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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

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ABSTRACT

Background: The efficacy and safety of glatiramer acetate (GA) 20 mg/mL once-daily subcutaneous injections (GA20) in relapsing-remitting multiple sclerosis (RRMS) is well-established. However, injection-related adverse events (IRAEs) may impede treatment adherence and tolerability. GA 40 mg/mL three-times weekly (GA40) also has a favorable efficacy and safety profile.
Objective: To evaluate the safety, tolerability, and patient experience when converting from GA20 to GA40.
Methods/trial design: GLACIER was an open-label, randomized, parallel-group trial conducted at 31 sites in the US between June 2013 and December 2013. Stable RRMS patients on GA20 were randomized in a 1:1 ratio to continue with GA20 or convert to GA40. The adjusted mean annualized rate of IRAEs was the primary endpoint for this study. Additionally, the severity of IRAEs, rate of injection-site reactions (ISRs), and patient-reported MS impact and treatment satisfaction were compared for the two treatment groups over the 4-month core study.
Results: A total of 209 patients were randomized to convert to GA40 ($n=108$) or continue with GA20 ($n=101$). The adjusted mean annualized rate of IRAEs was reduced by 50% with GA40 (35.3 events per year; $n=108$) versus GA20 (70.4 events per year; $n=101$) (risk ratio (RR)=0.50; 95% confidence interval [CI]=0.34–0.74; $p=0.0006$). There was a 60% reduction in the rate of moderate/severe events (GA40 ($n=108$): 0.9 events per year versus GA20 ($n=101$): 2.2 events per year; RR=0.40; $p=0.0021$). Perception of treatment convenience improved for GA40-treated patients soon after converting and was sustained.
Conclusions: The GLACIER study demonstrates a favorable IRAE and convenience profile of GA40 for RRMS patients.
Trial registration: NCT01874145 available at clinicaltrial.gov.

1. Introduction

Disease-modifying therapies (DMTs) that reduce the frequency of relapses, reduce accumulation of disability, and control symptoms have improved the care of patients with relapsing-remitting multiple sclerosis (RRMS) (Damal et al., 2013; Compston and Coles, 2002). Glatiramer acetate (GA), a first-line therapy approved for the treatment of RRMS (TEVA Neuroscience, Inc. 2014), has a well-characterized long-term safety profile (TEVA Neuroscience, Inc. 2014; Boster et al., 2011), with more than 2 million patient-years of overall exposure to GA 20 mg/mL administered once daily by subcutaneous injection (GA20) (data on file), and reduces the frequency of relapses and magnetic resonance imaging (MRI) disease activity (Johnson et al., 1995; Martinelli Boneschi et al.,

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2003; Comi et al., 2001; Bornstein et al., 1987).

Several first-line treatment regimens for RRMS require long-term, frequent injection of the drug, making adherence a challenge for many patients despite satisfactory efficacy (Verdun di Cantogno et al., 2011; Devonshire et al., 2011). Factors contributing to non-adherence and reduced tolerability in MS treatment include problems with injecting, perceived lack of efficacy, and perhaps most importantly, the high incidence of injection-related adverse events (IRAEs) (Devonshire et al., 2011; Treadaway et al., 2009; Costello et al., 2008). IRAEs associated with injectable DMTs and GA include systemic immediate post-injection reactions (IPIRs) such as flushing and anxiety and, more often, local injection-site reactions (ISRs), such as pain and redness (TEVA Neuroscience, Inc. 2014). More severe ISRs, such as lipoatrophy and skin necrosis, occur less frequently (Costello et al., 2008). Modified treatment regimens – alternative dosages and low-frequency administration schedules – have the potential to reduce the rate and severity of IRAEs. Therefore, modifying the treatment regimen of drugs with proven, long-term efficacy can result in better adherence and tolerability while maintaining efficacy and improving treatment convenience and patient experience (Remington et al., 2013; Tan et al., 2011). The value of such alternative regimens is enhanced given the importance of treatment adherence in ensuring optimal clinical outcomes (Tan et al., 2011; Al-Sabbagh et al., 2008).

In 2014, based largely on the results of the Glatiramer Acetate Low-frequency Administration (GALA) study, GA 40 mg/mL administered three-times weekly by subcutaneous injection (GA40) was approved for the treatment of RRMS by regulatory authorities in an increasing number of countries worldwide. The low-frequency GA40 was shown to have favorable efficacy and safety profiles (Khan et al., 2013).

Previous GA40 trials only enrolled patients who were naïve to GA treatment and did not examine those converting from GA20 to GA40. The GLACIER (GLatiramer Acetate low frequenCy safety and patIent ExpeRience) study was performed to assess the safety and tolerability of GA40 compared with GA20 in clinically stable patients who had been treated continuously with GA20 for a minimum of 6 months before screening. This study provides insight into whether GA40 provides improved safety, tolerability, and patient experience compared with the established GA20 regimen.

2. Materials and methods

2.1. Study design and patients

The GLACIER study was an open-label, randomized, parallel-group study conducted at 31 sites in the United States between June 2013 and December 2013. Investigators were neurologists, and sites consisted of individual and group neurology practices, neurology and MS research centers, and independent clinic trial facilities. All institutional review boards or ethics committees of the participating centers approved the protocol, and all patients gave written informed consent before any study-related procedures were performed.

Key eligibility criteria required patients to be least 18 years of age, with a confirmed and documented RRMS diagnosis (according to the revised McDonald criteria (Polman et al., 2011)) and an Expanded Disability Status Scale (EDSS) score of ≤ 5.5 at screening and baseline visits. All patients were required to be on continuous GA20 treatment for ≥ 6 months before screening and to be neurologically stable and relapse-free for ≥ 60 days before randomization.

Patients with progressive forms of MS, or those with neuromyelitis optica, were excluded. Other exclusion criteria included treatment with experimental or investigational drugs; concomitant use of other MS disease-modifying drugs; chronic (> 30 days) systemic corticosteroid treatment within 6 months of screening; and prior use of mitoxantrone, cladribine, alemtuzumab, rituximab, or natalizumab.

At the baseline visit, eligible patients were randomized in a 1:1 ratio to either continue with GA20 or convert to GA40. The computerized randomization sequence was generated and maintained by the Clinical Supply Chain department at Teva Pharmaceuticals (Netanya, Israel), and randomization was conducted centrally using the Interactive Response Technology system. Patients were randomized according to the randomization scheme of constrained blocks by site, and treatment group assignment was not biased by patient or trial center preferences. Investigators and participants were not blinded or masked to the open-label treatment assignment. Patients were treated with either a single-use, pre-filled syringe containing GA20 or GA40 (Teva Pharmaceutical Industries) in a 1-mL suspension of 40 mg of mannitol USP/Ph.Eur dissolved in water. Five scheduled site visits occurred during the core phase at months −1 (screening), 0 (baseline), 1, 2, and 4 (termination). Eligible patients from both treatment arms who completed the core phase were offered the opportunity to participate in an extension phase, during which they would receive GA40 treatment.

2.2. Procedures

The primary endpoint was the rate of IRAEs in each treatment arm. Secondary endpoints included the rate of ISRs, patient-reported impact of MS on physical and psychological well-being using the Multiple Sclerosis Impact Scale-29 (MSIS-29) questionnaire, and patient perceptions of convenience and overall satisfaction using subscales of the Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9). Additional endpoints included baseline patient expectations for efficacy, safety, and convenience of GA40 compared with GA20.

Assessments of IRAEs were performed throughout the study based on the patient's diary card recordings of occurrence and severity of IRAEs. IRAEs included all local ISRs or symptoms or events related to IPIRs, such as flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, or urticaria. Severity was defined by the patient as mild if the IRAE is ‘easily tolerated,’ moderate if the IRAE ‘interferes with normal daily activity’, or severe if the IRAE ‘prevents normal daily activity’.

Study drug compliance was evaluated during each visit after the initial dispensation of the study drug, and study drug accountability records were completed. Compliance was calculated as a percentage by dividing the number of used syringes by the number of total syringes expected to be used, multiplied by 100. The incidence of patients in each arm of the study with $\geq 75\%$ overall compliance to the study drug was an exploratory trial outcome.

The MSIS-29 questionnaire and TSQM-9 were performed at baseline and Months 1, 2, and 4. The validated, 29-item MSIS-29 questionnaire was used to assess patient-reported impact of MS on physical well-being and psychological well-being. Responses were scored using a five-point Likert scale range, with higher aggregate scores corresponding to greater impact on well-being. The validated TSQM-9 was used to assess patient-reported perceptions of convenience (items 4–6) and overall satisfaction (items 1–3), with higher scores representing more positive perceptions.

Patients' expectations of convenience were assessed at baseline using a study-specific questionnaire, in which patients reported whether they expected GA40 to be less, equally, or more convenient compared with GA20. Similarly, patients reported whether they expected GA40 to be less, equally, or more safe, as well as effective, compared with GA20.

Safety assessments included adverse events (AEs), vital signs, electrocardiographic (ECG) measurements, and standard clinical