Thai Food and Drug Administration (Thai FDA)

Public assessment report

Copaxone®

International non-proprietary name: Glatiramer acetate

I. INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS). MS is a common disease, affecting approximately 2,500,000 people worldwide, the majority being in the temperate areas in Europe and North America. There are not many cases of MS in Thailand. In approximately 85% of the patients, disease onset is characterized by an acute attack indicating unifocal or multifocal CNS involvement, usually followed by a recovery phase. At a variable interval of time, new attacks affect optic nerve, spinal cord, and brain and the disease enters a relapsing remitting (RR) course. Relapses may be followed by some level of residual disability. After 20 years, about two thirds of patients switch to an insidious secondary progressive multiple sclerosis (SPMS) course. The current therapeutic approach involves symptomatic treatment, treatment of acute relapses, and disease modifying therapies. Symptomatic treatment refers to all therapies applied to improve symptoms and complications caused by the disease e.g. fatigue, spasticity, ataxia, walking disability, weakness, bladder and bowel disturbances among others. In general, these treatments are nonspecific. More MS specific treatments are those that intend to facilitate remyelination or axonal conductivity. The standard-of-care for acute relapses is methylprednisolone that shortens the duration of relapses but has no influence on the sequel of the relapse. Treatment aimed to modify the course of the disease includes immunomodulators (interferons and glatiramer acetate), monoclonal antibodies, α4β-integrin antagonists, sphingosine analogues (fingolimod), immunosuppressants and cytotoxic agents. These therapies aim to prevent relapses and to diminish the accumulation of disability. Due to the risk of opportunistic infections and secondary malignancies, many of these are second line options.

The active ingredient of Copaxone is glatiramer acetate (GA), which consists of the acetate salts of synthetic polypeptides containing 4 naturally occurring amino acids: L-glutamic acid, L-alanine, Ltyrosine and L-lysine. This complex mixture is comprised of antigenic sequences that modulate the immune system in patients with multiple sclerosis (MS) towards an anti-inflammatory phenotype. The amino acid ratio in GA was designed to mimic that of myelin basic protein, a component of the myelin sheath of nerves. The active substance belongs to the Antineoplastic and immunomodulating agents, other immunostimulants pharmacotherapeutic group (ATC code: L03AX13)

Copaxone 20 mg/ml was approved in Israel and the US in 1996 and in the United Kingdom followed by the entire European Union (EU) during 2000-2001. Copaxone 40 mg/ml was approved in 2014 in EU and USA. Currently, Copaxone® is indicated in the EU for the treatment of relapsing forms of multiple sclerosis including patients who have experienced a well-defined first clinical episode and are determined to be at high risk of developing clinically definite multiple sclerosis (CDMS) and for the reduction in frequency of relapses in ambulatory patients (i.e. who can walk unaided) with relapsing-remitting multiple sclerosis (RRMS).

Copaxone® has been approved for marketing in 59 countries (20 mg/ml) and 56 countries (40 mg/ml) worldwide, including Thailand for both 20 mg and 40 mg PFS, for the treatment of relapsing forms of Multiple Sclerosis. Overall, more than 2.7 million patient-years of exposure to the drug have accumulated. Copaxone® is available as a 20 mg/mL solution for injection, pre-filled syringe, injected subcutaneously daily, and as a 40 mg/mL solution for injection in a pre-filled syringe (PFS), administered by subcutaneous injection three times a week. Silom is proposing Glatiramer Acetate (GA) Injection 40 mg/mL in a pre-filled pen (PFP) as an additional alternative presentation to GA Injection 20 mg/mL and 40 mg/mL solution for injection in a PFS. GA Injection 40 mg/mL in a pre-

filled pen will be administered by subcutaneous injection by patients with relapsing forms of multiple sclerosis, in the same dose as GA Injection 40 mg/mL PFS.

One of the applications concerns glatiramer acetate in an additional presentation, pre-filled pen (PFP), of a solution of 40mg/ml in pre-filled syringes, which has been approved in Europe. The new PFP presentation contains the same formulation and primary container closure system as the GA Injection 40 mg/mL solution for injection in a pre-filled syringe.

The Copaxone-Pen 40 mg/mL injection in a pre-filled pen (PFP) application is an extension application to the existing application for Copaxone 40 mg/mL injection in a pre-filled syringe (PFS).

No new non-clinical studies were conducted in support of this line-extension application, since the pharmacodynamic, pharmacokinetic and toxicological properties of glatiramer acetate are well known.

The applicant has submitted the data from three clinical studies to support this application: a pivotal study and two supportive studies. A certificate of compliance with Good Clinical Practice (GCP) guidelines is provided in the clinical study reports.

The Thai FDA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites in Europe, the Thai FDA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside Thailand, the Thai FDA has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those foreign sites.

II. QUALITY ASPECTS

II.1 Introduction

Name:	Copaxone (Glatiramer Acetate)
Dosage form and strength:	20 mg/ml solution for injection in pre-filled syringe
Proposed dosage range:	subcutaneous injection once daily

Name:	Copaxone (Glatiramer Acetate)
Dosage form and strength:	40 mg/ml solution for injection in pre-filled syringe
Proposed dosage range:	subcutaneous injection three times a week with at least 48 hours apart

Name:	Copaxone (Glatiramer Acetate)

Dosage form and strength:	40 mg/ml solution for injection in pre-filled pen
Proposed dosage range:	subcutaneous injection three times a week with at least 48 hours apart

II.2 Drug substance

Glatiramer acetate

International non-proprietary name (INN):	N/A
United States Adopted Name (USAN):	Glatiramer acetate
Chemical names:	L-glutamic acid, polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt) [USAN] L-alanine, polymer with L-glutamic acid, L-lysine and L-tyrosine, acetate (salt) L-lysine, polymer with L-alanine, L-glutamic acid and L-tyrosine, acetate (salt) L-tyrosine, polymer with L-alanine, L-glutamic acid and L-lysine, acetate (salt)
Molecular formula:	Poly[L-Glu^{13-15}, L-Ala^{39-46}, L-$Tyr^{8.6-10}$, L-Lys^{30-37}].n$CH3CO_2H$
Relative molecular mass:	The average molecular weight of the glatiramer acetate is between 5,000 and 9,000 daltons with at least 68 percent of the molecules within the range of 2,500 to 20,000 daltons.
Physical characteristics:	White to slightly yellowish lyophilised material
Solubility:	Soluble in water, insoluble in acetone

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis. No materials of animal or human origin are used in the production of the active substance.

Appropriate proof-of-structure data have been supplied for the active substance. All potential impurities have been identified and monitored appropriately.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for all working standards.

The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Drug product

Pharmaceutical development

The objective of the pharmaceutical development of 40 mg/ml products was the achievement of a safe and efficacious dosage form for subcutaneous administration three times per week.

The excipients used in the manufacturing of the 40 mg/mL presentation are the same as those used for 20 mg/mL presentation. These are controlled in accordance with requirements of their respective current Ph Eur monograph. Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients are of animal/human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the product

Satisfactory batch formulae have been provided for manufacture of the drug product, together with an appropriate account of the manufacturing process. The manufacturing process has been validated. It show that the manufacturing process to be suitably controlled and consistently capable of producing drug product that meets the required quality requirements.

Drug product specification

The drug product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data have been provided from commercial -scale batches that comply with the release specification. The Applicant confirms that the same reference standards will be used for testing the 40 mg/mL product as employed in the testing of the 20 mg/mL presentation. This is acceptable.

Stability of the drug product

Stability studies were performed in accordance with current guidelines on batches of the drug product, packed in the packaging proposed for marketing. The data from these studies support a proposed shelf-life of 3 years for Copaxone 20 mg/ml and 2 years for Copaxone 40 mg/ml with the following storage conditions: 'Keep the pre-filled syringes in the outer carton, in order to protect from light. Store in a refrigerator (2 ^{o}C – 8 ^{o}C). Do not freeze', with a permitted 1 month excursion to 15 – 25 ^{o}C.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended for this application.

III. NON-CLINICAL ASPECTS

No new non-clinical studies were conducted in support of 40 mg/ml application since the pharmacodynamic, pharmacokinetic and toxicological properties of glatiramer (GA) are well known from 20 mg/ml application. As GA is a widely used, well-known active substance, no further studies are required and the applicant has not provided any. An overview based on a literature review is, thus, appropriate. There are no major non-clinical objections to the grant of a marketing authorization for Copaxone 20 and 40 mg/ml solution for injection, pre-filled syringe and pen.

The dossier for the original 20 mg/ml application included written summaries and tabulated data providing complete documentation of the nonclinical program conducted to support the application. Furthermore, the applicant has conducted a thorough review of relevant nonclinical information that was published since the original application in other countries, and has incorporated this information in the present Overview, rewritten in the format of the CTD.

Toxicology

The NOAEL for systemic effects, after chronic s.c. dosing of rats (up to 104 weeks) and monkeys (up to 52 weeks), was defined as 7.5 and 10 mg/kg/day, respectively. These dose levels are approximately 1.75-fold and 5.5-fold higher, respectively, than the equivalent human dose of GA (40 mg) based on a body surface area comparison. At higher dose levels there was an increased rate of glomerulonephritis in male rats that were treated for 104 weeks. In monkeys that were treated at doses above 10 mg/kg/day, there were some signs of hyperimmune stimulation.

In a two-year carcinogenicity study, mice were given up to 60 mg/kg/day GA by sc injection (equivalent to 15 times the human therapeutic dose of 20 mg, on a mg/m2 basis). In males of the high dose group (60 mg/kg/day) but not in females nor in males of the lower dose levels (up to 30 mg/kg/day), there was an increased incidence of fibrosarcoma at injection sites. These sarcomas were associated with skin damage that is precipitated by repetitive injections of irritant over a limited skin area. No other increases in tumour incidence were noted. No increase in the incidence of tumours was recorded in the two-year carcinogenicity study in rats that were dosed with up to 30 mg/kg/day GA by sc injection (equivalent to 15 times the human therapeutic dose of 20 mg on a mg/m2 basis). For the 40 mg dose, this would reduce to 7.5 times.

It should be noted that clinical safety margins may not be relevant on a body surface area comparison since GA undergoes almost instantaneous degradation in vivo at the site of injection and very little (if any) intact drug appears systemically after s.c. administration. Hence, the level of GA in the systemic circulation is not indicative of drug activity.

Based on the assumption that the systemic exposure of the proposed product does not exceed levels previously approved, there are no pre clinical objections to the proposed line extension application.

Environmental Risk Assessment (ERA)

It may be concluded that the marketing of the proposed product will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pharmacokinetic studies in patients have not been performed. In vitro data and limited data from healthy volunteers indicate that with subcutaneous administration of glatiramer acetate, the active substance is readily absorbed and that a large part of the dose is rapidly degraded to smaller fragments already in subcutaneous tissue. Important to note, the biological and pharmacological effect of GA is mediated by immune system modulation and is independent of blood concentrations.

IV.2 Pharmacodynamics

No new study data was submitted, which is acceptable.

IV.3 Clinical efficacy

Clinical studies have been conducted to support the 20 mg/ml application.

RRMS:

A total of 269 patients have been treated with Copaxone in three controlled trials. The first was a two-year study involving 50 patients (Copaxone n=25, placebo n=25) who were diagnosed with relapsing-remitting MS by the then-applicable standard criteria, and who had at least two attacks of neurological dysfunction (exacerbations) during the preceding two years. The second study applied the same inclusion criteria and included 251 patients treated for up to 35 months (Copaxone n=125, placebo n=126). The third study was a nine-month study involving 239 patients (Copaxone n=119, placebo n=120) where inclusion criteria were similar to those in the first and second studies with the additional criterion that patients had to have at least one gadolinium-enhancing lesion on the screening MRI.
In clinical trials in MS patients receiving Copaxone, a significant reduction in the number of relapses, compared with placebo, was seen.
In the largest controlled study, the relapse rate was reduced by 32% from 1.98 under placebo to 1.34 under glatiramer acetate.

Exposure data are available for up to twelve years in 103 patients treated with Copaxone.
Copaxone has also demonstrated beneficial effects over placebo on MRI parameters relevant to relapsing-remitting MS.
Copaxone 20 mg/mL: In the controlled study 9001/9001E, which enrolled 251 patients, who were followed for up to 35 months (including a blinded phase extension 9001E of the 9001 study), the cumulative percentage of patients who developed 3-month confirmed disability progression was 29.4% for placebo and 23.2% for Copaxone-treated patients (p=0.199).
There is no evidence that Copaxone treatment has an effect on relapse duration or severity.
There is currently no evidence for the use of Copaxone in patients with primary or secondary progressive disease.

Single clinical event suggestive of MS:

One placebo-controlled study involving 481 patients (Copaxone n=243, placebo n=238) was performed in patients with a well-defined, single, unifocal neurological manifestation and MRI features

highly suggestive of MS (at least two cerebral lesions on the T2-weighted MRI above 6 mm diameter). Any disease other than MS that could better explain signs and symptoms of the patient had to be excluded. The placebo-controlled period was followed by an open label treatment: Patients who either presented with MS symptoms or were asymptomatic for three years, whichever came first, were assigned to active drug treatment in an open-label phase for an additional period of two years, not exceeding a maximal total treatment duration of 5 years. Of the 243 patients initially randomised to Copaxone, 198 continued Copaxone treatment in the open-label phase. Of the 238 patients initially randomised to placebo, 211 switched to Copaxone treatment in the open-label phase.
During the placebo-controlled period of up to three years, Copaxone delayed the progression from the first clinical event to clinically definite multiple sclerosis (CDMS) according to Poser criteria in a statistically significant and clinically meaningful manner, corresponding to a risk reduction of 45% (Hazard Ratio = 0.55; 95% CI [0.40; 0.77], p-value=0.0005). The proportion of patients who converted to CDMS was 43% for the placebo group and 25% in the Copaxone group.
The favourable effect of treatment with Copaxone over placebo was also demonstrated in two secondary MRI endpoints, i.e. number of new T2 lesions and T2 lesion volume.
Post-hoc subgroup analyses were performed in patients with various baseline characteristics to identify a population at high risk to develop the second attack. For subjects with baseline MRI with at least one T1 Gd-enhancing lesion and 9 or more T2 lesions, conversion to CDMS was evident for 50% of the placebo subjects vs. 28% of the Copaxone subjects in 2.4 years. For subjects with 9 or more T2 lesions at baseline, conversion to CDMS was evident for 45% of the placebo subjects vs. 26% on Copaxone in 2.4 years. However, the impact of early treatment with Copaxone on the long term evolution of the disease is unknown even in these high-risk subgroups as the study was mainly designed to assess the time to the second event. In any case, treatment should only be considered for patients classified at high risk.
The effect shown in the placebo-controlled phase was sustained in the long-term follow-up period of up to 5 years. The time progression from the first clinical event to CDMS was prolonged with earlier Copaxone treatment as compared to delayed treatment, reflecting a 41% risk reduction with earlier versus later treatment (Hazard Ratio = 0.59; 95% CI [0.44; 0.80], p-value=0.0005). The proportion of subjects in the Delayed Start group who progressed was higher (49.6%) compared to those in the Early Start group (32.9%).
A consistent effect in favour of early treatment over delayed treatment across time was shown for the annualised number of lesions over the entire study period in new T1 Gd-enhancing lesions (reduced by 54%; p<0.0001), new T2 lesions (reduced by 42%; p<0.0001) and new T1 hypointense lesions (reduced by 52%; p<0.0001). An effect in reductions in favour of early versus delayed treatment was also observed for the total number of new T1 Gd-enhancing lesions (reduced by 46%; p=0.001), T1 Gd-enhancing lesion volume (a mean difference of -0.06 ml; p<0.001), as well as the total number of new T1 hypointense lesions (reduced by 46%; p<0.001) measured over the entire study period.
No appreciable differences between the Early Start and Delayed Start cohorts were observed for either hypointense T1 lesion volume or brain atrophy over 5 years. However, analysis of brain atrophy at last observed value (adjusted to treatment exposure) showed a reduction in favour of early treatment with GA (the mean difference of percent change in brain volume was 0.28%; p=0.0209).

Clinical studies have been conducted to support the 40 mg/ml application.

The clinical data for 40 mg/ml application consists of a pivotal study (GALA, MS-GA-301).

- The GALA study was randomized, parallel-group study performed in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) injection 40 mg administered three times a week(TIW) compared to placebo in a double-blind design.

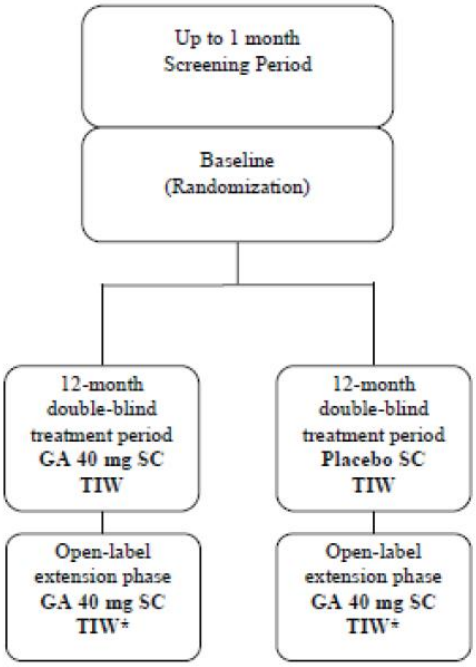
The GALA study evaluated the proposed product at the proposed regimen (40 mg/mL three times a week, i.e. 120 mg a week) over 12 months, with a 12-month open-label extension. This study was placebo controlled and did not include a comparison with the currently approved dosing regimen (20 mg/mL daily injection, i.e. 140 mg a week).

Pivotal study: GALA (MS-GA-301)

This was a multinational (20 countries), multicenter (136 sites), randomized, parallel-group study performed in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) injection 40 mg administered three times a week (TIW) compared to placebo in a double-blind design.

The study consisted of 3 phases:
-Screening phase: up to 1 month.
- Placebo-Controlled (PC) Phase: 12 months of GA 40 mg or matching placebo, administered TIW by sc injection.
- Open-Label (OL) Extension: All subjects were offered the opportunity to continue treatment with GA 40 mg administered TIW, until this dose strength would be commercially available for the treatment of RRMS subjects or until the development of this GA dose regimen would be stopped by the Sponsor.

Overall study design



*All subjects completing the double-blind PC phase were offered the opportunity to continue treatment with GA 40 mg administered three times a week (TIW), until this dose strength would be commercially available for the treatment of RRMS subjects or until the development of this GA dose regimen would be stopped by the Sponsor.

Patients experiencing a relapse were reconsented prior to restarting test medication.

Subjects were included in the study if all of the following criteria were met (main criteria only):

- Subjects must have a confirmed and documented multiple sclerosis (MS) diagnosis as defined by the Revised McDonald criteria [Ann Neurol 2005: 58:840-846], with a relapsing-remitting disease course.
- Subjects must be ambulatory with an Expanded Disability Status Scale (EDSS) score of 0-5.5 in both screening and baseline visits.
- Subjects must have experienced one of the following:
    - At least one documented relapse in the 12 months prior to screening, or
    - At least two documented relapses in the 24 months prior to screening, or
    - One documented relapse between 12 and 24 months prior to screening with at least one documented T1-gadolinium (Gd) enhancing lesion on magnetic resonance imaging (MRI) performed within 12 months prior to screening.
- Subjects had to be 18-55 years of age, inclusive.

Main Criteria for Exclusion: progressive forms of MS; use of experimental/investigational drugs, immunosuppressive agents or cytotoxic agents within the 6 months prior to screening; use of natalizumab or any other monoclonal antibodies, or cladribine within 2 years prior to screening; previous treatment with immunomodulators (including interferon β 1a and 1b, and intravenous [IV] immunoglobulin) within 2 months prior to screening; previous use of GA or any other glatiramoid; chronic (more than 30 consecutive days) systemic (IV, per os [PO] or intramuscular [IM]) corticosteroid treatment within 6 months prior to screening visit; Previous total body irradiation or total lymphoid irradiation; a known history of sensitivity to Gd, inability to successfully undergo MRI scanning, or known drug hypersensitivity to mannitol; clinically significant or unstable medical or surgical condition /-/ which may include hepatic, renal or metabolic diseases, systemic disease, acute infection, current malignancy or recent history (5 years) of malignancy, major psychiatric disorder, history of drug and/or alcohol abuse and allergies; endovascular treatment for chronic cerebrospinal venous insufficiency (CCSVI).

Both treatment groups were comparable with respect to baseline demographics, MS disease characteristics and MRI parameters. 97.6 % of the study population was caucasian, 67.9 % were females with a mean age of 37.6. Mean time from first symptoms was 7.7 years and the majority of subjects had 1 or 2 relapses in the 2 years prior to screening. Baseline EDSS score was approximately 2.7, which is realtively low on a scale of 0 to 10 (9 meaning patient confined to bed). There was slightly more patients with T1 gadolinium-enhanced lesions or T2 lesionsat baseline; this should be discussed.

Results

Approximately 1350 patients were planned to be enrolled, and to be randomized in a 2:1 ratio to the two treatment arms. The total number randomized was 1404 (943 on GA 40 mg TIW and 461 on placebo).

Randomisation was not stratified on any variables. 6.7% of patients in the placebo group and 8.9% in the GA group did not complete the placebo-controlled phase of the study.
The most common single reason for early discontinuation was withdrawal of consent; in 17 subjects (3.7%) in the placebo group and 34 subjects (3.6%) in the GA 40 mg TIW group. The second most common reason was due to AE in 6 subjects (1.3%) in the placebo group and 29 subjects (3.1%) in the GA 40 mg TIW group. One subject in the placebo group died during the PC phase of the study.
Primary Endpoint(s): The total number of confirmed relapses during the 12-month double-blind placebo-controlled treatment phase.
A relapse was defined as the appearance of one or more new neurological abnormalities or the reappearance of one or more previously observed neurological abnormalities lasting at least 48 hours and immediately preceded by an improving neurological state of at least 30 days from onset of previous relapse.
This criterion is different from the clinical definition of relapse: 'at least 24 hours duration of symptoms'. Since 'in-study' relapse definition had to be supported by an objective neurological evaluation (see next paragraph), a neurological deficit had to sustain long enough to eliminate pseudo-relapses.
An event was counted as a relapse only when the subject's symptoms were accompanied by observed objective neurological changes, consistent with at least one of the following:

- An increase of at least 0.5 in the EDSS score as compared to previous evaluation.
- An increase of one grade in the actual score of 2 or more of the 7 FS, as compared to previous evaluation.
- An increase of 2 grades in the actual score of one FS as compared to the previous evaluation.

Results of the principal analysis of the primary endpoint, the total number of confirmed relapses during the 12-month double-blind PC treatment phase, demonstrated a statistically significant treatment effect of GA 40 mg TIW over placebo: the risk ratio [95% confidence interval, CI] was 0.656 [0.539; 0.799], reflecting a 34.4% reduction in total number or relapses in the GA 40 mg TIW group ($p<0.0001$).

Secondary Endpoints:

1. *The cumulative number of new/enlarging T2 lesions at Months 6 and 12:* the analysis demonstrated a statistically significant treatment effect of GA 40 mg TIW over placebo; the risk ratio [95% CI] was 0.653 [0.546; 0.780], reflecting a 34.7% reduction in the cumulative number of new/enlarging T2 lesions in the GA 40 mg TIW group ($p<0.0001$).
2. *The cumulative number of enhancing lesions on T1-weighted images at Months 6 and 12:* the analysis demonstrated a statistically significant treatment effect of GA 40 mg TIW over placebo; the risk ratio [95% CI] was 0.552 [0.436; 0.699], reflecting a 44.8% reduction in the cumulative number of enhancing lesions on T1-weighted images in the GA 40 mg TIW group ($p<0.0001$).

3. *The percentage change in brain volume from baseline to Month 12 (indicative of brain atrophy):* the analysis did not demonstrate a statistically significant treatment effect of GA 40 mg TIW over placebo; the adjusted mean difference [95% CI] was -0.061 [-0.154; 0.033, p=0.2058] (p=0.2058).

Relapse-Related Exploratory Endpoints:

- Time to First Confirmed Relapse during the PC phase: a favorable effect for GA 40 mg TIW over placebo was demonstrated with a 39.4% reduction in the hazard for first relapse during the PC phase (p<0.0001).
- Proportion of Relapse-Free Subjects during the PC phase: a favorable effect for GA 40 mg TIW over placebo was demonstrated with almost a 2-fold increase in the odds of being relapse-free during the PC phase (p<0.0001).
- The Total Number of Severe Relapses defined as Confirmed Relapses Requiring Hospitalization and/or IV Steroids during the PC Phase: a favorable effect for GA 40 mg TIW over placebo was demonstrated with a 35.6% reduction in the total number of confirmed severe relapses during the PC phase (p<0.0001).

An analysis of the primary endpoint in patients with at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gadoliniumenhancing lesion.

Disability-Related Exploratory Endpoints, change in EDSS and AI scores: There was no appreciable difference between the GA 40 mg TIW and placebo treatment groups for the proportion of subjects with confirmed EDSS progression, or change from baseline to Month 12 in either EDSS score or AI (p≥0.2449).

FS and EDSS were assessed based on a slightly modified neurological examination than the one described by Kurtzke. The study employed Neurostatus, a standardized neurological examination and assessment of the Kurtzke EDSS to quantify disability in seven FS.

Anti-GA Antibodies, Peripheral Blood Lymphocytes Proliferation and Pharmacogenetic Ancillary studies were performed.

Safety

The overall incidence of AEs was higher in the GA 40 mg TIW group (72.1% [680 subjects]) compared to the placebo group (61.6% [284 subjects]). General disorders and administration site conditions were reported in 10.0% of the patients in the placebo group and 43.1 % in the GA 40mg TIW group. The most common AEs reported in the GA 40 mg TIW group were in the categories of injection site reactions (ISR) and immediate post injection reaction (IPIRs).

The most commonly reported AEs (other than ISR and IPIRs), reported by ≥2% of subjects in the GA 40 mg TIW group, and with an incidence higher than placebo by ≥1%, were (in no particular order): nasopharyngitis, influenza-like illness, respiratory tract infection viral, pyrexia, nausea and chills. Adverse events were higher in patients switching from placebo to active treatment in the open label phase (delayed start).

The AEs reported in this study by GA-treated subjects are consistent with the known AE profile of glatiramer acetate. However it is noted that cardiac disorders and vascular disorders occurred at a much greater incidence in the glatiramer group.

IV.4 Clinical safety

In support of the safety data in the proposed GA 40 mg/ml TIW SmPC, relevant observations are presented in this section. Safety analysis is focused on data from RRMS patients who participated in the GALA study in which placebo or GA 40 mg/ml was administered three times a week. Safety data for other doses and regimens, (GA 20 mg/ml a day and 40 mg//ml a day), derived from the completed studies GA/9006 and GA/9016 (FORTE), are presented within this document for comparison purposes. Thus, GA 40 mg/ml TIW is compared directly to placebo TIW, and indirectly to daily doses of GA 20/ml and 40 mg/ml.

Two cohorts were defined:

For the analysis of safety data, two cohorts were defined:

1. A double-blind (DB) phase cohort comprising four groups of subjects with RRMS
2. An open-label (OL) phase cohort comprising four groups of subjects with RRMS from the OL phase of study 9016 (FORTE) and study MS-GA-301 (GALA) (there was no OL phase in the 9006 study).

All subjects received GA 40 mg/ml (daily in study 9016 or TIW in study MS-GA-301) during the OL phase of their respective studies. These groups were designated as 'early start' (ES) if the subjects had received GA 40 mg/ml (either daily or TIW) during the DB phase, or 'delayed start' (DS) if subjects had received GA 20 mg/day or placebo TIW during the DB phase and had not started GA 40 mg/ml (either daily or TIW) until the OL phase.

Supportive studies

1. Proof of concept study (GA-9006)

This was a multi-center, randomized, double-blind parallel group study comparing a new higher dose formulation of glatiramer acetate (GA) 40mg to the 20mg formulation in RelapsingRemitting MS (RR-MS) patients.

Eligible subjects were equally randomized into one of the two treatment arms, either GA 20mg or GA 40mg. Both doses were administered subcutaneously, **once daily**, for treatment duration of **36 weeks**.

Efficacy

The total number of T1-Gd enhanced lesions measuered on the Intent-to-treat (ITT) cohort showed a 38% reduction in favor of GA 40mg as compared to GA 20mg in the cumulative number of Gd-enhancing lesions at months 7, 8 and 9 (p= 0.0898). Post-hoc analysis demonstrated that this advantage was apparent as early as 3 months following study randomization, showing a significant reduction of 52% in favor of the 40mg dose as compared to 20mg (p-value=0.0051).

Analyses of confirmed relapses were performed on the ITT cohort. The mean (±SD) number of confirmed relapses on-study was 0.52 ±0.59 for subjects on GA 20mg and 0.30 ±0.59 for subjects on GA 40mg. Mean Annualized number of confirmed relapses was 0.81±0.98 on 20mg as compared to 0.49±1.1 on 40mg

Safety
The overall incidence of Immediate Post injection Reactions (IPIR) on 40mg was 32.6% (mostly moderate) compared to 22.7% (mostly mild) on 20mg. All events resolved with no sequelae. This incidence is consistent with GA 20mg experience. The largest difference between the groups with regards to IPIR symptoms (flushing, palpitations, tachycardia, dyspnoea and chest pain) was in palpitations, 10.9% for subjects on GA 40mg compared to 2.3% for subjects on GA 20mg.

2. FORTE study, a Multinational, Multicenter, Randomized, Parallel-Group, Double-Blind Study to Compare the Efficacy, Tolerability and Safety of Glatiramer Acetate Injection 40 mg/ml to that of Glatiramer Acetate Injection 20 mg/ml Administered Once Daily by Subcutaneous Injection in Subjects with Relapsing Remitting Multiple Sclerosis (RRMS).
RRMS (McDonald criteria 2005) eligible subjects were equally randomized into one of the two treatment arms, either GA 40 mg or GA 20 mg administered subcutaneously, once daily, for treatment duration of up to 12 months, followed by an open-label (OL) phase of treatment with a daily injection of GA 40 mg for 12 months. The objectives of the study were to compare GA 40 mg to GA 20 mg for efficacy, as determined by the rate of confirmed relapses during the DB phase, as well as MRI-related parameters, tolerability, and safety. Scheduled visits at the sites for the DB phase were performed at screening, baseline, Months 1, 2, 3, 6, 9, 12 (end of DB phase), and Months 15, 18, 21, and 24 of the OL phase.
Of the 1155 subjects randomized to study treatment, 1024 subjects completed the DB phase and 1005 subjects (98.1%) continued treatment with GA 40 mg in the OL phase (482 subjects in the original GA 40 mg group and 523 subjects initially randomized to GA 20 mg).
Premature termination from the DB phase was reported for 52 subjects (8.9%) on GA 20 mg and 79 (13.9%) on GA 40 mg. The main reasons for termination were due to AE (GA 20 mg: 28/586 subjects [4.8%]; GA 40 mg: 51/569 [9.0%]) and consent withdrawal (GA 20 mg: 10/586 subjects [1.7%]; GA 40 mg: 12/569 [2.1%]). One subject died in a traffic accident and 5 subjects (0.4%) withdrew due to pregnancy. Following the results of the DB phase in which the primary endpoint was not reached, 891 subjects (88.7%) terminated due to Teva's decision to terminate the OL phase. Termination due to AE was reported for 30 subjects (3.0%) in the OL phase.
The study included 828 females (71.7%) and 327 males (28.3%). The mean (SD) age was 36.34 (8.99) years, and the majority of subjects were Caucasian (1100/1155 subjects; 95.2%). Mean (SD) BMI was 25.3 (5.5) kg/m2. The two treatment groups were comparable with respect to baseline demographic variables. Overall, the mean (SD) time from MS diagnosis was 6.6 (6.4) years, and the

mean (SD) number of exacerbations recorded in the 2 years prior to screening was 2.0 (1.0) years. Baseline MS disease characteristics and MRI measures were comparable for the two treatment groups.

Efficacy

The results of the principal analysis on relapse rate during the DB phase, using Quasi-Likelihood (over-dispersed) Poisson Regression, adjusted to the exposure in the DB phase, with prior 2-year relapse rate and baseline EDSS score and country as covariates did not demonstrate a statistically significant difference between the dose groups. The analysis yielded a RR (Rate Ratio) [95%CI] of the 40 mg dose over the 20 mg dose of: 1.0732 [0.8799, 1.3090]; p-value=0.4859.

Because the primary endpoint did not achieve significance, testing of the secondary endpoints did not ensure preservation of the overall type-I error.

Safety

The overall incidence (% of subjects) and incidence rate (IR) of adverse events (AEs) was comparable in both the GA 20 mg and GA 40 mg treatment groups (85.2%, IR=90.9 vs. 86.1%, IR=95.6, respectively) during the DB phase. A slightly higher incidence and IR were reported in the OL phase for subjects initially randomized to GA 20 mg who switched to GA 40 mg (55.4%; IR=97.9) compared to those who were on GA 40 mg in both phases (52.7%; IR=92.1).

The most common AEs in both study phases were related to injection site (IS) reactions, and symptoms associated with Immediate Post-Injection Reaction (IPIR).

Double-blind phase: generally, severe IS reactions were reported in similar incidence in both groups, except for IS mass which had 6 severe cases on GA 40 mg compared to one case on GA 20mg. IS mass was the leading cause for early termination due to AEs in the GA 40 mg group, 14 subjects in the GA 40 mg group (2.5%; IR=2.7) vs.2 subjects in the GA 20 mg group (0.3%; IR=0.4). One subject on GA 20 mg vs. 6 subjects on GA 40 mg had a change from baseline in QTcB greater than 60 msec during the DB phase. None of these changes reached a level of QTcB >500 msec. Fifty-one (9.0%; IR=9.9) subjects on GA 40 mg vs. 28 (4.8%; IR=5.1) subjects on GA 20 mg terminated the DB phase of the study due to AEs. AEs of IS reactions, IPIR symptoms, skin reactions and oedemas were the most common AEs leading to early termination.

Adverse events were clearly higher in patients switching from GA 20mg to GA 40mg in the open label phase (delayed start).

Note from the assessor

The overall incidence of subjects reporting AEs during the DB phase was lower in the TIW dose groups (both GA 40 mg and placebo) compared to the daily dose groups (GA 40 mg/day and GA 20 mg/day). A total of 72.1% subjects in the GA 40 mg TIW group and 61.6% subjects in the Placebo TIW group reported AEs, compared to 86.2% and 87.2% in the GA 20 mg/day and GA 40 mg/day groups, respectively.

General disorders and administration site conditions was the SOC with the highest incidence of subjects reporting AEs in all three GA dose groups, and this incidence was noticeably lower in the GA

40 mg TIW group (43.1%) compared to the daily dosage groups (63.2% in the GA 20 mg/day group and 67.2% in the GA 40 mg/day group); only 12.1% of subjects in the Placebo TIW group had AEs in this SOC; this difference relates to ISRs reported among the GA subjects and is consistent with the known AE profile of GA. ISR was the HLT with the highest incidence of subjects reporting AEs in all three GA dose groups, and this incidence was noticeably lower in the GA 40 mg TIW group (35.5%) compared to the daily dosage groups (59.2% in the GA 40 mg/day group and 57.5% in the GA 20 mg/day group). The second highest incidence was reported for the SOC "Infections and infestations" with a high incidence of upper respiratory tract infections in all groups (including placebo).
The incidence of subjects reporting AEs in all other SOCs and HLT was generally lower in the GA 40 mg TIW group compared to both the GA 20 mg/day group and the GA 40 mg/day group.

DB Phase Cohort: Summary of Adverse Events

Preferred Term/Grouped AEs n (%) of subjects	GA 9006 and GA 9016		MS-GA-301(GALA)	
	GA 20 mg/ml/day (N=630)	GA 40 mg/ml/day (N=615)	Placebo TIW (N=461)	GA 40 mg/ml TIW (N=943)
All AEs	543 (86.2)	536 (87.2)	284 (61.6)	680 (72.1)
Treatment-related AEs	424 (67.0)	440 (72.0)	71 (15.0)	450 (48.0)
Serious AEs	26 (4.1)	26 (4.2)	21 (4.6)	42 (4.5)
Deaths	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
Withdrawal due to AEs	31 (4.9)	57 (9.3)	6 (1.3)	29 (3.1)

The incidence of subjects who discontinued due to AEs in the DB phase groups was higher in the GA daily dose groups (9.3% and 4.9% subjects on GA 40 mg/day and GA 20 mg/day, respectively) compared to the GA 40 mg TIW (3.1% subjects) and placebo TIW (1.3% subjects) groups.
The only AEs which led to early discontinuation in ≥1% of subjects in the GA 40 mg/day, GA 20 mg/day or GA 40 mg TIW groups were: IS erythema (1.8%, 0.6% and 0.3%, respectively), IS pain (1.0%, 0.6% and 0.4%, respectively), and dyspnea (1.1%, 0.8% and 0.1%, respectively).
The most common AEs leading to early discontinuation in the DB phase cohort were ISR and/or IPIR symptoms. The most common AE, after ISRs and IPIRs which led to early termination was swelling face, which was reported by 0.8% subjects in the GA 40 mg/day group and 0.5% subjects in the GA 20 mg/day group.
No data was provided on the incidence of adverse events according to disease stage, concomitant use or other baseline characteristics.
A number of reported adverse events that could be linked to the administration of a higher dose such as:increased incidence immediate post-injection reactions (IPIR) and anaphylactic reactions

- increased risk of QTc prolongation and cardiovascular events that should be differentiated from IPIR
- drug induced liver injury
- increased incidence of infections, esentially for the respiratory tract

IV.5 Pharmacovigilance system (DDPS)

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

IV.6 Safety Management Program

SMP protocols for 20 and 40 mg/ml products are submitted.