Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMETHODS. Supplemental Methods

Study Steering Committee

- Jeffrey Cohen MD (Chair), Mellen Center for Multiple sclerosis Treatment and Research, Cleveland Clinic, Cleveland, USA
- Frederik Barkhof MD (Director, Image Analysis Centre), Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, Netherlands
- Anna Belova MD, Research Institute of Traumatology and Orthopaedy, Functional Diagnostics, Nizhniy Novgorod, Russia Federation
- Krzysztof Selmaj MD, Neurology Center Lodz, Lodz, Poland
- Christian Wolf, Lycalis sprl, Brussels, Belgium

Data and Safety Monitoring Board

- Gavin Giovannoni MD (Chair), Centre for Neuroscience and Trauma, Barts and The London Medical School, London, UK
- Ernst Wilhelm Radü MD, Medical Image Analysis Center (MIAC), Basel, Switzerland
- Andreas Völp PhD, Psy Consult Scientific Services, Frankfurt, Germany

Study Sites and Principal Investigators

Belarus
Yuri Vladimirovich Alekseenko, Health Care Institution:Vitebsk Regional Clinical Hospital, Elena Ivanovna Mikhailova, Gomel Regional Clinical Hospital, Sergey Demyanovich Kulesh, Grodno Regional Clinical Hospital, Sergey Alexeevich Likhachev, State Institution: Republican Research and Clinical Centre of Neurology and Neurosurgery, Galina Ivanovna Naumova Health Care Institution: Vitebsk Regional Diagnostic Centre, Vladimir Vladimirovich Ponomarev, Minsk City Clinical Hospital #5, Alexander Sergyeevich Fedulau, Health Care Institution: 9th City Clinical Hospital

Bosnia and Herzegovina
Sanja Grgic, Clinical Center Banja Luka, Enra Suljic, Clinical Center of University of Sarajevo, Osman Sinanovic, Tuzla University Hospital Center

Bulgaria
Nadezhda Deleva, Multiprofile Hospital for Active Treatment "Sveta Marina", Varna, Lyubomir Haralanov, Multiprofile Hospital for Active Treatment “National Cardiology Hospital”, Sofia, Ivan Milanov, Multiprofile Hospital for Active Treatment of Neurology and Psychiatry "Sveti Naum", Sofia, Boyko Stamenov, University Multiprofile Hospital for Active Treatment "Dr. Georgi Stranski", Pleven, Ivaylo Tarnev, University Multiprofile Hospital for Active Treatment "Aleksandrovska", Sofia, Maria Manova, University Multiprofile Hospital for Active Treatment "Sveti Georgi", Plovdiv, Plamen Tsvetanov, Military Medical Academy – Multiprofile Hospital for Active Treatment, Pleven, Krasimir Genov, Military Medical Academy - Multiprofile Hospital for Active Treatment, Sofia

Czech Republic
Petr Kanovsky, University Hospital Olomouc, Michal Dufek, St Anne´s University Hospital Brno, Olga Zapletalova, University Hospital Ostrava, Marta Vachova, Hospital Teplice, o.z., Michaela Tyblova, 1st Faculty of Medicine and General University Hospital, Eva Medova, University Hospital Kralovske Vinohrady, Pavel Stourac, University Hospital Brno

Croatia
Anton Vladić, Clinical Hospital Sveti Duh, Marija Bošnjak Pašić, CHC Zagreb, Silva Butković Soldo, CHC Osijek, Vanja Basic Kes, Clinical Hospital 'Sestre Milosrdnice'

Estonia
Katrin Gross-Paju, West Tallinn Central Hospital, Georgi Zjablov, East Viru Central Hospital

Germany
Matthias Schwab, Medical University of Jena

Georgia
Maia Beridze, DEKA Ltd., Ann Gauarashvili, Clinic "Curatio", JSC, Marina Janelidze, S.Khechinashvili University Clinic of Tbilisi State Medical University, Roman Shakarishvili P.Sarajishvili Institute of Neurology, Alexander Tsiskaridze, Medical Center CITO

Italy
Rocco Totaro, San Salvatore Hospital of L'Aquila, Giacomo Lus, University Hospital Polyclinic of the Second University of Naples

Mexico
Alejandra Gonzalez Duarte Briseño, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Laura Ordoñez Boschetti, Consultorio de Medicina Especializada del Sector Privado, Guillermo Punzo Bravo, Clínica Neurológica de Morelia, Luis Roberto Partida Medina, Centro De Investigación Médico Biológica y Terapia Avanzada (CIMBYTA)

Moldova
Mihail Gavriliuc, Institute of Neurology and Neurosurgery, Stanislav Groppa, Emergency Hospital, University of Continuous Medical and Pharmacy Education, Tamara Birsan, "Sf. Arhanghel Mihail" Municipal Clinical Hospital, Olesea Odainic, Institute of Neurology and Neurosurgery

Poland
Krystyna Pierzchala, Non-public Health Care Facility Wladyslaw Pierzchala, Grzegorz Opala, Private Medical Practice, Ewa Motta, Dendryt Medical Center, Andrzej Tutaj, Provincial Specialist Hospital, Ryszard Zimnoch, J. Sniadecki Provincial Hospital Bialystok, Janusz Zbrojkiewicz, NEURO MEDIC Janusz Zbrojkiewicz Non-Public Healthcare Facility, Jerzy Kotowicz, Healthcare Facility Outpatient Clinic of the Medical Professionals Association, Krzysztof Selmaj, Neurology Center Lodz, Jan Ilkowski, Neuro-Kard Non-Public Healthcare Facility, Ilkowski and Partners, Medical Doctors Partnership Poznan, Jerzy Kamienowski, Materia Medica Non-public Health Care Facility, Zbigniew Stelmasiak, Private Specialist Neurologic Clinic

Romania
Ana Varvara Campeanu, Neurology Clinic of the Fundeni Clinical Institute, Ioan Buraga, Colentina Clinical Hospital Bucharest, Adina Maria Roceanu, "Dr Roceanu Adina Maria" Medical Private Practice, Sorin Tuta, Quantum Medical Center, Cristina Elena Mitu, Quantum Medical Center, Lacramioara Perju-Dumbrava, Cluj Napoca Emergency Clinical County Hospital

Russia
Natalia Maslova, Smolensk State Medical Academy, Igor Stolyarov, N.P. Bechtereva Institute of the Human Brain of the Russian Academy of Sciences, Valentina Alifirova, Siberian State

Medical University, Rim Magzhanov, Kuvatov Republican Clinical Hospital, Irina Poverennova, Samara Kalinin Regional Clinical Hospital, Stella Sivertseva, Medical Sanitary Unit "Nephtyanik", Fatima Stuchevskaya, Municipal Multi-Specialty Hospital #2, Eduard Yakupov, Vashe Zdorovye Research Medical Center Ltd., Anna Belova, City Clinical Hospital #3, Irina Sokolova, Municipal Treatment and Prevention Institution “City Hospital #33”, Alexander Skoromets, First Pavlov State Medical University of St. Petersburg, Larisa Volkova, Sverdlovsk Regional Clinical Hospital #1, Nadezhda Korotkevich Kemerovo Regional Clinical Hospital, Gennadiy Mishin, City Hospital #2, Nadezhda Malkova, Siberian District Medical Center, Alexander Fedyanin, Altaj Regional Clinical Hopital, Zhanna Chephranova, State Medical Institution: St. Joseph Belgorod Regional Hospital, Olga Patrusheva, Arkhangelsk Regional Clinical Hospital, Evgeny Evdoshenko, City Clinical Hospital #31, Saint-Petersburg, Lesya Chichanovskaya, Tver Regional Clinical Hospital, Olga Doronina, LLC City Neurological Center “Sibneuromed”, Galina Loginova, Penza Regional Clinical Hospital n. a. N. N. Burdenko, Elena Pasechnik, Kaluga Regional Hospital, Elena Rybina, Lipetsk Regional Clinical Hospital, Center for Multiple Sclerosis, Mikhail Sherman, Outpatient Clinic #2 under Kirov City Hospital #1, Andrey Yurchenko, Bryansk Regional Hospital # 1, Igor Zavalishin, Research Center for Neurology

Serbia
Evica Dinčić, Military Medical Academy, Čongor Nadj, Clinical Centre Vojvodina, Tatjana Boskovic- Matic, Clinical Centre Kragujevac

South Africa
Franclo Henning, Tygerberg Hospital, Chris Francois Retief, Wilgers Hospital, Judy Green, St Augustine Medical Mews

Ukraine
Tetiana Kobys, Kyiv City Clinical Hospital #4, Svitlana Pogorila, Central Hospital of Military and Medical Department under the Security Service of Ukraine, Tetiana M. Muratova, Center for Reconstructive and Restorative Medicine (University Clinic) within Odesa State Medical University, Liudmyla Dziak, Dnipropetrovsk Medical Academy under the Ministry of Health of Ukraine, Serhiy Kareta, Public Treatment and Prophylaxis Institution: Chernihiv Regional Hospital, Volodymyr Pryshchepa, O.F. Herbachevskyi Regional Clinical Hospital within Zhytomyr Regional Council, Tetyana Litovchenko, Kharkiv Medical Academy of Postgraduate Education, Yanosh Sanotskyy, Lviv Regional Clinical Hospital, Valeriy Pashkovskyy, Bukovyna State Medical University, Olena Statinova, Donetsk M. Gorky National Medical University, Sergii Moskovko, Vinnytsia M.I. Pyrohov National Medical University, Marta Khavunka, Public City Clinical Hospital #5, Andriy Aleksyeyev, Public Treatment and Prophylaxis Institution: Donetsk Central City Hospital #17, Olena Tovazhnyanska, Kharkiv National Medical University, Nataliya Lytvynenko, State Higher Educational Institution of Ukraine: Ukrainian Medical Academy of Dentistry, Volodymyr Smolanka Regional Clinical Center for Neurosurgery and Neurology, Valerii Shkolnyk, Dnipropetrovsk Medical Academy under the Ministry of Health of Ukraine, Olga Shulga, Volyn Regional Clinical Hospital, Valentyna Drobotenko, Cherkassy Regional Hospital, Galyna Chmyr, Ivano-Frankivsk Regional Clinical Hospital, Kostyantyn Loganovskyi, State Institution: National Research Center of Radiation Medicine of the National Academy of Medical Sciences of Ukraine, Tetyana Nehrych, Lviv Danylo Halytsky National Medical University, Volodymyr Shepotinnyk, Public Medical Institution: I.K. Matsuk Mariupol City Hospital #4

United Kingdom

Brendan McLean, Royal Cornwall Hospital, Clive Hawkins, University Hospital of North Staffordshire, Jason Ramtahal, Torbay Hospital, Basil Sharrack, Royal Hallamshire Hospital

United States
Gary Birnhaum, Minneapolis Clinic of Neurology, Jeffrey Cohen, Cleveland Clinic, Concetta Forchetti, Alexian Brothers Neurosciences Institute, Gaby Thai, University of California in Irvine, Liliana Montoya, Neurostudies, Inc., Pari Nikpey, Charlottesville Medical Research, Hermanth Rao, The Neurological Institute, PA, Richard Singer, Neurology Clinical Research, Inc., Jeffrey Gross, Associated Neurologists of Southern Connecticut, P.C., Lawrence Goldstick, Neurology Specialists, Samuel Hunter, Brain and Nerve Neurology, Advanced Neurosciences Institute, Elizabeth Zarate-Rowell, Diligent Clinical Trials, Inc., Robert Tillett, Norton Neurology Services, MS Center, Kenneth Carnes, Raleigh Neurology Associates

MRI Protocol

MRI procedures

A standardized MRI protocol was developed by the Image Analysis Center (IAC) in Amsterdam in collaboration with BioClinica, who were responsible for site selection, quality control, data storage, and communication with sites. The IAC performed the visual and quantitative image analysis. An MRI manual was prepared to instruct sites how to perform scans, anonymize them, and transfer image data for central reading. If necessary, repeat scans were requested. Before a site was permitted to screen trial patients, they were required to successfully perform a test scan with use of image equipment with minimum field strength of 1.0 Tesla.

The scanning protocol included T_1-weighted spin-echo scans (TR 400-700ms, TE 5-25ms, 2 excitations) before gadolinium administration; dual-echo T_2-weighted scans (TR 2000-3000ms, TE 20-40ms & 70-120ms, 1 excitation) and T_1-weighted scans (TR 400-700ms, TE 5-25ms, 2 excitations) after gadolinium administration. Axial slices oriented according to internal landmarks were prescribed with 3 mm slice thickness and 1 mm in-plane resolution. Gadolinium was administered as an intravenous infusion of 0.1 mmol/kg. To minimize the risk of nephrogenic systemic fibrosis, the use of gadolinium contrast agents with a cyclical molecular structure was recommended, and a normal estimated glomerular filtration rate was required.

Planning of MRI scans

MRI time-points included screening, baseline, and months 7, 8, and 9. The screening MRI scan had to be taken when the patient was neurologically stable and after the wash-out period for the respective multiple sclerosis treatments as detailed in the exclusion criteria had passed. If a patient had a historical MRI performed within 3 months of signing informed consent for the trial, on which $\geq$1 gadolinium-enhancing lesion are present, this scan could be used for eligibility and no additional screening MRI was needed for that patient. If an otherwise eligible patient had no gadolinium-enhancing lesion at the first screening MRI, the patient could be kept in screening and a repeat scan performed at least 30 days after the first screening MRI. If this scan also did not reveal a gadolinium-enhancing lesion, MRI could be repeated once more at least 30 days later. If none of these three scans revealed any gadolinium-enhancing lesions, the patient was considered a screen failure and not randomized.

During the double-blind trial, the baseline MRI scan could be done up to two days before the other baseline assessments. Subsequent MRI scans could be obtained two days before or after the other assessments of the corresponding visit, as long as the MRI scan was taken within the overall window of ±7 days of the scheduled visit. In the event a scan was missed or determined to be of inadequate quality, a repeat scan was performed as soon as possible.

In the event of a relapse, it was attempted to have the trial-related efficacy MRI scans obtained before steroid therapy was initiated. If this was not possible, the MRI scan was taken 14 days or more after the last steroid dose. If the delayed MRI scan occurred within the window of the next planned MRI scan, this next MRI scan was omitted to avoid two scans being taken at around the same time.

MRI safety assessments

Each MRI scan performed for the study was reviewed for safety by a local neuroradiologist. The investigator was only notified in case the local neuroradiologist or the central MRI reader detected unexpected, MS-unrelated findings on the MRI scan. In addition, automated flags were generated by the central readers at IAC for all MRI scans that demonstrated > 15 gadolinium-enhancing lesions and notification was sent to the investigator. Otherwise, the site staff remained blinded regarding the MRI scanning results.

MRI efficacy assessments

Identification of gadolinium-enhancing lesions on T_1-weighted images was done by means of a double-blind read by two independent experienced readers, trained according to the standard-operating procedures of the IAC. In case of discrepancy, a third reader adjudicated and made a final decision. The readers also marked hyperintense lesions on T_2-weighted images and hypointense lesions on post-gadolinium T_1-weighted images. On each follow-up scan, the number of total and new gadolinium-enhancing lesions on T_1-weighted images and new hyperintense lesions on T_2-weighted lesions (determined using registration and subtraction) were assessed. At baseline and month 9, the volumes of hyperintense lesions on T_2-weighted images and hypointense lesions on T_1-weighted images were quantified by trained technicians, again using subtraction images for the follow-up time-point. Normalized brain volume at baseline and percentage brain volume change at month 9 were determined using SIENA(X).

Sample Size Estimation

Based on the European/Canadian Glatiramer Acetate Trial,[1] we estimated that the average number of gadolinium-enhancing lesions during months 7–9 would be 1.75 times higher with placebo treatment compared to GA treatment. The upper limit of the equivalence margin was set at 1.375, representing 50% of the treatment effect versus placebo observed in the Europeans/Canadian Glatiramer Acetate Trial. The lower limit of the equivalence margin was set at 0.727 to create a symmetrical margin in the log-scale. According to the results of Comi et al.[1] and Tubridi et al.,[2] the standard deviation of the endpoint (log(m7,G) + log(m8,G) + log(m9,G))/3 and (log(m7,C) + log(m8,C) + log(m9,C))/3 will be approximately 1.1, multiple correlation between the endpoint and the logarithms of the screening and baseline counts is expected to be 0.3. Simulations then showed that a study with 300 evaluable subjects in the GTR and in the GA arms will have approximately 92% power to show equivalence. A placebo group of 70 evaluable subjects will lead to approximately 98% power to show assay sensitivity. The probability (power) of showing both assay sensitivity and equivalence will be approximately 90%.

References

1. Comi G, Filippi M, Wolinsky JS, the European/Canadian Glatiramer Acetate Study Group. 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. *Ann Neurol.* 2001;49(3):290-297.
2. Tubridy N, Ader HJ, Barkhof F, Thompson AJ, Miller DH. 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.* 1998;64(1):50-55.

Washout Periods for MS Disease Treatments Prior to Screening

1 year:
- mitoxantrone (participant was excluded if mitoxantrone cumulative lifetime dose was above 100 mg/m^2

6 months:
- fingolimod
- immunoglobulins and/or monoclonal antibodies (including natalizumab)
- leflunomide
- putative MS treatments
- chronic oral or injected corticosteroids or injected ACTH (more than 30 consecutive days)

3 months:
- azathioprine
- methotrexate
- plasma exchange
- any other experimental intervention, in particular experimental drugs

1 month:
- interferon-β1a or 1b
- short-term oral or injectable corticosteroids for treatment of a relapse
- short-term ACTH

eTable 1: Major protocol violations

End Point	GTR (n=353)	GA (n=357)	Placebo (n=84)
At least one major protocol violation #	13 (3.7%)	6 (1.7%)	2 (2.4%)
Missing more than 7 consecutive injections during the first 7 months of double-blind treatment	11 (3.1%)	5 (1.4%)	1 (1.2%)
Not receiving the randomized treatment during the first 7 months	0 (0.0%)	1 (0.3%)	0 (0.0%)
Subject not having >=1 and <=5 or <=15 T1-GdE lesions at randomization	2 (0.6%)	0 (0.0%)	1 (1.2%)
Received disallowed concomitant medications during the first 7 months of double-blind treatment	0 (0.0%)	1 (0.3%)	0 (0.0%)

Subjects could have more than one major violation

eTable 2: Post-hoc analysis of total number of new gadolinium-enhancing lesions during months 7–9 on T_1-weighted images

End Point	GTR (n=353)	GA (n=357)	Placebo (n=84)
Study sensitivity: mean (95% CI) §	0.39 (0.29 to 0.52)	0.36 (0.27 to 0.48)	0.74 (0.52 to 1.06)
(GTR+GA)/placebo ratio (95%CI)	0.505 (0.384 to 0.665)		
Equivalence: mean (95% CI) ¥	0.41 (0.31 to 0.54)	0.38 (0.29 to 0.50)	
GTR/GA ratio (95% CI)	1.086 (0.880 to 1.340)		

§ Estimates represent total lesions during months 7–9 and were derived from the random effects generalized linear model with a negative binomial distribution and logarithmic link function, including all three treatment groups.

¥ Estimates represent total lesions during months 7–9 and were derived from the random effects generalized linear model with a negative binomial distribution and logarithmic link function, including the GTR and GA treatment groups.

eTable 3: Adverse events reported for ≥1% of patients in the GTR or GA Groups or for more than two patients in the placebo group summarized by MedDRA System Organ Class and Preferred Term (Safety Set)

Events classified by System Organ Class Preferred Term – no. (%) of patients	GTR (n=353)	GA (n=357)	Placebo (n=84)
Any event	**180 (51.0%)**	**194 (54.3%)**	**47 (56.0%)**
General disorders and administration site conditions	**107 (30.3%)**	**115 (32.2%)**	**17 (20.2%)**
Injection site reaction	58 (16.4%)	62 (17.4%)	6 (7.1%)
Immediate post-injection reaction	24 (6.8%)	18 (5.0%)	0 (0.0%)
Injection site swelling	14 (4.0%)	12 (3.4%)	3 (3.6%)
Injection site pain	11 (3.1%)	13 (3.6%)	1 (1.2%)
Injection site erythema	8 (2.3%)	7 (2.0%)	0 (0.0%)
Injection site pruritus	8 (2.3%)	5 (1.4%)	0 (0.0%)
Pyrexia	6 (1.7%)	6 (1.7%)	2 (2.4%)
Asthenia	5 (1.4%)	5 (1.4%)	2 (2.4%)
Influenza like illness	1 (0.3%)	8 (2.2%)	1 (1.2%)
Injection site haematoma	1 (0.3%)	0 (0.0%)	3 (3.6%)
Injection site bruising	0 (0.0%)	0 (0.0%)	3 (3.6%)
Infections and infestations	**46 (13.0%)**	**67 (18.8%)**	**20 (23.8%)**
Nasopharyngitis	13 (3.7%)	23 (6.4%)	6 (7.1%)
Influenza	6 (1.7%)	5 (1.4%)	2 (2.4%)
Upper respiratory tract infection	6 (1.7%)	6 (1.7%)	3 (3.6%)
Bronchitis	5 (1.4%)	5 (1.4%)	0 (0.0%)
Respiratory tract infection viral	5 (1.4%)	3 (0.8%)	2 (2.4%)
Respiratory tract infection	2 (0.6%)	4 (1.1%)	4 (4.8%)
Urinary tract infection	2 (0.6%)	4 (1.1%)	0 (0.0%)
Nervous system disorders	**36 (10.2%)**	**43 (12.0%)**	**13 (15.5%)**
Headache	16 (4.5%)	12 (3.4%)	7 (8.3%)
Multiple sclerosis relapse	4 (1.1%)	6 (1.7%)	0 (0.0%)
Dizziness	2 (0.6%)	7 (2.0%)	0 (0.0%)
Paraesthesia	2 (0.6%)	4 (1.1%)	2 (2.4%)
Gastrointestinal disorders	**15 (4.2%)**	**12 (3.4%)**	**4 (4.8%)**
Nausea	5 (1.4%)	3 (0.8%)	0 (0.0%)
Skin and subcutaneous tissue disorders	**15 (4.2%)**	**10 (2.8%)**	**0 (0.0%)**
Rash	4 (1.1%)	2 (0.6%)	0 (0.0%)
Urticaria	4 (1.1%)	2 (0.6%)	0 (0.0%)

GA = brand glatiramer acetate, GTR = generic glatiramer acetate

eTable 3: Continued

Events classified by System Organ Class Preferred Term – no. (%) of patients	GTR * (n=353)	GA * (n=357)	Placebo (n=84)
Psychiatric disorders	**14 (4.0%)**	**17 (4.8%)**	**1 (1.2%)**
Depression	6 (1.7%)	7 (2.0%)	0 (0.0%)
Anxiety	1 (0.3%)	4 (1.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	**12 (3.4%)**	**18 (5.0%)**	**8 (9.5%)**
Back pain	2 (0.6%)	5 (1.4%)	2 (2.4%)
Arthralgia	1 (0.3%)	5 (1.4%)	2 (2.4%)
Respiratory, thoracic and mediastinal disorders	**11 (3.1%)**	**16 (4.5%)**	**0 (0.0%)**
Dyspnoea	3 (0.8%)	4 (1.1%)	0 (0.0%)
Cough	2 (0.6%)	4 (1.1%)	0 (0.0%)
Blood and lymphatic system disorders	**9 (2.5%)**	**6 (1.7%)**	**2 (2.4%)**
Lymphadenopathy	2 (0.6%)	4 (1.1%)	0 (0.0%)
Eye disorders	**9 (2.5%)**	**5 (1.4%)**	**0 (0.0%)**
Vascular disorders	**7 (2.0%)**	**8 (2.2%)**	**3 (3.6%)**
Hypertension	4 (1.1%)	5 (1.4%)	2 (2.4%)
Injury, poisoning and procedural complications	**6 (1.7%)**	**9 (2.5%)**	**4 (4.8%)**
Cardiac disorders	**5 (1.4%)**	**4 (1.1%)**	**1 (1.2%)**
Tachycardia	4 (1.1%)	3 (0.8%)	0 (0.0%)
Metabolism and nutrition disorders	**5 (1.4%)**	**4 (1.1%)**	**3 (3.6%)**
Hypercholesterolaemia	4 (1.1%)	3 (0.8%)	1 (1.2%)
Ear and labyrinth disorders	**4 (1.1%)**	**5 (1.4%)**	**0 (0.0%)**
Immune system disorders	**4 (1.1%)**	**1 (0.3%)**	**0 (0.0%)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (1.1%)**	**3 (0.8%)**	**1 (1.2%)**
Reproductive system and breast disorders	**4 (1.1%)**	**6 (1.7%)**	**2 (2.4%)**
Investigations	**4 (1.1%)**	**6 (1.7%)**	**2 (2.4%)**
Hepatobiliary disorders	**2 (0.6%)**	**1 (0.3%)**	**1 (1.2%)**
Endocrine disorders	**1 (0.3%)**	**0 (0.0%)**	**0 (0.0%)**
Renal and urinary disorders	**1 (0.3%)**	**3 (0.8%)**	**0 (0.0%)**
Congenital, familial and genetic disorders	**0 (0.0%)**	**1 (0.3%)**	**0 (0.0%)**
Surgical and medical procedures	**0 (0.0%)**	**1 (0.3%)**	**0 (0.0%)**

* GA = brand glatiramer acetate, GTR = generic glatiramer acetate

eTable 4: Local injection site reactions† summarized by MedDRA System Organ Class and Preferred Term (Safety Set)

Local injection site reaction – no. (%) of patients	GTR * (n=353)	GA * (n=357)	Placebo (n=84)
General disorders and administration site conditions			
Any event†	**81 (22.9%)**	**83 (23.2%)**	**14 (16.7%)**
Injection site reaction	58 (16.4%)	62 (17.4%)	6 (7.1%)
Injection site swelling	14 (4.0%)	12 (3.4%)	3 (3.6%)
Injection site pain	11 (3.1%)	13 (3.6%)	1 (1.2%)
Injection site erythema	8 (2.3%)	7 (2.0%)	0 (0.0%)
Injection site pruritus	8 (2.3%)	5 (1.4%)	0 (0.0%)
Injection site induration	3 (0.8%)	3 (0.8%)	0 (0.0%)
Injection site hypoaesthesia	2 (0.6%)	1 (0.3%)	0 (0.0%)
Injection site oedema	2 (0.6%)	2 (0.6%)	0 (0.0%)
Injection site haematoma	1 (0.3%)	0 (0.0%)	3 (3.6%)
Injection site bruising	0 (0.0%)	0 (0.0%)	3 (3.6%)
Injection site haemorrhage	0 (0.0%)	0 (0.0%)	1 (1.2%)

* GA = brand glatiramer acetate, GTR = generic glatiramer acetate

† Includes all reported injection site related PTs, except injection site atrophy

eTable 5: Immediate post-injection reactions and related symptoms summarized by MedDRA System Organ Class and Preferred Term (Safety Set).

IPIR or IPIR-Related Symptom – no. (%) of patients *	GTR † (n=353)	GA † (n=357)	Placebo (n=84)
Any event	**34 (9.6%)**	**27 (7.6%)**	**2 (2.4%)**
General disorders and administration site conditions			
At least one AE	27 (7.6%)	18 (5.0%)	1 (1.2%)
Immediate post-injection reaction	24 (6.8%)	18 (5.0%)	0 (0.0%)
Chest pain	3 (0.8%)	0 (0.0%)	0 (0.0%)
Chest discomfort	1 (0.3%)	0 (0.0%)	0 (0.0%)
Non-cardiac chest pain	0 (0.0%)	0 (0.0%)	1 (1.2%)
Cardiac disorders			
At least one AE	4 (1.1%)	3 (0.8%)	1 (1.2%)
Tachycardia	4 (1.1%)	3 (0.8%)	0 (0.0%)
Palpitations	0 (0.0%)	0 (0.0%)	1 (1.2%)
Respiratory, thoracic and mediastinal disorders			
At least one AE	4 (1.1%)	4 (1.1%)	0 (0.0%)
Dyspnoea	3 (0.8%)	4 (1.1%)	0 (0.0%)
Tachypnoea	1 (0.3%)	0 (0.0%)	0 (0.0%)
Skin and cutaneous tissue disorders			
At least one AE	2 (0.6%)	1 (0.3%)	0 (0.0%)
Erythema	2 (0.6%)	1 (0.3%)	0 (0.0%)
Investigations			
At least one AE	1 (0.3%)	0 (0.0%)	0 (0.0%)
Heart rate increased	1 (0.3%)	0 (0.0%)	0 (0.0%)
Vascular disorders			
At least one AE	0 (0.0%)	2 (0.6%)	0 (0.0%)
Flushing	0 (0.0%)	2 (0.6%)	0 (0.0%)

* Reported terms were selected based on brand glatiramer acetate labeling and literature review.

† GA = brand glatiramer acetate, GTR = generic glatiramer acetate, IPIR – immediate post-injection reaction

eFigure: Frequency Distribution of local injection site reaction scores (Safety Set)
Patients completed a diary for 14 consecutive days at the initiation of treatment (Panels A and B) and month 3 (Panels C and D), recording which of five injection site symptoms (pain, itchiness, redness, swelling, or lumps) were present after 5 minutes (Panels A and C) or 24 hours (Panels B and D). The local injection site reaction score represents the number (from 0 to 5) of symptoms present. GA = brand glatiramer acetate, GTR = generic glatiramer acetate, LISR = local injection site reaction, NA = not available.