CBG MEB

Public Assessment Report

Scientific discussion

Sclerthon 20 mg/ml, solution for injection, pre-filled syringe

(glatiramer acetate)

NL/H/3212/001/DC

Date: 6 June 2016

This module reflects the scientific discussion for the approval of Sclerthon 20 mg/ml, solution for injection, pre-filled syringe. The procedure was finalised on 11 March 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
ARR	Annual Relapse Rates
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EAE	Experimental Autoimmune Encephalitis
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EDSS	Expanded Disability Status Scale
EEA	European Economic Area
ERA	Environmental Risk Assessment
FAS	Full Analysis Set
GLP	Good Laboratory Practice
GMR	Geometric Mean Ratio
GTR	Glatiramer
GTR.ace	Glatiramer acetate
ICH	International Conference of Harmonisation
LS	Least Squares
MAH	Marketing Authorisation Holder
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
PBMC	Peripheral Blood Mononuclear Cell
PPS	Per Protocol Set
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
RRMS	Relapsing-remitting Multiple Sclerosis
SAE	Serious Adverse Event
SD	Standard Deviation
sIL-1Ra	Soluble Interleukin-1 Receptor antagonist
SmPC	Summary of Product Characteristics
SOC	System-Organ Class
TSE	Transmissible Spongiform Encephalopathy
T1-GdE	T1-weighted Gadolinium Enhancing

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sclerthon 20 mg/ml, solution for injection, pre-filled syringe from Synthon B.V.

The product is indicated for the treatment of relapsing forms of multiple sclerosis (MS).
Glatiramer acetate is not indicated in primary or secondary progressive MS.

A comprehensive description of the indications and posology is given in the SmPC. See section 5.1 of the approved SmPC for important information on the population for which efficacy has been established.

The mechanism(s) by which glatiramer acetate exerts its effects in patients with MS is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in several animal species through immunisation against central nervous system derived material containing myelin and often used as an experimental animal model of MS. Studies in animals and in MS patients suggest that upon its administration, glatiramer acetate-specific suppressor T cells are induced and activated in the periphery.

This decentralised procedure concerns a hybrid application claiming similarity with the innovator product Copaxone 20 mg/ml solution for injection, pre-filled syringe. A first marketing authorization in the EU under Directive 65/65 for a product containing glatiramer acetate was granted on 9 August 2000 through a UK national procedure. This marketing authorization was for Copaxone powder for solution in vials containing 20 mg glatiramer acetate.
In the Netherlands Copaxone 20 mg/ml (NL License RVG 30086) has been registered since 29 March 2004 through Mutual Recognition Procedure UK/H/0453/002.

The Concerned Member States (CMS) involved in this procedure were Austria and Luxembourg.

Dossier requirements
Although the product is not a biological medicinal product as such, the company followed a strategy similar to the dossier requirements of bio-similar applications and has provided next to quality data, also non-clinical and clinical data in support of similarity. The results of the GATE study were submitted, a 9-month equivalence trial in which the efficacy, safety and tolerability of Sclerthon was compared to Copaxone in subjects with relapsing-remitting multiple sclerosis (RRMS) followed by an open-label 15-month Sclerthon treatment part.

Scientific advice
The MAH has sought scientific advice on the dossier requirements both at centralized and national level in several Member States. Glatiramer acetate is a heterogeneous mixture of peptide compounds of four amino acids found in myelin basic protein, namely glutamic acid, lysine, alanine, and tyrosine. The complexity of the drug substance presents particular challenges for demonstration of equivalence with the innovator product and for testing production consistency. Since it is unknown which specific components (or parts thereof) are responsible for the therapeutic effect, it was generally agreed that simple pharmacokinetic studies would not be appropriate for bridging the current product to the innovator product Copaxone. The company was therefore advised by the EMA that the product should be subjected to a detailed comparative characterization study with Copaxone, and to consider any additional data necessary to prove similarity.

View of an interested party
In the Netherlands interested parties have the right to give their views during pending applications. These views should be taken into consideration during assessment and decision-making of the respective application procedure. An interested party took this opportunity and presented its views about ‘the pending marketing authorization applications for medicinal products with the active substance glatiramer acetate’ during two hearings.

In the view of the interested party, submission of an application of glatiramer acetate based on article 10(3) is not possible since glatiramer acetate comprises of a polypeptide mixture of which the specific sequences cannot be deciphered with current technologies and as the active moiety(ies) are unidentifiable. Moreover, according to the interested party, 'the product is the process' and therefore the use of a different production method will preclude the conclusion that glatiramer as synthesized by another company (test product) shares the same active moiety and will expose the patient to the same molecule as Copaxone (reference product). Therefore, according to the interested party, the only appropriate legal pathway would be Article 8(3) of the Directive, i.e. an application based on a full dossier.
Additionally, the interested party sent a letter, dated 18 January 2016, to the CMD(h) which partly refers to concerns previously expressed, and contains an update on their position on the GATE study, a new publication of comparative gene expression experiments and comparative physicochemical tests between Copaxone and a product authorized in the USA. These views have been taken into consideration during the assessment of the application for Sclerthon 20 mg/ml.

The concerns raised were carefully assessed upon, and the relevant concerns were addressed in the questions to the MAH during the evaluation procedure. These were successfully resolved.

Legal basis – hybrid application
The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application.

While assessing the legal basis of the application, the complexity of the drug substance, presenting particular challenges for demonstrating equivalence was recognized. Moreover it was recognised that, because of the complexity of the substance, the production process of the drug substance is an important factor as the compositional reproducibility is linked to the tightly controlled manufacturing process. However, based on the data provided, it was concluded that article 10(3) is an appropriate legal basis for glatiramer 'generic' applications, taking into account previous scientific advices given by the EMA, the CMD(h) discussion and the wording of the Notice to Applicants, volume 2A, chapter 1, section 5.3.2.1:

If additional information concerning changes to the nature of the active substance cannot establish the absence of a significant difference with regard to safety or efficacy then it would be necessary to submit the results of appropriate pre-clinical tests and clinical trials in accordance with the requirements of Article 10(3) (see section 5.3.5). To the extent that the active substance may be considered as a new active substance as defined in Annex III at the end of this Chapter, the applicant may consider the submission of an application in accordance with Article 8(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Sclerthon 20 mg/ml is a clear, colourless to slightly yellow/brownish solution free from visible particles. The solution for injection has a pH of 5.5 - 7.0 and an osmolarity of about 265 mOsmol/L.
1 ml of solution for injection contains 20 mg glatiramer acetate, equivalent to 18 mg of glatiramer base per pre-filled syringe.

The solution is packed in a single use glass syringe barrel with an integrated needle. A rubber stopper (bromobutyl, type 1) is fitted in the barrel for closure and acts as piston during injection. A driving rod is screwed in the rubber stopper. The needle is covered with a needle shield.

The excipients are mannitol and water for injections.

II.2 Drug Substance

The drug substance is a white to off-white hygroscopic powder containing glatiramer acetate. It is soluble in water and insoluble in heptane. The drug substance is not described in any pharmacopoeia. Glatiramer acetate consists of the acetate salt of a mixture of synthetic polypeptides containing four

naturally occurring amino acids in a specific ratio but random order: L-Tyrosine, L-Alanine, L-Glutamic acid, and L-Lysine. Polymorphism is not considered relevant since the drug product concerns a solution for injection in which glatiramer acetate is dissolved.

Manufacturing process
The synthesis of glatiramer acetate results in the complex heterogeneous mixture of random polypeptide chains. In view of the heterogeneity of the substance and the limitations of release controls the MAH has fixed the drug substance manufacturing conditions rigorously in the dossier within narrow ranges to assure consistency of the commercial product, and assure similarity between the clinical batch used in the GATE trial and the commercial product. The MAH provided sufficient detail in the process description. Process validation data on the manufacture of three batches have been submitted, meeting in-process and drug substance specifications. The manufacturing process is adequately validated for two manufacturing scales.

Quality control of drug substance
The MAH has performed an extensive (physico)chemical and biological characterization program comparing the active substance present in Sclerthon and Copaxone 20 mg/mL, using a panel of chemical and biological assays.
The main comparative study involved eight commercial scale batches of either formulation, as well as negative controls, i.e. polymers in similar composition but different synthesis processes to support the discriminatory power of the methods. Overall the presented results of reported experiments show strong similarities in the primary and higher order structures of the different active substance batches investigated, i.e. results either overlap or Sclerthon batches were within a variability seen for Copaxone batches.
Additional evidence for similarity is presented by a characterization study in which nine different mass fractions have been isolated from Copaxone and Sclerthon which are further subjected to chemical and biological tests. Altogether, the similarities between test and reference batches in the results present strong evidence for overall equivalence in the peptides composition of the two lots.

Stability of drug substance
A degradation study has been performed. The suitability of the applied method to monitor deviations in chain length fractions and formation of degradation products has been shown. A retest period of 36 months is applied when stored at -20°C ± 5°C.

II.3 Medicinal Product

Pharmaceutical development
A formulation has been developed having the same quantitative and qualitative composition in excipients and drug substance compared with originator product. The drug product manufacturing process is sufficiently supported with adequate development studies. The choice for sterilisation by filtration is justified, since steam sterilization affected the quality of the drug substance. At release, the drug product is at least tested to the requirement as laid down in the pharmacopoeia monograph for parenteral preparations: Ph. Eur. 2.6.1 - Sterility and Ph. Eur. 2.6.14 - Bacterial endotoxins. A filling overage is used to compensate for the amount of solution which remains in the syringe and needle.
During validation the extractable volume test according Ph. Eur. 2.9.17 was carried out and the results were satisfactory. The target filling volume is regarded as acceptable for this product.
The MAH submitted the results of a head-to-head comparison of Sclerthon and Copaxone batches that were used in the clinical study (GATE Study). The data demonstrate comparability of the test and reference batches.

Manufacturing process
The manufacture of the drug product is a conventional process. The manufacturing process has been laid down in sufficient detail. Sufficient validation data for drug product manufacturing scales were provided to allow for the proposed production scales. Studies were presented to support the production scale.

Control of excipients
All the excipients used in the manufacturing of the drug product are of pharmacopoeial grade (Ph. Eur.). These specifications are acceptable.

Quality control of drug product
The drug product specification includes the following parameters: appearance, colour, clarity, pH, particle contamination, extractable volume, assay, identification, molecular weight distribution, impurities, potency, sterility and bacterial endotoxins.
In addition to chemical release tests the drug product is also controlled by a cell based assay for biological activity. The *in vitro* bioassay is adequately described and validation data have been provided. An immunoassay is included in batch control as well. Overall the biological properties are considered sufficiently controlled.

Stability of drug product
The MAH has provided results of real time studies for 36 months, accelerated studies for 6 months and an 'in use study' (incorporation of a temperature switch from 5°C ± 3 °C to 25°C/60%RH and 25°C/60%RH to 5°C ± 3 °C). No out of specification results nor trends are observed in any of the results submitted. Photostability has been demonstrated.
In addition, available results for the potency (cell-based assay) have been included. At all evaluated stability time-points, batches showed biological activity and complied with the proposed specification limit for potency.

A shelf life of 3 years at 2°C to 8°C has been granted. Within this period the product can be stored between 15°C and 25°C, once, for up to one month. After this one month period it must be returned to storage in a refrigerator (2°C to 8°C).

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the Member States consider that Sclerthon 20 mg/ml has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
The Member States took into consideration that there are inherent limitations for drawing a conclusion on similarity/comparability of highly heterogeneous mixtures such as glatiramer. For instance, in many tests patterns are compared providing 'fingerprints' rather than an absolute result. Also the presence of individual related impurities at lower level can not be sufficiently addressed for a compound consisting of numerous possible combinations. Therefore the similarity needed to be further supported with (non)clinical data. These are presented in section III and IV of this report.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The MAH provided data from an experimental autoimmune encephalitis (EAE) mouse model to demonstrate pharmacological comparability of Sclerthon and Copaxone. Although the EAE model is a well established model for MS and has been used to study the activity of drugs for the treatment of MS, the value of this model for comparability purposes is limited. The EAE mouse model shows considerable inter- and intra-assay variability. It is therefore difficult to draw firm conclusions on the comparability of two glatiramer products on the basis of these data.

The submitted quality data from an *ex vivo* T-cell assay and a PBMC assay is limited. The cell-based assay using the monocytic THP-1 cell line presented in the quality dossier as a potency assay was used to demonstrate comparable biological activity of Copaxone and Sclerthon at a functional level. This cell-based assay has been sufficiently characterised. Relative potencies were comparable. No statistical differences between Sclerthon and Copaxone batches were found.

III.2 Pharmacokinetics

The available data for Copaxone demonstrate that generating further pharmacokinetic and drug disposition data for glatiramer acetate is highly unlikely to provide new and relevant data regarding the drug disposition characteristics of the hybrid medicinal product. Analogous to Copaxone, upon subcutaneous dosing Sclerthon will undergo local metabolism/degradation at the site of injection and local and systemic exposure are likely to be an extensive mixture of peptides. However, methodological complications such as those encountered for Copaxone will equally apply for the hybrid formulation. Consequently, no new pharmacokinetic studies have been performed for Sclerthon.

III.3 Toxicology

Comparative toxicity studies were performed in rats. In two 28-days studies and one 90-days study, Sclerthon and Copaxone were administered subcutaneously by daily injection to four different injection sites in a roulating schedule (one site each day). Dose levels in the first 28-days study and the 90-days study were 10 and 40 mg/kg/day.
Dosing solutions were not analysed and test substances were not retained (after expiry date). Instead the MAH provided in-use stability studies demonstrating the stability of Sclerthon and Copaxone under the conditions of the toxicology studies performed.
Local reactions occurred, which can be expected for SC administration of a foreign substance. Macroscopic findings consisted of dark red foci and dark red discoloration of the subcutis/muscle. Microscopically, the tissue response showed progression through acute phase – hemorrhage, fibrous necrosis, lymphoid and granulocytic infiltrate and myofiber degeneration/myonecrosis, to chronic phase – myofiber regeneration and fibroplasia, which by the end of the recovery period had completely resolved.
In addition, liver and kidney effects were observed. In the liver minimal to moderate perilobular fibrosis and an increase in relative liver weight was observed. In the kidney slightly higher severity of tubular basophilia, hyaline cast(s) and glomerulopathy was seen. Furthermore, in the 90-day study, mild perivascular (lympho)plasmacytic infiltrates were noted in injection sites, kidneys, liver and parotid glands. Slight changes in biochemical and haematological parameters were considered to reflect the histopathological changes and disappeared after treatment had subsided.
The toxicity profile did not differ between Sclerthon and Copaxone.
In the second 28-days study, next to Sclerthon and Copaxone additional groups were included which were treated with Sclerthon containing variable amounts of brominated Sclerthon. This study showed that the presence of Br-Tyr up to 13.5 times the maximal exposure in humans does not affect the outcome in terms of local or systemic toxicological effects.
The MAH generated gene expression data in THP-1 cells exposed *in vitro* to Sclerthon and Copaxone. Five different batches of Sclerthon versus 5 batches of Copaxone in THP-1 cells have been studied.
The genomic data provided by the MAH clearly indicate that at the level of gene expression no differences suggesting a functionally relevant difference between Copaxone and Sclerthon can be observed when tested in the monocytic cell line THP-1, which can be considered a relevant cell type for investigating glatiramer.
The findings contrast with the findings in a similar setup where Copaxone was compared with another glatiramer compound (Probioglat). In that study, performed by originator company Teva, 162 out of 47000+ probesets were differentially expressed between Copaxone and Probioglat (Kolitz et al., 2015[1]). The authors claim that Probioglat induced a more pro-inflammatory response in the THP-1 cells than Copaxone. Similar shifts in expression in the genes involved (*CCL5, CCL2, MMP9, MMP1, CXCL10, CD14, ICAM1* and *BIRC3*) were not observed in the study submitted by the MAH described above (*CXCL10* was down-regulated by both Copaxone and Sclerthon). Another article by Hasson et. al.[2] showed differences between Copaxone and a glatiramer formulation called Polimunol. However, the comparison was imprecise due to the use of a single Polimunol batch vs. three Copaxone batches. In addition the cut-off of a 1.1-fold difference in gene expression as used in the analysis by Hasson et al (2016) is not considered biologically relevant. The gene array study with THP-1 cells submitted by the MAH compared 5 Sclerthon batches with 5 Copaxone batches. In the analysis a 1.4-fold change

[1] Kolitz et al. Gene expression studies of a human monocyte cell line identify dissimilarities between differently manufactured glatiramoids. Scientific Reports | 5:10191 | DOI: 10.1038/srep10191
[2] T. Hasson et al. Functional effects of the antigen glatiramer acetate are complex and tightly associated with its composition. Journal of Neuroimmunology 290 (2016) 84–95

cut-off value was used at a p-value of <0.05. According to the literature, these combination criteria typically provide more biologically meaningful sets of genes.
It is not known whether the Polimunol batch is representative for the product applied for. However, in view of the methodological issues as described above, no further clarification was asked for.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Sclerthon 20 mg/ml is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

The MAH has submitted non-clinical data in support of this hybrid application. The cell-based assay in THP-1 cells indicates that Sclerthon and Copaxone induce production of sIL-1Ra in human monocytes to a comparable extent and thus exhibit a similar response in this cell type. Genomic data provided by the MAH did not indicate meaningful differences suggesting a functionally relevant difference between Copaxone and Sclerthon at the level of gene expression when tested in the monocytic cell line THP-1.
The absence of pharmacokinetic data is justified, as new findings are not likely.
Regarding toxicity, no relevant differences were observed in toxicology studies in rats.

Many of the studies employing the EAE mouse model to evaluate the pharmacological activity of glatiramer and Copaxone batches have been performed under GLP. The toxicology studies were also conducted under GLP.

IV. CLINICAL ASPECTS

IV.1 Introduction

Glatiramer acetate is a known active substance with established efficacy and tolerability in patients with RRMS.
A clinical overview has been provided, which is based on scientific literature. In addition, a clinical study has been conducted by the MAH to compare the efficacy, safety and tolerability of test product Sclerthon to reference product Copaxone. The study is discussed below.

IV.2 Pharmacokinetics and pharmacodynamics

Available data on Copaxone show that glatiramer parent compound molecules cannot be quantified in body fluids or tissues. Given the nature of the product, accurate detection methods to monitor exposure to glatiramer in the systemic circulation (or in other readily available biological matrices) are not available. *In vitro* data and limited pharmacokinetic data from healthy volunteers available for Copaxone indicate that after subcutaneous administration of glatiramer, the active substance is readily absorbed and a large part of the dose is rapidly degraded to smaller fragments already in the subcutaneous tissues. No pharmacokinetic or pharmacodynamic studies have therefore been performed with Sclerthon.

IV.3 Clinical efficacy

- **GATE study**

Design and objectives

The GATE study was a multicentre, randomized, double-blind, placebo-controlled, parallel-group, 9-month equivalence trial comparing the efficacy, safety and tolerability of Sclerthon (Synthon B.V.) to Copaxone (Teva Pharmaceuticals Ltd) in subjects with relapsing-remitting multiple sclerosis (RRMS) followed by an open-label 15-month Sclerthon treatment part.

Ambulatory RRMS patients aged 18-55 years with ≥1 relapse in the year prior to screening and 1-15 T1-GdE brain lesions were randomized in a 4.3:4.3:1 ratio to receive 20 mg Sclerthon, 20 mg Copaxone, or placebo by daily subcutaneous injection for 9 months. A total of 796 subjects were randomized.

The objective of the double-blind part of this trial was to demonstrate that the efficacy of the test formulation is equivalent to Copaxone in subjects with RRMS. The primary endpoint of the double-blind part was the number of T1-GdE lesions on brain MRI during Months 7 to 9.
The objectives for the open-label part of the trial were to evaluate efficacy, safety and tolerability of long-term (two years) Sclerthon treatment and to evaluate efficacy, safety and tolerability of switching to Sclerthon treatment after previous Copaxone use.

Additional efficacy endpoints included other MRI parameters, annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS), and free from disease activity. Safety and tolerability were assessed through monitoring of adverse events, injection site reactions, vital signs and routine blood laboratory tests.

Statistical methods

In the GATE study, the sensitivity of the trial was evaluated by showing superiority of both active treatments versus placebo. The MAH used also another argument for assay sensitivity: that in both active groups both in the FAS and Per Protocol Set (PPS) analysis, the upper limit of the 95% CI for the geometric mean ratio (GMR) of the number of T1-GdE lesions during months 7 to 9 of Sclerthon and Copaxone combined over placebo was less than 1. This is considered a less relevant argument since as discussed in the scientific advice a combined analysis of Copaxone and Sclerthon versus placebo is not recommended.

Equivalence margins

To ensure a minimum effect of active treatment was maintained, the upper limit of the equivalence margin was set at half of 1.75, i.e. 1.375. Symmetrical margins in the log scale results in a lower limit of 0.727 after back-transformation. With the calculated sample size and expected variability as derived from literature (Comi et al., 2001[3]; Tubridy et al., 1998[4]), the upper limit of 1.375 for the 95% CI would allow an estimated maximal difference of approximately 10% between (the point estimates of) the number of lesions in the active treatment groups.
Sormani and Bruzzi (2013[5]) performed meta-analyses in which a correlation was established between MRI lesions and relapse rates, allowing a translation of MRI endpoints into relapse rates which are typically used as endpoint in regulatory trials for new MS drugs. The meta-analyses indicate that with a relative difference in point-estimate of 10% (ratio 1.10) for T1-GdE lesions, the associated difference in relapse rate between the Sclerthon group and Copaxone group will be smaller than 7%. This should be considered in context of the published reduction in relapse rate of Copaxone when compared to placebo which is approximately 30% (Comi et al., 2001; Johnson et al., 1995[6]). This implies that more

[3] Comi,G., Filippi,M., and Wolinsky,J.S. (2001). European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic

[4] Tubridy,N., Ader,H.J., Barkhof,F., Thompson,A.J., and Miller,D.H. (1998). Exploratory treatment trials in multiple sclerosis using MRI: sample size calculations for relapsing-remitting and secondary progressive subgroups using placebo controlled parallel groups. J. Neurol. Neurosurg. Psychiatry 64, 50-55.

[5] Sormani,M.P. and Bruzzi,P. (2013). MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. Lancet Neurol 12, 669-76.

[6] Johnson,K.P., Brooks,B.R., Cohen,J.A., Ford,C.C., Goldstein,J., Lisak,R.P., Myers,L.W., Panitch,H.S., Rose,J.W., and Schiffer,R.B. (1995). Copolymer 1 reduces relapse rate and improves disability in relapsing-

than 75% of the Copaxone effect on relapse rate (7% of 30%) will be retained. In conclusion, the pre-defined equivalence margins for the primary endpoint T1-GdE lesions correspond to a maximal allowed relative difference in relapses that is considered clinically acceptable.
For the evaluation of superiority, the guidelines require the Full Analysis Set (FAS) as the primary population for the analysis since this generally gives a conservative estimation of treatment effect. For equivalence analysis, the guidelines advice analysis based on the per protocol set (PPS), since this is generally more sensitive to detect treatment differences (ICH E9, Statistical Principles for Clinical Trials 1998). In the GATE trial both superiority over placebo (for assay sensitivity), and equivalence to Copaxone were evaluated. Overall, the FAS was selected for analysis of the primary population for analysis of efficacy, which included all subjects who were randomized and received at least one dose of study drug. Analysis on the PPS was also performed. Relevant differences between the FAS and PPS were to be further investigated.

The described methods for assessing superiority over placebo and equivalence to Copaxone are considered adequate and acceptable.

In the CHMP scientific advice it was considered that MRI measures will be acceptable to detect effect and establish equivalence of two products containing glatiramer in a shorter study duration, in case that the quality data indicate a high level of similarity. Also the current CHMP guideline on multiple sclerosis (EMA/CHMP/771815/2011, Rev. 2) states that MRI endpoints may be sufficient for demonstrating similarity of two products in the context of biosimilar and generic applications. The concept is that for bridging purposes showing similar biological activity is sufficient irrespective of the discussion between the relationship of MRI lesions and relapses. The study was designed as recommended during scientific advice and is considered adequate to investigate similar biological activity between investigational and reference product.

Results

Double-blind period
The Full Analyses Set (FAS) consisted of 794 subjects with 353 randomized to Sclerthon, 357 randomized to Copaxone, and 84 randomized to placebo. In each treatment group, the mean duration of exposure was 0.7 years. Subjects in the placebo group were not exposed to glatiramer acetate during the double-blind part of the trial.
A total of 735 patients (92.5%) completed the 9-month double-blind treatment period. Drop out rates were similar in the Sclerthon (25 pts, 7.0%) and the Copaxone group (33 pts, 9.2%), and both were higher than in the placebo group (3 pts, 3.6%). The treatment groups were very similar at randomization for demographic and other baseline characteristics as well as for MS disease characteristics.

Assay sensitivity
Assay sensitivity of the study was demonstrated since both active treatment arms were superior to placebo. The geometric mean ratio (GMR) of Copaxone was 0.466 [CI95% 0.3426; 0.633] and for Sclerthon the GMR was 0.510 [CI95% 0.374; 0.696].

Equivalence analysis
The results on the primary endpoint (number of MRI lesions in months 7, 8 and 9) indicated similar biological activity of Sclerthon to Copaxone (see tables below).

remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 45, 1268-1276

Table 1 Number of T1-GdE Lesions at Months 7 to 9 (Full Analysis Set) - *GTR = Sclerthon*

	GTR N = 353	Copaxone® N = 357	Placebo N = 84
Month 7			
n	327	329	81
Mean (SD)	1.2 (2.62)	1.1 (2.50)	2.1 (3.05)
Geometric mean	0.88	0.85	1.29
Median	0.0	0.0	1.0
Min / Max	0.0 / 30.0	0.0 / 22.0	0.0 / 13.0
Month 8			
n	320	313	79
Mean (SD)	1.2 (2.55)	1.0 (2.21)	1.7 (2.29)
Geometric mean	0.89	0.83	1.17
Median	0.0	0.0	1.0
Min / Max	0.0 / 30.0	0.0 / 22.0	0.0 / 11.0
Month 9			
n	315	301	76
Mean (SD)	1.1 (2.81)	0.8 (1.44)	2.3 (2.87)
Geometric mean	0.84	0.77	1.50
Median	0.0	0.0	1.0
Min / Max	0.0 / 34.0	0.0 / 9.0	0.0 / 14.0

Table 2 Primary efficacy analysis: Geometric Mean Ratio of the number of gadolinium-enhancing lesions during Months 7, 8 and 9 of GTR (Sclerthon) over Copaxone (Full Analysis Set and Per Protocol Set)

	Point Estimate	95% CI
Full Analysis Set		
Geometric Mean Ratio GTR / Copaxone®	1.097	[0.884; 1.362]
Per Protocol Set		
Geometric Mean Ratio GTR / Copaxone®	1.099	[0.881; 1.370]

Table 3 Change from Baseline to Month 7 and Month 9 in the Number and Volume of T2 Lesions (Full Analysis Set) – *GTR = Sclerthon*

	GTR N = 353	Copaxone® N = 357	Placebo N = 84
Number of T2 Lesions			
Change to Month 7			
n	320	325	80
Mean (SD)	6.6 (9.19)	5.5 (7.31)	7.8 (9.61)
Median	4.0	3.0	5.0
Min / Max	-1.0 / 73.0	-2.0 / 60.0	-1.0 / 52.0
LS Mean[1]	5.77	4.65	6.91
95% CI	[4.06; 7.48]	[2.96; 6.34]	[4.61; 9.21]
Change to Month 9			
n	308	296	75
Mean (SD)	9.2 (13.94)	7.3 (9.43)	11.1 (11.39)
Median	5.0	4.0	7.0
Min / Max	-1.0 / 147.0	-2.0 / 71.0	0.0 / 50.0
LS Mean[1]	7.87	5.93	9.77
95% CI	[5.39; 10.34]	[3.44; 8.41]	[6.44; 13.10]
Volume of T2 Lesions (mm^3)			
Change to Month 7			
N	318	323	79
Mean (SD)	349.7 (2188.87)	328.4 (1665.96)	7.2 (4603.45)
Median	176.5	105.0	268.0
Min / Max	-24503.0 / 11551.0	-9892.0 / 13440.0	-38374.0 / 7890.0
LS Mean[1]	305.66	282.58	-43.99
95% CI	[-190.77; 802.09]	[-209.21; 774.38]	[-714.43; 626.44]
Change to Month 9			
N	304	294	74
Mean (SD)	466.0 (2255.91)	449.2 (1656.73)	388.2 (4979.83)
Median	277.0	163.0	443.0
Min / Max	-22481.0 / 10426.0	-9892.0 / 9084.0	-38374.0 / 13006.0
LS Mean[1]	377.62	358.18	297.93
95% CI	[-160.52; 915.77]	[-181.24; 897.61]	[-428.80; 1024.66]

[1] LS mean: estimated least squares means derived from an ANCOVA model assuming normal distribution and including the stratification variables geographical region and number of T1-GdE lesions at screening (one versus 2 to 15) as covariates.

The least-squares mean number of T1-GdE lesions at Month 7 to 9 was 0.447 in the Sclerthon group and 0.408 in the Copaxone group. The point estimate of the Sclerthon/Copaxone T1-GdE lesion ratio was 1.095 with a 95% CI of [0.883; 1.360] for the FAS (see table 4). The point estimate of the Sclerthon/Copaxone T1-GdE lesion ratio was 1.099 with a 95% CI of [0.881; 1.370] for the PPS. The pre-defined equivalence interval was [0.727; 1.375], as this was agreed at scientific advice as narrow enough to serve this equivalence exercise. Since in both analyses the 95% CIs were enclosed within this predefined equivalence interval, it was concluded that Sclerthon was equivalent to Copaxone.

Table 4 Results of the sensitivity analysis for equivalence testing (double-blind part – full analysis set) – *GTR = Sclerthon*

	Analyses	N	Least Squares Mean (SEM)		Ratio GTR/Copaxone® [95% CI]
			GTR	Copaxone®	
	Pre-planned analysis (NB)	668	0.447 (0.0634)	0.408 (0.0590)	1.095 [0.883;1.360]
Use of alternative distributions:					
	Poisson	668	0.446 (0.0633)	0.408 (0.0589)	1.093 [0.881;1.357]
	Poisson, ar(1)	668	0.412 (0.0604)	0.381 (0.0568)	1.083 [0.867;1.353]
Influence of excluding subjects with extreme values (NB distribution) defined as :					
	More than 10 T1-GdE at M7,8,9	655	0.437 (0.0602)	0.401 (0.0566)	1.090 [0.885;1.342]
	More than 15 T1-GdE at M7,8,9	662	0.443 (0.0621)	0.406 (0.0580)	1.090 [0.882;1.347]
	More than 15 T1-GdE at baseline	658	0.439 (0.0627)	0.393 (0.0575)	1.117 [0.897;1.391]
	Absolute residuals ≥ 6	661	0.444 (0.0621)	0.404 (0.0577)	1.099 [0.889;1.358]
Influence of missing values (NB distribution) using:					
	Complete cases	587	0.464 (0.0676)	0.399 (0.0602)	1.163 [0.926;1.462]
	LOCF	656	0.441 (0.0633)	0.395 (0.0580)	1.116 [0.897;1.389]

Other endpoints

The outcomes on the secondary endpoints relapses and EDSS (Expanded Disability Status Scale) were less clear. Considering the study duration of 9 months this may be expected for the EDSS.

The total number of confirmed relapses was 84 reported in 72 subjects in the Sclerthon group, 115 reported in 94 subjects in the Copaxone group, and 26 reported in 22 subjects in the placebo group.

The LS mean [95% CI] for the Annual Relapse Rates (ARR) was 0.31 [0.20; 0.48] in the Sclerthon group, 0.40 [0.26; 0.62] in the Copaxone group, and 0.38 [0.22; 0.66] in the placebo group. It seems that the study duration was too short to ensure assay sensitivity on these endpoints since outcomes for the two active arms and placebo did not differ significantly. Further, the study was not powered for demonstrating efficacy in ARR. Also the patient population in the study can be considered rather mild in MS severity as the mean number of relapses within 2 years prior to the study was relatively low across treatment groups. The annual relapse rate has been declining in the MS population for the last two decades, making it more difficult to demonstrate efficacy in terms of relapse rates.

Moreover, the concept is that for bridging purposes showing similar biological activity is sufficient irrespective of the discussion between the relationship of MRI lesions and relapses. Therefore it has been agreed that MRI measures are acceptable and therefore the primary objective of the study has been achieved.

Follow-up period
728 subjects entered the open-label part of the study and 670 patients completed it. All patients switched to Sclerthon at the start of the open-label phase. 93.8% in the Sclerthon/Sclerthon group completed the study, as compared to 92.9% of the Copaxone/Sclerthon group and 81.5% of the placebo/Sclerthon group.

At open-label baseline, the mean number (SD) of T1-GdE lesions was 1.1 (2.77) in the Sclerthon/Sclerthon group, 0.8 (1.43) in the Copaxone/Sclerthon group and 2.2 (2.82) in the placebo/Sclerthon group. At the end of the open-label phase at 24 months, the mean number of T1-GdE lesions was 0.7 (1.70) in the Sclerthon/Sclerthon group, 0.6 (1.38) in the Copaxone/Sclerthon group and 0.9 (2.19) in the placebo/Sclerthon group. As can be seen, the mean number of T1-GdE lesions continued to decline during the open-label phase in all treatment groups.

The mean change in the EDSS scale at month 12, and 18 as compared to the open-label phase baseline was 0.0 in all treatment groups. At month 24, it was 0.0 in the Sclerthon/Sclerthon group and Copaxone/Sclerthon group and 0.1 in the placebo/Sclerthon group. When examining the entire study duration from double-blind period baseline to 24 months, similar numbers are observed. As glatiramer acetate had not demonstrated an effect on disability progression, these results were to be expected.

During the open-label phase, the LS mean (95% CI) for the Annual Relapse rate was 0.21 (0.13; 0.34) in the Sclerthon/Sclerthon group, 0.24 (0.15; 0.39) in the Copaxone/Sclerthon group, and 0.23 (0.12; 0.42) in the placebo/Sclerthon group. Corresponding ARR (95% CI) for the total study duration from double-blind period baseline to 24 months was 0.25 (0.18; 0.37), 0.31 (0.22; 0.45) and 0.30 (0.19; 0.47) for Sclerthon/Sclerthon, Copaxone/Sclerthon and placebo/Sclerthon, respectively.

IV.4 Clinical safety

In the double-blind part of the GATE study the number of subjects reporting adverse events (AEs) or drug-related AEs was comparable for all three treatment groups. In the Sclerthon group, 51.0% of subjects reported AEs, 35.4% of subjects reported drug-related AEs. Serious adverse events (SAEs) were reported for 12 subjects (3.4%), these include three subjects who reported drug related SAEs. Twelve subjects (3.4%) in the Sclerthon group discontinued the study drug and/or the trial due to AEs. There were no deaths reported in the trial.

The MedDRA system-organ class (SOC) with the highest frequency of AEs was General disorders and administration site conditions. The percentage of subjects with at least one AE in this SOC was 30.3% in the Sclerthon group, which is comparable to the reported incidence of 32.2% in the Copaxone group and slightly higher than the 20.2% in the placebo group
The common AEs reported in the general disorders and administration site conditions SOC were also the terms that were most frequently being considered as drug-related events.
For the remaining SOCs, the frequency was similar across treatment groups, and the frequency for individual AEs was not consistently higher in any treatment group.

In the follow-up period 35.9% of patients had at least one adverse event. Drug related AEs occurred in 10.9% of the patients. These figures are lower than in the Sclerthon and Copaxone arm in the double-blind phase of the study. The SOC with the highest frequency of AEs was Infections and infestations, with nasopharyngitis as the most frequently reported AE. The incidence of injection site reactions was considerably lower than in the double-blind study period.
No deaths occurred during the follow-up period. There were 22 patients with serious adverse events (3.0%). SAEs considered treatment related were angioedema, psoriasis, peripheral artery thrombosis and anaphylactic reaction. 10 subjects (1.4%) discontinued the trial due to an AE.
There were no notable differences in tolerability between patients who continued to use Sclerthon during the follow-up phase and patients who switched from Copaxone to Sclerthon.

The MAH had also submitted the results of immunogenicity assessment during the total study duration. The proportion of patients with glatiramer anti-drug antibodies (ADAs) was >90% from month 3 onwards in the Sclerthon and Copaxone treatment groups. These data indicated that the antibody formation remained rather stable during the 24 month study duration and there were no notable

differences between the treatment groups (Sclerthon/Sclerthon, Copaxone/Sclerthon and placebo/Sclerthon).
The clinical relevance of the glatiramer ADAs remained unclear, however the ADAs were comparable between Copaxone and Sclerthon.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Sclerthon 20 mg/ml.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Anxiety • Benign neoplasms of the skin and soft tissues • Convulsions • Hypersensitivity • Immediate Post Injection Reaction • Injection site necrosis and atrophy • Injection site reactions (excluding necrosis and atrophy)
Important potential risks	• Glomerulonephropathies • Liver injury
Missing information	• Elderly patients • Paediatric patients (below 18 years of age) • Patients with renal or hepatic impairment • Pregnant or breast feeding women

The Member States agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this hybrid authorisation, reference is made to the clinical studies and experience with the innovator product Copaxone. In support of the application, the MAH conducted a multicentre, randomized, double-blind, placebo-controlled, parallel-group, 9-month, equivalence trial comparing the efficacy and safety and tolerability of Sclerthon to the reference product Copaxone. Subjects with relapsing-remitting multiple sclerosis (RRMS) were included. The double-blind phase was followed by an open-label 15-month Sclerthon treatment part.

An interested party presented its view on a number of issues, most importantly the lack of assay sensitivity regarding ARR, lack of consistency between the MRI lesion outcome and the ARR results, and differences in the safety results of the GATE study.

In principle therapeutic efficacy would require comparison on both MRI and clinical endpoints in MS, and such would be required for comparison of non-similar MS products. For bridging purposes however, showing similar biological activity (i.e in MRI endpoints) is considered sufficient and was recommended in several scientific advices.
The evidence submitted from the clinical study demonstrated similar biological activity of Sclerthon and Copaxone on the primary endpoint (number of T1-GdE lesions in months 7, 8 and 9) within the agreed equivalence margins. The MAH has also provided a sufficient explanation for not detecting a trend in annualized relapse rate (ARR): the study was not sensitive enough to establish an effect on ARR as the sample size was too small and study duration too short. Further, the annual relapse rate in a mild MS population (as included in the study) is low in general. Moreover, as the clinical study was performed for bridging purposes, showing similar biological activity was considered sufficient irrespective of the discussion between the relationship of MRI lesions and relapses.

In general, the safety data presented suggested that the profile of Sclerthon was similar to that of Copaxone, also at long-term. This was indicated by similar incidence of adverse events (AEs), including severe AEs, serious AEs, AEs related to the investigational medicinal product and AEs leading to discontinuation of trial or investigational medicinal product. Similarity in immune-response was demonstrated as well. Risk management is adequately addressed for this medicinal product.
Overall, based on the objections raised by the interested party, the Member States did not identify a reason to reconsider the conclusions.

V. USER CONSULTATION

The MAH has provided a justification for not carrying out user testing. The current package leaflet (PL) of the reference product Copaxone 20 mg/ml marketed in the UK has been used as a basis for the proposed PL of Sclerthon 20 mg/ml solution for injection in pre-filled syringe. The two leaflets were compared to evaluate the differences. In addition, a successful user test of an Eplerenone 25 mg and 50 mg film-coated tablets PL was presented. This user test is referred to in order to support the changes related to house style. The justification is considered acceptable. The package leaflet does not require further user testing.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sclerthon 20 mg/ml solution for injection pre-filled syringe has a proven chemical-pharmaceutical quality and is a hybrid form of Copaxone. The reference product Copaxone 20 mg/ml solution for injection, pre-filled syringe has an established favourable efficacy and safety profile in RRMS.

The application was discussed in the Board meetings of the RMS on 30 October 2014 and 29 October 2015. The Board discussed whether the requirements of the quality, non-clinical and clinical dossier were met for this hybrid application in accordance with Article 10(3) of Directive 2001/83/EC.
With regard to non-clinical and clinical aspects, no relevant dissimilarities to the reference product were seen. Moreover, the quality results regarding similarity presented strong evidence for overall equivalence in the peptides composition and for equivalence in the interbatch variability.
The application was discussed in the CMD(h) meeting of February 2016 in order to address any remaining issues.

Comparability between test and reference is considered adequately substantiated. This has been concluded upon based on both extensive (physico)chemical and biological characterisation program comparing the active substance present in Sclerthon and Copaxone 20 mg/ml, using a panel of chemical and biological assays as well as the clinical data results from the GATE study. Moreover, comparability was corroborated by additional similarity data resulting from a further quality characterisation study, data from an experimental autoimmune encephalitis (EAE) mouse model, data from an *ex vivo* T-cell assay and a PBMC assay as well as gene expression data in THP-1 cells. Taken together, comparability between test and reference is considered adequately shown.

Based on all data presented, the Board concluded that Sclerthon 20 mg/ml can be regarded as therapeutic equivalent to the reference product. ‘Therapeutical equivalence’ means that the efficacy and safety of this hybrid formulation is similar to the efficacy and safety of the reference product. Agreement on this conclusion was reached between Member States.

The Member States considered that Sclerthon is a legitimate hybrid form of the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 11 March 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Addition of secondary packaging sites; addition of batch release site.	NL/H/3212/ 001/IA/001/ G	IA/G	25-4-2016	25-5-2016	Approval	No
Change in pack size of the finished product.	NL/H/3212/ 001/IB/002/ G	IB/G	25-4-2016	25-5-2016	Approval	No