LOW FREQUENCY GLATIRAMER ACETATE THERAPY

This application claims priority of U.S. Provisional Applications Nos. 61/337,612, filed February 11, 2010 and 61/274,687, filed August 20, 2009, the contents of each of which are hereby incorporated by reference in their entirety.

Throughout this application various publications are referenced by their full citations. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

BACKGROUND OF THE INVENTION

Multiple Sclerosis (MS) is a chronic, debilitating disease of the central nervous system (CNS). MS has also been classified as an autoimmune disease. MS disease activity can be monitored by magnetic resonance imaging (MRI) of the brain, accumulation of disability, as well as rate and severity of relapses.

There are five main forms of multiple sclerosis:

1) *Benign Multiple Sclerosis*:
Benign multiple sclerosis is a retrospective diagnosis which is characterized by 1-2 exacerbations with complete recovery, no lasting disability and no disease progression for 10-15 years after the initial onset. Benign multiple sclerosis may, however, progress into other forms of multiple sclerosis.

2) *Relapsing-Remitting Multiple Sclerosis (RRMS)*:

Patients suffering from RRMS experience sporadic exacerbations or relapses, as well as periods of remission. Lesions and evidence of axonal loss may or may not be visible on MRI for patients with RRMS.

3) *Secondary Progressive Multiple Sclerosis (SPMS)*:
SPMS may evolve from RRMS. Patients afflicted with SPMS have relapses, a diminishing degree of recovery during remissions, less frequent remissions and more pronounced neurological deficits than RRMS patients. Enlarged ventricles, which are markers for atrophy of the corpus callosum, midline center and spinal cord, are visible on MRI of patients with SPMS.

4) *Primary Progressive Multiple Sclerosis (PPMS)*;
PPMS is characterized by a steady progression of increasing neurological deficits without distinct attacks or remissions. Cerebral lesions, diffuse spinal cord damage and evidence of axonal loss are evident on the MRI of patients with PPMS.

5) *Progressive-Relapsing Multiple Sclerosis (PRMS)*:
PRMS has periods of acute exacerbations while proceeding along a course of increasing neurological deficits without remissions. Lesions are evident on MRI of patients suffering from PRMS (Multiple sclerosis: its diagnosis, symptoms, types and stages, 2003, albany.net/.about .tjc/multiple-sclerosis.html; What are the Types of Multiple Sclerosis?, 2005, <imaginis.com/multiple-sclerosis/types-of-ms.asp?mode=1>).

Chronic progressive multiple sclerosis is a term used to collectively refer to SPMS, PPMS, and PRMS (Types of Multiple Sclerosis (MS), 2005, <themcfox.com/multiple-sclerosis/types-of-ms/types-of-multi-ple-sclerosis.htm>). The relapsing forms of multiple sclerosis are SPMS with superimposed relapses,

RRMS and PRMS.

Glatiramer acetate (GA), a mixture of polypeptides which do not all have the same amino acid sequence, is marketed under the tradename Copaxone®. GA comprises the acetate salts of polypeptides containing L-glutamic acid, L-alanine, L-tyrosine and L-lysine at average molar fractions of 0.141, 0.427, 0.095 and 0.338, respectively. The average molecular weight of Copaxone® is between 5,000 and 9,000 daltons. ("Copaxone", Physician's Desk Reference, (2005), Medical Economics Co., Inc., (Montvale, N.J.), 3115.) Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine, L-tyrosine, acetate (salt).

Its structural formula is:

(Glu,Ala,Lys,Tyr)x.X CH_3COOH

($C_5H_9NO_4 \cdot C_3H_7NO_2 \cdot C_6H_{14}N_2O_2 \cdot C_9H_{11}NO_3$) x·x CHO

CAS-147245-92-9

Copaxone® ("Copaxone", Full Prescribing Information, (February, 2009), FDA Marketing Label) (20mg glatiramer acetate daily injection) is an approved therapy for patients with relapsing remitting multiple sclerosis (RRMS), including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

GA has also been disclosed for use in the treatment of other autoimmune diseases (U.S. Patent Publication No. 2002/0055466 A1 (R. Aharoni et al.), inflammatory non-autoimmune diseases (U.S. Patent Publication No. 2005/0014694 A1 (V. Wee Yong et al.); and U.S. Patent Application No. 2002/0077278 A1, published Jun. 20, 2002 (Young et al.)) and other diseases (U.S. Patent Publication Nos. 2003/0004099 A1 and 2002/0037848

A1 (Eisenbach-Schwartz, et al.); U.S. Pat. No. 6,514,938 B1, issued Feb. 4, 2003 (Gad et al.); PCT International Publication No. WO 01/60392, published Aug. 23, 2001 (Gilbert et al.); PCT International Publication No. WO 00/27417, published May 19, 2000 (Aharoni et al.); and PCT International Publication No. WO 01/97846, published Dec. 27, 2001 (Moses et al.).

The 20mg/day subcutaneous (s.c.) dose has been shown to reduce the total number of enhancing lesions in MS patients as measured by MRI (G. Comi et al., European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetere on Magnetic Resonance Imaging-Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis, Ann. Neurol. 49:290-297 (2001)).

Safety data accumulated for GA in clinical trials shows that the drug product is safe and well tolerated.

Disclosed is an effective low frequency dosage regimen of GA administration to patients suffering from a relapsing form of multiple sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

SUMMARY OF THE INVENTION

This invention provides a method of alleviating a symptom of relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis comprising administering to the human patient three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection so as to thereby alleviate the symptom of the patient.

This invention also provides a method of increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis which comprises reducing the frequency of subcutaneous injections of a pharmaceutical composition comprising a therapeutically effective dose of glatiramer acetate to three times over a period of seven days with at least one day between every injection.

In another embodiment, the therapeutically effective dose of glatiramer acetate is 40mg/ml.

This invention also provides a use of glatiramer acetate in the preparation of a medicament for treating relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis wherein the administration pattern of the medicament

is three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention additionally provides a use of glatiramer acetate in the preparation of a medicament for treating relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis wherein the medicament is prepared for an administration pattern of three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention yet also provides a use of glatiramer acetate in the preparation of a medicament for increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis wherein the administration pattern of the medicament is three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention further provides a use of glatiramer acetate in the preparation of a medicament for increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple

sclerosis wherein the medicament is prepared for an administration pattern of three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention provides glatiramer acetate for use in treating relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis by three subcutaneous injections over a period of seven days with at least one day between every subcutaneous injection.

This invention also provides glatiramer acetate for use in increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis by three subcutaneous injections over a period of seven days with at least one day between every subcutaneous injection.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a method of alleviating a symptom of relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis comprising administering to the human patient three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection so as to thereby alleviate the symptom of the patient.

In another embodiment, there are three injections for every seven days and there must be at least one day between each injection. In a further embodiment, possible injection schedules include Day 1, Day 3, Day 5; Day 1, Day 3, Day 6; Day 1, Day 3, Day 7; Day 1, Day 4, Day 6; Day 1, Day 4, Day 7; Day 1, Day 5, Day 7; Day 2, Day 4, Day 6; Day 2, Day 4, Day 7; Day 2, Day 5, Day 7; or Day 3, Day 5, Day 7.

In an embodiment, alleviating a symptom comprises reducing the frequency of relapses.

In yet another embodiment, alleviating a symptom comprises reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient.

In another embodiment, alleviating a symptom comprises reducing the mean number of new T_2 lesions in the brain of the patient.

In a further embodiment, alleviating a symptom comprises reducing the cumulative number of enhancing lesions on T_1-weighted images in the patient.

In another embodiment, alleviating a symptom comprises reducing brain atrophy in the patient.

In another embodiment, alleviating a symptom comprises increasing the time to a confirmed relapse in the patient.

In another embodiment, alleviating a symptom comprises reducing the total number of confirmed relapses in the patient.

In another embodiment, alleviating a symptom comprises reducing the progression of MRI-monitored disease activity in the patient.

In another embodiment, alleviating a symptom comprises reducing total volume of T_2 lesions in the patient.

In another embodiment, alleviating a symptom comprises reducing the number of new hypointense lesions on enhanced T_1 scans in the patient.

In another embodiment, alleviating a symptom comprises reducing the total volume of hypointense lesions on enhanced T_1 scans in the patient.

In another embodiment, alleviating a symptom comprises reducing the level of disability as measured by EDSS Score in the patient.

In another embodiment, alleviating a symptom comprises reducing the change in EDSS Score in the patient.

In another embodiment, alleviating a symptom comprises reducing the change in Ambulation Index in the patient.

In another embodiment, alleviating a symptom comprises reducing the level of disability as measured by EuroQoL (EQ5D) questionnaire in the patient.

In another embodiment, alleviating a symptom comprises reducing the level of disability as measured by the work productivity and activities impairment – General Health (WPAI-GH) questionnaire in the patient.

In an additional embodiment, the pharmaceutical composition is in a prefilled syringe for self administration by the patient.

In yet another embodiment, the therapeutically effective dose of glatiramer acetate is 40mg/ml. In a further embodiment, the therapeutically effective dose of glatiramer acetate is 40mg/0.75ml.

In a further embodiment, the patient has not received glatiramer acetate therapy prior to initiation of the subcutaneous injections.

In an embodiment, the pharmaceutical composition is in the form of a sterile solution.

In another embodiment, the pharmaceutical composition further comprises mannitol.

In yet another embodiment, the pharmaceutical composition has a pH in the range of 5.5 to 8.5.

In an embodiment, the pharmaceutical composition has a pH in the range of 5.5 to 7.0.

In an embodiment the frequency of an immediate post injection reaction or the frequency of an injection site reaction is reduced relative to daily subcutaneous administration of 20mg glatiramer acetate.

This invention also provides a method of increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis which comprises reducing the frequency of subcutaneous injections of a pharmaceutical composition comprising a therapeutically effective dose of glatiramer acetate to three times over a period of seven days with at least one day between every injection.

In another embodiment, increasing the tolerability of GA treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an immediate post injection reaction.

In yet another embodiment, the immediate post injection reaction is palpitations, feeling hot, flushing, hot flushes, tachycardia, dyspnoea, chest discomfort, chest pain, non-cardiac chest , asthenia, back pain, bacterial infection, chills, cyst, face edema, fever, flu syndrome, infection, injection site erythema, injection site hemorrhage, injection

site induration, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site urticaria, injection site welt, neck pain, pain, migrane, syncope, tachycardia, vasodilatation, anorexia, diarrhea, gastroenteritis, gastrointestinal disorder, nausea, vomiting, ecchymosis, peripheral edema, arthralgia, agitation, anxiety, confusion, foot drop, hypertonia, nervousness, nystagmus, speech disorder, tremor, vertigo, bronchitis, dyspnea, laryngismus, rhinitis, erythema, herpes simplex, pruritus, rash, skin nodule, sweating, urticaria, ear pain, eye disorder, dysmenorrheal, urinary urgency, or vaginal moniliasis.

In an additional embodiment, increasing the tolerability of GA treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an injection site reaction.

In a further embodiment, the injection site reaction is erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, or welt that occurs immediately around the site of injection.

In an embodiment, a single clinical attack includes a clinical episode of optic neuritis, blurring of vision, diplopia, involuntary rapid eye movement, blindness, loss of balance, tremors, ataxia, vertigo, clumsiness of a limb, lack of coordination, weakness of one or more extremity, altered muscle tone, muscle stiffness, spasms, tingling, paraesthesia, burning sensations, muscle pains, facial pain, trigeminal neuralgia, stabbing sharp pains, burning tingling pain, slowing of speech, slurring of words, changes in rhythm of speech, dysphagia, fatigue, bladder problems (including urgency, frequency, incomplete emptying and incontinence),

bowel problems (including constipation and loss of bowel control), impotence, diminished sexual arousal, loss of sensation, sensitivity to heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning.

In another embodiment, prior to administration the patient has at least 1 cerebral lesion detectable by an MRI scan and suggestive of multiple sclerosis.

In yet another embodiment, the lesion is associated with brain tissue inflammation, myelin sheath damage or axonal damage.

In an additional embodiment, the lesion is a demyelinating white matter lesion visible on brain MRI.

In a further embodiment, the white matter lesions are at least 3 mm in diameter.

This invention also provides a use of glatiramer acetate in the preparation of a medicament for treating relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis wherein the administration pattern of the medicament is three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention additionally provides a use of glatiramer acetate in the preparation of a medicament for treating relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a

patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis wherein the medicament is prepared for an administration pattern of three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention yet also provides a use of glatiramer acetate in the preparation of a medicament for increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis wherein the administration pattern of the medicament is three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention further provides a use of glatiramer acetate in the preparation of a medicament for increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis wherein the medicament is prepared for an administration pattern of three subcutaneous injections of a therapeutically effective dose of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection.

This invention provides glatiramer acetate for use in treating relapsing-remitting multiple sclerosis in a human patient suffering from relapsing-remitting multiple sclerosis or a

patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis by three subcutaneous injections over a period of seven days with at least one day between every subcutaneous injection.

This invention also provides glatiramer acetate for use in increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis or a patient who has experienced a first clinical episode and is determined to be at high risk of developing clinically definite multiple sclerosis by three subcutaneous injections over a period of seven days with at least one day between every subcutaneous injection.

DEFINITIONS

As used herein, immediate post injection reaction (IRPR) refers to a reaction such as, palpitations, feeling hot, flushing, hot flushes, tachycardia, dyspnoea, chest discomfort, chest pain, and non-cardiac chest pain that occurs immediately following injection. Reactions may also include asthenia, back pain, bacterial infection, chills, cyst, face edema, fever, flu syndrome, infection, injection site erythema, injection site hemorrhage, injection site induration, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site urticaria, injection site welt, neck pain, pain, migrane, syncope, tachycardia, vasodilatation, anorexia, diarrhea, gastroenteritis, gastrointestinal disorder, nausea, vomiting, ecchymosis, peripheral edema, arthralgia, agitation, anxiety, confusion, foot drop, hypertonia, nervousness, nystagmus, speech disorder, tremor, vertigo, bronchitis, dyspnea, laryngismus, rhinitis, erythema, herpes simplex, pruritus, rash, skin nodule, sweating, urticaria, ear pain, eye

disorder, dysmenorrheal, urinary urgency, and vaginal moniliasis.

As used herein, injection site reaction (ISR) refers to a reaction such as erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, and welt that occurs immediately around the site of injection.

As used herein, "tolerability" relates to the level of discomfort associated with GA treatment. Tolerability is associated with the frequency and severity of post injection reactions and injection site reactions. Tolerability influences the period that a patient can follow GA treatment.

As used herein, the term Gd-enhancing lesions, refers to lesions that result from a breakdown of the blood-brain barrier, which appear in contrast studies using gandolinium contrast agents. Gandolinium enhancement provides information as to the age of a lesion, as Gd-enhancing lesions typically occur within a six week period of lesion formation.

As used herein, the term T_1-weighted MRI images refers to an MR-image that emphasizes T_1 contrast by which lesions may be visualized. Abnormal areas in a T_1-weigted MRI image are "hypointense" and appear as dark spots. These spots are generally older lesions.

As used herein, the term T_2-weighted MRI image, refers to an MR-image that emphasizes T_2 contrast by which lesions may be visualized. T_2 lesions represent new inflammatory activity.

As used herein, the term "unit dosage" refers to physically discrete units suited as single administration dose for a subject to be treated, containing a therapeutically effective

quantity of active compound in association with the required pharmaceutical carrier, e.g., a syringe.

As used herein, clinically isolated syndrome (CIS) refers to 1) a single clinical attack suggestive of MS and 2) at least one lesion suggestive of MS. As an example, the patient has at least 1 cerebral lesion detectable by an MRI scan and suggestive of multiple sclerosis. As an additional example the lesion is associated with brain tissue inflammation, myelin sheath damage or axonal damage. As another example the lesion is a demyelinating white matter lesion visible on brain MRI. In a further example, the white matter lesions are at least 3 mm in diameter.

The term "single clinical attack" is used synonymously with "first clinical episode", "first clinical attack", and "first clinical event" which, for example, presents as a clinical episode of optic neuritis, blurring of vision, diplopia, involuntary rapid eye movement, blindness, loss of balance, tremors, ataxia, vertigo, clumsiness of a limb, lack of coordination, weakness of one or more extremity, altered muscle tone, muscle stiffness, spasms, tingling, paraesthesia, burning sensations, muscle pains, facial pain, trigeminal neuralgia, stabbing sharp pains, burning tingling pain, slowing of speech, slurring of words, changes in rhythm of speech, dysphagia, fatigue, bladder problems (including urgency, frequency, incomplete emptying and incontinence), bowel problems (including constipation and loss of bowel control), impotence, diminished sexual arousal, loss of sensation, sensitivity to heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning.

As used herein, the criteria, as defined by Poser et al. Neurology, March 1983, 13 (3): 227-230, used to determine if a

subject meets the condition consistent with clinically definite multiple sclerosis (CDMS) are:

- Two attacks and clinical evidence of two separate lesions or
- Two attacks; clinical evidence of one lesion and paraclinical evidence of another separate lesion.

An attack (also referred to as an exacerbation, flare, or relapse,) is defined clinically as the sudden appearance or worsening of a symptom or symptoms of neurological dysfunction, with or without objective confirmation.

Clinical evidence of a lesion is defined as signs of neurological dysfunction demonstrable by neurological examination. An abnormal sign constitutes clinical evidence even if no longer present, but was recorded in the past by a competent examiner.

Paraclinical evidence of a lesion is defined as the demonstration by means of various tests and procedures of the existence of a lesion of the CNS that has not produced clinical signs but that may or may not have caused symptoms in the past. Such evidence may be derived from the hot-bath test, evoked response studies, neuroimaging, and expert neurological assessment. These tests are considered to be extensions of the neurological examination and not laboratory procedures.

As used herein, the term "glatiramoid" refers a complex mixture of the acetate salts of synthetic polypeptides, non-uniform with respect to molecular weight and sequence.

This invention is illustrated in the Examples section which follows. This section is set forth to aid in an understanding of the invention but is not intended to, and should not be

construed to, limit in any way the invention as set forth in the claims which follow thereafter.

Experimental Details

Example 1:

A multinational, multicenter, randomized, phase III parallel-group study performed in subjects with Relapsing-Remitting Multiple Sclerosis (RRMS) to assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) injection 40mg/ml administered three times weekly by subcutaneous injection over placebo in a double-blind design.

Methods:

The study is designed to select three days a week for injection. Three injections are administered for every seven days and there must be at least one day between each injection.

Study Duration:

- Screening phase: 1 month
- Placebo Controlled (PC) Phase: 12 months of 40mg/ml or matching placebo administered three times weekly by subcutaneous injection.
- Open Label (OL) Extension: All subjects will continue treatment with the GA 40mg/ml administered three times a week, until this dose is commercially available for the treatment of relapsing remitting multiple sclerosis (RRMS) patients or until the development of this dose for MS is stopped by the Sponsor.

Study Population:

Subjects with RRMS

Number of Subjects:

1350 subjects

Study Objective(s):

To assess the efficacy, safety and tolerability of Glatiramer Acetate (GA) injection 40mg/ml administered three times weekly compared to placebo in a double-blind study design.

Study Design:

Eligible subjects are randomized in a 2:1 ratio (40mg:placebo) and assigned to one of the following three treatment arms:

1. 40mg s.c. GA three times weekly (900 subjects)
2. Matching placebo three times weekly (450 subjects)

During the PC phase, subjects are evaluated at study sites for a total of 7 scheduled visits at months: -1 (screening), 0 (baseline), 1, 3, 6, 9, and 12 (End of PC phase).

Subjects successfully completing the study are offered the opportunity to enter into an open label extension in which all subjects will continue treatment with 40mg/ml GA dose. This is done until the 40mg/ml GA dose is commercially available for the treatment of relapsing remitting multiple sclerosis (RRMS) patients or until the development of this dose regimen is stopped by the Sponsor.

The termination visit of the PC phase will serve as the baseline visit of the OL phase. This phase will include scheduled visits every 3 months for the first 12 months, then scheduled visits every 6 months and will be completed with a termination visit.

During the study, the following assessments are performed (regardless of the treatment assignment) at the specified time points:

- Vital signs are measured at each study visit.
- A physical examination is performed at months -1 (screening), 0 (baseline) 6, 12 (end of PC phase) and every 6 months thereafter. In addition, a physical examination will be performed at the termination visit of the OL phase.
- The following safety clinical laboratory tests are performed:
  - o Complete blood count (CBC) with differential - at all scheduled visits in the PC phase, and every 12 months thereafter. In addition this test will be performed at the termination visit of the OL phase.
  - o Serum chemistry (including electrolytes, creatinine, urea and liver enzymes) and urinalysis - at all scheduled visits in the PC phase, and every 12 months thereafter. In addition this test will be performed at the termination visit of the OL phase.
  - o Serum β-hCG in women of child-bearing potential is performed at months -1 (screening), 0 (baseline), 12 (end of PC phase), and every 12 months thereafter. In addition this test will be performed at the termination visit of the OL phase.
- ECG is performed at months -1 (screening), 0 (baseline), 12 (end of PC phase), and every 12 months thereafter. In addition an ECG will be performed at the termination visit of the OL phase.
- Chest X-ray is performed at month -1 (screening) if not performed within 6 months prior to screening visit.
- Adverse Events (AEs) are monitored throughout the study.
- Concomitant Medications are monitored throughout the study.

- Neurological evaluations, including Neurostatus [Functional Systems (FS), Expanded Disability Status Scale (EDSS), Ambulation Index (AI)] are performed at months -1 (screening), 0 (baseline), 3, 6, 9, 12 (end of PC phase) and every 6 months thereafter. In addition, a neurological examination are performed at the termination visit of the OL phase.

- The general health status is assessed by the EuroQoL (EQ5D) questionnaire at months 0 (baseline) and 12 (end of PC phase).

- Additional quality of life parameters are assessed by the WPAI (Work Productivity and Activities Impairment) Questionnaire at month 0 (baseline), 3, 6, 9 and 12 (end of PC phase).

- All subjects undergo MRI scans at months 0 (13-7 days prior to baseline visit), 6 and 12 (end of PC phase). Following the results of the PC phase, the Sponsor may decide to perform an MRI scan at the termination visit of the OL phase.

- Relapses are confirmed/monitored throughout the study.

Ancillary Studies:

- Blood samples for determination of anti-GA antibodies are collected for all subjects at months 0 (baseline), 1, 3, 6, 9, 12 (end of PC phase), 18 and 24.

- Blood samples for evaluation of PBL proliferation in response to GA, as well as other immunological parameters, are collected in a subset of subjects at months 0 (baseline), 1, 3, 6, and 12 (end of PC phase).

- Blood samples for Pharmacogenetic (PGx) analysis are collected for all subjects twice during the study, preferably at month 0 (baseline) and month 1.

The allowed treatment for a multiple sclerosis relapse will be intravenous methylprednisolone 1 gr/day for up to 5 consecutive days.

Re-consent criteria

In case of a confirmed diagnosis of MS relapse (as defined in the protocol), **or** in case of an increase in EDSS of 1.5 points or more, sustained for at least 3 months, during the placebo-controlled phase, the following actions are taken:

- The subject is reminded of the current available MS medications/treatments and the opportunity to terminate the study.
- The subject is requested to re-sign an informed consent form if he/she chooses to continue to participate in the study, in the same treatment assignment.

The study is closely monitored through the study course by the sponsor's personnel as well as by an external independent data monitoring committee (DMC) in order to ensure subjects' welfare.

Inclusion/Exclusion:

Inclusion Criteria:

- Subjects must have a confirmed and documented 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 EDSS score of 0-5.5 in both screening and baseline visits.
- Subjects must be in a relapse-free, stable neurological condition and free of corticosteroid treatment [intravenous (IV), intramuscular (IM) and/or per os (PO)] or ACTH 30 days prior to screening (month -1) and between screening (month -1) and baseline (month 0) visits.
- Subjects must have had experienced one of the following:
    - o At least one documented relapse in the 12 months prior to screening, or
    - o At least two documented relapses in the 24 months prior to screening, or
    - o One documented relapse between 12 and 24 months prior to screening with at least one documented T_1-Gd enhancing lesion in an MRI performed within 12 months prior to screening.
- Subjects must be between 18 and 55 years of age, inclusive.
- Women of child-bearing potential must practice an acceptable method of birth control [acceptable methods of birth control in this study include: surgical sterilization, intrauterine devices, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy or a double-barrier method (condom or diaphragm with spermicide)].
- Subjects must be able to sign and date a written informed consent prior to entering the study.
- Subjects must be willing and able to comply with the protocol requirements for the duration of the study.

Exclusion Criteria:

- Subjects with progressive forms of MS.
- Use of experimental or investigational drugs, and/or participation in drug clinical studies within the 6 months prior to screening.
- Use of immunosuppressive (including Mitoxantrone (Novantrone®) or cytotoxic agents within 6 months prior to the screening visit.
- Previous use of either natalizumab (Tysabri®) or any other monoclonal antibodies within 2 years prior to screening.
- Use of cladribine within 2 years prior to screening.
- Previous treatment with immunomodulators (including IFNβ 1a and 1b, and IV Immunoglobulin (IVIg) within 2 months prior to screening.
- Previous use of GA or any other glatiramoid.
- Chronic (more than 30 consecutive days) systemic (IV, PO or IM) corticosteroid treatment within 6 months prior to screening visit.
- Previous total body irradiation or total lymphoid irradiation.
- Previous stem-cell treatment, autologous bone marrow transplantation or allogenic bone marrow transplantation.
- Known human immunodeficiency virus (HIV) positive status.
- Pregnancy or breastfeeding.
- Subjects with a clinically significant or unstable medical or surgical condition that would preclude safe and complete study participation, as determined by medical history, physical exams, ECG, abnormal laboratory

tests and chest X-ray. Such conditions 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 that could be detrimental according to the investigator's judgment.

- A known history of sensitivity to Gadolinium.
- Inability to successfully undergo MRI scanning.
- A known drug hypersensitivity to mannitol.

Route and Dosage Form:

- Glatiramer Acetate 40mg in 1ml for subcutaneous injection in a pre-filled syringe (PFS), administered three times a week.
- Matching placebo injection (mannitol in 1ml WFI) for subcutaneous injection in a pre-filled syringe (PFS).

Outcome Measures:

Primary Outcome Measure:

- The total number of confirmed relapses during the 12 month PC phase.

Secondary Outcome Measure:

- The number of new T_2 lesions at month 12 (end of PC phase) as compared to baseline scan.
- The cumulative number of enhancing lesions on T_1-weighted images taken at months 6 and 12 (end of PC phase).
- Brain atrophy as defined by the percent brain volume change from baseline to month 12 (end of PC phase).

Exploratory Endpoints: The following assessments are presented in an exploratory manner.

- The time to the first confirmed relapse during the placebo-controlled phase.
- The proportion of relapse-free subjects during the placebo-controlled phase.
- The total number of confirmed relapses during the placebo-controlled phase requiring hospitalization and/or IV steroids.
- The proportion (%) of subjects with confirmed EDSS progression during the placebo-controlled phase (progression of at least 1 EDSS point sustained for at least 3 months).
- Change from baseline to month 12 (end of placebo-controlled phase) in EDSS Score.
- Change from baseline to month 12 (end of placebo-controlled phase) in Ambulation Index.
- The total volume of T_2 lesions at month 12 (end of placebo-controlled phase)
- The number of new hypointense lesions on enhanced T_1 scans at month 12 (end of placebo-controlled phase) as compared to the baseline scan.
- The total volume of hypointense lesions on enhanced T_1 scans at month 12 (end of placebo-controlled phase).
- Brain atrophy as defined by the percentage change from baseline to month 12 (end of placebo-controlled phase) in normalized gray matter volume and in normalized white matter volume.
- The general health status, as assessed by the EuroQoL (EQ5D) questionnaire.
- Assessment of the effect of general health and symptom severity on work, using the work productivity and

activities impairment - General Health (WPAI-GH) questionnaire.

Safety and Tolerability Outcome Measures:

Safety:

- Adverse events
- Vital signs
- ECG findings
- Clinical laboratory parameters

Tolerability:

- Proportion of subjects (%) who prematurely discontinued from the study, reason of discontinuation and the time to withdrawal.
- Proportion of subjects (%) who prematurely discontinued from the study due to AEs and the time to withdrawal.

Statistical Considerations:

The sample size considerations for the study are based on the following assumptions:

- An individual subject's number of confirmed relapses during a one year period reflects a Poisson process with an individual rate of λi, and this individual subject rates λi are exponentially distributed with mean $1/\theta$, where θ is the population's annualized relapse rate. This approach models the total number of confirmed relapses as an Over Dispersed Poisson distribution.
- The expected annualized relapse rate in an untreated subject population is $\theta=0.35$ relapses per year.

- Treatment with 40mg s.c. GA three times weekly reduces the subject population annualized relapse rate by 30% or more when compared to the placebo group. That is, the expected annualized relapse rate of the GA treated populations is θ=0.245 relapses per year or less.

In addition, the following are also incorporated in the sample size calculation:

- 15% of the subjects drop out during the treatment duration. This drop out rate is taken into account in the calculations, as on the average, a subject who drops out of the study contributes 6 months of exposure to the treatment

Hochberg's step-up modification to Bonferroni's method is used to maintain the experiment-wise type-I error when comparing multiple treatment arms to placebo, and the p-values for the IAs are calculated using the O'brien-Fleming alpha spending functions.

A simulation study accounting for the above underlying assumptions used the Quasi-Likelihood (over-dispersed) Poisson Regression (SAS® PROC GENMOD), revealed that a total of 1350 subjects (900 subjects in the 40mg GA arm, and 450 subjects to the placebo arm) provide approximately 90% power to detect a significant difference in the total number of confirmed relapses as described above.

The analysis of the total numbers of confirmed relapses during the study period is based on baseline adjusted Quasi-Likelihood (over-dispersed) Poisson Regression.

The analysis of the number of new T_2 lesions at month 12 and of the cumulative number of enhancing lesions on T_1-weighted

images taken at months 6 and 12 is based on baseline-adjusted Negative Binomial Regression.

The analysis of Brain Atrophy will be based on Analysis of Covariance (ANCOVA).

Results

Primary Outcome Measure:

Treatment with 40mg s.c. GA three times weekly reduces the subject population annualized relapse rate by 30% or more when compared to the placebo group. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the subject population annualized relapse rate.

Secondary Outcome Measures:

- Treatment with 40mg s.c. GA three times weekly significantly reduces the number of new T_2 lesions at month 12. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the number of new T_2 lesions at month 12.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the cumulative number of enhancing lesions on T_1-weighted images taken at months 6 and 12. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the cumulative number of enhancing lesions on T_1-weighted images taken at months 6 and 12.

- Treatment with 40mg s.c. GA three times weekly significantly reduces brain atrophy as defined by the percent brain volume change from baseline to month 12. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing brain atrophy as defined by the percent brain volume change from baseline to month 12.

Exploratory Endpoints:

- Treatment with 40mg s.c. GA three times weekly significantly increases the time to the first confirmed relapse during the placebo-controlled phase. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at increasing the time to the first confirmed relapse during the placebo-controlled phase.

- Treatment with 40mg s.c. GA three times weekly significantly increases the proportion of relapse-free subjects during the placebo-controlled phase. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at increasing the proportion of relapse-free subjects during the placebo-controlled phase.

- Treatment with 40mg s.c. GA three times weekly significantly increases the proportion of relapse-free subjects during the placebo-controlled phase. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at increasing the proportion of relapse-free subjects during the placebo-controlled phase.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the total number of confirmed relapses during the placebo-controlled phase requiring hospitalization and/or IV steroids. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the total number of confirmed relapses during the placebo-controlled phase requiring hospitalization and/or IV steroids.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the progression of MRI-monitored disease activity in the patient. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the progression of MRI-monitored disease activity in the patient.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the total volume of T_2 lesions at month 12. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing total volume of T_2 lesions at month 12.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the number of new hypointense lesions on enhanced T_1 scans at month 12 as compared to the baseline scan. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the number of new hypointense lesions on enhanced T_1 scans at month 12 as compared to the baseline scan.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the total volume of hypointense lesions on enhanced T_1 scans at month 12. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the total volume of hypointense lesions on enhanced T_1 scans at month 12.

- Treatment with 40mg s.c. GA three times weekly significantly reduces brain atrophy as defined by the percentage change from baseline to month 12 in normalized gray matter volume and in normalized white matter volume. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing brain atrophy as defined by the percentage change from baseline to month 12 in normalized gray matter volume and in normalized white matter volume.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the level of disability as measured by EDSS Score. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the level of disability as measured by EDSS Score.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the proportion (%) of subjects with confirmed EDSS progression during the placebo-controlled phase (progression of at least 1 EDSS point sustained for at least 3 months). Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing proportion (%) of subjects with confirmed EDSS progression during the

placebo-controlled phase (progression of at least 1 EDSS point sustained for at least 3 months).

- Treatment with 40mg s.c. GA three times weekly significantly reduces the change from baseline to month 12 (end of placebo-controlled phase) in EDSS Score. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the change from baseline to month 12 (end of placebo-controlled phase) in EDSS Score.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the change from baseline to month 12 (end of placebo-controlled phase) in Ambulation Index. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the change from baseline to month 12 (end of placebo-controlled phase) in Ambulation Index.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the level of disability as measured by EuroQoL (EQ5D) questionnaire. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the level of disability as measured by EuroQoL (EQ5D) questionnaire.

- Treatment with 40mg s.c. GA three times weekly significantly reduces the level of disability as measured by the work productivity and activities impairment - General Health (WPAI-GH) questionnaire. Treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the level of disability as measured by the work productivity

and activities impairment - General Health (WPAI-GH) questionnaire.

Discussion

A significant drawback to GA therapy is the requirement of daily injections, which can be inconvenient. Moreover, in all clinical trials, injection-site reactions were seen to be the most frequent adverse reactions and were reported by the majority of patients receiving GA. In controlled studies, the proportion of patients reporting these reactions, at least once, was higher following treatment with GA (70%) than placebo injections (37%). The most commonly reported injection-site reactions, which were more frequently reported in GA vs. placebo-treated patients, were erythema, pain, mass, puritus, edema, inflammation and hypersensitivity.

However, several obstacles and limitations with potential approaches for addressing the drawbacks exist to current GA therapy. Subcutaneous drug delivery is limited, firstly, by the acceptable injection volume. Typically no more than 1 to 2ml of solution is permitted (Kansara V, Mitra A, Wu Y, Subcutaneous Delivery. Drug Deliv Technol, June 2009; 9(6):38-42). Secondly, the potential exists for drug degradation at the site of injection resulting in reduced bioavailability. Thirdly, based on the physiochemical properties of the drug, potent compounds may become locally trapped in the interstitial space which can lead to further localized irritation, precipitation of the drug and concentration-dependent adverse effects (Kansara V, Mitra A, Wu Y, Subcutaneous Delivery. Drug Deliv Technol, June 2009; 9(6):38-42). Finally, due to the complex pharmacokinetic behavior of a drug, variation in the frequency of administration is unpredictable and requires empirical testing. For example, although controlled clinical trials have demonstrated the

efficacy of IFNβ-1b in the treatment of MS, patient compliance, efficacy and tolerability are affected by the dosage regimen used. Merely increasing the dose of IFNβ-1b is insufficient to increase efficacy, the frequency of administration must also be increased (Luca Durelli, J Neurol (2003) 250 [Suppl 4]).

Accordingly, the subject application discloses an effective low frequency dosage regimen of GA administration to patients suffering from a relapsing form of multiple sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. Based on the performance of the dosage regimen in these studies, the administration of three s.c. injections over a period of seven days with at least one day between every injection is also expected to work in the treatment of patients who have experienced a clinically isolated syndrome (CIS). This is based on the fact that the 20mg daily s.c. injection has been shown to work in PCT International Application No. PCT/US2008/013146 (see International Publication No. WO 2009/070298 and also U.S. Patent Application Publication No. US 2009-0149541 A1).

What is claimed is:

1. A medicament comprising glatiramer acetate for use in treating a patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the medicament is to be administered in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

2. Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection for uses in treating a patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.

3. The medicament for use according to claim 1 or glatiramer acetate for use according to claim 2, wherein the treating comprises reducing the frequency of relapses, reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient, reducing the mean number of new T_2 lesions in the brain of the patient, reducing the cumulative number of enhancing lesions on T_1-weighted images, reducing brain atrophy in the patient, increasing the time to a confirmed relapse in the patient, reducing the total number of confirmed relapses in the patient, reducing the progression of MRI-monitored

disease activity in the patient, reducing the total volume of T_2 lesions in the patient, reducing the number of new hypointense lesions on enhanced T_1 scans in the patient, reducing the total volume of hypointense lesions on enhanced T_1 scans, reducing the level of disability as measured by EDSS Score in the patient, reducing the change in EDSS Score in the patient, reducing the change in Ambulation Index in the patient, reducing the level of disability as measured by EuroQoL (EQ5D) questionnaire in the patient, or reducing the level of disability as measured by the work productivity and activities impairment - General Health (WPAI-GH) questionnaire in the patient.

4. The medicament for use according to claim 1, or glatiramer acetate for use according to claim 2, wherein frequency of immediate post injection reaction or of injection site reaction relative to frequency experienced with daily subcutaneous administration of 20mg glatiramer acetate is reduced.

5. The medicament for use according to claim 1 or glatiramer acetate for use according to claim 2, wherein the tolerability in the patient is increased relative to daily subcutaneous administration of a 20mg dose of glatiramer acetate, wherein the increased tolerability comprises reduced frequency of immediate post injection reaction or reduced frequency of injection site reaction, each relative to the frequency experienced with daily subcutaneous administration of 20 mg glatiramer acetate.

6. The medicament or glatiramer acetate, for use according to claim 4 or claim 5, wherein the immediate post injection reaction is palpitations, feeling hot, flushing, hot flushes, tachycardia, dyspnoea, chest discomfort, chest pain, non-cardiac chest, asthenia, back pain, bacterial infection, chills, cyst, face edema, fever, flu syndrome, infection, injection site erythema, injection site hemorrhage, injection site induration, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site urticaria, injection site welt, neck pain, pain, migrane, syncope, tachycardia, vasodilatation, anorexia, diarrhea, gastroenteritis, gastrointestinal disorder, nausea, vomiting, ecchymosis, peripheral edema, arthralgia, agitation, anxiety, confusion, foot drop, hypertonia, nervousness, nystagmus, speech disorder, tremor, vertigo, bronchitis, dyspnea, laryngismus, rhinitis, erythema, herpes simplex, pruritus, rash, skin nodule, sweating, urticaria, ear pain, eye disorder, dysmenorrheal, urinary urgency, or vaginal moniliasis.

7. The medicament or glatiramer acetate, for use according to claim 4 or claim 5, wherein the injection site reaction is erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, or welt that occurs immediately around the site of injection.

8. The medicament for use according to any one of claim 1 or claims 3-8, wherein the medicament is a pharmaceutical composition comprising 40 mg/ml glatiramer acetate.

9. The medicament for use according to any one of claim 1 or claims 3-8 or glatiramer acetate for use according to any one claims 2-7, wherein the treating comprises reducing the frequency of relapses in the patient.

10. The medicament for use according to any one of claim 1 or claims 3-8 for use in reducing frequency of relapses in a human patient suffering from relapsing-remitting multiple sclerosis.

11. Glatiramer acetate for use according to any one of claims 2-7 for reducing frequency of relapses in a human patient suffering from relapsing-remitting multiple sclerosis.

12. The medicament for use according to any one of claim 1 or claims 3-8 for use in treating a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.

13. Glatiramer acetate for use according to any one of claims 2-7 for treating a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.

14. The medicament for use according to any one of claims 1, 3-9, 10 or 12, or glatiramer acetate for use according to any one of claims 2-7, 9, 11 or 13, wherein the patient has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, and wherein the patient has at least 1 cerebral lesion

detectable by an MRI scan and suggestive of multiple sclerosis.

15. The medicament for use according to any one of claims 1, 3-10, 12 or 14, or glatiramer acetate for use according to any one of claims 2-7, 9, 11 or 13-14, wherein the glatiramer acetate is administered using a prefilled syringe by self administration.