detailed manufacturing description and flow scheme have been provided.

All critical process parameters have been identified and are controlled by appropriate in-process controls.

The film-coated tablets are packaged into thermoformed aluminium/aluminium blister packs, which are then introduced into wallet kits and packaged into carton boxes. Confirmation is provided that the primary packaging components of the packaging materials in contact with the drug product comply with Directive 2002/72/EEC (and amendments) and Ph. Eur. monograph 3.1.11.

The manufacturing process has been validated during development by a number of studies for the major steps of the manufacturing process and has been demonstrated to be capable and to be able to reproducibly produce finished product of the intended quality. Process validation on the first three production scale batches will be performed post opinion.

Product specification

The finished product release specifications include appropriate tests for appearance (visual), identification (HPLC, UV), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur.), uniformity of dosage units (HPLC), water content (KF) and microbial contamination (Ph. Eur.). The proposed specifications include all required tests relevant for this dosage form.

All tests included in the specification have been satisfactorily described and validated. Appropriate data have been presented to justify the release specifications for each quality characteristic that is controlled.

The batch analysis data on three pilot scale batches manufactured during development and three production scale batches of the commercial formulation show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation.

The analytical methods have been adequately described and validated in accordance with ICH guidelines, and have shown to be stability-indicating.

Stability of the product

Stability studies have been carried out under long term (30°C±2°C/65%±5% RH) and accelerated (40°C±2°C/60%±5% RH) storage conditions according to ICH requirements, on three production scale batches stored in the primary packaging as proposed for marketing. Up to 24 months long-term and up to 6 months accelerated stability data have been provided.

Samples were tested for appearance (visual), assay (HPLC), degradation products (HPLC), dissolution (Ph.Eur.), water content (KF), microbial purity (Ph. Eur.) and relative humidity (water activity).

No significant tendencies in any of the parameters tested have been observed. All stability results presented remained within the proposed specifications during 24 months of storage.

In addition, a photostability study has been performed on one production scale batch as defined in the ICH Q1B guideline. No changes regarding appearance, assay, individual impurities and total impurities have been observed, indicating that the film-coated tablets are not sensitive to light.

The stability results presented are satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The excipients are commonly used in this type of formulation and comply with Ph. Eur. and/or the European Food Colors Directive. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions 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.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Teriflunomide is a selective, non-competitive and reversible inhibitor of mitochondrial dihydroorotate dehydrogenase (DHO-DH), which blocks the *de novo* synthesis of pyrimidines. As a consequence, the activation and proliferation of rapidly dividing T and B lymphocytes is arrested, which is hypothesised to interfere with MS manifestation.

Teriflunomide is the active main metabolite of leflunomide. The non-clinical development of teriflunomide was originally guided by experience gained with the parent compound leflunomide in

terms of study designs and anticipated target organ toxicities. Nevertheless, an independent self-standing development of teriflunomide was later pursued non-clinically, because of the intended use of teriflunomide as treatment in multiple sclerosis as opposed to the different indication of leflunomide.

Pivotal toxicology studies were performed in compliance with GLP. Apart from the *in vivo* evaluation of cardiovascular function in dogs, all safety pharmacology studies of the core battery also adhered to GLP regulations. Other safety pharmacological investigations were conducted prior to implementation of ICH guidelines in accordance with internal procedures of the applicant and did not follow current GLP standards, but were adequately reported to support the safety pharmacological profile of the active substance.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Anti-proliferative effects of teriflunomide on lymphocytes were analysed *in vitro* using mouse splenic lymphocytes, rat splenocytes and human peripheral blood mononuclear cells (PBMC). Inhibition of proliferation by teriflunomide (1-100 µM) depended on species, selected cell type/cell line, mitogenic stimulus and other experimental conditions. In assays conducted during leflunomide and teriflunomide development, animal cells appeared to be more sensitive to teriflunomide activity than human cells. The strongest interference with lymphocyte proliferation was determined in rat splenocytes (145-fold higher than human PBMCs). A 4- and 8-fold higher potency was found in mouse splenocytes and in whole blood samples of dogs, respectively. No significant influences on cellular viability were noted.

Teriflunomide was reported earlier to inhibit DNA and RNA synthesis and the expression of nuclear antigens. Reversal of this effect by addition of uridine or cytidine to the lymphocyte cultures indicated that teriflunomide interferes with *de novo* pyrimidine synthesis. The high affinity interaction of teriflunomide with DHO-DH including its species-specificity was also previously demonstrated.

Teriflunomide (0.004 - 10 nM) did not reveal more than 50 % inhibition when investigated against a battery of over 100 receptors and ion channels *in vitro*, which were either prepared from relevant tissues or expressed in recombinant cells. Inhibitory effects were only noted on cyclooxygenase-1 (-37 %) and purine receptors (-44 %). Moreover, teriflunomide weakly displaced ligand binding to serotonergic 5-HT_{1D}-receptors (-22 %), progesterone receptors and thyroid hormone receptors (-21 %) and slightly inhibited nitric oxide synthase (-24 %).

The primary pharmacodynamic activities of teriflunomide were investigated *in vivo* in rodent models (mouse and rats) of experimental autoimmune encephalitis (EAE). In these studies, effects of teriflunomide on neurological deficits, neuronal function, spinal cord pathologies and lymphocyte populations were assessed testing different prophylactic and therapeutic treatment regimens; a delayed onset and diminished severity of the disease were observed.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies were not performed in animals.

Safety pharmacology programme

Safety pharmacological evaluations of the CNS function revealed no influence of teriflunomide on general behaviour, body temperature and pro- or anticonvulsant liability. In rats, a significantly reduced locomotor activity was noted at oral doses ≥ 10 mg/kg; this observation was not made in a comparable study in mice. Of note, impaired motility was also evident in single dose toxicity studies testing p.o. and i.p. administrations in mice and rats. In repeated dose toxicity with i.v. dosing over 1 month in rats and 3 months oral administration in dogs, stilted gait and ataxia were observed in some animals, respectively.

In safety pharmacology studies of cardiovascular function, a slight inhibition of hERG currents at ≤ 100 µM teriflunomide was seen, which coincided with the shortening of the action potential duration in rabbit Purkinje fibres at 100 µM. Conversely, administration of 300 µM teriflunomide was observed to lead to weak facilitation of hERG-mediated repolarisation *in vitro*. No influence on cardiac conduction was apparent in safety pharmacology and toxicology studies in dogs or during thorough clinical evaluation of the teriflunomide effects on the QT interval.

Teriflunomide did not affect respiratory function in guinea pigs at the highest dose of 10 mg/kg p.o.

In a supplementary study in rats, dose-dependently increased diuresis and excretion of electrolytes were observed at oral teriflunomide doses of ≥ 3 mg/kg.

Pharmacodynamic drug interactions

Pharmacodynamic drug interactions of teriflunomide were not studied in the non-clinical setting.

2.3.3. Pharmacokinetics

The pharmacokinetic characteristics after single p.o. or i.v. administration of teriflunomide were evaluated in male mice, rats, rabbits and dogs using formulations that were subsequently also analysed in toxicological investigations. These results were complemented with toxicokinetic data, which document teriflunomide pharmacokinetics following repeated dosing. Protein binding properties of teriflunomide were investigated *in vitro*.

Teriflunomide was maximally absorbed in mice, rats, rabbits and dogs within 1 h, 6 h, 4-8 h or 1-4 h post dose culminating in levels of 36 µg/ml, 48.4 µg/ml, 25.9 µg/ml or 58.9 µg/ml, respectively. Teriflunomide showed almost 100% oral bioavailability in mice, rats and dogs, whereas it showed clearly lower levels (~66 %) in rabbits. Extensive protein binding between 96 and more than 99 % was determined in animals and man.

Following repeated oral administration of teriflunomide to mice and rats for up to 3 and 6 months, respectively, systemic exposure generally increased linearly with dose. The exposure increased in a greater than dose-proportional manner in dogs after repeated oral administration for up to 12 months and in pregnant rabbits treated orally for up to 7 days. Accumulation of teriflunomide was noted in all species after repeated doses reaching steady-state after approximately 1 month in mice and dogs and after 3 months in rats. There were no gender differences across test species.

Teriflunomide demonstrated rapid distribution after single dosing in rats. Highest concentrations were identified in skin, gastrointestinal tract, liver and kidney, while the lowest levels were determined in brain, spinal cord and eyes. The brain or spinal cord to blood ratio was ≤ 2 % and ≤ 5 %, respectively, following experimental induction of EAE indicating limited penetration of the active substance into the

CNS. There was no particular enrichment of teriflunomide in any region of the brain and no differences between pigmented and non-pigmented rat strains were observed.

The calculated volume of distribution (V_{ss} = 0.11 l/kg) was based on an assumption that drug elimination occurs solely from the central compartment. This could not be confirmed for teriflunomide, leading to an underestimation of the true V_{ss}.

Metabolism of teriflunomide involves oxidation, hydrolysis, and glucuronide and sulphate conjugation reactions. 4-trifluoro-methylaniline (4-TFMA) oxanilic acid was the main metabolite in all species representing about 7 %, 43 %, 5 %, 38 % and 18 % of the oral dose in mouse, rat, rabbit, dog and human, respectively. Apart from this metabolite, significant levels of the sulphate-conjugate of mono-hydroxylated teriflunomide were determined in rabbits and dogs. Moreover, mono-hydroxylated derivatives of teriflunomide and 4-TFMA sulphate were additionally found in dogs, whereas 4-TFMA 2-hydroxy malonamic acid was measured in rats. Among minor metabolites, a significant level of the metabolite A813226 was determined in rats. 4-TFMA concentrations of ~3 ng/ml were detected after oral administration in mice, rats and dogs and at a concentration of ≤ 0.626 ng/ml in rabbits. Of note, all human metabolites were identified in at least one animal species.

Independent of the administration route, teriflunomide was found to be almost completely excreted in all species, within 14 days in mice, rats and rabbits and within 28 days in dogs. This indicated drug accumulation, which was also noted after multiple administrations in these animal species. Increased drug persistence was further corroborated by a low plasma clearance in all species and a terminal half-life of 18-37 h in mice, rats and dogs. The terminal half-life was substantially shorter in rabbits (~4-5 h). Following oral administration in mass-balance studies, the major radioactivity was predominantly eliminated by faeces in mice (> 70 %) and by urine in rabbits (> 62 %), rats and dogs (51 %, respectively). Unchanged teriflunomide accounted for the main part of radioactivity in faeces of mice (> 65 %, p.o.), rats (22 %, p.o.) and dogs (26 %, p.o.) as well as in urine of rabbits (~20 %, p.o.).

A significant amount of teriflunomide was found to be excreted into milk (> 23%) in lactating rats.

2.3.4. Toxicology

Single dose toxicity

In single dose toxicity studies in mice and rats, similar clinical signs and mortality rates were observed after administering teriflunomide orally (p.o.) or via the intraperitoneal route (i.p.). In both species, teriflunomide doses of ≥ 200 mg/kg p.o. and ≥ 100 mg/kg i.p. were lethal. Clinical effects comprised impaired motility and various behavioural abnormalities, which were also observed in CNS safety pharmacology and repeated dose toxicity studies. Effects on the gastrointestinal mucosa were seen in rats at doses ≥ 200 mg/kg p.o. Signs of liver toxicity, presented as swollen liver lobes or liver deposits, were observed at doses ≥ 100 mg/kg i.p. In addition, faecal discolouration was seen in mice and diarrhoea in both species.

Repeat dose toxicity

Teriflunomide was investigated in repeat dose toxicity studies up to three months in mice, six months in rats and twelve months in dogs (major findings observed in pivotal studies are listed in table 1).

Table 1 Major findings in the repeat dose toxicity studies

Study No./ GLP	**Species; No., sex/ group**	**Duration/ route**	**Daily dose [mg/ kg]**	**NOEL/ NOAEL [mg/kg/ day]**	**Major findings**
2004-0511 **GLP**	CD-1 mice; 10 M/F	3 months; p.o.	0, 5, 25, 50, 75	nd	≥ 5 mg/kg: lymphoid necrosis/atrophy in spleen 25 mg/kg: Mortality ↑ (2 M/3F); hyporeactivity, scabby wounds and/or pale skin; RBC ↓; MCHC ↓; haemoglobin ↓; haematocrit ↓; reticulocytes ↑; extramedullary haematopoiesis in spleen ↑; K^+ ↓ (M/F) 25, 50 mg/kg: BM haematopoietic cells ↓; thymus + lymph nodes ↓; intestinal glandular epithelia ↓; hepatocellular hypertrophy ↑; testicular tubules ↓; ovary weight ↓ ≥ 50 mg/kg: Mortality ↑ (all animals)
2003-1492 **GLP**	SD rats; 15 M/F	6 months; p.o.	0, 0.3, 1.5/9[a], 3, 6	0.3 (NOAEL)	≥ 0.3 mg/kg: globulin, total protein ↓ (M/F); albumin/globulin ratio ↑ (M/F) ≥ 1.5 mg/kg: BW ↓ (M/F); MCH/MCHC ↓ (M/F) ≥ 3 mg/kg: thymus ↓ (M/F); germinal centres in lymphoid tissue ↓ (M/F); plasma cells in submandibular lymph nodes ↓ (M/F); haemosiderin in spleen ↑ (M/F); K^+ ↓ (F); creatinine ↓ (F) ≥ 6 mg/kg: haemoglobin ↓ (M/F); reticulocytes ↑ (M/F) 9 mg/kg: RBC ↓ (M/F); haematocrit ↓ (M/F) 9 mg/kg, AE in 2 M: Mortality; intestinal mucosa ↓; haematopoietic cells in BM ↓; activity ↓; lack of grooming; ptosis; dermal atonia; pallor; defecation ↓; body temperature ↓; discharge around the eyes, nose, mouth or forelimbs; BW ↓
2003-	Beagle	12 months	0, 0.2,	0.2	≥ 0.8 mg/kg: Liver weight ↑ (M/F);

1491 **GLP**	dogs; 4 M/F	; p.o.	0.8, 2/4[b]	(NOEL)	pancreatic acinar cells ↓; splenic haemosiderin (M/F) <u>4 mg/kg:</u> RBC/haemoglobin/ haematocrit ↓ (M/F); methemoglobin ↑ (M); MCHC ↓ (M); lymphocyte/basophil ↓; protein/globulin ↓ (M/F); albumin ↓ (F); TLI ↓ (M/F) <u>4 mg/kg, AE in 1 F:</u> Mortality; inflammatory changes (larynx/pharynx, retropharyngeal lymph nodes); thymus weight ↓ mesenteric lymph nodes ↓; anaemia; platelets ↓; lymphocytes/monocytes ↓; albumin ↓; cholesterol/triglycerides ↑; BM hypercellularity; fever; lethargy; red mucoid faeces; diarrhoea; discharge on the left eye; reddened ears and gums; salivation ↑, BW ↓

M = Male; F = Female; ALT = Alanine transaminase; AST = Aspartate transaminase; AP = Alkaline phosphatase; BM = Bone marrow; MCV = Mean corpuscular volume; MCHC = Mean corpuscular haemoglobin concentration; nd = not determined; RBC = Red blood cells; TLI = Trypsin-like immunoreactivity; ↑ = increase; ↓ = decrease

In addition, 3 month repeated dose oral toxicity studies and multiple intravenous injections for one month were analysed in rats and dogs. Systemic teriflunomide exposure in these investigations increased dose-dependently without significant differences between genders. Accumulation of teriflunomide was noted in all species. Overall, lower exposure levels were achieved in toxicity investigations and no safety margins could be established with regard to human therapeutic concentrations indicating a generally higher sensitivity of animals compared to humans.

The teriflunomide metabolites 4-TFMA and A813226 were toxicologically qualified in single and multiple dose toxicology studies in mice and rats and in genotoxicity studies *in vitro* and *in vivo*. Similar to toxicity results obtained with teriflunomide, signs of increased turnover of red blood cells and oxidative damage (decreased levels of erythrocytes, haematocrit and haemoglobin with concomitantly increased reticulocyte counts and methaemoglobin values as well as Heinz and Howell-Jolly body formation) were apparent in these investigations. Furthermore, hemosiderosis and extramedullar haematopoiesis were detected as secondary effects. Accordingly, macroscopic findings in premature descendents that had received high doses of 4-TFMA or A813226 in single dose toxicity studies comprised discoloured lungs and livers indicative of haemorrhages.

Genotoxicity

Teriflunomide was tested negative for gene mutations in the Ames test and in mammalian cells *in vitro*. It was also negative in three *in vivo* tests: *in vivo* bone marrow micronucleus test in mice, *in vivo* chromosome aberration test in Chinese hamsters and 14-day repeated dose bone marrow chromosome aberration test in rats. Positive results were obtained only in the *in vitro* chromosome aberration test in human lymphocytes.

The metabolite 4-TFMA was positive in one bacterial strain in the Ames test with sensitivity for base substitutions, in the HPRT assay in V79 cells and also in a chromosomal aberration assay in V79 cells. Although 4-TFMA demonstrated a mutagenic and clastogenic potential *in vitro*, it did not cause

clastogenicity *in vivo* up to lethal doses or induce DNA synthesis *in vivo* in rat liver up to MTD with oral administration. The metabolite A813226 was intensively tested for its mutagenic potential in a variety of *in vitro* and in *vivo* assays with additional *in vitro* mechanistic investigations for its capacity to inhibit DHO-DH and was devoid of any biologically relevant genotoxic potential. The impurity A782068 was tested in the Ames test with negative results for mutagenic potential.

Carcinogenicity

Carcinogenicity potential of teriflunomide was tested in 2-year studies in mice and rats after oral administration of doses up to 12 mg/kg/d in mice and 4 mg/kg/day in rats. Survival in high dose mice was slightly reduced and dosing of males was ceased in that group at week 95 as survival fell below 20/sex. The main reasons were ulcer and inflammation of skin and gastrointestinal tract. Effects such as atrophy of thymus were observed in mid and high dose males. Survival was also reduced in rats and treatment of the high dose male group was ceased at week 92 because of mortality. The major non-neoplastic effects observed in rat were bone marrow hypocellularity and decrease in splenic lymphocytes. There were some slight but not significant increases in adenomas in treated rats compared to controls. Pituitary gland adenomas in male rats were slightly increased, but numbers were still within historical control ranges and statistical significance was not consistent among all control groups. This was also the case for C-cell adenoma in thyroid gland in females.

No treatment related neoplastic effects were observed in either of the species.

Reproduction Toxicity

The reproductive and developmental toxicity of teriflunomide was evaluated in fertility and embryo-foetal development study in rats, embryo-foetal development studies in rats and rabbits and a pre- and post-natal development study in rats. Furthermore, the toxicity of teriflunomide was investigated in an exploratory study in juvenile rats.

Teriflunomide did not adversely affect male and female fertility (mating performance, fertility and gestation parameters), although sperm counts were reduced. In the female fertility study, effects on early embryonic and foetal development were seen (total post implantation loss, increase in early resorption, decrease in number of foetuses per litter, decrease in foetal weights and increase of external malformations). The NOAELs for male and female fertility were established at 10 and 8.6 mg/kg/day, respectively.

In the embryo-foetal development studies in the rat and rabbit, embryotoxicity and teratogenicity of teriflunomide was observed. In pregnant rats and rabbits treated with teriflunomide during the period of organogenesis embryo-lethality and malformations occurred at doses >1 mg/kg/day. Maternal NOAELs were established at 1 mg/kg/day in the rat and rabbit. Findings of maternal toxicity in both species included decrease in maternal weight and food consumption.

In the exploratory prenatal and postnatal development study, exposure to teriflunomide from implantation to weaning did induce maternal toxicity (body weight loss) at 0.6 mg/kg/day. Compound-related clinical effects were observed in the F1 generation pups in the 0.6 mg/kg and 1 mg/kg group (malrotated digits, decreased ossification). In the pivotal study, no maternal toxicity occurred at the highest dose, i.e. 0.3 mg/kg/day. However, in the F1 offspring, teriflunomide induced malformations at 0.3 mg/kg/day, but did not affect survival, behaviour and reproductive performance. A no-teratogenic risk level for teriflunomide in humans was established at 0.25 µg/ml. This value was derived from the NOAEL exposure in the embryo-foetal toxicity study in rabbits (60 µg·h/ml) plus a 10-fold safety

margin. Thus, the AUC_{0-24} considered as posing a no-teratogenic risk for humans is 6 µg·h/ml, which corresponds to a trough concentration of 0.25 µg/ml (i.e. 6 µg·h/ml/24 h).

No specific toxicities of teriflunomide were observed in an exploratory study in juvenile rats.

Toxicokinetic data

Systemic exposure after oral teriflunomide administration for up to 12 months increased dose-dependently in mice, rats and dogs. In pregnant rabbits, exposure increased in a greater than dose-proportional manner while in pregnant rats, less than dose-proportionally increased exposure was determined. No gender differences were evident, but accumulation of teriflunomide was observed in all species upon repetitive dosing. Compared to teriflunomide, exposure to the 4-TFMA metabolite was considerably lower and amounted to less than 0.01 to 0.07 % of the $AUC_{0-24\ h}$ of teriflunomide in the different animal species.

Local Tolerance

Teriflunomide did not show any irritation or sensitisation potential when administered by i.v., i.a. or p.v. injections or after dermal or ocular applications in rabbits. The sensitisation properties of teriflunomide were studied in guinea pig and no evidence of sensitisation was observed. The phototoxic potential of teriflunomide was assessed in mouse 3T3 fibroblast cells *in vitro.* No phototoxicity was evident up to the maximally soluble concentration of 200 µg/ml.

2.3.5. Ecotoxicity / environmental risk assessment

The applicant submitted an environmental risk assessment of teriflunomide. With respect to the assessment of persistence, bioaccumulation potential and toxicity, results of two studies on the n-octanol/water partition coefficient were provided. Phase I and parts of phase II assessment were included in the ERA.

Table 2 Summary of main study results

Substance (EMEA / H / C / 2514 / Aubagio):Teriflunomide			
CAS-number (if available): 163451-81-8			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 U.S. FDA protocol 3.02	0.925 (pH 7) 2.66 (pH 3)	Potential PBT N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0058	µg/L	> 0.01 threshold N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Ready Biodegradability Test	OECD 301	1% degradation within 28 days	

2.3.6. Discussion on non-clinical aspects

The anti-proliferative potency of teriflunomide including its efficacy in well-established animal models of multiple sclerosis using both prophylactic and therapeutic administrations was reliably documented in the dossier. While the fact that teriflunomide was only developed in the multiple sclerosis indication did not justify not performing secondary pharmacology studies, the CHMP considered that the data of Arava indicate that leflunomide and thus presumably also its active metabolite teriflunomide, do not have any activity other than the primary mechanism of action as an immunomodulatory agent. Therefore, further secondary pharmacodynamics studies were not required.

No clinically relevant effects on CNS, cardiovascular or respiratory function were observed in the safety pharmacological investigations. The CHMP considered that the effects on motility seen in rats and mice constituted a peripheral rather than centrally-mediated effect, as only minor amounts of teriflunomide penetrated the blood/brain-barrier (brain/blood ratio was ≤ 2 %). With respect to cardiovascular safety, the CHMP considered that no influence on cardiac conduction was apparent in safety pharmacology and toxicology studies in dogs or during thorough clinical evaluation of the teriflunomide effects on the QT interval and hence, the *in vitro* findings were regarded to be without relevance for the intended clinical therapy. The CHMP noted that the increased diuresis observed in a supplementary study was in agreement with pollakiuria, which was frequently seen during clinical treatment and consequently included as a common adverse reaction in the Product Information.

Pharmacodynamic drug interaction studies were not performed in animals since they were not considered pertinent by the applicant for the evaluation of the pharmacological profile or the mechanism of action of teriflunomide. Considering the specific mechanism of action of teriflunomide and the confirmed absence of significant interaction with a panel of more than 100 receptors, this was agreed by the CHMP.

Teriflunomide showed consistently high oral bioavailability in mice, rats and dogs and revealed comparably extensive protein binding of more than 96 % in animals and man. The calculated volume of distribution was based on an assumption that drug elimination occurs solely from the central compartment. As this could not be confirmed for teriflunomide, the initial calculation led to an underestimation of the true Vss. Therefore, the CHMP considered that this warranted a reference within section 5.2 of the SmPC as follows: "... However, this *(the volume of distribution)* is most likely an underestimation since extensive organ distribution was observed in rats."

All human metabolites were identified in at least one animal species and teriflunomide was found to be predominantly excreted by faeces in mice, rats, dogs and humans. However, drug accumulation of teriflunomide was noted following multiple administrations. In view of the reproduction toxicity of the compound as further discussed below, the CHMP considered that women who are pregnant or are planning a pregnancy should be advised to perform a rapid elimination procedure as outlined in section 4.4 of the SmPC.

While it is not known whether teriflunomide is excreted in human milk, it was found to be excreted into milk in lactating rats. Considering the potential for serious adverse reactions in nursing infants, the CHMP was of the view that teriflunomide must not be administered during breast-feeding, which is reflected in sections 4.3 and 4.6 of the SmPC.

The CHMP acknowledged that animals in toxicity studies could not be exposed to equivalent or higher levels of teriflunomide compared to those achieved during clinical therapy and that for this reason, no safety margins could be established. Nevertheless, the toxicity findings predominantly reflected the anti-proliferative action of the compound on rapidly dividing cells, such as decreased erythropoiesis

and granulopoiesis in bone marrow, atrophy of lymphoid organs, epithelial degeneration in oral cavity and gastrointestinal tract as well as tubular degeneration in testes and atrophy of ovary. Consequent to the haematopoietic changes in bone marrow, anaemia, leukopenia, lymphocytopenia and thrombocytopenia developed, which presumably caused comorbidities like impaired coagulation, haemorrhages, hemosiderosis and bacterial infections. As compensatory mechanisms indicative of regeneration, increased haematopoiesis in bone marrow and in extramedullary regions of the spleen were found. The CHMP considered that the major non-clinical findings were adequately reflected in section 5.3 of the SmPC.

Furthermore, enlarged livers were identified in mice, rats and dogs with concomitant elevations of transaminases in some of these species. Mechanistic studies implied that teriflunomide exerts a low hepatotoxic potential by uncoupling the mitochondrial respiratory chain from ATP synthesis leading to increased formation of superoxide anions. The resulting oxidative damage might additionally account for the increased formation of Heinz bodies in red blood cells and incidence of methaemoglobinemia, which was also observed with the minor metabolites 4-TFMA and A813226. The CHMP considered plausible that the cytotoxic activity resides in the aniline moiety of teriflunomide and its metabolites, because oxidative damage including methaemoglobinemia is known from toxicity studies with aniline (e.g. Khan *et al*., 1997). Since transaminase elevations were also detected in clinical trials with teriflunomide, they were included in the risk management plan and patients with severe hepatic impairment are contraindicated as reflected in section 4.3 of the SmPC.

In the chronic toxicity study in dogs, minimal to moderate pancreatic acinar degeneration, necrosis of individual acinar cells, fibrosis and infiltration of inflammatory cells were detected at oral teriflunomide doses ≥ 0.8 mg/kg/day. These cellular alterations were accompanied by reduced TLI in the study animals, whereas other pancreatic enzyme levels remained unchanged. The pancreas toxicity could be evoked by the mitochondrial toxicity of teriflunomide via inhibition of mitochondrial DHO-DH leading to pyrimidine deficiency, mitochondrial DNA depletion and oxidative stress. Duct cells of the exocrine pancreas might be sensitive for mitochondrial toxicity, since these cells contain numerous mitochondria. The duct cells lining the ampulla of Vater might be even more sensitive to this toxic effect, since they are continuously exposed due to the enterohepatic circulation of teriflunomide. However, similar to dogs, pancreatic enzymes were found to be generally unaffected in clinical trials and there was no clear correlation between incidences of pancreatitis and teriflunomide administration. As dogs seem to be more responsive to teriflunomide treatment than humans or are at least of comparable sensitivity, the significance of the rather mild pancreatic toxicity findings in dogs is uncertain.

With respect to the minor teriflunomide metabolites 4-TFMA and A813226 the CHMP noted that the toxicity findings were similar to those related to teriflunomide. The CHMP considered that the impaired erythropoiesis might be explained by the anti-proliferative activities of the metabolites and could additionally reflect their ability to uncouple the mitochondrial respiratory chain from ATP synthesis resulting in oxidative haemolysis, which has been implicated in mechanistic studies with the parent compound. Despite the potential to contribute to the toxicities of teriflunomide, the general levels of A813226 (approximately 3 %) and 4-TFMA (0.01-0.07 % in the different species) were low in relation to exposure of the parent compound and therefore, these findings were considered of minor relevance for clinical practice.

The CHMP considered that teriflunomide was extensively tested for genotoxicity *in vitro* and *in vivo* as described in section 2.3.4. All tests were negative except for the *in vitro* chromosome aberration assay in human lymphocytes. The applicant proposed nucleotide imbalance through the pharmacological mechanism, DHO-DH inhibition, as the probable reason for the positive *in vitro* results. In order to

confirm the proposed mechanism, two repeated experiments with uridine supplementation at 500 and 1000 µM were performed in an *in vitro* study. Although the evidence provided for the proposed induction of nucleotide imbalance as the probable reason for the positive results in the *in vitro* clastogenicity test was not convincing (as significant effect of uridine supplementation on reduction of chromosome damage and cytotoxicity was not observed), the CHMP did not consider this *in vitro* finding relevant for the *in vivo* situation. In particular, the CHMP took into account that all *in vivo* tests were clearly negative up to the MTD providing sufficiently high exposure for teriflunomide and the metabolite 4-TFMA. Moreover, teriflunomide was negative for induction of gene mutation in bacteria and mammalian cells and therefore, it was considered not to be a direct DNA reactive substance. Overall, the CHMP was of the view that teriflunomide did not possess a clinically relevant genotoxic potential, which was further substantiated by the absence of treatment-related neoplastic effects in long-term studies in mice and rats.

The CHMP also considered that metabolites 4-TFMA and A813226 did not show clinically relevant genotoxic potential. While 4-TFMA caused mutagenicity and clastogenicity *in vitro*, the findings were negative in *in vivo* tests. The reason why effects *in vivo* were not observed up to lethal doses might be that concentrations positive *in vitro* are most probably not achievable *in vivo* below acute lethal doses in animal experiments. As 4-TFMA exposure is very low in humans, 4-TFMA was not considered to pose a biologically relevant mutagenic potential in humans.

The CHMP considered that the relevant genotoxicity findings were adequately reflected in section 5.3 of the SmPC.

The long term carcinogenicity studies with oral administration of teriflunomide in mice and rats did not reveal treatment-related neoplastic effects and the CHMP concluded that there was no relevant evidence of a carcinogenic potential of teriflunomide.

The CHMP considered that the lack of evidence of carcinogenicity was reflected adequately in section 5.3 of the SmPC.

In reproduction toxicity investigations, no adverse effects of teriflunomide on male and female fertility were apparent, although a reduced sperm count was evident. However, in the female fertility study teriflunomide did not reach the anticipated concentrations in half of the animals at study initiation. Nevertheless, the dosing schedule ensured that the other half of animals were sufficiently dosed and the maternal toxicities observed in the high dose group suggested appropriate dose selection in compliance with the ICH S5 recommendations.

The CHMP considered that teriflunomide was embryo-toxic and teratogenic in rats and rabbits at doses in the human therapeutic range. In the embryo-foetal toxicity studies in rats and rabbits, teriflunomide evoked embryo-lethality and malformations at daily doses > 1 mg/kg. In the pre- and postnatal development study, malformations were detected in the F1 generation at daily doses of 0.3 mg/kg. However, no effects on survival, behaviour and reproductive performance of the F1 generation were observed. The no-teratogenic risk level for teriflunomide in humans is proposed in the SmPC as 0.25 µg/ml. Applying an additional 10-fold safety factor, this corresponds to an $AUC_{0\text{-}24h}$ of 6 µg·h/ml/day. Consequently, women of childbearing potential must use effective contraception during teriflunomide therapy as reflected in sections 4.3 and 4.6 of the SmPC. Due to the aforementioned drug persistence, CHMP additionally advised that women of childbearing potential continue contraception even after a stop of teriflunomide dosing until plasma concentrations have reached 0.02 µg/ml, which can be accelerated by a rapid elimination procedure with cholestyramine or activated charcoal powder as reflected in section 4.6 of the SmPC.

In the male fertility study, teriflunomide did not affect the mean numbers of corpora lutea, implantation sites, post-implantation loss, mean number of live foetuses, foetal sex ratio and mean foetal weight. Moreover, no compound-related external malformations and/or anomalies were noted in any dose group. As the estimated female drug exposure across the semen is approximately 100-fold lower than the plasma exposure at the recommended daily oral dose of teriflunomide, the CHMP considered that the risk of male-mediated embryo-foetal toxicity is low. This information is reflected in sections 4.6 and 5.3 of the SmPC.

Local tolerance of teriflunomide was extensively investigated by the applicant. The results of these studies, showing no irritation, sensitisation or phototoxic potential, contributed to defining the safety profile of the compound, but were seen as of minor relevance in view of the intended oral therapy in patients.

In terms of the environmental risk, the CHMP considered that the n-octanol/water partition coefficient for teriflunomide was below 4.5 in two studies and hence agreed that there was no need for further screening of teriflunomide for persistence, bioaccumulation or toxicity and that the environmental risk assessment may be stopped in phase I.

2.3.7. Conclusion on the non-clinical aspects

The CHMP was of the opinion that, in view of the presumptively higher sensitivity of animals as compared to man, results of non-clinical safety studies have limitations to predict safety risks in humans. Nevertheless, the CHMP took into consideration that the adverse effects observed in the non-clinical program of teriflunomide were appropriately reflected in the Product Information and Risk Management Plan and considered that there were no non-clinical issues precluding granting of a marketing authorisation.

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 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.

- Table 3 Tabular overview of clinical studies

Study /Study period Location /Study goals	**Design / Duration/ population**	**Study arms N randomised/n-completed**	**Endpoints**
Study 2001 2001-2003 Canada / France Efficacy Monotherapy To assess the effect on MRI	RD MC (16) DB PC PA Duration 36 weeks RMS, ≥ 2 clinical relapses in past 3 years and at least 1 relapse in past year, EDSS ≤ 6, no concurrent treatment	Placebo n=61/57 2 tablets QD for 7 d then 1 tablet QD Teriflunomide 7 mg QD n=61/58 Starting 14 mg QD for 7 d Maintenance 7 mg QD	Primary average number of unique active lesions per MRI scan Secondary other MRI based variables

Study /Study period Location /Study goals	Design / Duration/ population	Study arms N randomised/n-completed	Endpoints
activity, clinical efficacy and safety of teriflunomide 7 and 14 mg	Age: Median (range) 40 (19-64) M/F: 27/91 Stratification according to baseline EDSS (≤3.5 versus >3.5) and center	Teriflunomide 14 mg QD n=57/45 Starting 28 mg QD for 7 d Maintenance 14 mg QD	
EFC6049 (TEMSO) 2004-2010 EU, American countries Efficacy/safety Monotherapy	RD MC (126) DB PC PA Duration 108 weeks RMS, ≥ 1 clinical relapse past year or at least 2 relapses in past 2 year, EDSS ≤ 5.5, no concurrent treatment Age: Median (range) 38 (18-55) M/F: 303/785 Baseline EDSS (≤3.5 versus >3.5) and center	Placebo 1 tablet QD n=363/259 Teriflunomide 7 mg QD n=356/274 Teriflunomide 14 mg QD n=258/263	Primary ARR Secondary Disability (EDSS) MRI derived variables: BOD/Gd+ lesions/ hypointense T1-lesion/T1 lesions per MRI scan FIS/ SF-Q/WPAI/ EuroQoL EQ-5D/ MSFC
EFC10891 (TENERE) 2009-2011 EU, Canada, Tunisia Efficacy/safety Monotherapy Superiority study	RD MC (53) SB AC PA Duration 48-114 weeks RMS, EDSS ≤ 5.5, no other concurrent treatment Age: Median (range) 35 (18-65) M/F: 105/219 Baseline EDSS (≤3.5 versus >3.5) and country	IFN-β 1a Up to 44 ug sc 3*week n=101/71 Teriflunomide 7 mg QD n=109/89 Teriflunomide 14 mg QD n=111/89	Primary Time to failure (either relapse or permanent study treatment discontinuation for any cause, whichever came first) Secondary ARR FIS/ TSQM
EFC10531 (TOWER) 2008-2012 EU, American Countries, Asia, Australia Efficacy/safety Monotherapy	RD MC DB PC Duration 48-152 weeks RMS, EDSS ≤ 5.5, no concurrent treatment Age: 18-55 Baseline (≤3.5 versus >3.5) and center	Placebo 1 tablet QD n=389/388 Teriflunomide 7 mg QD n=408/407 Teriflunomide 14 mg QD n=372/370	Primary ARR Secondary Disability (EDSS) Fatigue/Health-related quality of life
PDY6045 Add-ON to IFN-β 1a 2007-2009 Canada, Germany, Italy, Spain, and the US. Tolerability and safety	RD MC (28) DB PC PA Duration 24 weeks RMS, EDSS ≤ 5.5, no other concurrent treatment Age: Median (range) 41 (19-54) M/F: 35/81	Placebo 1 -2 tablets QD n=41/38 Teriflunomide 7 mg QD n=37/34 Teriflunomide 14 mg QD n=40/38	Primary Adverse event Physical examinations Laboratory evaluations, ECGs Abdominal ultrasound pancreas Secondary MRI N of GD+ lesions
PDY6046 Add-ON to GA 2007-2009 Austria, Canada, Germany, Italy, the UK and the USA Tolerability, safety,	RD MC (24) DB PC PA Duration 24 weeks RMS, EDSS ≤ 5.5, no other concurrent treatment Age: Median (range) 43	Placebo 1 -2 tablets once daily n=41/39 Teriflunomide 7 mg QD n=42/37 Teriflunomide 14 mg QD	

Study /Study period Location /Study goals	Design / Duration/ population	Study arms N randomised/n-completed	Endpoints
pharmacokinetics, and pharmacodynamic	(19-55) M/F: 26/97	n=40/34	

Legend
AC=Active-controlled, ARR=annual relapse rate (n of relapse /person years), BOD=Burden of Disease, Db=Double blind, EDSS=Expanded Disability Status Scale, FIS= Fatigue Impact Scale, EQ-5D=European Qulaity of Life scale, FU=Follow-up, MC (16) = multicenter (n of centers), MSFC=Multiple Sclerosis Functional Composite, GA=Glatiramer, PA=parallel group study, PC=Placebo-controlled, Rd-randomised, RRMS=Relapsing remitting MS, SB= Single blind, SF-36= Short Form (36) Health Survey, TSQM=Treatment Satisfaction Questionnaire for Medication, WPAI= Work Productivity and Activities Impairment

Failure was defined as either relapse or permanent study treatment discontinuation for any cause, whichever came first
BOD = MRI variable burden of disease i.e. total volume of all abnormal brain tissue i.e. total volume of T2 lesion component + T1 hypointense lesions.

2.4.2. Pharmacokinetics

A total of 55 studies were performed to study pharmacokinetics and pharmacodynamics of teriflunomide, 18 of which were clinical pharmacology studies conducted in healthy subjects, special populations and MS patients.

Absorption

The absolute bioavailability was calculated by cross study comparison. Bioavailability of teriflunomide was high (approximately 100%) after oral intake due to its high permeability. Plasma teriflunomide concentrations peaked at a median time of 1 to 4 hours, independent of dose and dosing day.

Based on the PopPK analysis (Study POH0290), for the proposed dose of 14 mg teriflunomide, the steady-state C_{max} was 45.3 µg/ml and the steady-state AUC_{0-24} was 1070 µg/ml. Based on the observed data in the different studies in MS patients, the steady state $C_{trough/min}$ ranged from 37.4 to 65.8 µg/ml.

Food significantly reduced C_{max} by 18% for both doses, but did not significantly reduce the exposure ($AUC_{0-72)}$. The t_{max} (1.5-4.2 h versus 6.25-20 h, with and without food, respectively) was prolonged 2-4 fold.

Dose proportionality with single doses of 7 and 14 mg, reflected in C_{max} and AUC values, was shown in healthy subjects and with repeated oral dosing in MS patients based on the C_{trough} values. Of note, the dose-proportional increase in the plasma levels was not reflected in efficacy.

From the mean predicted pharmacokinetic parameters calculated from the population pharmacokinetic (PopPK) analysis using data from healthy volunteers and MS patients, there was a slow approach to steady-state concentration (i.e., approximately 100 days (3.5 months) to attain 95% of steady-state concentrations) and the estimated AUC accumulation ratio was approximately 34-fold.

Distribution

In vitro and in vivo human data showed that teriflunomide was extensively bound to plasma protein (>99%) and was mainly distributed in the plasma. Drug interactions due to displacement from other proteins are considered unlikely.

Data from the single i.v. administration of teriflunomide (Study HWA486/1024) showed a limited Vss of 11 l. This was in line with the PopPK analysis results using data from the Phase 3 studies 2001 and EFC6049/TEMSO.

Elimination

The primary biotransformation pathway for teriflunomide was hydrolysis. Secondary pathways involved oxidation, N-acetylation and sulfate conjugation. Teriflunomide was moderately metabolized into several metabolites. TFMA was not detected in the human *in vivo* metabolism study (BEX6038), but was detected in low amounts in plasma after repeated doses in clinical studies. TFMA glycolanilide and 4-TFMA oxalinic acid were formed *in vitro* after incubation of teriflunomide in human liver microsomes (Study HMR014997). 4-TFMA oxalinic acid was also formed after incubation of 4-TFMA *in vitro* in human hepatocytes (Study HMR017949).

Most of the metabolites were undetectable in humans and the metabolites which could be detected were not considered of relevance due to their minute amounts.

Based on individual prediction of pharmacokinetic parameters using the PopPK model of teriflunomide in healthy volunteers and MS patients, teriflunomide half-life was approximately 19 days after repeated doses of 14 mg. After a single i.v. administration, the total body clearance of teriflunomide was 30.5 ml/h.

Teriflunomide was eliminated via faeces by 37.5% of the administered dose (35.7% was the unchanged drug) and via urine by 22.6% (≤1.3% was the unchanged drug). Non-clinical data (from intra-duodenal administration of teriflunomide in rats) and the human *in vivo* observation of the presence of unchanged drug excreted in faeces at time points after 72 hours indicated that biliary secretion and possibly direct gastro-intestinal secretion leading to entero-hepatic recycling are involved in elimination process. The direct secretion might be mediated by the efflux transporter BCRP, as teriflunomide is its substrate.

Based on the PopPK analysis, bilirubin showed an effect of a 1.7-fold increase of mean $AUC_{0\text{-}24SS}$ between patients with a bilirubin value greater than 17 µmol/l (n=17) and patients with bilirubin value lower than 17 µmol/l (n=393).

The elimination of teriflunomide can be accelerated by the oral administration of cholestyramine or activated charcoal, presumably by interrupting the reabsorption processes at the intestinal level. Teriflunomide concentrations measured during an 11-day procedure to accelerate teriflunomide elimination with either 4 g cholestyramine every 8 hours, 8 g cholestyramine every 8 hours, or 50 g activated charcoal every 6 hours following cessation of teriflunomide treatment indicated that these regimens were effective in accelerating teriflunomide elimination, leading to more than 98% decrease in plasma teriflunomide concentrations, with cholestyramine being faster than activated charcoal.

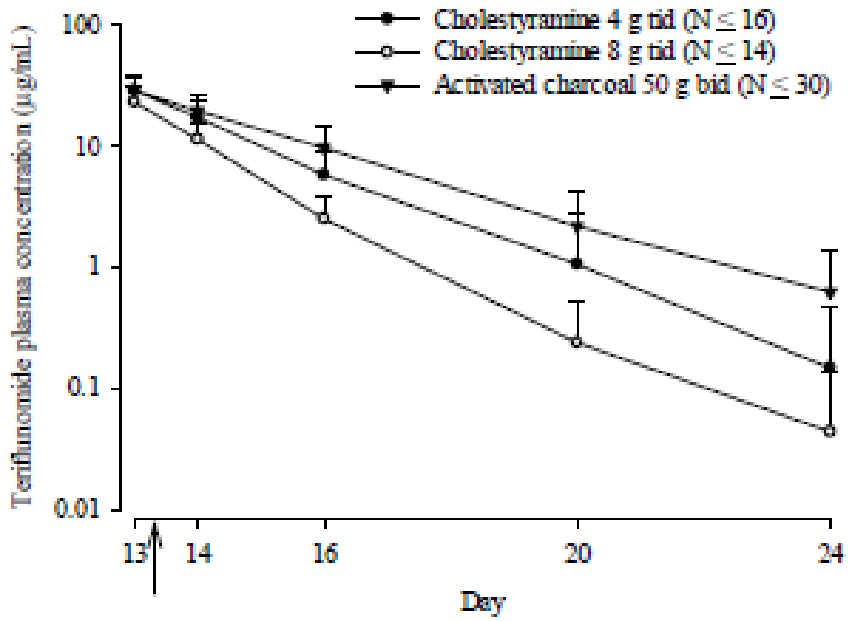
Fig. 1

Percent decrease in teriflunomide concentrations over 11 days after rapid elimination procedure (INT6040, INT10563, INT10564, and TES10852)

Treatment Description	N	Percent	%CV
Teriflunomide + Cholestyramine 8 g tid	47	99.8	0.432
Teriflunomide + Cholestyramine 4 g tid	42	99.6	0.805
Teriflunomide + Activated charcoal 50 g bid	30	97.8	2.53

CV=coefficient of variation; bid=twice a day; tid=three times a day.

- **Mean (standard deviation) teriflunomide plasma concentration-time profiles before and during rapid elimination procedure**



Note: Arrow represents the start of the rapid elimination procedure (which lasted 11 days)

Special populations

Several sources of intrinsic variability were identified in healthy subjects and MS patients based on the PopPK analysis: age, body weight, gender, race, and albumin and bilirubin levels, but their impact remained limited (≤31%). No data were available on children. Mild and moderate hepatic impairment had no impact on the pharmacokinetics of teriflunomide. No impact on the pharmacokinetics of teriflunomide was seen in patients with severe renal impairment.

Pharmacokinetic interaction studies

The *in vivo* data on the pharmacokinetic interaction of rifampin (an inducer for CYP2B6, 2C8, 2C9, 2C19, 3A P-gp and BCRP) with teriflunomide showed a reduction of teriflunomide AUC by about 40%.

The *in vivo* data on the pharmacokinetic interaction of teriflunomide with other drugs showed that teriflunomide moderately inhibited CYP2C8 and weakly inhibited CYP3A, but did not inhibit CYP2B6, CYP2C9, CYP2C19, and CYP2D6. Repeated doses of teriflunomide decreased mean C_{max} and AUC of

caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 *in vivo*.

Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, indicating that teriflunomide is not an inhibitor or an inducer of CYP2C9.

In vitro, teriflunomide was observed to be an inhibitor of CYP1A2 and CYP2C9.

There was an increase in mean C_{max} and AUC (1.43- and 1.54-fold, respectively) of cefaclor (an OAT3 substrate) following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3 in vivo. An increase in mean C_{max} and AUC (2.65- and 2.51-fold, respectively) was also observed for rosuvastatin (a multiple substrate for OAT3, BCRP, OATP1B1/B3) following repeated doses of teriflunomide.

2.4.3. Pharmacodynamics

Mechanism of action

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence teriflunomide reduces the proliferation of dividing cells that need de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

Primary and Secondary pharmacology

Primary pharmacology studies and systematic dose-finding studies were not performed. The doses of teriflunomide 7 mg/day and teriflunomide 14 mg/day were selected based on the doses active in animal EAE models and on pharmacokinetic data obtained with leflunomide (Arava). Teriflunomide exposure after a single 20 mg dose of leflunomide was about 70% of that after a single 20 mg dose of teriflunomide (Study 1001).

The pharmacodynamics and PK/PD relationship were investigated in three studies.

- Study TES10852: a placebo and positive-controlled study on the effect of teriflunomide on ventricular repolarization in healthy subjects.
- Study POH0295: an exploratory analysis of the PK-PD based on the data from studies HMR1726D/2001 and EFC6049/TEMSO.
- Study PDY11684: a secondary pharmacology study to evaluate teriflunomide effects on the immune response to vaccination in patients with relapsing MS

Study (PDY11684) was on-going at the time of the initial MAA. It was aimed to investigate whether teriflunomide treatment affects the immune response to vaccination in patients with relapsing MS. It was hypothesized that memory response to a recall antigen may be preserved, since memory T cells may not need de novo pyrimidine synthesis following re-activation to trigger antibody response.

In Study TES10852, the effect of teriflunomide on ventricular repolarization was evaluated in terms of change from time-matched baseline in QT (primary variable), calculated using Fridericia's formula (QTcF). This was analysed as the largest time-matched mean difference (LTMMD) between teriflunomide and placebo over Day 12, using specific time points over 12h. Teriflunomide effects on

secondary variables, e.g. heart rate, were measured. The clinical laboratory parameters, such as uric acid elimination on 24-hour urine collection and serum uric acid levels were also analysed.

No QTcF prolongation was observed at a mean Cmax steady state concentration of 30 µg/ml (a concentration within the range observed in MS patients). Heart rate was not affected by teriflunomide, either. A decrease in serum uric acid levels and increased urinary clearance were observed, which was in line with data from Phase 2/3 studies and also supported by literature (Toncev et al. 2002).

The PK-PD relationship was explored in Study POH0295 using data from studies HMR1726D/2001 and EFC6049/TEMSO. The relationship between the mean teriflunomide concentration after 8 weeks of treatment (independent variable) and several efficacy and safety variables (dependent variables) was modelled. Different models were used depending on the properties of the dependent variable (continuous/categorical). Results on the efficacy variables indicated that there was no significant relationship between mean teriflunomide concentrations and annual relapse rate or MRI burden of disease. A statistically significant decrease in risk of disability progression, as mean teriflunomide concentration increases, was found. For the number of Gadolinium-enhanced T1 lesions and the number of unique active lesions, the relationship to mean teriflunomide concentration could not be reliably predicted.

With respect to safety variables, no significant relationship was seen between mean teriflunomide concentrations and lipase, systolic blood pressure and creatinine clearance. A trend towards effect dependent on the dose was observed in some other safety variables, e.g. alanine aminotransferase, neutrophils, lymphocytes, amylase, diastolic blood pressure, alopecia, phosphate and uric acid.

Pharmacodynamic interactions with other medicinal products were investigated in two studies (Study PDY6045 and Study LTS6047) as a tertiary objective. Study PDY6045 evaluated the effects of a 7 mg and 14 mg dose of teriflunomide compared with placebo, in combination with a stable dose of IFN-beta, on interferon neutralizing antibodies for 24 weeks. Study LTS6047 was an extension of study PDY6045 and PDY6046 (add-on treatment with glatiramer acetate), with continued double-blind design for at least another 24 weeks. The number and proportion of patients with IFN-beta neutralizing antibodies (NAb) by visit and by treatment group for PDY6045 + LTS6047 were tabulated. Pharmacodynamic-neutralizing antibodies relationship was investigated on efficacy parameters such relapse rate and MRI variables.

Overall, in both studies, no significant effects on the proportion of NAb negative patients (NAb <20 Titre) were observed with add-on treatment of INF-beta and teriflunomide (for both doses) or placebo at week 24 and 48. No conclusions on the correlation between neutralizing antibody and efficacy could be made due to the low power of the studies (small sample size).

2.4.4. Discussion on clinical pharmacology

In general, the CHMP was of the view that the documentation adequately characterised the pharmacokinetic and pharmacodynamic profile of teriflunomide.

In their review, the CHMP considered that the steady-state levels of teriflunomide were reached in about 3-3.5 months and therefore, relapse prevention could be suboptimal in the period towards the steady state, which might warrant a loading dose. In this context, the applicant presented a cumulative occurrence of relapses over time for the TEMSO study and combined for the TEMSO + TOWER study. The results indicated an early separation of the curves between the placebo and teriflunomide groups. In addition, the applicant presented data on the cumulative mean number of

combined unique active lesions over the study period in study 2001. The combined unique lesions were decreased in teriflunomide-treated patients already at 6 weeks, reaching significance by 12 weeks. With an initial loading dose (double dose at week 1) administered in this study, the plasma through concentrations were not significantly changed as compared to subjects without an initial loading dose. Taken together, the evidence presented by the applicant was considered to provide reassurance that there was no delay in the onset of action and hence, a loading dose was not requested by the CHMP.

The CHMP also considered the effect of food on the pharmacokinetic parameters of teriflunomide, i.e. significantly reduced Cmax, prolonged tmax and no significant reduction in exposure (AUC0-72). In view of the long-half life (about 20 days), once daily administration and use in chronic treatment, the CHMP agreed that the product can be taken with or without food as reflected in section 4.2 of the SmPC.

Given the long half-life of teriflunomide, rapid elimination procedure by administration of cholestyramine or activated charcoal was accepted.

No significant difference on the pharmacokinetics of teriflunomide was observed between the healthy subjects and those with severe renal impairment. The CHMP considered that this was in line with the observation that only less than 2% of the unchanged drug is excreted in the urine. Overall, the CHMP was of the view that no dose adjustment in patients with mild, moderate or severe renal impairment would be needed. Nevertheless, the CHMP pointed out that as patients with severe renal impairment undergoing dialysis were not evaluated, teriflunomode should be contraindicated in this population.

With respect to hepatic impairment, no significant differences in exposure were observed in subjects with mild and moderate condition. Therefore, no dose adjustment was considered necessary in these patients. There was no clinical trial experience with the use of teriflunomide in patients with severe hepatic impairment and the applicant proposed a contraindication for these patients. This approach was agreed by the CHMP and reflected in the Product Information accordingly.

The CHMP considered the available population PK analysis data and concluded that no dose modifications or precautions according to body weight, age, gender, race and albumin were necessary. The finding of an increase of mean AUC0-24SS in patients with bilirubin levels greater than 17 µmol/l was not considered to have clinical implications for MS patients.

In vitro, teriflunomide was shown to be an inhibitor of CYP1A2 and CYP2C9, while this was not observed in the *in vivo* studies. The CHMP considered that it might be attributed to a combined effect of inhibition and induction during the repeated administration of teriflunomide for 11-12 days. As inhibition normally occurs for the first few days and induction later, inhibition of CYP1A2 and CYP2C9 might have been masked by the inducing effect. Based on calculated inhibition values provided by the applicant, the CHMP considered that teriflunomide was not likely to exert inhibitory effect on CYP1A2 and CYP2C9 metabolism. The CHMP considered that teriflunomide co-administration with caffeine weakly induced CYP1A2. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetin, alosetron, theophylline and tizanidine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of efficacy of these products. This was reflected in section 4.5 of the SmPC.

Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, suggesting that teriflunomide is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was co-administered with warfarin as compared with warfarin alone. Therefore, the CHMP considered that when warfarin is co-

administered with teriflunomide, close INR follow-up and monitoring should be ensured, as reflected in section 4.5 of the SmPC.

Based on the increase in mean rosuvastatin Cmax and AUC observed following repeated doses of teriflunomide, a dose reduction by 50% for rosuvastatin was recommended in case co-administration is needed.

With respect to pharmacodynamics, the CHMP considered that inhibition of proliferation of stimulated T- and B-cells has a role in the mechanism of action. However, the claim suggesting that teriflunomide exerts its effects only on stimulated lymphocytes and not on slowly dividing or resting cells dependent on pyrimidine was not supported with sufficient data. In this regard, the CHMP also pointed out that the adverse event profile, for example incidence of alopecia, was indicative of a lesser specificity that suggested by the applicant. The applicant acknowledged that there was evidence in literature which indicates that teriflunomide exerts inhibitory effects not only in activated T- and B-lymphocytes, but also in other proliferating cell types. Furthermore, the CHMP highlighted that references to reduced numbers of activated lymphocytes specifically in the central nervous system were not substantiated and requested that this should reflected accordingly in the text of section 5.1 of the SmPC.

The CHMP considered that teriflunomide did not show clinically relevant effects on ventricular repolarization or heart rate. The increase in uric acid clearance which was observed in the QT study was not considered to pose a safety concern.

The results of study POH0295 evaluating the PK-PD relationship did not show consistent pattern with respect to efficacy. In general, the dose-effect on the several efficacy and safety parameters, with the exception of primary pharmacological effects, was weak and when present, of limited predictive value. The CHMP noted that the lack of relationship between teriflunomide concentration and annual relapse rate was in line with the lack of dose-effect relationship in the clinical studies. This issue is further discussed in the Clinical Efficacy section, with respect to the choice of dose applied for.

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology data submitted were considered satisfactory.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose-finding study in the indication of relapsing multiple sclerosis was performed. Teriflunomide doses of 7 and 14 mg tested in the phase II and phase III clinical trials were selected by the applicant based on doses active in the animal EAE models and on pharmacokinetic and clinical data obtained with the parent compound leflunomide.

Teriflunomide exposure after a single 20 mg dose of leflunomide was ~70% of that after a single 20 mg dose of teriflunomide. Leflunomide was shown to be effective in patients with rheumatoid arthritis at doses of 10 and 20 mg. In the phase 2 of development of leflunomide, higher incidences of adverse events were observed with the dose of 25 mg and consequently, the decision was made to test the doses of 10 mg and 20 mg of leflunomide in Phase 3 studies. These results were also taken into account for the development of teriflunomide and the decision was made not to test doses of teriflunomide higher than 14 mg.

The applicant made a presumption of a 1:1 transmission of effective doses developed in RA to MS referring to the hypothesis that in both indications, the effect of teriflunomide on the DHO-DH enzyme would result in a clinical effect.

The CHMP discussion regarding absence of formal dose-finding studies is summarised in section 2.6.3.

2.5.2. Main studies

The applicant developed teriflunomide as a disease-modifying drug for multiple sclerosis, with the primary aim to investigate teriflunomide as a monotherapy in the treatment of patients with relapsing forms of MS. The following studies were considered by the CHMP as the most important for this marketing authorization application.

Of note, the patient populations within studies 2001, TEMSO, TOWER and TENERE were comparable and there were no relevant differences between the treatment arms in these studies with respect to medical history and concomitant diseases.

HMR1726D/2001 - A phase II study of the safety and efficacy of teriflunomide (HMR1726) in multiple sclerosis with relapses

Methods

Study Participants

Male or female subjects aged between 18 and 65 years, with clinically definite MS with at least 2 documented relapses as defined by the Poser criteria in the 3 years prior to screening could be enrolled in the study. At least 1 relapse had to be documented in the last year and the patients had to have a screening MRI scan fulfilling the criteria for a diagnosis of MS and an Expanded Disability Status Scale (EDSS) score between 0 and 6 inclusively.

Treatments

The trial included a 4-week, treatment-free screening period with MRI scans at week -4 (visit 1) and baseline (visit 3), a 36-week double-blind treatment period (visits 4 to 10) with 6 additional MRI scans performed every 6 weeks and a 6-week, post-treatment observation period with a final MRI scan at week 42 (visit 11).

Adults with clinically definite MS with relapses, based on MRI scans taken during the screening phase, were randomized (1:1:1) to 1 of 3 treatment groups (placebo, 7 mg or 14 mg teriflunomide once daily). Study medication was to be administered orally once daily with or without food. Subjects were encouraged to take their tablets (placebo, 7 or 14 mg teriflunomide) at the same time each day. In each of the 3 groups, subjects were to take a daily loading dose of 2 tablets for the first 7 days of the treatment period, followed by a maintenance dose of 1 tablet daily for the remaining days of the treatment phase.

Objectives

The primary objective of the study was to determine the safety and efficacy of teriflunomide in multiple sclerosis with relapses. The secondary objectives were focused on the effect of teriflunomide on additional MRI variables, clinical and quality of life measures. Furthermore, the PK-PD relationship was investigated.

Outcomes/endpoints

The primary efficacy endpoint was defined as the average number of unique active lesions per MRI scan for the double-blind treatment period of the study (sum of unique newly active lesions and of unique persistently active lesions for all scans divided by the number of scans on which the sum was based). This average was based on all scans performed during the treatment period.

Secondary endpoints were based on MRI scans (average number of new T1 lesions per scan, average number of new T2 lesions per scan, average number of newly active lesions per scan (T1 and T2 combined), average number of persistently active lesions per scan (T1 and T2 combined), number of subjects with no new lesion, number of subjects with no newly enhancing lesion, number of subjects with no new unique active lesion, percentage of scans per subject showing no enhancement, percentage change from baseline to endpoint in the burden of disease and percentage change from baseline in atrophy at week 36), clinical assessments (focusing on changes in EDSS score, MSFC score and relapses) and quality of life variables (fatigue impact scale and MSQOL-54).

Sample size

Fifty four evaluable subjects per treatment group were considered sufficient to detect with 90% power an effect size of 0.32 using a 2-sided Wilcoxon rank-sum test and at α-level of 0.05. This effect size for the Wilcoxon rank-sum test corresponds to a parametric effect size of 0.67. Anticipating a 10% dropout rate, it was considered necessary to randomize 60 subjects per treatment group for a total of 180 subjects.

Blinding and randomisation

The study was conducted in a double-blind fashion. The patients were randomised in a 1:1:1 ratio with blocks of six. Randomization of subjects was stratified on the basis of EDSS scores. Subjects with a score ≤ 3.5 were randomized in ascending order beginning with the lowest number; subjects with a score >3.5 were randomized in descending order beginning with the highest number.

Randomisation occurred at visit 3 after completion of all baseline assessments.

Statistical methods

The primary analysis populations were defined as follows:

• Efficacy-evaluable: All randomized subjects for whom there was at least 1 on-treatment MRI assessment

• Safety-evaluable: All randomized subjects who received at least 1 dose of study medication

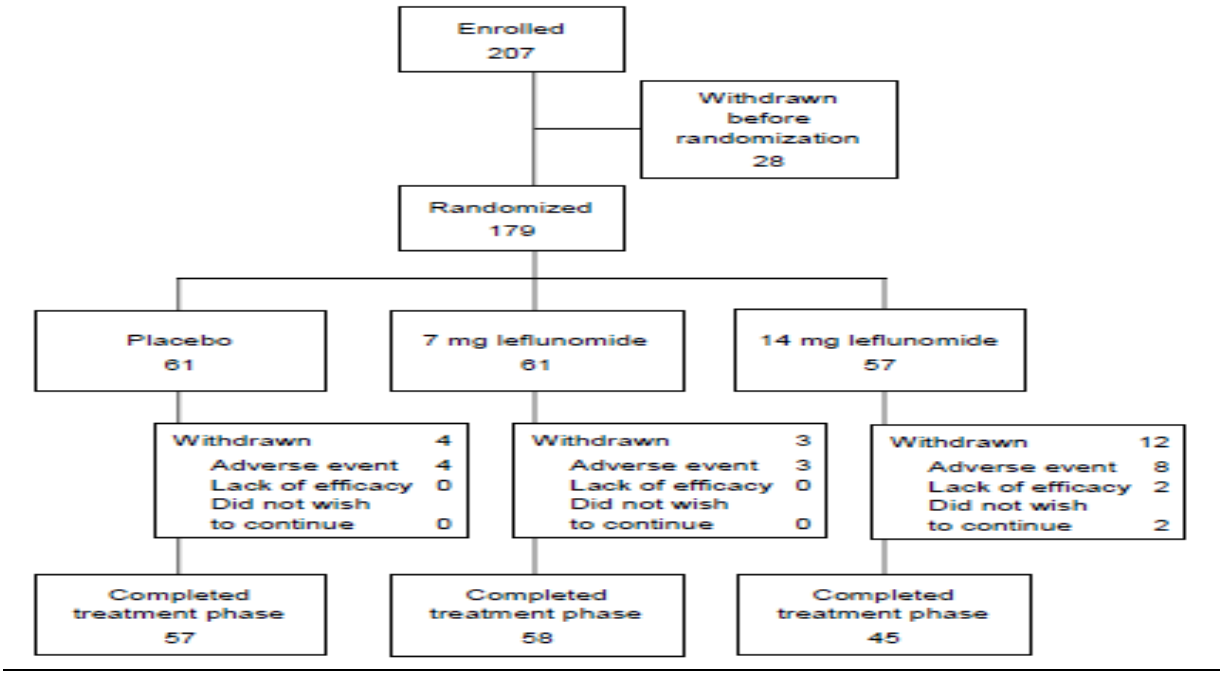
The primary efficacy variable (average number of unique active lesions per MRI scan for the treatment period) was analysed for differences between treatment groups using rank analysis of covariance with treatment, stratum (EDSS at baseline ≤ 3.5 vs. >3.5) and pooled centre as fixed effects and the ranked average pre-randomization number of unique active lesions as covariate. Dunnett's test for comparing 2 groups with placebo was used.

Results

Participant flow

The study participant flow is shown in figure 2.

Fig. 2



Recruitment

The study took place between 26 April 2001 and 17 March 2003.

Conduct of the study

Major protocol deviations were identified in 30 (16.9%) of the 177 treated subjects in the efficacy-evaluable population: 8/61 (13.1%) in the placebo group, 9/60 (15.0%) in the 7 mg teriflunomide group and 13/56 (23.2%) in the 14 mg teriflunomide group. The most common deviation was the wrong application of gadolinium or the use of other drugs for the treatment of relapses that interfered with the interpretation of the MRI scans. This was the case for 8/61 (13.1%) subjects in the placebo group, 7/60 (11.7%) subjects in the 7 mg teriflunomide group and 10/56 (17.9%) subjects in the 14 mg teriflunomide group.

Baseline data and Numbers analysed

179 patients with relapsing MS from two countries were randomized in a 1:1:1 ratio to placebo, 7 mg teriflunomide or 14 mg teriflunomide for a 36-week double-blind treatment period. Most of the included patients were patients with relapsing-remitting multiple sclerosis (155 patients); there were also around 12.4% patients in every treatment group with secondary progressive MS (SPMS). Generally, the included patients were patients with a rather mild disease form (median baseline EDSS: 2.0-2.5, number of relapses in the last year: 1).

Outcomes and estimation

With respect to the primary endpoint, the mean number of unique active lesions per MRI scan during the treatment period was 2.69 for placebo, 1.06 for 7 mg teriflunomide and 0.98 for 14 mg teriflunomide. Both teriflunomide treatment arms demonstrated statistically significant differences in comparison to placebo (placebo vs. 7 mg teriflunomide: p = 0.0234, placebo vs. 14 mg teriflunomide: p = 0.0052) in the primary analysis population, i.e. the efficacy-evaluable population. These results were supported by analyses in the ITT population and the completer population. In a sensitivity

analysis based on the PP population, the teriflunomide 7 mg treatment arm did not reach statistical significance when compared to placebo (p = 0.1099). For the 14 mg teriflunomide dose, borderline statistical significance in comparison to placebo (p = 0.0490) was achieved.

The average numbers of MRI lesions during the treatment period were significantly lower for patients treated with teriflunomide 14 mg in comparison to the placebo group for most of the lesion types analysed (except new enlarging T2 lesions, persistently enlarging T2 lesions and unique persistently active lesions (T1 and T2)). Sensitivity analyses were performed in the completer and the PP population. Analyses did not always support the results of the primary analysis.

The number of subjects with no unique newly active lesions during the treatment period did not reach statistical significance in any of the active treatment groups when compared to placebo, but was higher on active treatment (12 (19.7%) placebo subjects, 21 (35.0%) 7 mg teriflunomide subjects and 20 (35.7%) 14 mg teriflunomide subjects).

Median percent change from baseline to endpoint in burden of disease (defined as the sum of all regions of interest identified on T2 scans) did not reach statistical significance for the 7 mg teriflunomide group (p = 0.0959) when compared to placebo, but reached statistical significance for the 14 mg teriflunomide group (p = 0.0215) in comparison to placebo.

Generally, the annual relapse rate was rather low in all treatment groups (0.81 for placebo, 0.58 for teriflunomide 7 mg and 0.55 for teriflunomide 14 mg). The numbers of patients with MS relapses and the number of patients with relapses requiring steroid treatment were lowest in the 14 mg group. There was a trend for positive results for the two doses on proportion of patients with MS relapses (37.7%, 35.0% and 23.2% respectively for placebo, 7mg and 14 mg). This was not statistically significant.

The proportion of patients with EDSS progression was statistically significantly lower in the 14 mg group than on placebo, but the 7 mg group was higher than the placebo group without statistically significant difference (subjects with progression on EDSS: placebo 21.3%, 7 mg teriflunomide 28.8%, and 14 mg teriflunomide 7.4%, respectively).

There were no clinically relevant changes from baseline on any of the patient-reported outcomes or quality of life scores (FIS, MSFC, SF-36 or EQ-5D).

EFC6049 (TEMSO) - A randomized, double-blind, placebo-controlled, parallel-group design study to evaluate the efficacy and safety of teriflunomide (HMR1726D) in reducing the frequency of relapses and delaying the accumulation of physical disability in subjects with multiple sclerosis with relapses

Methods

Study Participants

To be eligible to participate in the study, the patients had to be between 18-55 years old, meeting the McDonald´s criteria (2005) for MS diagnosis, with an EDSS score of ≤5.5, exhibiting a relapsing clinical course with or without progression. The patients had to have at least 1 relapse over the 1 year preceding the trial or at least 2 relapses over the 2 years preceding the trial. Patients with significantly impaired bone marrow function or significant anaemia, leukopenia, or thrombocytopenia, patients with congenital or acquired immunodeficiency, malignancies or patients with liver or renal function impairment could not be enrolled. In addition, patients were not eligible for entry into the study if they met any of the following criteria: known history of active tuberculosis, persistent severe infection,

HIV positivity, chronic pancreatitis, pregnancy and breast-feeding. Prior or concomitant use of natalizumab, cladribin, mitoxantron or other immunosuppressive drugs was not allowed. Prior use of interferons, cytokine therapy or glatiramer acetate therapy was acceptable only if discontinued more than four months before participation in the study.

Treatments

One tablet of placebo, 7 mg teriflunomide or 14 mg teriflunomide was to be taken orally once daily in the morning for 108 weeks. The study medications were to be taken with or without food. A dosing interruption less than or equal to 15 days was allowed for patients undergoing surgical procedures involving general anaesthesia; the patients undergoing surgical procedures involving local or regional anaesthesia were to continue with the study medication without interruption.

During the study (or for 4 weeks prior to entry) the following treatments were not permitted: systemic corticosteroids (except for treatment of acute MS exacerbations as per protocol specifications), ACTH, cholestyramine, phenytoin, warfarin, tolbutamide and St. John's Wort products containing hyperforin in an unknown percentage or greater than 1% of the extract.

The relapses during the study were to be treated with corticosteroids if clinically necessary. The preferred standardized treatment consisted of 1 g intravenous methylprednisolone sodium succinate daily for 3 to 5 days. Study MRI was not to be performed until after a minimum of 14 days following the completion of a course of corticosteroids.

Objectives

The primary objective of the study was to determine the effect of teriflunomide in reducing the frequency of relapses in subjects with relapsing MS.

The secondary objectives comprised evaluating the effect of teriflunomide on delaying the accumulation of disability at 2 years as assessed by the EDSS, evaluating the effects of teriflunomide on MRI variables, evaluating the effect of teriflunomide on subject-reported fatigue as assessed by the Fatigue Impact Scale (FIS) and the safety and tolerability of teriflunomide by means of adverse event reporting, physical examinations, vital signs and laboratory evaluations.

Outcomes/endpoints

The primary efficacy endpoint of this study was the annualized relapse rate, defined as the number of confirmed relapses per patient-year.

The key secondary efficacy endpoint was time to disability progression, defined as the time to at least 1 point increase on EDSS score from baseline, if the baseline EDSS score was ≤5.5, or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was >5.5; this increase in EDSS score was to be persistent for at least 12 weeks.

Other secondary efficacy variables included the proportion of patients free of disability progression at 6 months, 1 year and 2 years, estimated by Kaplan-Maier curves, FIS total score and domain scores, burden of disease (key MRI secondary variable), total number of Gd-enhancing T1-lesions per MRI scan over the treatment period, total volume of Gd-enhancing T1-lesions per MRI scan over the treatment period, volume of hypointense post-Gd T1 lesions (black holes), volume of T2 lesion component and a number of exploratory MRI variables.

Sample size

The sample size estimation was based on the primary (ARR) and key secondary efficacy comparisons. From the available data on the approval of interferon beta products, it was assumed that the 2-year relapse rates were 2.20 and 1.66 for the placebo and teriflunomide groups, respectively. From recently available data on Tysabri trials, the placebo 2-year relapse rate was estimated to be 1.48. Assuming the number of relapses follows approximately a Poisson distribution with a common SD of 1.252, a study with 360 randomized subjects per treatment arm, or a total of 1080 randomized subjects, could have ≥95% power to detect a 25% relative risk reduction in the 2-year relapse rate at the 2-tailed significance level of $\alpha = 0.050$. This calculation incorporated a potential 20% 2-year dropout rate. In addition, a study with a sample size of 360 subjects per treatment arm would lead to an 80% powered log-rank test to detect a 37% hazard rate reduction of an assumed disability progression hazard rate of 0.1783 in the placebo group and 0.1116 in the teriflunomide group (i.e., 30% probability to disability progression for placebo patients by the end of 2 years, 20% for teriflunomide patients). This calculation also incorporated a 20% 2-year dropout rate.

Randomisation

After completing a screening phase of up to four weeks, patients were centrally randomized via an interactive voice response system in a 1:1:1 ratio with blocks of six. The randomization was stratified, based on centre and by patient's EDSS score (≤3.5 or >3.5) to ensure the balance in baseline disability between the 3 treatment groups.

Blinding (masking)

The study medication teriflunomide (7 mg and 14 mg) and placebo were supplied as identical white to slightly yellow film-coated biconvex tablets sealed in child-resistant blister packs.

In addition to the standard blinding procedures, the following measures were taken to further enhance blinding and reduce bias. At each study site, the study staff included a minimum of 2 neurologists (treating neurologist and examining neurologist), a magnetic resonance imaging (MRI) radiologist and technologist, a clinical coordinator and a technician/staff nurse (qualified to perform MSFC). The site personnel were blinded to study treatment and this included the treating neurologist. Central readings of all brain MRI and computerized tomography (CT) scan images were performed by the MRI analysis centre (MRI-AC) at the University of Texas Health Science Centre at Houston (USA). The study sites were required to perform and pass a qualifying or certification scan to ensure that the data acquisition was consistent and adequate for the study.

Statistical methods

All efficacy analyses were performed using the ITT population, defined as all randomized patients who had at least 1 day of study medication exposure. The patients were included in the treatment group to which they were randomized. Analyses of the safety endpoints were performed using the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The patients were included in the treatment group according to the actual treatment received.

The analyses of the primary efficacy and key secondary efficacy variables were also performed using the PP population, defined as a subset of the ITT population containing patients without a major efficacy-related protocol deviation.

The primary analysis for the ARR (primary efficacy endpoint) was performed using a Poisson regression model with robust error variance to accommodate the potential over-dispersed data appropriately. The

model included the total number of confirmed relapses with onset between randomization date and last dose date as the response variable, a 3-level treatment group (placebo, teriflunomide 7 mg and teriflunomide 14 mg), EDSS strata (baseline EDSS score ≤3.5 versus >3.5) and region (Eastern Europe, Western Europe and Americas) as covariates. To account for different treatment durations among patients, the log-transformed standardized treatment duration was included in the model as an "offset" variable for appropriate computation of relapse rate. The robust error variances were estimated by specifying the patient identifier in the repeated statement using SAS PROC GENMOD, which is equivalent to the Generalized Estimating Equation (GEE) model. Two-sided 95% confidence intervals (CI) of the rate ratio were calculated for the comparisons of each active treatment versus placebo. The estimated relapse rates and 2-sided 95% CI and the gross estimates of ARR were generated for each treatment group.

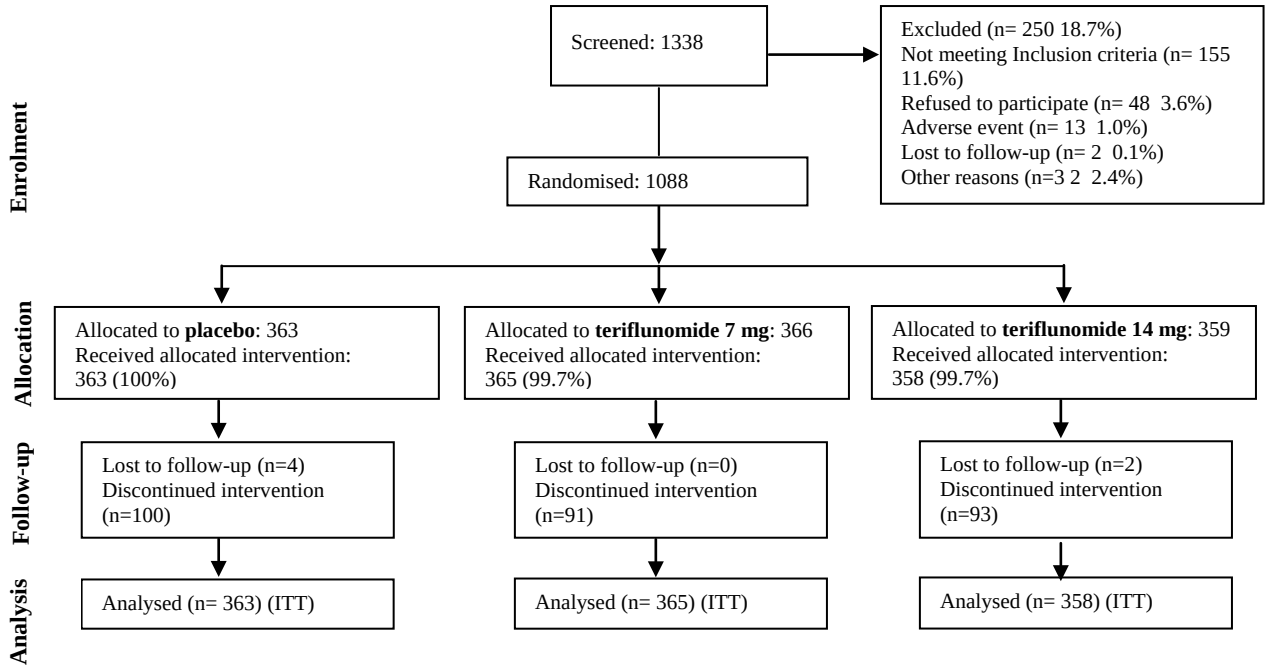
The key secondary analysis for the time to disability progression (sustained for at least 12 weeks) was performed using the log-rank test with time to disability progression as the dependent variable, the treatment group as test variable and region and baseline EDSS strata as stratification factors. Hazard ratios were estimated using Cox regression model with treatment group, region and baseline EDSS strata as covariates.

The Kaplan-Meier graphs were generated and Kaplan-Meier method was used to estimate the disability progression rate and its 95% CI at 6 months, 1 year and 2 years for each treatment group.

Results

Participant flow

The study participant flow is shown in figure 3.
Fig. 3



Patient completion rates and reasons for discontinuation are presented in table 4.

Table 4

		Teriflunomide	
	Placebo (N=363)	**7 mg (N=366)**	**14 mg (N=359)**
Randomized and not treated	0	1 (0.3%)	1 (0.3%)
Reason: protocol violation	0	1 (0.3%)	1 (0.3%)
Randomized and treated	363 (100%)	365 (99.7%)	358 (99.7%)
Completed study treatment period	259 (71.3%)	274 (74.9%)	263 (73.3%)
Did not complete study treatment period	104 (28.7%)	91 (24.9%)	95 (26.5%)
Completed study including EPTD follow-up	290 (79.9%)	296 (80.9%)	283 (78.8%)
Reason for study treatment discontinuation			
Adverse event	29 (8.0%)	37 (10.1%)	38 (10.6%)
Lack of efficacy	24 (6.6%)	14 (3.8%)	17 (4.7%)
Protocol violation	3 (0.8%)	2 (0.5%)	5 (1.4%)
Lost to follow-up	4 (1.1%)	0	2 (0.6%)
Death	0	0	0
Progressive disease	11 (3.0%)	4 (1.1%)	2 (0.6%)
Subject did not wish to continue	33 (9.1%)	32 (8.7%)	26 (7.2%)
Other	0	2 (0.5%)	5 (1.4%)
Patients who completed EPTD follow-up	31 (8.5%)	22 (6.0%)	20 (5.6%)
Completed study treatment but not entered extension	22 (6.1%)	22 (6.0%)	10 (2.8%)
Completed study treatment and entered extension	237 (65.3%)	252 (68.9%)	253 (70.5%)

EPTD: Early permanent treatment discontinuation

Note: EPTD follow-up was implemented during protocol amendment 4 (12 February 2007) in EFC6049. patients who discontinued study medication before the amendment are not included

Note: Percentages are calculated using the number of randomized patients as denominator.

Recruitment

The study took place between 24 September 2004 and 08 July 2010.

Conduct of the study

There were 9 amendments to the protocol: amendment 1 was introduced before the randomization of any patients and 8 amendments during the study.

Baseline data

A summary of the patient population enrolled in the study is presented in the tables below:

Table 5 Demography and baseline disease characteristics

		teriflunomide		
	Placebo (N=363)	**7 mg (N=365)**	**14 mg (N=358)**	**All (N=1086)**
Demography				
Age (years)				
Mean (SD)	38.4 (9.0)	37.5 (9.0)	37.8 (8.2)	37.9 (8.8)
Median (range)	39.0 (18 : 55)	39.0 (18 : 55)	38.0 (18 : 55)	38.0 (18 : 55)
Sex [n (%)]				
Female	275 (75.8%)	254 (69.6%)	254 (70.9%)	783 (72.1%)
Male	88 (24.2%)	111 (30.4%)	104 (29.1%)	303 (27.9%)
Race [n (%)]				
Number	362	364	357	1083
Caucasian/White	356 (98.3%)	354 (97.3%)	346 (96.9%)	1056 (97.5%)
Black	3 (0.8%)	1 (0.3%)	1 (0.3%)	5 (0.5%)
Asian/Oriental	1 (0.3%)	6 (1.6%)	8 (2.2%)	15 (1.4%)
Multiracial	1 (0.3%)	2 (0.5%)	2 (0.6%)	5 (0.5%)
Other	1 (0.3%)	1 (0.3%)	0	2 (0.2%)
Region [n (%)]				
Americas	82 (22.6%)	83 (22.7%)	80 (22.3%)	245 (22.6%)
Eastern Europe	114 (31.4%)	116 (31.8%)	108 (30.2%)	338 (31.1%)
Western Europe	167 (46.0%)	166 (45.5%)	170 (47.5%)	503 (46.3%)
BMI				
Number	358	363	352	1073
Mean (SD)	24.63 (5.01)	24.64 (4.54)	24.55 (4.67)	24.61 (4.74)
Median (range)	23.63 (16.2 : 48.2)	23.77 (15.5 : 44.3)	23.67 (16.8 : 42.6)	23.68 (15.5 : 48.2)
Baseline disease characteristics				
Time since first MS symptoms (years)				
Mean (SD)	8.56 (7.14)	8.78 (6.84)	8.70 (6.74)	8.68 (6.90)
Median (range)	6.33 (0.3 : 35.7)	7.00 (0.3 : 32.6)	7.17 (0.4 : 31.6)	6.83 (0.3 : 35.7)
Time since first MS diagnosis (years)				
Number	363	364	358	1085
Mean (SD)	5.13 (5.59)	5.29 (5.36)	5.59 (5.49)	5.33 (5.48)
Median (range)	3.25 (0.1 : 31.6)	3.75 (0.1 : 27.6)	3.71 (0.1 : 30.1)	3.50 (0.1 : 31.6)
Time since most recent relapse onset (months)				
Mean (SD)	6.28 (3.62)	6.29 (3.29)	6.50 (3.71)	6.35 (3.54)
Median (range)	5.00 (0.0 : 22.0)	5.00 (1.0 : 22.0)	6.00 (2.0 : 22.0)	5.00 (0.0 : 22.0)
Baseline EDSS score				
Mean (SD)	2.68 (1.34)	2.69 (1.33)	2.67 (1.25)	2.68 (1.30)

		teriflunomide		
	Placebo (N=363)	**7 mg (N=365)**	**14 mg (N=358)**	**All (N=1086)**
Median (range)	2.50 (0.0 : 6.0)	2.50 (0.0 : 6.0)	2.50 (0.0 : 5.5)	2.50 (0.0 : 6.0)
Randomized EDSS strata at baseline [n (%)]				
≤3.5	287 (79.1%)	280 (76.7%)	276 (77.1%)	843 (77.6%)
>3.5	76 (20.9%)	85 (23.3%)	82 (22.9%)	243 (22.4%)
Actual EDSS strata at baseline [n (%)]				
≤3.5	281 (77.4%)	280 (76.7%)	276 (77.1%)	837 (77.1%)
>3.5	82 (22.6%)	85 (23.3%)	82 (22.9%)	249 (22.9%)
Number of relapses in the last 2 years				
Mean (SD)	2.2 (1.0)	2.3 (1.2)	2.2 (1.0)	2.2 (1.1)
Median (range)	2.0 (1 : 7)	2.0 (1 : 12)	2.0 (1 : 9)	2.0 (1 : 12)
1	71 (19.6%)	74 (20.3%)	71 (19.8%)	216 (19.9%)
2	186 (51.2%)	187 (51.2%)	191 (53.4%)	564 (51.9%)
3	76 (20.9%)	64 (17.5%)	70 (19.6%)	210 (19.3%)
≥4	30 (8.3%)	40 (11.0%)	26 (7.3%)	96 (8.8%)
Number of relapses in the last 1 year				
Number	277	283	271	831
Mean (SD)	1.4 (0.7)	1.4 (0.7)	1.3 (0.7)	1.4 (0.7)
Median (range)	1.0 (0 : 6)	1.0 (0 : 6)	1.0 (0 : 4)	1.0 (0 : 6)
0	10 (3.6%)	9 (3.2%)	18 (6.6%)	37 (4.5%)
1	163 (58.8%)	173 (61.1%)	170 (62.7%)	506 (60.9%)
2	86 (31.0%)	88 (31.1%)	71 (26.2%)	245 (29.5%)
3	16 (5.8%)	10 (3.5%)	10 (3.7%)	36 (4.3%)
≥4	2 (0.7%)	3 (1.1%)	2 (0.7%)	7 (0.8%)
Number of baseline Gadolinium-enhancing lesions				
Number	359	359	355	1073
Mean (SD)	1.66 (3.55)	1.51 (3.97)	1.81 (5.17)	1.66 (4.28)
Median (range)	0.00 (0.0 : 26.0)	0.00 (0.0 : 38.0)	0.00 (0.0 : 50.0)	0.00 (0.0 : 50.0)
0	222 (61.8%)	232 (64.6%)	230 (64.8%)	684 (63.7%)
≥1	137 (38.2%)	127 (35.4%)	125 (35.2%)	389 (36.3%)
Baseline burden of disease (ml)				
Number	358	359	355	1072
Mean (SD)	19.34 (18.94)	20.42 (20.59)	18.08 (17.49)	19.28 (19.06)
Median (range)	12.75 (0.1 : 83.7)	13.98 (0.2 : 146.3)	12.39 (0.3 : 88.8)	13.05 (0.1 : 146.3)
MS subtype [n (%)]				
Relapsing Remitting	329 (90.6%)	332 (91.0%)	332 (92.7%)	993 (91.4%)
Secondary Progressive	22 (6.1%)	17 (4.7%)	12 (3.4%)	51 (4.7%)
Progressive Relapsing	12 (3.3%)	16 (4.4%)	14 (3.9%)	42 (3.9%)

		teriflunomide		
	Placebo (N=363)	**7 mg (N=365)**	**14 mg (N=358)**	**All (N=1086)**
With previous MS medication in the last 2 years [n (%)]				
Yes	90 (24.8%)	102 (27.9%)	102 (28.5%)	294 (27.1%)
No	273 (75.2%)	263 (72.1%)	256 (71.5%)	792 (72.9%)

Table 6 Frequency analysis of EDSS score at baseline (ITT population)

		teriflunomide	
	Placebo	7 mg	14 mg
Baseline EDSS score n(%)	(N=363)	(N=365)	(N=358)
0	17 (4.7%)	16 (4.4%)	11 (3.1%)
1	36 (9.9%)	27 (7.4%)	27 (7.5%)
1.5	36 (9.9%)	47 (12.9%)	50 (14.0%)
2	61 (16.8%)	73 (20.0%)	71 (19.8%)
2.5	53 (14.6%)	40 (11.0%)	37 (10.3%)
3	30 (8.3%)	31 (8.5%)	42 (11.7%)
3.5	48 (13.2%)	46 (12.6%)	38 (10.6%)
4	42 (11.6%)	41 (11.2%)	46 (12.8%)
4.5	14 (3.9%)	14 (3.8%)	19 (5.3%)
5	9 (2.5%)	16 (4.4%)	5 (1.4%)
5.5	16 (4.4%)	13 (3.6%)	12 (3.4%)
6	1 (0.3%)	1 (0.3%)	0

Table 7 MS medications taken within 2 years prior to first IP intake (ITT population)

		teriflunomide		
	Placebo (N=363)	7 mg (N=365)	14 mg (N=358)	All (N=1086)
No previous treatment with MS medication	273 (75.2%)	263 (72.1%)	256 (71.5%)	792 (72.9%)
Previous treatment with MS medication	90 (24.8%)	102 (27.9%)	102 (28.5%)	294 (27.1%)
INTERFERON BETA-1A	58 (16.0%)	74 (20.3%)	62 (17.3%)	194 (17.9%)
INTERFERON BETA-1A SUBCUTANEOUS QOD	39 (10.7%)	52 (14.2%)	37 (10.3%)	128 (11.8%)
INTERFERON BETA-1A INTRAMUSCULAR WEEKLY	23 (6.3%)	24 (6.6%)	29 (8.1%)	76 (7.0%)
INTERFERON BETA-1A UNSPECIFIED	1 (0.3%)	3 (0.8%)	3 (0.8%)	7 (0.6%)
INTERFERON BETA-1B	18 (5.0%)	22 (6.0%)	27 (7.5%)	67 (6.2%)
GLATIRAMER ACETATE	36 (9.9%)	23 (6.3%)	43 (12.0%)	102 (9.4%)
MITOXANTRONE	0	0	0	0
NATALIZUMAB	0	0	0	0

IP: Investigational product
WHO-DD dictionary - March, 2010
Prior medications are those the patients used prior to first IP intake.
Note: A patient can be counted in several categories.

Numbers analysed

A total of 1088 patients were randomized in this study. Of the 1088 patients, 2 patients were not treated with study medication due to protocol violations and were excluded from the ITT population. A total of 29 patients were excluded from the per-protocol population due to various protocol violations.

Table 8 Analysis populations (randomized population)

		teriflunomide	
	Placebo	7 mg	14 mg
Randomized population	363 (100%)	366 (100%)	359 (100%)
Efficacy population			
ITT population	363 (100%)	365 (99.7%)	358 (99.7%)
PP population	353 (97.2%)	356 (97.3%)	350 (97.5%)
Safety population	360	368	358

Note: The safety patients are tabulated according to treatment actually received (as treated)

For the other populations, patients are tabulated according to their randomized treatment

PGM=PRODOPS/HMR1726/EFC6049/CSR/REPORT/PGM/dis_populations_r_t.sas OUT=REPORT/OUTPUT/dis_populations_r_t_i.rtf (18AUG2010 - 17:53)

Outcomes and estimation

Results of the primary analysis, i.e. analysis of the MS relapse in the ITT population are presented in table 9 below.

Table 9 Analysis of MS relapse

		teriflunomide	
	Placebo (N=363)	7 mg (N=365)	14 mg (N=358)
Number of patients with ≥1 relapses			
Yes	184 (50.7%)	154 (42.2%)	141 (39.4%)
No	179 (49.3%)	211 (57.8%)	217 (60.6%)
Number of relapses			
0	179 (49.3%)	211 (57.8%)	217 (60.6%)
1	97 (26.7%)	92 (25.2%)	86 (24.0%)
2	48 (13.2%)	49 (13.4%)	33 (9.2%)
3	22 (6.1%)	10 (2.7%)	16 (4.5%)
4	11 (3.0%)	2 (0.5%)	4 (1.1%)
≥ 5	6 (1.7%)	1 (0.3%)	2 (0.6%)
Total number of relapses	335	233	227
Total patient-years followed	627.7	633.7	615.0
Unadjusted annualized relapses rate [a]	0.534	0.368	0.369
Adjusted annualized relapse rate [b]			
Estimate (95% CI)	0.539 (0.466, 0.623)	0.370 (0.318, 0.432)	0.369 (0.308, 0.441)
Relative risk (95% CI)		0.688 (0.563, 0.839)	0.685 (0.554, 0.847)
P-value		0.0002	0.0005
Individual patient annualized replase rate [c]			
N	363	365	358
Mean (SD)	0.731 (1.553)	0.646 (2.240)	0.597 (2.163)
Median	0.475	0.000	0.000
Min : Max	0.00 : 21.49	0.00 : 36.53	0.00 : 36.53

[a] The total number of relapses that occurred during the treatment divided by the total number of patient-years treated in the study.

[b] Derived using Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline and region as covariates, and log-transformed standardized study duration as an offset variable

[c] The number of relapse for each patient divided by the number of years treated in the study

Results of the primary analysis in the ITT population were confirmed by secondary analyses in the PP population and the sensitivity analysis of MS relapse in the ITT population. In the PP population, the adjusted ARR was 0.545 (95% CI: 0.471 to 0.631) in the placebo group, 0.367 (95% CI: 0.314 to 0.428) in the teriflunomide 7 mg group and 0.366 (95% CI: 0.305 to 0.438) in the teriflunomide 14

mg group. Both active treatment arms showed a statistically significant improvement in the primary endpoint ARR when compared to placebo (p=0.0001 for teriflunomide 7 mg and p=0.0002 for teriflunomide 14 mg). In the sensitivity analysis with additional data collected during the follow-up period, the adjusted ARR was 0.505 (95% CI: 0.438 to 0.583) in the placebo group, 0.358 (95% CI: 0.308 to 0.416) in the teriflunomide 7 mg group, and 0.358 (95% CI: 0.300 to 0.427) in the teriflunomide 14 mg group. Both active treatment arms showed a statistically significant improvement in the primary endpoint ARR when compared to placebo (p=0.0006 for teriflunomide 7 mg and p=0.0012 for teriflunomide 14 mg).

Analysis of the key secondary endpoint, i.e. time to disability progression sustained for 12 weeks (ITT population) is presented in table 10.

Table 10 Time to disability progression sustained for 12 weeks

		teriflunomide	
	Placebo (N=363)	7 mg (N=365)	14 mg (N=358)
Number of patients with disability progression	86 (23.7%)	68 (18.6%)	62 (17.3%)
Number of patients who were censored	277 (76.3%)	297 (81.4%)	296 (82.7%)
Probability of disability progression (95% CI) at[a]			
24 weeks	0.086 (0.057, 0.116)	0.058 (0.033, 0.083)	0.062 (0.036, 0.088)
48 weeks	0.160 (0.121, 0.200)	0.131 (0.094, 0.167)	0.113 (0.079, 0.148)
108 weeks	0.273 (0.223, 0.323)	0.217 (0.171, 0.263)	0.202 (0.156, 0.247)
Hazard ratio (95% CI)[b]		0.763 (0.555, 1.049)	0.702 (0.506, 0.973)
P-value[c]		0.0835	0.0279

Note: The time-to-event variable is defined as the time (days) from the date of randomization to the date of the first disability progression. For patients who have no disability progression on or before last during treatment EDSS evaluation, it will be censored at the date of last during-treatment EDSS evaluation.

[a] Derived from Kaplan-Meier estimates

[b] Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

[c] Derived from log-rank test with stratification of EDSS strata at baseline and region

PGM=PRODOPS/HMR1726/EFC6049/CSR/REPORT/PGM/eff_time2event_i_t.sas OUT=REPORT/OUTPUT/eff_dp_i_t_i.rtf (18AUG2010 - 18:22)

Neither of the teriflunomide treatment arms reached statistical significance when compared to placebo for the endpoint time to disability progression sustained for 24 weeks (p=0.1459, p=0.1259) as presented in table 11. Although the comparison of teriflunomide vs placebo did not reach statistical significance, a similar trend as for 12 weeks sustained disability progression was observed, with a slightly increased HR.

Table 11 Time to disability progression sustained for 24 weeks

	Placebo (N=363)	teriflunomide 7 mg (N=365)	teriflunomide 14 mg (N=358)
Number of patients with disability progression	58 (16.0%)	44 (12.1%)	43 (12.0%)
Number of patients who were censored	305 (84.0%)	321 (87.9%)	315 (88.0%)
Probability of disability progression (95% CI) at[a]			
24 weeks	0.049 (0.026, 0.072)	0.035 (0.015, 0.054)	0.047 (0.025, 0.070)
48 weeks	0.089 (0.059, 0.119)	0.092 (0.060, 0.123)	0.096 (0.064, 0.128)
108 weeks	0.187 (0.143, 0.231)	0.139 (0.101, 0.178)	0.138 (0.100, 0.177)
Hazard ratio (95% CI)[b]		0.750 (0.507, 1.110)	0.749 (0.505, 1.111)
P-value[c]		0.1459	0.1259

Note: The time-to-event variable is defined as the time (days) from the date of randomization to the date of the first disability progression. For patients who have no disability progression on or before last during treatment EDSS evaluation, it will be censored at the date of last during-treatment EDSS evaluation.

[a] Derived from Kaplan-Meier estimates

[b] Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

[c] Derived from log-rank test with stratification of EDSS strata at baseline and region

PGM=PRODOPS/HMR1726/EFC6049/CSR/REPORT/PGM/eff_time2event_i_t.sas OUT=REPORT/OUTPUT/eff_dp24_i_t_i.rtf (18AUG2010 - 18:23)

No difference in effect was demonstrated on the patient reported outcomes – FIS and MSFC or on quality of life variables SF-36 and EQ-5D between teriflunomide and placebo.

The overall MRI findings supported the primary results of both teriflunomide dose groups. Both teriflunomide doses improved several MRI parameters of disease activity, with a greater improvement observed for the 14 mg dose, as presented in table 12. Change from baseline in BOD at Week 108 was lower in both 7 mg and 14 mg teriflunomide groups compared with placebo ($p=0.0317$ and $p=0.0003$, respectively). Patients in both teriflunomide groups had fewer Gd-enhancing T1 lesions per scan than those in the placebo group ($p<0.0001$ for both doses). A post-hoc analysis comparing the 2 doses of teriflunomide showed that the 14 mg dose showed a greater improvement than the 7 mg dose ($p=0.0024$). The change from baseline in T1 hypointense lesion volume was reduced by teriflunomide 14 mg compared with placebo ($p=0.0161$) while no statistically significant difference was observed between the 7 mg dose and the placebo group.

Table 12 MRI findings

	Placebo (N=363)	teriflunomide 7 mg (N=365)	teriflunomide 14 mg (N=358)
Change from baseline at week 108 (MMRM)[a]			
Number	256	262	260
LS Mean (SE)	0.096 (0.009)	0.079 (0.009)	0.066 (0.009)
LS Mean Difference from placebo (SE)		-0.016 (0.012)	-0.030 (0.013)
95% CI		(-0.041, 0.008)	(-0.055, -0.006)
P-value		0.1916	0.0161
LS Mean Difference from 7 mg (SE)			-0.014 (0.012)
95% CI			(-0.038, 0.011)
P-value			0.2664
Number of Gd-enhancing lesions per scan			
Estimate (95% CI)	1.331 (1.059, 1.673)	0.570 (0.434, 0.748)	0.261 (0.167, 0.407)
Relative risk vs placebo (95% CI)		0.428 (0.310, 0.592)	0.196 (0.120, 0.321)
P-value		<.0001	<.0001
Relative risk vs 7 mg (95% CI)			0.457 (0.276, 0.757)
P-value			0.0024

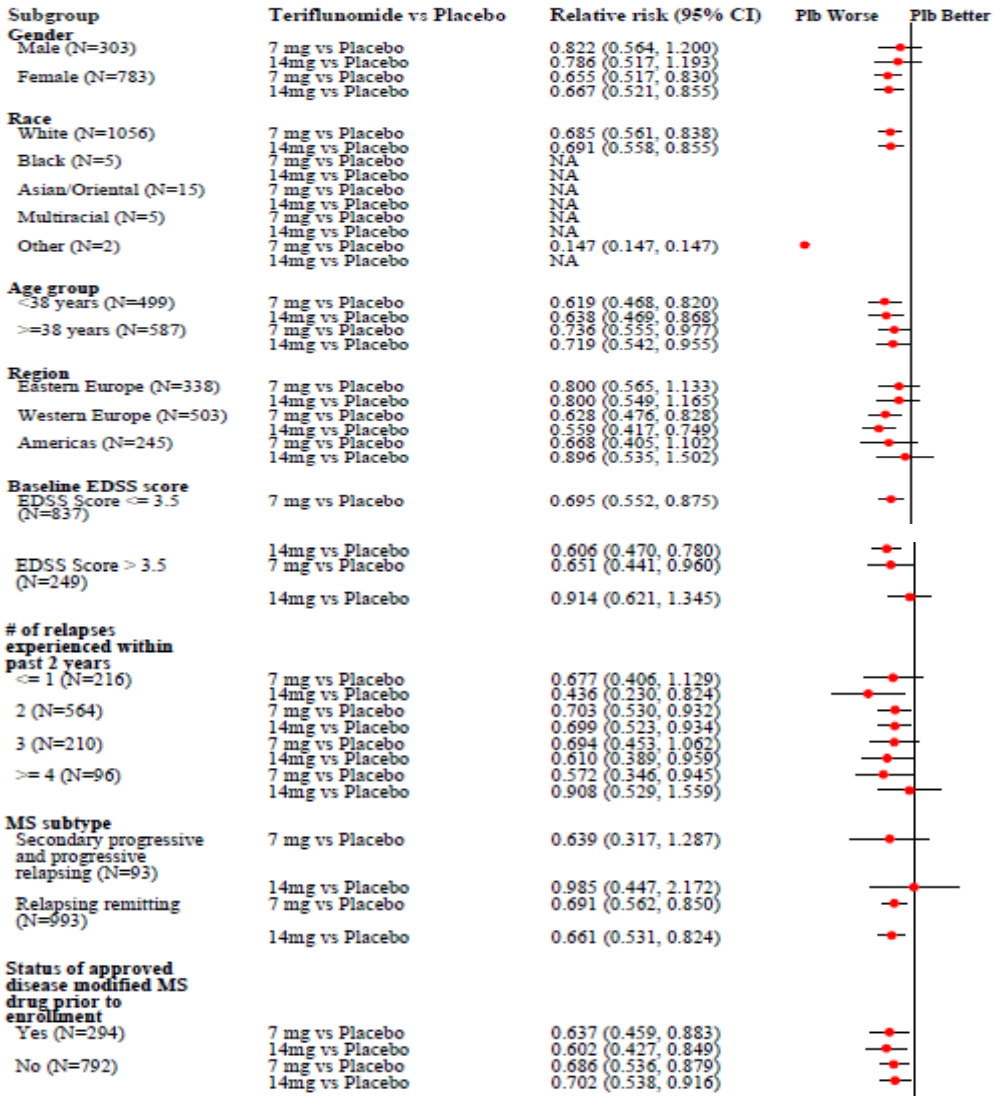
[a] Based on cubic root transformed data

	Placebo (N=363)	teriflunomide 7 mg (N=365)	teriflunomide 14 mg (N=358)
BOD (ml)			
Baseline			
Number	358	359	355
Mean (SD)	19.337 (18.939)	20.416 (20.594)	18.076 (17.488)
Change from baseline at week 108			
Number	256	262	260
Mean (SD)	2.208 (7.002)	1.308 (6.799)	0.723 (7.591)
Change from baseline at week 108 (MMRM)[a]			
Number	256	262	260
LS Mean (SE)	0.132 (0.018)	0.080 (0.018)	0.043 (0.018)
LS Mean Difference from placebo (SE)		-0.053 (0.024)	-0.089 (0.025)
95% CI		(-0.101, -0.005)	(-0.137, -0.041)
P-value		0.0317	0.0003
LS Mean Difference from 7 mg (SE)			-0.036 (0.024)
95% CI			(-0.084, 0.012)
P-value			0.1388
Volume of hypointense T1 lesions (ml)			
Baseline			
Number	358	359	355
Mean (SD)	3.256 (3.644)	3.361 (3.960)	2.910 (3.246)
Change from baseline at week 108			
Number	256	262	260
Mean (SD)	0.533 (1.063)	0.499 (1.154)	0.331 (1.012)

Ancillary analyses

Subgroup analyses of the MS relapse and the disability progression sustained for 12 weeks are presented in figures 4 and 5.

Fig. 4 Summary of MS relapse by all subgroups (ITT population)



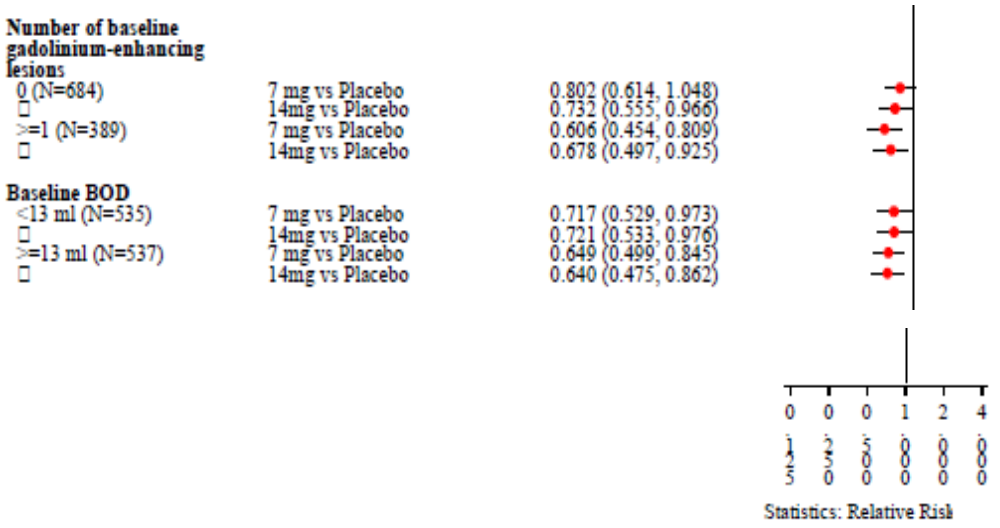
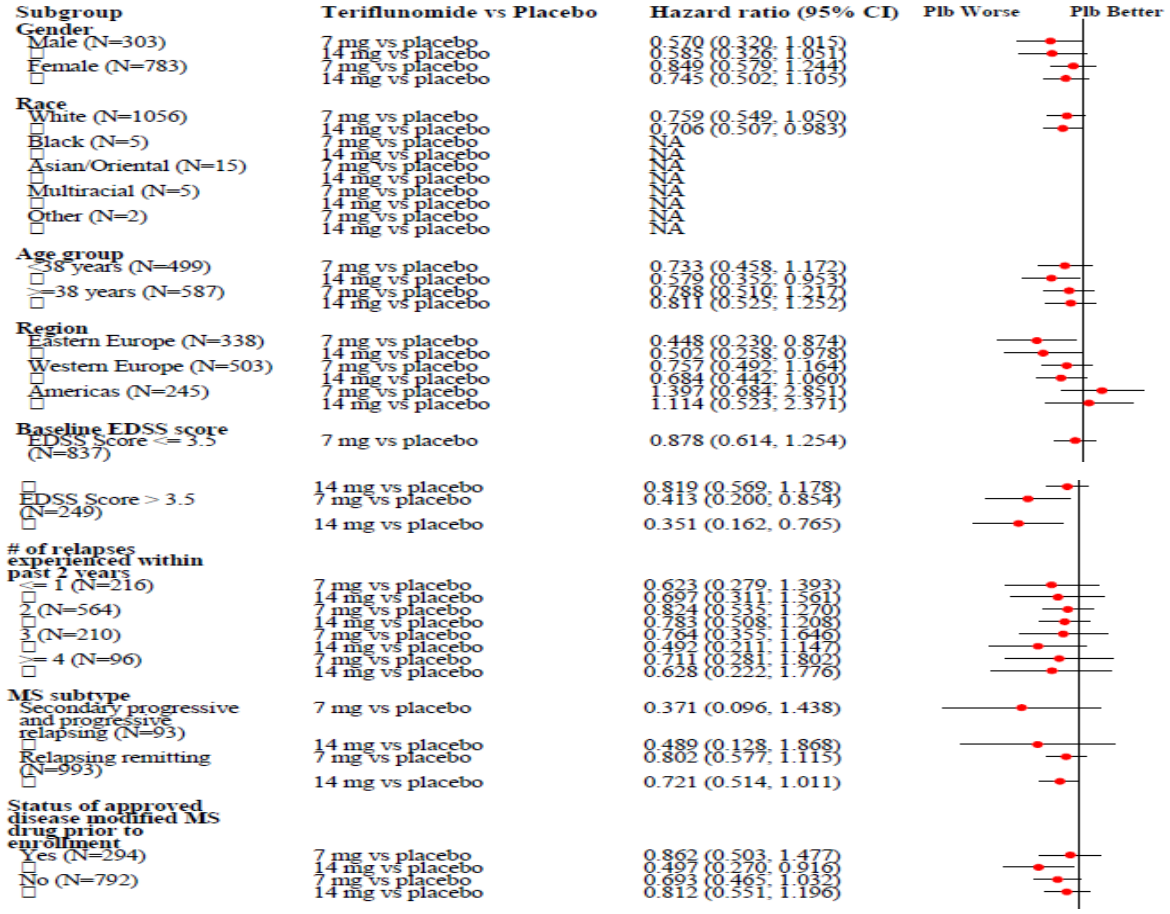
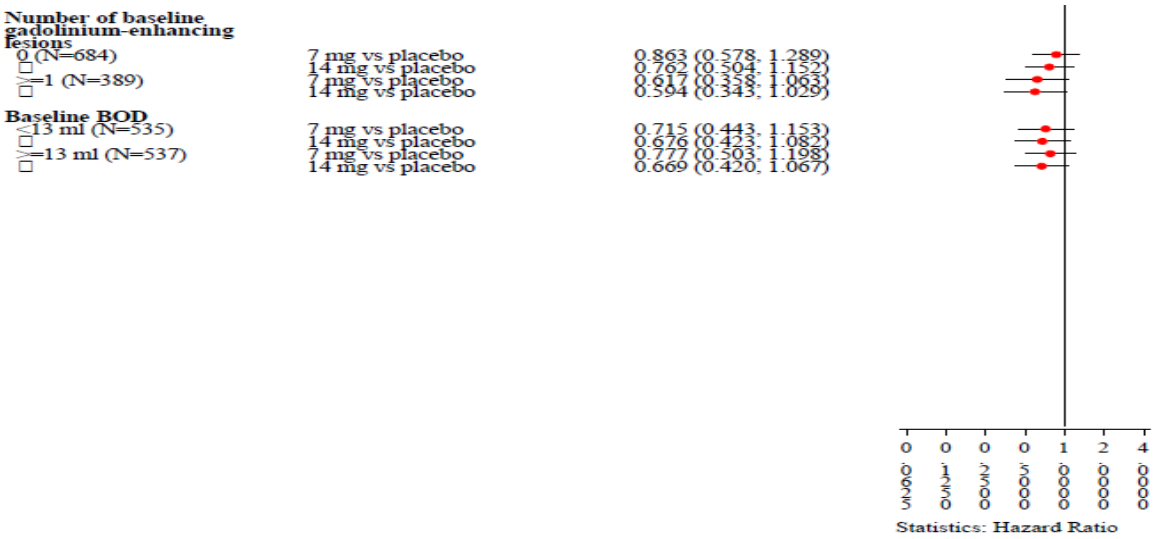


Fig. 5 Summary of time to disability progression sustained for 12 weeks by all subgroups (ITT population)





The applicant also provided results (table 13) for the subgroup of patients with high activity of the disease, based on the following definition of high disease activity: patients with at least 2 relapses in past year and 1 Gd lesion at baseline.

Table 13 ARR and 12 weeks disability progression in subgroups based on disease activity

	Annualized relapse rate Relative risk ratio (95% CI)		12 weeks disability progression Hazard ratio (95% CI)	
Subgroup	7 mg vs. Placebo	14 mg vs. Placebo	7 mg vs. Placebo	14 mg vs. Placebo
TEMSO / Clinical&imaging criteria				
Low-to-moderate (N=959)	0.721 (0.577, 0.900)	0.657 (0.522, 0.827)	0.810 (0.576, 1.139)	0.711 (0.501, 1.010)
High (N=127)	0.508 (0.320, 0.806)	0.810 (0.513, 1.278)	0.610 (0.247, 1.508)	0.648 (0.264, 1.592)

EFC10531 (TOWER) – A multi-center, double-blind, parallel-group, placebo-controlled study of the efficacy and safety of teriflunomide in patients with relapsing multiple sclerosis

Methods

Study Participants

To be eligible to participate in the study, the patients had to be between 18-55 years old, meeting the McDonald´s criteria (2005) for MS diagnosis, with an EDSS score of ≤5.5, exhibiting a relapsing clinical course with or without progression. The patients had to have at least 1 relapse in the 12 months preceding randomization, or at least 2 relapses in the 24 months preceding the randomization visit. Patients with significantly impaired bone marrow function or significant anaemia, leukopenia or thrombocytopenia, patients with congenital or acquired immunodeficiency, malignancies or patients with liver or renal function impairment could not be enrolled. In addition, patients were not eligible for entry into the study if they met any of the following criteria: known history of active tuberculosis, persistent severe infection, HIV positivity, chronic pancreatitis, pregnancy and breast-feeding. Prior or concomitant use of natalizumab, cladribin, mitoxantron or other immunosuppressive drugs was not

allowed. Prior use of interferons, cytokine therapy, glatiramer acetate or i.v. immunoglobulin therapy was acceptable only if discontinued more than three months before participation in the study.

Treatments

One tablet of placebo, 7 mg teriflunomide or 14 mg teriflunomide was to be taken orally once daily in the morning for 48-152 weeks, depending on time of enrollement. The study medications were to be taken with or without food. A dosing interruption of less than or equal to 15 days was allowed.

Concomitant use of systemic corticosteroids for the treatment of MS relapse was allowed during the study, if clinically necessary and according to the investigator´s judgment. The preferred standardized treatment was methylprednisolone sodium succinate 1 g, intravenously daily for 3 to 5 days.

Objectives

The primary objective of the study was to assess the effect of teriflunomide in comparison to placebo on frequency of MS relapses in patients with relapsing MS.

The secondary objectives comprised evaluating the effect of teriflunomide in comparison to placebo on disability progression in patients with relapsing forms of MS, the effect of teriflunomide on fatigue and health-related quality of life and the safety and tolerability of teriflunomide.

Outcomes/endpoints

The primary efficacy endpoint of this study was the annualized relapse rate, defined as the number of confirmed relapses per patient-year.

The key secondary efficacy endpoint was time to disability progression, defined as the time to at least 1 point increase on EDSS score from baseline, if the baseline EDSS score was ≤5.5, or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was >5.5; this increase in EDSS score was to be persistent for at least 12 weeks.

Other secondary endpoints were patient reported-fatigue assessed by the Fatigue Impact Scale (FIS), time to first confirmed relapse, proportion of patients without relapse, proportion of patients free of disability progression at 6 months, 1 year and 2 years, change from baseline in EDSS and the 36-item Short Form generic health survey (SF-36) scores.

Sample size

The sample size calculations were based on a 1:1:1 randomization ratio for teriflunomide 14 mg, teriflunomide 7 mg and placebo, and the primary and key secondary efficacy variables of ARR and time to (first) sustained disability progression, respectively, with the assumptions of: placebo ARR of 0.74 (based on recently available MS data, where the placebo 2-year relapse rate was estimated to be 1.48); a 25% relative risk reduction in ARR, (i.e, ARR of 0.55, for teriflunomide); number of relapses follows approximately Poisson distribution with over dispersion parameter of 1.3 (estimated with recently available data on Tysabri trials and protocol 2001, LTS6048); a 1.5-year recruitment period with linear recruitment rate, thus the average exposure duration for ongoing patients is 1.75 years; a 2-tailed 5% significance level and expected drop-out rate of 20%. Based on these assumptions, a total of 1110 patients (370 per treatment group) were needed for the study and had 94% power to detect a 25% relative risk reduction in ARR. In addition, the study had 75% power to detect a 37% hazard ratio reduction in time to disability progression using log-rank test. The sample size and power estimate was computed using EAST 4.0 with the assumptions of a hazard rate of 0.1783 in the placebo group, and 0.1116 in the teriflunomide group (i.e., 30% probability of disability progression for placebo patients

by the end of 2 years, and 20% for teriflunomide patients). The sample size was also adjusted for a 20% drop out rate.

Randomisation

After a screening phase of up to 4 weeks and completion of all baseline procedures, the patients were centrally randomized in a 1:1:1 ratio to 1 of the 3 treatment groups. Randomization was stratified by site and baseline EDSS score (≤3.5 versus >3.5).

Blinding (masking)

The trial was conducted in a double-blind fashion, with all investigational products identical in appearance. Similar procedures to maintain the blind were implemented as in the first placebo-controlled trial, EFC6049/TEMSO.

Statistical methods

Efficacy analyses were based on the ITT population consisting of all randomized patients, who had at least 1 day exposure to the investigational product. Safety analyses were based on the safety population which included all patients randomized and exposed to the investigational product, as treated. The analyses of the primary efficacy and key secondary efficacy variables were also performed using the per-protocol (PP) population, defined as a subset of the ITT population containing patients without a major efficacy-related protocol deviation.

The primary analysis for the ARR (primary efficacy endpoint) was performed using a Poisson regression model with robust error variance including the number of confirmed relapses with their onset between randomization date and last dose date as the response variable, treatment, region and EDSS strata as covariates. To account for different treatment durations among patients, the log-transformed standardized treatment duration was included in the model as an “offset” variable for appropriate computation of relapse rate. The robust error variances were estimated by specifying the patient identifier in the repeated statement using SAS PROC GENMOD, which is equivalent to the Generalized Estimating Equation (GEE) model. A supportive analysis for ARR was performed using negative binomial model with the same model specification as in the Poisson regression model above. Two-sided 95% confidence intervals of the rate ratio as well as risk difference were provided for the comparison of each active treatment versus placebo. The estimated relapse rates and 2-sided 95% confidence intervals were provided for each treatment group.

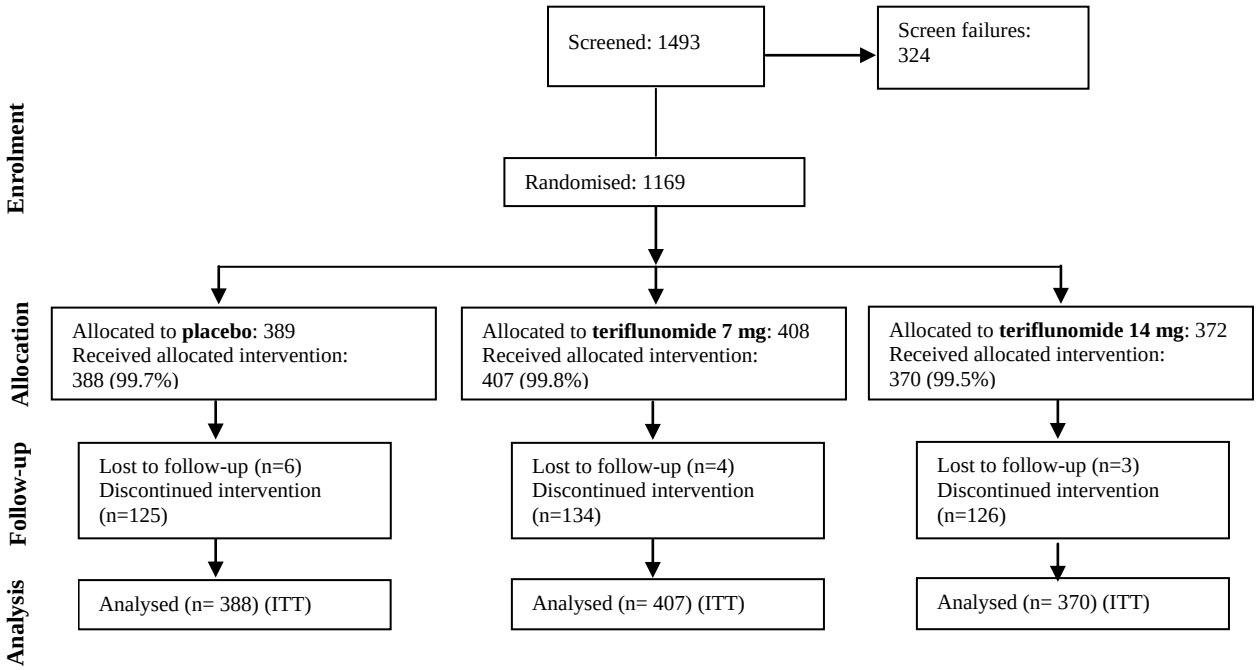
The key secondary analysis for the time to disability progression (sustained for at least 12 weeks) was performed using log-rank test with time to first disability progression as the dependent variable, treatment as test variable, and region and EDSS strata as strata variables.

The Kaplan-Meier plots were generated and the Kaplan-Meier method was used to estimate the probability (95% CI) of disability progression at 6 months, 1 year, 2 years and 2.5 years for each treatment group.

Results

Participant flow

The study participant flow is shown in the figure 6.
Fig. 6



Patient completion rate and reasons for discontinuation are presented in table 14.

Table 14

	Placebo (N=389)	teriflunomide 7 mg (N=408)	teriflunomide 14 mg (N=372)
Randomized and not treated	1 (0.3%)	1 (0.2%)	2 (0.5%)
Randomized and treated	388 (99.7%)	407 (99.8%)	370 (99.5%)
Completed study treatment period	263 (67.6%)	273 (66.9%)	244 (65.6%)
Did not complete study treatment period	125 (32.1%)	134 (32.8%)	126 (33.9%)
Reason for study treatment discontinuation			
Adverse event	26 (6.7%)	54 (13.2%)	58 (15.6%)
Lack of efficacy	37 (9.5%)	30 (7.4%)	20 (5.4%)
Poor compliance to protocol	15 (3.9%)	3 (0.7%)	4 (1.1%)
Lost to follow-up	6 (1.5%)	4 (1.0%)	3 (0.8%)
Other reason	41 (10.5%)	43 (10.5%)	41 (11.0%)
Patient's decision to permanently discontinue treatment	87 (22.4%)	90 (22.1%)	76 (20.4%)
Completed study including EPTD follow-up period	274 (70.4%)	289 (70.8%)	258 (69.4%)
Patients who participated the EPTD follow-up period	23 (5.9%)	26 (6.4%)	35 (9.4%)
Patients who completed the EPTD follow-up period	11 (2.8%)	16 (3.9%)	14 (3.8%)
Patients who did not complete the EPTD follow-up period	12 (3.1%)	10 (2.5%)	21 (5.6%)
Reason for EPTD follow-up discontinuation			
Lost to follow-up	0	4 (1.0%)	1 (0.3%)
Subject did not wish to continue	11 (2.8%)	5 (1.2%)	17 (4.6%)
Other reason	1 (0.3%)	1 (0.2%)	3 (0.8%)

Recruitment

The study took place between 26 August 2008 and 17 April 2012.

Conduct of the study

There were 5 amendments to the protocol, the most crucial one being amendment 4, which among others, changed the timepoint for confirmation of disability progression from 24 weeks to 12 weeks to align the analysis with the TEMSO study.

Baseline data

A summary of the patient population enrolled in the study is presented in the tables below:

Table 15 Demographics (randomized population)

	Placebo (N=389)	teriflunomide 7 mg (N=408)	teriflunomide 14 mg (N=372)	All (N=1169)
Age (years)				
Number	389	408	372	1169
Mean (SD)	38.1 (9.1)	37.4 (9.4)	38.2 (9.4)	37.9 (9.3)
Median	39.0	38.0	38.0	38.0
Min : Max	18 : 56	18 : 55	18 : 56	18 : 56
Age Group [n (%)]				
Number	389	408	372	1169
<38	177 (45.5%)	201 (49.3%)	174 (46.8%)	552 (47.2%)
≥38	212 (54.5%)	207 (50.7%)	198 (53.2%)	617 (52.8%)
Sex [n (%)]				
Number	389	408	372	1169
Male	116 (29.8%)	108 (26.5%)	114 (30.6%)	338 (28.9%)
Female	273 (70.2%)	300 (73.5%)	258 (69.4%)	831 (71.1%)
Race [n (%)]				
Number	389	408	372	1169
Caucasian/White	318 (81.7%)	329 (80.6%)	313 (84.1%)	960 (82.1%)
Black	7 (1.8%)	8 (2.0%)	7 (1.9%)	22 (1.9%)
Asian/Oriental	60 (15.4%)	60 (14.7%)	49 (13.2%)	169 (14.5%)
Other	4 (1.0%)	11 (2.7%)	3 (0.8%)	18 (1.5%)
Region [n (%)]				
Number	389	408	372	1169
Eastern Europe	117 (30.1%)	124 (30.4%)	116 (31.2%)	357 (30.5%)
Western Europe and Africa	121 (31.1%)	127 (31.1%)	120 (32.3%)	368 (31.5%)
Asia and Australia	67 (17.2%)	65 (15.9%)	55 (14.8%)	187 (16.0%)
America	84 (21.6%)	92 (22.5%)	81 (21.8%)	257 (22.0%)

Table 16 Baseline disease characteristics – randomized population

	Placebo (N=389)	teriflunomide 7 mg (N=408)	teriflunomide 14 mg (N=372)	All (N=1169)
Time since first diagnosis of MS (years)				
Number	389	408	371	1168
Mean (SD)	4.92 (5.66)	5.30 (5.45)	5.27 (5.90)	5.16 (5.66)
Median	2.92	3.50	3.25	3.17
Min : Max	0.1 : 33.8	0.0 : 29.1	0.0 : 32.7	0.0 : 33.8
Time since first symptoms of MS (years)				
Number	389	408	371	1168
Mean (SD)	7.64 (6.70)	8.18 (6.75)	8.18 (6.73)	8.00 (6.72)
Median	5.75	6.33	6.92	6.25
Min : Max	0.2 : 35.3	0.1 : 34.4	0.2 : 36.9	0.1 : 36.9
Time since most recent relapse onset (months)				
Number	389	408	371	1168
Mean (SD)	5.29 (3.41)	5.18 (3.41)	5.33 (3.32)	5.26 (3.38)
Median	4.00	4.00	5.00	4.00
Min : Max	1.0 : 23.0	1.0 : 20.0	1.0 : 20.0	1.0 : 23.0
Number of relapses within past 1 year				
Number	388	408	371	1167
Mean (SD)	1.4 (0.8)	1.4 (0.7)	1.4 (0.7)	1.4 (0.7)
Median	1.0	1.0	1.0	1.0
Min : Max	0 : 7	0 : 5	0 : 5	0 : 7

0	9 (2.3%)	9 (2.2%)	5 (1.3%)	23 (2.0%)
1	251 (64.7%)	263 (64.5%)	240 (64.7%)	754 (64.6%)
2	105 (27.1%)	105 (25.7%)	99 (26.7%)	309 (26.5%)
3	13 (3.4%)	26 (6.4%)	22 (5.9%)	61 (5.2%)
≥4	10 (2.6%)	5 (1.2%)	5 (1.3%)	20 (1.7%)
Number of relapses within past 2 years				
Number	389	408	370	1167
Mean (SD)	2.1 (1.1)	2.1 (1.1)	2.1 (1.2)	2.1 (1.2)
Median	2.0	2.0	2.0	2.0
Min : Max	1 : 8	1 : 8	1 : 9	1 : 9
1	129 (33.2%)	137 (33.6%)	121 (32.7%)	387 (33.2%)
2	162 (41.6%)	148 (36.3%)	155 (41.9%)	465 (39.8%)
3	56 (14.4%)	82 (20.1%)	50 (13.5%)	188 (16.1%)
≥4	42 (10.8%)	41 (10.0%)	44 (11.9%)	127 (10.9%)
MS subtype [n (%)]				
Number	389	408	370	1167
Relapsing Remitting	379 (97.4%)	393 (96.3%)	366 (98.9%)	1138 (97.5%)
Secondary Progressive	4 (1.0%)	3 (0.7%)	2 (0.5%)	9 (0.8%)
Progressive Relapsing	6 (1.5%)	12 (2.9%)	2 (0.5%)	20 (1.7%)
With previous MS medication in the last 2 years [n (%)]				
Number	389	408	372	1169
Yes	135 (34.7%)	123 (30.1%)	126 (33.9%)	384 (32.8%)
No	254 (65.3%)	285 (69.9%)	246 (66.1%)	785 (67.2%)
Baseline EDSS score				
Number	389	408	372	1169
Mean (SD)	2.69 (1.36)	2.71 (1.39)	2.71 (1.35)	2.70 (1.37)
Median	2.50	2.50	2.50	2.50
Min : Max	0.0 : 5.5	0.0 : 5.5	0.0 : 6.5	0.0 : 6.5
Randomized EDSS strata at baseline [n (%)]				
Number	389	408	372	1169
≤3.5	299 (76.9%)	309 (75.7%)	277 (74.5%)	885 (75.7%)
>3.5	90 (23.1%)	99 (24.3%)	95 (25.5%)	284 (24.3%)
Actual EDSS strata at baseline [n (%)]				
Number	389	408	372	1169
≤3.5	294 (75.6%)	301 (73.8%)	276 (74.2%)	871 (74.5%)
>3.5	95 (24.4%)	107 (26.2%)	96 (25.8%)	298 (25.5%)

PGM=PRODOPS/HMR1726/EFC10531/CSR_01/REPORT/PGM/dem_disease_r_t.sas OUT=REPORT/OUTPUT/dem_disease_r_t_i.rtf (24MAY2012 - 16:30)

Table 17 MS medications taken within 2 years prior to first IP intake - Number of patients by standardized medication name - Randomized population

	Placebo (N=389)	teriflunomide 7 mg (N=408)	teriflunomide 14 mg (N=372)	All (N=1169)
Previous treatment with MS medication	135 (34.7%)	123 (30.1%)	126 (33.9%)	384 (32.8%)
Interferon beta-1a	59 (15.2%)	63 (15.4%)	64 (17.2%)	186 (15.9%)
Interferon beta-1a subcutaneous QOD	34 (8.7%)	30 (7.4%)	36 (9.7%)	100 (8.6%)
Interferon beta-1a intramuscular weekly	26 (6.7%)	41 (10.0%)	28 (7.5%)	95 (8.1%)
Interferon beta-1a unspecified	3 (0.8%)	0	2 (0.5%)	5 (0.4%)
Glatiramer acetate	52 (13.4%)	47 (11.5%)	37 (9.9%)	136 (11.6%)
Interferon beta-1b	38 (9.8%)	27 (6.6%)	35 (9.4%)	100 (8.6%)
Fingolimod	1 (0.3%)	2 (0.5%)	3 (0.8%)	6 (0.5%)
Interferon beta	2 (0.5%)	1 (0.2%)	1 (0.3%)	4 (0.3%)
Natalizumab	1 (0.3%)	0	0	1 (<0.1%)
Mitoxantrone	0	0	0	0
No previous treatment with MS medication	254 (65.3%)	285 (69.9%)	246 (66.1%)	785 (67.2%)

IP: Investigational product
WHO-DD dictionary - March, 2012
Prior medications are those the patients used prior to first IP intake.
Note: A patient can be counted in several categories.
Table sorted by decreasing frequency of standardized medication name incidence in the overall treatment group
PGM=PRODOPS/HMR1726/EFC10531/CSR_01/REPORT/PGM/dem_prevmsmed_r_t.sas
OUT=REPORT/OUTPUT/dem_prevmsmed_r_t_i.rtf (13JUN2012 - 9:05)

Numbers analysed

The analysis populations are summarised in table 18.

Table 18

	Placebo	teriflunomide 7 mg	teriflunomide 14 mg
Randomized population	389 (100%)	408 (100%)	372 (100%)
Efficacy population			
ITT population	388 (99.7%)	407 (99.8%)	370 (99.5%)
PP population	381 (97.9%)	400 (98.0%)	352 (94.6%)
PK population	385	408	371
Safety population	385	409	371

Note: The safety and PK patients are tabulated according to treatment actually received (as treated).
For the other populations, patients are tabulated according to their randomized treatment.
PGM=PRODOPS/HMR1726/EFC10531/CSR_01/REPORT/PGM/dis_populations_r_t.sas OUT=REPORT/OUTPUT/dis_populations_r_t_i.rtf (07JUN2012 - 17:20)

Outcomes and estimation

Results of the primary analysis, i.e. analysis of the MS relapse in the ITT population, are presented in table 19.

Table 19 Analysis of MS relapse

	Placebo (N=388)	teriflunomide 7 mg (N=407)	teriflunomide 14 mg (N=370)
Number of patients with >= 1 relapses			
Yes	186 (47.9%)	144 (35.4%)	122 (33.0%)
No	202 (52.1%)	263 (64.6%)	248 (67.0%)
Number of relapses			
0	202 (52.1%)	263 (64.6%)	248 (67.0%)
1	116 (29.9%)	83 (20.4%)	79 (21.4%)
2	46 (11.9%)	39 (9.6%)	36 (9.7%)
3	13 (3.4%)	17 (4.2%)	4 (1.1%)
4	7 (1.8%)	3 (0.7%)	2 (0.5%)
>= 5	4 (1.0%)	2 (0.5%)	1 (0.3%)
Total number of relapses	296	235	177
Total patient-years followed	608.4	614.0	573.6
Unadjusted annualized relapses rate [a]	0.487	0.383	0.309
Adjusted annualized relapse rate [b]			
Estimate (95% CI)	0.501 (0.432, 0.581)	0.389 (0.332, 0.457)	0.319 (0.267, 0.381)
Relative risk (95% CI)		0.777 (0.630, 0.958)	0.637 (0.512, 0.793)
P-value[c]		0.0183	0.0001
Risk difference (95% CI)		-0.112 (-0.205, -0.018)	-0.182 (-0.270, -0.093)
P-value[d]		0.0189	0.0001
Individual patient annualized relapse rate [e]			
N	388	407	370
Mean (SD)	0.694 (1.379)	0.563 (1.398)	0.479 (2.477)
Median	0.000	0.000	0.000
Min : Max	0.00 : 13.04	0.00 : 13.04	0.00 : 45.66

[a] The total number of relapses that occurred during the treatment divided by the total number of patient-years treated in the study.
[b] Derived using Poisson model with the total number of confirmed relapses onset between randomization date and last dose date as the response variable, treatment, EDSS strata at baseline and region as covariates, and log-transformed treatment duration as an offset variable
[c] Chi-square test from estimating the rate ratios.
[d] Z test from estimating the risk difference.
[e] The number of relapse for each patient divided by the number of years treated in the study
PGM=PRODOPS/HMR1726/EFC10531/CSR_01/REPORT/PGM/eff_relap_t.sas OUT=REPORT/OUTPUT/eff_relap_po_i_t_i.rtf (24MAY2012 - 16:35)

Results of the primary analysis in the ITT population were confirmed by analyses in the PP population.

Analysis of the key secondary endpoint, i.e. time to disability progression sustained for 12 weeks (ITT population) is presented in table 20.

Table 20 Time to disability progression sustained for 12 weeks

	Placebo (N=388)	teriflunomide 7 mg (N=407)	teriflunomide 14 mg (N=370)
Number of patients with disability progression	65 (16.8%)	65 (16.0%)	44 (11.9%)
Number of patients who were censored	323 (83.2%)	342 (84.0%)	326 (88.1%)
Probability of disability progression (95% CI) at [a]			
24 weeks	0.080 (0.052, 0.107)	0.053 (0.030, 0.076)	0.027 (0.009, 0.044)
48 weeks	0.142 (0.106, 0.179)	0.121 (0.087, 0.155)	0.078 (0.049, 0.108)
108 weeks	0.197 (0.152, 0.241)	0.211 (0.161, 0.261)	0.158 (0.112, 0.204)
132 weeks	0.210 (0.159, 0.260)	0.222 (0.168, 0.276)	0.158 (0.112, 0.204)
Hazard ratio (95% CI)[b]		0.955 (0.677, 1.347)	0.685 (0.467, 1.004)
P-value[c]		0.7620	0.0442

Note: The time-to-event variable is defined as the time (days) from the date of randomization to the date of the first disability progression. For patients who have no disability progression on or before last during treatment EDSS evaluation, it will be censored at the date of last during-treatment EDSS evaluation.

[a] Derived from Kaplan-Meier estimates

[b] Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

[c] Derived from log-rank test with stratification of EDSS strata at baseline and region.

PGM=PRODOPS/HMR1726/EFC10531/CSR_01/REPORT/PGM/eff_dp_i_t.sas OUT=REPORT/OUTPUT/eff_dp_i_t_i.rtf (24MAY2012 - 16:34)

Neither of the teriflunomide treatment arms reached statistical significance when compared to placebo for the endpoint time to disability progression sustained for 24 weeks (p=0.8218, p=0.4456) as presented in table 21.

Table 21 Time to disability progression sustained for 24 weeks

		teriflunomide	
	Placebo (N=388)	7 mg (N=407)	14 mg (N=370)
Number of patients with disability progression	41 (10.6%)	45 (11.1%)	33 (8.9%)
Number of patients who were censored	347 (89.4%)	362 (88.9%)	337 (91.1%)
Probability of disability progression (95% CI) at [a]			
24 weeks	0.055 (0.031, 0.078)	0.034 (0.016, 0.053)	0.027 (0.009, 0.044)
48 weeks	0.093 (0.063, 0.124)	0.090 (0.060, 0.120)	0.065 (0.038, 0.093)
108 weeks	0.119 (0.084, 0.155)	0.149 (0.106, 0.192)	0.117 (0.078, 0.155)
132 weeks	0.133 (0.089, 0.177)	0.149 (0.106, 0.192)	0.117 (0.078, 0.155)
Hazard ratio (95% CI)[b]		1.054 (0.690, 1.610)	0.843 (0.533, 1.334)
P-value[c]		0.8218	0.4456

Note: The time-to-event variable is defined as the time (days) from the date of randomization to the date of the first disability progression. For patients who have no disability progression on or before last during treatment EDSS evaluation, it will be censored at the date of last during-treatment EDSS evaluation.

[a] Derived from Kaplan-Meier estimates

[b] Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

[c] Derived from log-rank test with stratification of EDSS strata at baseline and region

PGM=PRODOPS/HMR1726/EFC10531/CSR_01/REPORT/PGM/eff_dp_i_t.sas OUT=REPORT/OUTPUT/eff_dp24_i_t_i.rtf (24MAY2012 - 16:42)

With respect to time to first multiple sclerosis relapse, the estimated proportion of patients free of confirmed relapses at Week 48 was 60.6% in the placebo group, 71.9% in the teriflunomide 7 mg group, and 76.3% in the teriflunomide 14 mg group. The statistically significant hazard reduction was 30.2% (p=0.0016) for the teriflunomide 7 mg group and 36.9% (p<0.0001) for the teriflunomide 14 mg group.

The changes from baseline in EDSS score for the ITT population were analysed and a statistically significant treatment difference was observed for the 14 mg teriflunomide dose at Week 48 (LS mean difference from placebo (SE) = -0.139 (0.069); 95% CI: -0.274 to -0.004; p=0.0429). These results were consistent with the analyses in the PP population.

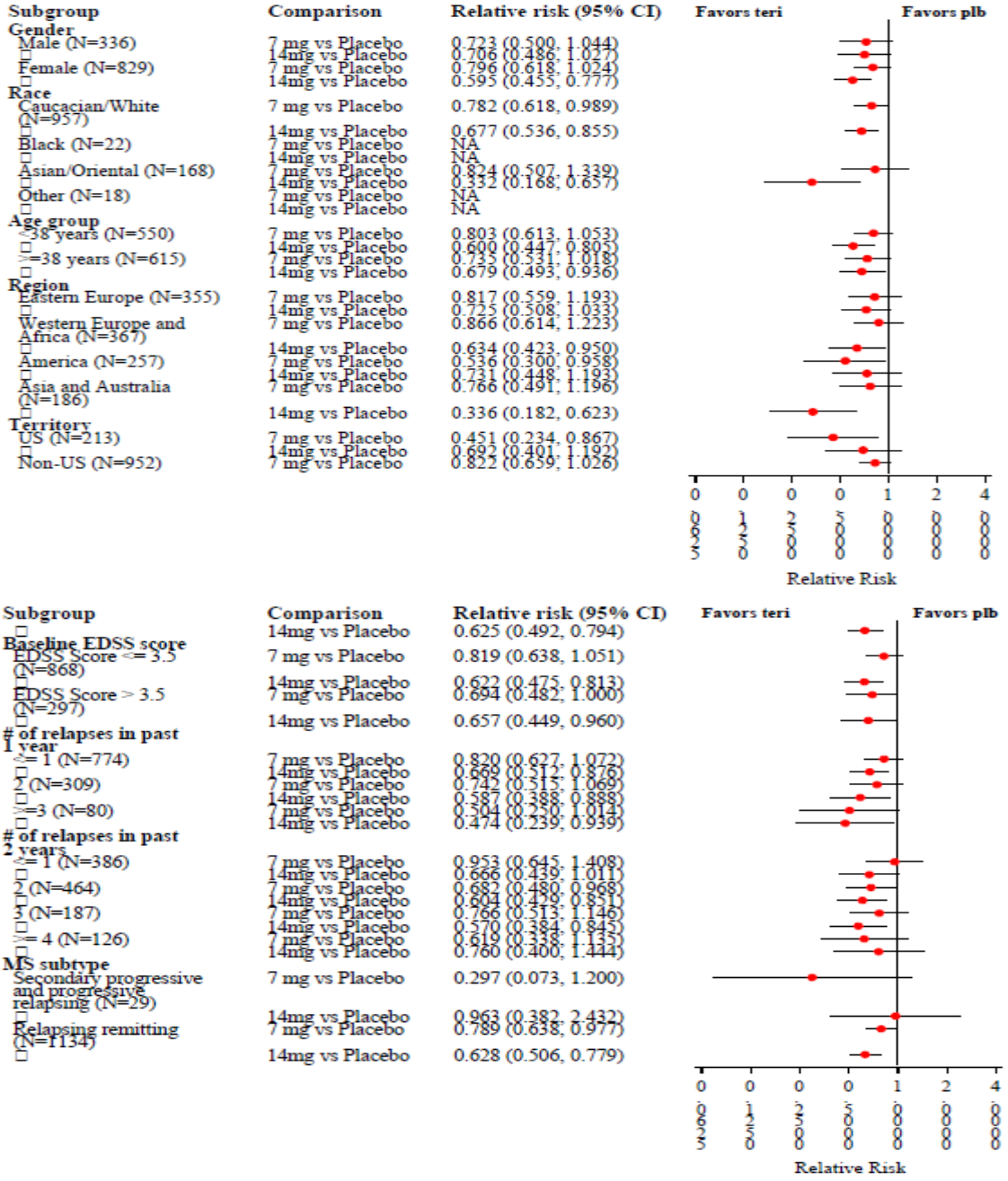
Analysis of the change from baseline values in FIS total score showed that data numerically favoured the teriflunomide dose groups compared with placebo. Based on ANCOVA analysis of FIS total score, the treatment difference was statistically significant at a nominal 0.05 level (without multiplicity adjustment) in the 14 mg dose group versus placebo (p=0.0429).

Analysis of SF-36 of both physical and mental components using the MMRM analysis showed a trend for effect in favour of 14 mg teriflunomide versus placebo. Based on ANCOVA analysis, the SF-36 mental health summary score showed a statistically significant treatment difference at a nominal 0.05 level (without multiplicity adjustment) in change from baseline to last visit in the 14 mg teriflunomide group (p=0.0224).

Ancillary analyses

Subgroup analyses of the MS relapse and the disability progression sustained for 12 weeks are presented in tables 6 and 7.

Fig. 7 Summary of MS relapse by all subgroups (ITT population)



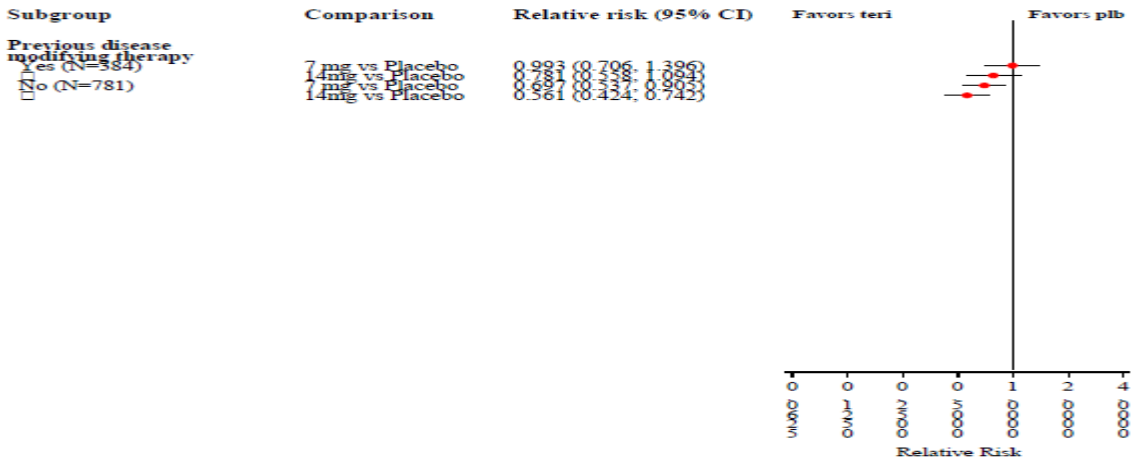
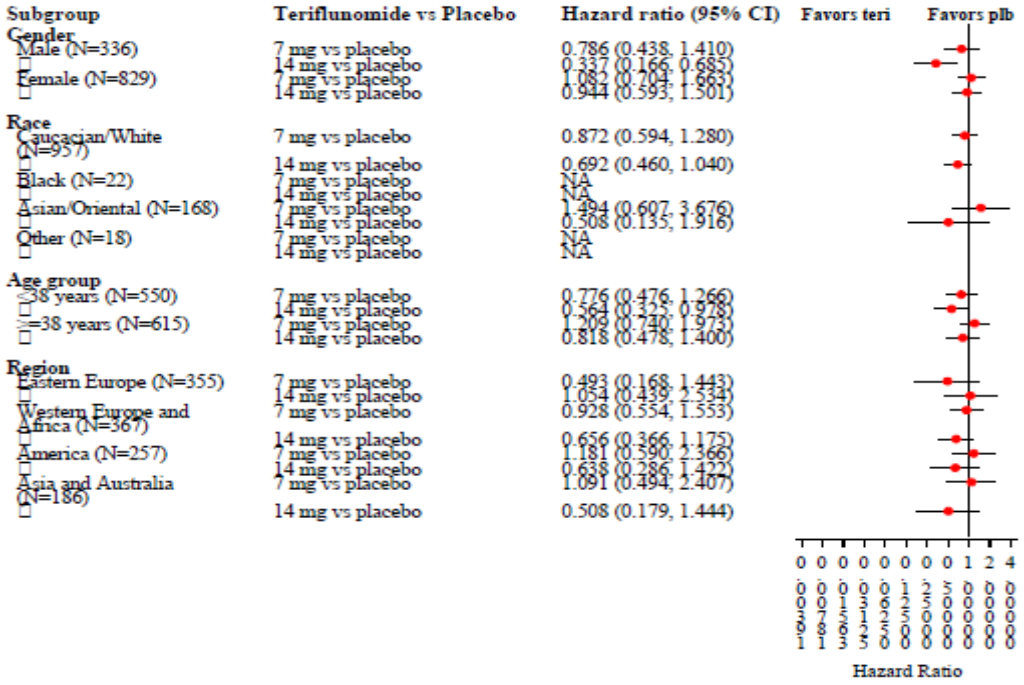
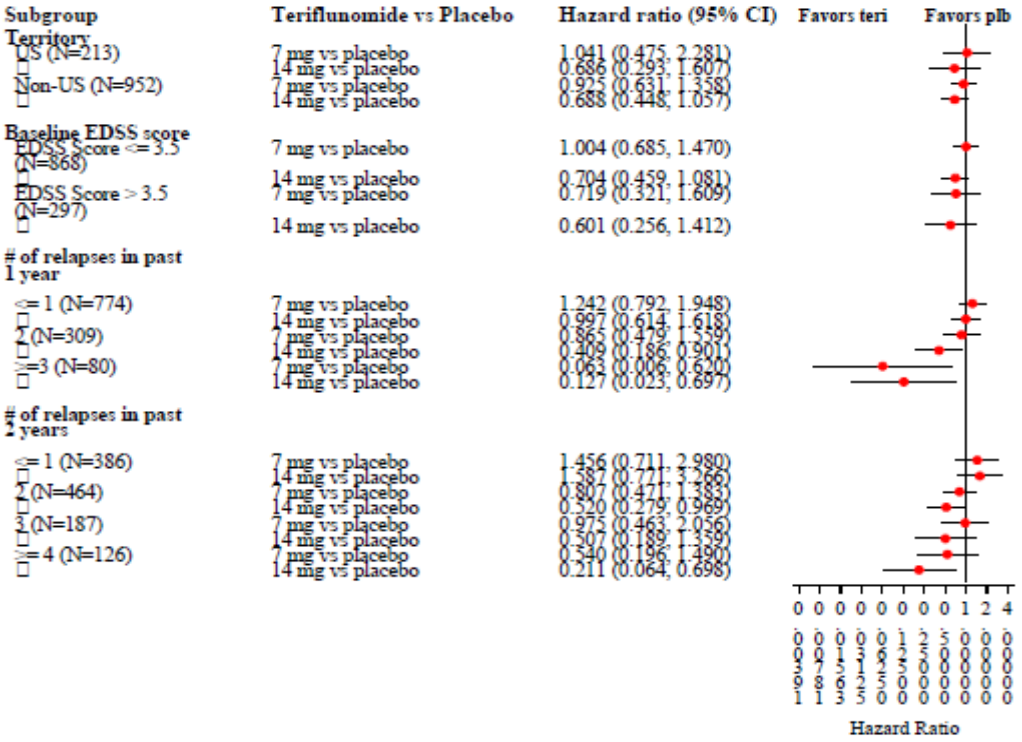


Fig. 8 Summary of time to disability progression sustained for 12 weeks by all subgroups (ITT population)





EFC10891 (TENERE) - A multi-center, randomized, parallel-group, rater-blinded study comparing the effectiveness and safety of teriflunomide and interferon beta-1a in patients with relapsing multiple sclerosis

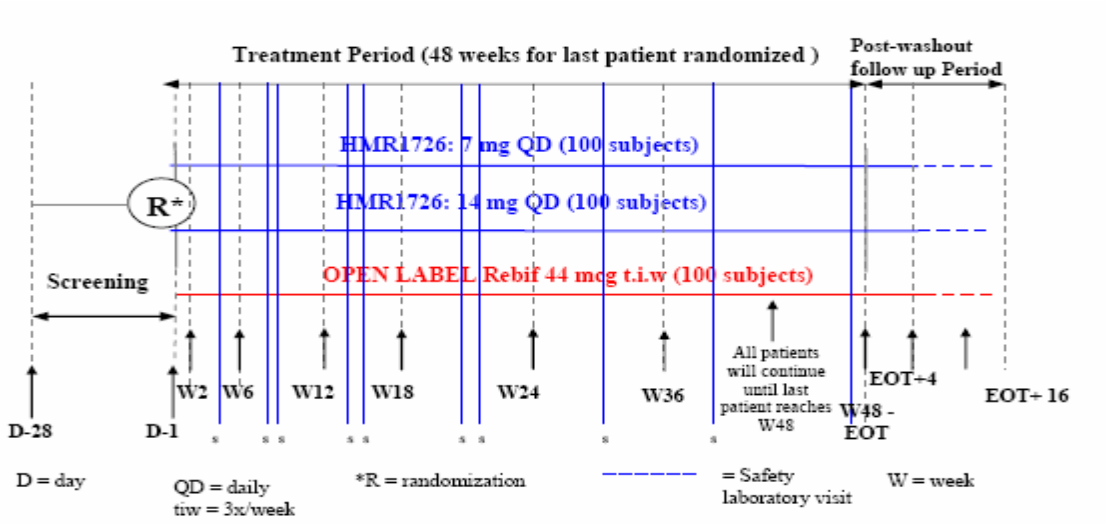
Methods

Study Participants

To be eligible to participate in the study, the patients had to be over 18 years old, meeting the McDonald´s criteria (2005) for MS diagnosis, with an EDSS score of ≤5.5 at the time of the screening visit. The exclusion criteria were generally in line with those established within the two placebo-controlled trials.

Treatments

Fig. 9



Patients allocated to teriflunomide were administered either one tablet 7 mg teriflunomide or 14 mg teriflunomide, which was to be taken orally once daily in the morning for a minimum of 48 weeks. The study medications were to be taken with or without food. Patients randomised to the active comparator were administered interferon-beta 1a in subcutaneous injections three times a week. Patients began the study with ascending doses of Rebif 8.8 mcg for the first 2 weeks, 22 mcg for the next 2 weeks and then 44 mcg. If a patient did not tolerate the 44 mcg dose, reduction back to the 22 mcg dose was permitted.

Objectives

The primary objective of the study was to assess the effectiveness of two doses of teriflunomide in comparison to interferon-beta 1a, evaluated by the time to failure.

The secondary objectives comprised evaluating the effect of the two doses of teriflunomide in comparison to interferon-beta 1a on frequency of relapses, fatigue, patient's satisfaction with treatment and safety and tolerability.

Outcomes/endpoints

The primary efficacy endpoint of this study was the time to failure, defined as the first occurrence of confirmed relapse or permanent study treatment discontinuation for any cause, whichever occurred first.

The secondary efficacy endpoints included the annualized relapse rate (ARR), Fatigue Impact Scale (FIS) and Treatment Satisfaction Questionnaire for Medication (TSQM).

Sample size

The sample size estimation was based on the comparison between teriflunomide and interferon beta 1a with regard to the primary endpoint: time to failure. With 100 randomized patients per arm, the study had 81% power to detect a difference between teriflunomide and interferon-beta 1a in time to failure at the 2-tailed significance level of α=0.025, assuming that the hazard rate was 0.4186 and 0.7440 for teriflunomide and interferon-beta 1a, respectively, and that the recruitment duration was approximately 1.5 years. The significance level was specified for the multiplicity consideration.

Randomisation

Patients were centrally randomized via an interactive voice response system in a 1:1:1 ratio. The randomization was stratified, based on geographical region and by patient's baseline EDSS score (≤3.5 or >3.5).

Blinding (masking)

This study was double-blind with respect to the two oral treatment groups and was open-label between the oral treatment groups and the injection group.

For proper evaluation of the efficacy endpoints during the core period of the study, there were two neurologists at each study centre. The treating neurologist was responsible for subject eligibility evaluation, supervision of study medication administration, recording and treating of AEs and assessing relapses, and monitoring of safety assessments, including routine laboratory results and concomitant medications. The examining neurologist was responsible for conducting all functional system score and EDSS score assessments. Throughout the study, the examining neurologist remained unaware of the patient's treatment assignment and the safety profile (AEs, concomitant medications and laboratory results). When evaluating a patient, the patient was instructed to properly dress to cover any injection site locations.

Statistical methods

All efficacy analyses were performed using all randomized patients (ITT population). Analyses of safety end points were performed using the all treated population, which included patients that took at least 1 dose of study medication.

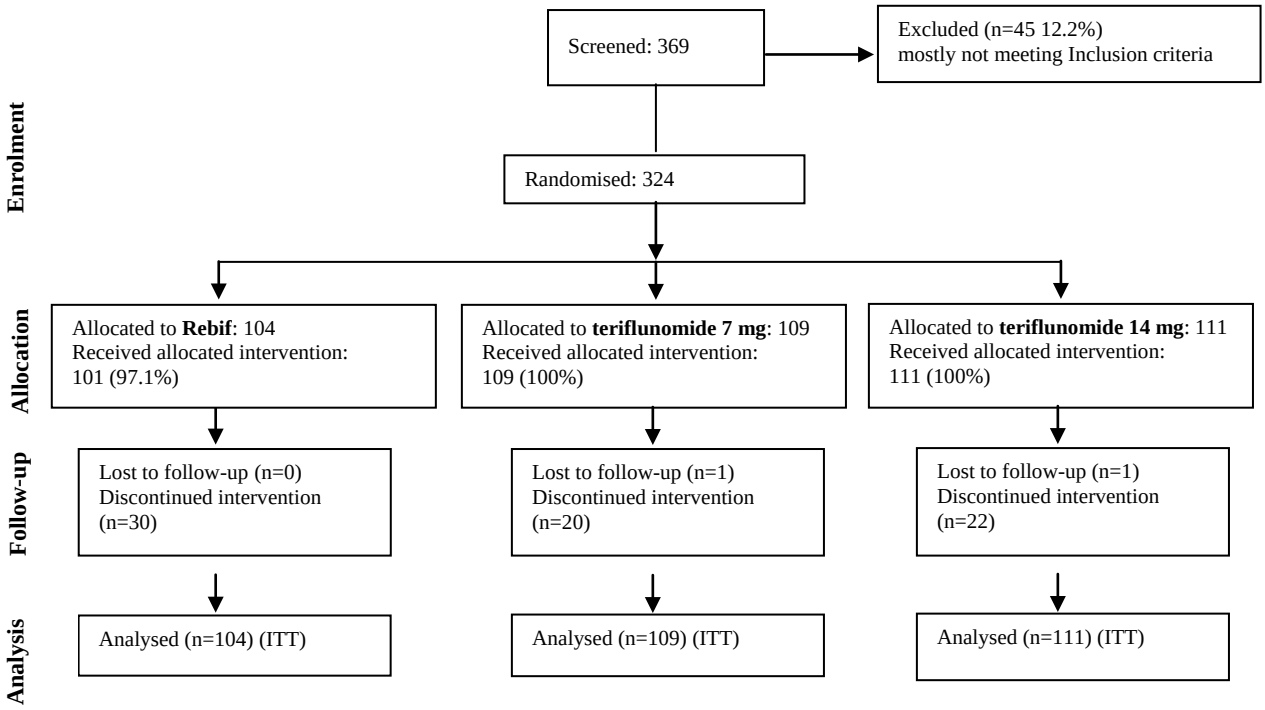
The primary analysis for the time to failure was performed using the log-rank test with time to failure as the dependent variable, treatment group (teriflunomide 7 mg, teriflunomide 14 mg and interferon-beta 1a) as test variable, and pre-defined geographical region and baseline EDSS (EDSS score ≤3.5 versus >3.5) as stratum variables. Kaplan-Meier estimates and curves of the cumulative incidence were used to estimate the rate of failure patients across time points.

Results

Participant flow

The study participant flow is shown in the figure 10.

Fig. 10



Patient completion rate and reasons for discontinuation are presented in table 22.

Table 22

	teriflunomide 7 mg (N=109)	teriflunomide 14 mg (N=111)	Rebif (N=104)
Randomized and not treated	0	0	3 (2.9%)
Randomized and treated	109 (100%)	111 (100%)	101 (97.1%)
Completed study treatment period	89 (81.7%)	89 (80.2%)	71 (68.3%)
Did not complete study treatment period	20 (18.3%)	22 (19.8%)	30 (28.8%)
Patient's request for treatment discontinuation	11 (10.1%)	14 (12.6%)	11 (10.6%)
Reason for study treatment discontinuation			
Adverse event	9 (8.3%)	12 (10.8%)	22 (21.2%)
Lack of efficacy	7 (6.4%)	4 (3.6%)	2 (1.9%)
Poor compliance to protocol	0	0	1 (1.0%)
Lost to follow-up	1 (0.9%)	1 (0.9%)	0
Other reason	3 (2.8%)	5 (4.5%)	5 (4.8%)
Patients who did not participate in EPTD follow-up period	13 (11.9%)	13 (11.7%)	17 (16.3%)
Patients who completed the EPTD follow-up period	3 (2.8%)	3 (2.7%)	4 (3.8%)
Patients who did not complete the EPTD follow-up period	1 (0.9%)	4 (3.6%)	4 (3.8%)
Reason for EPTD follow-up discontinuation			
Lost to follow-up	0	2 (1.8%)	0
Death	0	0	0
Subject did not wish to continue	1 (0.9%)	2 (1.8%)	2 (1.9%)
Other reason	0	0	2 (1.9%)

EPTD: Early permanent treatment discontinuation
Note: Not all discontinued patients had an EPTD page completed.
Note: Percentages are calculated using the number of randomized patients as denominator.

Recruitment

The study took place between 16 April 2009 and 14 September 2011.

Conduct of the study

There was 1 amendment, to the study protocol, elaborating on the scope of the extension part of the study.

Baseline data

A summary of the patient population enrolled in the study is presented in tables 23 and 24.

Table 23 Demographics and patient characteristics at baseline (randomized population)

	Rebif (N=104)	teriflunomide 7 mg (N=109)	teriflunomide 14 mg (N=111)	All (N=324)
Demography				
Age (years)				
Mean (SD)	37.0 (10.6)	35.2 (9.2)	36.8 (10.3)	36.3 (10.0)
Median (range)	34.5 (18 : 58)	35.0 (19 : 58)	35.0 (18 : 65)	35.0 (18 : 65)
Sex [n (%)]				
Female	71 (68.3%)	70 (64.2%)	78 (70.3%)	219 (67.6%)
Male	33 (31.7%)	39 (35.8%)	33 (29.7%)	105 (32.4%)
Race [n (%)]				
Caucasian/White	104 (100%)	109 (100%)	111 (100%)	324 (100%)
Region [n (%)]				
Americas	7 (6.7%)	8 (7.3%)	6 (5.4%)	21 (6.5%)
Eastern Europe	35 (33.7%)	39 (35.8%)	41 (36.9%)	115 (35.5%)
Western Europe and Africa	62 (59.6%)	62 (56.9%)	64 (57.7%)	188 (58.0%)
BMI				
Number	100	109	110	319
Mean (SD)	24.93 (4.80)	25.26 (5.77)	25.00 (5.19)	25.07 (5.27)
Median (range)	23.84 (16.0 : 43.0)	24.17 (15.5 : 50.9)	23.97 (16.5 : 44.8)	24.06 (15.5 : 50.9)
Baseline disease characteristics				
Time since first MS symptoms (years)				
Mean (SD)	7.71 (7.60)	7.02 (6.91)	6.64 (7.63)	7.11 (7.38)
Median (range)	5.71 (0.3 : 37.4)	4.17 (0.1 : 27.6)	4.42 (0.3 : 37.8)	4.58 (0.1 : 37.8)
Time since first MS diagnosis (years)				
Mean (SD)	3.82 (5.69)	3.72 (5.19)	3.68 (6.24)	3.74 (5.71)
Median (range)	1.00 (0.1 : 30.3)	0.67 (0.1 : 23.4)	0.75 (0.1 : 36.5)	0.88 (0.1 : 36.5)
Time since most recent relapse onset (months)				
Number	104	109	110	323
Mean (SD)	9.79 (10.72)	9.00 (13.96)	7.90 (10.34)	8.88 (11.79)
Median (range)	6.00 (1.0 : 58.0)	5.00 (1.0 : 115.0)	5.00 (1.0 : 64.0)	5.00 (1.0 : 115.0)
Baseline EDSS score				
Mean (SD)	2.04 (1.19)	2.04 (1.22)	2.33 (1.35)	2.14 (1.26)
Median (range)	2.00 (0.0 : 5.5)	1.50 (0.0 : 5.5)	2.00 (0.0 : 5.5)	2.00 (0.0 : 5.5)
Randomized EDSS strata at baseline [n (%)]				
≤3.5	93 (89.4%)	96 (88.1%)	95 (85.6%)	284 (87.7%)
>3.5	11 (10.6%)	13 (11.9%)	16 (14.4%)	40 (12.3%)
Actual EDSS strata at baseline [n (%)]				

	Rebif (N=104)	teriflunomide 7 mg (N=109)	teriflunomide 14 mg (N=111)	All (N=324)
≤3.5	94 (90.4%)	97 (89.0%)	95 (85.6%)	286 (88.3%)
>3.5	10 (9.6%)	12 (11.0%)	16 (14.4%)	38 (11.7%)
Number of relapses in the last 2 years				
Mean (SD)	1.7 (1.1)	1.7 (0.9)	1.7 (0.9)	1.7 (1.0)
Median (range)	2.0 (0 : 6)	2.0 (0 : 4)	2.0 (0 : 4)	2.0 (0 : 6)
0	11 (10.6%)	7 (6.4%)	7 (6.3%)	25 (7.7%)
1	39 (37.5%)	42 (38.5%)	41 (36.9%)	122 (37.7%)
2	30 (28.8%)	39 (35.8%)	41 (36.9%)	110 (34.0%)
3	18 (17.3%)	17 (15.6%)	20 (18.0%)	55 (17.0%)
≥4	6 (5.8%)	4 (3.7%)	2 (1.8 %)	12 (3.7%)
Number of relapses in the last 1 year				
Mean (SD)	1.2 (1.0)	1.3 (0.8)	1.4 (0.8)	1.3 (0.8)
Median (range)	1.0 (0 : 5)	1.0 (0 : 3)	1.0 (0 : 4)	1.0 (0 : 5)
0	22 (21.2%)	13 (11.9%)	13 (11.7%)	48 (14.8%)
1	47 (45.2%)	60 (55.0%)	56 (50.5%)	163 (50.3%)
2	28 (26.9%)	29 (26.6%)	34 (30.6%)	91 (28.1%)
3	4 (3.8%)	7 (6.4%)	6 (5.4%)	17 (5.2%)
≥4	3 (2.9%)	0	2 (1.8%)	5 (1.5%)
MS subtype [n (%)]				
Relapsing Remitting	104 (100%)	109 (100%)	108 (97.3%)	321 (99.1%)
Secondary Progressive	0	0	1 (0.9%)	1 (0.3%)
Progressive Relapsing	0	0	2 (1.8%)	2 (0.6%)
With previous MS medication in the last 2 years [n (%)]				
Yes	25 (24.0%)	23 (21.1%)	13 (11.7%)	61 (18.8%)
No	79 (76.0%)	86 (78.9%)	98 (88.3%)	263 (81.2%)

Table 24 MS medications taken within 2 years prior to randomization – number of patients by standardized medication name (randomized population)

	teriflunomide			
	7 mg (N=109)	14 mg (N=111)	Rebif (N=104)	All (N=324)
Previous treatment with MS medication	23 (21.1%)	13 (11.7%)	25 (24.0%)	61 (18.8%)
Glatiramer acetate	10 (9.2%)	7 (6.3%)	12 (11.5%)	29 (9.0%)
Interferon beta-1b	9 (8.3%)	5 (4.5%)	10 (9.6%)	24 (7.4%)
Interferon beta-1a	6 (5.5%)	3 (2.7%)	6 (5.8%)	15 (4.6%)
Interferon beta-1a intramuscular weekly	6 (5.5%)	2 (1.8%)	5 (4.8%)	13 (4.0%)
Interferon beta-1a unspecified	0	1 (0.9%)	1 (1.0%)	2 (0.6%)
Interferon beta-1a subcutaneous QOD	0	0	0	0
Mitoxantrone	0	0	0	0
Fingolimod	0	0	0	0
Natalizumab	0	0	0	0
No previous treatment with MS medication	86 (78.9%)	98 (88.3%)	79 (76.0%)	263 (81.2%)

WHO-DD dictionary -March, 2011

Prior medications are those the patients used prior to first IP intake.

Note: A patient can be counted in several categories.

Table sorted by decreasing frequency of standardized medication name incidence in the overall treatment group.

Numbers analysed

A total of 324 patients were randomized in this study (table 25). Three patients in the Rebif treatment group were randomized, but were not treated with study medication and were excluded from the safety population.

Table 25 Summary of analysis populations

	teriflunomide		
	7 mg	14 mg	Rebif
Randomized population	109 (100%)	111 (100%)	104 (100%)
Efficacy population			
Intent-to Treat (ITT)	109 (100%)	111 (100%)	104 (100%)
PK population	110	110	61
Safety population	110	110	101

Note: The safety patients are tabulated according to treatment actually received (as treated).

For the other populations, patients are tabulated according to their randomized treatment.

Outcomes and estimation

Results of the primary analysis, i.e. analysis of the time to failure (confirmed relapse or permanent study treatment discontinuation) in the ITT population are presented in table 26.

Table 26 Analysis of time to failure

	teriflunomide		
	7 mg (N=109)	14 mg (N=111)	Rebif (N=104)
Number of patients with primary outcome [a]	53 (48.6%)	42 (37.8%)	44 (42.3%)
Relapse	46 (42.2%)	26 (23.4%)	16 (15.4%)
Permanent treatment discontinuation	7 (6.4%)	15 (13.5%)	25 (24.0%)
Other reason for failure [b]	0	1 (0.9%)	3 (2.9%)
Number of patients who were censored	56 (51.4%)	69 (62.2%)	60 (57.7%)
Kaplan-Meier estimates of probability of failure (95% CI) at			
24 weeks	0.257 (0.175, 0.339)	0.243 (0.163, 0.323)	0.298 (0.210, 0.386)
48 weeks	0.358 (0.268, 0.448)	0.333 (0.246, 0.421)	0.365 (0.273, 0.458)
96 weeks	0.588 (0.461, 0.714)	0.411 (0.309, 0.514)	0.444 (0.343, 0.544)
Hazard ratio (95% CI)[c]	1.122 (0.752, 1.674)	0.861 (0.564, 1.314)	
P-value[d]	0.5190	0.5953	-

[a] First occurrence of confirmed relapse, permanent treatment discontinuation for any cause or other reason for failure whichever occurs first.

[b] Includes patients who were never treated or received the wrong treatment.

[c] Derived using Cox proportional hazard model with treatment, EDSS strata at baseline and region as covariates.

[d] Derived using Log-rank test with stratification of EDSS strata at baseline and region.

Note: one additional patient in the 7 mg group received the wrong treatment which was identified after database lock. This patient is not counted as other reason for failure in the table, but as a censored patient.

The total number of confirmed MS relapses between the date of randomisation and the last dose were 58, 35 and 25 relapses corresponding to an unadjusted ARR of 0.426, 0.265 and 0.223 per patient-year in the 7 mg teriflunomide, 14 mg teriflunomide and Rebif group, respectively. Most of the patients across the treatment groups experienced no relapse (teriflunomide 7 mg: 63 (57.8%), teriflunomide 14 mg 85 (76.6%), Rebif 88 (84.6%)).

With respect to a reported impact on fatigue, only patients in the teriflunomide 7 mg treatment group benefited in comparison to Rebif. According to TSQM score measurement, the patients expressed greater satisfaction with treatment in the teriflunomide groups than in the Rebif group: LS-mean global satisfaction score at Week 48 (higher score indicating better satisfaction) of 68.292 (p=0.0239 versus Rebif), 68.818 (p=0.0162 versus Rebif), and 60.975 for 7 mg, 14 mg and Rebif, respectively. This global satisfaction was related to a better satisfaction on each of the dimensions used in that instrument (effectiveness, side effect and convenience).

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 27 Summary of Efficacy for trial HMR1726D/2001

Title: A phase II study of the safety and efficacy of teriflunomide (HMR1726) in multiple sclerosis with relapses				
Study identifier	HMR1726D/2001			
Design	multinational, placebo-controlled, double-blind, parallel-group, randomized, stratified on the basis of the EDSS score (EDSS score ≤3.5 versus >3.5)			
	Duration of main phase: Duration of screening phase: Duration of extension phase:		36 weeks 4 weeks not applicable (subject of a separate protocol)	
Hypothesis	Superiority			
Treatments groups	Teriflunomide 7 mg		taken orally once daily; loading dose 14 mg/day (first 7 days); maintenance dose 7 mg/ day N= 61/60 (randomized/ efficacy evaluable)	
	Teriflunomide 14 mg		taken orally once daily; loading dose 28 mg/day (first 7 days); maintenance dose 14 mg/ day N= 57/56 (randomized/ efficacy evaluable)	
	Placebo		taken orally once daily N= 61/61 (randomized/ efficacy evaluable)	
Endpoints and definitions	Primary endpoint	No. of unique active lesions per MRI scan	The average number of unique active lesions per MRI scan for the double-blind treatment period of the study	
Results and Analysis				
Analysis description	Primary Analysis **-** analysis of covariance (ANCOVA) was used on the ranked average number of unique active lesions per scan during the double-blind phase with treatment, stratum and pooled centre as fixed effects and the ranked pre-randomization number of unique active lesions as covariate. The Dunnett test for 2 groups compared with a control was used to adjust for multiple comparisons.			
Analysis population and time point description	Efficacy-evaluable population (all randomized subjects for whom there was at least 1 on-treatment MRI assessment); time point – week 36			
Descriptive statistics and estimate variability	Treatment group	Teriflunomide 7 mg	Teriflunomide 14 mg	Placebo
	Number of subjects	60	56	61
	No. of unique active lesions per scan Adjusted mean ±SEM	 1.06 0.38	 0.98 0.39	 2.69 0.39

Effect estimate per comparison	Risk of treatment failure	Comparison groups	Teriflunomide 7 mg vs placebo
		Difference in the number of unique active lesions per scan	-1.63
		95% CI	(-2.70, -0.55)
		P-value	0.0234
	Risk of treatment failure	Comparison groups	Teriflunomide 14 mg vs placeob
		Difference in the number of unique active lesions per scan	-1.71
		95% CI	(-2.79, -0.63)
		P-value	0.0052

Table 28 Summary of Efficacy for trial EFC6049 (TEMSO)

Title: A randomized, double-blind, placebo-controlled, parallel-group design study to evaluate the efficacy and safety of teriflunomide (HMR1726D) in reducing the frequency of relapses and delaying the accumulation of physical disability in subjects with multiple sclerosis with relapses			
Study identifier	EFC6049 (TEMSO)		
Design	multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, stratified (by centre and by baseline EDSS score)		
	Duration of main phase: Duration of screening phase: Duration of extension phase:		108 weeks 4 weeks not applicable (subject of a separate protocol)
Hypothesis	Superiority		
Treatments groups	Teriflunomide 7 mg		taken orally as a single daily dose for 108 weeks N= 366/ 365 (randomized/ treated)
	Teriflunomide 14 mg		taken orally as a single daily dose for 108 weeks N= 359/ 358 (randomized/ treated)
	Placebo		taken orally as a single daily dose for 108 weeks N= 363/ 363 (randomized/ treated)
Endpoints and definitions	Primary endpoint	ARR	Annualized relapse rate (defined as the number of confirmed relapses per patient-year)
	Key secondary endpoint	Time to disability progression	Time to disability progression (defined as the time to at least 1 point increase on EDSS score from baseline, if the baseline EDSS score was ≤5.5, or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was >5.5; this increase in EDSS score was to be persistent for at least 12 weeks.)
Results and Analysis			

Analysis description	**Primary Analysis** The primary analysis for the ARR (primary efficacy endpoint) was performed using a Poisson regression model with robust error variance to accommodate the potential over-dispersed data appropriately. The model included the total number of confirmed relapses with onset between randomization date and last dose date as the response variable, a 3-level treatment group, EDSS strata and region as covariates. To account for different treatment durations among patients, the log-transformed standardized treatment duration was included in the model as an "offset" variable for appropriate computation of relapse rate. Two-sided 95% confidence intervals (CI) of the rate ratio were calculated for the comparisons of each active treatment versus placebo. The estimated relapse rates and 2-sided 95% CI and the gross estimates of ARR were generated for each treatment group.			
Analysis population and time point description	Intent to treat population; timepoint – week 108			
Descriptive statistics and estimate variability	Treatment group	Teriflunomide 7 mg	Teriflunomide 14 mg	Placebo
	Number of subject	365	358	363
	Adjusted ARR 95% CI	0.370 (0.318, 0.432)	0.369 (0.308, 0.441)	0.539 (0.466, 0.623)

Effect estimate per comparison	ARR	Comparison groups	Teriflunomide 7 mg vs Placebo
		Relative risk	0.688
		95% CI	(0.563, 0.839)
		P-value	0.0002
	ARR	Comparison groups	Teriflunomide 14 mg vs Placebo
		Relative risk	0.685
		95% CI	(0.554, 0.847)
		P-value	0.0005

Analysis description	**Key secondary analysis** The time to disability progression (sustained for at least 12 weeks) was analyzed using the log-rank test with time to disability progression as the dependent variable, the treatment group as test variable, and region and baseline EDSS strata as stratification factors. Hazard ratios were estimated using Cox regression model with treatment group, region, and baseline EDSS strata as covariates. The Kaplan-Meier graphs were generated and Kaplan-Meier method was used to estimate the disability progression rate and its 95% CI for each treatment group.)			
Analysis population and time point description	Intent to treat population; timepoint week 108			
Descriptive statistics and estimate variability	Treatment group	Teriflunomide 7 mg	Teriflunomide 14 mg	Placebo
	Number of subject	365	358	363

	Probability of disability progression week 108 95% CI	0.217 (0.171, 0.263)	0.202 (0.156, 0.247)	0.273 (0.223, 0.323)
Effect estimate per comparison	Risk of disability progression	Comparison groups	7 mg vs Placebo	
		Hazard ratio	0.763	
		95% CI	(0.555, 1.049)	
		P-value	0.0835	
	Risk of disability progression	Comparison groups	14 mg vs Placebo	
		Hazard ratio	0.702	
		95% CI	(0.506, 0.973)	
		P-value	0.0279	

Table 29 – Summary of Efficacy for trial EFC10531 (TOWER)

Title: A multi-center double-blind parallel-group placebo-controlled study of the efficacy and safety of teriflunomide in patients with relapsing multiple sclerosis			
Study identifier	EFC10531 (TOWER)		
Design	multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, stratified (by centre and by baseline EDSS score)		
	Duration of main phase: Duration of screening phase: Duration of extension phase:	48-152 weeks (depending on time of enrollment) 4 weeks not applicable (subject of a separate protocol)	
Hypothesis	Superiority		
Treatments groups	Teriflunomide 7 mg	taken orally as a single daily dose for 48 weeks N= 408/ 407 (randomized/ treated)	
	Teriflunomide 14 mg	taken orally as a single daily dose for 108 weeks N= 372/ 370 (randomized/ treated)	
	Placebo	taken orally as a single daily dose for 108 weeks N= 389/ 388 (randomized/ treated)	
Endpoints and definitions	Primary endpoint	ARR	Annualized relapse rate (defined as the number of confirmed relapses per patient-year)
	Key secondary endpoint	Time to disability progression	Time to disability progression (defined as the time to at least 1 point increase on EDSS score from baseline, if the baseline EDSS score was ≤5.5, or time to at least 0.5 increase on EDSS score from baseline, if the baseline EDSS score was >5.5; this increase in EDSS score was to be persistent for at least 12 weeks.)
Results and Analysis			

Analysis description	**Primary Analysis** The primary analysis for the ARR (primary efficacy endpoint) was performed using a Poisson regression model with robust error variance to accommodate the potential over-dispersed data appropriately. The model included the total number of confirmed relapses with onset between randomization date and last dose date as the response variable, a 3-level treatment group, EDSS strata and region as covariates. To account for different treatment durations among patients, the log-transformed standardized treatment duration was included in the model as an "offset" variable for appropriate computation of relapse rate. Two-sided 95% confidence intervals (CI) of the rate ratio were calculated for the comparisons of each active treatment versus placebo. The estimated relapse rates and 2-sided 95% CI and the gross estimates of ARR were generated for each treatment group.			
Analysis population and time point description	Intent to treat population; timepoint – week 48			
Descriptive statistics and estimate variability	Treatment group	Teriflunomide 7 mg	Teriflunomide 14 mg	Placebo
	Number of subject	407	370	388
	Adjusted ARR 95% CI	0.389 (0.332, 0.457)	0.319 (0.267, 0.381)	0.501 (0.432, 0.581)
Effect estimate per comparison	ARR	Comparison groups	Teriflunomide 7 mg vs Placebo	
		Relative risk	0.777	
		95% CI	(0.630, 0.958)	
		P-value	0.0183	
	ARR	Comparison groups	Teriflunomide 14 mg vs Placebo	
		Relative risk	0.637	
		95% CI	(0.512, 0.793)	
		P-value	0.0001	
Analysis description	**Key secondary analysis** The time to disability progression (sustained for at least 12 weeks) was analyzed using the log-rank test with time to disability progression as the dependent variable, the treatment group as test variable, and region and baseline EDSS strata as stratification factors. Hazard ratios were estimated using Cox regression model with treatment group, region, and baseline EDSS strata as covariates. The Kaplan-Meier graphs were generated and Kaplan-Meier method was used to estimate the disability progression rate and its 95% CI for each treatment group.			
Analysis population and time point description	Intent to treat population; timepoint week 48			
Descriptive statistics and estimate variability	Treatment group	Teriflunomide 7 mg	Teriflunomide 14 mg	Placebo
	Number of subject	407	370	388

	Probability of disability progression week 24 95% CI 48 95% CI 108 95% CI 132 95% CI	 0.053 (0.030, 0.076) 0.121 (0.087, 0.155) 0.211 (0.161, 0.261) 0.222 (0.168, 0.276)	 0.027 (0.009, 0.044) 0.078 (0.049, 0.108) 0.158 (0.112, 0.204) 0.158 (0.112, 0.204)	 0.080 (0.052, 0.107) 0.142 (0.106, 0.179) 0.197 (0.152, 0.241) 0.210 (0.159, 0.260)
Effect estimate per comparison	Risk of disability progression	Comparison groups	7 mg vs Placebo	
		Hazard ratio	0.955	
		95% CI	(0.677, 1.347)	
		P-value	0.7620	
	Risk of disability progression	Comparison groups	14 mg vs Placebo	
		Hazard ratio	0.685	
		95% CI	(0.467, 1.004)	
		P-value	0.0442	

Table 30 – Summary of Efficacy for trial EFC10891 (TENERE)

Title: A multi-center, randomized, parallel-group, rater-blinded study comparing the effectiveness and safety of teriflunomide and interferon beta-1a in patients with relapsing multiple sclerosis			
Study identifier	EFC10891 (TENERE)		
Design	multicenter, multinational, randomized, double-blind (for teriflunomide doses), open-label (for interferon-beta 1a), parallel-group, stratified by country and baseline disability (EDSS score ≤3.5 versus >3.5)		
	Duration of main phase: Duration of screening phase: Duration of extension phase:		minimum of 48 and maximum of 118 weeks of treatment 4 weeks 48 weeks (for patients providing additional consent on the extension)
Hypothesis	Superiority		
Treatments groups	Teriflunomide 7 mg		taken orally as a single daily dose each day of the treatment period N= 109/109 (randomized/ treated)
	Teriflunomide 14 mg		taken orally as a single daily dose each day of the treatment period N= 111/111 (randomized/ treated)
	Rebif (8.8 mcg for the first two weeks, 22 mcg for the next two weeks and 44 mcg thereafter)		taken as a subcutaneous injection three times per week during the treatment period N= 104/101 (randomized/ treated)
Endpoints and definitions	Primary endpoint	Time to failure	Failure was defined as the first occurrence of relapse or permanent study treatment discontinuation for any cause, whichever occurred first. A relapse was defined as the appearance of a new clinical sign/ symptom, stable for at least 30 days that persisted for a minimum of 24 hours in the absence of fever.
Results and Analysis			

Analysis description	**Primary Analysis** Time to failure was analyzed using log-rank test with time to failure as the dependent variable, treatment group as test variable, pre-defined geographical region and baseline EDSS as stratum variables. Kaplan-Meier estimates and curves of the cumulative incidence were used to estimate the rate of failure across time points.			
Analysis population and time point description	Intent to treat population; time points – week 24, 48, 96			
Descriptive statistics and estimate variability	Treatment group	Teriflunomide 7 mg	Teriflunomide 14 mg	Rebif
	Number of subjects	109	111	104
	Probability of treatment failure at week 24 95% CI week 48 95% CI week 96 95% CI	 0.257 (0.175, 0.339) 0.358 (0.268, 0.448) 0.588 (0.461, 0.714)	 0.243 (0.163, 0.323) 0.333 (0.246, 0.421) 0.411 (0.309, 0.514)	 0.298 (0.210, 0.386) 0.365 (0.273, 0.458) 0.444 (0.343, 0.544)
Effect estimate per comparison	Risk of treatment failure	Comparison groups	Teriflunomide 7 mg vs Rebif	
		Hazard ratio	1.122	
		95% CI	(0.752, 1.674)	
		P-value	0.5190	
	Risk of treatment failure	Comparison groups	Teriflunomide 14 mg vs Rebif	
		Hazard ratio	0.861	
		95% CI	(0.564, 1.314)	
		P-value	0.5953	

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

The Applicant performed an integrated analysis of the EFC6049/TEMSO and EFC10531/TOWER studies. Exclusion of the TENERE study from this analysis was motivated by the different design (lack of placebo arm, lack of complete blinding and a different primary endpoint).

The main clinical results of the integrated analysis are presented in the table 31 and figures 11, 12 and 13.

Table 31

	Teriflunomide 14 mg	**Placebo**
Overall population	**N=728**	**N=751**
Annualised relapse rate (primary endpoint)	0.354 (p<0.0001)	0.534
Percent disability of 3-month sustained progression at week 132	17.9% (p=0.0029)	25.2%
Hazard ratio (95% CI)	0.695 (0.542, 0.892	

	Teriflunomide 14 mg	**Placebo**
Percent disability of 6-month sustained progression at week 132	14.0% (p=0.055)	20.7%
Hazard ratio (95% CI) [1]	0.759 (0.570, 1.011)	

Figure 11 Subgroup analysis of MS relapse for teriflunomide 14 mg (pooled analysis: TEMSO and TOWER)

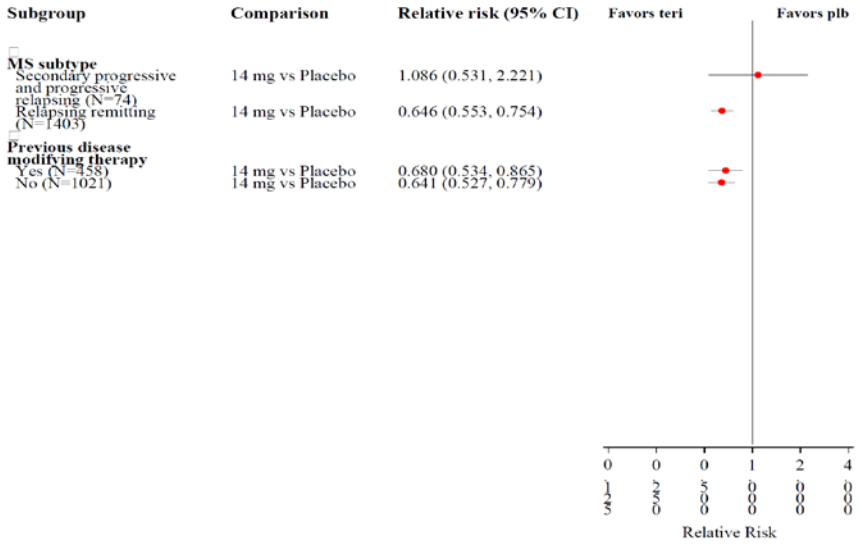


Figure 12 Subgroup analysis of MS relapse for teriflunomide 7 mg (pooled analysis: TEMSO and TOWER)

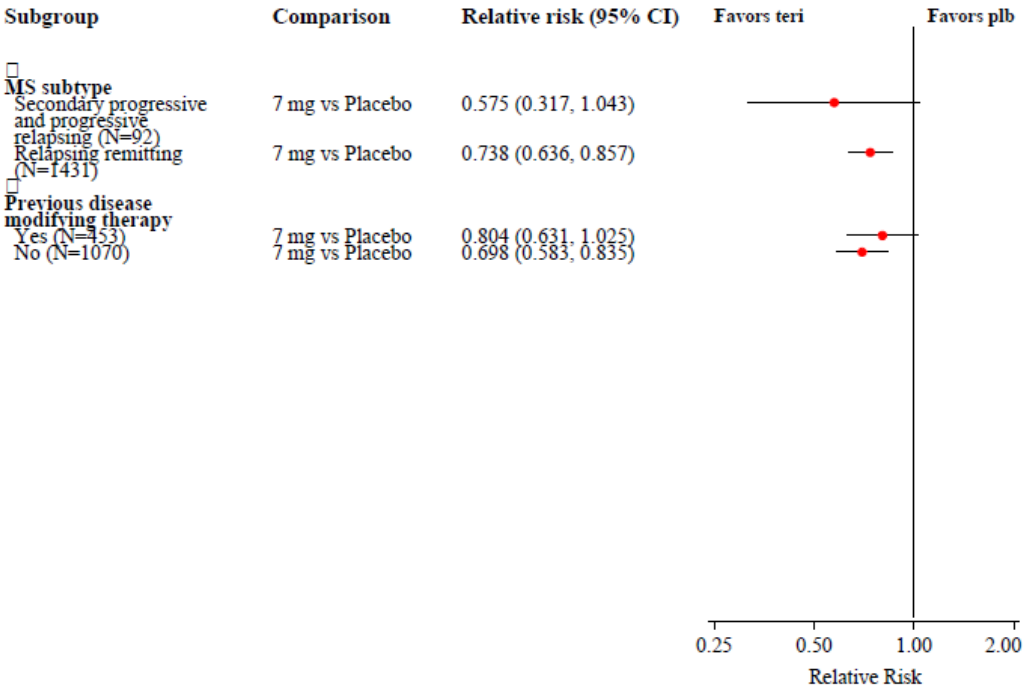
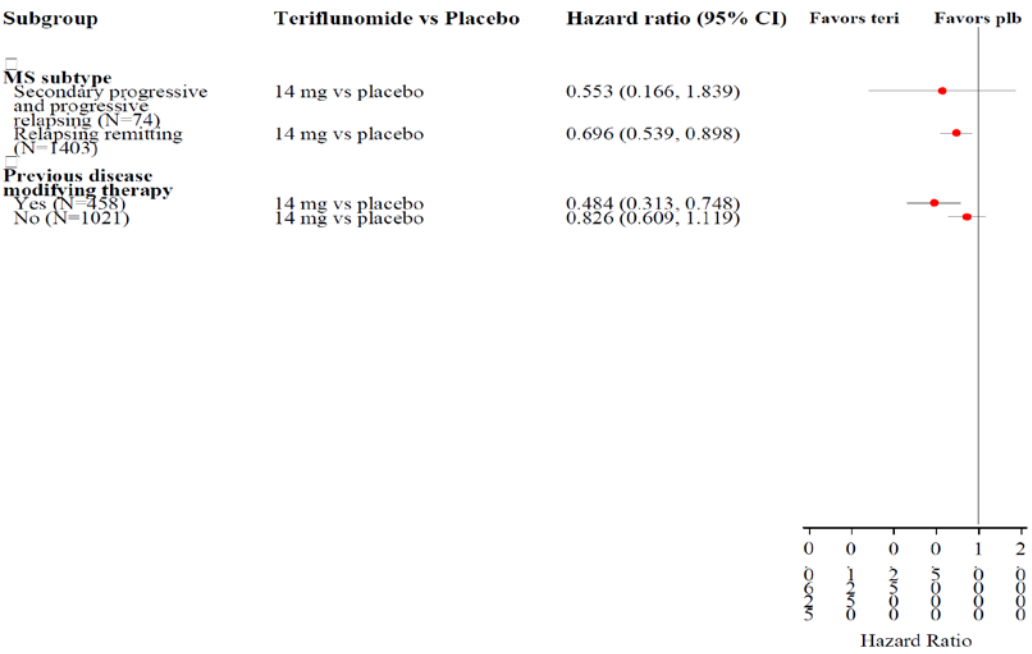


Figure 13: Subgroup analysis of time to 3 month sustained disability progression for teriflunomide 14 mg (pooled analysis: TEMSO and TOWER)



The assessment of MRI outcome parameters was not part of the TOWER trial and therefore, an integrated analysis on the MRI outcomes was not possible.

Clinical studies in special populations

No specific studies in special populations were performed.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The CHMP considered that formally, no adequate dose-finding studies in the indication of relapsing-remitting MS were performed and that the choice of doses for the clinical programme was based on pre-clinical data and comparisons with leflunomide (parent compound), which is indicated in the treatment of rheumatoid arthritis. In this context, the CHMP requested that the rationale for the presumption of a 1:1 transmission off effective doses across indications should be provided. The applicant argued that both diseases, multiple sclerosis and rheumatoid arthritis, are conditions with an inflammatory component and that the effect of teriflunomide on the DHO-DH enzyme would lead to efficacy. The CHMP acknowledged that DHO-DH inhibition results in beneficial immunosuppressive and consequently anti-proliferative effects in the disease, but was of the view that further arguments as to why comparable dosing is expected to have the minimal and the optimal effect in both diseases would have been of additional value, such as detailed discussion with respect to the patho-mechanisms of both diseases. However, the CHMP also considered that both the 7 and 14 mg doses were observed to be effective in MS on the chosen primary endpoint ARR, with a trend showing slightly improved efficacy with the 14 mg dose. In view of an additional trend of increase incidence of some adverse events in the 14 mg dose compared to the 7 mg dose, the CHMP concluded that, overall, the range of doses tested in the clinical programme of teriflunomide for RRMS was considered justified.

The main clinical studies were performed as multicentre, randomised and placebo- or active-controlled. Studies 2001, TEMSO and TOWER were conducted in a double blind fashion, while in the TENERE study with Rebif as comparator, the treatment was double-blind only with respect to the two teriflunomide groups (7 mg vs 14 mg) and open label for teriflunomide vs Rebif. The CHMP considered the differences in the route of administration and the dosing regimen of teriflunomide (p.o., daily) and Rebif (s.c., three times a week) and, taking into account additional measures to maintain the blind (blinded examining physician different from the treating physician; patients instructed to cover injection sites), agreed that the incomplete blinding of the study was acceptable. The choice of the comparator product Rebif, approved for treatment of patients with relapsing forms of MS in Europe since 1998, was considered appropriate. However, the CHMP pointed out that a formal scientific advice on the development of teriflunomide as monotherapy of multiple sclerosis, recommending a 3-arm trial comparing efficacy and safety of the test drug with placebo and comparator, was not followed by the applicant.

The efficacy endpoints were chosen in accordance with the current EMA guideline for multiple sclerosis. The primary endpoint in the two phase III pivotal trials was the annualized relapse rate and time to disability progression was chosen as the key secondary endpoint. This was considered appropriate by the CHMP. Disability progression was measured in terms of time to a 3-month sustained change in EDSS score of at least 1 point increase on EDSS score from baseline (if the baseline EDSS score was ≤5.5) or at least 0.5 point increase on EDSS score from baseline (if the baseline EDSS score was >5.5). The CHMP pointed out that according to the Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis (CPMP/EWP/561/98 Rev.1)., "accurate and reliable definition of sustained worsening is important and should include two consecutive examinations carried out by the same physician at least 6 months apart", but acknowledged that the 6-month sustained disability progression was chosen as an additional secondary endpoint.

The inclusion criteria for participation in the study were considered adequate to reflect the intended target population, i.e. patients with relapsing multiple sclerosis. The 2001 (for TEMSO) and 2005 (for TOWER) McDonald criteria to define the established MS were considered standard criteria and endorsed. The approach to include also patients with a very low EDSS score was considered acceptable by the CHMP, as the initiation of a disease-modifying therapy early in the disease is supported.

Efficacy data and additional analyses

In the proof-of-concept phase II study 2001, an effect on the lesions detected with MRI was seen, which was considered sufficient to proceed with phase III studies. Demonstrating a convincing effect on relapse rate could not be expected in this study due to its short duration and a small sample size, but a positive trend with respect to relapses as well as disability was observed.

Efficacy of teriflunomide was supported by results of two placebo controlled studies (TEMSO and TOWER) on the ARR and time to 3-month sustained disability progression.

TEMSO was the first phase III trial performed with two doses of teriflunomide in relapsing forms of multiple sclerosis and in general, its results indicated significant reduction in the frequency of relapse in both doses tested (teriflunomide 7 mg and teriflunomide 14 mg) as compared to placebo. The relative effect size observed, i.e. a 30% reduction in ARR was comparable to the effect-size seen with beta interferons and glatiramer. The results also showed a statistically significant effect in time to 3-month sustained disability progression for the 14 mg dose. Although none of the teriflunomide treatment arms reached statistical significance in comparison to placebo for the time to 6-month sustained disability progression, a similar trend was observed as for the 3-month sustained disability

progression, with a slightly increased hazard ratio. Overall, the efficacy of the 14 mg dose applied for was considered to be higher than the 7 mg dose tested in parallel.

The results were supported by a second pivotal trial (TOWER). Furthermore, results from the integrated analysis of both trials indicated consistency in the efficacy data, based on the ARR and time to sustained disability progression. The assessment of MRI outcome parameters was not part of the TOWER trial and thus, an integrated analysis on the MRI outcomes was not possible.

With the TENERE study, the applicant aimed to show superiority of teriflunomide over interferon-beta 1a (Rebif). However, this trial did not show statistically significant differences on the primary endpoint. No non-inferiority comparison vs Rebif was planned. In the TENERE study, the primary endpoint treatment failure included both relapse and treatment discontinuation. For this study, the CHMP considered that it was important to examine separately the two components of treatment failure. Furthermore, it was important to demonstrate that there was no difference in the distribution of study duration in the different treatment arms, as otherwise the interpretation of main results would be difficult e.g. if withdrawals due to AE were early, there would not be much time to be at risk of relapse. These analyses were requested as they were considered to provide further supportive data for efficacy: The results of the separate outcomes, discontinuation and confirmed relapse, indicated that more patients in the Rebif treated group compared to the teriflunomide treated groups were considered treatment failure due to discontinuation, while more patients in the teriflunomide treated groups had relapses compared to patients treated with Rebif. This could suggest that Rebif is more effective in preventing relapses in those patients who are able to remain on treatment, while teriflunomide seemed to be better tolerated. However, this conclusion might be confounded by differences in exposure duration between treatment conditions. Therefore, additional analyses were requested to take this possibility into account. The additional data provided by the company suggested that duration of exposure was indeed longer in the teriflunomide treatment groups compared to the Rebif treatment group, probably due to the fact that discontinuations in the Rebif treated group occurred earlier than the relapses in the teriflunomide treated groups. However, imputation of the missing data for non-completers suggested that even if duration of exposure to the medications were equal, this would not alter the results of the primary analysis.

Subgroup analyses were performed for the endpoints time to failure and MS relapse. With regard to relapses, all subgroups provided better results in favour of Rebif.

With respect to the MS type of patients enrolled in the studies, the CHMP considered that the majority of patients in the study programme were patients with RRMS and the number of patients with secondary progressive MS and superimposed relapses was very limited. Therefore, further justification that efficacy could be reasonably extrapolated from the RRMS to the broader population presenting with RMS was requested, based on mechanistic considerations and available literature.

The applicant claimed that differences between progressive forms of MS and RRMS would be more attributable to different degrees of inflammation, demyelination and axonal loss than to qualitative differences. However, referring to Kappos (Effect of drug in secondary disease progression in patients with multiple sclerosis; Kappos L, Multiple Sclerosis 2004; 10: 46-55), the CHMP considered that “it is particularly important to differentiate these two forms (SPMS and RRMS) of the disease”. As the process in SPMS relates more to a cellular/axon loss than to simple inflammation, the CHMP was of the view that a pathophysiological difference between RRMS and SPMS cannot be neglected and therefore, with respect to mechanistic considerations, the applicant´s argumentation was less convincing. Overall, the CHMP felt that extrapolation of efficacy data from RRMS patients to patients with RMS was not supported by the information provided.

In addition, when judging whether efficacy could be sufficiently ensured in the broad indication in RMS, the CHMP took into account also results from the two phase III studies, TEMSO and TOWER. Pre-planned subgroup analyses for patients with SPMS and PRMS were presented by the applicant and discussed by the CHMP. In their evaluation, the CHMP considered that for the purpose of extrapolation to the still relapsing patients with SPMS and PRMS, results on annualised relapse rate were more important than those on disability progression. Based on the TEMSO study, results on the SPMS+PRMS subgroup did not indicate that teriflunomide 14 mg would be favoured over placebo (Relative risk: 0.985; (0.447, 2.172). Similar observation was made in the TOWER study (Relative risk: 0.963 (0.382, 2.432). Results based on the pooled analyses of studies TEMSO and TOWER were even less re-assuring, as they favoured placebo over teriflunomide for the relapse rate (Relative risk: 1.086 (0.531, 2.221). The CHMP considered that a more positive trend was seen with the 7 mg dose, but taking into account that, in the overall population, the efficacy was considered to be better for the 14 mg dose on both the MS relapse rate and disability progression parameters, these findings were not considered sufficient to support efficacy in the SPMS+PRMS subgroup. Overall, the CHMP was of the view that the above provided subgroup analyses, together with the lack of support by the mechanistic considerations, did not allow to conclude that efficacy could be reasonably extrapolated from the RRMS to the broader population presenting with RMS.

In order to identify and substantiate patient population which would benefit most from treatment with teriflunomide, the applicant provided a number of subgroup analyses based on baseline characteristics, such as disease severity and disease activity. An effect on relapse rate and disability progression (time to 3-month sustained disability progression) was sufficiently shown across a number of treatment groups of patients, including patients with high disease activity.

With respect to the definition of high disease activity “patients with at least 2 relapses in past year and 1 Gd lesion at baseline” used by the applicant, the CHMP considered that it is analogous to the second part of the indication for Tysabri and Gilenya, and although a general consensus over the definition of high disease activity is currently lacking, this approach was accepted. The point estimate for the hazard ratio for time to disability progression was 0.648 for the teriflunomide 14 mg treatment group in comparison to placebo, and for the annualized relapse rate, results also pointed into the right direction. Reference to treatment effects in this subgroup was considered essential to the prescribing physician and was thus included in section 5.1 of the SmPC. The CHMP considered that no data were available in patients who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or patients having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years. This was reflected in section 5.1 of the SmPC.

The CHMP considered that no subgroup was identified, where the effect would be more robust or more convincing compared to others.

Additional expert consultation

In the course of the procedure, the CHMP identified need for input from the SAG Neurology on the two following questions:

- **Question 1**

How does the SAG Neurology view the efficacy of teriflunomide compared to placebo and to other MS products? Does the SAG consider that a beneficial effect on progression of disability has been clearly established?

- **Question 2**

Considering the efficacy and safety profiles of teriflunomide in the context of other products, what are the views of the SAG Neurology on the patient population(s) in whom treatment with teriflunomide is likely to be most beneficial and appropriate (taking into account stage / duration of illness, baseline disability/ disease activity, rate of disability progression, response to other treatments etc.)?

Overall, the SAG Neurology considered that the efficacy over placebo on disease activity (relapse and MRI parameters) was demonstrated. However, there was no consensus in the panel over the effect on disability progression, in particular as both studies failed on the time to 6 month sustained disability secondary endpoint. Although there is no rigorous way of making comparisons across products based on the available data, the SAG Neurology felt that the efficacy of teriflunomide was at best comparable to interferon beta, as illustrated by the results of the TENERE study.

The SAG Neurology was concerned about the safety profile of teriflunomide, in particular with respect to decrease in lymphocyte counts, elevation of liver enzymes, peripheral neuropathy, effect on pregnancy/fertility; and to what extent these risks could be sufficiently monitored and managed in clinical practise. As a result, there was no consensus in the panel as to whether there is a population in whom teriflunomide would have a favourable benefit/risk balance.

The SAG Neurology considered that sub-group analyses did not point toward a particular group of patients where the product would be most efficacious. However, in view of the mild efficacy and the safety concerns, the panel considered that teriflunomide should preferably be used only in patients with mildly active RRMS.

A majority of members also felt that the use of teriflunomide should be reserved to patients who are intolerant to current 1st line therapy. A minority of members disagreed with this, considering that the risks were manageable with appropriate risk minimisation measures taking account of the knowledge gained with leflunomide (Arava).

2.5.4. Conclusions on the clinical efficacy

Overall, the clinical efficacy data submitted were considered satisfactory and supportive of the indication of teriflunomide for the treatment of adult patients with relapsing remitting multiple sclerosis.

2.6. Clinical safety

Patient exposure

The safety database for teriflunomide as monotherapy in patients with relapsing MS included data from two completed randomized, double-blind, placebo-controlled studies (2001 and EFC6049/TEMSO), two ongoing long-term safety studies (LTS6048 and LTS6050) and one completed randomized, active-controlled study (EFC10891/TENERE). The core placebo-controlled analysis was based on the completed studies in Pool A, focused on the placebo-controlled segments of studies 2001 and EFC6049/TEMSO including 844 patients with relapsing MS treated with teriflunomide 7 mg (429 patients) per day or 14 mg (415 patients) per day over a treatment period of up to 2 years. A similar

number of patients were exposed to placebo (421). The median treatment exposure was 755 days across treatment groups.

The clinical development programme of teriflunomide included a total of 29 clinical studies (18 clinical pharmacology studies and 11 Phase 2 or Phase 3 studies). As of 8 September 2011, 23 studies were completed and 5 were ongoing.

The active-treatment analysis (Pool B) included patients exposed to teriflunomide based on Phase 2 and 3 studies and their extensions; this was a subset of 1355 patients treated with teriflunomide 7 mg and 14 mg, including the 844 patients on active treatment from Pool A, with exposure of up to 10.4 years. The median duration of study treatment was 2.7 years for each treatment group. In Pool B, the baseline demographic characteristics were homogenous between teriflunomide 7 mg and 14 mg and were overall similar to those of Pool A. Pool B provided safety information over a prolonged treatment period, including a subset of patients with about 10 years of follow-up.

Patients exposed to the study medication were predominantly female (72.3%), primarily Caucasian (96.9%) and with a median age of 39 years. The geographic regions included in Pool A were America (mainly, North America [27.6%]), Eastern Europe (26.7%) and Western Europe (41.3%), all being equally represented across the treatment groups.

291 additional placebo patients were switched to active treatment in the extension studies and 220 patients were treated with teriflunomide in study EFC10891/TENERE with more than 10 years follow-up.

Additionally, blinded data from studies ongoing at the time of the MAA submission, i.e. study EFC10531/TOWER (1165 patients randomized and treated, results available during the course of the procedure), study EFC6260/TOPIC (467 patients randomized and treated) in early MS (patients with CIS) and study EFC6058/TERACLES (68 patients randomized and treated) in patients with stable doses of IFN-β 1-a were also part of the safety analysis. Further data on 158 patients from the 1-year adjunct studies (75 patients that received teriflunomide in addition to IFN-β [Studies PDY6045+LTS6047] and 83 patients in addition to GA [Studies PDY6046+LTS6047]) were presented separately. The median duration of study treatment was similar (336 to 337 days) in all treatment groups for studies PDY6045+LTS6047 and PDY6046+LTS6047.

The safety database for teriflunomide included over 4394 cumulative patient-years of exposure (2294.68 patient-years for the 7 mg teriflunomide group and 2099.75 patient-years for the 14 mg teriflunomide group) including 77 patients who received the compound for at least 8 years.

Adverse events

The most frequently reported treatment–emergent AEs (TEAEs) (with PT ≥10% in any treatment group) and with a significant difference for teriflunomide as compared to placebo were alopecia, ALT increased, diarrhoea and nausea. A clear dose effect was seen for these events.

In Pool A, the proportion of patients with at least 1 TEAE was similar across teriflunomide and placebo groups. Treatment-emergent SAEs were reported in 12.8% of patients in the placebo group, 12.8% of patients in the 7 mg teriflunomide group and 15.7% of patients in the 14 mg teriflunomide group. The frequency of serious TEAEs and TEAEs leading to permanent treatment discontinuation was reported with a slightly higher incidence on teriflunomide 14 mg compared to the 7 mg and placebo groups.

In Pool B, the proportion of patients with at least 1 treatment-emergent SAE was 23.2% and 20.7% in the 7 mg and 14 mg teriflunomide groups, respectively. The most frequently reported SAEs were within the “Investigations” and “Infections and infestations” SOCs.

A similar proportion of TEAEs was reported in the 7 mg and 14 mg teriflunomide groups in the single-dose non-placebo-controlled phase 1 studies. In the repeated-dose studies, where teriflunomide was administered using a loading dose of 70 mg for 3 to 4 days to obtain rapidly steady state concentrations, and followed by a repeated high dose of 14 mg to maintain the steady state, the proportion of TEAEs with teriflunomide (32.3%) was comparable to placebo (33.1%). A higher frequency of events was reported during the rapid elimination procedure either after teriflunomide (52.0%) or after placebo (63.9%). Relatively few serious TEAEs and TEAEs leading to treatment discontinuations were reported either in the single-dose or repeated-dose studies.

The overall frequencies of the most common and common TEAEs seen in the other studies (EFC10891/TENERE, PDY6045+LTS6047, pooled single and repeated dose studies, study INT10564, EFC10531/TOWER, EFC6260/TOPIC, EFC6058/TERACLES) were similar to those seen in Pool A and Pool B. The overall percentage of patients with TEAEs was similar in the teriflunomide treatment groups as compared to Rebif in the TENERE study.

In the placebo-controlled Pool A, the 5 SOCs with the most frequently reported TEAEs were as follows (by decreasing frequency in the 14 mg teriflunomide group):

- Infections and infestations (57.5%, 59.7%, 61.7% on placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively)
- Gastrointestinal disorders (34.4%, 39.9%, 45.3% on placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively)
- Nervous system disorders (45.4%, 45.7%, 45.1% on placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively)
- Skin and subcutaneous tissue disorders (21.9%, 28.9%, 37.1% on placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively)
- Musculoskeletal and connective tissue disorders (39.2%, 38.2%, 35.7% on placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively)

The incidence rate and relative risk ratio of common TEAEs (≥2% at the MedDRA HLT level in any of the treatment groups) based on the Pool A safety population is presented in table 32.

Table 32 The incidence rate and relative risk ratio of common TEAEs – Safety population – Pool A

	Placebo	teriflunomide		Relative risk ratio (95% CI)	
HLT: High Level Term	(N=421)	7 mg (N=429)	14 mg (N=415)	7 mg vs placebo	14 mg vs placebo
HLT: Liver function analyses	44 (10.5%)	73 (17.0%)	74 (17.8%)	**1.63** (1.15 to 2.31)	**1.71** (1.21 to 2.42)
HLT: Diarrhoea (excl infective)	35 (8.3%)	62 (14.5%)	72 (17.3%)	**1.74** (1.17 to 2.57)	**2.09** (1.43 to 3.05)
HLT: Nausea and vomiting symptoms	38 (9.0%)	50 (11.7%)	69 (16.6%)	1.29 (0.87 to 1.93)	**1.84** (1.27 to 2.67)
HLT: Alopecias	18 (4.3%)	49 (11.4%)	61 (14.7%)	**2.67** (1.58 to 4.51)	**3.44** (2.07 to 5.71)
HLT: Paraesthesias and dysaesthesias	43 (10.2%)	52 (12.1%)	61 (14.7%)	1.19 (0.81 to 1.74)	**1.44** (1.00 to 2.08)
HLT: Viral infections NEC	8 (1.9%)	19 (4.4%)	27 (6.5%)	**2.33** (1.03 to 5.27)	**3.42** (1.57 to 7.45)
HLT: Neutropenias	3 (0.7%)	10 (2.3%)	19 (4.6%)	3.27 (0.91 to 11.80)	**6.42** (1.92 to 21.55)
HLT: Vascular hypertensive disorders NEC	8 (1.9%)	15 (3.5%)	19 (4.6%)	1.84 (0.79 to 4.29)	**2.41** (1.07 to 5.44)
HLT: Menstruation with increased bleeding	2 (0.5%)	5 (1.2%)	13 (3.1%)	2.45 (0.48 to 12.58)	**6.59** (1.50 to 29.04)
HLT: Muscle pains	6 (1.4%)	17 (4.0%)	13 (3.1%)	**2.78** (1.11 to 6.98)	2.20 (0.84 to 5.73)
HLT: Mononeuropathies	3 (0.7%)	4 (0.9%)	11 (2.7%)	1.31 (0.29 to 5.81)	**3.72** (1.05 to 13.24)
HLT: Tinea infections	2 (0.5%)	6 (1.4%)	10 (2.4%)	2.94 (0.60 to 14.50)	**5.07** (1.12 to 23.01)

	Placebo	teriflunomide		Relative risk ratio (95% CI)	
HLT: High Level Term	(N=421)	7 mg (N=429)	14 mg (N=415)	7 mg vs placebo	14 mg vs placebo
HLT: Flatulence, bloating and distension	4 (1.0%)	14 (3.3%)	9 (2.2%)	**3.43** (1.14 to 10.35)	2.28 (0.71 to 7.35)
HLT: Erythemas	2 (0.5%)	10 (2.3%)	6 (1.4%)	**4.91** (1.08 to 22.26)	3.04 (0.62 to 14.99)

Among the common TEAEs, the following PTs were reported with higher frequency in one or both teriflunomide groups, as compared to placebo with a difference of ≥1%:

Headache, diarrhoea, alopecia, nausea, alanine aminotransferase increased, influenza, upper respiratory tract infection, paraesthesia, urinary tract infection, arthralgia, bronchitis, sinusitis, dizziness, rash, neutropenia, vomiting, hypertension, toothache, musculoskeletal pain, pharyngitis, anxiety, viral gastroenteritis, cystitis, oral herpes, aspartate aminotransferase increased, rhinitis, seasonal allergy, myalgia, GGT increased, eczema, pruritus, acne, sciatica, multiple sclerosis, pollakiuria, weight decreased, carpal tunnel syndrome, menorrhagia, pain, neutrophil count decreased, hyperaesthesia, post-traumatic pain, palpitations, tooth infection, tinea pedis, tonsillitis, laryngitis, muscle spasticity, neuralgia, faecal incontinence, flatulence, erythema, white blood cell count decreased, leukopenia and abdominal distension.

There were no unexpected findings in the adverse event profile in patients receiving teriflunomide in Pool B; the adverse events were comparable to those observed in Pool A. Within this safety population, the most commonly reported adverse reactions in the teriflunomide 14 mg group versus placebo were: influenza (11.8% versus 9.3%), upper respiratory tract infection (10.8% versus 9.0%), urinary tract infection (10.6% versus 9.5%), paraesthesia (10.6% versus 7.8%), diarrhoea (17.3% versus 8.3%), ALT increased (14.0% versus 7.1%), nausea (14.2% versus 6.9%) and alopecia (14.7% versus 4.3%). In general, diarrhoea, nausea and alopecia, were mild to moderate, transient and infrequently led to treatment discontinuation.

Adverse events of special interest (AESI) were defined as events of potential risk of occurrence based on the current available preclinical and clinical data, the class effect and the potential mechanism of action of teriflunomide. These AE groups are presented in table 33 together with their incidence rates and relative risk ratios.

Table 33 - Incidence rate and relative risk ratio of TEAEs of special interest - Safety population - Pool A

		Teriflunomide		Relative risk ratio (95% CI)	
AESI	Placebo (N=421)	7 mg (N=429)	14 mg (N=415)	7 mg vs placebo	14 mg vs placebo
Nausea	29 (6.9%)	40 (9.3%)	59 (14.2%)	1.35 (0.86 to 2.14)	2.06 (1.35 to 3.15)
Diarrhoea	35 (8.3%)	62 (14.5%)	72 (17.3%)	1.74 (1.17 to 2.57)	2.09 (1.43 to 3.05)
Hepatic Disorders	59 (14.0%)	88 (20.5%)	84 (20.2%)	1.46 (1.08 to 1.98)	1.44 (1.07 to 1.96)
Pulmonary Disorders	1 (0.2%)	0	0	0.00 (NC)	0.00 (NC)
Peripheral Neuropathy	20 (4.8%)	16 (3.7%)	25 (6.0%)	0.79 (0.41 to 1.49)	1.27 (0.72 to 2.25)
Malignancy	4 (1.0%)	1 (0.2%)	2 (0.5%)	0.25 (0.03 to 2.19)	0.51 (0.09 to 2.75)
Hypertension	13 (3.1%)	22 (5.1%)	23 (5.5%)	1.66 (0.85 to 3.25)	1.79 (0.92 to 3.50)
Bone Marrow Disorders	11 (2.6%)	44 (10.3%)	36 (8.7%)	3.93 (2.06 to 7.50)	3.32 (1.71 to 6.43)
Infections and infestations	242 (57.5%)	256 (59.7%)	256 (61.7%)	1.04 (0.93 to 1.16)	1.07 (0.96 to 1.20)
Hypersensitivity	61 (14.5%)	82 (19.1%)	85 (20.5%)	1.32 (0.97 to 1.79)	1.41 (1.05 to 1.91)
Pancreatic Disorders	13 (3.1%)	14 (3.3%)	10 (2.4%)	1.06 (0.50 to 2.22)	0.78 (0.35 to 1.76)
Alopecia	18 (4.3%)	49 (11.4%)	63 (15.2%)	2.67 (1.58 to 4.51)	3.55 (2.14 to 5.89)
Cardiac Arrhythmias	1 (0.2%)	1 (0.2%)	0	0.98 (0.06 to 15.64)	0.00 (NC)
Convulsions	1 (0.2%)	2 (0.5%)	3 (0.7%)	1.96 (0.18 to 21.56)	3.04 (0.32 to 29.14)
Hemorrhages	31 (7.4%)	29 (6.8%)	39 (9.4%)	0.92 (0.56 to 1.50)	1.28 (0.81 to 2.00)
Embolic and Thrombotic Events	4 (1.0%)	5 (1.2%)	7 (1.7%)	1.23 (0.33 to 4.54)	1.78 (0.52 to 6.02)

The asymptotic CIs for the relative risk ratio are provided. MedDRA version 14.0

Overview of TEAEs for hepatic disorders and ALT increase (based on laboratory data) for Pool A safety population is presented in table 34.

Table 34

n (%)	Placebo (N=421)	teriflunomide 7 mg (N=429)	teriflunomide 14 mg (N=415)
Patients with any TEAE	377 (89.5%)	390 (90.9%)	382 (92.0%)
Patients with any serious AE	55 (13.1%)	55 (12.8%)	67 (16.1%)
Patients with any serious TEAE	54 (12.8%)	55 (12.8%)	65 (15.7%)
Patients with any TEAE leading to permanent treatment discontinuation	32 (7.6%)	39 (9.1%)	49 (11.8%)
>1 - ≤3 ULN	124/420 (29.5%)	204/428 (47.7%)	205/413 (49.6%)
>3 - ≤5 ULN	15/420 (3.6%)	15/428 (3.5%)	16/413 (3.9%)
>5 - ≤20 ULN	9/420 (2.1%)	9/428 (2.1%)	7/413 (1.7%)
>20 ULN	2/420 (0.5%)	1/428 (0.2%)	2/413 (0.5%)
ALT >3 ULN and TBILI >2 ULN	1	1	1

Serious adverse event / deaths / other significant events

In the placebo-controlled Pool A, treatment-emergent SAEs were reported in 12.8% of patients in the placebo group, 12.8% of patients in the 7 mg teriflunomide group and 15.7% of patients in the 14 mg teriflunomide group. There was no difference between groups in the proportion of patients with serious hepatic disorders. Serious cholecystitis and cholelithiasis were more frequent in patients treated with teriflunomide 7 mg (1.9%) than in those treated with placebo or teriflunomide 14 mg (0.2% each). Two patients treated with teriflunomide 14 mg experienced moderate neutropenia or neutrophil count decrease. Both patients recovered while continuing treatment with teriflunomide. Serious infections and infestations were reported with a similar frequency in both the placebo (2.1%) and 14 mg teriflunomide (2.2%) groups and with a slightly lower incidence in the 7 mg teriflunomide group (1.4%). Overall, one case of pancreatitis was reported in the placebo group whereas two patients in the 7 mg teriflunomide group had serious asymptomatic increases in lipase (up to 5.2 x ULN), and recovered. The rate of neoplasms (benign, malignant and unspecified) as a whole was 1.0% in the placebo group, 0.2% in the 7 mg teriflunomide group and 0.5% in the 14 mg teriflunomide group. Among them, 3 patients, all treated with placebo, had malignant tumours including breast cancer, thyroid cancer and cervical cancer (1 case each) and 1 patient treated with teriflunomide 14 mg was diagnosed with cervix carcinoma in situ (stage 0), which resolved following surgical ablation of the tumour. One case of ongoing depression followed by a suicide attempt was reported in a patient treated with placebo, two patients treated with teriflunomide 7 mg experienced major depression and 1 suicide attempt was reported in a patient treated with teriflunomide 14 mg. Angina pectoris and myocardial infarction (1 case each) were reported in the placebo group. Both patients recovered with corrective treatment. The proportion of patients with serious TEAEs in the “Skin and subcutaneous tissue disorders” SOC (0.2% on placebo and in each teriflunomide group), in the “Musculoskeletal and connective tissue disorders” SOC (1.0% on placebo and on teriflunomide 14 mg and 1.2% on teriflunomide 7 mg) and in the “Investigations” SOC (3.1% on placebo and 2.1% and 2.9% on teriflunomide 7 mg and 14 mg, respectively) was largely similar across all treatment groups. Serious gastrointestinal disorders were more frequent in the teriflunomide groups (1.9% each) than in the

placebo group (0.2%). Two patients were hospitalized, one of whom had a history of gastrointestinal reflux and concomitant use of NSAID therapy. Serious TEAEs in the “Renal and urinary disorders” SOC (renal colic and urethral stenosis) were reported in two patients in the 14 mg teriflunomide group (versus no patients in the other 2 groups).

In Pool B, the proportion of patients with at least one treatment-emergent SAE was 23.2% and 20.7% in the 7 mg and 14 mg teriflunomide groups, respectively. The most frequently reported SAEs were from the SOC “Investigations” (4.3% and 4.4% in the 7 mg and 14 mg teriflunomide groups, respectively), mainly due to ALT increased. Serious TEAEs in the “Infections and infestations” SOC were reported in 3.9% and 3.6% of patients on teriflunomide 7 mg and teriflunomide 14 mg, respectively.

In study EFC10891/TENERE, the proportion of patients with serious TEAEs was similar between teriflunomide 14 mg and Rebif (5.5% and 6.9%, respectively), but higher with teriflunomide 7 mg (10.9%).

Deaths

No deaths were reported in Pool A, adjunct studies or Phase 1 studies. In Pool B, four deaths were reported during the long-term studies in patients treated with teriflunomide for 3 to 9 years. In addition, four deaths were reported in the ongoing studies including 2 completed suicides, a road traffic accident and a septicemia due to Gram-negative organism complicated with disseminated intravascular coagulopathy (in the 14 mg teriflunomide group).

The deaths reported during the overall clinical programme are summarised in figure 14.

Fig. 14 Reported deaths

	Treament group		
	Teriflunomide	**Control / Placebo**	**Blinded**
Pool A (placebo-controlled for up to 2 years)	No deaths		Not applicable
Pool B (LT extension for up to 10 years)	- **1 'death of unknown cause'** (unwitnessed) at 7 mg; cerebral autopsy findings consistent with acute attack of MS - **3 from cardiac origin** (see Table 29 for more details) observed at 7 mg (n =1), 14 mg (n = 2)	Not applicable	Not applicable
TENERE	No deaths		Not applicable
Phase 1, Clinical pharmacology and Adjunct studies	No deaths		Not applicable
Ongoing studies (as of 25 Nov 2011)	- **1 sepsis** (Gram-negative) at 14 mg	- **1 suicide** (no prior history of depression)	- **1 motor vehicle accident** - **1 suicide** (history of depression

Hepatic disorders

ALT elevations less than 3xULN were more common with teriflunomide, with a frequent onset during the first 6 months of treatment and recovery on-treatment for most patients. The overview of TEAEs for hepatic disorders and ALT increase (based on laboratory data) based on the pool A safety population is presented in table 35.

Table 35 Overview of TEAEs for hepatic disorders and ALT increase

n (%)	Placebo (N=421)	teriflunomide 7 mg (N=429)	teriflunomide 14 mg (N=415)
Patients with any TEAE	377 (89.5%)	390 (90.9%)	382 (92.0%)
Patients with any serious AE	55 (13.1%)	55 (12.8%)	67 (16.1%)
Patients with any serious TEAE	54 (12.8%)	55 (12.8%)	65 (15.7%)
Patients with any TEAE leading to permanent treatment discontinuation	32 (7.6%)	39 (9.1%)	49 (11.8%)
>1 - ≤3 ULN	124/420 (29.5%)	204/428 (47.7%)	205/413 (49.6%)
>3 - ≤5 ULN	15/420 (3.6%)	15/428 (3.5%)	16/413 (3.9%)
>5 - ≤20 ULN	9/420 (2.1%)	9/428 (2.1%)	7/413 (1.7%)
>20 ULN	2/420 (0.5%)	1/428 (0.2%)	2/413 (0.5%)
ALT >3 ULN and TBILI >2 ULN	1	1	1

In the SOC “Hepatobiliary disorders”, there was a slight imbalance with serious cholecystitis and cholelithiasis more frequently reported in patients treated with teriflunomide 7 mg (1.9%) than in those treated with placebo or teriflunomide 14 mg (0.2% each).

Pancreatic disorders

In placebo-controlled Pool A, the distribution of patients with pancreatic disorders TEAEs was similar across the treatment groups (3.1%, 3.3%, and 2.4% in the placebo, 7 mg teriflunomide, and 14 mg teriflunomide groups, respectively). Median time to onset of pancreatic disorders was 299 days on placebo, 155 days on teriflunomide 7 mg and 71 days on teriflunomide 14 mg. One case of pancreatitis confirmed by cholangiopancreatography was diagnosed in a patient treated with placebo in pool A. Isolated cases of pancreatic abnormalities were reported in pool B. The analysis of laboratory values showed that in Pool A, elevation of pancreatic lipase and amylase (>2 to ≤5 x ULN or >5 x ULN) was reported in a small number of patients in the placebo and the 7 mg teriflunomide groups. No increases in pancreatic lipase >2 x ULN or in pancreatic amylase >5 x ULN were reported in patients in the 14 mg teriflunomide group. There were no mean increases compared to baseline for serum amylase and lipase values. In EFC10531/TOWER Phase 3 study the incidence of patients with pancreatic disorders TEAEs was similar across the treatment groups (1.3%, 1.5%, and 1.3% in the placebo, 7 mg teriflunomide, and 14 mg teriflunomide groups, respectively) and there were no mean increases (as compared to baseline) in serum amylase and lipase confirming the results of the first phase 3 study, EFC6049/ TEMSO.

Bone marrow disorders

In Pool A, the proportion of patients with TEAEs for bone marrow disorders was higher in both teriflunomide groups (10.3% and 8.7% in the 7 mg teriflunomide and 14 mg teriflunomide groups, respectively) than in the placebo group (2.6%). The effect of teriflunomide on bone marrow was evidenced by a decrease affecting primarily WBC counts (<15% from baseline levels, mainly neutrophil and lymphocyte count decrease) and a dose effect was observed. The decrease in mean count from baseline occurred during the first 6 weeks, then stabilised over time while on-treatment but at decreased levels. There were isolated cases of more significant decrease, predominantly in WBCs; most of these cases resolved rapidly and the patients continued treatment.

Infections

In Pool A, the proportion of patients with TEAEs related to infections and infestations was comparable across the treatment groups. The analysis of relative risk did not show an increased risk with either

teriflunomide 7 mg or teriflunomide 14 mg compared to placebo. A low and similar incidence of serious infections was reported across groups (2.1%, 1.4% and 2.2% in the placebo, 7 mg teriflunomide and 14 mg teriflunomide groups, respectively). Infections mainly involved the upper respiratory tract. Viral infections were reported with a higher frequency in the 7 mg and 14 mg teriflunomide groups compared to placebo (4.4%, 6.5% and 1.9%, respectively), with a trend towards a dose-effect relationship. None of the TEAEs were considered serious or led to treatment discontinuation.

With respect to opportunistic infections, non-serious herpetic infections were reported with a higher frequency with teriflunomide as compared to placebo. Two opportunistic infections were reported as serious TEAE (1 case of herpes zoster on placebo and 1 case of CMV hepatitis infection on teriflunomide 14 mg) in Pool A and 1 reported in Pool B (1 case of oral herpes with teriflunomide 7 mg). In addition, in Pool B, 1 case of suspected tuberculosis primary infection was reported on teriflunomide 14 mg. No systemic opportunistic infections, such as pneumocystis, toxoplasma, mycobacterium, syphilis, mucocutaneous candidiasis, histoplasmosis, or aspergillosis were reported. No cases of progressive PML were observed in the entire teriflunomide programme. Of note, one fatal septicaemia due to Gram-negative organism was reported in a patient on teriflunomide 14 mg in the study EFC10531/TOWER.

Hypersensitivity/skin disorders

In Pool A, the proportion of patients with TEAEs potentially related to hypersensitivity and skin disorders was higher in the teriflunomide groups compared to placebo (14.5%, 19.1% and 20.5%, for the placebo, 7 mg teriflunomide and 14 mg teriflunomide groups, respectively). Urticaria, erythema, pruritus, and pruritic rash were observed with low incidences, but were more frequent in the teriflunomide groups compared to placebo in a dose-dependent manner. One patient in the 7 mg teriflunomide group discontinued due to intense generalised rash. Two patients in the 14 mg group discontinued treatment, 1 due to pruritus and 1 due to urticaria.

In Pool B, six patients in the 7 mg teriflunomide group had serious TEAEs identified in the MedDRA search for potential hypersensitivity reactions. Most of them were considered related to underlying disease conditions and were not suggestive of teriflunomide-related hypersensitivity reactions. No severe generalised major skin disorders (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome) were observed during the studies with teriflunomide.

Malignancy

In Pool A, in a total of 7 cases (4 cases on placebo, 1 case on teriflunomide 7 mg and 2 cases on teriflunomide 14 mg), most cases of medically confirmed malignant tumours including breast cancer, thyroid cancer and cervix carcinoma in situ (1 case each) were reported in the placebo group. One case of cervix carcinoma in situ was identified in a patient receiving teriflunomide 14 mg and no case was identified in the 7 mg teriflunomide group. All patients recovered following appropriate therapy.

In Pool B, a total of 22 cases of TEAEs for benign and malignant neoplasm were identified using the specific narrow SMQ search for malignancy: 14 (2.0%) on teriflunomide 7 mg and 8 (1.2%) on teriflunomide 14 mg. Among these 22 patients with benign and malignant tumours, 12 were diagnosed with medically confirmed malignancies (10 patients in the teriflunomide 7 mg group and 2 patients in the 14 mg teriflunomide group). The median time to onset was 5.2 years and 2.95 years for teriflunomide 7 mg and teriflunomide 14 mg, respectively.

Hypertension

In Pool A, an increased frequency of hypertension was observed in the placebo-controlled studies (1.9%, 3.5% and 4.3% on placebo, teriflunomide 7 mg and 14 mg, respectively). New-onset hypertension occurred in 2.8% and 3.5% of patients in the 7 mg and 14 mg teriflunomide groups compared to 1.1% of patients in the placebo group. Exacerbation of pre-existing hypertension was also more frequent in patients treated with teriflunomide compared to placebo (9.5% and 10.6% in teriflunomide 7 and 14 mg compared to 8.9% in placebo). A tendency to normalization of blood pressure with the cessation of study treatment was observed in the follow-up period.

Cardiac arrhythmias

Electrocardiographic evaluations performed in the clinical programme, including a thorough ECG study (Study TES10852) did not indicate risk of cardiac rhythm abnormalities with teriflunomide exposure as compared to placebo. No effect on heart rate was observed and no categorical increases of QTcF >480 ms or QTcF increases from baseline >60 ms were observed. Isolated events of cardiac arrhythmia were reported in teriflunomide-treated patients; these were asymptomatic premature cardiac complexes commonly seen in the general population and asymptomatic atrial fibrillation.

Interstitial lung disease

No risk of ILD with teriflunomide treatment became apparent in the teriflunomide clinical programme. No AEs potentially attributed to ILD were reported in the teriflunomide groups in Pool A. There were 2 cases of suspected ILD in the extension studies (Pool B), which were unlikely related to teriflunomide treatment.

Haemorrhages

In placebo-controlled Pool A, the proportion of patients with haemorrhages was 7.4% on placebo, 6.8% on teriflunomide 7 mg and 9.4% on teriflunomide 14 mg. The slightly higher percentage in the 14 mg group was mainly related to cases of menorrhagia or metrorrhagia in the 14 mg teriflunomide group. Most cases were incidental or had plausible explanations such as myomas.

Peripheral neuropathy

In Pool A, overall TEAEs potentially related to peripheral neuropathy were reported in 4.8% of patients in the placebo group, 3.7% in the 7 mg teriflunomide group and 6.0% in the 14 mg teriflunomide group. No significant difference in the incidence of peripheral neuropathy was reported across the treatment groups in Pool A (0.5% on placebo, 0.5% and 0.7% on teriflunomide 7 mg and teriflunomide 14 mg, respectively). Several non-serious cases of polyneuropathy were seen with teriflunomide treatment, while none was observed in patients on placebo.

Alopecia

In Pool A, the proportion of patients with TEAEs related to alopecia was higher in the two teriflunomide groups compared to the placebo group, and a dose-effect relationship was observed (4.3%, 11.4%, and 15.2% on placebo, teriflunomide 7 mg and teriflunomide 14 mg, respectively). The majority of the events were reported in female patients. Most cases were of mild and moderate intensity with spontaneous resolution within 4 months on treatment. No cases of complete hair loss were reported in the entire clinical programme. In the safety analysis of Pool B, no increased risk of alopecia with long-term administration was observed.

Laboratory findings

Laboratory data were reviewed to identify possible trends resulting from exposure to teriflunomide. Similar proportions of patients in the placebo group and the teriflunomide groups (in Pool A) experienced abnormalities in metabolic functions. Mean changes from baseline in values of metabolic functions were minimal over time and did not vary between treatment groups. Increase in CPK >1 - ≤2.5 ULN occurred most frequently on teriflunomide 7 mg (23.0%) compared to placebo (8.2%) and teriflunomide 14 mg (17.5%); however, these calculations were based on a small subset of patients in each treatment group.

No effect of teriflunomide on metabolic functions (e.g. glucose metabolism, cholesterol panel) was observed. No change in glomerular renal function assessed by creatinine, creatinine clearance or BUN was observed with teriflunomide. Decrease in plasma level of total uric acid with teriflunomide resulted from the uricosuric effect of teriflunomide.

Approximately 10% decrease in plasma level of inorganic phosphorus was observed with teriflunomide treatment, also considered to be due to increased renal tubular elimination.

Further laboratory data (liver enzymes, haematology and pancreatic enzymes) are described in the section regarding adverse events of special interest.

Safety in special populations

Subgroup safety analyses from all studies were provided. The following subgroups were analysed for their effects on the incidence of any TEAEs, serious TEAEs and TEAEs leading to treatment discontinuation for patients taking 7 mg or 14 mg teriflunomide compared to placebo

- Age group (<38 years or ≥38 years)
- Gender group (Male or Female)
- Racial group (Caucasian, Black, Asian/Oriental, Other)
- BMI (<25, ≥25 to <30, ≥30 kg/m2)
- Baseline EDSS score (≤3.5, >3.5)

Overall, there were no intrinsic factors that would increase the risk of experiencing any TEAEs or any serious TEAE for patients taking 7 mg or 14 mg teriflunomide compared to placebo.

Patients <38 years on teriflunomide 14 mg versus placebo showed an increased risk of AEs leading to discontinuation compared to the patients with age ≥38 years. However, due to the small number of discontinuation for TEAE, this result may have been an accidental finding.

Teriflunomide was not specifically investigated in the elderly and there was only one subject in the clinical programme aged 65 who was exposed to teriflunomide.

There is no relevant use of teriflunomide in children aged from birth to less than 10 years for the treatment of multiple sclerosis. The safety and efficacy of teriflunomide in children aged 10 to 18 years was not established at the time of the initial marketing authorisation application.

Recommendations for patients with renal and hepatic impairment are discussed under clinical pharmacology aspects.

Safety related to drug-drug interactions and other interactions

Effect of teriflunomide on CYP2C8 substrate: repaglinide

There was an increase in mean repaglinide Cmax and AUC (1.7- and 2.4-fold, respectively), followingrepeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of CYP2C8 in

vivo. Therefore, medicinal products metabolised by CYP2C8, such as repaglinide, paclitaxel, pioglitazone or rosiglitazone, should be used with caution during treatment with teriflunomide.

Effect of teriflunomide on oral contraceptive: 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel

There was an increase in mean ethinylestradiol Cmax and AUC0-24 (1.58- and 1.54-fold, respectively) and levonorgestrel Cmax and AUC0-24 (1.33- and 1.41-fold, respectively) following repeated doses of teriflunomide. While this interaction of teriflunomide is not expected to adversely impact the efficacy of oral contraceptives, consideration should be given to the type or dose of oral contraceptives used in combination with teriflunomide.

Effect of teriflunomide on CYP1A2 substrate: caffeine

Repeated doses of teriflunomide decreased mean Cmax and AUC of caffeine (CYP1A2 substrate) by 18% and 55%, respectively, suggesting that teriflunomide may be a weak inducer of CYP1A2 in vivo. Therefore, medicinal products metabolised by CYP1A2 (such as duloxetin, alosetron, theophylline and tizanidine) should be used with caution during treatment with teriflunomide, as it could lead to the reduction of the efficacy of these products.

Effect of teriflunomide on warfarin

Repeated doses of teriflunomide had no effect on the pharmacokinetics of S-warfarin, indicating that teriflunomide is not an inhibitor or an inducer of CYP2C9. However, a 25% decrease in peak international normalised ratio (INR) was observed when teriflunomide was coadministered with warfarin as compared with warfarin alone. Therefore, when warfarin is co-administered with teriflunomide, close INR follow-up and monitoring is recommended.

Effect of teriflunomide on organic anion transporter 3 (OAT3) substrates:

There was an increase in mean cefaclor Cmax and AUC (1.43- and 1.54-fold, respectively), following repeated doses of teriflunomide, suggesting that teriflunomide is an inhibitor of OAT3 in vivo. Therefore, when teriflunomide is coadministered with substrates of OAT3, such as cefaclor, benzylpenicillin, ciprofloxacin, indometacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, caution is recommended.

Effect of teriflunomide on BCRP and /or organic anion transporting polypeptide B1 and B3 (OATP1B1/B3) substrates:

There was an increase in mean rosuvastatin Cmax and AUC (2.65- and 2.51-fold, respectively), following repeated doses of teriflunomide. However, there was no apparent impact of this increase in plasma rosuvastatin exposure on the HMG-CoA reductase activity. For rosuvastatin, a dose reduction by 50% is recommended for coadministration with teriflunomide. For other substrates of BCRP (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration of teriflunomide should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.

Discontinuation due to adverse events

In Pool A, the proportion of patients with TEAEs leading to permanent treatment discontinuation was 7.6%, 9.1% and 11.8% in the placebo, 7 mg teriflunomide and 14 mg teriflunomide groups, respectively. The most common TEAE leading to treatment discontinuation was ALT increased (1.9%,

2.6%, and 1.9% in the placebo, 7 mg teriflunomide, and 14 mg teriflunomide groups, respectively). Per study protocols, treatment was to be discontinued for confirmed ALT increase above 3 x ULN.

In Pool B, the proportion of patients with TEAEs leading to withdrawals was similar between the treatment groups (15.6% and 15.3% on teriflunomide 7 mg and 14 mg, respectively), with reasons consistent with those observed in Pool A.

2.6.1. Discussion on clinical safety

In the clinical development programme, the cumulative exposure to teriflunomide in the monotherapy trials was over 4394 patient-years up to the database lock point for this submission. The inclusion of EFC10531/TOWER study increased the exposure to more than 6200 patient-years, with a safety profile considered similar to the safety profile established with the previous studies and without any unexpected safety findings.

In the pivotal Phase 2 and 3 trials included in Pool A and Pool B, 1355 patients were exposed to teriflunomide 7 mg and 14 mg with a maximum exposure of up to 10.4 years. The median duration of study treatment was 2.7 years for both teriflunomide 7 mg and 14 mg in Pool B. In addition, 462 subjects were exposed to teriflunomide in the Phase 1 studies with single doses up to 100 mg and repeated doses up to 70 mg/day.

The CHMP considered that the extent and duration of exposure, in particular the total number of MS patients treated for at least 6 months at dose levels intended for clinical use, was adequate to assess clinical safety of a drug intended for long-term treatment and in line with the NfG on population exposure to assess clinical safety (CPMP/ICH/375/95).

The demographic characteristics of the safety population were very similar for Pool A as compared to Pool B. The safety population was primarily Caucasian (>96%), with a median age of 38 to 39 years and with a predominance of females (>70%). The geographic regions represented were mainly Western Europe, North America and Eastern Europe.

The most common clinical AEs reported with teriflunomide with a dose-effect relationship were diarrhoea, alopecia, nausea and ALT increased (less than 3x ULN). These events were generally of mild intensity and infrequently led to treatment discontinuation.

The CHMP considered that the safety database was not sufficient to entirely exclude a risk of drug induced liver disorders. Hepatic toxicity is a known risk of teriflunomide, which was supported by the data that >1 - ≤3 x ULN increase in ALT was observed in 29.5% placebo vs. 47.7% and 49.6% teriflunomide 7 and 14 mg, respectively. With the argument that the median time to onset of hepatic disorders was 127 days in the 14 mg teriflunomide group, the applicant initially proposed a hepatic monitoring schedule consisting of screening at baseline, and then monthly for six months and quarterly thereafter for a year or as indicated by clinical signs and symptoms. The CHMP was of the view that the reversibility of mild hepatic toxicity was not convincingly demonstrated and moreover, that once hepatic injury is detected, it needs to be closely monitored, since ALT levels may further increase or decrease. As most mild elevations are asymptomatic, a quarterly monitoring after the first 6 months of treatment was not considered sufficient to ensure timely detection of hepatic toxicity. In conclusion, the CHMP requested that liver enzymes should be assessed every two weeks during the first six months of treatment and every eight weeks thereafter or as indicated by clinical sign and symptoms; this was reflected in section 4.8 of the SmPC. A pre-existing severe hepatic impairment was considered to preclude the use of teriflunomide and was therefore included as a contraindication.

Since teriflunomide is highly protein bound and cleared via hepatic metabolism and biliary secretion, plasma levels of teriflunomide can be expected to be increased in patients with hypoproteinaemia. As patients with severe hypoproteinaemia were excluded from the pivotal studies, teriflunomide poses an unknown risk for this patient group, because insufficient clinical experience is available. Therefore, teriflunomide should not be used in patients with conditions of severe hypoproteinaemia, as reflected in sections 4.3 and 4.4 of the SmPC.

Pancreas was identified as a target organ in a 12-month toxicity study in dogs; this finding was of uncertain relationship to the pharmacologic activity of teriflunomide in humans. In clinical studies with close laboratory monitoring and imaging, there was no mean increase (compared to baseline) in serum amylase and lipase. The CHMP considered that the available clinical data did not suggest a critically increased risk of clinical pancreatitis in patients treated with therapeutic doses of teriflunomide. Based on the evidence available for leflunomide (parent compound), pancreatic disorders were reflected in the RMP as an important identified risk.

The proportion of patients with bone marrow disorders was higher in both teriflunomide treatment groups compared to placebo. Isolated cases of significant cytopenias were observed, such as cases of more significant decreases of white blood cell count and thrombocytopenia.

The most frequently reported TEAEs in Pool A were infections, with a slightly higher incidence in both teriflunomide groups compared to placebo. The most frequently reported events were upper respiratory tract infections, especially nasopharyngitis. The frequency of non-serious herpetic infections was higher on teriflunomide as compared to placebo. The incidence of serious infections and infections leading to treatment discontinuation was similar across all groups. Apart from sporadic cases of tuberculosis and cytomegalovirus hepatitis infection on teriflunomide treatment, no signals of severe systemic opportunistic infections, including PML, were be detected.

With respect to the fatal case of a gram-negative sepsis, the CHMP was of the opinion that the immunosuppressant potential of teriflunomide was possibly responsible for the fatal outcome in the 20 year old female patient. This case of multi-organ failure with fatal outcome was considered to suggest a possible susceptibility of MS patients to develop a severe infection due to lack of efficient immune response.

No signals for severe hypersensitivity reactions such as Stevens - Johnson syndrome, systemic anaphylactic reactions or severe skin reactions were detected more frequently in the teriflunomide groups compared to placebo during the entire clinical programme. In patients treated with the parent compound leflunomide, very rare cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported and therefore, the CHMP considered that a specific reference to skin reactions should be made in section 4.4 of the SmPC and hypersensitivity reactions, including severe skin reactions were reflected in the RMP as an important identified risk.

There was no indication of a carcinogenic risk in a 2-year oral carcinogenicity study in rats and mice. The frequency of cancer as solid tumors in placebo-controlled clinical trials was not higher on teriflunomide as compared to placebo and no unusual pattern was observed. Although it is known that the risk of malignancy, particularly lymphoproliferative disorders, is increased with the use of some immunosuppressive agents, the CHMP considered re-assuring that no cases of lymphoproliferative or haematological malignancies were observed in the clinical programme of teriflunomide.

The effect of teriflunomide on blood pressure was regularly monitored during the teriflunomide clinical development programme. Blood pressure measurements were performed at each visit in the Phase 2 and 3 studies. Diastolic and systolic blood pressure elevations were more frequent on teriflunomide.

Nevertheless, in patients who developed hypertension, the introduction or modification of antihypertensive treatment usually led to good control of blood pressure. There were no reports of hypertensive emergencies, or of acute life-threatening or long-term complications. The CHMP considered that the potential elevation of blood pressure is adequately reflected in sections 4.4 and 4.8 of the SmPC.

With respect to cardiac rhythm abnormalities, the CHMP considered that the available data did not indicate an increased risk of cardiac arrhythmia.

In an adjunct study with glatiramer acetate, one case of interstitial lung disease, possibly related to teriflunomide, was reported and two cases unlikely related to teriflunomide were reported in the extension studies. Based on the extent of patient exposure, a rare risk of drug-induced pulmonary toxicity could not be excluded. While pulmonary toxicity was not suggested by the clinical database of teriflunomide, the interstitial lung disease was considered an important identified risk based on an effect from observations with the parent compound leflunomide.

Adverse events potentially related to peripheral neuropathy, polyneuropathy, paraesthesias and neuralgia were reported in all treatment groups, but more frequently in teriflunomide treated patients. This observation was supported by pool A and pool B data as well as additional data from the TOWER study. In several cases, the event was considered serious and study discontinuation due to peripheral neuropathy was also reported. The CHMP concluded that peripheral neuropathy should be reflected as an important potential risk in the RMP and that treatment discontinuation should be considered, together with performing the accelerated elimination procedure, as reflected in section 4.4 of the SmPC.

The CHMP considered the eight cases of death reported in the entire development programme, five of which were evaluated as possibly related to other concomitant pre-existing diseases or underlying MS itself and three cases as possibly related to the drug exposure. Overall, considering the fatal cases observed, the CHMP was of the view that close monitoring was essential with respect to the increased risk of severe infections during treatment with teriflunomide as well as of potential severe cardiac problems such as acute heart failure and myocardial infarction. The respective pharmacovigilance activities are reflected in the RMP.

With regard to laboratory data, teriflunomide led to a decrease (of at most 15%) in neutrophils and lymphocytes and smaller mean decreases in platelet and RBC counts and to greater increase in ALT, AST and SGGT than placebo. The CHMP considered that the review of other haematology and clinical chemistry variables, blood pressure, pulse rate, body temperature, body weight and ECG recordings did not reveal any clinically relevant safety findings attributable to treatment with teriflunomide.

The CHMP also considered that the safety will be further confirmed with more long-term data from the ongoing studies.

No post-marketing experience was available, as teriflunomide was not marketed in any country; however, the post-marketing experience with Arava (leflunomide, parent compound of teriflunomide) was considered relevant for the safety profile of teriflunomide. In general, the safety database from the clinical experience with teriflunomide in MS patients did not present new and unknown AEs, but was rather a confirmation of the experience with leflunomide. However, the overall safety database of leflunomide is much larger; thus, the CHMP was of the view that the leflunomide safety data should also be taken into account, especially those effects related to the mechanism of action, i.e. reduction of pyrimidine dependent cell proliferation, and potentially linked to safety issues due to immunosuppression (opportunistic infections and PML). In this context, the CHMP considered that the

risk management plan and product information of teriflunomide should cover all important identified and potential risks of leflunomide.

Overall, the available safety data suggested that teriflunomide 14 mg has a manageable safety profile and, provided appropriate post-authorisation measures, can be used safely in the proposed indication.

From the safety database all the adverse reactions reported in clinical trials were included in the SmPC.

Of note, while the applicant only applied for authorisation of the 14 mg dose, the CHMP discussed available efficacy and safety data of both doses. Based on the data presented, the CHMP noted that while the 14 mg dose was numerically more efficacious in terms of annualized relapse rate and delay in disability progression, the data on the 7 mg dose also suggested efficacy. As the lower dose might present an option of reducing dose for tolerability reasons, the CHMP recommended that the applicant should submit an application for the 7 mg strength in the post-authorisation phase.

2.6.2. Conclusions on the clinical safety

The safety of teriflunomide is considered to be acceptable when used in accordance with the conditions defined in the Product Information. Appropriate measures including additional pharmacovigilance activities and risk minimization measures were put in place to ensure safe and effective use of the product in the recommended indication.

The safety aspects are further discussed in the context of the overall benefit-risk balance.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The applicant submitted a signed Summary of the Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the respective GVP module, the CHMP considered the Summary of the Pharmacovigilance System acceptable.

Risk Management Plan

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

Table 36 RMP Summary Table

Safety Concerns	Pharmacovigilance Activities	Risk Minimisation Activities
Important Identified Risks		
Hepatic effects	Routine: Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials Targeted questionnaire Additional: Non-interventional long-term safety study (EU-PASS)	Routine: Product Labeling, PIL SPC section 4.2 Posology and method of administration indicates that treatment should be initiated and supervised by a physician experienced in MS and mentions that ALT and SGPT should be controlled before starting treatment and monitored periodically during treatment. Severe hepatic impairment is a contraindication listed in the SPC section 4.3 Contraindications. The SPC section 4.4 Special warnings and precautions for use, provides information on frequency and pattern of liver enzyme elevation with teriflunomide during clinical trials, and gives recommendations to minimize this risk (e.g. at baseline, monitored periodically during treatment, and in case of signs/symptoms suggestive of hepatic dysfunction; treatment to be discontinued if liver injury is suspected; consider treatment discontinuation in case of confirmed liver enzyme elevation > 3x ULN). Also mentions that terifluonomide should not be used in patients with severe hypoproteinaemia, and that it is recommended to avoid alcohol consumption during treatment with teriflunomide due to a potential for additive hepatotoxic effects. ALT increased is listed as a very

		common ADR in the SPC section 4.8 Undesirable effects; gamma-glutamyltransferase increased, and AST increased are listed as common ADRs Additional: Communication Plan Physicians + patients (HCP education/discussion guide and Patient Education card)
Hypertension	Routine: Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials	Routine: Product Labeling, PIL SPC section 4.2 Posology and method of administration indicates that treatment should be initiated and supervised by a physician experienced in MS and mentions that blood pressure should be controlled before starting treatment and monitored periodically during treatment. The SPC section 4.4 Special warnings and precautions for use provides information on blood pressure elevation observed with teriflunomide in clinical trials, and advises to appropriately manage blood pressure elevation before, during, and after treatment with teriflunomide. In the SPC section 4.8 Undesirable effects, hypertension is listed as a common ADR. Additional: Communication Plan Physicians + Patients (HCP education/discussion guide and Patient Education Card)
Hematologic Effects	Routine: Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials	Routine: Product Labeling, PIL SPC section 4.2 Posology and method of administration indicates that treatment should be initiated and supervised by a physician experienced in MS and mentions that complete blood cell count should be controlled before starting treatment and monitored based on signs and

		symptoms during treatment. The SPC section 4.4 Special warnings and precautions for use provides information on blood cell count decrease (including pattern of occurrence) observed wih teriflunomide in clinical trials. It also provides recommendations to minimize the risk of hematological effects (e.g. blood cell count available at baseline as a precaution, and to be assessed during treatment as indicated by clinical signs and symptoms). It also mentions that the risk of haematological disorders is increased in patients with pre-existing blood cell count abnormalities and that the accelerated elimination procedure should be considered in case of occurrence of haematolgoical disorders. In the SPC section 4.8 Undesirable effects, neutropenia, neutrophil count decreased, WBC count decreased. Anemia and mild thrombocytopenia are listed as uncommon ADRs. The SPC section 5.3 Preclinical safety data informs about decreased blood cell count observed in animals <u>Additional:</u> Communication Plan Physicians + Patients (HCP education/discussion guide and patient Education Card)
Infections	<u>Routine:</u> Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials <u>Additional:</u> Non-interventional long-term safety study (EU-PASS	Routine: Product Labeling, PIL: SPC section 4.2 Posology and method of administration indicates that treatment should be initiated and supervised by a physician experienced in MS The SPC section 4.4 Special warnings and precautions for use mentions that initiation of treatment with teriflunomide should be delayed in

		patients with severe active infection until resolution. It also provides information on incidence of serious infections and mentions that if a patient develops a serious infection suspending treatment with teriflunomide should be considered. The benefits and risks of reinitiating treatment with teriflunomide should be assessed and an accelerated elimination procedure may be considered. Patients on teriflunomide should be instructed to report symptoms of infections to a physician. It mentions that co-administration with other immunosuppressive therapies has not been evaluated. It also mentions that patients with a positive tuberculosis screen should be treated by standard medical practice prior to treatment with teriflunomide. In the SPC section 4.8 Undesirable effects, influenza, upper respiratory tract infection, and urinary tract infection are listed as very common ADRs. Bronchitis, sinusitis, pharyngitis, cystitis, gastroenteritis viral, oral herpes, tooth infection, laryngitis, and tinea pedis, are listed as common ADRs. <u>Additional:</u> Communication Plan Physicians + Patients (HCP education/discussion guide and patient Education Card)
Interstitial lung disease (based on effects observed with leflunomide)	<u>Routine:</u> Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials Targeted questionnaire <u>Additional:</u> Non-interventional long-term safety study (EU-	<u>Routine: Product Labeling</u> In the SPC section 4.4 Special warnings and precautions for use, it is mentioned that the risk of interstitial lung diseases is increased in patients with a history of ILD which is a potentially fatal disorder and may occur acutely during therapy. Pulmonary symptoms, such as cough and dyspnoea, may be a reason for discontinuation of the therapy and for

	PASS)	further investigation, as appropriate. The SPC section 4.8 Undesirable effects lists interstitial lung disease as a very rare undesirable effect
Hypersensivity reactions, including severe skin reactions	<u>Routine:</u> Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials	Routine: Product Labeling, PIL Hypersensitivity to the active substance (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients is a contraindication listed in the SPC section 4.3 Contraindications. In the SPC section 4.4 Special warnings and precautions for use, it is mentionned that in case of ulcerative stomatitis, teriflunomide administration should be discontinued. If skin and/or mucosal reactions are observed which raise the suspicion of severe generalised major skin reactions (Stevens-Johnson syndrome, or toxic epidermal necrolysis-Lyell's syndrome), teriflunomide and any other possibly associated treatment must be discontinued, and an accelerated washout procedure initiated immediately. In such cases patients should not be re- exposed to teriflunomide In the SPC section 4.8 Undesirable effects, rash and acne is a common ADRs with teriflunomide.
Pancreatic effects	<u>Routine:</u> Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials Targeted questionnaire <u>Additional:</u> Non-interventional long-term safety study (EU-	<u>Routine: Product Labeling, PIL.</u> The SPC section 5.3 Preclinical safety data mentions pancreas as one of the major target organs of toxicity. The SPC section 4.8 Undesirable effects lists pancreatitis as a very rare undesirable effect

	PASS)	
Important Potential Risks		
Teratogenicity	Routine: Targeted questionnaire (pregnancy forms) Additional: International Pregnancy registry (EU/ROW) Pregnancy registry (US/Canada)	Routine: Product Labeling, PIL The SPC section 4.2 Posology and method of administration indicates that treatment should be initiated and supervised by a physician experienced in MS The SPC section 4.6 Fertility, pregnancy and lactation states also that treatment with teriflunomide is not recommended during pregnancy or in women with child-bearing potential not using contraception. It also states that women of child-bearing potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception before initiaiting teriflunomide treatment. It mentions the availability of the accelerated elimination procedure in patients treated with teriflunomide who wish to become pregnant. The accelerated elimination procedure is described in more detail in SPC section 4.4 Special warnings and precautions for use and in the 'Elimination' section of SPC 5.2 Pharmacokinetic properties. The SPC section 5.3 Preclinical safety data informs that teriflunomide was embryotoxic and teratogenic in animals in the human therapeutic range. Additional: Communication Plan Physicians + Patients (HCP education/discussion guide and patient education card)
Serious opportunistic infections, including	Routine: Routine pharmacovigilance and periodic assessment in	Routine: Product Labeling The SPC section 4.2 Posology and method of administration indicates

PML	PSURs Ongoing clinical trials Targeted questionnaire (PML) <u>Additional:</u> Non-interventional long- term safety study (EU- PASS)	that treatment should be initiated and supervised by a physician experienced in MS The SPC section 4.4 Special warnings and precautions for use provides recommendations to minimize the risk of serious infections (do not start treatment in case of active infection; report symptoms of infections to physician; in case of serious infection, consider suspending treatment, and undergoing the accelerated elimination procedure and reassess benefit-risk before reinitiating treatment). It also mentions that co- administration with other immunosuppressive therapies has not been evaluated. The SPC section 5.1 Pharmacodynalic properties highlights the immunomodulatory properties of teriflunomide, and its effect on lymphocytes. <u>Additional:</u> Communication Plan Physicians + Patients (HCP education/discussion guide and patient education card)
Cardiovascular effects	<u>Routine:</u> Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials <u>Additional:</u> Non-interventional long- term safety study (EU- PASS)	None
Malignancies (including lymphoproliferative disorders)	<u>Routine:</u> Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials	Routine: Product Labeling The SPC section 4.8 Undesirable effects mentions that the risk of malignancy, particularly lymphoproliferative disorders, is increased with use of some

	Additional: Non-interventional long- term safety study (EU- PASS)	immunosuppressive agents.
Peripheral neuropathy	Routine: Routine pharmacovigilance and periodic assessment in PSURs Ongoing clinical trials Targeted questionnaire Additional: Non-interventional long- term safety study (EU-PASS)	Routine: Product Labeling, PIL. The SPC section 4.4 Special warnings and precautions for use mentions that if a patient taking teriflunomide develops a confirmed peripheral neuropathy, discontinuing terfiflunomide therapy and performing the accelerated elimination procedure had to be considered. In the SPC section 4.8 Undesirable effects, paresthesia is listed as a very common ADR, and sciatica, carpal tunnel syndrome, hyperesthesia and neuralgia are listed as common ADRs with teriflunomide. It also reports the actual incidences for TEAEs suggestive of peripheral neuropathy
Renal failure	Routine: Routine pharmacovigilance and periodic assessment in PSURs	Routine: Product Labeling The SPC section 4.2 Posology and method of administration indicates that no dosage adjustment is necessary for patients with mild, moderate or severe not undergoing dialysis renal impairment. Patients with severe renal impairment undergoing dialysis were not evaluated. Therefore teriflunomide is not recommended in this population. Severe renal insufficiency is a contraindication listed in the SPC section 4.3 Contraindications. The SPC section 5.2 Pharmacokinetic properties mentions that severe renal impairment had no impact on the pharmacokinetic of teriflunomide. Therefore no dose adjustment is anticipated in mild, moderate and severe renal-impaired patients

Potential off-label use in adults	Routine: Routine pharmacovigilance and periodic assessment in PSURs Additional: Non-interventional long- term safety study (EU-PASS)	None
Risk of interaction (with CYP2C8 and CYP1A2 substrates, BCRP substrates, OATP1B1/B3 substrates, OAT3 substrates, warfarin, oral contraceptive)	Routine: Routine pharmacovigilance and periodic assessment in PSURs	Routine: Product Labeling, PIL. The SPC section 4.5 Interaction with other medicines informs about - the increased plasma exposure of repaglinide (a CYP2C8 substrate) when co-administered with teiflunomide; recommends using with caution drugs metabolized by CYP2C8 (e.g. repaglinide, paclitaxel, pioglitazone or rosiglitazone) during treatment with teriflunomide. - the increased plasma exposure of cefaclor (a OAT3 substrate) when co-administered with teriflunomide; recommends using with caution substrates of OAT3, such as cefaclor, penicillin G, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine, during treatment with teriflunomide. - the increased plasma exposure of rosuvastatin (a BCRP and OATP1B1/B3 substrate) when co-administered with teriflunomide; recommends for rosuvastatin, a dose reduction by 50% for coadministration with teriflunomide; recommends caution for other substrates of BCRP (eg, methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the OATP family especially HMG-Co reductase inhibitors (eg, simvastatin, atorvastatin pravastatin,

		methotrexate, nateglinide, repaglinide, rifampin) concomitant administration of teriflunomide and close patient monitoring for signs and symptoms of excessive exposure to the drugs and considering reduction of the dose of these drugs. - the decreased plasma exposure of caffeine (a CYP1A2 substrate) when co-administered with teiflunomide; recommends using with caution drugs metabolized by CYP1A2 (e.g. duloxetin, alosetron, theophylline and tizanidine) during treatment with teriflunomide, as their efficacy could be reduced - a 25% decrease in INR when warfarin was administered with teriflunomide, and therefore recommends close INR follow-up and monitoring, when warfarin is co-administered with teriflunomide - the increased plasma exposure of thinylestradiol and levonorgestrel when administered with teriflunomide; it also clarifies that while this is not likely to adversely impact the efficacy of oral contraceptives, consideration should be given to the type or dose of oral contraceptives used in combination with teriflunomide
Important missing information		
Use in children	<u>Routine:</u> Routine pharmacovigilance and periodic assessment in PSURs <u>Additional:</u> Pediatric clinical study planned (EFC11759) Non-interventional long- term safety study (EU-PASS)	Routine: Product Labeling, PIL. The SPC section 4.2 Posology and method of administration indicates that the safety and efficacy of teriflinomide in children and adolescent aged 0 to 18 years has not yet been established.

Use in combination with MS treatments (other than IFN-β and glatiramer acetate)	Routine: Routine pharmacovigilance and periodic assessment in PSURs Additional: Non-interventional long- term safety study (EU- PASS)	Routine: Product Labeling, PIL The SPC section 4.4 Special warnings and precautions for use indicates that co-administration with antineoplastic or immunosuppressive therapies used for treatment of MS has not been evaluated. It also states that safety studies, in which teriflunomide was concomitantly administered with interferon beta, and glatiramer acetate did not reveal any specific safety concerns, and that the long term safety of these combinations in MS has not been established. In addition, recommendations on how to switch to or from teriflunomide treatment is provided for patients already treated or planned to be treated with other MS treatments.

The CHMP, having considered the data submitted, was of the opinion that the pharmacovigilance activities in addition to the use of routine pharmacovigilance, as summarised in the EU-RMP Summary table, are needed to investigate further some of the safety concerns.

The CHMP, having considered the data submitted, was of the opinion that the following additional risk minimisation activities were required:

Communication Plan for Physicians and Patients, including:

- Educational material for Healthcare professionals
- Educational card for patients

2.8. User consultation

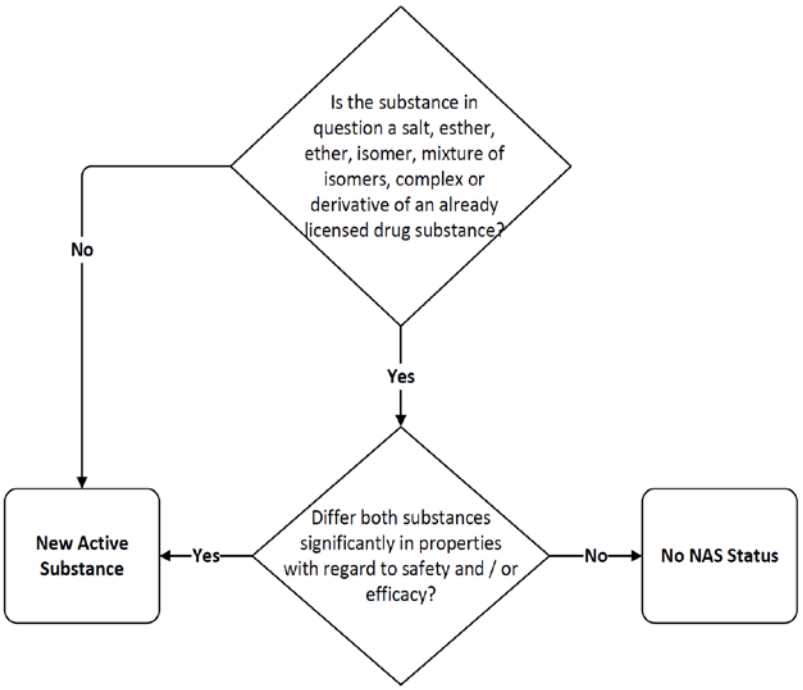
The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9. New active substance status

To determine whether a certain drug substance can be regarded as a New Active Substance (NAS) the requirements of Article 10(2)(b) of Directive 2001/83/EC have to be taken into account:

"The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy".

According to this, the NAS assessment has to follow a stepwise approach as illustrated in the following scheme:



Thus, in first instance the chemical relationship of teriflunomide and its parent compound leflunomide has to be studied (see section 2.9.1 below). If a positive NAS-categorisation is however not regarded justified from a chemical point of view, then other evidence from clinical and non-clinical data will have to be taken into account (see section 2.9.2).

2.9.1. Chemical differences - Classification of teriflunomide as derivative of leflunomide

From a chemical point of view, it can be easily concluded that both, teriflunomide and leflunomide are not related as different salts, esters, ethers, isomers, mixtures of isomers or complexes. The relevant question is, whether teriflunomide and leflunomide can be regarded as derivatives. In the chemical literature various definitions are given for the term *"derivative"*:

Examples for the definition of the term *"derivative"*:

- *"Any compound that may, at least theoretically, be formed from another compound to which it is structurally related."*[1]
- *"A chemical compound that may be produced from another compound of similar structure in one or more steps."*[2]

1 Oxford Dictionary of Biochemistry and Molecular Biology, 2nd ed., 2012.

2 The American Heritage Medical Dictionary, Houghton Mifflin Harcourt; Updated edition (2007)

Both definitions are based on two elements: The conversion, at least theoretical, from one to the other and their structural relationship.

i. Chemical interconversion

Teriflunomide is the main active *in vivo* metabolite of leflunomide. Upon administration of leflunomide, 70 % of the drug administered converts into teriflunomide. The only difference between the molecules is the opening of the isoxazole ring. This is considered a simple structural modification and a technically simple one-step synthetic transformation. The ring-opening of 3-unsubstituted isoxazoles to afford α-cyanoenol (or isomeric cyanocarbonyl) derivatives has been known since the pioneering work of Claisen in 1891[3]. The reaction proceeds rapidly and cleanly via a E2-elimination mechanism, without other intermediates, upon treatment with base at ambient temperature. These conditions would also, for example, hydrolyse an ester to its corresponding carboxylic acid. Since the ring-opening of 3-unsubstituted isoxazoles is so facile and selective, several synthetic processes have been developed which take advantage of this transformation as the first step, effectively using 3-unsubstituted isoxazoles as latent α-cyanocarbonyl compounds[4]. In the case under consideration, leflunomide could be easily converted to teriflunomide by treatment with base. The electron-withdrawing amide carbonyl moiety at the 4-position will facilitate this process. This conversion has already been demonstrated *in vivo* in human plasma. In addition, teriflunomide is listed as a potential impurity of leflunomide in the Ph.Eur. monograph of leflunomide.

The applicant argues that the fact that teriflunomide is a metabolite of leflunomide should not be taken into account, and that similarity must be assessed based on the chemical quality aspects and the similarity coefficients. However, it should not be overruled that a derivative is a compound that may, at least theoretically, be formed from another compound. In this respect, it is noted that the applicant uses a synthetic route not involving leflunomide for the synthesis of teriflunomide, but this should not constitute an argument to conclude that teriflunomide is not a derivative of teriflunomide. Most of the molecules can be synthetized by different syntheses (e.g.generics), and applicants may choose to use one or another route. There is no scientific reason to conclude that in this case teriflunomide is not a derivative because the route of synthesis employed by the applicant does not use the parent compound, whereas, instead, the opening of the isoxazole ring of leflunomide as a synthethic step would entail that teriflunomide is a derivative.

As mentioned above, teriflunomide is an *in vivo* metabolite of leflunomide. Upon administration of leflunomide *in vivo*, the isoxazole ring of leflunomide is opened and teriflunomide is formed[5]. Therefore, regardless of the substance administered (leflunomide or teriflunomide) it is the same molecule (teriflunomide) the one exerting the pharmacological, immunological or metabolic action in view of restoring, correcting or modifying physiological functions, and does not present, in clinical use, a new chemical entity to patients.

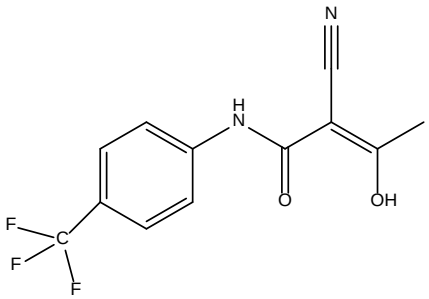
3 "Isoxazoles" in The Chemistry of Heterocyclic Compounds, Paola Grünanger and Paola Vita-Finzi, 1991, John Wiley and Sons Inc., Chapter 1.4.6.1, p 298.

4 McGregor, D. N. et al, Tetrahedron, 1969, 25, 389-395; Wakefield, B. J. and Wright, D. J., Adv. Heterocycl. Chem., 1979, 25, 147-204; Cillar, J. A. et al, J. Chem. Soc. Perkin Trans. 1, 1985, 2581-2584; Perez, C. et al, Tetrahedron, 52, 987-992).

5 Breedveld, F. C. and Dayer, J-M., Ann. Rheum. Dis., 2000, 59, 841-849.

ii. Structural similarity

teriflunomide



leflunomide

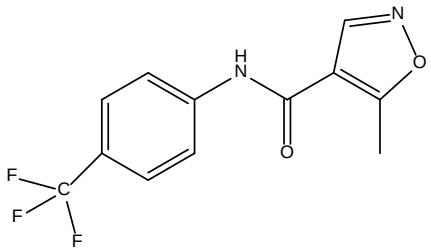


Figure 15 Molecular structures of teriflunomide and leflunomide.

In the latest response document, the applicant objected that simple *"zero-dimensional"* calculations like those exclusively based on molecular weight differences are not suitable for similarity assessment. Indeed, it is agreed that single aspects of a chemical substance, like molecular weight, functional groups, or the total number of certain chemical elements are not a sufficient indicator for similarity comparisons when assessed alone. However, the final conclusion of the QWP report is clearly based on the entirety of different molecular properties assessed in combination:

- The leflunomide molecule is composed of an amide substituted with a 4-(trifluoromethyl) phenyl in the N-position and 5-methylisoxazol ring linked to the carbonyl side of the amide. Teriflunomide molecule also consists of an amide substituted with a 4-(trifluoromethyl) phenyl in the N-position, whereas the carbonyl side of the amide is substituted by a linear chain, which results from ring opening of the 5-methylisoxazol ring. Thus, both molecules share the 4-(trifluoromethyl)phenyl and amide groups, which represent more than 69 % of their molecular structure. The only difference between the two molecules is the opening of the isoxazole ring that can be technically performed in a simple one-step transformation.
- Both leflunomide and teriflunomide have the identical molecular formula ($C_{12}H_9F_3N_2O_2$) and, hence, the same relative molecular mass, number of carbons and hydrogens as well as heteroatoms, i.e. fluorines, nitrogens and oxygens. Moreover, both molecules are structural isomers.
- Like other derivatives or pro-drugs, some physico-chemical properties are different between teriflunomide and leflunomide (see table 1). Beneficially altering these properties is one reason pro-drugs are developed. In addition, it should be taken into consideration that different polymorphs or solvates of a substance can have different chemical and physical properties, and this would not result on them being a different drug substance. Nonetheless, the compounds share many similarities in the physico-chemical properties that are particularly relevant to their in vivo performance (e.g. the insolubility in water, bioavailability and the categorisation in BCS class II).

Table 37 Comparison of the physico-chemical properties of teriflunomide and leflunomide.

Physico-chemical property	Teriflunomide	Leflunomide
Description	White to almost white powder	White to almost white powder
Melting range	228-232 ºC	165-167 ºC
pKa value, 23 ^{oC}	3.1	10.8
Partition coefficient, logP	2.7	1.95
Hygroscopicity	Not hygroscopic	Not hygroscopic
Aqueous solubility	Practically insoluble in water	Practically insoluble in water
Biopharmaceutics classification system (BCS)	Class II	Class II
Oral bioavailability	100%	80%
Stability	photostable	Unstable to light

Taking all these aspects into consideration, it can be concluded that the differences between both molecules (namely, opening of the isoxazole ring) are minor, and both molecules are structurally similar.

Similarity assessment based on similarity calculations

The applicant makes reference to the assessment of similarity in the context of orphan medicinal products. For the comparison of leflunomide vs. teriflunomide some similarity calculations performed by the company and in addition by an independent expert are presented using the Tanimoto coefficients in combination with structure-based molecular fingerprints. The applicant concluded that the calculated Tanimoto values clearly suggest a classification as different molecular structures.

In view of the applicant's claim the CHMP has performed the structural similarity evaluation as per the orphan drug legislation. However, such similarity assessment is not meant to define whether an active substance is to be considered new active substance or not, but only whether two active substance are to be considered similar within the meaning of Article 3(3)(c) of Commission Regulation (EC) No 847/2000. This evaluation takes into consideration the molecular structural features, the 1D descriptors and the similarity coefficients using different fingerprints. The outcome of the evaluation is that considering all these elements, namely the 1D descriptors (molecular structure, molecular formula, atoms of carbon, hydrogen and heteroatoms, relative molecular mass, functional groups, number of rings, phenyl rings etc.) and the supportive information from the similarity coefficients calculated, it can be concluded that both molecules are similar in the context of the orphan drug legislation (see separate QWP report on structural similarity). Five different fingerprints (2D descriptors FCFP_4, ECFP_4, MDL Public Keys, FCFC_4 and ECFC_4) and one unidentified fingerprint from an external expert were used to convert the chemical structures into a binary form, and three different similarity coefficients (Tanimoto, Dice and Cosine) based on these fingerprints were calculated. As expected there is variability in the values of the similarity coefficients (Tanimoto, Dice, Cosine) obtained with the different types of fingerprints. However, taking into account all calculated values it was considered that the molecules are similar based on the principles that QWP uses to establish structural similarity in the context of the orphan drug legislation (see Appendix 1 -QWP report).

The different values of similarity coefficients obtained are related to the type of fingerprint selected. Therefore, the similarity assessment should not just focus on one single aspect (i.e. fingerprint and one similarity calculation), but should be based on different molecular descriptors, which are assessed in combination.

Conclusion on Chemical Differences

Based on all these aspects (chemical interconversion and structural relationship/similarity assessment), CHMP came to the conclusion that teriflunomide is a structurally related metabolite of leflunomide, a derivative of an already authorised active substance. Both molecules share the same structural features, differences in molecular structure are only minor.

2.9.2. Significant difference in safety and/or efficacy to justify the new active substance status

2.9.2.1. Introduction

With respect to Directive 2001/20/EC, Directive 2010/63/EU, the ICH E6 (R1) guideline on GCP (CPMP/ICH/135/95) and the Declaration of Helsinki (1996) the Applicant suggested that comparative non-clinical and clinical investigations to prove a NAS claim would be unethical and even illegal. However, the CHMP pointed out that the *"Reflection paper on considerations given to designation of a single-stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance"* (EMA/651649/2010) explicitly indicates that significant difference in safety and/or efficacy to justify the NAS claim could be substantiated based on non-clinical evidence if it is conclusive or likely to result in significant changes in clinical efficacy or safety:

"2.3.1 Evidence likely to be sufficient

- *Compelling preclinical data where it is not feasible to conduct head to head clinical studies, e.g. differences in reproductive toxicity or carcinogenicity, or the reference active substance is not authorised for the proposed indication.*

2.3.2 Evidence unlikely to be sufficient

- *Preclinical differences that are inconclusive or unlikely to result in significant changes in clinical efficacy or safety."*

The CHMP was of the view that the non-clinical evidence would not necessarily have to be based on direct comparative animal testing, provided that findings based on indirect non-clinical comparisons were compelling and of clinical relevance.

The non-clinical and clinical evidence provided by the applicant to demonstrate differences between teriflunomide and leflunomide is summarised and discussed below.

2.9.2.2. Potential non-clinical and clinical differences between teriflunomide and leflunomide

Despite the same pharmacological mechanism of action of teriflunomide and leflunomide, possible clinical differences in the efficacy of both substances cannot be deduced from available data, because the proposed therapy of multiple sclerosis with teriflunomide completely differs from the treatment of

rheumatoid arthritis for which leflunomide received MA. Therefore, the applicant focussed on potentially different pharmacokinetic, non-clinical and clinical safety properties of the two agents, which are summarised below.

CYP1A2-mediated metabolism

Teriflunomide is formed as major metabolite of leflunomide by opening of the isoxazole ring catalysed predominantly by the cytochrome P450 isozyme CYP1A2 for which different genetic polymorphisms exist. As CYP1A2 plays only a minor role in the metabolism of teriflunomide, it can be anticipated that CYP1A2 genetic heterogeneity is not associated with side effects of teriflunomide. This absence of CYP1A2-mediated metabolism might reduce the propensity of teriflunomide for interactions with other drugs during MS therapy (e.g. ciprofloxacin, fluoroquinolones) and for pharmacogenomic variability.

However, the two enzymes CYP2C19 and CYP3A4 are additionally involved in the opening of the isoxazole ring of leflunomide. The relationship between genetic polymorphism and PK parameters is weakened if more than one enzyme contributes to the metabolism of a drug, as the deficit of one enzyme may be balanced by the other (Porcelli S *et al*. 2011). Subjects who may lack two enzyme systems (1A2 or 2C19; 3A4 shows no polymorphism at all) are rather rare.

Moreover, the pharmacogenomic study of Bohanec Grabar *et al*. (2008) cited by the applicant bears two major deficits:

1) No PK data of leflunomide were reported and no PK data of metabolites (including teriflunomide) were analysed, whereas the sample size for the aimed toxicological evaluation was rather small.

2) The genotype of the CYP1A2*1F allele was determined and from this information the CYP1A2 activity was concluded. Indeed there are several published studies that indicate that this allele is associated with increased inducibility. The individual induction depends highly on environmental and dietary factors (Le Marchand *et al*. 1997). However no genotype/phenotype relationship has been established for this enzyme system yet.

Regarding extrinsic factors, the results of interaction studies of leflunomide or teriflunomide with rifampin (weak CYP 1A2 inducer, inducer of CYP2C19 und CYP3A4) did not indicate any benefit for teriflunomide. Studies investigating the impact of CYP1A2 inhibitors on teriflunomide formation have not been provided. In summary, no reliable information has been provided, that the missing metabolism of teriflunomide step via CYP1A2 leads to a clinically relevant benefit.

Hepatotoxic potential

Apart from teriflunomide, the biotransformation of leflunomide generates five additional metabolites that are not formed from teriflunomide. The *in silico* analyses of these five metabolites using DEREK, MultiCase and Leadscope software identified a hepatotoxic risk for methyl-hydroxy leflunomide, methyl-hydroxy leflunomide glucuronide and leflunomide due to their isoxazole amide scaffold. As the isoxazole amide moiety is lost during ring opening, a similar hepatotoxic potential was not assumed for teriflunomide and the other metabolites of leflunomide.

The *in silico* findings were further pursued *in vitro*. Both teriflunomide and leflunomide showed comparably low cytotoxicity in rat and human primary hepatocytes *in vitro* (TC_{50} = ~200 – 500 µM), whereas leflunomide was more cytotoxic than teriflunomide in the human hepatocellular carcinoma cell line HepG2. This cytotoxicity was further addressed in mechanistic investigations in isolated mitochondria, where leflunomide was 10-fold more potent than teriflunomide to inhibit state III

complexes of the respiratory chain and 2- to 5-fold more potent to uncouple state II respiration. This uncoupling effect might be responsible for the identified reductions in ATP levels with concomitantly increased generation of superoxide anions as evident in rat hepatoma H4IIE cells.

In terms of clinical safety, the CHMP considered that in comparison to leflunomide, the potentially lower hepatotoxic potential of teriflunomide is of minor clinical relevance with no significant benefits for patients treated with teriflunomide. Liver toxicity, most prominent in patients with pre-existent liver disease or concomitant use of other hepatotoxic drugs, seems to be one of the most serious safety issues of teriflunomide. Most rheumatoid arthritis patients, who experienced severe liver injury with leflunomide treatment had one or multiple underlying risk factors for hepatotoxicity including concomitant NSAID or methotrexate therapy, previous or concurrent alcohol abuse, or viral or autoimmune hepatitis. This presumably accounts for the fewer or milder hepatic side effects during clinical treatment with teriflunomide compared to leflunomide therapy.

Genotoxicity of 4-TFMA

Clinical determinations of the urinary excretion rate of 4-TFMA oxanilic acid suggest that the initial formation of the potentially genotoxic metabolite 4-TFMA by direct hydrolysis of leflunomide is very extensive until all leflunomide has been converted to teriflunomide. This is in agreement with more than 4-fold higher mean maximum plasma concentrations measured after administration of 20 mg leflunomide in RA patients (23.3 ng/ml) compared to 14 mg teriflunomide in MS patients (5.3 ng/ml). However, genotoxic effects of 4-TFMA were only determined *in vitro* at a LOEL of 50 µg/ml and were not confirmed in animals, most probably because this level is not achievable *in vivo* below acutely lethal doses. Accordingly, it remains highly questionable if the safety margins calculated based on the *in vitro* LOEL and the mean maximum plasma concentrations in patients of at least 2000 after leflunomide or 9000 after teriflunomide administration indeed translate into a clinically meaningful difference.

Carcinogenic potential

Malignant lymphoma, bronchio-alveolar adenoma and carcinoma were detected in a carcinogenicity study with leflunomide in mice, but not in rats. In contrast, no carcinogenic potential of teriflunomide was evident in either species. The Applicant aimed to attribute the carcinogenicity seen with leflunomide in mice to 4-TFMA. Nonetheless, as detailed in the section on genotoxicity of 4-TFMA above, the LOEL for genotoxicity of 4-TFMA is regarded not achievable beyond lethal doses *in vivo*. The CHMP also highlighted that while rats are known to be more sensitive to aromatic amines like 4-TFMA than mice, carcinogenicity studies with leflunomide and teriflunomide in rats were both negative. Consequently, the putative differences in terms of carcinogenicity seen only in mice remain elusive and were hence not considered to be relevant for human therapy.

Cataract formation

Cataract formation was detected at leflunomide mid and high doses (≥ 3 mg/kg/day) in the oral carcinogenicity study in rats. Despite these lens opacities occurred at a more than 3-fold higher incidence compared to controls, they are a common age-related phenomenon in this species. Moreover, a dose-relation was only implied for female rats, whereas incidences of cataracts were randomly scattered across male dose groups treated with leflunomide. Likewise, cataracts were irregularly distributed across both genders in rats that had received teriflunomide in a carcinogenicity

study, albeit at lower incidences. Interestingly, leflunomide did not promote cataract formation in a 41 day study in rats. Although a drug-related effect of leflunomide could not be absolutely excluded, the clinical relevance of the cataract formation remains disputable, as no particular human risk has been identified since marketing authorisation of leflunomide.

Pancreatic toxicity, chronic progressive nephropathy and amyloidosis

Pancreatic toxicity comprising minimal to moderate acinar degeneration, necrosis of individual acinar cells, fibrosis and infiltration of inflammatory cells were observed at teriflunomide doses ≥ 0.8 mg/kg/day in the 12 months toxicity study in dogs, but not after leflunomide treatment. Following teriflunomide administration, pancreatic toxicities were only accompanied by reduced trypsin-like immunoreactivity in the study animals, whereas pancreatic levels of amylase or lipase remained unchanged. In the clinical program, pancreatic enzyme levels were generally unaffected and there was no clear correlation between incidences of pancreatitis and teriflunomide administration. As dogs appear to be more susceptible to teriflunomide treatment than humans, the clinical significance of the rather mild pancreatic toxicity findings after teriflunomide administration of dogs is uncertain.

In a carcinogenicity study in mice, chronic progressive nephropathy (CPN) was limited to females of the 12 mg/kg/day teriflunomide high dose group only. On the contrary, no such findings were apparent with leflunomide in carcinogenicity investigations in this species. Similarly, moderate amyloidosis of several organs (mainly stomach, intestine, pancreas, liver, kidney, spleen, lymph node, salivary and adrenal glands, thyroid/parathyroid) was seen with teriflunomide, but not leflunomide, in both genders of the high dose group in the carcinogenicity study in mice.

The applicant ascribed the CPN and amyloidosis findings to the inflammatory lesions provoked by the anti-inflammatory activity of teriflunomide. However, teriflunomide treatment neither caused CPN in male mice, nor in rats and amyloidosis was restricted to mice. Likewise, no CPN or amyloidosis was evident in the carcinogenicity study of leflunomide in mice or rats, although teriflunomide and leflunomide share the same pharmacodynamic activity. As CPN is very common in rodents and both CPN and amyloidosis are well known to develop spontaneously with age, thus complicating toxicity evaluations, their clinical relevance is highly debatable [6,7,8].

2.9.3. Regulatory aspects

Consistency with former decisions on other compounds

The applicant has raised the issue of consistency by referring to the CHMP's assessment of similar active substances in the past.

Reference is made to Chapter 1 of Volume 2A of the Notice to Applicants where it is stated that the decision whether a different form of the active substance is to be regarded as a new active substance should be taken by the competent authorities on a case-by-case basis.

[6] Hard: Mechanisms of chemically induced renal carcinogenesis in the laboratory rodent. *Toxicol Pathol* 1998, 26 (1): 104-112.

[7] Hard and Khan: A Contemporary overview of chronic progressive nephropathy in the laboratory rats, and its significance for human risk assessment. *Toxicol Pathol* 2004, 32: 171-180.

[8] Frith and Chandra: Incidence, distribution and morphology of amyloidosis in Charles Rivers CD-1 mice. *Toxicol Pathol* 1991, 19: 123-127.

In 2010 the CHMP started developing a draft reflection paper that provides clarification on the criteria to be applied in the scientific assessment of a new active substance status by the Competent Authorities.

It has to be explained that the CHMP commenced with **systematic** evaluation of the NAS status within the assessment procedure, which translates into an explicit statement of the scientific conclusion on the NAS claim, leading to the decision on granting of the Marketing Authorisation following the judgement in Case T-275/09[9]. In this case the Court of Justice (ECJ) has recognised that an evaluation of the NAS by the CHMP is a preparatory act to the decision to grant the marketing authorisation.[10] As a development the CHMP has adopted a policy of systematic scientific evaluation of the NAS as a step within the MA assessment procedure which is reflected in the final "Reflection paper on considerations given to designation of a single-stereo isomeric form (enantiomer), a complex, a derivative, or a different salt or ester as new active substance in relation to the relevant reference active substance" (EMA/651649/2010).

With respect to the applicant´s reference to products Neoclarityn (authorised in 2001) and (Invega authorised in 2007), it needs to be highlighted that no systematic NAS assessment was conducted at the time of the MAA of these products for the reasons described above.

The CHMP also noted that the applicant has re-produced a table from the literature of pharmacologically active metabolites and parent drugs where each active metabolite was considered a new drug[11]. It should be noted, that the scientific publication[12] from which the table provided was extracted states: *"Actually, active metabolites having improved pharmacological activity or lower toxicity than those parent compounds were already marketed as new drugs"*. This further supports the CHMP position, i.e. requesting the applicant to provide clinical and non-clinical evidence to demonstrate significant differences in safety and/or efficacy between teriflunomide and leflunomide.

2.9.4. Conclusion

Overall, the CHMP is of the opinion that teriflunomide is a derivative of leflunomide, since the only difference between both molecules is the opening of the isoxazole ring. This is considered to be a simple structural modification, which occurs by a single metabolic step *in vivo* and can be also achieved *in vitro* via a simple one-step synthetic transformation. Furthermore, the evidence provided by the applicant to demonstrate significant differences in properties with regard to safety and efficacy indicated rather minor differences between teriflunomide and leflunomide with unknown or questionable clinical relevance, as detailed in section 2.9.2. Therefore, the available underlying data to the MAA did not allow concluding that teriflunomide qualifies as a NAS.

[9] Case T-275/09 Sepracor Pharmaceuticals (Ireland) Ltd v EC, not yet published.
[10] Ibid, paragraph 31.
11 Applicant's responses to the 2nd D180 LoI-Table 1 page 15.
12 JM..Kang et al. Pharmacologically activemetabolites of currently marketed drugs: potential resources for new drug discovery and development. The pharmaceutical society of Japan. 2010; 130: 1325-1337.[13] Römpp Chemie Lexikon, 9th edition, Thieme 1995, ISBN 3-13-102759-2.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Teriflunomide is an immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHO-DH), required for the de novo pyrimidine synthesis. As a consequence, teriflunomide reduces the proliferation of dividing cells that need de novo synthesis of pyrimidine to expand. The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but this is mediated by a reduced number of lymphocytes.

The anti-proliferative potency of teriflunomide including its efficacy in well-established animal models of multiple sclerosis using both prophylactic and therapeutic administrations was reliably documented in the dossier. A delayed onset and diminished severity of the disease were observed in these studies.

Efficacy of teriflunomide, as monotherapy, in the treatment of adult patients with relapsing remitting multiple sclerosis was supported with data generated in a proof-of-concept study and phase III clinical trials.

In study 2001, an effect was observed on the change from baseline to week 36 in mean number of unique active lesions per MRI. The difference from baseline to end of study was 5.2% for placebo and -2.5% for teriflunomide 14 mg. The difference between teriflunomide 14 mg and placebo was statistically significant (p=0.0215). With respect to the secondary clinical endpoints, the proportion of patients with MS relapses was 37.7% and 23.2% for placebo and teriflunomide 14 mg, respectively. Although there was a positive trend for the 14 mg dose, this difference was not statistically significant. The proportion of patients with EDSS progression was 21.3% and 7.4% for placebo and teriflunomide 14 mg, respectively. The difference versus placebo was statistically significant for the 14 mg teriflunomide group.

In the TEMSO study, the effect was observed on the annual relapse rate, which was 0.539 and 0.369 for placebo and 14 mg teriflunomide, respectively. The proportion of subjects with 3-month sustained disability progression was 23.7% and 17.3% for placebo and 14 mg, respectively and the difference for the hazard ratio of 0.702 was statistically significant for the 14 mg group (p=0.0279). The MRI findings supported the results of the study. No efficacy was demonstrated on the patient reported outcomes (FIS and MSFC) or on quality of life variables (SF-36 and EQ-5D).

Results of the TEMSO study were supported by a second placebo-controlled study TOWER. The effect was shown on the adjusted ARR, 0.501 in the placebo group and 0.319 in the 14 mg teriflunomide group. This corresponded to a statistically significant relative risk reduction of 36.3% (p=0.0001) in the teriflunomide 14 mg group. Teriflunomide 14 mg also statistically significantly reduced the time to 12-week sustained disability progression compared to placebo with a relative reduction in the hazard ratio of 31.5% (p=0.0442). The estimated percentage of patients with 12-week sustained disability progression at week 48 was 14.2% and 7.8% in the placebo and 14 mg teriflunomide groups, respectively. With respect to time to first multiple sclerosis relapse, the estimated proportion of patients free of confirmed relapses at Week 48 was 60.6% in the placebo group and 76.3% in the teriflunomide 14 mg group. The statistically significant hazard reduction was 36.9% (p<0.0001) for the teriflunomide 14 mg group.

The results from the integrated analysis of both trials indicated consistency in the efficacy data, based on the ARR and time to 3-month sustained disability progression.

In general, the effect observed in the TEMSO and TOWER study was perceived in the range of the treatment effects seen for interferon beta and glatiramer acetate.

Oral administration was considered a benefit as compared to products with a subcutaneous or intramuscular administration.

Uncertainty in the knowledge about the beneficial effects

In the TENERE study, the estimated cumulative rate of treatment failure was 41.1% and 44.4% at 96 weeks for the 14 mg teriflunomide group and Rebif, respectively. With respect to the risk of treatment failure 14 mg teriflunomide group vs Rebif, the hazard ratio was 0.861 (p-value: 0.5953). Overall, this active controlled study failed in its primary objective, which was to demonstrate superiority over Rebif. The CHMP considered that this rendered the TENERE study inconclusive, as due to the uncertainty about assay sensitivity, it could not be concluded that teriflunomide had a similar efficacy to Rebif. The rate of permanent treatment discontinuation (as a component of the primary endpoint) was higher in the Rebif group than in teriflunomide: 13.5% and 24.0% in the 14 mg teriflunomide and Rebif groups, respectively. On the other hand, the rate of relapse (as a component of the primary endpoint) was lower in the Rebif group than in the 14 mg teriflunomide group, 23.4%, and 15.4% in the 14 mg teriflunomide and Rebif group, respectively. The ARR was 0.259 and 0.216 for the 14 mg teriflunomide group and Rebif, respectively. Analysing the components of the primary endpoint, i.e. reasons for treatment failure, the CHMP considered that for teriflunomide these were attributed to lack of efficacy (relapses), whereas for Rebif, treatment failure was mostly due to poor tolerability. This was considered indicative of lower efficacy of teriflunomide.

With respect to the MS type of patients enrolled in the studies, the CHMP considered that the majority of patients in the study programme were patients with RRMS and the number of patients with secondary progressive MS and superimposed relapses was limited. Furthermore, the CHMP considered that extrapolation of efficacy was not supported by the mechanistic considerations and that the data from the respective subgroup analyses did not show sufficient evidence of efficacy in terms of effect on the relapse rate in patients with SPMS and PRMS (and superimposed relapses), as discussed in detail in section 2.5.3. Overall, the CHMP concluded that efficacy could not be reasonably extrapolated from the RRMS to the broader population presenting with RMS.

In order to identify and substantiate the patient population which would benefit most from treatment with teriflunomide, the applicant provided a number of subgroup analyses based on baseline characteristics, such as disease severity and disease activity. An effect on relapse rate and disability progression (time to 3-month sustained disability progression) was sufficiently shown across a number of treatment groups of patients, including patients with high disease activity. With respect to the definition of the high disease activity “patients with at least 2 relapses in past year and 1 Gd lesion at baseline” used by the applicant, the CHMP considered that it is analogous to the second part of the indication for Tysabri and Gilenya, and although a general consensus over the definition of high disease activity is currently lacking, this approach was accepted.

Risks

Unfavourable effects

In clinical studies, teriflunomide caused adverse effects on the liver with potentially serious consequences. Teriflunomide caused elevations of liver enzymes, typically within the first six months of treatment, followed by stabilisation. A total of six patients in the clinical studies met the criteria for Hy's law; these cases were attributed to the teriflunomide treatment. Therefore, the CHMP considered that there was a risk of serious hepatic adverse reactions. The data on reversibility of the hepatic toxicity upon treatment continuation with teriflunomide was not considered sufficiently solid to support a specific claim that hepatic toxicity could be reversible upon treatment continuation with 14 mg teriflunomide in cases of mild elevations (ALT ≤ 3 ULN).

The proportion of patients with bone marrow disorders was higher for teriflunomide compared to placebo. Teriflunomide led to a decrease in neutrophils and lymphocytes of at most 15% and smaller mean decreases in platelet and RBC counts. Isolated cases of significant cytopenias, e.g. thrombocytopenia, and cases of more significant decrease in white blood cell count were observed. The effect of teriflunomide on the immune system and a trend for a higher proportion of serious infections in the teriflunomide groups (respiratory tract, lung infections and possible herpes viral infections) was discerned.

Diastolic and systolic blood pressure elevations were more frequent on teriflunomide as compared to placebo. Even though no increased risk was observed for cardiac arrhythmias they should be seen as adverse cardiovascular events potentially associated with blood pressure elevation.

Alopecia, diarrhoea, nausea, ALT increase, nasopharyngitis, paraesthesia, back pain, pain in limb, arthralgia, rash and abdominal pain were reported more common in the teriflunomide groups than in the placebo group.

The safety database of leflunomide was also taken into account considering that the effect of leflunomide is completely mediated by its metabolite teriflunomide.

Uncertainty in the knowledge about the unfavourable effects

With respect to opportunistic infections, the frequency of non-serious herpetic infections was higher on teriflunomide as compared to placebo. However, no signals of serious systemic opportunistic infections, including progressive multifocal leukoencephalopathy, were detected in the clinical programme of teriflunomide. Despite the non-serious nature of cases observed and the lack of clinical signal to date, since teriflunomide is an immunomodulator, serious opportunistic infections were considered to be a potential risk.

Teriflunomide was observed to cause lymphopenia and also neutropenia, early after initiation of treatment. It is not known whether the number of circulating lymphocytes strictly reflects the immunocompetence of the patient. The low lymphocyte and neutrophil counts were observed throughout teriflunomide treatment, with a tendency to decrease even further. A tendency to return towards normal range after treatment discontinuation was observed. However, the long-term risks of serious infections associated with this effect are not known.

Events potentially related to peripheral neuropathy, polyneuropathy, paraesthesias and neuralgia were reported in all treatment groups, but more frequently in teriflunomide treated patients. Notwithstanding the clinical presentation of the events was highly variable, polyneuropathy was

considered as a potential risk of teriflunomide.

Although no signal of malignancy was observed in the clinical studies, since teriflunomide impacts the immune system, and in light of the limited long-term experience, malignancy was considered as a potential risk to be followed carefully during the post-marketing period.

The CHMP considered that teriflunomide was embryo-toxic and teratogenic in rats and rabbits at doses in the human therapeutic range. Thus, teriflunomide was considered to have a potential to cause serious birth defects, when administered during pregnancy. Consequently, women of childbearing potential must use effective contraception during therapy and use of teriflunomide during pregnancy is contraindicated.

Discussion on the benefit-risk balance

With respect to benefits of teriflunomide, the CHMP was of the view that the data presented by the applicant showed modest but clinically relevant efficacy results and supported the use of teriflunomide as a first-line treatment in the RRMS patient population. The relative effect size observed in the placebo-controlled studies was considered comparable to the effect-size seen in the earlier MS studies with interferon beta and glatiramer (around 30% risk reduction for ARR). With respect to disability progression, teriflunomide was observed to show an effect on the 3-month sustained disability progression endpoint.

Direct comparison with an interferon beta (Rebif) as an active comparator failed to show superiority. This study was considered inconclusive by the CHMP, since in the absence of placebo, the study lacked assay sensitivity and no conclusions on similar effects of teriflunomide and Rebif could be made.

The applicant provided a number of subgroup analyses based on baseline characteristics, such as disease severity and disease activity. Based on these, an effect on relapse rate and disability progression (time to 3-month sustained disability progression) was sufficiently shown across the treatment groups of patients, including those with existing high disease activity. The CHMP was of the view that no subgroup was identified, in which the benefits would be considered more robust or more convincing in comparison to others.

The safety profile of teriflunomide was comparable to the known safety profile of the parent compound leflunomide and no new unexpected safety issues emerged in the clinical programme of teriflunomide. This was not unexpected given that teriflunomide is almost the sole active metabolite of leflunomide. Consequently, the safety database of leflunomide was taken into account in the benefit-risk balance assessment. In particular, the CHMP considered the safety issues such as opportunistic infections, cases of PML and malignancies. While no signals of these were detected in the clinical programme of teriflunomide, the risk of their occurrence cannot be completely excluded, since both teriflunomide and leflunomide, being immunomodulators, have an impact on the immune system. Of note, the safety data from the clinical programme of teriflunomide already included single cases of tuberculosis and herpes simplex infections, which were considered an indicator of risk of opportunistic infections.

The most prominent adverse events observed were liver toxicity, gastrointestinal events, bone marrow suppression, infections and alopecia. While gastrointestinal events were mostly considered as mild and moderate and were rarely a reason for treatment discontinuation, liver toxicity, although asymptomatic, was a reason for treatment cessation in most cases. The data indicated that liver toxicity could be reversible, but required a rather long recovery time (up to two years). The

CHMP considered that patients with severe hepatic impairment must not be treated with teriflunomide, which was reflected in section 4.3 of the SmPC. Furthermore, liver enzymes should be assessed before initiation of therapy and in regular intervals afterwards and treatment should be discontinued if liver injury is suspected.

The haematological effects (decrease in white blood cells, red blood cells and platelet counts) were considered to warrant assessment of the complete blood cell count before starting treatment and during therapy based on signs and symptoms (e.g. infections). Patients with significantly impaired bone marrow function or significant anaemia, leukopenia, neutropenia or thrombocytopenia must not be treated with teriflunomide, which is reflected in section 4.3 of the SmPC.

With respect to infections, the most frequently reported events were upper respiratory tract infections, especially nasopharyngitis. The risk of infection was considered attributable to the effect of teriflunomide on the immune system. Based on the data available, the CHMP considered that, in case of an infection, treatment with teriflunomide should not be started until the patient recovers.

Alopecia was considered a severe AE, despite its non-threatening feature, as it can be socially debilitating, particularly for female subjects.

The CHMP also considered the reproductive toxicity. While the extent of teratogenic effect is not known, studies in animals showed reproductive toxicity. Teriflunomide was considered to have a potential to cause serious birth defects, when administered during pregnancy. Therefore, women of childbearing potential are required to use effective contraception and use of teriflunomide during pregnancy is contraindicated.

The oral route of administration was considered an advantage above the first line interferon beta and glatiramer acetate, which have to be injected either subcutaneously or intramuscularly.

The CHMP considered that all identified and potential risks, including the ones based on the experience with leflunomide were adequately addressed in the Risk Management Plan and the Product Information.

The overall benefit/risk of Aubagio in the RRMS indication was considered favourable.

3.1. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Aubagio in the treatment of adult patients with relapsing remitting multiple sclerosis is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where Aubagio is marketed, at launch and after launch, all healthcare professionals who are expected to use Aubagio are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Educational material for Healthcare professionals
- Educational card for patients

The educational material for HealthCare Professionals (HCP) will include the following key elements:

1. HCPs should discuss with their patients the specific safety concerns of Aubagio detailed below including the tests and precautions needed for safe use as follows:

- Risk of hepatic effects
    - liver function tests are needed prior to treatment and periodically during treatment

    - To educate the patient about the signs and symptoms of liver disease and the need to report to their HCP if they experience any of them

- Potential risk of teratogenicity
    - To check pregnancy status before starting treatment
    - To educate female patients of child-bearing potential on the need for effective contraception before starting, and during treatment with teriflunomide
    - To inform their doctor immediately if they stop contraception, or prior to changing contraceptive measures
    - If female patients become pregnant despite using contraceptive measures, they should stop teriflunomide and contact their doctor immediately who should:
        - Consider and discuss with the patient the accelerated elimination procedure
        - encourage them to enrol in a pregnancy registry (in countries where a pregnancy registry is on-going),
- Risk of hypertension
    - to check for a history of hypertension and that blood pressure should be appropriately managed during treatment
    - the need for blood pressure checks before treatment and periodically during treatment,
- Risk of hematologic effects
    - the need for complete blood cell counts before treatment and periodically during treatment based on signs and symptoms
- Risk of infections/serious infections
    - To discuss the need to contact the doctor in the event of signs/symptoms of infection, or if the patient takes other medicines that affect the immune system

2. A reminder to provide patients with a Patient Education Card, including filling-in their contact details, and to provide replacement Patient Education Cards as necessary;

3. To encourage patients to contact their MS physician and/or General Practitioner if they experience any of the signs and symptoms discussed in the Patient Education Card;

4. Information on the optional service of a periodic reminder to patients about the continued need for effective contraception during treatment.

The educational card for the patients will include the following key elements:

1. A reminder for both patients and all HCPs involved in their treatment that the patient is being treated with teriflunomide, a drug which:

- Requires concomitant use of effective contraception in women of child-bearing potential
- Requires a pregnancy status check before treatment
- Affects liver function
- Affects blood cell counts and the immune system

2. Information to educate the patient:

- To pay attention to certain signs and symptoms which might indicate liver disease or infection, and if any of these occur, to contact their doctor/HCP promptly
- Of the need for the procedures/tests before and during teriflunomide treatment
- To remind female patients to tell their doctor if breastfeeding
- For women of child-bearing potential
    - to emphasise the need for effective contraception during treatment with teriflunomide
    - to stop treatment with teriflunomide immediately if they suspect they might be pregnant and also to contact their doctor immediately
- To remind patients to show the Patient Education Card to Doctors/HCPs involved with their medical care (especially in the event of medical emergencies and/or if new Doctors/HCPs are involved.)
- To record the first date of prescription and the contact details of their prescriber

3. To encourage the patients to read the PIL thoroughly

4. If they become pregnant:

- To remind both patients and HCPs about the accelerated elimination procedure
- To remind both patients and HCP about the Pregnancy Registry (in countries where pregnancy registry is on-going)

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

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that teriflunomide which is a derivative of leflunomide is not qualified as a new active substance, as it does not differ significantly in properties with regard to safety and/or efficacy from the previously authorised substance.

Re-examination of the CHMP opinion of 21 March 2013

Following the CHMP conclusion that teriflunomide, the active substance of Aubagio, is not qualified as a new active substance, the applicant submitted detailed grounds for the re-examination of the CHMP Opinion.

Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation to the CHMP.

Applicant´s position:

On 21 March 2013 the CHMP issued a positive opinion for the approval of Aubagio (teriflunomide) for the treatment of adult patients with relapsing remitting multiple sclerosis, but denied the NAS status.

In particular, the applicant expressed disagreement with this conclusion, on the basis that

i) teriflunomide is not a derivative of leflunomide, and, in any event,

ii) significant differences in terms of safety and efficacy between both compounds have been demonstrated.

I) Teriflunomide is not a derivative of leflunomide

Applicant´s position: (summarized)

The applicant provided the following arguments in support of their claim that teriflunomide is not a derivative of leflunomide:

1.1 Proper interpretation of the term derivative under article 10.2(b) of Directive 2001/83/EC

(a) Assessment based on chemical composition of the product and not in vivo metabolism.

The CHMP however concluded in first instance that teriflunomide is not a new active substance for purposes of Article 10(2)(b) of Directive 2001/83/EC, which stipulates:

"The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy."

That definition expressly refers to a "medicinal product which has the same qualitative and quantitative composition …" as a reference product (emphasis added). It is thus based on the chemical composition of the product, and not on the possible metabolism in vivo, after administration to the patient. The fact that one active substance is an active metabolite of another (after administration to the patient) is thus not relevant.

This also clearly follows from the definition of "active substance" under Article 1(3a) of Directive 2001/83/EC: "Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product

intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis." (emphasis added)

The definition is based on the good manufacturing guidelines, which refer to the active substances as used in manufacturing. The CHMP concluded in first instance that teriflunomide is a derivative of leflunomide and therefore it is not a new active substance for purposes of Article 10(2)(b) of Directive 2001/83/EC.

Consequently, whether the active substance in a new medicinal product is a "salt, ester, ether, isomer, mixture of isomers, complex or derivative" of an existing active substance must be assessed on the basis of the chemical characteristics of the substance as it is present in the finished medicinal product.

The fact that a substance is an in vivo metabolite of another is irrelevant.

(b) Metabolites are not listed in Article 10(2)(b)

Metabolites are not listed in the group of compounds covered by the presumption rule.

(c) Interpretation in light of the structure of Article 10(2)(b)

Article 10(2)(b) includes different salts, esters, ethers, isomers, mixtures of isomers, complexes and derivatives in the presumption rule. It is clear that the terms salts, esters, ethers, isomers, mixtures of isomers and complexes cover molecules that (i) include the same chemical structure, but bound to a different salt, ester, ether, or complex, or (ii) have the same atom connectivity but in a different isomeric form. The common characteristic of all these forms is thus that they contain the same structure or the same atom connectivity.

The inclusion of the term "derivative" in this list can thus only be intended to cover chemical forms that also contain the same structure or the same atom connectivity. It is thus a residual category that is meant to cover other chemical forms than salts, esters, etc. that contain the same structure (or the same atom connectivity).*(d) In the alternative, the chemical similarity must be sufficiently strong to justify a presumption of being the same active substance*

Subsidiarily, even if it was admitted that the term "derivative" be interpreted -- as was done by the CHMP and the QWP -- on the basis of a broader chemical meaning, teriflunomide would still not qualify as a derivative of leflunomide. In particular, both the CHMP and the QWP have adopted a concept of structural similarity that is so broad that it would cover many substances that are clearly not similar. The threshold for structural similarity coefficients must be higher if any meaningful similarity comparison is to be performed.

The following definitions in reference chemistry textbooks illustrate the broad chemical meaning of the term derivative:

Römpp Chemie Lexikon:

"Derivate (von lat.: derivare = ableiten). Bez. für Abkömmlinge einer chem. Verb., die aus dieser häufig in nur einem Reaktionsschritt gebildet werden. (Derivatisierung), u. die zu zu ihr in einem engen chemischen Verwandtschaftsgrad stehen. So sind z.B. Hydrazone u. Oxime D. der Aldehyde u. Ketone od. Ester u. Amide D. der Carbonsäuren u. können zu deren Charakterisierung herangezogen werden."[13]

In free translation: *"Derivatives (from Latin derivare = derive). Description for descendants of a chemical compound, which are formed from it in often a single reaction step (derivatisation), and which have a close degree of chemical relationship with it. For example hydrazones and oximes are derivatives of the aldehydes or ketones or esters and amides derivatives of the carboxilic acids and can be used for their characterisation."* (emphasis added)

Oxford Dictionary of Biochemistry and Molecular Biology:

"*Derivative: Any compound that may, at least theoretically, be formed from another compound to which it is structurally related."*[14] *(emphasis added)*

Oxford Dictionary of Chemistry

"Derivative: A compound that is derived from some other compound and usually maintains its general structure, e.g. trichloromethane (chloroform) is a derivative of methane."[15] (emphasis added)

These definitions have two elements in common. A derivative can be chemically derived from another substance, and it has a structural/chemical similarity with that substance.

The importance of the structural similarity is also confirmed in the EU orphan medicines rules. The relevance of the criteria laid down under this legislation has been confirmed by the European Commission, which, in its letter of 24 January 2013 to the CHMP, stated that the analysis "whether teriflunomide and leflunomide have the same chemical structure … should take full consideration of the definition of "similar active substance" provided for under Article 3(2)(c) of Regulation 847/2000." Commission Regulation 847/2000 defines a "similar active substance" as follows, for purposes of the orphan market exclusivity:

> "an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism.
>
> This includes: (1) isomers, mixture of isomers, complexes, esters, salts and non-covalent derivatives of the original active substance that differs from the original active substance only with respect to minor changes in the molecular structures, such as a structural analogue; …" (emphasis added)

If similar molecular structure is needed for a derivative to be a similar active substance, it is a fortiori needed for it to qualify as the same active substance.

[13] Römpp Chemie Lexikon, 9th edition, Thieme 1995, ISBN 3-13-102759-2.
[14] Definition of "Derivative", Oxford Dictionary of Biochemistry and Molecular Biology, http://www.oxfordreference.com/view/10.1093/acref/9780198529170.001.0001/acref-9780198529170-e-4977?rskey=EUbyVJ&result=3&q=Derivative (consulted on 5 December 2012)
[15] Definition of "Derivative", Oxford Dictionary of Chemistry, http://www.oxfordreference.com/view/10.1093/acref/9780199204632.001.0001/acref-9780199204632-e-1252?rskey=EUbyVJ&result=1&q=Derivative (consulted on 5 December 2012)

As explained above, this broad chemical approach of the term “derivative” cannot be accepted as this term must be understood in the context of the enumeration of article 10(2)(b) of Directive 2001/83/EC, which solely refers to substances sharing the same structure (or atom connectivity). Nevertheless, if this alternative interpretation is accepted, a derivative does not need to contain the same chemical compound. The structural similarity must, however, be sufficiently clear and strong to justify a presumption of being the same active ingredient. There is not sufficient similarity between the two molecules to consider teriflunomide as a derivative of leflunomide

1.2 Teriflunomide does not include the leflunomide molecule

Teriflunomide clearly does not contain the compound leflunomide. It has an open chain where leflunomide is a heterocyclic compound with an isoxazole ring.

Based on the main interpretation that derivatives must contain the same structure or the same atom connectivity (extended, for instance, by a clathrate) -- as outlined above in section [1.1 (c)] -- teriflunomide cannot be a derivative of leflunomide. The presumption rule can thus not apply, so that teriflunomide must be considered as a new active substance.

This conclusion is the only one that respects the spirit of article 10(2)(b) of Directive 2001/83/EC, while taking due consideration to the public health impact of the NAS assessment.

1.3. In the alternative, there is no sufficient structural similarity between teriflunomide and leflunomide

Teriflunomide as used in Aubagio® is not chemically derived from leflunomide. The QWP and the CHMP however concluded that the opening of the isoxazole ring “is considered a simple structural modification and a technically simple one-step synthetic transformation”. This statement is incorrect. To convert leflunomide chemically into teriflunomide requires a complex reaction scheme shown below (see Figure 16) where the isoxazole ring must first be opened in a base-catalyzed reaction to produce two sequential intermediates to form the teriflunomide enol which must be adjacent to the amide group.

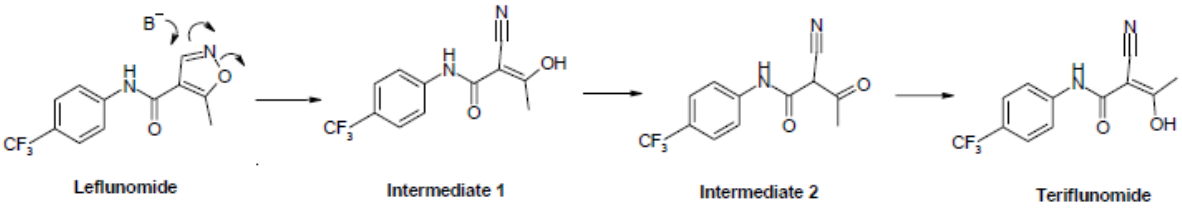


Figure 16 - Chemical steps required for the conversion of leflunomide into teriflunomide

Irrespective of the production method used, it is clear that teriflunomide is structurally different from leflunomide. There is no close degree of chemical relationship between the two substances. Leflunomide is a heterocyclic compound with an isoxazole ring, while teriflunomide is an open chain compound with a keto-enol and nitrile functionalities.

The following sections demonstrate the major structural differences between teriflunomide and leflunomide supporting that teriflunomide is a NAS. Teriflunomide should thus be considered a new active substance.

1.4. Teriflunomide is structurally different from leflunomide

The QWP report of 15 March 2013 concluded that teriflunomide and leflunomide are structurally similar and that “considering the 1D descriptors (molecular structure, molecular formula, atoms of carbon,

hydrogen and heteroatoms, relative molecular mass, functional groups, number of rings, phenyl rings, etc) and the supportive information from the similarity coefficients using different fingerprints, it can be concluded that from a structural point of view, the differences between both molecules (namely, opening of the isoxazole ring) are minor. Both molecules are structurally similar in the context of the orphan drug legislation."

Sanofi considers that the CHMP has not sufficiently recognized the significant impact that the opening of the isoxazole ring of leflunomide has on the entire molecule framework. Several external experts agree with Sanofi that teriflunomide and leflunomide are clearly different chemical entities.

Evidence of the structural differences between leflunomide and teriflunomide include the data from the Module 3 General Properties and Elucidation of Structure and Other Characterization) of each submission or prior response documents provided for each drug substance, namely:

Spectroscopic properties (NMR, IR, MS and UV)

Tanimoto coefficient, descriptors, fingerprints and formula differences Physico-chemical differences (Solubility, Melting Point)

Structural Biology (conformational differences, protein binding, electrostatic interactions, molecular polarization, descriptors and fingerprints topological representations and amide bond reactivity differences)

Physicochemical properties

The information presented in this section by Sanofi clearly demonstrate that leflunomide and teriflunomide are entirely distinct molecules with unique spectroscopic, Tanimoto, physico-chemical and structural biology features. These are significant structural differences that do not support a finding that the two compounds are so structurally similar that they can be considered derivatives. It follows that teriflunomide must be considered a new active substance.

CHMP position

To determine whether a certain drug substance can be regarded as a New Active Substance (NAS) the requirements of Article 10(2)(b) of Directive 2001/83/EC that defines what can be considered as the same active substance have to be taken into account:

"The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy".

Based on this provision, the Notice to Applicants (NtA, Volume 2A, Chapter 1) in Annex III provides for a guiding interpretation of what can be regarded as a New Active Substance:

"A new chemical, biological or radiopharmaceutical active substance includes:

- *a chemical, biological or radiopharmaceutical substance not previously authorised as a medicinal product in the European Union.*
- *an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union but differing in properties with regards to safety and efficacy from that chemical substance previously authorised.*
- *[…]"*

As stated in the initial CHMP opinion, from a chemical point of view, it can be easily concluded that both, teriflunomide and leflunomide are not related as different salts, esters, ethers, isomers, mixtures of isomers or complexes. The relevant question is, whether teriflunomide and leflunomide can be regarded as derivatives.

As presented above, the applicant has provided several definitions of the term "derivative" which reflect the vague nature of the term. E.g. the applicant avoids to emphasise the word "usually" in the definition cited from Oxford Dictionary of Chemistry above. However this word is important because it implies that there are circumstances in which the general structure of the compound is not maintained after derivatization.

In fact, there are other dictionaries which do not take into consideration the structural aspect for the definition of derivative, for example:

-McGraw-Hill Dictionary of Scientific and Technical Terms[16]:

"Derivative [CHEM]: A substance that is made from another substance".

As the legislation does not provide a definition of the term "derivative" this has to be interpreted also in light of its linguistic meaning. Semantically, a "derivative" is something that is derived from something else.

Scientific rationale for interpretation of the term "derivative"

In order to understand the regulatory interpretation of the term "derivative" it is important to note that all the terms in Article 10(2)(b) "*salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance*" share a common denominator: they may under certain circumstances expose the patient to exactly the same molecule as an already approved medicinal product does, as explained below:

- Salts usually dissociate in aqueous solution and the active part is no longer associated with the counter ion but is rather surrounded by solvent molecules and ions present in the solution. An abridged application may be based on another salt than the reference product. The new salt shall be considered to be the same active substance unless it differs significantly in properties with regards to safety and/or efficacy.
- Preparing esters and ethers of an original molecule is a commonly used method to prepare pro-drugs intended to release the original molecule *in vivo*. If justified by differences with respect to safety and/or efficacy, they can be granted NAS status.
- Isomers should in this context be understood as enantiomers. Isomers related to each other as enantiomers have the same connectivity but are non-superimposable mirror images of each other. They have the same chemical and physical properties (apart from the rotation of plane polarized light), i.e. act in exactly the same manner, except when they interact with other chiral structures. Whether they differ with respect to safety and/or efficacy may differ case by case. Enantiomers are therefore not NAS in themselves. There is a particular situation, which is the reason for mentioning "mixture of isomers" in Article 10(2)(b). That is where a racemate is the active substance of an approved medicinal product and a new application for only one of the two enantiomers is made. In this case, the enantiomer represents half of the active content in the original product. The patients are therefore in both cases exposed to this

[16] 'derivative' 2003, in *McGraw-Hill Dictionary of Scientific and Technical Terms*, McGraw-Hill, New York, NY, USA, viewed 24 June 2013, <from http://www.credoreference.com/entry/mhscience/derivative>

structure. The enantiomer can get NAS status provided that it is justified by differences with respect to safety and/or efficacy.

If this understanding of "isomer" in Article 10(2)(b) would not prevail, the consequence would be that the NAS status of teriflunomide versus leflunomide must be assessed based on their relationship as structural isomers (both having the same molecular formula: $C_{12}H_9F_3N_2O_2$). Also in this situation justification based on differences with respect to safety and/or efficacy would be needed.

- Complexes intended to release *in vivo* an already approved active substance that is entrapped by the complex would not be considered NAS, unless differences with respect to safety and/or efficacy are demonstrated.

Based on this it can be concluded that derivative in the context of Article 10(2)(b) and the Annex III of the NtA should be primarily understood as those substances:

a. where the original substance *in vivo* will be derived from the new applied substance in such a manner that the patients are exposed to the original substance (the applied substance is a prodrug). Esters and ethers are separately mentioned in the article, but other kind of pro-drugs are covered by the term "derivative".

b. where the new applied substance is the same substance as the one the patients were exposed to when treated with the original substance. i.e. where the new substance is identical to what is *in vivo* derived from the original substance (the applied substance is a metabolite).

Besides this primary understanding of derivative, a secondary understanding has resided on whether the applied molecule can be considered as a simple *in vitro* structural modification of an already approved molecule.

The active substance contained in Aubagio, teriflunomide falls under the primary understanding of the term derivative since it is an *in vivo* metabolite of leflunomide. Upon administration of leflunomide, *in vivo*, the isoxazole ring present in the molecule of leflunomide is opened and 70% of the drug administered converts into teriflunomide (teriflunomide is derived *in vivo*). Therefore, regardless of the substance administered (leflunomide or teriflunomide) the patient is exposed to the same molecule.

In addition, teriflunomide also falls within the secondary understanding of the term derivative (*in vitro* derivative). It can be easily derived by a one step in vitro hydrolysis from leflunomide. The reaction proceeds rapidly and cleanly *via* an E_2-elimination mechanism, without other intermediates, upon treatment with base at ambient temperature. This is considered a simple structural modification. The keto-enol tautomerism is an equilibrium reaction which does not mean that the conversion can be regarded as a complex reaction.

Therefore, from a quality point of view, the CHMP considers that teriflunomide is a derivative of an already authorised active substance.

The interpretation from the applicant based on "what is used in the medicinal product production" cannot be accepted as it would preclude the use of different salts, esters, ethers in generic applications. It would not be possible to fulfil the criteria "the same qualitative and quantitative composition" with another salt, ester, ether, respectively. The substances will in many cases be similar as they are present in the formulation. As explained above, the primary understanding of Article

10(2)(b) of Directive 2001/83/EC is that the new substance may under certain circumstances expose the patient to exactly the same molecule as an already approved medicinal product does.

Even though Aubagio is not an orphan medicinal product, in response to the applicant's claim during the initial evaluation, the CHMP performed the structural similarity evaluation as per the orphan drug legislation (Article 3(3)(b) of Commission Regulation (EC) No 847/2000). The CHMP concluded that considering the 1D descriptors (molecular structure, molecular formula, atoms of carbon, hydrogen and heteroatoms, relative molecular mass, functional groups, number of rings, phenyl rings, etc) and the supportive information from the similarity coefficients using different fingerprints, from a structural point of view, the differences between leflunomide and teriflunomide molecules (namely, opening of the isoxazole ring) are minor. Both molecules are structurally similar in the context of the orphan drug legislation.

However, such similarity assessment is not meant to define whether an active substance is to be considered new active substance or not, but only whether two active substances are to be considered similar within the meaning of Article 3(3)(c) of Commission Regulation (EC) No 847/2000.

Teriflunomide is a structural analogue of leflunomide. Both molecules share the same molecular structure, namely the 4-(trifluoromethyl) phenyl and the amide groups, and only differ on the part of the structure which is subject to the opening of the isoxazol ring.

The compounds share many similarities in their properties. For example, both compounds are practically insoluble in water and belong to the class II biopharmaceutics classification system. They are also similarly lipophilic and bioavailable. However, since leflunomide and teriflunomide are different chemical entities it is anticipated that they might show some differences in spectroscopic and physicochemical properties. Indeed, the observed differences in some physico-chemical properties e.g. melting point could also be found for different polymorphs and isomers of the same active substance and for different esters/acids. The aim to develop pro-drugs is to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically active agents.

Therefore the differences in physicochemical or spectroscopic properties are acknowledged but could only lead to the conclusion on NAS if this translates to an improved safety and/or efficacy of the product. As described above, the *in vivo* transformation of leflunomide into teriflunomide precludes considering teriflunomide as a NAS unless a significant difference in safety and efficacy is demonstrated.

The described differences in structural conformation between parent compound and the derivative (X-Ray, electron density, 3D molecular representation) may appear mainly in the crystalline state. However, since the molecules have to be dissolved before exerting their biological action, these differences are not considered relevant for the performance of the product *in vivo* and thus for the NAS assessment.

Conclusion on Chemical aspects

Based on the above, the CHMP considers that for the purpose of assessment of the NAS status teriflunomide is a derivative of leflunomide since it exposes the patients to the same molecule as treatment with leflunomide does.

This conclusion is further emphasised by the fact that teriflunomide can be easily derived by a one step in-vitro hydrolysis from leflunomide. This is considered a simple structural modification and a technically simple one-step synthetic transformation.

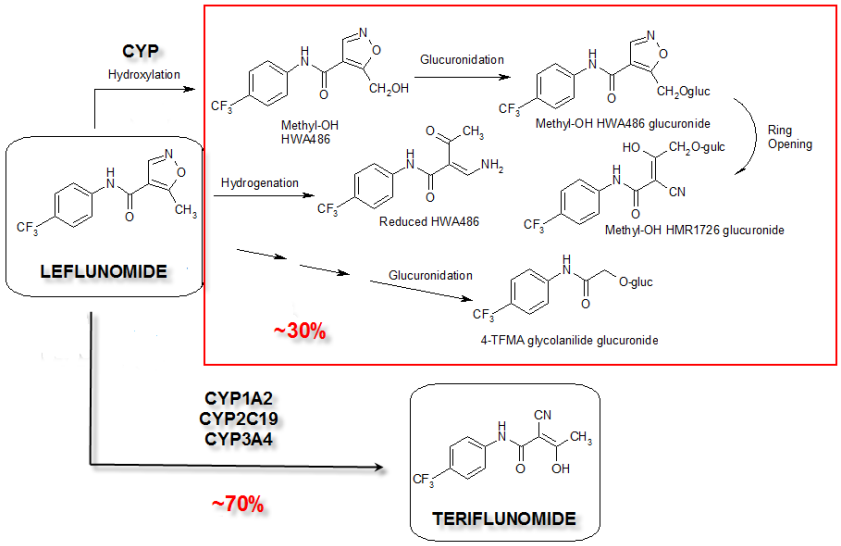
II) Significant differences in safety and/or efficacy

Applicant´s position:

The following arguments were presented by the applicant to justify that significant differences in terms of safety and/or efficacy exist between teriflunomide and leflunomide.

Considering the pharmacokinetics of teriflunomide and leflunomide, the applicant pointed at formation of leflunomide-specific metabolites that are not formed after teriflunomide administration, some of which have a potential for hepatotoxicity based on in silico analyses. In particular, the applicant highlighted that approximately 30% of the leflunomide dose is converted to substances (metabolites) that are not observed following teriflunomide administration (fig. 17)

Fig. 17



In this context, the applicant highlighted that the extra step of leflunomide to teriflunomide, involving CYP-mediated metabolism, may increase the potential for adverse reactions due to polymorphisms and resulting heterogeneity in metabolism and drug interactions.

Poor and intermediate CYP2C19 metabolizer RA patients were seen to present with lower teriflunomide concentration[17].

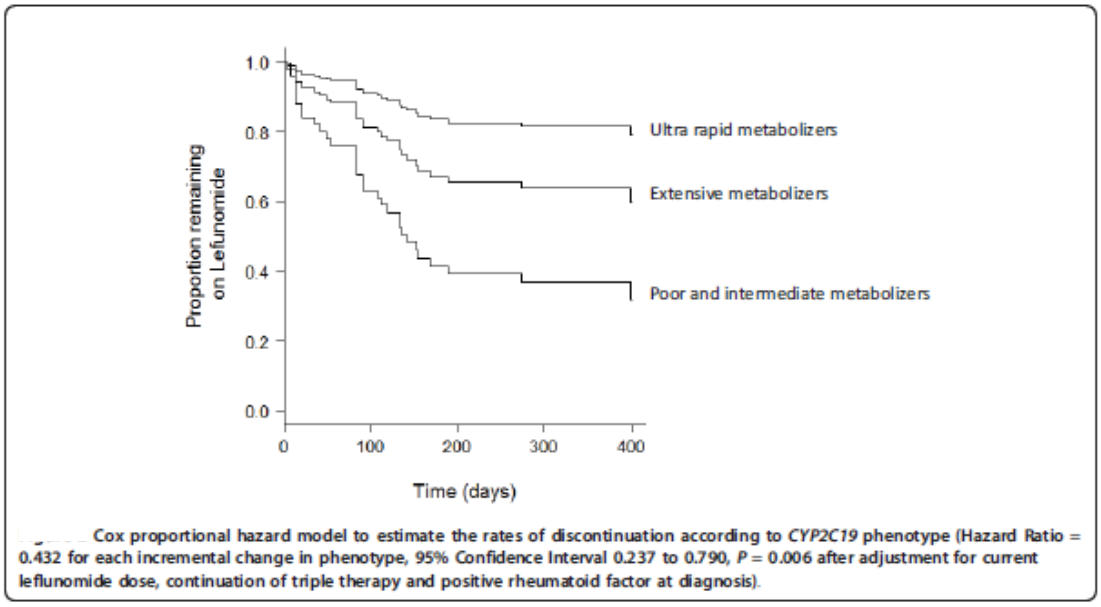
Consistently with this observation, CYP2C19 phenotype was also shown to be significantly associated with the likelihood of treatment cessation. In their grounds for re-examination, the applicant made a specific reference to a recent publication by Wiese et al.[18], which investigated the polymorphisms in cytochrome P450 2C19 enzyme and cessation of leflunomide in patients with rheumatoid arthritis.

Overall, the results of the study indicated that CYP2C19 phenotype was significantly associated with the likelihood of cessation, with ultra-rapid metabolizers (UM patients) ceasing less frequently than intermediate/poor metabolizer (IM/PM) patients with RA under leflunomide treatment because of adverse events (fig. 18).

[17] Bohanec Grabar P, Grabnar I, Rozman B, Logar D, Tomsic M, Suput D, Trdan T, Peterlin Masic L, Mrhar A, Dolzan V: Investigation of the influence of CYP1A2 and CYP2C19 genetic polymorphism on A771726 pharmacokinetics in leflunomide treated patients with rheumatoid arthritis. Drug Metab Dispos 2009, 37:2061-2068

[18] Wiese MD, Schnabl MJ, O'Doherty D et al. Polymorphisms in cytochrome P450 2C19 enzyme and cessation of leflunomide in patients with rheumatoid arthritis. Arthritis Res. Ther. 2012;14(4): R163

Fig. 18 Retention rates in 78 Rheumatoid Arthritis patients treated with leflunomide by metabolizer status



Cox proportional hazard model to estimate the rates of discontinuation according to *CYP2C19* phenotype (Hazard Ratio = 0.432 for each incremental change in phenotype, 95% Confidence Interval 0.237 to 0.790, $P = 0.006$ after adjustment for current leflunomide dose, continuation of triple therapy and positive rheumatoid factor at diagnosis).

The company summarised that the study was a retrospective cohort study with 252 RA patients treated with leflunomide, of whom 78 patients were selected based on age, diagnosis of RA, DNA sample availability and sufficient clinical data. Leflunomide treatment was administered in combination with other medicines such as methotrexate, sulfasalazin and hydroychoroquine.

The key results are summarised in table 38 below:

Table 38

Association of phenotypes and genotypes with cessation due to side effects

SNP	Phenotype/Genotype	Proportion ceased due to side effects (%)	Hazard Ratio (95% Confidence Interval), *P*-value*
CYP2C19 (*CYP2C19*2* (rs4244285), *CYP2C19*17* (rs12248560))	Poor/Intermediate metabolizers	8/15 (53.3%)	0.432 (0.237 to 0.790), $P = 0.006$†
	Extensive metabolizers	18/39 (46.2%)	
	Ultra-rapid metabolizers	5/21 (23.8%)	

Of note, 42.3% of patients discontinued leflunomide treatment due to adverse events. Poor/intermediate metabolisers discontinued treatment due to AEs significantly more frequently than extensive/ultra-rapid metabolisers. The AEs leading to discontinuations comprised diarrhea (8), nausea/vomiting (7), elevated transaminases (6), shortness of breath/cough/pneumonitis (5), dizziness/fainting (4), rash (3), haematological events (3), abdominal cramps/bloating (3), hair loss (2), fatigue (2) and other single AE causes (9).

With respect to safety, the applicant referred to the conclusion of the authors, i.e. that if the side effects from leflunomide were solely caused by teriflunomide, intermediate/poor metabolizers would be expected to have a lower incidence of toxicity. The observation of the IM/PM patients not showing a lower incidence of toxicity indicated either direct toxicity by leflunomide, or that an alternate pathway competes with the conversion of leflunomide to teriflunomide and results in formation of another metabolite which contributes to side effects.

As opposed to leflunomide, an association between this genetic heterogeneity and teriflunomide adverse events is not expected, as CYP-mediated metabolism is limited in teriflunomide.

The applicant claimed that these findings are clinically relevant in terms of safety and drug interactions.

To put these findings into perspective of the MS setting where teriflunomide was developed, the applicant further highlighted that there is a number of concomitant medications, which are CYP2C19 inhibitors, frequently used in RRMS patients, such as anti-depressant, antibiotics and antifungals, NSAIDs and anti-convulsant, proton-pump inhibitors & H2-receptor antagonists and modafinil (table 39).

Table 39 Selected inhibitors of CYP2C19 (drugs highlighted in red reflect drugs in therapeutic classess most frequently prescribed to MS patients)

INHIBITORS	
Strong: • Moclobemide (antidepressant) • Fluvoxamine (SSRI) • Chloramphenicol (bacteriostatic antimicrobial) Weak: Several anticonvulsants • Oxcarbazepine • Felbamate • Topiramate • Valproate • Carbamazepine	Unspecified potency: Proton pump inhibitors • Lansoprazole • Omeprazole • Pantoprazole • Rabeprazole • Cimetidine (H2-receptor antagonist) • Fluoxetine (SSRI) • Indomethacin (NSAID) • Ketoconazole (antifungal) • Modafinil (eugeroic) • Probenecid (uricosuric) • Ticlopidine (antiplatelet) • JWH-018 • Isoniazid

As an additional argument, raised already in the initial MAA, the applicant pointed out that conducting direct comparative clinical studies purely for the reasons of substantiating the NAS would be unethical, specifically highlighting the fact that exposing RA patients to teriflunomide or MS patients to leflunomide would not be justifiable due to expected lack of benefits of such study to patients enrolled.

At the same time the applicant re-iterated the arguments and data presented in the initial dossier (i.e. non-clinical safety data regarding hepatotoxic potential, genotoxic/carcinogenic potential, cataracts, pancreas and inflammation and clinical pharmacology data on PK and pharmacogenomics) and claimed that the overall data provided form a sufficient basis for concluding that there is a significant difference in safety between teriflunomide and leflunomide.

CHMP position

The CHMP considered the arguments presented by the applicant and re-confirmed their previous position that in order for teriflunomide to be qualified as a new active substance there should be significant differences in terms of safety and/or efficacy and that these differences should be viewed as clinically relevant.

There are reported differences in (non-)clinical pharmacokinetics and toxicity findings between teriflunomide and leflunomide (including hepatic profiles in silico and in vitro, carcinogenic, cataractogenic, inflammatory and pancreatic profiles in vivo), which might well indicate that both are two different substances. Although it is plausible that these could translate into clinical differences, the CHMP maintained their previous position on interpretation of the non-clinical safety data and the need to further substantiate the relevance of the available evidence.

In this regard, differences in the metabolism/PK of both teriflunomide and leflunomide in combination with the pharmacogenomics data were viewed as potentially translating into clinical relevance. The fact that up to 30% of leflunomide is converted to other metabolites not formed following teriflunomide administration and that these metabolites are not inert components, but potentially hepatotoxic, and/or likely to participate in drug interactions was considered of clinical relevance. As it was the fact that the metabolism of leflunomide and teriflunomide follow two different metabolic pathways, with involvement of cytochromes to a large extent in the case of leflunomide conversion to teriflunomide.

To further explore the relevance of the differences, the CHMP discussed results of the Wiese study taking into account its limitations, including the use of concomitant medication, selection of the patients and the statistical analysis. It was reported that poor/ intermediate CYP 2C19 metabolisers were numerically at higher risk of treatment cessation than the other subgroups due to safety reasons. Recognising the exploratory nature of this study, its results were nevertheless considered to indicate that the polymorphism related variability in the relative transformation of leflunomide into its active metabolite teriflunomide vs the alternative non-inert metabolites, has clinical consequences, as the alternative metabolites may contribute to some adverse drug reactions. Results were also considered to indicate that cytochrome involvement in leflunomide metabolism might be a relevant source of drug-drug interactions.

A number of publications, including the Grabar study presented by the applicant, suggested that genetic variability in leflunomide-metabolizing enzymes influences teriflunomide concentrations, which was considered to give further support to the previous findings.

Based on the combination of the biological plausibility, experimental findings, the differences in metabolism pathway of leflunomide vs teriflunomide, with the concept of different levels of CYP-mediated metabolism, and the findings in the clinical setting (i.e. retention of treatment highest in the UM patients), the CHMP considered that if teriflunomide is administered, this variability and the potential for some adverse reaction will be reduced, leading to a significant difference between leflunomide and teriflunomide safety profile.

Conclusions on significant differences in safety and/or efficacy

Overall, the CHMP was of the opinion that based on the totality of data described and discussed above, it can be concluded that there is a significant difference between teriflunomide and leflunomide in safety.

Overall conclusion on grounds for re-examination

Overall, the CHMP was of the opinion that teriflunomide is a derivative of leflunomide, since the only difference between both molecules is the opening of the isoxazole ring. This is considered to be a simple structural modification, which occurs by a single metabolic step *in vivo* and can be also achieved *in vitro* via a simple one-step synthetic transformation.

However, this simple structural modification leads in vivo to a substantially different biotransformation profile. For that reason, based on the combination of biological plausibility and the non-cliinical and clinical evidence available, the CHMP considered that in terms of safety, there is a significant difference between teriflunomide and leflunomide.

Therefore, the available underlying data to the MAA allowed concluding that teriflunomide qualifies as a NAS.

Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision that teriflunomide which is a derivative of leflunomide is qualified as a new active substance, as it differs significantly in properties with regard to safety from the previously authorised substance.

Divergent positions to the majority recommendation are appended to this report.

Appendix

DIVERGENT POSITIONS

The undersigned members of the CHMP did not agree with the CHMP's conclusion that the active substance contained in Aubagio, teriflunomide, is a new active substance.

The reasons for divergent positions were as follows:

Teriflunomide is a structurally closely related *in vivo* derivative of leflunomide. In this case, the legislation (Art. 10(2)(b) of Dir. 2001/83/EC) and the pertinent CHMP reflection paper (EMA/651649/2010) require the demonstration of significant differences with regard to safety and/or efficacy to consider the derivative a NAS. In this regard, the level of scientific evidence provided by the applicant is considered to be insufficient to demonstrate the significant difference required by the legislation for the following reasons:

- A relevant difference regarding propensity for drug-drug interactions or a relevant effect of metabolizer status on efficacy or safety of leflunomide vs. teriflunomide is possible, but could not be definitely confirmed from the data provided
  - The opening of the isoxazole-ring of leflunomide to form teriflunomide is catalysed by different isozymes of the cytochrome P450 family (CYP1A2, CYP2C19 and CYP3A4) and deficiency in one of these enzymes due to genetic polymorphisms or due to drug/drug interactions is expected to be compensated for by the other enzymes. Interaction studies of leflunomide or teriflunomide with rifampicin (weak inducer of CYP1A2, inducer of CYP2C19 und CYP3A4) did not relevantly affect teriflunomide serum concentrations and did not indicate any benefit for teriflunomide.
  - About 70 % of leflunomide is transformed into teriflunomide, the remaining 30% are converted into five additional metabolites. It has not been established that these metabolites exert relevant pharmacological or even toxicological activities *in vivo* in both animals and humans.
- Results from two published studies (Grabar et al., 2009, and Wiese et al., 2012) do not sufficiently support the relevance of CYP2C19 metabolizer status on the safety of leflunomide vs. teriflunomide as claimed by the Applicant. Deficiencies of these studies hampering their interpretation include retrospective design, potential recruitment bias, small sample size (especially in important subgroups), limited or lack of exposure data and unclear or retrospective and selective evaluation of adverse events based on patient recollection. In addition, results regarding the impact of metaboliser status on toxicity of leflunomide are conflicting. Information on patient characteristics, leflunomide doses or number and type of relevant co-medications for the analysed metaboliser subgroups, which could have well affected the frequency and type of adverse events, is absent and whilst a causal effect may be hypothesised, it cannot be confirmed on the basis of the data presented for assessment. Moreover, the statistical analysis in the Wiese study is considered to be flawed for the purpose of confirmatory inference. Firstly, the analysis method will exaggerate the presented putative associations because of the modelling assumptions that cannot reasonably be assessed on the basis of the small sample size. Secondly, it has not been confirmed that the analyses were pre-specified and not data-driven with consequent concerns over bias.
- The results from non-clinical studies presented by the applicant do not sufficiently support a clinically relevant difference in the safety profiles of leflunomide and teriflunomide.
- With respect to hepatic and pancreatic toxicity, genotoxic/carcinogenic potential, and the risk to develop cataract or chronic progressive nephropathy and amyloidosis, safety issues highlighted by

the applicant, differences between leflunomide and teriflunomide were only detected in certain non-clinical *in silico* and *in vitro* tests or were inconclusively limited to single gender, species, or even dose groups *in vivo* or were attributable to other circumstances (e.g. aging of the animals in long-term studies). As these findings were not confirmed by other non-clinical *in vivo* investigations or by clinical data, the minor differences are consequently of unknown or questionable clinical relevance.

London, 27 June 2013

Daniela Melchiorri	Ian Hudson
Barbara van Zwieten-Boot	Robert Hemmings
Romaldas Maciulaitis	Harald Enzmann
Nela Vilceanu	Pierre Demolis
Karsten Bruins Slot	