Public Assessment Report

Scientific discussion

Sclerthon 40 mg/ml, solution for injection, pre-filled syringe

(glatiramer acetate)

NL/H/3779/001/DC

Date: 18 January 2018

This module reflects the scientific discussion for the approval of Sclerthon 40 mg/ml, solution for injection, pre-filled syringe. The procedure was finalised on 3 October 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references can be found on page 14.

List of abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
ARR	Annual Relapse Rate
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMDh	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
EEA	European Economic Area
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practices
GTR	Glatiramer
ICH	International Conference of Harmonisation
IPIR	Immediate Post-Injection Reaction
ISR	Injection Site Reaction
MAH	Marketing Authorisation Holder
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NMT	Not More Than
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RRMS	Relapsing-Remitting Multiple Sclerosis
sIL-1Ra	Soluble Interleukin-1 Receptor antagonist
SmPC	Summary of Product Characteristics
T1-GdE	T1-weighted Gadolinium Enhancing
TIW	Thrice a Week
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Sclerthon 40 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.

The recommended dosage in adults is 40 mg of glatiramer acetate (one pre-filled syringe), administered as a subcutaneous injection three times a week with at least 48 hours apart.

This decentralised procedure concerns a hybrid application claiming similarity with the innovator product Copaxone 40 mg/ml, solution for injection, pre-filled syringe (NL License RVG 113849) which has been registered in the Netherlands by Teva Pharmaceuticals Ltd through procedure UK/H/0453/004 since 23 December 2014. For expiry of data protection reference is made to Copaxone 20 mg powder for solution in vials which has been authorised in the EEA for more than ten years through a UK national procedure (PL10921/0019). 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.
Since both authorisations for Copaxone are considered to belong to the same global marketing authorisation this approach is acceptable.

The concerned member state (CMS) involved in this procedure was Austria

The MAH has registered a lower glatiramer acetate strength, 20 mg/ml solution for injection, pre-filled syringe through decentralised procedures NL/H/3211-3212/001.
In the Netherlands the 20 mg/ml formulation was granted a marketing authorisation pursuant to Article 10(3) of Directive 2001/83/EC on 10 May 2016.
Public Assessment Reports are published:

- Brabio 20 mg/ml - https://db.cbg-meb.nl/Pars/h115980.pdf (NL/H/3211/001/DC)
- Sclerthon 20 mg/ml - https://db.cbg-meb.nl/Pars/h115987.pdf (NL/H/3212/001/DC)

In this report the 20 mg/ml formulation is referred to as GTR Synthon 20 mg/ml.

Dossier requirements
The MAH submitted the following data to demonstrate therapeutic equivalence between Sclerthon 40 mg/ml and Copaxone 40 mg/ml:

- Analytical and *in vivo* and *in vitro* biological studies comparing Copaxone 20 mg/ml, Copaxone 40 mg/ml, GTR Synthon 20 mg/ml and Sclerthon 40 mg/ml.
- Preclinical toxicological studies
- The GATE clinical study comparing Copaxone 20 mg/ml to GTR Synthon 20 mg/ml strength (data from the MAH).
- The GALA clinical study comparing Copaxone 40 mg/ml to placebo (published data from the

Copaxone dossier).

- Published data on clinical trials (four published clinical studies, used in the application for the 40 mg/ml strength of the innovator Copaxone, including a report for a meta-analysis with weekly doses of 120 mg, 140 mg and 280 mg Copaxone).

Scientific advice

No specific scientific advice has been sought for this application. However, the MAH has sought scientific advice on the dossier requirements for their 20 mg/ml product both at centralised and national level in several Member States which are also applicable for the current application. 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 characterisation 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 authorisation applications for medicinal products with the active substance under the name glatiramer acetate' in July 2016 in a letter, with a request for an oral hearing.

In August 2017 the interested party provided new information, stating that additional clinical data was needed to support the application of Sclerthon 40 mg/ml. The interested party considers that Sclerthon 40 mg/ml should not be approved in absence of adequate additional clinical studies, see also paragraph 'Legal base – hybrid application' below. The concerns raised were carefully assessed, and the relevant concerns were addressed during the evaluation procedure.

CMDh discussion

An oral hearing was held with the MAH in September 2017, in which the CMDh raised questions to the MAH with regard to the therapeutic equivalence of Sclerthon 40 mg/ml versus Copaxone 40 mg/ml based on the data provided.

Legal base – hybrid application

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as bioequivalence cannot be demonstrated by bioavailability studies and additional information is needed in view of the complexity of the drug substance.

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 the active moiety(ies) are therefore 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 synthesised 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.

The complexity of the drug substance is recognised, presenting particular challenges for demonstrating equivalence. Moreover it is 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, Article 10(3) is an appropriate legal basis for the glatiramer 'generic' applications, taking into account previous scientific advices given by the Scientific Advice Working party of CHMP and by

national competent authorities, CMDh discussions and the wording of the Notice to Applicants, volume 2A, chapter 1, 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 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 300 mOsmol/l.
1 ml of solution for injection contains 40 mg glatiramer acetate, equivalent to 36 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 a piston during injection. A driving rod is screwed in the rubber stopper. The needle is covered with a needle shield.
The volume of solution in the syringe is 1.0 ml.

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 development of drug substance
The MAH has performed an extensive physicochemical and biological characterisation programme comparing the active substance present in GTR Synthon 20 mg/ml 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 GTR Synthon batches were within a variability seen for Copaxone batches.
Additional evidence for similarity is presented by a characterisation study for two lots in which nine different mass fractions have been isolated from Copaxone and GTR Synthon 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.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided.

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
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The manufacturing process results in a specified content of 34.2-37.8 mg base. Comparative batch studies show that the test batches contain a similar peptide content as reference batches (Copaxone 40 mg/ml). The choice for sterilisation by filtration is justified, since steam sterilisation 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 to Ph.Eur. 2.9.17 was carried out and the results were satisfactory. The target filling volume is regarded as acceptable for this product. Pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process has been laid down in sufficient detail. The manufacture of the drug product is a conventional process. Validation data for drug product manufacturing scales were provided. The batch size of the batches used during this process validation has a sufficient volume.

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 finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, colour, clarity, pH, particle contamination, extractable volume, assay, identification, molecular weight distribution, impurities, potency, immunoassay, sterility and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from sufficient batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
The MAH has provided results of stability studies with three batches from both manufacturers. The batches have been stored for 36 months at long-term (5°C ± 3°C) and 6 months at accelerated conditions (25°C/60% RH). The batches have also been used for 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 or 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.

On basis of the data submitted, a shelf life was granted of three years. The labelled storage conditions are “Store in a refrigerator (2°C to 8°C)”. Within the shelf life period storage of one month at room temperature is allowed. If not used, after this one month period it must be returned to storage in a refrigerator (2°C to 8°C).

Specific measures for 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 40 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.

To show therapeutic equivalence between Sclerthon 40 mg/ml and Copaxone 40 mg/ml the MAH applied an appropriate bridging strategy, including quality and in vivo and in vitro studies comparing Copaxone 20 mg/ml, Copaxone 40 mg/ml, GTR Synthon 20 mg/ml and Sclerthon 40 mg/ml. Therapeutic equivalence is further discussed in section IV.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The MAH provided data obtained with different glatiramer acetate and glatiramer batches and Copaxone batches in two *in vitro*, one *ex vivo* and two *in vivo* bioassays to evaluate the mode of action and biological activity. Sclerthon 40 mg/ml batches were only studied in the THP-1 cell assay and in the experimental autoimmune encephalitis (EAE) mouse model. The submitted data from an *ex vivo* T-cell assay showed considerable variability and for the human peripheral blood mononuclear cell (PBMC) assay limited data is available to demonstrate comparable biological activity of Copaxone and Sclerthon at a functional level. However, the cell-based assay using the human monocytic THP-1 cell line, presented also in the quality dossier as a potency assay, was used to demonstrate comparable biological activity of Copaxone and Sclerthon batches at a functional level. This cell-based assay has been sufficiently characterised and comparable bioactivity was found.

A microarray study, comparing five batches of Sclerthon and Copaxone, demonstrated comparable gene modulation and no relevant differences between the Sclerthon and Copaxone batches used in a human monocytic cell line THP-1.

In addition, the MAH provided data from the 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 conclusions on the comparability of two glatiramer products on the basis of these *in vivo* data.

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 Sclerthon. Analogous to Copaxone, upon subcutaneous dosing Sclerthon will undergo local metabolism/degradation at the site of injection and local and systemic exposure is likely to be an extensive mixture of peptides. Methodological complications such as those encountered for Copaxone will equally apply for Sclerthon. 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 subcutaneous 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 - haemorrhage, 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 glatiramer. This study showed that the presence of Br-Tyr up to 6.8 times the maximal exposure in humans does not affect the outcome in terms of local or systemic toxicological effects.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Sclerthon 40 mg/ml is intended for 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 Sclerthon 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.

The MAH further supported this hybrid application with the following existing clinical data:

- The GATE clinical study comparing Copaxone 20 mg/ml to GTR Synthon 20 mg/ml (see annex I).
- The GALA clinical study comparing Copaxone 40 mg/ml to placebo (data from the Copaxone dossier).
- Published data on clinical trials (four published clinical studies, partly used in the application for the 40 mg/ml strength of the innovator Copaxone, including a report for a meta analysis with weekly doses of 120 mg, 140 mg and 280 mg Copaxone).

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

Therapeutic equivalence of the MAH's glatiramer acetate 20 mg/ml product has been accepted earlier based on elaborate quality, non-clinical and clinical data. In the assessment of the GTR Synthon 20 mg/ml dossier, comparability based on *in vitro* data was not considered sufficient and hence a therapeutic equivalence study was mandatory. Extrapolation of the results of the GATE study data to the 40 mg/ml strength cannot be simply based on reference to Copaxone since no direct comparison in terms of efficacy between Copaxone 20 mg daily and Copaxone 40 mg thrice in one week (TIW) is available. The MAH has therefore used a number of arguments to support a bridging rationale (figure 1). In summary:

- Bridge 1 (quality and *in vitro* and *in vivo** studies plus the clinical GATE study**) confirms the therapeutic equivalence of the critical and complex drug substance between the MAH's product and the innovator product at the level of the 20 mg/ml product;
- Bridge 2 (includes quality, *in vitro* and *in vivo** studies) confirms the equivalence of the MAH's 20 mg/ml drug product to the MAH's 40 mg/ml drug product and;
- Bridge 3 (includes quality, *in vitro* and *in vivo** studies) confirms the equivalence of the MAH's 40 mg/ml drug product to Copaxone 40 mg/ml.

* As indicated in the Non-Clinical section above the *in vivo* data are only of limited value. See for the discussion on the *in vitro* studies the Quality an Non-Clinical sections above.
** For the clinical assessment of the GATE study, see annex I.

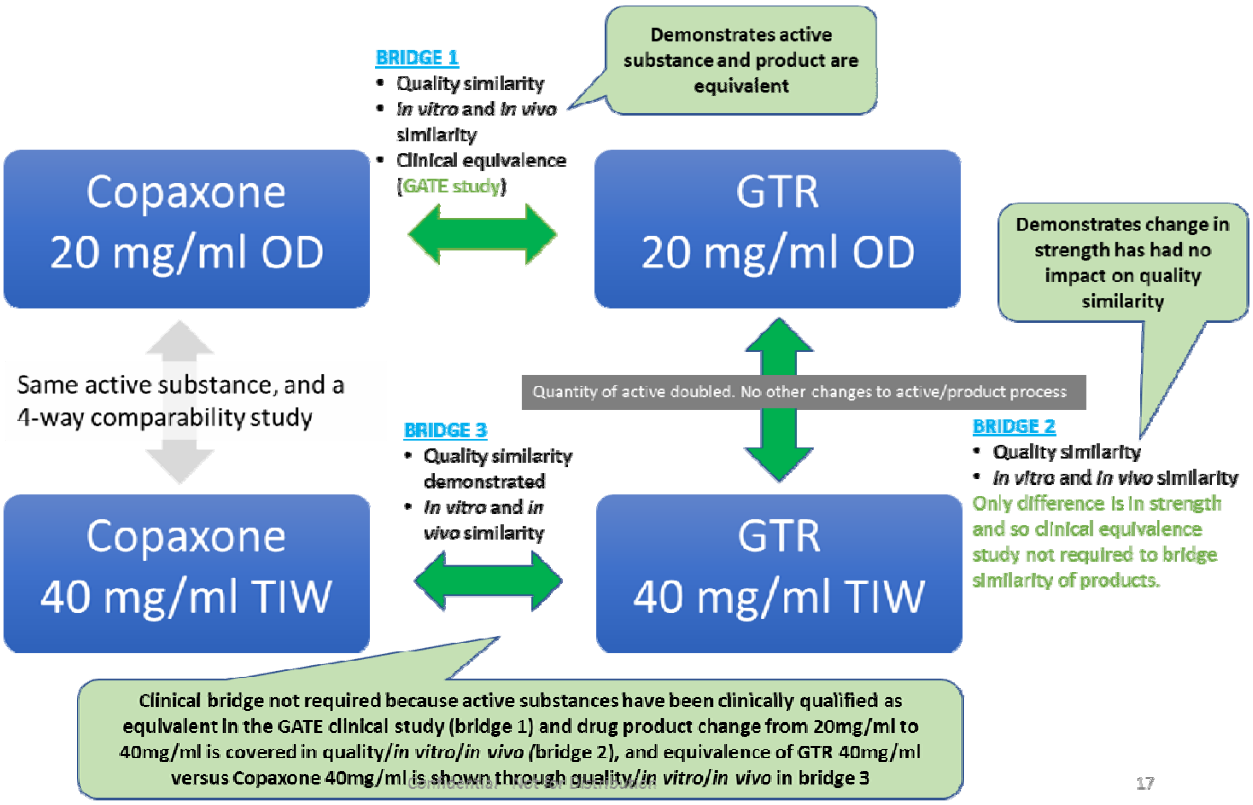

Figure 1: Bridging strategy to demonstrate therapeutic equivalence between Sclerthon 40 mg/ml (GTR 40 mg/ml TIW) and Copaxone 40 mg/ml. GTR Synthon 20 mg/ml is referred to as GTR 20 mg/ml OD.

Clinical equivalence between Copaxone 20 mg/ml and GTR Synthon 20 mg/ml
The data to support bridge 1 are the data which formed the basis for the approval of GTR Synthon. Comparability between test and reference is considered adequately substantiated. This has been concluded based on both extensive (physico)chemical and biological characterisation programs comparing the active substance present in GTR Synthon 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, it is concluded that GTR Synthon 20 mg/ml can be regarded as therapeutic equivalent to Copaxone 20 mg/ml.

Clinical equivalence between GTR Synthon 20 mg/ml and Sclerthon 40 mg/ml
Since Sclerthon 40 mg/ml and GTR Synthon 20 mg/ml differ in a higher concentration only and the MAH has demonstrated the lack of difference in higher order structures and biological activity, it is agreed that no difference in immunogenicity and change in efficacy could be expected to occur when the same drug substance is applied with a higher concentration. This is accepted as supportive argumentation for bridge 2.

Clinical equivalence between Sclerthon 40 mg/ml and Copaxone 40 mg/ml
The full characterisation data show that the drug substance for all four products (GTR Synthon 20 mg/ml, Sclerthon 40 mg/ml, Copaxone 20 mg/ml and Copaxone 40 mg/ml) shows strong similarities in primary structure, physicochemical properties, higher order structures and biological activity when tested with a sensitive characterisation package.

With regard to the literature data, the following additional studies have been provided:
- The study by Cohen et al compared Copaxone 20 mg/ml subcutaneous daily to Copaxone 40 mg/ml subcutaneous daily in a study of 9 months with Magnetic Resonance Imaging (MRI) as

primary endpoint (Cohen et al., 2007)

- The FORTE study compared Copaxone 20 mg/ml subcutaneous daily to Copaxone 40 mg/ml subcutaneous daily in Relapsing-Remitting Multiple Sclerosis (RRMS) patients treated for 12 months.
- The GLACIER study was conducted in RRMS patients who switched from the 20 mg/ml Copaxone daily regimen to the 40 mg/ml strength thrice in one week (TIW). It was concluded that tolerability is acceptable and hence this switching can be applied in clinical practice (Wolinsky et al., 2015).

The FORTE study and the study of Cohen et al. are of limited value for the assessment of therapeutic equivalence of Copaxone 20 mg/ml and Copaxone 40 mg/ml since assay sensitivity of these studies is questioned and even if accepted, the confidence intervals are too wide for deciding on equivalence. Moreover, the dose regime in those studies was once daily and not thrice a week.

The GALA study, randomised RRMS patients to either receive Copaxone 40 mg/ml three times per week (N=943) or matched placebo (N=461) during a 12 months double-blind phase. Copaxone 40 mg/ml TIW showed to be superior to placebo on clinical (annual relapse rate - ARR) and MRI parameters. This evidence is considered pivotal for the approval of the Copaxone 40 mg/ml TIW (published data from the Copaxone dossier). The MAH has discussed this study as providing evidence for efficacy and safety of Copaxone 40 mg/ml TIW, which in combination with the provided evidence for similarity with Sclerthon 40 mg/ml may lead to the assumption that Sclerthon 40 mg/ml will have the same clinical effect. This can be accepted as supportive argumentation for the bridge 3 according to the scheme provided.

IV.4 Clinical safety

The safety profile of glatiramer acetate is known from the experience with Copaxone and from the data available in the GTR Synthon 20 mg/ml dossier (see annex I).

The most common adverse events (AEs) are Immediate Post-Injection Reactions (IPIRs) and Injection Site Reactions (ISRs). Their management is well covered in the SmPC of Copaxone and GTR Synthon 20 mg/ml respectively.

With respect to the safety of Sclerthon 40 mg/ml, there are no data with the product applied for.
Copaxone 40 mg/ml has a comparable safety profile as Copaxone 20 mg/ml in terms of number, type and severity of reported (S)AEs and local tolerability. No clinically relevant abnormalities in vital signs and laboratory values were observed.

Study comparing Copaxone 20 mg/ml to 40 mg/ml daily - Cohen et al., 2007
In the study of Cohen et al. Copaxone was well tolerated. Injections site reactions were the most frequently reported adverse events for both doses, occurring in 38 subjects (86.4%) in the Copaxone 20 mg/ml daily group and in 39 subjects (84.8%) in the Copaxone 40 mg/ml daily group. Thirty-nine IPIRs occurred in 10 (22.7%) subjects on Copaxone 20 mg/ml daily vs 52 IPIRs in 15 (32.6%) subjects on Copaxone 40 mg/ml daily. The IPIRs in the Copaxone 20 mg/ml daily group were mostly categorised as mild and the IPIR in the Copaxone 40 mg/ml daily group as moderate.

Study comparing Copaxone 20 mg/ml to 40 mg/ml daily - FORTE study
In the FORTE study, the safety profile of Copaxone 20 mg/ml daily and Copaxone 40 mg/ml daily was similar to that observed in previous studies with Copaxone. There were no differences seen in AE frequency between the treatment arms. The number of patients with ISRs was similar between the treatment arms (55.6% in the Copaxone 20 mg/ml daily group vs 58% in the Copaxone 40 mg/ml daily group). The incidence of IPIR was low: 36 patients (6.1%) in Copaxone 20 mg/ml and 43 patients (7.6%) in Copaxone 40 mg/ml. There were no safety concerns in either treatment group with regard to laboratory results, electrocardiogram and vital signs.

Study comparing Copaxone 40 mg/ml TIW to placebo - GALA study
In the GALA study the safety profile of Copaxone 40 mg/ml three times per week was consistent with the known safety profile of the Copaxone 20 mg/ml formulation. The most common AEs were ISRs (35.2% of Copaxone 40 mg/ml three times per week patients vs. 5.0% of placebo patients), 99.9% of these were of mild or moderate severity. At least one symptom related to systemic immediate post-

injection reactions occurred in 7.6% of patients who received Copaxone 40 mg/ml three times per week and 1.7% of patients who received placebo. AEs leading to discontinuation of treatment occurred in 3.1% of patients in the Copaxone 40 mg/ml group and 1.3% of patients in the placebo group. The highest rate of discontinuation was attributed to ISRs, which led to discontinuation of Copaxone 40 mg/ml three times per week in 1.0% of patients. There was no increase in the incidence of infections or malignant diseases, or clinically significant changes or safety concerns, in either treatment group with regard to laboratory values, electrocardiogram (ECG) readings, and vital signs.

Study comparing Copaxone 40 mg/ml TIW to Copaxone 20 mg/ml daily - GLACIER study

The GLACIER study demonstrated that the rate of reporting injection related adverse events is reduced in the Copaxone 40 mg/ml TIW group compared to the Copaxone 20 mg/ml daily group. The adjusted mean annualised rate of injection related adverse events (IRAEs) was reduced by 50% with Copaxone 40 mg/ml TIW (35.3 events per year) versus Copaxone 20 mg/ml daily (70.4 events per year). The proportion of patients experiencing at least one IRAE was similar between the groups, 58.3% for Copaxone 40 mg/ml TIW versus 56.4% for Copaxone 20 mg/ml daily. The adjusted mean annualised rate of injection site reactions was reduced by 50% with Copaxone 40 mg/ml TIW (35.2 events per year) versus Copaxone 20 mg/ml daily (70.4 events per year). The proportion of patients experiencing at least one injection site reaction was similar between the groups, 56.5% for Copaxone 40 mg/ml TIW versus 56.4% for Copaxone 20 mg/ml daily. The rates of injection site atrophy and necrosis were minimal (≤0.1 events per year), with no observable difference between treatment groups. The annualised IPIR rate was 1.9 events per year for Copaxone 40 mg/ml TIW and 3.9 events per year for Copaxone 20 mg/ml daily.

Glatiramer anti-drug antibodies

The ADAs were comparable between Copaxone 20 mg/ml and GTR Synthon (see annex I). This may also be expected to be the case for 40 mg/ml TIW. The motivation of the MAH is based on the claim that the active ingredient in GTR Synthon 20 mg/ml and Sclerthon 40 mg/ml is the same, the excipients are the same, the structure and characteristics of the peptide mix remain the same, and that immunogenicity does not seem to be dose dependant (according to non-clinical studies with Copaxone). Moreover in the SmPC of Copaxone it is mentioned that "*There is no evidence to suggest that these glatiramer acetate-reactive antibodies are neutralising or that their formation is likely to affect the clinical efficacy of Copaxone*."

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 40 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 od age) • Patients with renal or hepatic impairment • Pregnant or breastfeeding 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 authorisation reference is made to clinical studies and experience with the innovator. The MAH has provided sufficient data and argumentation to justify that the data from the quality, *in vivo* and *in vitro* studies comparing Copaxone 20 mg/ml and 40 mg/ml, GTR Synthon 20 mg/ml and Sclerthon 40 mg/ml is eligible to be used in this hybrid application, in combination with the GATE and GALA clinical studies, and published data on clinical trials with weekly doses of 120 mg, 140 mg and 280 mg Copaxone.
Sclerthon 40 mg/ml and GTR Synthon 20 mg/ml contain an identical drug substance and excipient formulation and do not differ in higher order structures and biological activity which may lead to difference in immunogenicity and efficacy and safety. This is further supported by highly comparable quality attributes and biological activities of Sclerthon 40 mg/ml and Copaxone 40 mg/ml, GTR Synthon 20 mg/ml and Copaxone 20 mg/ml. This, in combination with the additional clinical argumentation for bridging Sclerthon 40 mg/ml to Copaxone 40 mg/ml, is sufficient. Risk management is adequately addressed for this medicinal product.

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 40 mg/ml marketed in the United Kingdom has been used as a basis for the proposed PL of Sclerthon 40 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 40 mg/ml, solution for injection, pre-filled syringe has a proven chemical-pharmaceutical quality and is a hybrid form of Copaxone. The reference product has an established favourable efficacy and safety profile.

The application was discussed in the Board meetings of the RMS on 25 Augustus 2016, 29 June 2017 and 6 September 2017. The Board discussed the strategy of the MAH to demonstrate therapeutic equivalence between Sclerthon 40 mg/ml and Copaxone 40 mg/ml. It was concluded that, based on the provided data, it was adequately shown that Sclerthon 40 mg/ml is therapeutically equivalent to Copaxone 40 mg/ml.
Comparability of Sclerthon 40 mg/ml versus Copaxone 40 mg/ml was also discussed at the CMDh meeting of September 2017 in an oral hearing with the company.

Comparability between test and reference is considered adequately substantiated based on both extensive (physico)chemical and biological characterisation programs comparing the active substance present in Sclerthon and Copaxone 40 mg/ml, using a panel of chemical and biological assays as well as clinical data. Moreover, comparability was corroborated by an adequate bridging strategy for which sufficient quality, biological and clinical data has been submitted.

Based on all data presented, the Board concluded that Sclerthon 40 mg/ml can be regarded as therapeutically equivalent to the reference product. ‘Therapeutic 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 3 October 2017.

REFERENCES

Cohen, J.A., Rovaris, M., Goodman, A.D., Ladkani, D., Wynn, D., and Filippi, M. Randomized, double-blind, dose-comparison study of glatiramer acetate in relapsing-remitting MS. Neurology 2007; 68(12):939-944

Comi, G., Cohen, J.A., Arnold, D.L., Wynn, D., and Filippi, M. Phase III dose-comparison study of glatiramer acetate for multiple sclerosis. Ann. Neurol. 2011; 69:75-82

Khan, O., Rieckmann, P., Boyko, A., Selmaj, K., and Zivadinov, R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol. 2013; 73(6):705-713

Public assessment reports - glatiramer acetate 20 mg/ml, solution for injection, pre-filled syringe:

- Brabio - https://db.cbg-meb.nl/Pars/h115980.pdf
- Sclerthon - https://db.cbg-meb.nl/Pars/h115987.pdf

Wolinsky, J.S., Borresen, T.E., Dietrich, D.W., Wynn, D., Sidi, Y., Steinerman, J.R., Knappertz, V. and Kolodny, S. GLACIER: An open-label, randomized, multicenter study to assess the safety and tolerability of glatiramer acetate 40 mg three-times weekly versus 20 mg daily in patients with relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2015; 4(4): 370-376 - Journal Article;-Research Support, Non-U.S. Gov't

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

Annex I - Clinical assessment of the GATE study

I. Clinical efficacy

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 Glatiramer acetate 20 mg/ml (GTR, Synthon B.V.) to Copaxone (Teva Pharmaceuticals Ltd) in subjects with relapsing-remitting multiple sclerosis (RRMS) followed by an open-label 15-month GTR Synthon 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 GTR Synthon, 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 doubleblind 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) GTR Synthon treatment and to evaluate efficacy, safety and tolerability of switching to GTR Synthon treatment after previous Copaxone use.

Additional efficacy endpoints included other MRI parameters, 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 GTR Synthon 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 GTR Synthon 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 GTR Synthon 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 than 75% of the Copaxone effect on relapse rate (7% of 30%) will be retained. In conclusion, the predefined 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 GTR Synthon, 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 GTR Synthon (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 GTR Synthon 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 GTR Synthon to Copaxone (see tables below).

Table 1 Number of T1-GdE Lesions at Months 7 to 9 (Full Analysis Set) – GTR = Glatiramer acetate Synthon

	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 (Glatiramer acetate Synthon) 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 = Glatiramer acetate Synthon

	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 GTR Synthon group and .408 in the Copaxone group. The point estimate of the GTR Synthon/Copaxone T1-GdE lesion ratio was .095 with a 95% CI of [0.883; 1.360] for the FAS (see table 4). The point estimate of the GTR Synthon/Copaxone T1-GdE lesion ratio was 1.099 with a 95% CI of [0.881; 1.370] for the PPS. The predefined 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 GTR Synthon was equivalent to Copaxone.

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

	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 GTR Synthon 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 GTR Synthon 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 GTR Synthon at the start of the open-label phase. 93.8% in the GTR Synthon/GTR Synthon group completed the study, as compared to 92.9% of the Copaxone/GTR Synthon group and 81.5% of the placebo/GTR Synthon group.
At open-label baseline, the mean number (SD) of T1-GdE lesions was 1.1 (2.77) in the GTR Synthon/GTR Synthon group, 0.8 (1.43) in the Copaxone/GTR Synthon group and 2.2 (2.82) in the placebo/GTR Synthon 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 GTR Synthon/GTR Synthon group, 0.6 (1.38) in the Copaxone/GTR Synthon group and 0.9 (2.19) in the placebo/GTR Synthon 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 GTR Synthon/GTR Synthon group and Copaxone/GTR Synthon group and 0.1 in the placebo/GTR Synthon 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 GTR Synthon/GTR Synthon group, 0.24 (0.15; 0.39) in the Copaxone/GTR Synthon group, and 0.23 (0.12; 0.42) in the placebo/GTR Synthon 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 GTR Synthon/GTR Synthon, Copaxone/GTR Synthon and placebo/GTR Synthon, respectively.

II. 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 GTR Synthon 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 GTR Synthon 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 GTR Synthon 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 GTR Synthon and Copaxone arm in the doubleblind 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 GTR Synthon during the follow-up phase and patients who switched from Copaxone to GTR Synthon.

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 GTR Synthon 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 (GTR Synthon/GTR Synthon, Copaxone/GTR Synthon and placebo/GTR Synthon).

The clinical relevance of the glatiramer ADAs remained unclear, however the ADAs were comparable between Copaxone and GTR Synthon.

III. 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 GTR Synthon 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 GTR Synthon 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 GTR Synthon 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 GTR Synthon 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.

References

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 resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann. Neurol. 2001;49:290-297
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 metaanalysis 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 relapsingremitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 45, 1268-1276