Docket No. 2609/80798-A/JPW/GJG/ML

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, VA 22313-1450

Date: August 19, 2010

Sir:

Transmitted herewith for filing is the utility patent application of:

Ety Klinger

_____ for
Inventor(s)

LOW FREQUENCY GLATIRAMER ACETATE THERAPY
Title of Invention

including the following:

X Application (44 pages in total), including 37 pages of specification; 6 page(s) of claims; 1 page(s) of abstract; 0 page(s) of sequence listing; and 0 sheet(s) of drawings

X Oath or Declaration of Applicant(s) (X signed ____ unsigned)

X Power of Attorney (X signed ____ unsigned)

X Preliminary Amendment (___ including claim to benefit of earlier U.S. Provisional Application(s))

The following are also enclosed:

X Assignment to Teva Pharmaceutical Industries, Ltd.

____ Verified Statement to establish small entity status under 37 C.F.R. §1.9 and §1.27

____ Information Disclosure Statement, including Form PTO-1449 (Copies of citations are included: Yes_____; No_____)

____ Non-Publication Request (Form PTO/SB/135 must be attached)

____ Computer Readable Form (CRF) of Sequence Listing and Statement Verifying Identity of CRF and Sequence Listing

____ Certified copy of previously filed foreign application(s) as follows:

Country	Application No.	Filing Date

____ Applicant(s) hereby claim(s) priority based upon the aforementioned foreign application(s) under 35 U.S.C. §119

JPW Rev. 10-2-08

___ Two copies of this Patent Application Transmittal Letter

_X_ Return Receipt Postcard

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dated August 19, 2010

___ Other (identify): _____

The filing fee is calculated as follows:

NUMBER OF CLAIMS AS FILED, MINUS ALL CLAIMS CANCELED BY ANY ACCOMPANYING PRELIMINARY AMENDMENT

	Number Filed		Number Extra*		Rate Small Entity	Rate Other Entity		Fee Small Entity	Fee Other Entity
Total Claims	26	-20 =	6	X	$26	$52	=	$	$ 312
Independent Claims	2	-3 =	0	X	$110	$220	=	$	$ 0
Pages in Excess of 100	0	-100=	0	÷ by 50 † X	$135	$270	=	$	$ 0
Multiple Dependent Claims Present: __Yes _X_No					$195	$390	=	$	$ 0
Non-English Specification: __Yes _X_No					$130.	$130.	=	$	$ 0
					Basic Fee			$ 165.	$ 330.
					Search Fee			$ 270.	$ 540.
					Examination Fee			$ 110.	$ 220.
					Total Fee			$	$1,402.00

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_X_ A check in the amount of $1,402.00 is enclosed.

___ Please charge Deposit Account No._____ in the amount of $_____

___ The Commissioner is hereby authorized to charge any additional fees required or credit any overpayment to Deposit Account No. 03-3125 as follows:

___ Filing fees under 37 C.F.R. §1.16
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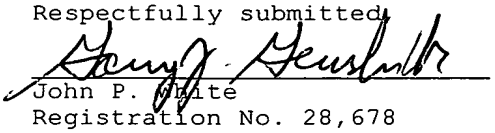
Respectfully submitted,



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JPW Rev. 10-2-08

Docket No. 2609/80798-A/JPW/GJG/ML

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Ety Klinger

Serial No.: Not Yet Known

Filed: Herewith

For: LOW FREQUENCY GLATIRAMER ACETATE THERAPY

30 Rockefeller Plaza
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August 19, 2010

Commissioner for Patents
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SIR:

EXPRESS MAIL CERTIFICATE OF MAILING FOR ABOVE-IDENTIFIED APPLICATION

"Express Mail" mailing label number: EM 520 849 611 US

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I hereby certify that this paper or fee is being deposited to the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

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Respectfully submitted,

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S817_A

Docket Number: 80798-A/JPW/GJG/ML

DECLARATION AND POWER OF ATTORNEY

As a below-named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

LOW FREQUENCY GLATIRAMER ACETATE THERAPY

the specification of which:
(check one)

__X__ *is attached hereto.*

_____ *was filed on* _____ *as*

Application Serial No. _____

and was amended _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International Application which designated at least one country other than the United States, listed below. I have also identified below any foreign application for patent or inventor's certificate, or PCT International Application having a filing date before that of the earliest application from which priority is claimed:

Prior Foreign Application(s)			*Priority Claimed*	
Number	*Country*	*Filing Date*	*Yes*	*No*
N/A			___	___
			___	___
			___	___
			___	___
			___	___

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

Provisional Application No.	*Filing Date*	*Status*
61/274,687	August 20, 2009	pending
61/337,612	February 11, 2010	pending

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s), or Section 365(c) of any PCT International Application(s) designating the United States listed below. Insofar as this application discloses and claims subject matter in addition to that disclosed in any such prior Application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56, which became available between the filing date(s) of such prior Application(s) and the national or PCT international filing date of this application:

Application Serial No.	*Filing Date*	*Status*
N/A		

And I hereby appoint

John P. White (Reg. No. 28,678); Christopher C. Dunham (Reg. No. 22,031); Norman H. Zivin (Reg. No. 25,385); William E. Pelton (Reg. No. 25,702); Robert D. Katz (Reg. No. 30,141); Paul Teng (Reg. No. 40,837); and Gary J. Gershik (Reg. No. 39,992).

and each of them, all c/o Cooper & Dunham LLP, 30 Rockefeller Plaza, 20th Floor, New York, New York 10112, my attorneys, each with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith and to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty.

5817.A

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Declaration and Power of Attorney *Page 3*

Please address all communications, and direct all telephone calls, regarding this application to:

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first joint inventor Ety Klinger
Inventor's signature [signature] *Date of signature* Aug 15, 2010
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JPW Rev. 8/13/08

Application
for
United States Letters Patent

To all whom it may concern:

Be it known that

Ety Klinger

have invented certain new and useful improvements in

LOW FREQUENCY GLATIRAMER ACETATE THERAPY

of which the following is a full, clear and exact description.

LOW FREQUENCY GLATIRAMER ACETATE THERAPY

This application claims the benefit of U.S. Provisional Application Nos. 61/274,687, filed August 20, 2009 and 61/337,612, filed February 11, 2010. The contents 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 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.

2. The method of claim 1, wherein alleviating a symptom comprises reducing the frequency of relapses.

3. The method of claim 1 or 2, wherein alleviating a symptom comprises reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient.

4. The method of any one of claims 1-3, wherein alleviating a symptom comprises reducing the mean number of new T_2 lesions in the brain of the patient.

5. The method of any one of claims 1-4, wherein alleviating a symptom comprises reducing the cumulative number of enhancing lesions on T_1-weighted images.

6. The method of any one of claims 1-5, wherein alleviating a symptom comprises reducing brain atrophy in the patient.

7. The method of any one of claims 1-6, wherein alleviating a symptom comprises increasing the time to a confirmed relapse in the patient.

8. The method of any one of claims 1-7, wherein alleviating a symptom comprises reducing the total number of confirmed relapses in the patient.

9. The method of any one of claims 1-8, wherein alleviating a symptom comprises reducing the progression of MRI-monitored disease activity in the patient.

10. The method of any one of claims 1-9, wherein alleviating a symptom comprises reducing total volume of T_2 lesions in the patient.

11. The method of any one of claims 1-10, wherein alleviating a symptom comprises reducing the number of new hypointense lesions on enhanced T_1 scans in the patient.

12. The method of any one of claims 1-11, wherein alleviating a symptom comprises reducing the total volume of hypointense lesions on enhanced T_1 scans.

13. The method of any one of claims 1-12, wherein alleviating a symptom comprises reducing the level of disability as measured by EDSS Score in the patient.

14. The method of any one of claims 1-13, wherein alleviating a symptom comprises reducing the change in EDSS Score in the patient.

15. The method of any one of claims 1-14, wherein alleviating a symptom comprises reducing the change in Ambulation Index in the patient.

16. The method of any one of claims 1-15, wherein alleviating a symptom comprises reducing the level of disability as measured by EuroQoL (EQ5D) questionnaire in the patient.

17. The method of any one of claims 1-16, wherein 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.

18. The method of any one of claims 1-17, wherein the pharmaceutical composition is in a prefilled syringe for self administration by the patient.

19. The method of any one of claims 1-17, wherein the therapeutically effective dose of glatiramer acetate is 40mg.

20. The method of any one of claims 1-19, wherein the patient has not received glatiramer acetate therapy prior to initiation of the subcutaneous injections.

21. The method of any one of claims 1-20, wherein 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.

22. 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.

23. The method of claim 22, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an

immediate post injection reaction.

24. The method of claim 22 or 23, 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.

25. The method of claim 22, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an injection site reaction.

26. The method of claim 22 or 24, wherein the injection site reaction is erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, or welt that occurs immediately around the site of injection.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

ABSTRACT

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.

Dkt. 2609/80798-A/JPW/GJG/ML

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ety Klinger
U.S. Serial No.	:	Not Yet Known
Filed	:	Herewith
For	:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY

30 Rockefeller Plaza
New York, New York 10112
August 19, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Please enter this Preliminary Amendment prior to examination of the above-identified application.

In the Claims:

Please replace the pending claims with the new claim set below, pursuant to 37 C.F.R. §1.121:

1. (Original) 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.

2. (Original) The method of claim 1, wherein alleviating a symptom comprises reducing the frequency of relapses.

3. (Currently Amended) The method of claim 1~~ or 2~~, wherein alleviating a symptom comprises reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient.

4. (Currently Amended) The method of~~ any one of claims 1-3~~ claim 1, wherein alleviating a symptom comprises reducing the mean number of new T_2 lesions in the brain of the patient.

5. (Currently Amended) The method of~~ any one of claims 1-4~~ claim 1, wherein alleviating a symptom comprises reducing the cumulative number of enhancing lesions on T_1-weighted images.

6. (Currently Amended) The method of~~ any one of claims 1-5~~

claim 1, wherein alleviating a symptom comprises reducing brain atrophy in the patient.

7. (Currently Amended) The method of ~~any one of claims 1-6~~ claim 1, wherein alleviating a symptom comprises increasing the time to a confirmed relapse in the patient.

8. (Currently Amended) The method of ~~any one of claims 1-7~~ claim 1, wherein alleviating a symptom comprises reducing the total number of confirmed relapses in the patient.

9. (Currently Amended) The method of ~~any one of claims 1-8~~ claim 1, wherein alleviating a symptom comprises reducing the progression of MRI-monitored disease activity in the patient.

10. (Currently Amended) The method of ~~any one of claims 1-9~~ claim 1, wherein alleviating a symptom comprises reducing total volume of T_2 lesions in the patient.

11. (Currently Amended) The method of ~~any one of claims 1-10~~ claim 1, wherein alleviating a symptom comprises reducing the number of new hypointense lesions on enhanced T_1 scans in the patient.

12. (Currently Amended) The method of ~~any one of claims 1-11~~ claim 1, wherein alleviating a symptom comprises reducing the total volume of hypointense lesions on enhanced T_1 scans.

13. (Currently Amended) The method of ~~any one of claims 1-12~~ claim 1, wherein alleviating a symptom comprises reducing the level of disability as measured by EDSS Score in the patient.

14. (Currently Amended) The method of ~~any one of claims 1-13~~ claim 1, wherein alleviating a symptom comprises reducing the change in EDSS Score in the patient.

15. (Currently Amended) The method of ~~any one of claims 1-14~~ claim 1, wherein alleviating a symptom comprises reducing the change in Ambulation Index in the patient.

16. (Currently Amended) The method of ~~any one of claims 1-15~~ claim 1, wherein alleviating a symptom comprises reducing the level of disability as measured by EuroQoL (EQ5D) questionnaire in the patient.

17. (Currently Amended) The method of ~~any one of claims 1-16~~ claim 1, wherein 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.

18. (Currently Amended) The method of ~~any one of claims 1-17~~ claim 1, wherein the pharmaceutical composition is in a prefilled syringe for self administration by the patient.

19. (Currently Amended) The method of ~~any one of claims 1-17~~ claim 1, wherein the therapeutically effective dose of glatiramer acetate is 40mg.

20. (Currently Amended) The method of ~~any one of claims 1-19~~ claim 1, wherein the patient has not received glatiramer acetate therapy prior to initiation of the subcutaneous injections.

21. (Currently Amended) The method of ~~any one of claims 1-20~~ claim 1, wherein 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.

22. (Original) 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.

23. (Original) The method of claim 22, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an immediate post injection reaction.

24. (Currently Amended) The method of claim 22~~ or 23~~, 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.

25. (Original) The method of claim 22, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing form of multiple sclerosis comprises reducing the frequency of an injection site reaction.

26. (Currently Amended) The method of claim 22~~ or 24~~, wherein the injection site reaction is erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, or welt that occurs immediately around the site of injection.

27-32. (Canceled)

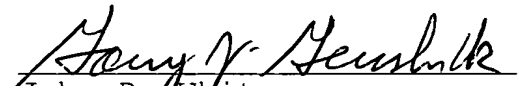
Remarks

By this Preliminary Amendment, applicants have canceled claims 27-32 and amended claims 3-21, 24 and 26 solely to reduce the filing fees. Accordingly, claims 1-26 are presented for examination.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed filing fee of $1,402.00, is deemed necessary in connection with the filing of this Preliminary Amendment. If any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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PATENT APPLICATION SERIAL NO._____

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE
FEE RECORD SHEET

08/23/2010 SZEWDIE1 00000003 12886684

01 FC:1011	330.00 OP
02 FC:1111	540.00 OP
03 FC:1311	220.00 OP
04 FC:1202	312.00 OP

PTO-1556
(5/87)

*U.S. Government Printing Office: 2002- 489-267/69033

PTO/SB/06 (12-04)

Filing Date: 081910

Approved for use through 7/31/2006. OMB 0651-0032

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	12/806,684

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY			OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))							330
SEARCH FEE (37 CFR 1.16(k), (i), or (m))							540
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))							220
TOTAL CLAIMS (37 CFR 1.16(i))	26 minus 20 =	6	X 26 =		OR	X 52 =	312
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =		X 110 =			X 220 =	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $270 ($135 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			N/A			N/A	
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1402

APPLICATION AS AMENDED – PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDI-TIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)	OR	RATE ($)	ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/806,684	08/19/2010	1614	1402	2609/80798-A/JPW/GJG/ML	26	2

CONFIRMATION NO. 3109

23432
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

FILING RECEIPT

OC000000043394851

Date Mailed: 09/10/2010

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Ety Klinger, Tel Aviv, ISRAEL;

Assignment For Published Patent Application

Teva Pharmaceutical Industries, Ltd.

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Robert Katz--30141
Gary Gershik--39992
Paul Teng--40837

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/274,687 08/20/2009
and claims benefit of 61/337,612 02/11/2010

Foreign Applications

If Required, Foreign Filing License Granted: 09/08/2010

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/806,684**

Projected Publication Date: 02/24/2011

Non-Publication Request: No

Early Publication Request: No

Title

Low frequency glatiramer acetate therapy

Preliminary Class

514

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office	Application Number	12/806,684
	Filing Date	August 19, 2010
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	First Named Inventor	Ety Klinger
	Art Unit	1614
	Examiner Name	
	Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	3	2005-0014694	01-20-2005	Yong et al.
	4	2009-0149541 A1	06-11-2009	Stark et al.
	5	2007-0037740	02-15-2007	Pinchasi et al.
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	10	6,054,430	04-25-2000	Konfino, et al.
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	15	6,939,539	09-06-2005	Konfino, et al.
	16	7,199,098	04-03-2007	Konfino, et al.
	17	2005-0171286	08-04-2005	Konfino et al.
	18	7,022,663	04-04-2006	Gilbert et al.
	19	6,214,791	04-10-2001	Arnon, et al.
	20	6,342,476	01-29-2002	Konfino, et al.
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	22	7,033,582	04-25-2006	Yong, et al.
	23	6,800,285	10-05-2004	Rodriguez et al.

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]

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	Filing Date	August 19, 2010
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	First Named Inventor	Ety Klinger
	Art Unit	1614
	Examiner Name	
	Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	24	2005/0019322 A1	01-27-2005	Rodriguez, et al.
	25	7,279,172	10-09-2007	Aharoni et al.
	26	7,425,332	09-16-2008	Aharoni et al.
	27	6,514,938	02-04-2003	Gad et al.
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	43	2006-0264354 A1	11-23-2006	Aharoni et al.
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]

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Form PTO-1449 (Substitute) **U.S. Department of Commerce Patent and Trademark Office**

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Ety Klinger
Art Unit	1614
Examiner Name	
Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	45	6,844,314	01-18-2005	Eisenbach-Schwartz et al.
	46	2002-0037848-A1	03-28-2002	Eisenbach-Schwartz et al.
	47	2006-0240463 A1	04-24-2006	Lancet
	48	12/861,655	08-23-2010	Stark et al.
	49	12/231,292	08-29-2008	Aharoni et al.
	50	12/761,367	04-15-2010	Altman et al.
	51	12/785,125	05-21-2010	Altman et al.

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	52	WO 00/027417	05-18-2000	Aharoni et al.	
	53	WO 05/041933	06-12-2003	Rosenberger	
	54	WO 2004/043995	05-27-2004	Bejan et al.	
	55	WO 2006/050122	05-11-2006	Ray et al.	
	56	WO 2008/006026	01-10-2008	Iyer et al.	
	57	WO 2009/070298	06-04-2009	Stark et al.	
	58	WO 00/20010	04-13-2000	Flechter, et al.	

EXAMINER SIGNATURE **DATE CONSIDERED**

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office		
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	**Application Number**	12/806,684
	Filing Date	August 19, 2010
	First Named Inventor	Ety Klinger
	Art Unit	1614
	Examiner Name	
	Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	International Search Report issued October 4, 2010 in connection with PCT International Application No. PCT/US10/02283, filed August 19, 2010 (Klinger)	
	2	Written Opinion of the International Searching Authority issued October 4, 2010 in connection with PCT International Application No. PCT/US10/02283, filed August 19, 2010 (Klinger)	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a checkmark here if English language Translation is attached.

2609/80798-A-PCT

JPW/GK/ACK

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
JOHN P. WHITE
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

RECEIVED
COOPER DUNHAM
OCT - 5 2010
DOCKET CLERK

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 80798-A-PCT/JPW/WS	Date of mailing *(day/month/year)* 04 OCT 2010 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/02283	International filing date *(day/month/year)* 19 August 2010 (19.08.2010)
Applicant TEVA PHARMACEUTICAL INDUSTRIES LTD.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19: 12-4-10
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders** IDS Based on Search 12-28-10 (80798-A)

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 80798-A-PCT/JPW/WS	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/02283	International filing date *(day/month/year)* 19 August 2010 (19.08.2010)	(Earliest) Priority Date *(day/month/year)* 20 August 2009 (20.08.2009)
Applicant TEVA PHARMACEUTICAL INDUSTRIES LTD.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/02283

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-21, 26
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/02283

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/12; A01N 37/44; A61K 31/195 (2010.01)
USPC - 514/566
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A01N 37/12; A01N 37/44; A61K 31/195 (2010.01)
USPC -- 514/566

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8): A01N 37/12; A01N 37/44; A61K 31/195 (2010.01)
USPC -- 514/2, 18, 564, 561, 557, 553

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO PubWEST: (PGPB, USPT, EPAB, JPAB)
glatiramer acetate, multiple sclerosis, subcutaneous, injection, relapse, Gd, inflammation, palpitation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/0014694 A1 (YONG, et al.) 20 January 2005 (20.01.2005), entire document, especially, [Abstract], para [0038], [0039], [0052], [0062], [0105], [0172]-[0174], [0180]-[0181]	1, 2, 22-25, 27-32
Y		3
Y	US 2009/0149541 A1 (STARK, et al.) 11 June 2009 (11.06.2009), entire document, especially, para [0027]-[0029]; Figs. 6-9	3
A	US 2007/0037740 A1 (PINCHASI, et al.) 15 February 2007 (15.02.2007), entire document	1-3, 22-25, 27-32
A	US 2009/0048181 A1 (SCHIPPER, et al.) 19 February 2009 (19.02.2009), entire document	1-3, 22-25, 27-32

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2010 (28.09.2010)	04 OCT 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: JOHN P. WHITE
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	04 OCT 2010
Applicant's or agent's file reference 80798-A-PCT/JPW/WS	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/02283	19 August 2010 (19.08.2010)	20 August 2009 (20.08.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 37/12; A01N 37/44; A61K 31/195 (2010.01)
USPC - 514/566

Applicant TEVA PHARMACEUTICAL INDUSTRIES LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	27 September 2010 (27.09.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/02283

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/02283

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-21, 26

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4-21, 26 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-21 and 26 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 4-21, 26

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/02283

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	3	YES
	Claims	1, 2, 22-25, 27-32	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-3, 22-25, 27-32	NO
Industrial applicability (IA)	Claims	1-3, 22-25, 27-32	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 2, 22-25 and 27-32 lack novelty under PCT Article 33(2) as being anticipated by US 2005/0014694 A1 (YONG, et al.).

Regarding claims 1 and 27, Yong teaches 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. (see [Abstract], para [0052], [0105], [0172], [0173]).

Regarding claim 2, Yong further teaches the method of claim 1, wherein alleviating a symptom comprises reducing the frequency of relapses (para [0173], [0174], [0180], [0181]).

Regarding claims 22, 28 and 29, Yong teaches 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 (see [Abstract], para [0052], [0105], [0172], [0173]).

Regarding claim 23, Yong further teaches the method of claim 22, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing sclerosis comprises reducing the form of frequency multiple of an immediate post injection reaction (para [0062]).

Regarding claim 24, Yong further teaches the method of claims 22 or 23, wherein the immediate post injection reaction is an infection (para [0038], [0039]).

Regarding claim 25, Yong further teaches the method of claim 22, wherein increasing the tolerability of glatiramer acetate treatment in the human patient suffering from a relapsing sclerosis comprises reducing the injection site reaction (para [0062], [0173], inflammation).

Regarding claims 30-32, Yong teaches Glatiramer acetate for use in treating relapsing remitting multiple sclerosis or 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 (see [Abstract], para [0052], [0105], [0172], [0173]).

Claim 3 lacks an inventive step under PCT Article (33) as being obvious over Yong in view of US 2009/0149541 A1 to Stark, et al. (herein Stark).

Regarding claim 3, Yong does not expressly teach the further claim limitation taught by Stark of wherein alleviating a symptom comprises reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient (see para [0027]-[0029]; Figs. 6-9). It would have been obvious to a person of ordinary skill in the art to reduce the amount of Gd-enhancing lesions in order to control the onset of multiple sclerosis, since these lesions in the brain were a well-known symptom of multiple sclerosis.

Claims 1-3, 22-25 and 27-32 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Electronic Acknowledgement Receipt

EFS ID:	9189472
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Adam Krol
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	07-JAN-2011
Filing Date:	19-AUG-2010
Time Stamp:	16:21:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	110107_2609_80798_A_IDS_JPW_GJG_ACK.pdf	389172 454445cec868b2f080dfc9f856989457f6262d33	no	8

Warnings:

Information:

2	Information Disclosure Statement (IDS) Filed (SB/08)	110107_2609_80798_A_Exhibit A_JPW_GJG_ACK.pdf	622899 17efb7273bc316d974c5e2ac7dfa26b3099a dd83	no	4
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Foreign Reference	110107_2609_80798_A_Exhibit 1_JPW_GJG_ACK.pdf	444817 0018eb88b84251f9bfc278e1b770fad7f630 e6ac	no	4
Warnings:					
Information:					
4	Foreign Reference	110107_2609_80798_A_Exhibit 2_JPW_GJG_ACK.pdf	355337 57744b1958beca6aa3db1f7eab3aa36fa33f cf6f	no	4
Warnings:					
Information:					
5	Foreign Reference	110107_2609_80798_A_Exhibit 3_JPW_GJG_ACK.pdf	4233559 8efdfec0293ce7261db142440c719fdfb4dd e58a	no	58
Warnings:					
Information:					
6	Foreign Reference	110107_2609_80798_A_Exhibit 4_JPW_GJG_ACK.pdf	3989890 866c6e2ce7bbeace5bbb41664f8af90e1dc ded4d	no	62
Warnings:					
Information:					
7	Foreign Reference	110107_2609_80798_A_Exhibit 5_JPW_GJG_ACK.pdf	1422449 13a6b052cc93211eaf225fc84556a54553db 80d2	no	26
Warnings:					
Information:					
8	Foreign Reference	110107_2609_80798_A_Exhibit 6_JPW_GJG_ACK.pdf	3497513 413cd638867d3702d2e6ecbf0cfedeeda51 362f2	no	47
Warnings:					
Information:					
9	Foreign Reference	110107_2609_80798_A_Exhibit 7_JPW_GJG_ACK.pdf	1849519 c2675dee482030665ae982bc917f5e0a560 418ab	no	28
Warnings:					
Information:					
10	Foreign Reference	110107_2609_80798_A_Exhibit 8_JPW_GJG_ACK.pdf	4248205 a7ee10b3c0a7e8e31ff083f4b789c46d2f8fe 707	no	73

Warnings:					
Information:					
11	Foreign Reference	110107_2609_80798_A_Exhibit 9_JPW_GJG_ACK.pdf	1605162 d53ae5e92a55caaca9e96082892cd977fa4ef070	no	26
Warnings:					
Information:					
			Total Files Size (in bytes):	22658522	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 2609/80798-A/JPW/GJG/ACK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Ety Klinger

Serial No. : 12/806,684

Filed : August 19, 2010 Group Art Unit: 1614

Conf. No. : 3109

For : LOW FREQUENCY GLATIRAMER ACETATE THERAPY

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
January 7, 2011

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, Applicant directs the Examiner's attention to the following items, which are listed on the Substitute PTO-1449 form attached hereto as **Exhibit A**. Items 1-2 were issued in connection with the counterpart PCT International Application, and items 3-6 were cited in item 1.

Copies of items 3 to 51 have not been included in accordance with 37 C.F.R. § 1.98(a)(2)(ii).

Copies of items 1-2 and 52-58 are attached hereto as **Exhibits 1-9**, respectively.

1. International Search Report issued October 4, 2010 in connection with PCT International Application No.

PCT/US10/02283, filed August 19, 2010 (Klinger) **(Exhibit 1)**;

2. Written Opinion of the International Searching Authority issued October 4, 2010 in connection with PCT International Application No. PCT/US10/02283, filed August 19, 2010 (Klinger) **(Exhibit 2)**;

3. U.S. Patent Application Publication US-2005-0014694, published January 20, 2005 (Yong et al.);

4. U.S. Patent Application Publication No. US 2009-0149541 A1, published June 11, 2009 (Stark et al.);

5. U.S. Patent Application Publication US 2007-0037740, published February 15, 2007 (Pinchasi et al.);

6. U.S. Patent Application Publication US 2009-0048181, published February 19, 2009 (Schipper et al.);

7. U.S. Patent No. 5,800,808, issued September 1, 1998 (Konfino, et al.);

8. U.S. Patent No. 5,981,589, issued November 9, 1999 (Konfino, et al.);

9. U.S. Patent No. 6,048,898, issued April 11, 2000 (Konfino, et al.);

10. U.S. Patent No. 6,054,430, issued April 25, 2000 (Konfino, et al.);

11. U.S. Patent No. 6,342,476, issued January 29, 2002 (Konfino, et al.);

12. U.S. Patent No. 6,362,161, issued March 26, 2002, (Konfino et al.);

13. U.S. Patent No. 6,620,847, issued September 16, 2003 (Konfino, et al.);

14. U.S. Patent Application Publication US-2004-0106554, published June 3, 2004 (Konfino et al.);

15. U.S. Patent No. 6,939,539, issued September 6, 2005 (Konfino, et al.);

16. U.S. Patent No. 7,199,098, issued April 3, 2007 (Konfino, et al.);

17. U.S. Patent Application Publication No. US-2005-0171286, published August 4, 2005 (Konfino et al.);

18. U.S. Patent No. 7,022,663, issued April 4, 2006 (Gilbert et al.);

19. U.S. Patent No. 6,214,791, issued April 10, 2001 (Arnon, et al.);

20. U.S. Patent No. 6,342,476, issued January 29, 2002 (Konfino, et al.);

21. U.S. Patent Application Publication US-2002-0077278, published June 20, 2002 (Yong et al.);

22. U.S. Patent No. 7,033,582, issued April 25, 2006 (Yong, et al.);

23. U.S. Patent No. 6,800,285, issued October 5, 2004 (Rodriguez et al.);

24. U.S. Patent Application Publication No. US-2005/0019322 A1, published January 27, 2005 (Rodriguez, et al.);

25. U.S. Patent No. 7,279,172, issued October 9, 2007 (Aharoni et al.);

26. U.S. Patent No. 7,425,332, issued September 16, 2008 (Aharoni et al.);

27. U.S. Patent No. 6,514,938, issued February 4, 2003 (Gad et al.);

28. U.S. Patent No. 6,800,287, issued October 5, 2004 (Gad et al.);

29. U.S. Patent No. 7,074,580, issued July 22, 2006 (Gad et al.);

30. U.S. Patent No. 7,163,802 B2 issued January 16, 2007 (Gad et al.);

31. U.S. Patent Application Publication No. US-2007-0048794 A1, published March 1, 2007 (Gad et al.);

32. U.S. Patent Application Publication No. US 2010-0210817 A1, published August 19, 2010 (Gad et al.);

33. U.S. Patent No. 7,429,374, issued September 30, 2008 (Ety Klinger);

34. U.S. Patent Application Publication No. US 2009-0053253 A1, published February 26, 2009 (Klinger);

35. U.S. Patent Application Publication No. 2007-0173442, published July 26, 2007 (Vollmer);

36. U.S. Patent Application Publication No. US-2005-0170004, published August 4, 2005 (Rosenberger);

37. U.S. Patent No. 7,560,100, issued June 14, 2009 (Pinchasi et al.);

38. U.S. Patent Application Publication No. US-2007-0054857 published March 8, 2007 (Pinchasi et al.);

39. U.S. Patent Application Publication No. 2007-0037740 A1, published February 15, 2007 (Pinchasi et al.);

40. U.S. Patent Application Publication No. 2010-0167983 A1, published July 1, 2010 (Kreitman et al.);

41. U.S. Patent No. 7,495,072, issued February 24, 2009 (Dolitzky);

42. U.S. Patent Application Publication No. US-2006-0172942 A1, published August 3, 2006 (Dolitzky);

43. U.S. Patent Application No. 2006-0264354 A1, published November 23, 2006 (Aharoni et al.);

44. U.S. Patent Application Publication No. US 2007-0059798, published March 15, 2007 (Gad);

45. U.S. Patent No. 6,844,314, issued January 18, 2005 (Eisenbach-Schwartz et al.);

46. U.S. Patent Application Publication No. US-2002-0037848-A1, published March 28, 2002 (Eisenbach-Schwartz et al.);

47. U.S. Patent Application Publication No. US-2006-0240463 A1, published April 24, 2006 (Lancet);

48. U.S. Serial No. 12/861,655, filed August 23, 2010 (Stark et al.);

49. U.S. Serial. No. 12/231,292, filed on August 29, 2008 (Aharoni et al.);

50. U.S. Serial No. 12/761,367, filed April 15, 2010 (Altman et al.);

51. U.S. Serial No. 12/785,125, filed May 21, 2010 (Altman et al.);

52. PCT International Publication No. WO 00/027417, published May 18, 2000 (Aharoni et al.) **(Exhibit 3)**;

53. PCT International Publication No. WO 05/041933, published June 12, 2003 (Rosenberger) **(Exhibit 4)**;

54. PCT International Publication No. WO 2004/043995, published May 27, 2004 (Bejan et al.) **(Exhibit 5)**;

55. PCT International Publication No. WO 2006/050122, published May 11, 2006 (Ray et al.) **(Exhibit 6)**;

56. PCT International Publication No. WO 2008/006026, published January 10, 2008 (Iyer et al.) **(Exhibit 7)**;

57. PCT International Publication No WO 2009/070298, published June 4, 2009 (Stark et al.) **(Exhibit 8)**; and

58. PCT International Publication No. WO 00/20010, published April 13, 2000 (Flechter, et al.) **(Exhibit 9)**.

The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO 1449.

This Information Disclosure Statement is being submitted under 37 C.F.R. § 1.97(b)(3), before the mailing of a first Office Action on the merits in connection with the subject application. Accordingly, no fee is required for filing this Information Disclosure Statement.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

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Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on January 7, 2011.

1/7/11

Adam C. Krol Date
Reg. No. 64,351

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/806,684	08/19/2010	Ety Klinger	2609/80798-A/JPW/GJG/ML

CONFIRMATION NO. 3109

23432
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

PUBLICATION NOTICE

Title: Low frequency glatiramer acetate therapy

Publication No.US-2011-0046065-A1
Publication Date:02/24/2011

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/806,684	08/19/2010	Ety Klinger	2609/80798-A/JPW/GJG/ML	3109

23432 7590 02/06/2012

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EXAMINER
ULM, JOHN D

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
02/06/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/806,684	KLINGER, ETY	
	Examiner	Art Unit	
	JOHN ULM	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-26* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-26* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/07/11*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1) Claims 1 to 26 are pending in the instant application. Claims 3 to 21, 24 and 26 have been amended and claims 27 to 32 canceled as requested by Applicant in the preliminary amendment filed concurrently with the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2) Claims 1 to 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description and enablement requirements. These claims encompass subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims encompass a method of alleviating a symptom of relapsing-remitting multiple sclerosis (RRMS) or increasing the tolerability of GA treatment in a human patient suffering from relapsing-remitting multiple sclerosis by the administration thereto of as few as three subcutaneous injections of 40mg of glatiramer acetate (a.k.a. copolymer-1) on alternate days durimng a one week period. However, neither the instant specification nor the art of record provides evidence that any measurable benefit has been shown, or can reasonably be predicted, to result from the administration of as

few as three doses of glatiramer acetate to an individual suffering from RRMS. Therefore, the claimed method is neither enabled nor described in the specification because Applicant had failed to demonstrate a correlation between the administration of only three 40mg doses of glatiramer acetate to an individual suffering from RRMS and any measurable benefit consequent thereto as of the effective filing date of the instant application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3) Claims 14 to 17 and 22 to 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3.1) Claim 14 is vague and indefinite because the there is no antecedent basis for “the change in EDSS Score”.

3.2) Claims 15 to 17 are vague and indefinite because the there is no antecedent basis for “the level of disability”.

3.3) Claims 22 to 26 are vague and indefinite because the limitations “increasing the tolerability” and “reducing the frequency” are both relative terms for which no points of reference are given. In addition, there is no antecedent basis for “the frequency”.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4) Claims 1 to 17 and 20 to 26 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by the Flechter et al. publication (Clinical Neuropharmacology 25(1);11-15, Jan-Feb 2002). Flechter et al. fairly taught a method of treating RRMS by the administration of a therapeutically effective amount of copolymer-1 (glatiramer acetate) in an alternate-day administration schedule for up to two years. Such a schedule would require the administration of copolymer-1 on three alternate days out of every other week, expressly meeting the limitations of claim 1. In so far as certain of the dependent claims require specific therapeutic outcomes, such outcomes would have been inherent to the treatment protocol of Flechter et al., as shown by the fact that the instant specification fails to identify any particular dosage that had been shown to be effective in achieving a specific outcome.

The discovery of an inherent property of a prior art process can not serve as a basis for patenting that process. See *Ex parte Novitski*, 26 USPQ2d 1389 (Bd. Pat. App. & Inter. 1993) (The Board rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of *P. cepacia*. A U.S. patent to Dart disclosed inoculation using *P. cepacia* type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating.).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5) Claims 18 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over the Flechter et al. publication cited above. These claims potentially distinguish from the method of Flechter et al. in that they require the therapeutically effective dose of glatiramer acetate to be contained in a prefilled syringe for self administration by the patient. The text in the second full paragraph on page 12 of Flechter et al. disclosed that the copolymer-1 employed therein was supplied as a sterile lyophilized material in single-dose vials and that patients or family members were instructed how to prepare and administer the drug. Weather the vial of Flechter et al. was capable of functioning as a syringe is not indicated, however, the transfer of that material into a syringe, as would have been required for administration, would have resulted in the production of a prefilled syringe for self administration by the patient.

6) Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over the Flechter et al. publication (Clinical Neuropharmacology 25(1);11-15, Jan-Feb 2002) in view of the Cohen et al. publication (Neurology 68:939-944, 20 Mar. 2007). In so far as these claims encompass a method of treating a subject suffering from RRMS by the administration thereto of 40 mg of glatiramer acetate on alternate days, this treatement

protocol would have been obvious to one of ordinary skill in the art in view of this combination of references.

Flechter et al. has been cited because it fairly taught a method of treating RRMS by the administration of a 20 mg dose of copolymer-1 (glatiramer acetate) to a subject suffering therefrom in an alternate-day administration schedule for up to two years. Flechter et al. did not identify a 40 mg dose of copolymer-1 (glatiramer acetate) as an effective dosage for the treatment of RRMS. As indicated by the abstract therein, the Cohen et al. publication fairly taught that the overall efficacy results described therein suggested that a 40 mg dose of copolymer-1 may be more effective than the currently approved 20 mg daily dose in reducing MRI activity and clinical relapse in an individual suffering from RRMS. To have combined the more effective 40 mg dosage of copolymer-1 described in Cohen et al. with the alternate-day administration schedule of Flechter et al. to reduce the frequency of injections that an RRMS patient is subjected to by half would have been *prima facie* obvious to one of ordinary skill in the art of neurology in view of this combination of references.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re*

Ockert, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101. 7)

7) Claims 1 to 9, 11 to 16 and 18 to 23 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 to 12 and 14 to 17 to 23 of copending Application No. 13/308,299. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 to 26 are provisionally rejected on the ground of nonstatutory double patenting over claims 13 and 18 to 20 of copending Application No. 13/308,299. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming essentially the same subject matter.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN ULM whose telephone number is (571)272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John D. Ulm/
Primary Examiner, Art Unit 1649

Notice of References Cited	Application/Control No. 12/806,684	Applicant(s)/Patent Under Reexamination KLINGER, ETY	
	Examiner JOHN ULM	Art Unit 1649	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
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	L	US-			
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	FLECHTER at al. Copolymer 1 (Glatiramer Acetate) in relapsing Forms of Multiple Sclerosis: Open Multicenter Study of Alternate-Day Administration, Jan-Feb 2002, Clinical Neuropharmacology 25(1):11-15
	V	COHEN et al. Randomized, Double-blind, Dose-comparison Study of Glatiramer Acetate in relapsing-remitting MS, 20 Mar. 2007, Neurology 68:939-944
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

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 See HELP RANGE before carrying out any RANGE search.

=> s alternate-day administration
         27643 ALTERNATE
        658134 DAY
       1825709 ADMINISTRATION
L1          46 ALTERNATE-DAY ADMINISTRATION
               (ALTERNATE(W)DAY(W)ADMINISTRATION)

=> d 1-46 ti so

L1   ANSWER 1 OF 46     MEDLINE .RTM.  on STN
TI   A case of small intestinal GIST maintained as a long stable disease
by
     imatinib mesylate 400 mg/day,   ***alternate***  -  ***day***
***administration***   for 2
     weeks followed by a 2 week interval.
SO   Gan to kagaku ryoho. Cancer & chemotherapy, (2011 Oct) Vol. 38, No.
10,
     pp. 1695-8.
     Journal code: 7810034. ISSN: 0385-0684. L-ISSN: 0385-0684.
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L1 ANSWER 2 OF 46 MEDLINE .RTM. on STN
TI Alternate day rosuvastatin, an underutilized option in statin intolerant
hyperlipidemic patients: a case report and literature review.
SO Tennessee medicine : journal of the Tennessee Medical Association, (2011
Feb) Vol. 104, No. 2, pp. 49-51.
Journal code: 9609310. ISSN: 1088-6222. L-ISSN: 1088-6222.

L1 ANSWER 3 OF 46 MEDLINE .RTM. on STN
TI Effects of steroid avoidance and novel protocols on growth in paediatric
renal transplant patients.
SO Pediatric nephrology (Berlin, Germany), (2010 Apr) Vol. 25, No. 4, pp.
747-52. Electronic Publication: 2009-10-21. Ref: 32
Journal code: 8708728. E-ISSN: 1432-198X. L-ISSN: 0931-041X.

L1 ANSWER 4 OF 46 MEDLINE .RTM. on STN
TI Does perioperative high-dose prednisolone have clinical benefits for
generalized myasthenia gravis?.
SO European journal of cardio-thoracic surgery : official journal of the
European Association for Cardio-thoracic Surgery, (2006 Jun) Vol. 29, No.
6, pp. 908-13. Electronic Publication: 2006-05-03.
Journal code: 8804069. ISSN: 1010-7940. L-ISSN: 1010-7940.

L1 ANSWER 5 OF 46 MEDLINE .RTM. on STN
TI Cost-effective G-CSF therapy strategies for cyclical neutropenia:
mathematical modelling based hypotheses.
SO Journal of theoretical biology, (2006 Feb 21) Vol. 238, No. 4, pp. 754-63.
Electronic Publication: 2005-08-22.
Journal code: 0376342. ISSN: 0022-5193. L-ISSN: 0022-5193.

L1 ANSWER 6 OF 46 MEDLINE .RTM. on STN
TI ***Alternate*** - ***day*** ***administration*** of pegvisomant maintains normal serum
insulin-like growth factor-I levels in patients with acromegaly.
SO The Journal of clinical endocrinology and metabolism, (2005 Mar) Vol. 90,
No. 3, pp. 1588-93. Electronic Publication: 2004-12-07.
Journal code: 0375362. ISSN: 0021-972X. L-ISSN: 0021-972X.

L1 ANSWER 7 OF 46 MEDLINE .RTM. on STN
TI Chronic treatment with tadalafil improves endothelial function in men with
increased cardiovascular risk.
SO European urology, (2005 Feb) Vol. 47, No. 2, pp. 214-20; discussion 220-2.
Journal code: 7512719. ISSN: 0302-2838. L-ISSN: 0302-2838.

L1 ANSWER 8 OF 46 MEDLINE .RTM. on STN

TI Alternate-day oral therapy with TS-1 for advanced gastric cancer.
SO International journal of clinical oncology / Japan Society of Clinical
    Oncology, (2004 Jun) Vol. 9, No. 3, pp. 143-8.
    Journal code: 9616295. ISSN: 1341-9625. L-ISSN: 1341-9625.

L1 ANSWER 9 OF 46 MEDLINE .RTM. on STN
TI Diagnosis and clinical management of chronic graft-versus-host disease.
SO International journal of hematology, (2004 Apr) Vol. 79, No. 3, pp. 221-8.
    Ref: 21
    Journal code: 9111627. ISSN: 0925-5710. L-ISSN: 0925-5710.

L1 ANSWER 10 OF 46 MEDLINE .RTM. on STN
TI A prospective trial of steroid withdrawal after renal transplantation in
    children: results obtained 1990 and 2002.
SO Transplantation proceedings, (2004 Mar) Vol. 36, No. 2 Suppl, pp.
    216S-219S.
    Journal code: 0243532. ISSN: 0041-1345. L-ISSN: 0041-1345.

L1 ANSWER 11 OF 46 MEDLINE .RTM. on STN
TI A case of type 4 gastric cancer with peritoneal dissemination successfully
    treated over 2 years by ***alternate*** - ***day***
administration of TS-1.
SO Gan to kagaku ryoho. Cancer & chemotherapy, (2004 Feb) Vol. 31, No. 2, pp.
    237-40.
    Journal code: 7810034. ISSN: 0385-0684. L-ISSN: 0385-0684.

L1 ANSWER 12 OF 46 MEDLINE .RTM. on STN
TI Is alternate daily dose of atorvastatin effective in treating patients
    with hyperlipidemia? The Alternate Day Versus Daily Dosing of Atorvastatin
    Study (ADDAS).
SO American heart journal, (2002 Oct) Vol. 144, No. 4, pp. 674-7.
    Journal code: 0370465. E-ISSN: 1097-6744. L-ISSN: 0002-8703.

L1 ANSWER 13 OF 46 MEDLINE .RTM. on STN
TI Cyclic neutropenia.
SO Seminars in hematology, (2002 Apr) Vol. 39, No. 2, pp. 89-94. Ref: 37
    Journal code: 0404514. ISSN: 0037-1963. L-ISSN: 0037-1963.

L1 ANSWER 14 OF 46 MEDLINE .RTM. on STN
TI Copolymer 1 (glatiramer acetate) in relapsing forms of multiple sclerosis:
    open multicenter study of ***alternate*** - ***day***
administration .
SO Clinical neuropharmacology, (2002 Jan-Feb) Vol. 25, No. 1, pp. 11-5.
    Journal code: 7607910. ISSN: 0362-5664. L-ISSN: 0362-5664.

L1 ANSWER 15 OF 46 MEDLINE .RTM. on STN
TI Synthetic glucocorticoid therapy--recent progress.
SO Nihon rinsho. Japanese journal of clinical medicine, (2000 Nov) Vol. 58,
No. 11, pp. 2353-63. Ref: 7
Journal code: 0420546. ISSN: 0047-1852. L-ISSN: 0047-1852.

L1 ANSWER 16 OF 46 MEDLINE .RTM. on STN
TI Relationship of plasma buprenorphine and norbuprenorphine to withdrawal
symptoms during dose induction, maintenance and withdrawal from sublingual
buprenorphine.
SO Addiction (Abingdon, England), (1998 Apr) Vol. 93, No. 4, pp. 549-59.
Journal code: 9304118. ISSN: 0965-2140. L-ISSN: 0965-2140.

L1 ANSWER 17 OF 46 MEDLINE .RTM. on STN
TI Synergism between sirolimus and 1,25-dihydroxyvitamin D3 in vitro and in
vivo.
SO Journal of neuroimmunology, (1997 Nov) Vol. 79, No. 2, pp. 138-47.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L1 ANSWER 18 OF 46 MEDLINE .RTM. on STN
TI A European phase II study of recombinant human granulocyte
colony-stimulating factor (lenograstim) in the treatment of severe chronic
neutropenia in children. Lenograstim Study Group.
SO European journal of pediatrics, (1997 Sep) Vol. 156, No. 9, pp. 693-700.
Journal code: 7603873. ISSN: 0340-6199. L-ISSN: 0340-6199.

L1 ANSWER 19 OF 46 MEDLINE .RTM. on STN
TI Growth and height in children after liver transplantation.
SO Transplant international : official journal of the European Society for
Organ Transplantation, (1996) Vol. 9 Suppl 1, pp. S160-3.
Journal code: 8908516. ISSN: 0934-0874. L-ISSN: 0934-0874.

L1 ANSWER 20 OF 46 MEDLINE .RTM. on STN
TI Prevention of murine experimental allergic encephalomyelitis: cooperative
effects of cyclosporine and 1 alpha, 25-(OH)2D3.
SO Journal of neuroimmunology, (1995 Sep) Vol. 61, No. 2, pp. 151-60.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L1 ANSWER 21 OF 46 MEDLINE .RTM. on STN
TI Prominent subepithelial deposits detected on 2nd renal biopsy in a boy
with membranoproliferative glomerulonephritis type I: a case report.
SO Nihon Jinzo Gakkai shi, (1995 Apr) Vol. 37, No. 4, pp. 247-52.
Journal code: 7505731. ISSN: 0385-2385. L-ISSN: 0385-2385.

L1 ANSWER 22 OF 46 MEDLINE .RTM. on STN
TI Alternate-day dosing during buprenorphine treatment of opioid dependence.
SO Life sciences, (1994) Vol. 54, No. 17, pp. 1215-28.
Journal code: 0375521. ISSN: 0024-3205. L-ISSN: 0024-3205.

L1 ANSWER 23 OF 46 MEDLINE .RTM. on STN
TI Bone mineral content of the third lumbar vertebra during 18 months of
prednisolone treatment for giant cell arteritis.
SO Clinical rheumatology, (1993 Dec) Vol. 12, No. 4, pp. 455-60.
Journal code: 8211469. ISSN: 0770-3198. L-ISSN: 0770-3198.

L1 ANSWER 24 OF 46 MEDLINE .RTM. on STN
TI Myasthenia gravis and steroid therapy.
SO Rinsho shinkeigaku = Clinical neurology, (1992 Feb) Vol. 32, No. 2, pp.
131-7.
Journal code: 0417466. ISSN: 0009-918X. L-ISSN: 0009-918X.

L1 ANSWER 25 OF 46 MEDLINE .RTM. on STN
TI Enhancement by tyrosine methyl ester of gastric carcinogenesis induced by
N-methyl-N'-nitro-N-nitrosoguanidine in Wistar rats.
SO International journal of cancer. Journal international du cancer, (1991
Jul 9) Vol. 48, No. 5, pp. 785-8.
Journal code: 0042124. ISSN: 0020-7136. L-ISSN: 0020-7136.

L1 ANSWER 26 OF 46 MEDLINE .RTM. on STN
TI Intermittent long-term adrenocorticosteroid treatment of myasthenia gravis.
SO Journal of neurology, (1991 Feb) Vol. 238, No. 1, pp. 16-8.
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L1 ANSWER 27 OF 46 MEDLINE .RTM. on STN
TI Prophylaxis of uric acid stones with alternate day doses of alkaline potassium salts.
SO The Journal of urology, (1991 Jan) Vol. 145, No. 1, pp. 97-9.
Journal code: 0376374. ISSN: 0022-5347. L-ISSN: 0022-5347.

L1 ANSWER 28 OF 46 MEDLINE .RTM. on STN
TI Enhancement by neurotensin of experimental carcinogenesis induced in rat
colon by azoxymethane.
SO British journal of cancer, (1990 Sep) Vol. 62, No. 3, pp. 368-71.
Journal code: 0370635. ISSN: 0007-0920. L-ISSN: 0007-0920.
Report No.: NLM-PMC1971434.

L1 ANSWER 29 OF 46 MEDLINE .RTM. on STN
TI Double-blind, placebo-controlled trial of alternate-day furosemide therapy
in infants with chronic bronchopulmonary dysplasia.

SO The Journal of pediatrics, (1990 Jul) Vol. 117, No. 1 Pt 1, pp. 112-8.
Journal code: 0375410. ISSN: 0022-3476. L-ISSN: 0022-3476.

L1 ANSWER 30 OF 46 MEDLINE .RTM. on STN
TI [Initial experiences with substitution treatment of hypoparathyroidism
with synthetic human parathyroid hormone].
Erste Erfahrungen in der Substitutionsbehandlung des Hypoparathyreoidismus
mit synthetischem humanen Parathormon.
SO Monatsschrift Kinderheilkunde : Organ der Deutschen Gesellschaft fur Kinderheilkunde, (1990 Mar) Vol. 138, No. 3, pp. 141-6.
Journal code: 8206462. ISSN: 0026-9298. L-ISSN: 0026-9298.

L1 ANSWER 31 OF 46 MEDLINE .RTM. on STN
TI Use of buprenorphine in the treatment of opioid addiction. II. Physiologic
and behavioral effects of daily and ***alternate*** - ***day*** ***administration*** and
abrupt withdrawal.
SO Clinical pharmacology and therapeutics, (1990 Apr) Vol. 47, No. 4, pp.
525-34.
Journal code: 0372741. ISSN: 0009-9236. L-ISSN: 0009-9236.

L1 ANSWER 32 OF 46 MEDLINE .RTM. on STN
TI Promotion by nialamide of gastric carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine in Wistar rats.
SO Japanese journal of cancer research : Gann, (1989 Jun) Vol. 80, No. 6, pp.
521-5.
Journal code: 8509412. ISSN: 0910-5050. L-ISSN: 0910-5050.

L1 ANSWER 33 OF 46 MEDLINE .RTM. on STN
TI Promotion by neurotensin of gastric carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine in Wistar rats.
SO Cancer research, (1989 Feb 15) Vol. 49, No. 4, pp. 843-6.
Journal code: 2984705R. ISSN: 0008-5472. L-ISSN: 0008-5472.

L1 ANSWER 34 OF 46 MEDLINE .RTM. on STN
TI Fluocortolone: pharmacokinetics and effect on ACTH and cortisol secretion
during daily and ***alternate*** - ***day*** ***administration*** .
SO European journal of clinical pharmacology, (1988) Vol. 35, No. 2, pp.
177-81.
Journal code: 1256165. ISSN: 0031-6970. L-ISSN: 0031-6970.

L1 ANSWER 35 OF 46 MEDLINE .RTM. on STN
TI Enhancement by prolonged administration of caerulein of experimental carcinogenesis induced by N-methyl-N'-nitro-N-nitrosoguanidine in rat

stomach.
SO Cancer research, (1988 Nov 15) Vol. 48, No. 22, pp. 6332-5.
Journal code: 2984705R. ISSN: 0008-5472. L-ISSN: 0008-5472.

L1 ANSWER 36 OF 46 MEDLINE .RTM. on STN
TI Favorable results of thymectomy combined with prednisolone ***alternate*** - ***day*** ***administration*** in myasthenia gravis.
SO The Japanese journal of surgery, (1987 Jan) Vol. 17, No. 1, pp. 14-20.
Journal code: 1302176. ISSN: 0047-1909. L-ISSN: 0047-1909.

L1 ANSWER 37 OF 46 MEDLINE .RTM. on STN
TI Highly purified leucocyte interferons for renal transplant recipients.
SO Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, (1982 Mar)
Vol. 36, No. 2, pp. 94-7.
Journal code: 8213295. ISSN: 0753-3322. L-ISSN: 0753-3322.

L1 ANSWER 38 OF 46 MEDLINE .RTM. on STN
TI Polymyositis--treatment and prognosis. A study of 107 patients.
SO Acta neurologica Scandinavica, (1982 Apr) Vol. 65, No. 4, pp. 280-300.
Journal code: 0370336. ISSN: 0001-6314. L-ISSN: 0001-6314.

L1 ANSWER 39 OF 46 MEDLINE .RTM. on STN
TI Inhibition of collagen accumulation by glucocorticoids in rat lung after
intratracheal bleomycin instillation.
SO Cancer research, (1982 Feb) Vol. 42, No. 2, pp. 405-8.
Journal code: 2984705R. ISSN: 0008-5472. L-ISSN: 0008-5472.

L1 ANSWER 40 OF 46 MEDLINE .RTM. on STN
TI Angiotensin converting enzyme. V. Serum levels as monitors of disease
activity in corticosteroid-treated sarcoidosis.
SO European journal of respiratory diseases, (1980 Apr) Vol. 61, No. 2, pp.
113-22.
Journal code: 8006891. ISSN: 0106-4339. L-ISSN: 0106-4339.

L1 ANSWER 41 OF 46 MEDLINE .RTM. on STN
TI Efficacy of troleandomycin in outpatients with severe, corticosteroid-dependent asthma.
SO The Journal of allergy and clinical immunology, (1980 Dec) Vol. 66, No. 6,
pp. 438-46.
Journal code: 1275002. ISSN: 0091-6749. L-ISSN: 0091-6749.

L1 ANSWER 42 OF 46 MEDLINE .RTM. on STN
TI Adriamycin in the treatment of resectible and irresectible primary hepatocellular carcinoma.

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SO   Annals of the Academy of Medicine, Singapore, (1980 Apr) Vol. 9, No.
2,
     pp. 256-9.
     Journal code: 7503289. ISSN: 0304-4602. L-ISSN: 0304-4602.

L1   ANSWER 43 OF 46     MEDLINE .RTM.  on STN
TI   Effect on bone growth of daily versus alternate-day corticosteroid
     administration: an experimental study.
SO   The Journal of laboratory and clinical medicine, (1977 Jan) Vol. 89,
No.
     1, pp. 120-30.
     Journal code: 0375375. ISSN: 0022-2143. L-ISSN: 0022-2143.

L1   ANSWER 44 OF 46     MEDLINE .RTM.  on STN
TI   Eosinophilic gastroenteritis.
SO   Southern medical journal, (1976 Apr) Vol. 69, No. 4, pp. 427-9.
     Journal code: 0404522. ISSN: 0038-4348. L-ISSN: 0038-4348.

L1   ANSWER 45 OF 46     MEDLINE .RTM.  on STN
TI   Methylprednisolone therapy and allograft rejection. Comparison of
daily
     and   ***alternate***     ***day***     ***administration***  .
SO   Transplantation, (1970 Dec) Vol. 10, No. 6, pp. 552-5.
     Journal code: 0132144. ISSN: 0041-1337. L-ISSN: 0041-1337.

L1   ANSWER 46 OF 46     MEDLINE .RTM.  on STN
TI   [  ***Alternate***     ***day***     ***administration***   of
prednisone in the treatment of
     various pediatric diseases].
     Utilisation de la prednisone un jour sur deux dans le traitement de
     certaines affections pediatriques.
SO   Therapie, (1968 Jul-Aug) Vol. 23, No. 4, pp. 919-27.
     Journal code: 0420544. ISSN: 0040-5957. L-ISSN: 0040-5957.


=> s l1 and sclerosis
         93740 SCLEROSIS
L2           1 L1 AND SCLEROSIS

=> d ti so

L2   ANSWER 1 OF 1     MEDLINE .RTM.  on STN
TI   Copolymer 1 (glatiramer acetate) in relapsing forms of multiple
       ***sclerosis***  : open multicenter study of   ***alternate***  -
***day***     ***administration***  .
SO   Clinical neuropharmacology, (2002 Jan-Feb) Vol. 25, No. 1, pp. 11-5.
     Journal code: 7607910. ISSN: 0362-5664. L-ISSN: 0362-5664.


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App Flt	Rec #	Sel	U	Doc ID	DBNM	Pub Date	Title	Inventor
	1	☐	☑	US 20120015891 A1	PGPB	20120119	DEPOT SYSTEMS COMPRISING GLATIRAMER OR A PHARMACOLOGICALLY ACCEPTABLE SALT THEREOF	Marom; Ehud et al.
	2	☐	☑	US 20110182805 A1	PGPB	20110728	Nanoparticle fabrication methods, systems, and materials	DeSimone; Joseph M et al.
	3	☐	☑	US 20110171176 A1	PGPB	20110714	COMPLEMENT ANTAGONISTS AND USES THEREOF	Baas; Frank et al.
	4	☐	☑	US 20110112010 A1	PGPB	20110512	OCTANOIC ACID FORMULATIONS AND METHODS OF TREATMENT USING THE SAME	Hallett; Mark et al.
	5	☐	☑	US 20110082149 A1	PGPB	20110407	METABOLICALLY INERT ANTIFOLATES FOR TREATING DISORDERS OF ABNORMAL CELLULAR PROLIFERATION AND INFLAMMATION	Roberts; Michael J. et al.
	6	☐	☑	US 20110081338 A1	PGPB	20110407	METABOLICALLY INERT ANTIFOLATES FOR TREATING DISORDERS OF ABNORMAL CELLULAR PROLIFERATION AND INFLAMMATION	Roberts; Michael J. et al.
	7	☐	☑	US 20110044944 A1	PGPB	20110224	ANTI-INFLAMMATORY COMPOSITIONS FOR TREATING BRAIN INFLAMMATION	THEOHARIDES; Theoharis C.
	8	☐	☑	US 20110021590 A1	PGPB	20110127	AMINOPYRROLIDINONE DERIVATIVES AND USES THEREOF	Duggan; Mark E.
	9	☐	☑	US 20110015132 A1	PGPB	20110120	SYNERGISTIC 5'-METHYLTHIOADENOSINE COMBINATIONS	vila Zaragoza; Matias Antonio et al.
	10	☐	☑	US 20110009360 A1	PGPB	20110113	Nutraceutical Composition and Methods for Preventing or Treating Multiple Sclerosis	Kasper; Lloyd H. et al.
	11	☐	☑	US 20100305023 A1	PGPB	20101202	Method of Delaying The Onset of Clinically Definite Multiple Sclerosis	Stark; Yafit et al.
	12	☐	☑	US 20100291610 A1	PGPB	20101118	Regulating Stem Cells	Porat; Yael et al.

	13	☐	☑	US 20100255061 A1	PGPB	20101007	Posterior Segment Drug Delivery	de Juan, JR.; Eugene et al.
	14	☐	☑	US 20100209914 A1	PGPB	20100819	METHODS, SYSTEMS, AND KITS FOR EVALUATING MULTIPLE SCLEROSIS	Bigwood; Douglas et al.
	15	☐	☑	US 20100160250 A1	PGPB	20100624	METHOD FOR TREATING INFLAMMATORY CONDITIONS	Douglass, III; James G. et al.
+ 1	16	☐	☑	US 20100136007 A1	PGPB	20100603	CSF1R EXTRACELLULAR DOMAIN FUSION MOLECULES AND TREATMENTS USING SAME	LIN; Haishan et al.
	40	☐	☑	US 8080246 B2	USPT	20111220	Colony stimulating factor 1 receptor (CSF1R) extracellular domain fusion molecules	Lin; Haishan et al.
	17	☐	☑	US 20100130540 A1	PGPB	20100527	AZAQUINOLINONE DERIVATIVES AND USES THEREOF	Duggan; Mark E.
	18	☐	☑	US 20100129359 A1	PGPB	20100527	Methods to facilitate transmission of large molecules across the blood-brain, blood-eye, and blood-nerve barriers	Tobinick; Edward Lewis
	19	☐	☑	US 20100034771 A1	PGPB	20100211	Combination Of Cytokine And Cytokine Receptor For Altering Immune System Functioning	Ezerzer; Chai et al.
	20	☐	☑	US 20100028994 A1	PGPB	20100204	NANOPARTICLE FABRICATION METHODS, SYSTEMS, AND MATERIALS FOR FABRICATING ARTIFICIAL RED BLOOD CELLS	DeSimone; Joseph M. et al.
	21	☐	☑	US 20090325934 A1	PGPB	20091231	METHOD FOR TREATING NEUROLOGICAL AND NEUROPATHIC DISEASES USING RHO KINASE INHIBITOR COMPOUNDS	Navratil; Tomas et al.
	22	☐	☑	US 20090275496 A1	PGPB	20091105	Effective quantitation of complex peptide mixtures in tissue samples and improved therapeutic methods	Baldwin; Sam et al.
	23	☐	☑	US 20090215892 A1	PGPB	20090827	Octanol Formulations and Methods of Treatment Using the Same	Nahab; Fatta B. et al.
	24	☐	☑	US 20090149541 A1	PGPB	20090611	Method of delaying the onset of clinically definite multiple sclerosis	Stark; Yafit et al.
	25	☐	☑	US 20090136947 A1	PGPB	20090528	METHOD FOR CONDUCTING AN ASSAY FOR NEUTRALIZING ANTIBODIES	TOVEY; MICHAEL G. et al.
	26	☐	☑	US 20090060873 A1	PGPB	20090305	Novel synthetic triterpenoids and methods of use in the treatment and prevention of multiple scleroris	Sporn; Michael B. et al.

	27	☐	☑	US 20080118553 A1	PGPB	20080522	Tannate salt form of polypeptide mixtures, their preparation and use	Frenkel; Anton et al.
	28	☐	☑	US 20070264481 A1	PGPB	20071115	Isolated and fixed micro and nano structures and methods thereof	DeSimone; Joseph M. et al.
+ 1	29	☐	☑	US 20070048794 A1	PGPB	20070301	Copolymer 1 related polypeptides for use as molecular weight markers and for therapeutic use	Gad; Alexander et al.
	44	☐	☑	US 7615359 B2	USPT	20091110	Copolymer 1 related polypeptides for use as molecular weight markers and for therapeutic use	Gad; Alexander et al.
	30	☐	☑	US 20070037740 A1	PGPB	20070215	Combination therapy with glatiramer acetate and alphacalcidol for the treatment of multiple sclerosis	Pinchasi; Irit et al.
	31	☐	☑	US 20060198822 A1	PGPB	20060907	Treatment for multiple sclerosis	Booth; David Richmond et al.
+ 1	32	☐	☑	US 20060111272 A1	PGPB	20060525	Metabolically inert antifolates for treating disorders of abnormal cellular proliferation and inflammation	Roberts; Michael J. et al.
	42	☐	☑	US 7829708 B2	USPT	20101109	Metabolically inert antifolates for treating disorders of abnormal cellular proliferation and inflammation	Roberts; Michael J. et al.
+ 1	33	☐	☑	US 20060013905 A1	PGPB	20060119	Anti-inflammatory compositions for treating multiple sclerosis	Tehoharides; Theoharis C.
	41	☐	☑	US 7906153 B2	USPT	20110315	Anti-inflammatory compositions for treating multiple sclerosis	Theoharides; Theoharis C.
	34	☐	☑	US 20050186192 A1	PGPB	20050825	Autologous T-cell vaccines materials and methods	Zang, Jingwu Z.
	35	☐	☑	US 20050170004 A1	PGPB	20050804	Nanoparticles for drug delivery	Rosenberger, Vered et al.
	36	☐	☑	US 20040048871 A1	PGPB	20040311	Use of high dose intravenous methotrexate, with leucovorin rescue, to treat early multiple sclerosis and other diseases of the central nervous system	Rowe, Vernon D.
	37	☐	☑	US 20040013643 A1	PGPB	20040122	Methods for treatment of multiple sclerosis with statins	Mach, Francois
+ 1	38	☐	☑	US 20030091578 A1	PGPB	20030515	Autologous T-cell vaccines materials and methods	Zhang, Jingwu
	43	☐	☑	US 7658926 B2	USPT	20100209	Autologous T-cell vaccines materials and methods	Zang; Jingwu Z.

	+ 1	39	☐	☑	US 20030008875 A1	PGPB	20030109	Use of regularly scheduled high dose intravenous methotrexate therapy, with interim administration of immunomodulatory agents, to treat multiple sclerosis and other diseases of the central nervous system	Rowe, Vernon D.
		45	☐	☑	US 6903100 B2	USPT	20050607	USE OF REGULARLY SCHEDULED HIGH DOSE INTRAVENOUS METHOTREXATE THERAPY, WITH INTERIM ADMINISTRATION OF IMMUNOMODULATORY AGENTS, TO TREAT MULTIPLE SCLEROSIS AND OTHER DISEASES OF THE CENTRAL NERVOUS SYSTEM	Rowe; Vernon D.

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☐	L5	L4 same l1	1047
☐	L4	L2 or ms	2928855
☐	L3	L2 or ms	2928855
☐	L2	multiple sclerosis	58595
☐	L1	glatiramer	1693

END OF SEARCH HISTORY

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12806684	KLINGER, ETY
	Examiner	Art Unit
	JOHN ULM	1649

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Searched inventor's name in NPL & PALM; Searched Medline, WEST & Google for: sclerosis, glatimer acetate, copolymer 1, alternate-day, dosage	02/02/2012	JDU

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner


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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 14:45:56 ON 24 JAN 2012

=> file medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.24       0.24

FILE 'MEDLINE' ENTERED AT 14:46:09 ON 24 JAN 2012

 FILE LAST UPDATED: 24 Jan 2012 (20120124/UP).  FILE COVERS 1946 TO DATE.

 MEDLINE(R) is a registered trademark of the U.S. National Library of
 Medicine (NLM).

 MEDLINE and LMEDLINE have been updated with the 2011 Medical Subject
 Headings (MeSH) vocabulary and tree numbers from the U.S.  National
Library
 of Medicine (NLM).  Additional information is available at:


http://www.nlm.nih.gov/pubs/techbull/nd10/nd10_medline_data_changes_2011.
html.

 The 2011 Medline reload was completed on January 22, 2011.
 See HELP RLOAD for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

 See HELP RANGE before carrying out any RANGE search.

=> s glatiramer
L1          808 GLATIRAMER

=> s multiple sclerosis
         735608 MULTIPLE
          93740 SCLEROSIS
L2        47163 MULTIPLE SCLEROSIS
                (MULTIPLE(W)SCLEROSIS)

=> s l2 or MS
         160214 MS
L3       188180 L2 OR MS

=> s l1(p) l3
L4          693 L1(P) L3

=> s l4 and relapsing
          17031 RELAPSING
L5          370 L4 AND RELAPSING
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=> d 70-370 ti so

L5   ANSWER 70 OF 370     MEDLINE .RTM.  on STN
TI     ***Glatiramer***   acetate: a review of its use in
***relapsing***  -remitting
       ***multiple***     ***sclerosis***   and in delaying the onset of
clinically definite
       ***multiple***     ***sclerosis***  .
SO   Drugs, (2010 Aug 20) Vol. 70, No. 12, pp. 1545-77.
     Journal code: 7600076. ISSN: 0012-6667. L-ISSN: 0012-6667.

L5   ANSWER 71 OF 370     MEDLINE .RTM.  on STN
TI   Emerging therapies in   ***relapsing***  -remitting multiple
sclerosis.
SO   Reviews on recent clinical trials, (2010 Sep) Vol. 5, No. 3, pp.
179-88.
     Journal code: 101270873. E-ISSN: 1876-1038.

L5   ANSWER 72 OF 370     MEDLINE .RTM.  on STN
TI   Therapy of multiple sclerosis in children and adolescents.
SO   Clinical neurology and neurosurgery, (2010 Sep) Vol. 112, No. 7, pp.
     633-40.  Electronic Publication: 2010-05-14.
     Journal code: 7502039. E-ISSN: 1872-6968. L-ISSN: 0303-8467.

L5   ANSWER 73 OF 370     MEDLINE .RTM.  on STN
TI   Cyclophosphamide Treatment of MS: Current Therapeutic Approaches and
     Treatment Regimens.
SO   International MS journal / MS Forum, (2010 Jan) Vol. 17, No. 1, pp.
12-8.
     Journal code: 9804403. ISSN: 1352-8963. L-ISSN: 1352-8963.

L5   ANSWER 74 OF 370     MEDLINE .RTM.  on STN
TI   Effects of   ***glatiramer***   acetate on spasticity in previously
     interferon-beta-treated and treatment-naive patients with
       ***relapsing***  -remitting   ***multiple***     ***sclerosis***
: a prospective,
     nonrandomized, open-label, uncontrolled, observational pilot study.
SO   Clinical therapeutics, (2010 Jun) Vol. 32, No. 6, pp. 1061-6.
     Journal code: 7706726. E-ISSN: 1879-114X. L-ISSN: 0149-2918.

L5   ANSWER 75 OF 370     MEDLINE .RTM.  on STN
TI   The role of natalizumab in the treatment of multiple sclerosis.
SO   The American journal of managed care, (2010 Jun) Vol. 16, No. 6
Suppl, pp.
     S164-70.
     Journal code: 9613960. E-ISSN: 1936-2692. L-ISSN: 1088-0224.

L5   ANSWER 76 OF 370     MEDLINE .RTM.  on STN
TI     ***Glatiramer***   acetate for   ***multiple***
***sclerosis***  .
SO   Cochrane database of systematic reviews (Online), (2010) No. 5, pp.
     CD004678.  Electronic Publication: 2010-05-12. Ref: 135
     Journal code: 100909747. E-ISSN: 1469-493X. L-ISSN: 1361-6137.
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L5 ANSWER 77 OF 370 MEDLINE .RTM. on STN
TI Current and future disease-modifying therapies in multiple sclerosis.
SO International journal of clinical practice, (2010 Apr) Vol. 64, No. 5, pp.
637-50.
Journal code: 9712381. E-ISSN: 1742-1241. L-ISSN: 1368-5031.

L5 ANSWER 78 OF 370 MEDLINE .RTM. on STN
TI Efficacy of natalizumab in second line therapy of ***relapsing*** -remitting
multiple sclerosis: results from a multi-center study in German speaking
countries.
SO European journal of neurology : the official journal of the European
Federation of Neurological Societies, (2010 Jan) Vol. 17, No. 1, pp. 31-7.
Electronic Publication: 2009-07-09.
Journal code: 9506311. E-ISSN: 1468-1331. L-ISSN: 1351-5101.

L5 ANSWER 79 OF 370 MEDLINE .RTM. on STN
TI Freedom from disease activity in multiple sclerosis.
SO Neurology, (2010 Apr 27) Vol. 74 Suppl 3, pp. S3-7.
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 80 OF 370 MEDLINE .RTM. on STN
TI Risks vs benefits of ***glatiramer*** acetate: a changing perspective as new
therapies emerge for ***multiple*** ***sclerosis*** .
SO Therapeutics and clinical risk management, (2010) Vol. 6, pp. 153-72.
Electronic Publication: 2010-04-15.
Journal code: 101253281. E-ISSN: 1178-203X. L-ISSN: 1176-6336.
Report No.: NLM-PMC2857614.

L5 ANSWER 81 OF 370 MEDLINE .RTM. on STN
TI [Update on current care guidelines: diagnostics, treatment and rehabilitation of multiple sclerosis].
MS-taudin diagnoosi, laakehoito ja kuntoutus.
SO Duodecim; laaketieteellinen aikakauskirja, (2010) Vol. 126, No. 2, pp.
199-200.
Journal code: 0373207. ISSN: 0012-7183. L-ISSN: 0012-7183.

L5 ANSWER 82 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate and the glatiramoid class of immunomodulator drugs in
multiple ***sclerosis*** : an update.
SO Expert opinion on drug metabolism & toxicology, (2010 May) Vol. 6, No. 5,
pp. 643-60. Ref: 103
Journal code: 101228422. E-ISSN: 1744-7607. L-ISSN: 1742-5255.

L5 ANSWER 83 OF 370 MEDLINE .RTM. on STN

TI Effect of immunomodulatory medication on regional gray matter loss in
relapsing -remitting multiple sclerosis--a longitudinal MRI study.
SO Brain research, (2010 Apr 14) Vol. 1325, pp. 174-82. Electronic Publication: 2010-02-16.
Journal code: 0045503. E-ISSN: 1872-6240. L-ISSN: 0006-8993.

L5 ANSWER 84 OF 370 MEDLINE .RTM. on STN
TI Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients.
SO Journal of managed care pharmacy : JMCP, (2010 Apr) Vol. 16, No. 3, pp.
206-16.
Journal code: 9605854. ISSN: 1083-4087. L-ISSN: 1083-4087.

L5 ANSWER 85 OF 370 MEDLINE .RTM. on STN
TI Failure of ***glatiramer*** acetate to modify the peripheral T cell repertoire
of ***relapsing*** -remitting ***multiple*** ***sclerosis*** patients.
SO Clinical immunology (Orlando, Fla.), (2010 Apr) Vol. 135, No. 1, pp. 33-42. Electronic Publication: 2010-02-08.
Journal code: 100883537. E-ISSN: 1521-7035. L-ISSN: 1521-6616.

L5 ANSWER 86 OF 370 MEDLINE .RTM. on STN
TI [Immunomodulatory treatments for multiple sclerosis: lessons from direct
comparative studies].
Traitements de fond de la sclerose en plaques: enseignements des etudes
randomisees comparatives directes.
SO Revue neurologique, (2010 Jan) Vol. 166, No. 1, pp. 21-31. Electronic
Publication: 2009-07-10. Ref: 35
Journal code: 2984779R. ISSN: 0035-3787. L-ISSN: 0035-3787.

L5 ANSWER 87 OF 370 MEDLINE .RTM. on STN
TI [Current treatment for multiple sclerosis].
Traitements actuels de la sclerose en plaques.
SO Presse medicale (Paris, France : 1983), (2010 Mar) Vol. 39, No. 3, pp.
381-8. Electronic Publication: 2010-01-27.
Journal code: 8302490. ISSN: 0755-4982. L-ISSN: 0755-4982.

L5 ANSWER 88 OF 370 MEDLINE .RTM. on STN
TI Continuous long-term immunomodulatory therapy in ***relapsing*** ***multiple***
sclerosis : results from the 15-year analysis of the US prospective
open-label study of ***glatiramer*** acetate.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2010 Mar) Vol. 16,

No. 3, pp. 342-50. Electronic Publication: 2010-01-27.
Journal code: 9509185. E-ISSN: 1477-0970. L-ISSN: 1352-4585.
Report No.: NLM-PMC2850588.

L5 ANSWER 89 OF 370 MEDLINE .RTM. on STN
TI Effect of oral antihistamine on local injection site reactions with self-administered glatiramer acetate.
SO The Journal of neuroscience nursing : journal of the American Association of Neuroscience Nurses, (2010 Feb) Vol. 42, No. 1, pp. 40-6.
Journal code: 8603596. ISSN: 0888-0395. L-ISSN: 0888-0395.

L5 ANSWER 90 OF 370 MEDLINE .RTM. on STN
TI Natalizumab reduces clinical and MRI activity in multiple sclerosis patients with high disease activity: results from a multicenter study in Switzerland.
SO European neurology, (2010) Vol. 63, No. 2, pp. 101-6. Electronic Publication: 2010-01-16.
Journal code: 0150760. E-ISSN: 1421-9913. L-ISSN: 0014-3022.

L5 ANSWER 91 OF 370 MEDLINE .RTM. on STN
TI Healthcare resource utilization following switch or discontinuation in multiple sclerosis patients on disease modifying drugs.
SO Journal of medical economics, (2010 Mar) Vol. 13, No. 1, pp. 90-8.
Journal code: 9892255. E-ISSN: 1941-837X. L-ISSN: 1369-6998.

L5 ANSWER 92 OF 370 MEDLINE .RTM. on STN
TI Sleep disturbance and fatigue in mild ***relapsing*** remitting multiple sclerosis patients on chronic immunomodulant therapy: an actigraphic study.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2010 Feb) Vol. 16, No. 2, pp. 238-47. Electronic Publication: 2009-12-22.
Journal code: 9509185. E-ISSN: 1477-0970. L-ISSN: 1352-4585.

L5 ANSWER 93 OF 370 MEDLINE .RTM. on STN
TI Renewal of the T-cell compartment in ***multiple*** ***sclerosis*** patients treated with ***glatiramer*** acetate.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2010 Feb) Vol. 16, No. 2, pp. 218-27. Electronic Publication: 2009-12-09.
Journal code: 9509185. E-ISSN: 1477-0970. L-ISSN: 1352-4585.

L5 ANSWER 94 OF 370 MEDLINE .RTM. on STN
TI The mechanism of action of ***glatiramer*** acetate treatment in ***multiple*** ***sclerosis*** .
SO Neurology, (2010 Jan 5) Vol. 74 Suppl 1, pp. S25-30. Ref: 31
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 95 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate for the treatment of ***multiple*** ***sclerosis*** : evidence
for a dual anti-inflammatory and neuroprotective role.
SO Journal of the neurological sciences, (2009 Dec) Vol. 287 Suppl 1, pp.
S17-23.
Journal code: 0375403. E-ISSN: 1878-5883. L-ISSN: 0022-510X.

L5 ANSWER 96 OF 370 MEDLINE .RTM. on STN
TI Health and quality of life in patients with ***relapsing*** multiple
sclerosis: making the intangible tangible.
SO Journal of the neurological sciences, (2009 Dec) Vol. 287 Suppl 1, pp.
S11-6.
Journal code: 0375403. E-ISSN: 1878-5883. L-ISSN: 0022-510X.

L5 ANSWER 97 OF 370 MEDLINE .RTM. on STN
TI Immunoglobulin-like transcript 3, an inhibitor of T cell activation, is
reduced on blood monocytes during multiple sclerosis relapses and is
induced by interferon beta-1b.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2010 Jan) Vol. 16,
No. 1, pp. 30-8. Electronic Publication: 2009-12-09.
Journal code: 9509185. E-ISSN: 1477-0970. L-ISSN: 1352-4585.

L5 ANSWER 98 OF 370 MEDLINE .RTM. on STN
TI Recent developments in multiple sclerosis therapeutics.
SO BMC medicine, (2009) Vol. 7, pp. 74. Electronic Publication: 2009-12-07.
Journal code: 101190723. E-ISSN: 1741-7015. L-ISSN: 1741-7015.
Report No.: NLM-PMC3224941.

L5 ANSWER 99 OF 370 MEDLINE .RTM. on STN
TI Monoclonal antibodies in the treatment of multiple sclerosis.
SO Current medicinal chemistry, (2009) Vol. 16, No. 36, pp. 4858-68.
Ref:
142
Journal code: 9440157. E-ISSN: 1875-533X. L-ISSN: 0929-8673.

L5 ANSWER 100 OF 370 MEDLINE .RTM. on STN
TI Serum levels of CXCL13 are elevated in active multiple sclerosis.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2009 Nov) Vol. 15,
No. 11, pp. 1271-9. Electronic Publication: 2009-10-05.
Journal code: 9509185. E-ISSN: 1477-0970. L-ISSN: 1352-4585.

L5 ANSWER 101 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate in combination with minocycline in patients with
relapsing --remitting ***multiple*** ***sclerosis*** : results of a Canadian,

multicenter, double-blind, placebo-controlled trial.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2009 Oct) Vol. 15,
No. 10, pp. 1183-94. Electronic Publication: 2009-09-23.
Journal code: 9509185. E-ISSN: 1477-0970. L-ISSN: 1352-4585.

L5 ANSWER 102 OF 370 MEDLINE .RTM. on STN
TI Disease-modifying agents in the treatment of multiple sclerosis: a review
of long-term outcomes.
SO CNS & neurological disorders drug targets, (2009 Dec) Vol. 8, No. 6, pp.
512-9. Ref: 50
Journal code: 101269155. E-ISSN: 1996-3181. L-ISSN: 1871-5273.

L5 ANSWER 103 OF 370 MEDLINE .RTM. on STN
TI [***Glatiramer*** acetate in interferon beta non respondent
relapsing -remitting ***multiple*** ***sclerosis***
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Acetato de glatiramero en pacientes con esclerosis multiple
remitente-recurrente no respondedores al interferon beta.
SO Neurologia (Barcelona, Spain), (2009 Sep) Vol. 24, No. 7, pp. 435-8.
Journal code: 9005460. ISSN: 0213-4853. L-ISSN: 0213-4853.

L5 ANSWER 104 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate improves regulatory T-cell function by
expansion of
naive CD4(+)CD25(+)FOXP3(+)CD31(+) T-cells in patients with
multiple
sclerosis .
SO Journal of neuroimmunology, (2009 Nov 30) Vol. 216, No. 1-2, pp. 113-7.
Electronic Publication: 2009-07-31.
Journal code: 8109498. E-ISSN: 1872-8421. L-ISSN: 0165-5728.

L5 ANSWER 105 OF 370 MEDLINE .RTM. on STN
TI A reassessment of the plateauing relationship between T2 lesion load and
disability in MS.
SO Neurology, (2009 Nov 10) Vol. 73, No. 19, pp. 1538-42. Electronic
Publication: 2009-09-30.
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 106 OF 370 MEDLINE .RTM. on STN
TI Molecular profiling of ***glatiramer*** acetate early treatment effects in
multiple ***sclerosis*** .
SO Disease markers, (2009) Vol. 27, No. 2, pp. 63-73.
Journal code: 8604127. E-ISSN: 1875-8630. L-ISSN: 0278-0240.

L5 ANSWER 107 OF 370 MEDLINE .RTM. on STN
TI Effect of ***glatiramer*** acetate on conversion to clinically definite

multiple ***sclerosis*** in patients with clinically isolated syndrome
(PreCISe study): a randomised, double-blind, placebo-controlled trial.
SO Lancet, (2009 Oct 31) Vol. 374, No. 9700, pp. 1503-11. Electronic Publication: 2009-10-06.
Journal code: 2985213R. E-ISSN: 1474-547X. L-ISSN: 0140-6736.

L5 ANSWER 108 OF 370 MEDLINE .RTM. on STN
TI Diagnosing and managing multiple sclerosis.
SO The Practitioner, (2009 Sep) Vol. 253, No. 1721, pp. 25-30, 2-3.
Journal code: 0404245. ISSN: 0032-6518. L-ISSN: 0032-6518.

L5 ANSWER 109 OF 370 MEDLINE .RTM. on STN
TI 250 microg or 500 microg interferon beta-1b versus 20 mg ***glatiramer***
acetate in ***relapsing*** -remitting ***multiple*** ***sclerosis*** : a prospective,
randomised, multicentre study.
SO Lancet neurology, (2009 Oct) Vol. 8, No. 10, pp. 889-97. Electronic Publication: 2009-09-02.
Journal code: 101139309. E-ISSN: 1474-4465. L-ISSN: 1474-4422.

L5 ANSWER 110 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate treatment in PPMS: why males appear to respond favorably.
SO Journal of the neurological sciences, (2009 Nov 15) Vol. 286, No. 1-2, pp.
92-8. Electronic Publication: 2009-05-08.
Journal code: 0375403. E-ISSN: 1878-5883. L-ISSN: 0022-510X.

L5 ANSWER 111 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate for ***multiple*** ***sclerosis*** : a comprehensive review of
mechanisms and clinical efficacy.
SO Expert review of neurotherapeutics, (2002 May) Vol. 2, No. 3, pp. 285-94.
Journal code: 101129944. E-ISSN: 1744-8360. L-ISSN: 1473-7175.

L5 ANSWER 112 OF 370 MEDLINE .RTM. on STN
TI Comparing the cost-effectiveness of disease-modifying drugs for the first-line treatment of ***relapsing*** -remitting multiple sclerosis.
SO Journal of managed care pharmacy : JMCP, (2009 Sep) Vol. 15, No. 7, pp.
543-55.
Journal code: 9605854. ISSN: 1083-4087. L-ISSN: 1083-4087.

L5 ANSWER 113 OF 370 MEDLINE .RTM. on STN
TI Cost effectiveness of ***glatiramer*** acetate and natalizumab in
relapsing -remitting ***multiple*** ***sclerosis***
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SO Applied health economics and health policy, (2009) Vol. 7, No. 2, pp.
91-108.
Journal code: 101150314. ISSN: 1175-5652. L-ISSN: 1175-5652.

L5 ANSWER 114 OF 370 MEDLINE .RTM. on STN
TI Natalizumab in the treatment of multiple sclerosis.
SO Therapeutics and clinical risk management, (2009 Jun) Vol. 5, No. 3, pp.
585-94. Electronic Publication: 2009-08-03.
Journal code: 101253281. ISSN: 1176-6336. L-ISSN: 1176-6336.
Report No.: NLM-PMC2724189.

L5 ANSWER 115 OF 370 MEDLINE .RTM. on STN
TI Cost-effectiveness of four immunomodulatory therapies for
relapsing -remitting multiple sclerosis: a Markov model based on data a
Balkan country in socioeconomic transition.
SO Vojnosanitetski pregled. Military-medical and pharmaceutical review, (2009
Jul) Vol. 66, No. 7, pp. 556-62.
Journal code: 21530700R. ISSN: 0042-8450. L-ISSN: 0042-8450.

L5 ANSWER 116 OF 370 MEDLINE .RTM. on STN
TI Incidence and factors associated with treatment failure in the CLIMB multiple sclerosis cohort study.
SO Journal of the neurological sciences, (2009 Sep 15) Vol. 284, No. 1-2, pp.
116-9. Electronic Publication: 2009-05-09.
Journal code: 0375403. E-ISSN: 1878-5883. L-ISSN: 0022-510X.

L5 ANSWER 117 OF 370 MEDLINE .RTM. on STN
TI Benefits of ***glatiramer*** acetate in the treatment of ***relapsing*** -remitting
multiple ***sclerosis*** .
SO Expert review of pharmacoeconomics & outcomes research, (2009 Jun) Vol. 9,
No. 3, pp. 205-14. Ref: 66
Journal code: 101132257. E-ISSN: 1744-8379. L-ISSN: 1473-7167.

L5 ANSWER 118 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate and interferon beta-1b: a study of outcomes among
patients with ***multiple*** ***sclerosis*** .
SO Advances in therapy, (2009 May) Vol. 26, No. 5, pp. 552-62. Electronic
Publication: 2009-05-14.
Journal code: 8611864. E-ISSN: 1865-8652. L-ISSN: 0741-238X.

L5 ANSWER 119 OF 370 MEDLINE .RTM. on STN
TI Cost effectiveness and budget impact of natalizumab in patients with
relapsing multiple sclerosis.
SO Current medical research and opinion, (2009 Jun) Vol. 25, No. 6, pp.
1445-54.

Journal code: 0351014. E-ISSN: 1473-4877. L-ISSN: 0300-7995.

L5 ANSWER 120 OF 370 MEDLINE .RTM. on STN
TI Efficacy of treatment of ***MS*** with IFNbeta-1b or ***glatiramer*** acetate by monthly brain MRI in the BECOME study.
SO Neurology, (2009 Jun 9) Vol. 72, No. 23, pp. 1976-83. Electronic Publication: 2009-03-11.
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 121 OF 370 MEDLINE .RTM. on STN
TI Clinically isolated syndrome and multiple sclerosis: rethinking the arsenal.
SO Current treatment options in neurology, (2009 May) Vol. 11, No. 3, pp. 193-202.
Journal code: 9815940. ISSN: 1092-8480. L-ISSN: 1092-8480.

L5 ANSWER 122 OF 370 MEDLINE .RTM. on STN
TI Natalizumab is effective as second line therapy in the treatment of ***relapsing*** remitting multiple sclerosis.
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2009 Mar) Vol. 16, No. 3, pp. 424-6.
Journal code: 9506311. E-ISSN: 1468-1331. L-ISSN: 1351-5101.

L5 ANSWER 123 OF 370 MEDLINE .RTM. on STN
TI New options for early treatment of multiple sclerosis.
SO Journal of the neurological sciences, (2009 Feb 1) Vol. 277 Suppl 1, pp. S9-S11. Ref: 15
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 124 OF 370 MEDLINE .RTM. on STN
TI Immunosuppression followed by immunomodulation.
SO Journal of the neurological sciences, (2009 Feb 1) Vol. 277 Suppl 1, pp. S50-4. Ref: 21
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 125 OF 370 MEDLINE .RTM. on STN
TI Concepts of induction and escalation therapy in multiple sclerosis.
SO Journal of the neurological sciences, (2009 Feb 1) Vol. 277 Suppl 1, pp. S42-5. Ref: 26
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 126 OF 370 MEDLINE .RTM. on STN
TI What can be learned from open direct comparative trials in multiple sclerosis?.
SO Journal of the neurological sciences, (2009 Feb 1) Vol. 277 Suppl 1, pp. S25-8. Ref: 18
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 127 OF 370 MEDLINE .RTM. on STN
TI Lessons from randomised direct comparative trials.
SO Journal of the neurological sciences, (2009 Feb 1) Vol. 277 Suppl 1, pp.
S19-24. Ref: 23
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 128 OF 370 MEDLINE .RTM. on STN
TI Link of the mechanisms of action of glatiramer acetate to its long-term
clinical data.
SO Journal of the neurological sciences, (2009 Feb 1) Vol. 277 Suppl 1, pp.
S12-5. Ref: 20
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 129 OF 370 MEDLINE .RTM. on STN
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Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 130 OF 370 MEDLINE .RTM. on STN
TI Clinical trials in multiple sclerosis: current and future requirements -
potential pitfalls.
SO Journal of neurology, (2008 Dec) Vol. 255 Suppl 6, pp. 66-8.
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 131 OF 370 MEDLINE .RTM. on STN
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SO Neuropsychiatric disease and treatment, (2007 Apr) Vol. 3, No. 2, pp.
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Journal code: 101240304. ISSN: 1176-6328. L-ISSN: 1176-6328.
Report No.: NLM-PMC2654627.

L5 ANSWER 132 OF 370 MEDLINE .RTM. on STN
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SO Expert opinion on pharmacotherapy, (2009 Mar) Vol. 10, No. 4, pp. 657-68.
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L5 ANSWER 133 OF 370 MEDLINE .RTM. on STN
TI GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled
study.
SO Neurology, (2009 Mar 3) Vol. 72, No. 9, pp. 806-12.
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.
Report No.: NLM-PMC2821836.

L5 ANSWER 134 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate reduces the risk for experimental cerebral malaria: a
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SO Malaria journal, (2009) Vol. 8, pp. 36. Electronic Publication: 2009-02-27.
Journal code: 101139802. E-ISSN: 1475-2875. L-ISSN: 1475-2875.
Report No.: NLM-PMC2651188.

L5 ANSWER 135 OF 370 MEDLINE .RTM. on STN
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Journal code: 100968555. E-ISSN: 1471-2377. L-ISSN: 1471-2377.
Report No.: NLM-PMC2631506.

L5 ANSWER 136 OF 370 MEDLINE .RTM. on STN
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multiple sclerosis.
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2009 Feb) Vol. 16, No. 2, pp. 262-7. Electronic Publication: 2008-12-09.
Journal code: 9506311. E-ISSN: 1468-1331. L-ISSN: 1351-5101.

L5 ANSWER 137 OF 370 MEDLINE .RTM. on STN
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SO Neuroscience and behavioral physiology, (2009 Jan) Vol. 39, No. 1, pp.
47-51.
Journal code: 0330471. ISSN: 0097-0549. L-ISSN: 0097-0549.

L5 ANSWER 138 OF 370 MEDLINE .RTM. on STN
TI Fatigue characteristics in multiple sclerosis: the North American Research
Committee on Multiple Sclerosis (NARCOMS) survey.
SO Health and quality of life outcomes, (2008) Vol. 6, pp. 100. Electronic
Publication: 2008-11-14.
Journal code: 101153626. E-ISSN: 1477-7525. L-ISSN: 1477-7525.
Report No.: NLM-PMC2596785.

L5 ANSWER 139 OF 370 MEDLINE .RTM. on STN
TI [Long-term effects of ***glatiramer*** acetate in ***multiple*** ***sclerosis***].
Activite a long terme de l'acetate de glatiramere dans le traitement de la
sclerose en plaques : etat des connaissances.
SO Revue neurologique, (2008 Nov) Vol. 164, No. 11, pp. 917-26. Electronic

Publication: 2008-05-16.
Journal code: 2984779R. ISSN: 0035-3787. L-ISSN: 0035-3787.

L5 ANSWER 140 OF 370 MEDLINE .RTM. on STN
TI Multiple sclerosis and reproductive risks in women.
SO Reproductive sciences (Thousand Oaks, Calif.), (2008 Oct) Vol. 15, No. 8,
pp. 755-64. Ref: 63
Journal code: 101291249. E-ISSN: 1933-7205. L-ISSN: 1933-7191.

L5 ANSWER 141 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate after mitoxantrone induction improves MRI markers of
lesion volume and permanent tissue injury in ***MS*** .
SO Journal of neurology, (2008 Oct) Vol. 255, No. 10, pp. 1473-8. Electronic
Publication: 2008-10-07.
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 142 OF 370 MEDLINE .RTM. on STN
TI How effective is intravenous immunoglobulin for the treatment of
relapsing -remitting multiple sclerosis?.
SO Nature clinical practice. Neurology, (2008 Nov) Vol. 4, No. 11, pp. 588-9.
Electronic Publication: 2008-10-14.
Journal code: 101261799. E-ISSN: 1745-8358. L-ISSN: 1745-834X.

L5 ANSWER 143 OF 370 MEDLINE .RTM. on STN
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sclerosis-directed immuno-therapies.
SO Clinical neurology and neurosurgery, (2008 Nov) Vol. 110, No. 9, pp.
951-7. Electronic Publication: 2008-05-27. Ref: 48
Journal code: 7502039. ISSN: 0303-8467. L-ISSN: 0303-8467.

L5 ANSWER 144 OF 370 MEDLINE .RTM. on STN
TI Impact of co-prescribed ***glatiramer*** acetate and antihistamine therapy on
the likelihood of relapse among patients with ***multiple*** ***sclerosis*** .
SO The Journal of neuroscience nursing : journal of the American Association
of Neuroscience Nurses, (2008 Oct) Vol. 40, No. 5, pp. 281-90.
Journal code: 8603596. ISSN: 0888-0395. L-ISSN: 0888-0395.

L5 ANSWER 145 OF 370 MEDLINE .RTM. on STN
TI Comparison of subcutaneous interferon beta-1a with ***glatiramer*** acetate in
patients with ***relapsing*** ***multiple*** ***sclerosis*** (the REbif vs
Glatiramer Acetate in ***Relapsing*** ***MS*** Disease [REGARD] study): a
multicentre, randomised, parallel, open-label trial.
SO Lancet neurology, (2008 Oct) Vol. 7, No. 10, pp. 903-14. Electronic
Publication: 2008-09-11.

Journal code: 101139309. ISSN: 1474-4422. L-ISSN: 1474-4422.

L5 ANSWER 146 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate-associated, CD30+, primary, cutaneous, anaplastic large-cell lymphoma.
SO Archives of neurology, (2008 Oct) Vol. 65, No. 10, pp. 1378-9.
Journal code: 0372436. E-ISSN: 1538-3687. L-ISSN: 0003-9942.

L5 ANSWER 147 OF 370 MEDLINE .RTM. on STN
TI Clinical markers of therapeutic response to disease modifying drugs.
SO Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, (2008 Sep)
Vol. 29 Suppl 2, pp. S211-3. Ref: 18
Journal code: 100959175. ISSN: 1590-1874. L-ISSN: 1590-1874.

L5 ANSWER 148 OF 370 MEDLINE .RTM. on STN
TI CD4+CD25+FoxP3+PD1- regulatory T cells in acute and stable ***relapsing*** -remitting multiple sclerosis and their modulation by therapy.
SO The FASEB journal : official publication of the Federation of American
Societies for Experimental Biology, (2008 Oct) Vol. 22, No. 10, pp. 3500-8. Electronic Publication: 2008-06-27.
Journal code: 8804484. E-ISSN: 1530-6860. L-ISSN: 0892-6638.

L5 ANSWER 149 OF 370 MEDLINE .RTM. on STN
TI Managing adverse effects of disease-modifying agents used for treatment of
multiple sclerosis.
SO Current medical research and opinion, (2008 Sep) Vol. 24, No. 9, pp. 2679-90. Electronic Publication: 2008-08-08.
Journal code: 0351014. E-ISSN: 1473-4877. L-ISSN: 0300-7995.

L5 ANSWER 150 OF 370 MEDLINE .RTM. on STN
TI Concomitant radiochemotherapy in a patient with multiple sclerosis and
glioblastoma.
SO Clinical neuropathology, (2008 Sep-Oct) Vol. 27, No. 5, pp. 346-50.
Journal code: 8214420. ISSN: 0722-5091. L-ISSN: 0722-5091.

L5 ANSWER 151 OF 370 MEDLINE .RTM. on STN
TI Effects of ***glatiramer*** acetate on fatigue and days of absence from work
in first-time treated ***relapsing*** -remitting ***multiple*** ***sclerosis*** .
SO Health and quality of life outcomes, (2008) Vol. 6, pp. 67. Electronic
Publication: 2008-09-05.
Journal code: 101153626. E-ISSN: 1477-7525. L-ISSN: 1477-7525.
Report No.: NLM-PMC2542355.

L5 ANSWER 152 OF 370 MEDLINE .RTM. on STN
TI Predictors of the location of multiple sclerosis relapse.

SO Journal of neurology, neurosurgery, and psychiatry, (2008 Oct) Vol. 79,
No. 10, pp. 1190-3. Electronic Publication: 2008-01-25.
Journal code: 2985191R. E-ISSN: 1468-330X. L-ISSN: 0022-3050.

L5 ANSWER 153 OF 370 MEDLINE .RTM. on STN
TI Health-related quality of life in multiple sclerosis: current evidence,
measurement and effects of disease severity and treatment.
SO CNS drugs, (2008) Vol. 22, No. 10, pp. 827-39. Ref: 50
Journal code: 9431220. ISSN: 1172-7047. L-ISSN: 1172-7047.

L5 ANSWER 154 OF 370 MEDLINE .RTM. on STN
TI Interferon-beta1b for the treatment of multiple sclerosis.
SO Expert opinion on drug metabolism & toxicology, (2008 Aug) Vol. 4, No. 8,
pp. 1111-7. Ref: 26
Journal code: 101228422. ISSN: 1742-5255. L-ISSN: 1742-5255.

L5 ANSWER 155 OF 370 MEDLINE .RTM. on STN
TI ***Multiple*** ***sclerosis*** : ***glatiramer*** acetate induces anti-inflammatory T
cells in the cerebrospinal fluid.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2008 Jul) Vol. 14,
No. 6, pp. 749-58.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 156 OF 370 MEDLINE .RTM. on STN
TI Long-term (up to 22 years), open-label, compassionate-use study of
glatiramer acetate in ***relapsing*** -remitting ***multiple*** ***sclerosis*** .
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2008 May) Vol. 14,
No. 4, pp. 494-9. Electronic Publication: 2008-01-21.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 157 OF 370 MEDLINE .RTM. on STN
TI Paradoxically aggressive multiple sclerosis in the face of natalizumab
therapy.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2008 Jun) Vol. 14,
No. 5, pp. 708-10.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 158 OF 370 MEDLINE .RTM. on STN
TI Combination treatment of ***Glatiramer*** Acetate and Minocycline affects
phenotype expression of blood monocyte-derived dendritic cells in
Multiple ***Sclerosis*** patients.
SO Journal of neuroimmunology, (2008 Jul 15) Vol. 197, No. 2, pp. 140-6.
Electronic Publication: 2008-06-13.

Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L5 ANSWER 159 OF 370 MEDLINE .RTM. on STN
TI Reduction of free radicals in ***multiple*** ***sclerosis*** : effect of
glatiramer acetate (Copaxone).
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2008 Jul) Vol. 14,
No. 6, pp. 739-48. Electronic Publication: 2008-05-27.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 160 OF 370 MEDLINE .RTM. on STN
TI Mechanisms of action of disease-modifying agents and brain volume changes
in multiple sclerosis.
SO Neurology, (2008 Jul 8) Vol. 71, No. 2, pp. 136-44. Ref: 60
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 161 OF 370 MEDLINE .RTM. on STN
TI [Biological treatment of multiple sclerosis].
Biologisk behandling af multipel sklerose.
SO Ugeskrift for laeger, (2008 Jun 9) Vol. 170, No. 24, pp. 2156-9.
Journal code: 0141730. E-ISSN: 1603-6824. L-ISSN: 0041-5782.

L5 ANSWER 162 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate after induction therapy with mitoxantrone in
relapsing ***multiple*** ***sclerosis*** .
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2008 Jun) Vol. 14,
No. 5, pp. 663-70. Electronic Publication: 2008-04-18.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 163 OF 370 MEDLINE .RTM. on STN
TI Cost-effectiveness analyses of natalizumab (Tysabri) compared with other
disease-modifying therapies for people with highly active
relapsing -remitting multiple sclerosis in the UK.
SO PharmacoEconomics, (2008) Vol. 26, No. 7, pp. 617-27.
Journal code: 9212404. ISSN: 1170-7690. L-ISSN: 1170-7690.

L5 ANSWER 164 OF 370 MEDLINE .RTM. on STN
TI Immunomodulating drugs in multiple sclerosis: compliance, satisfaction and
adverse effects evaluation in a German multiple sclerosis population.
SO Current medical research and opinion, (2007 Jun) Vol. 23, No. 6, pp.
1209-15. Electronic Publication: 2007-04-23.
Journal code: 0351014. E-ISSN: 1473-4877. L-ISSN: 0300-7995.

L5 ANSWER 165 OF 370 MEDLINE .RTM. on STN
TI Combination therapy for the treatment of multiple sclerosis: challenges
and opportunities.

SO Current medical research and opinion, (2007 Jun) Vol. 23, No. 6, pp. 1199-208. Electronic Publication: 2007-04-23. Ref: 59
Journal code: 0351014. E-ISSN: 1473-4877. L-ISSN: 0300-7995.

L5 ANSWER 166 OF 370 MEDLINE .RTM. on STN
TI Recombinant interferon beta or ***glatiramer*** acetate for delaying
conversion of the first demyelinating event to ***multiple*** ***sclerosis*** .
SO Cochrane database of systematic reviews (Online), (2008) No. 2, pp. CD005278. Electronic Publication: 2008-04-16. Ref: 31
Journal code: 100909747. E-ISSN: 1469-493X. L-ISSN: 1361-6137.

L5 ANSWER 167 OF 370 MEDLINE .RTM. on STN
TI Natural naive CD4+CD25+CD127low regulatory T cell (Treg) development and
function are disturbed in multiple sclerosis patients: recovery of memory
Treg homeostasis during disease progression.
SO Journal of immunology (Baltimore, Md. : 1950), (2008 May 1) Vol. 180, No.
9, pp. 6411-20.
Journal code: 2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767.

L5 ANSWER 168 OF 370 MEDLINE .RTM. on STN
TI Anti-depressant use in association with interferon and ***glatiramer***
acetate treatment in ***multiple*** ***sclerosis*** .
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2008 Apr) Vol. 14,
No. 3, pp. 406-11. Electronic Publication: 2007-11-06.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 169 OF 370 MEDLINE .RTM. on STN
TI Combination therapies in multiple sclerosis.
SO Journal of neurology, (2008 Mar) Vol. 255 Suppl 1, pp. 51-60. Ref: 45
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 170 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate: evidence for a dual mechanism of action.
SO Journal of neurology, (2008 Mar) Vol. 255 Suppl 1, pp. 26-36. Ref: 53
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 171 OF 370 MEDLINE .RTM. on STN
TI A shift from adaptive to innate immunity: a potential mechanism of disease
progression in multiple sclerosis.
SO Journal of neurology, (2008 Mar) Vol. 255 Suppl 1, pp. 3-11. Ref: 23
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 172 OF 370 MEDLINE .RTM. on STN

TI Therapeutic outcome 3 years after switching of immunomodulatory therapies
in patients with ***relapsing*** -remitting multiple sclerosis in Argentina.
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2008 Apr) Vol. 15, No. 4, pp. 386-93.
Journal code: 9506311. E-ISSN: 1468-1331. L-ISSN: 1351-5101.

L5 ANSWER 173 OF 370 MEDLINE .RTM. on STN
TI Variation of serum uric acid levels in multiple sclerosis during relapses
and immunomodulatory treatment.
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2008 Apr) Vol. 15, No. 4, pp. 394-7. Electronic Publication: 2008-02-26.
Journal code: 9506311. E-ISSN: 1468-1331. L-ISSN: 1351-5101.

L5 ANSWER 174 OF 370 MEDLINE .RTM. on STN
TI Lobular panniculitis at the site of ***glatiramer*** acetate injections for
the treatment of ***relapsing*** -remitting ***multiple*** ***sclerosis*** . A report of
two cases.
SO Journal of cutaneous pathology, (2008 Apr) Vol. 35, No. 4, pp. 407-10.
Journal code: 0425124. E-ISSN: 1600-0560. L-ISSN: 0303-6987.

L5 ANSWER 175 OF 370 MEDLINE .RTM. on STN
TI Short-term combination of ***glatiramer*** acetate with i.v. steroid treatment
preceding treatment with GA alone assessed by MRI-disease activity in
patients with ***relapsing*** -remitting ***multiple*** ***sclerosis*** .
SO Journal of the neurological sciences, (2008 Mar 15) Vol. 266, No. 1-2, pp.
44-50. Electronic Publication: 2007-09-25.
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 176 OF 370 MEDLINE .RTM. on STN
TI Multiple sclerosis: interferon beta for some serious forms.
SO Prescrire international, (2007 Dec) Vol. 16, No. 92, pp. 252-7.
Journal code: 9439295. ISSN: 1167-7422. L-ISSN: 1167-7422.

L5 ANSWER 177 OF 370 MEDLINE .RTM. on STN
TI Mitoxantrone as induction treatment in aggressive ***relapsing*** remitting
multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients.
SO Journal of neurology, neurosurgery, and psychiatry, (2008 Jan) Vol. 79,
No. 1, pp. 52-6. Electronic Publication: 2007-09-10.
Journal code: 2985191R. E-ISSN: 1468-330X. L-ISSN: 0022-3050.

L5 ANSWER 178 OF 370 MEDLINE .RTM. on STN
TI Treatment of secondary progressive multiple sclerosis: current recommendations and future prospects.
SO BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, (1999 Oct) Vol. 12, No. 4, pp. 267-77.
Journal code: 9705305. ISSN: 1173-8804. L-ISSN: 1173-8804.

L5 ANSWER 179 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate could be a potential therapeutic agent for Parkinson's
disease through its neuroprotective and anti-inflammatory effects.
SO Medical hypotheses, (2007) Vol. 69, No. 6, pp. 1219-21. Electronic Publication: 2007-06-04.
Journal code: 7505668. ISSN: 0306-9877. L-ISSN: 0306-9877.

L5 ANSWER 180 OF 370 MEDLINE .RTM. on STN
TI A longitudinal observational study of a cohort of patients with ***relapsing*** -remitting ***multiple*** ***sclerosis*** treated with ***glatiramer*** acetate.
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2007 Nov) Vol. 14, No. 11, pp.
1266-74.
Journal code: 9506311. E-ISSN: 1468-1331. L-ISSN: 1351-5101.

L5 ANSWER 181 OF 370 MEDLINE .RTM. on STN
TI Mechanism of action of ***glatiramer*** acetate in treatment of ***multiple***
sclerosis .
SO Neurotherapeutics : the journal of the American Society for Experimental
NeuroTherapeutics, (2007 Oct) Vol. 4, No. 4, pp. 647-53. Ref: 67
Journal code: 101290381. ISSN: 1933-7213. L-ISSN: 1878-7479.

L5 ANSWER 182 OF 370 MEDLINE .RTM. on STN
TI Investigating ***glatiramer*** acetate for ***relapsing*** -remitting ***multiple***
sclerosis at the double dose--is more better?.
SO Nature clinical practice. Neurology, (2007 Oct) Vol. 3, No. 10, pp. 540-1.
Electronic Publication: 2007-09-04.
Journal code: 101261799. E-ISSN: 1745-8358. L-ISSN: 1745-834X.

L5 ANSWER 183 OF 370 MEDLINE .RTM. on STN
TI Erythema nodosum and ***glatiramer*** acetate treatment in ***relapsing*** -remitting ***multiple*** ***sclerosis***
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SO Multiple sclerosis (Houndmills, Basingstoke, England), (2007 Aug) Vol. 13,
No. 7, pp. 941-4.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 184 OF 370 MEDLINE .RTM. on STN

TI ***Glatiramer*** in the treatment of ***multiple*** ***sclerosis*** .
SO International journal of nanomedicine, (2006) Vol. 1, No. 3, pp. 283-9.
Ref: 52
Journal code: 101263847. ISSN: 1176-9114. L-ISSN: 1176-9114.
Report No.: NLM-PMC2426806.

L5 ANSWER 185 OF 370 MEDLINE .RTM. on STN
TI Pharmacogenetics of ***glatiramer*** acetate therapy for ***multiple***
sclerosis reveals drug-response markers.
SO Pharmacogenetics and genomics, (2007 Aug) Vol. 17, No. 8, pp. 657-66.
Journal code: 101231005. ISSN: 1744-6872. L-ISSN: 1744-6872.

L5 ANSWER 186 OF 370 MEDLINE .RTM. on STN
TI Development of ulcerative colitis in a patient with multiple sclerosis
following treatment with interferon beta 1a.
SO World journal of gastroenterology : WJG, (2007 Jul 14) Vol. 13, No. 26,
pp. 3638-40.
Journal code: 100883448. ISSN: 1007-9327. L-ISSN: 1007-9327.

L5 ANSWER 187 OF 370 MEDLINE .RTM. on STN
TI Multiple sclerosis: an essential review.
SO South Dakota medicine : the journal of the South Dakota State Medical
Association, (2007 Jun) Vol. 60, No. 6, pp. 231-3, 235. Ref: 14
Journal code: 101265265. ISSN: 0038-3317. L-ISSN: 0038-3317.

L5 ANSWER 188 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate: mechanisms of action in ***multiple*** ***sclerosis*** .
SO Autoimmunity reviews, (2007 Aug) Vol. 6, No. 7, pp. 469-75. Electronic
Publication: 2007-03-06. Ref: 37
Journal code: 101128967. ISSN: 1568-9972. L-ISSN: 1568-9972.

L5 ANSWER 189 OF 370 MEDLINE .RTM. on STN
TI Experimental models of neuroprotection relevant to multiple sclerosis.
SO Neurology, (2007 May 29) Vol. 68, No. 22 Suppl 3, pp. S32-7; discussion
S43-54. Ref: 50
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 190 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate in ***multiple*** ***sclerosis*** : a review.
SO CNS drug reviews, (2007 Summer) Vol. 13, No. 2, pp. 178-91. Ref: 70
Journal code: 9514898. ISSN: 1080-563X. L-ISSN: 1080-563X.

L5 ANSWER 191 OF 370 MEDLINE .RTM. on STN
TI Natalizumab (Tysabri) treatment for ***relapsing*** multiple sclerosis.
SO The neurologist, (2007 Jul) Vol. 13, No. 4, pp. 182-7. Ref: 34
Journal code: 9503763. ISSN: 1074-7931. L-ISSN: 1074-7931.

L5 ANSWER 192 OF 370 MEDLINE .RTM. on STN
TI Effects of education level and employment status on HRQoL in early ***relapsing*** -remitting multiple sclerosis.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2007 Jul) Vol. 13,
No. 6, pp. 783-91. Electronic Publication: 2007-02-16.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 193 OF 370 MEDLINE .RTM. on STN
TI Clinical response to ***glatiramer*** acetate correlates with modulation of
IFN-gamma and IL-4 expression in ***multiple*** ***sclerosis*** .
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2007 Jul) Vol. 13,
No. 6, pp. 754-62. Electronic Publication: 2007-03-15.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 194 OF 370 MEDLINE .RTM. on STN
TI Emerging therapies for MS.
SO Revue neurologique, (2007 Jun) Vol. 163, No. 6-7, pp. 688-96. Ref: 61
Journal code: 2984779R. ISSN: 0035-3787. L-ISSN: 0035-3787.

L5 ANSWER 195 OF 370 MEDLINE .RTM. on STN
TI [Immunosuppression with monoclonal antibodies in multiple sclerosis].
Immunosuppression par anticorps monoclonaux dans la sclerose en plaques.
SO Revue neurologique, (2007 Jun) Vol. 163, No. 6-7, pp. 682-7. Ref: 16
Journal code: 2984779R. ISSN: 0035-3787. L-ISSN: 0035-3787.

L5 ANSWER 196 OF 370 MEDLINE .RTM. on STN
TI Clinical follow-up of 304 patients with multiple sclerosis three years
after mitoxantrone treatment.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2007 Jun) Vol. 13,
No. 5, pp. 626-31. Electronic Publication: 2007-02-09.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 197 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate: mechanisms of action in ***multiple*** ***sclerosis*** .
SO International review of neurobiology, (2007) Vol. 79, pp. 537-70. Ref:
121

Journal code: 0374740. ISSN: 0074-7742. L-ISSN: 0074-7742.

L5 ANSWER 198 OF 370 MEDLINE .RTM. on STN
TI Cost-analysis of ***relapsing*** -remitting multiple sclerosis in Italy after
the introduction of new disease-modifying agents.
SO Clinical drug investigation, (2004) Vol. 24, No. 7, pp. 409-20.
Journal code: 9504817. ISSN: 1173-2563. L-ISSN: 1173-2563.

L5 ANSWER 199 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate could be a potential antidepressant through its neuroprotective and anti-inflammatory effects.
SO Medical hypotheses, (2007) Vol. 69, No. 1, pp. 145-8. Electronic Publication: 2006-12-29.
Journal code: 7505668. ISSN: 0306-9877. L-ISSN: 0306-9877.

L5 ANSWER 200 OF 370 MEDLINE .RTM. on STN
TI Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2007 May) Vol. 13,
No. 4, pp. 502-8. Electronic Publication: 2007-02-09.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 201 OF 370 MEDLINE .RTM. on STN
TI Production of brain-derived neurotrophic factor by mononuclear cells of
patients with ***multiple*** ***sclerosis*** treated with ***glatiramer*** acetate,
interferon-beta 1a, and high doses of immunoglobulins.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2007 Apr) Vol. 13,
No. 3, pp. 313-31. Electronic Publication: 2007-01-29.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 202 OF 370 MEDLINE .RTM. on STN
TI Cost-effectiveness of four immunomodulatory therapies for
relapsing -remitting multiple sclerosis: a Markov model based on
long-term clinical data.
SO Journal of managed care pharmacy : JMCP, (2007 Apr) Vol. 13, No. 3, pp.
245-61.
Journal code: 9605854. ISSN: 1083-4087. L-ISSN: 1083-4087.

L5 ANSWER 203 OF 370 MEDLINE .RTM. on STN
TI Randomized, double-blind, dose-comparison study of ***glatiramer*** acetate in
relapsing -remitting ***MS*** .
SO Neurology, (2007 Mar 20) Vol. 68, No. 12, pp. 939-44.
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 204 OF 370 MEDLINE .RTM. on STN

TI Cognitive function in ***relapsing*** multiple sclerosis: minimal changes in a
10-year clinical trial.
SO Journal of the neurological sciences, (2007 Apr 15) Vol. 255, No. 1-2, pp.
57-63. Electronic Publication: 2007-02-28.
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in Debrecen, Hungary].
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L5 ANSWER 206 OF 370 MEDLINE .RTM. on STN
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SO Expert opinion on drug metabolism & toxicology, (2006 Dec) Vol. 2, No. 6,
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SO Der Nervenarzt, (2006 Dec) Vol. 77, No. 12, pp. 1506-18.
Journal code: 0400773. ISSN: 0028-2804. L-ISSN: 0028-2804.

L5 ANSWER 208 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate-specific human CD8(+) T cells: increased IL-4
production in ***multiple*** ***sclerosis*** is reduced by ***glatiramer*** acetate
treatment.
SO Journal of neuroimmunology, (2006 Dec) Vol. 181, No. 1-2, pp. 133-40.
Electronic Publication: 2006-11-07.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L5 ANSWER 209 OF 370 MEDLINE .RTM. on STN
TI Sequential maintenance treatment with ***glatiramer*** acetate after
mitoxantrone is safe and can limit exposure to immunosuppression in very
active, ***relapsing*** remitting ***multiple*** ***sclerosis*** .
SO Journal of neurology, (2006 Sep) Vol. 253, No. 9, pp. 1160-4. Electronic
Publication: 2006-09-21.

Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 210 OF 370 MEDLINE .RTM. on STN
TI Intravenous immunoglobulins as therapeutic option in the treatment of
multiple sclerosis.
SO Journal of neurology, (2006 Sep) Vol. 253 Suppl 5, pp. V50-8. Ref: 50
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 211 OF 370 MEDLINE .RTM. on STN
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Les traitements actuels dans la sclerose en plaques.
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Ref:
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Journal code: 0404334. ISSN: 0035-2640. L-ISSN: 0035-2640.

L5 ANSWER 212 OF 370 MEDLINE .RTM. on STN
TI Interferon treatment may trigger primary headaches in multiple sclerosis
patients.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2006 Aug)
Vol. 12,
No. 4, pp. 476-80.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 213 OF 370 MEDLINE .RTM. on STN
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their laboratory analysis in multiple sclerosis].
Immunmodulalo terapia kovetkezteben kialakulo neutralizalo antitestek
jelentosege es laboratoriumi meghatarozasa sclerosis multiplexben.
SO Ideggyogyaszati szemle, (2006 May 20) Vol. 59, No. 5-6, pp. 156-62.
Ref:
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L5 ANSWER 214 OF 370 MEDLINE .RTM. on STN
TI A prospective open-label study of ***glatiramer*** acetate: over a decade of
continuous use in ***multiple*** ***sclerosis*** patients.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2006 Jun)
Vol. 12,
No. 3, pp. 309-20.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 215 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate in treatment-naive and prior
interferon-beta-1b-treated ***multiple*** ***sclerosis*** patients.
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Journal code: 0370336. ISSN: 0001-6314. L-ISSN: 0001-6314.

L5 ANSWER 216 OF 370 MEDLINE .RTM. on STN
TI Clinical course after change of immunomodulating therapy in ***relapsing*** -remitting multiple sclerosis.
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2006 May) Vol. 13, No. 5, pp. 471-4.
Journal code: 9506311. ISSN: 1351-5101. L-ISSN: 1351-5101.

L5 ANSWER 217 OF 370 MEDLINE .RTM. on STN
TI Early treatment.
SO Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, (2006 Mar)
Vol. 27 Suppl 1, pp. S8-12. Ref: 42
Journal code: 100959175. ISSN: 1590-1874. L-ISSN: 1590-1874.

L5 ANSWER 218 OF 370 MEDLINE .RTM. on STN
TI Epitope specificity of serum antibodies directed against the extracellular
domain of myelin oligodendrocyte glycoprotein: Influence of relapses and
immunomodulatory treatments.
SO Journal of neuroimmunology, (2006 May) Vol. 174, No. 1-2, pp. 147-56.
Electronic Publication: 2006-03-06.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L5 ANSWER 219 OF 370 MEDLINE .RTM. on STN
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SO Brain : a journal of neurology, (2006 May) Vol. 129, No. Pt 5, pp. 1293-305. Electronic Publication: 2006-03-02.
Journal code: 0372537. E-ISSN: 1460-2156. L-ISSN: 0006-8950.

L5 ANSWER 220 OF 370 MEDLINE .RTM. on STN
TI Immunomodulatory treatment in multiple sclerosis: experience at a Brazilian center with 390 patients.
SO Arquivos de neuro-psiquiatria, (2006 Mar) Vol. 64, No. 1, pp. 51-4.
Electronic Publication: 2006-04-05.
Journal code: 0125444. ISSN: 0004-282X. L-ISSN: 0004-282X.

L5 ANSWER 221 OF 370 MEDLINE .RTM. on STN
TI ***Relapsing*** ***MS*** patients' experiences with ***glatiramer*** acetate
treatment: a phenomenological study.
SO The Journal of neuroscience nursing : journal of the American Association
of Neuroscience Nurses, (2006 Feb) Vol. 38, No. 1, pp. 37-41.
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TI [Mitoxantrone as induction therapy in aggressive ***relapsing*** remitting
multiple sclerosis: a descriptive analysis of 100 consecutive patients].
Etude observationnelle de la mitoxantrone dans les formes remittentes
actives de sclerose en plaques: suivi a long terme d'une cohorte de 100
patients consecutifs.
SO Revue neurologique, (2006 Feb) Vol. 162, No. 2, pp. 185-94.
Journal code: 2984779R. ISSN: 0035-3787. L-ISSN: 0035-3787.

L5 ANSWER 223 OF 370 MEDLINE .RTM. on STN
TI The cardiac effects of mitoxantrone: do the benefits in multiple sclerosis
outweigh the risks?.
SO Expert opinion on drug safety, (2006 Mar) Vol. 5, No. 2, pp. 265-74.
Ref:
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Journal code: 101163027. E-ISSN: 1744-764X. L-ISSN: 1474-0338.

L5 ANSWER 224 OF 370 MEDLINE .RTM. on STN
TI Effects of oral ***glatiramer*** acetate on clinical and MRI-monitored disease
activity in patients with ***relapsing*** ***multiple*** ***sclerosis*** : a
multicentre, double-blind, randomised, placebo-controlled study.
SO Lancet neurology, (2006 Mar) Vol. 5, No. 3, pp. 213-20.
Journal code: 101139309. ISSN: 1474-4422. L-ISSN: 1474-4422.

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TI ***Glatiramer*** acetate induces pro-apoptotic mechanisms involving Bcl-2, Bax
and Cyt-c in peripheral lymphocytes from ***multiple*** ***sclerosis*** patients.
SO Journal of neurology, (2006 Feb) Vol. 253, No. 2, pp. 231-6. Electronic
Publication: 2005-09-30.
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 226 OF 370 MEDLINE .RTM. on STN
TI Cyclophosphamide therapy for MS.
SO International MS journal / MS Forum, (2005 Aug) Vol. 12, No. 2, pp. 52-8.
Journal code: 9804403. ISSN: 1352-8963. L-ISSN: 1352-8963.

L5 ANSWER 227 OF 370 MEDLINE .RTM. on STN
TI Mitoxantrone in the treatment of multiple sclerosis.
SO International MS journal / MS Forum, (2005 Nov) Vol. 12, No. 3, pp. 74-87.
Ref: 87
Journal code: 9804403. ISSN: 1352-8963. L-ISSN: 1352-8963.

L5 ANSWER 228 OF 370 MEDLINE .RTM. on STN

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SO Advances in neurology, (2006) Vol. 98, pp. 273-92. Ref: 93
Journal code: 0367524. ISSN: 0091-3952. L-ISSN: 0091-3952.

L5 ANSWER 229 OF 370 MEDLINE .RTM. on STN
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an Italian Co-operative Study.
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Vol. 26 Suppl 4, pp. S183-6.
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715-27. Ref: 105
Journal code: 8103137. ISSN: 0720-4299. L-ISSN: 0720-4299.

L5 ANSWER 231 OF 370 MEDLINE .RTM. on STN
TI Axonal metabolic recovery and potential neuroprotective effect of ***glatiramer*** acetate in ***relapsing*** -remitting ***multiple*** ***sclerosis*** .
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2005 Dec) Vol. 11,
No. 6, pp. 646-51.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 232 OF 370 MEDLINE .RTM. on STN
TI Early treatment and dose optimisation BENEFIT and BEYOND.
SO Journal of neurology, (2005 Sep) Vol. 252 Suppl 3, pp. iii44-iii50. Ref:
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Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 233 OF 370 MEDLINE .RTM. on STN
TI Clinical and immune responses correlate in ***glatiramer*** acetate therapy of
multiple ***sclerosis*** .
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2005 Nov) Vol. 12, No. 11, pp.
869-78.
Journal code: 9506311. ISSN: 1351-5101. L-ISSN: 1351-5101.

L5 ANSWER 234 OF 370 MEDLINE .RTM. on STN
TI History of modern multiple sclerosis therapy.
SO Journal of neurology, (2005 Sep) Vol. 252 Suppl 3, pp. iii3-iii9. Ref: 31

Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 235 OF 370 MEDLINE .RTM. on STN
TI Clinical implications of neuropathological findings in multiple sclerosis.
SO Journal of neurology, (2005 Sep) Vol. 252 Suppl 3, pp. iii10-iii14.
Ref:
43
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 236 OF 370 MEDLINE .RTM. on STN
TI The efficacy of ***glatiramer*** acetate in beta-interferon-intolerant ***MS***
patients.
SO Acta neurologica Scandinavica, (2005 Oct) Vol. 112, No. 4, pp. 234-7.
Journal code: 0370336. ISSN: 0001-6314. L-ISSN: 0001-6314.

L5 ANSWER 237 OF 370 MEDLINE .RTM. on STN
TI Lower brain-derived neurotrophic factor in serum of ***relapsing*** remitting
MS : reversal by ***glatiramer*** acetate.
SO Journal of neuroimmunology, (2005 Oct) Vol. 167, No. 1-2, pp. 215-8.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L5 ANSWER 238 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate in ***multiple*** ***sclerosis***: update on potential
mechanisms of action.
SO Lancet neurology, (2005 Sep) Vol. 4, No. 9, pp. 567-75. Ref: 82
Journal code: 101139309. ISSN: 1474-4422. L-ISSN: 1474-4422.

L5 ANSWER 239 OF 370 MEDLINE .RTM. on STN
TI Long-term follow up of glatiramer acetate compassionate use in Belgium.
SO Acta neurologica Belgica, (2005 Jun) Vol. 105, No. 2, pp. 81-5.
Journal code: 0247035. ISSN: 0300-9009. L-ISSN: 0300-9009.

L5 ANSWER 240 OF 370 MEDLINE .RTM. on STN
TI The distribution of the magnetic resonance imaging response to ***glatiramer*** acetate in ***multiple*** ***sclerosis***.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2005 Aug) Vol. 11,
No. 4, pp. 447-9.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 241 OF 370 MEDLINE .RTM. on STN
TI Disease-modifying drugs in childhood-juvenile multiple sclerosis: results
of an Italian co-operative study.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2005 Aug) Vol. 11,
No. 4, pp. 420-4.

Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 242 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate in ***multiple*** ***sclerosis***
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SO Expert review of neurotherapeutics, (2005 Jul) Vol. 5, No. 4, pp.
451-8.
Ref: 71
Journal code: 101129944. E-ISSN: 1744-8360. L-ISSN: 1473-7175.

L5 ANSWER 243 OF 370 MEDLINE .RTM. on STN
TI Putative mechanisms of action of statins in ***multiple***
sclerosis --comparison to interferon-beta and
glatiramer acetate.
SO Journal of the neurological sciences, (2005 Jun 15) Vol. 233, No. 1-
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173-7. Electronic Publication: 2005-04-20. Ref: 41
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 244 OF 370 MEDLINE .RTM. on STN
TI Antigen-specific therapies for the treatment of multiple sclerosis:
a
clinical trial update.
SO Expert opinion on investigational drugs, (1997 Nov) Vol. 6, No. 11,
pp.
1715-27.
Journal code: 9434197. E-ISSN: 1744-7658. L-ISSN: 1354-3784.

L5 ANSWER 245 OF 370 MEDLINE .RTM. on STN
TI Factors related with treatment adherence to interferon beta and
glatiramer acetate therapy in ***multiple***
sclerosis .
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2005 Jun)
Vol. 11,
No. 3, pp. 306-9.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 246 OF 370 MEDLINE .RTM. on STN
TI Bystander modulation of chemokine receptor expression on peripheral
blood
T lymphocytes mediated by glatiramer therapy.
SO Archives of neurology, (2005 Jun) Vol. 62, No. 6, pp. 889-94.
Journal code: 0372436. ISSN: 0003-9942. L-ISSN: 0003-9942.

L5 ANSWER 247 OF 370 MEDLINE .RTM. on STN
TI Can ***glatiramer*** acetate reduce brain atrophy development in
multiple
sclerosis ?.
SO Journal of the neurological sciences, (2005 Jun 15) Vol. 233, No. 1-
2, pp.
139-43. Electronic Publication: 2005-04-20. Ref: 36
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 248 OF 370 MEDLINE .RTM. on STN

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A sclerosis multiplex osszetett funkcionalis index alkalmazhatosaganak
vizsgalata Debrecenben.
SO Ideggyogyaszati szemle, (2005 Mar 20) Vol. 58, No. 3-4, pp. 113-8.
Journal code: 17510500R. ISSN: 0019-1442. L-ISSN: 0019-1442.

L5 ANSWER 249 OF 370 MEDLINE .RTM. on STN
TI Twenty-four-month comparison of immunomodulatory treatments - a retrospective open label study in 308 RRMS patients treated with beta
interferons or glatiramer acetate (Copaxone).
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2005 Jun) Vol. 12, No. 6, pp. 425-31.
Journal code: 9506311. ISSN: 1351-5101. L-ISSN: 1351-5101.

L5 ANSWER 250 OF 370 MEDLINE .RTM. on STN
TI Interferon-beta1b for multiple sclerosis.
SO Expert review of neurotherapeutics, (2005 Mar) Vol. 5, No. 2, pp. 153-64.
Ref: 72
Journal code: 101129944. E-ISSN: 1744-8360. L-ISSN: 1473-7175.

L5 ANSWER 251 OF 370 MEDLINE .RTM. on STN
TI Jessner-Kanof lymphocytic infiltration of the skin associated with glatiramer acetate.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2005 Apr) Vol. 11,
No. 2, pp. 245-8.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 252 OF 370 MEDLINE .RTM. on STN
TI Oral glatiramer acetate in experimental autoimmune encephalomyelitis:
clinical and immunological studies.
SO Annals of the New York Academy of Sciences, (2004 Dec) Vol. 1029, pp.
239-49.
Journal code: 7506858. ISSN: 0077-8923. L-ISSN: 0077-8923.

L5 ANSWER 253 OF 370 MEDLINE .RTM. on STN
TI [Immunomodulatory therapy in multiple sclerosis].
Immunmodulans kezeles sclerosis multiplexben.
SO Ideggyogyaszati szemle, (2004 Nov 20) Vol. 57, No. 11-12, pp. 401-16.
Ref: 77
Journal code: 17510500R. ISSN: 0019-1442. L-ISSN: 0019-1442.

L5 ANSWER 254 OF 370 MEDLINE .RTM. on STN
TI Current approved options for treating patients with multiple sclerosis.

SO Neurology, (2004 Dec 28) Vol. 63, No. 12 Suppl 6, pp. S8-14. Ref: 56
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 255 OF 370 MEDLINE .RTM. on STN
TI Selecting a disease-modifying agent as platform therapy in the long-term
management of multiple sclerosis.
SO Neurology, (2004 Dec 14) Vol. 63, No. 11 Suppl 5, pp. S19-27. Ref: 56
Journal code: 0401060. E-ISSN: 1526-632X. L-ISSN: 0028-3878.

L5 ANSWER 256 OF 370 MEDLINE .RTM. on STN
TI Neurologic consequence of delaying ***glatiramer*** acetate therapy for
multiple ***sclerosis*** : 8-year data.
SO Acta neurologica Scandinavica, (2005 Jan) Vol. 111, No. 1, pp. 42-7.
Journal code: 0370336. ISSN: 0001-6314. L-ISSN: 0001-6314.

L5 ANSWER 257 OF 370 MEDLINE .RTM. on STN
TI Localized panniculitis and subsequent lipoatrophy with subcutaneous
glatiramer acetate (Copaxone) injection for the treatment of ***multiple***
sclerosis .
SO American journal of clinical dermatology, (2004) Vol. 5, No. 5, pp. 357-9.
Journal code: 100895290. ISSN: 1175-0561. L-ISSN: 1175-0561.

L5 ANSWER 258 OF 370 MEDLINE .RTM. on STN
TI Importance of benefit-to-risk assessment for disease-modifying drugs used
to treat MS.
SO Journal of neurology, (2004 Sep) Vol. 251 Suppl 5, pp. v42-v49. Ref: 25
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L5 ANSWER 259 OF 370 MEDLINE .RTM. on STN
TI [Selected issues of immunomodulating treatment in multiple sclerosis].
Wybrane zagadnienia immunomodulacyjnego leczenia chorych na stwardnienie
rozsiane.
SO Neurologia i neurochirurgia polska, (2004 Jul-Aug) Vol. 38, No. 4, pp.
299-306. Ref: 37
Journal code: 0101265. ISSN: 0028-3843. L-ISSN: 0028-3843.

L5 ANSWER 260 OF 370 MEDLINE .RTM. on STN
TI Amelioration of proteolipid protein 139-151-induced encephalomyelitis in
SJL mice by modified amino acid copolymers and their mechanisms.
SO Proceedings of the National Academy of Sciences of the United States of
America, (2004 Aug 10) Vol. 101, No. 32, pp. 11743-8. Electronic

Publication: 2004-08-03.
Journal code: 7505876. ISSN: 0027-8424. L-ISSN: 0027-8424.
Report No.: NLM-PMC511046.

L5 ANSWER 261 OF 370 MEDLINE .RTM. on STN
TI Stepped-care approach to treating MS: a managed care treatment algorithm.
SO Journal of managed care pharmacy : JMCP, (2004 Jun) Vol. 10, No. 3 Suppl
B, pp. S26-32. Ref: 75
Journal code: 9605854. ISSN: 1083-4087. L-ISSN: 1083-4087.

L5 ANSWER 262 OF 370 MEDLINE .RTM. on STN
TI [The efficiency and cost-utility ratio of interferon beta in the treatment
of multiple sclerosis in Andalusia].
Eficiencia y relacion coste-utilidad del interferon beta en la esclerosis
multiple en Andalucia.
SO Revista de neurologia, (Jul 1-15 2004) Vol. 39, No. 1, pp. 1-6.
Journal code: 7706841. ISSN: 0210-0010. L-ISSN: 0210-0010.

L5 ANSWER 263 OF 370 MEDLINE .RTM. on STN
TI Mycophenolate mofetil in multiple sclerosis.
SO Clinical neuropharmacology, (2004 Mar-Apr) Vol. 27, No. 2, pp. 80-3.
Journal code: 7607910. ISSN: 0362-5664. L-ISSN: 0362-5664.

L5 ANSWER 264 OF 370 MEDLINE .RTM. on STN
TI The cost of multiple sclerosis and the cost effectiveness of disease-modifying agents in its treatment.
SO CNS drugs, (2004) Vol. 18, No. 9, pp. 561-74. Ref: 98
Journal code: 9431220. ISSN: 1172-7047. L-ISSN: 1172-7047.

L5 ANSWER 265 OF 370 MEDLINE .RTM. on STN
TI The PROMiSe trial: baseline data review and progress report.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2004 Jun) Vol. 10
Suppl 1, pp. S65-71; discussion S71-2. Ref: 7
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 266 OF 370 MEDLINE .RTM. on STN
TI Immunologic factors in primary progressive multiple sclerosis.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2004 Jun) Vol. 10
Suppl 1, pp. S16-21; discussion S21-2. Ref: 13
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 267 OF 370 MEDLINE .RTM. on STN
TI The effect of immunomodulatory treatment on multiple sclerosis fatigue.
SO Journal of neurology, neurosurgery, and psychiatry, (2004 Jul) Vol. 75,
No. 7, pp. 1045-7.
Journal code: 2985191R. ISSN: 0022-3050. L-ISSN: 0022-3050.

Report No.: NLM-PMC1739126.

L5 ANSWER 268 OF 370 MEDLINE .RTM. on STN
TI Non-specific immunosuppressants in the treatment of multiple sclerosis.
SO Clinical neurology and neurosurgery, (2004 Jun) Vol. 106, No. 3, pp. 263-9. Ref: 39
Journal code: 7502039. ISSN: 0303-8467. L-ISSN: 0303-8467.

L5 ANSWER 269 OF 370 MEDLINE .RTM. on STN
TI ***Multiple*** ***sclerosis*** : ***glatiramer*** acetate inhibits monocyte reactivity
in vitro and in vivo.
SO Brain : a journal of neurology, (2004 Jun) Vol. 127, No. Pt 6, pp. 1370-8.
Electronic Publication: 2004-04-16.
Journal code: 0372537. ISSN: 0006-8950. L-ISSN: 0006-8950.

L5 ANSWER 270 OF 370 MEDLINE .RTM. on STN
TI Are statins a treatment option for multiple sclerosis?.
SO Lancet neurology, (2004 Jun) Vol. 3, No. 6, pp. 369-71. Ref: 34
Journal code: 101139309. ISSN: 1474-4422. L-ISSN: 1474-4422.

L5 ANSWER 271 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate for the treatment of ***multiple*** ***sclerosis*** .
SO Expert opinion on pharmacotherapy, (2004 Apr) Vol. 5, No. 4, pp. 875-91.
Ref: 87
Journal code: 100897346. ISSN: 1465-6566. L-ISSN: 1465-6566.

L5 ANSWER 272 OF 370 MEDLINE .RTM. on STN
TI A comparison of the benefits of mitoxantrone and other recent therapeutic
approaches in multiple sclerosis.
SO Expert opinion on pharmacotherapy, (2004 Apr) Vol. 5, No. 4, pp. 747-65.
Ref: 161
Journal code: 100897346. ISSN: 1465-6566. L-ISSN: 1465-6566.

L5 ANSWER 273 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** : new preparation. No place in ***multiple*** ***sclerosis*** .
SO Prescrire international, (2004 Feb) Vol. 13, No. 69, pp. 10-2.
Journal code: 9439295. ISSN: 1167-7422. L-ISSN: 1167-7422.

L5 ANSWER 274 OF 370 MEDLINE .RTM. on STN
TI Lipoatrophy in patients with ***multiple*** ***sclerosis*** on ***glatiramer*** acetate.
SO The Canadian journal of neurological sciences. Le journal canadien des
sciences neurologiques, (2004 Feb) Vol. 31, No. 1, pp. 58-63.
Journal code: 0415227. ISSN: 0317-1671. L-ISSN: 0317-1671.

L5 ANSWER 275 OF 370 MEDLINE .RTM. on STN
TI Induction of IL-10 in rat peritoneal macrophages and dendritic cells by
glatiramer acetate.
SO Journal of neuroimmunology, (2004 Mar) Vol. 148, No. 1-2, pp. 63-73.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L5 ANSWER 276 OF 370 MEDLINE .RTM. on STN
TI Therapy with ***glatiramer*** acetate for ***multiple***
sclerosis .
SO Cochrane database of systematic reviews (Online), (2004) No. 1, pp.
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L5 ANSWER 277 OF 370 MEDLINE .RTM. on STN
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SO Journal of molecular recognition : JMR, (2003 Nov-Dec) Vol. 16, No. 6, pp.
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Journal code: 9004580. ISSN: 0952-3499. L-ISSN: 0952-3499.

L5 ANSWER 278 OF 370 MEDLINE .RTM. on STN
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functions and therapeutic efficacy.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2003 Dec) Vol. 9,
No. 6, pp. 592-9.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 279 OF 370 MEDLINE .RTM. on STN
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therapy in a six-year organized ***multiple*** ***sclerosis*** trial.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2003 Dec) Vol. 9,
No. 6, pp. 585-91.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 280 OF 370 MEDLINE .RTM. on STN
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immunomodulatory treatments for ***relapsing*** -remitting multiple sclerosis.
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Federation of Neurological Societies, (2003 Nov) Vol. 10, No. 6, pp. 671-6.
Journal code: 9506311. ISSN: 1351-5101. L-ISSN: 1351-5101.

L5 ANSWER 281 OF 370 MEDLINE .RTM. on STN
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SO Journal of immunology (Baltimore, Md. : 1950), (2003 Dec 1) Vol. 171, No.

11, pp. 6267-74.
Journal code: 2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767.

L5 ANSWER 282 OF 370 MEDLINE .RTM. on STN
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multiple ***sclerosis*** with ***glatiramer*** acetate.
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Journal code: 0150760. ISSN: 0014-3022. L-ISSN: 0014-3022.

L5 ANSWER 283 OF 370 MEDLINE .RTM. on STN
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Journal code: 9503763. ISSN: 1074-7931. L-ISSN: 1074-7931.

L5 ANSWER 284 OF 370 MEDLINE .RTM. on STN
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management.
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L5 ANSWER 285 OF 370 MEDLINE .RTM. on STN
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acetate treatment in ***multiple*** ***sclerosis*** .
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Journal code: 0372537. ISSN: 0006-8950. L-ISSN: 0006-8950.

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SO Neuroscience research, (2003 Oct) Vol. 47, No. 2, pp. 201-7.
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L5 ANSWER 287 OF 370 MEDLINE .RTM. on STN
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No. 8, pp. 1381-7. Ref: 17
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multiple ***sclerosis*** . Experience of the Moscow ***multiple*** ***sclerosis*** center].
Ispol'zovanie glatiramera atsetata (kopaksona) v lechenii bol'nykh rasseiannym sklerozom. Opyt Moskovskogo tsentra rasseiannogo skleroza.
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L5 ANSWER 289 OF 370 MEDLINE .RTM. on STN
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multiple ***sclerosis*** pathogenesis].
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zven'ia patogeneza rasseiannogo skleroza.
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Journal code: 9712194. ISSN: 1997-7298. L-ISSN: 1997-7298.

L5 ANSWER 290 OF 370 MEDLINE .RTM. on STN
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in ***multiple*** ***sclerosis*** : meta-analysis of three double-blind,
randomized, placebo-controlled clinical trials.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2003 Aug) Vol. 9,
No. 4, pp. 349-55.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 291 OF 370 MEDLINE .RTM. on STN
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onset ***multiple*** ***sclerosis*** .
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Journal code: 8101187. ISSN: 0174-304X. L-ISSN: 0174-304X.

L5 ANSWER 292 OF 370 MEDLINE .RTM. on STN
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Journal code: 8111343. ISSN: 0271-8235. L-ISSN: 0271-8235.

L5 ANSWER 293 OF 370 MEDLINE .RTM. on STN
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SO Current opinion in neurology, (2003 Jun) Vol. 16, No. 3, pp. 289-97. Ref:
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Journal code: 9319162. ISSN: 1350-7540. L-ISSN: 1080-8248.

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glatiramer acetate or interferon beta in Spain].
Analisis coste utilidad del tratamiento de la esclerosis multiple remitente-recidivante con acetato de glatiramero o interferon beta en
Espana.
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L5 ANSWER 295 OF 370 MEDLINE .RTM. on STN
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current status.
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L5 ANSWER 296 OF 370 MEDLINE .RTM. on STN
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sclerosis .
SO BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy, (2003) Vol. 17, No. 3, pp. 207-10. Ref: 35
Journal code: 9705305. ISSN: 1173-8804. L-ISSN: 1173-8804.

L5 ANSWER 297 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate (Copaxone) therapy for ***multiple*** ***sclerosis*** .
SO Pharmacology & therapeutics, (2003 May) Vol. 98, No. 2, pp. 245-55. Ref:
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Journal code: 7905840. ISSN: 0163-7258. L-ISSN: 0163-7258.

L5 ANSWER 298 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate (copolymer-1, copaxone) promotes Th2 cell development
and increased IL-10 production through modulation of dendritic cells.
SO Journal of immunology (Baltimore, Md. : 1950), (2003 May 1) Vol. 170, No.
9, pp. 4483-8.
Journal code: 2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767.

L5 ANSWER 299 OF 370 MEDLINE .RTM. on STN
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induces hyporesponsive T cells in patients with ***multiple*** ***sclerosis*** .
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Journal code: 100883537. ISSN: 1521-6616. L-ISSN: 1521-6616.

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glatiramer
    acetate in the management of ***multiple*** ***sclerosis*** .
Commentary:
    evaluating disease modifying treatments in ***multiple***
sclerosis .
SO BMJ (Clinical research ed.), (2003 Mar 8) Vol. 326, No. 7388, pp.
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    discussion 522.
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    Report No.: NLM-PMC150460.

L5 ANSWER 301 OF 370 MEDLINE .RTM. on STN
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      glatiramer acetate in the treatment of ***multiple***
sclerosis .
SO Clinical therapeutics, (2002 Dec) Vol. 24, No. 12, pp. 1998-2021.
Ref:
    138
    Journal code: 7706726. ISSN: 0149-2918. L-ISSN: 0149-2918.

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    Decision del tratamiento en la esclerosis multiple.
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    Journal code: 7706841. E-ISSN: 1576-6578. L-ISSN: 0210-0010.

L5 ANSWER 303 OF 370 MEDLINE .RTM. on STN
TI Interleukin 12 and interleukin 10 are affected differentially by
treatment
    of ***multiple*** ***sclerosis*** with ***glatiramer***
acetate (Copaxone).
SO Folia neuropathologica / Association of Polish Neuropathologists and
    Medical Research Centre, Polish Academy of Sciences, (2002) Vol. 40,
No.
    4, pp. 173-5.
    Journal code: 9437431. ISSN: 1641-4640. L-ISSN: 1509-572X.

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SO International journal of clinical practice. Supplement, (2002 Sep)
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    131, pp. 23-32.
    Journal code: 9712380. ISSN: 1368-504X. L-ISSN: 1368-504X.

L5 ANSWER 305 OF 370 MEDLINE .RTM. on STN
TI Disease-modifying therapy in ***relapsing*** --remitting multiple
sclerosis:
    efficacy is paramount.
SO International journal of clinical practice. Supplement, (2002 Sep)
No.
    131, pp. 3-7. Ref: 41
    Journal code: 9712380. ISSN: 1368-504X. L-ISSN: 1368-504X.

L5 ANSWER 306 OF 370 MEDLINE .RTM. on STN
TI The role of intravenous immunoglobulin in the treatment of multiple sclerosis.
SO Journal of the neurological sciences, (2003 Feb 15) Vol. 206, No. 2, pp.
123-30. Ref: 61
Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 307 OF 370 MEDLINE .RTM. on STN
TI Short-term correlations between clinical and MR imaging findings in ***relapsing*** -remitting multiple sclerosis.
SO AJNR. American journal of neuroradiology, (2003 Jan) Vol. 24, No. 1, pp.
75-81.
Journal code: 8003708. ISSN: 0195-6108. L-ISSN: 0195-6108.

L5 ANSWER 308 OF 370 MEDLINE .RTM. on STN
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of multiple sclerosis patients undergoing immunomodulatory treatment.
SO Journal of neurology, neurosurgery, and psychiatry, (2003 Jan) Vol. 74,
No. 1, pp. 123-6.
Journal code: 2985191R. ISSN: 0022-3050. L-ISSN: 0022-3050.
Report No.: NLM-PMC1738169.

L5 ANSWER 309 OF 370 MEDLINE .RTM. on STN
TI Effect of combined IFNbeta-1a and ***glatiramer*** acetate therapy on
GA-specific T-cell responses in ***multiple*** ***sclerosis*** .
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2002 Dec) Vol. 8,
No. 6, pp. 485-91.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 310 OF 370 MEDLINE .RTM. on STN
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with ***relapsing*** -remitting multiple sclerosis.
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Medical Decision Making, (2002 Nov-Dec) Vol. 22, No. 6, pp. 506-13.
Journal code: 8109073. ISSN: 0272-989X. L-ISSN: 0272-989X.

L5 ANSWER 311 OF 370 MEDLINE .RTM. on STN
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multiple sclerosis: a meta-analysis.
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557-63.
Journal code: 9506311. ISSN: 1351-5101. L-ISSN: 1351-5101.

L5 ANSWER 312 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate-specific T-helper 1- and 2-type cell lines produce
BDNF: implications for ***multiple*** ***sclerosis*** therapy. Brain-derived
neurotrophic factor.
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L5 ANSWER 313 OF 370 MEDLINE .RTM. on STN
TI Effect of ***glatiramer*** acetate on ***MS*** lesions enhancing at different
gadolinium doses.
SO Neurology, (2002 Nov 12) Vol. 59, No. 9, pp. 1429-32.
Journal code: 0401060. ISSN: 0028-3878. L-ISSN: 0028-3878.

L5 ANSWER 314 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate: a review of its use in ***relapsing*** -remitting
multiple ***sclerosis*** .
SO CNS drugs, (2002) Vol. 16, No. 12, pp. 825-50. Ref: 110
Journal code: 9431220. ISSN: 1172-7047. L-ISSN: 1172-7047.

L5 ANSWER 315 OF 370 MEDLINE .RTM. on STN
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with multiple sclerosis].
Rezul'taty otkrytykh postregistratsionnykh klinicheskikh ispytanii preparata kopakson u bol'nykh rasseiannym sklerozom.
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Journal code: 9712194. ISSN: 1997-7298. L-ISSN: 1997-7298.

L5 ANSWER 316 OF 370 MEDLINE .RTM. on STN
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Journal code: 101092952. ISSN: 1444-0903. L-ISSN: 1444-0903.

L5 ANSWER 317 OF 370 MEDLINE .RTM. on STN
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reproducible and sustained.
SO Neurology, (2002 Oct 22) Vol. 59, No. 8, pp. 1284-6.
Journal code: 0401060. ISSN: 0028-3878. L-ISSN: 0028-3878.

L5 ANSWER 318 OF 370 MEDLINE .RTM. on STN

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sclerosis: a systematic review.
SO Archives of internal medicine, (2002 Oct 28) Vol. 162, No. 19, pp. 2161-9.
Journal code: 0372440. ISSN: 0003-9926. L-ISSN: 0003-9926.

L5 ANSWER 319 OF 370 MEDLINE .RTM. on STN
TI Comparative assessment of immunomodulating therapies for
relapsing -remitting multiple sclerosis.
SO CNS drugs, (2002) Vol. 16, No. 8, pp. 563-78. Ref: 82
Journal code: 9431220. ISSN: 1172-7047. L-ISSN: 1172-7047.

L5 ANSWER 320 OF 370 MEDLINE .RTM. on STN
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Multiple Sklerose. Therapeutischer Nihilismus ist hier fehl am Platz.
SO MMW Fortschritte der Medizin, (2002 May 6) Vol. Suppl 2, pp. 52-7.
Journal code: 100893959. ISSN: 1438-3276. L-ISSN: 1438-3276.

L5 ANSWER 321 OF 370 MEDLINE .RTM. on STN
TI [Treatment of ***multiple*** ***sclerosis*** with ***glatiramer*** acetate. Current
aspects of mechanisms of action, pharmacokinetics, adverse effect profile
and clinical studies].
Behandlung der Multiplen Sklerose mit ***Glatiramer*** -Azetat. Aktuelles zu
Wirkungsmechanismen, Pharmakokinetik, Nebenwirkungsprofil und Studiensituation.
SO Der Nervenarzt, (2002 Apr) Vol. 73, No. 4, pp. 321-31. Ref: 82
Journal code: 0400773. ISSN: 0028-2804. L-ISSN: 0028-2804.

L5 ANSWER 322 OF 370 MEDLINE .RTM. on STN
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SO Neurologia (Barcelona, Spain), (2002 May) Vol. 17, No. 5, pp. 244-58.
Ref: 91
Journal code: 9005460. ISSN: 0213-4853. L-ISSN: 0213-4853.

L5 ANSWER 323 OF 370 MEDLINE .RTM. on STN
TI Differentiation of multiple sclerosis subtypes: implications for treatment.
SO CNS drugs, (2002) Vol. 16, No. 6, pp. 405-18. Ref: 76
Journal code: 9431220. ISSN: 1172-7047. L-ISSN: 1172-7047.

L5 ANSWER 324 OF 370 MEDLINE .RTM. on STN
TI [***Glatiramer*** for ***relapsing*** -remitting ***multiple*** ***sclerosis***].
Glatiramer bei schubformig-progredienter ***MS*** .
SO Medizinische Monatsschrift fur Pharmazeuten, (2002 Apr) Vol. 25, No. 4,
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Journal code: 7802665. ISSN: 0342-9601. L-ISSN: 0342-9601.

L5 ANSWER 325 OF 370 MEDLINE .RTM. on STN
TI Comparison of ***glatiramer*** acetate (Copaxone) and interferon beta-1b
(Betaferon) in ***multiple*** ***sclerosis*** patients: an open-label 2-year
follow-up.
SO Journal of the neurological sciences, (2002 May 15) Vol. 197, No. 1-2, pp.
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Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

L5 ANSWER 326 OF 370 MEDLINE .RTM. on STN
TI Mechanisms of action of interferons and ***glatiramer*** acetate in ***multiple***
sclerosis .
SO Neurology, (2002 Apr 23) Vol. 58, No. 8 Suppl 4, pp. S3-9. Ref: 59
Journal code: 0401060. ISSN: 0028-3878. L-ISSN: 0028-3878.

L5 ANSWER 327 OF 370 MEDLINE .RTM. on STN
TI Considerations in the treatment of ***relapsing*** -remitting multiple
sclerosis.
SO Neurology, (2002 Apr 23) Vol. 58, No. 8 Suppl 4, pp. S10-22. Ref: 107
Journal code: 0401060. ISSN: 0028-3878. L-ISSN: 0028-3878.

L5 ANSWER 328 OF 370 MEDLINE .RTM. on STN
TI Extended use of ***glatiramer*** acetate (Copaxone) is well tolerated and
maintains its clinical effect on ***multiple***
sclerosis relapse rate and
degree of disability. 1998 [classical article].
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Journal code: 0401060. ISSN: 0028-3878. L-ISSN: 0028-3878.

L5 ANSWER 329 OF 370 MEDLINE .RTM. on STN
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relapsing -remitting MS patients.
SO Neurology, (2002 Feb 12) Vol. 58, No. 3, pp. 417-21.
Journal code: 0401060. ISSN: 0028-3878. L-ISSN: 0028-3878.

L5 ANSWER 330 OF 370 MEDLINE .RTM. on STN
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sclerosis: comparative meta-analysis].
Terapeutyczny potencjal interferonu beta-1b i pokrewnych lekow w stwardnieniu rozsianym: porownawcza meta-analiza.
SO Neurologia i neurochirurgia polska, (2001) Vol. 35, No. 4 Suppl, pp. 125-38.
Journal code: 0101265. ISSN: 0028-3843. L-ISSN: 0028-3843.

L5 ANSWER 331 OF 370 MEDLINE .RTM. on STN

TI Copolymer 1 (***glatiramer*** acetate) in ***relapsing*** forms of ***multiple***
sclerosis : open multicenter study of alternate-day administration.
SO Clinical neuropharmacology, (2002 Jan-Feb) Vol. 25, No. 1, pp. 11-5.
Journal code: 7607910. ISSN: 0362-5664. L-ISSN: 0362-5664.

L5 ANSWER 332 OF 370 MEDLINE .RTM. on STN
TI A prospective, open-label treatment trial to compare the effect of IFNbeta-1a (Avonex), IFNbeta-1b (Betaseron), and ***glatiramer*** acetate
(Copaxone) on the relapse rate in ***relapsing*** --remitting ***multiple***
sclerosis : results after 18 months of therapy.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2001 Dec) Vol. 7,
No. 6, pp. 349-53.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 333 OF 370 MEDLINE .RTM. on STN
TI Risk-benefit assessment of ***glatiramer*** acetate in ***multiple*** ***sclerosis*** .
SO Drug safety : an international journal of medical toxicology and drug
experience, (2001) Vol. 24, No. 13, pp. 979-90.
Journal code: 9002928. ISSN: 0114-5916. L-ISSN: 0114-5916.

L5 ANSWER 334 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate and IFN-beta act on dendritic cells in ***multiple***
sclerosis .
SO Journal of neuroimmunology, (2001 Dec 3) Vol. 121, No. 1-2, pp. 102-10.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L5 ANSWER 335 OF 370 MEDLINE .RTM. on STN
TI Sample size estimations for MRI-monitored trials of MS comparing new vs
standard treatments.
SO Neurology, (2001 Nov 27) Vol. 57, No. 10, pp. 1883-5.
Journal code: 0401060. ISSN: 0028-3878. L-ISSN: 0028-3878.

L5 ANSWER 336 OF 370 MEDLINE .RTM. on STN
TI ***Multiple*** ***sclerosis*** : modulation of apoptosis susceptibility by
glatiramer acetate.
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Journal code: 0370336. ISSN: 0001-6314. L-ISSN: 0001-6314.

L5 ANSWER 337 OF 370 MEDLINE .RTM. on STN
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patients with ***relapsing*** -remitting ***multiple*** ***sclerosis*** : effect of
glatiramer acetate (copolymer 1).
SO Clinical and diagnostic laboratory immunology, (2001 Nov) Vol. 8, No. 6,
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Journal code: 9421292. ISSN: 1071-412X. L-ISSN: 1071-412X.
Report No.: NLM-PMC96249.

L5 ANSWER 338 OF 370 MEDLINE .RTM. on STN
TI Predictors of adherence to Copaxone therapy in individuals with
relapsing -remitting multiple sclerosis.
SO The Journal of neuroscience nursing : journal of the American Association
of Neuroscience Nurses, (2001 Oct) Vol. 33, No. 5, pp. 231-9.
Journal code: 8603596. ISSN: 0888-0395. L-ISSN: 0888-0395.

L5 ANSWER 339 OF 370 MEDLINE .RTM. on STN
TI ***Glatiramer*** acetate in the treatment of ***multiple*** ***sclerosis*** .
SO Expert opinion on pharmacotherapy, (2001 Jul) Vol. 2, No. 7, pp. 1149-65.
Ref: 79
Journal code: 100897346. ISSN: 1465-6566. L-ISSN: 1465-6566.

L5 ANSWER 340 OF 370 MEDLINE .RTM. on STN
TI Glatiramer acetate (GA) induces IL-13/IL-5 secretion in naive T cells.
SO Journal of neuroimmunology, (2001 Sep 3) Vol. 119, No. 1, pp. 137-44.
Journal code: 8109498. ISSN: 0165-5728. L-ISSN: 0165-5728.

L5 ANSWER 341 OF 370 MEDLINE .RTM. on STN
TI Short-term brain volume change in ***relapsing*** -remitting ***multiple***
sclerosis : effect of ***glatiramer*** acetate and implications.
SO Brain : a journal of neurology, (2001 Sep) Vol. 124, No. Pt 9, pp. 1803-12.
Journal code: 0372537. ISSN: 0006-8950. L-ISSN: 0006-8950.

L5 ANSWER 342 OF 370 MEDLINE .RTM. on STN
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relapsing ***multiple*** ***sclerosis*** : MRI and clinical correlates.
Multiple ***Sclerosis*** Study Group and the MRI Analysis Center.
SO Multiple sclerosis (Houndmills, Basingstoke, England), (2001 Feb) Vol. 7,
No. 1, pp. 33-41.
Journal code: 9509185. ISSN: 1352-4585. L-ISSN: 1352-4585.

L5 ANSWER 343 OF 370 MEDLINE .RTM. on STN

TI Autoimmune hyperthyroidism in ***multiple*** ***sclerosis*** under treatment with
glatiramer acetate--a case report.
SO European journal of neurology : the official journal of the European Federation of Neurological Societies, (2001 Mar) Vol. 8, No. 2, pp. 199.
Journal code: 9506311. ISSN: 1351-5101. L-ISSN: 1351-5101.

L5 ANSWER 344 OF 370 MEDLINE .RTM. on STN
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Journal code: 9506311. ISSN: 1351-5101. L-ISSN: 1351-5101.

L5 ANSWER 345 OF 370 MEDLINE .RTM. on STN
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Ref:
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Journal code: 0112037. ISSN: 0012-6543. L-ISSN: 0012-6543.

L5 ANSWER 346 OF 370 MEDLINE .RTM. on STN
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profile and suppression of T cell lines reactive against myelin basic
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SO Neuroscience letters, (2000 Aug 11) Vol. 289, No. 3, pp. 205-8.
Journal code: 7600130. ISSN: 0304-3940. L-ISSN: 0304-3940.

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placebo-controlled study of the effects of ***glatiramer*** acetate on
magnetic resonance imaging--measured disease activity and burden in
patients with ***relapsing*** ***multiple*** ***sclerosis*** . European/Canadian
Glatiramer Acetate Study Group.
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Journal code: 7707449. ISSN: 0364-5134. L-ISSN: 0364-5134.

L5 ANSWER 348 OF 370 MEDLINE .RTM. on STN
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L5 ANSWER 349 OF 370 MEDLINE .RTM. on STN
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SO Expert opinion on investigational drugs, (2000 May) Vol. 9, No. 5, pp.
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L5 ANSWER 350 OF 370 MEDLINE .RTM. on STN
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multiple ***sclerosis*** . An analysis by area under disability/time curves.
The Copolymer 1 ***Multiple*** ***Sclerosis*** Study Group.
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Journal code: 0375403. ISSN: 0022-510X. L-ISSN: 0022-510X.

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of the synthetic random polypeptide glatiramer acetate.
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12, pp. 7300-7.
Journal code: 2985117R. ISSN: 0022-1767. L-ISSN: 0022-1767.

L5 ANSWER 352 OF 370 MEDLINE .RTM. on STN
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Journal code: 9319162. ISSN: 1350-7540. L-ISSN: 1080-8248.

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multiple ***sclerosis*** patients observed for 6 years. Copolymer 1
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SO Multiple sclerosis (Houndmills, Basingstoke, England), (2000 Aug) Vol. 6,
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TI Meta-analysis of clinical trials with copolymer 1 in multiple sclerosis.
SO European neurology, (2000) Vol. 43, No. 4, pp. 189-93.

Journal code: 0150760. ISSN: 0014-3022. L-ISSN: 0014-3022.

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L5 ANSWER 356 OF 370 MEDLINE .RTM. on STN
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multiple sclerosis: effects of heterogeneity of disease course in placebo
cohorts.
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Report No.: NLM-PMC1736854.

L5 ANSWER 357 OF 370 MEDLINE .RTM. on STN
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Il trattamento della sclerosi multipla. Il presente ed il futuro. Gruppo
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L5 ANSWER 359 OF 370 MEDLINE .RTM. on STN
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Journal code: 0372436. ISSN: 0003-9942. L-ISSN: 0003-9942.

L5 ANSWER 360 OF 370 MEDLINE .RTM. on STN
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SO Archives of dermatology, (1999 Oct) Vol. 135, No. 10, pp. 1277-8.
Journal code: 0372433. ISSN: 0003-987X. L-ISSN: 0003-987X.

L5 ANSWER 361 OF 370 MEDLINE .RTM. on STN

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perspectives.
SO Current opinion in neurology, (1999 Jun) Vol. 12, No. 3, pp. 279-93.
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L5 ANSWER 362 OF 370 MEDLINE .RTM. on STN
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L5 ANSWER 363 OF 370 MEDLINE .RTM. on STN
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Ref: 19
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     maintains its clinical effect on   ***multiple***
***sclerosis***   relapse rate and
     degree of disability. Copolymer 1   ***Multiple***
***Sclerosis***   Study Group.
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L6   ANSWER 1 OF 25     MEDLINE .RTM.  on STN
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therapies emerge for ***multiple*** ***sclerosis*** .
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Electronic Publication: 2010-04-15.
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multiple ***sclerosis*** .
SO Disease markers, (2009) Vol. 27, No. 2, pp. 63-73.
Journal code: 8604127. E-ISSN: 1875-8630. L-ISSN: 0278-0240.

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SO Current medical research and opinion, (2009 Jun) Vol. 25, No. 6, pp. 1445-54.
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1266-74.
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SO Acta neurologica Scandinavica, (2005 Oct) Vol. 112, No. 4, pp. 234-7.
Journal code: 0370336. ISSN: 0001-6314. L-ISSN: 0001-6314.

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SO Journal of neurology, (2004 Sep) Vol. 251 Suppl 5, pp. v42-v49. Ref: 25
Journal code: 0423161. ISSN: 0340-5354. L-ISSN: 0340-5354.

L6 ANSWER 16 OF 25 MEDLINE .RTM. on STN
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current status.
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L6 ANSWER 18 OF 25 MEDLINE .RTM. on STN
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L6 ANSWER 20 OF 25 MEDLINE .RTM. on STN
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SO Journal of the neurological sciences, (2002 May 15) Vol. 197, No. 1-2, pp. 51-5.
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The Copolymer 1 ***Multiple*** ***Sclerosis*** Study Group.
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L6 ANSWER 23 OF 25 MEDLINE .RTM. on STN
TI Meta-analysis of clinical trials with copolymer 1 in multiple sclerosis.
SO European neurology, (2000) Vol. 43, No. 4, pp. 189-93.
Journal code: 0150760. ISSN: 0014-3022. L-ISSN: 0014-3022.

L6 ANSWER 24 OF 25 MEDLINE .RTM. on STN
TI Disability outcome measures in therapeutic trials of ***relapsing*** -remitting
multiple sclerosis: effects of heterogeneity of disease course in placebo
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SO Journal of neurology, neurosurgery, and psychiatry, (2000 Apr) Vol. 68,
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Report No.: NLM-PMC1736854.

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	23.96	24.20

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Patent and Trademark Office

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First Named Inventor	Ety Klinger
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Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
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EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	01/24/2012

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

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(Use several sheets if necessary)

Application Number	12/806,684
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First Named Inventor	Ety Klinger
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Examiner Name	
Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	01/24/2012

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Form PTO-1449 (Substitute) **U.S. Department of Commerce Patent and Trademark Office**

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Ety Klinger
Art Unit	1614
Examiner Name	
Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/J.U./	45	6,844,314	01-18-2005	Eisenbach-Schwartz et al.
/J.U./	46	2002-0037848-A1	03-28-2002	Eisenbach-Schwartz et al.
/J.U./	47	2006-0240463 A1	04-24-2006	Lancet
/J.U./	48	12/861,655	08-23-2010	Stark et al.
/J.U./	49	12/231,292	08-29-2008	Aharoni et al.
/J.U./	50	12/761,367	04-15-2010	Altman et al.
/J.U./	51	12/785,125	05-21-2010	Altman et al.

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]
/J.U./	52	WO 00/027417	05-18-2000	Aharoni et al.	
/J.U./	53	WO 05/041933	06-12-2003	Rosenberger	
/J.U./	54	WO 2004/043995	05-27-2004	Bejan et al.	
/J.U./	55	WO 2006/050122	05-11-2006	Ray et al.	
/J.U./	56	WO 2008/006026	01-10-2008	Iyer et al.	
/J.U./	57	WO 2009/070298	06-04-2009	Stark et al.	
/J.U./	58	WO 00/20010	04-13-2000	Flechter, et al.	

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	01/24/2012

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Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office		
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	Filing Date	August 19, 2010
	First Named Inventor	Ety Klinger
	Art Unit	1614
	Examiner Name	
	Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.U./	1	International Search Report issued October 4, 2010 in connection with PCT International Application No. PCT/US10/02283, filed August 19, 2010 (Klinger)	
/J.U./	2	Written Opinion of the International Searching Authority issued October 4, 2010 in connection with PCT International Application No. PCT/US10/02283, filed August 19, 2010 (Klinger)	

EXAMINER SIGNATURE	/John Ulm/	DATE CONSIDERED	01/24/2012

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WEST Search History

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DATE: Tuesday, January 24, 2012

Hide?	Set Name	Query	Hit Count
Prior Art			
		DB=PGPB,USPT; PLUR=YES; OP=ADJ	
☐	L1	alternate-day administration	7

END OF SEARCH HISTORY

L1: Records 1 through 7 of 7
Sorted by: Rec #
Sort is done only on each individual page

App Flt	Rec #	Sel	U	Doc ID	DBNM	Pub Date	Title	Inventor
	1	☐	☑	US 20090215676 A1	PGPB	20090827	Method of treatment	VAN DER LELY; Aart Jan
	2	☐	☑	US 20060058384 A1	PGPB	20060316	Treatment of IGA nephropathy with omega-3 fatty acids	Hogg; Ronald J.
	3	☐	☑	US RE41571 E	USPT	20100824	Method of providing sustained analgesia with buprenorphine	Reder; Robert F. et al.
	4	☐	☑	US RE41489 E	USPT	20100810	Method of providing sustained analgesia with buprenorphine	Reder; Robert F. et al.
	5	☐	☑	US RE41408 E	USPT	20100629	Method of providing sustained analgesia with buprenorpine	Reder; Robert F. et al.
	6	☐	☑	US 6844354 B1	USPT	20050118	Agent for prophylaxis and treatment of interstitial pneumonia and pulmonary fibrosis	Iizuka; Kunihiko et al.
	7	☐	☑	US 5225440 A	USPT	19930706	Attenuation of the opioid withdrawal syndrome by inhibitors of nitric oxide synthase	London; Edythe D. et al.

Docket No. 2609/80798-A/JPW/GJG/GTK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ety Klinger	
Serial No.	:	12/806,684	Examiner: John Ulm
Filed	:	August 19, 2010	Group Art Unit: 1649
Conf. No.	:	3109	
For	:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY	

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
August 6, 2012

BY EFS
Commissioner for Patents
Alexandria, VA

Sir:

AMENDMENT IN RESPONSE TO FEBRUARY 6, 2012 OFFICE ACTION AND PETITION FOR THREE-MONTH EXTENSION OF TIME

This Amendment is submitted in response to a February 06, 2012 Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the February 06, 2012 Office Action was originally due May 06, 2012. Applicant hereby requests a three-month extension of time. The fee for a three-month extension of time is ONE THOUSAND TWO HUNDRED SEVENTY DOLLARS ($1,270) and authorization is hereby given to charge this amount to Deposit Account No. 03-3125. With a three-month extension of time, a response to the February 06, 2012 is due August 6, 2012. Accordingly, this response is being timely filed.

Amendments to the Claims

Pursuant to 37 C.F.R. §1.121(c), this listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently Amended) A method of ~~alleviating a symptom of~~ reducing the frequency of relapses ~~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 has MRI features consistent with ~~is determined to be at high risk of developing clinically definite~~ multiple sclerosis comprising administering to the human patient a therapeutically effective dosage regimen of three subcutaneous injections of ~~a therapeutically effective dose of~~ 1ml of a pharmaceutical composition comprising 40mg of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, the regimen being sufficient ~~so as~~ to ~~thereby alleviate the symptom of~~ reduce the frequency of relapses in the patient.

2. (Cancelled)

3. (Currently Amended) The method of claim 1, ~~wherein alleviating a symptom comprises~~ further comprising reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient.

4. (Currently Amended) The method of claim 1, ~~wherein alleviating a symptom comprises~~ further comprising reducing the mean number of new T_2 lesions in the brain of the patient.

5. (Currently Amended) The method of claim 1, ~~wherein alleviating a symptom comprises~~ further comprising reducing the cumulative number of enhancing lesions on T_1-weighted images.

6-17. (Canceled)

18. (Previously Presented) The method of claim 1, wherein the pharmaceutical composition is in a prefilled syringe for self administration by the patient.

19. (Canceled)

20. (Previously Presented) The method of claim 1, wherein the patient has not received glatiramer acetate therapy prior to initiation of the subcutaneous injections.

21. (Previously Presented) The method of claim 1, wherein 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.

22-32. (Canceled)

33. (New) The method of claim 3, further comprising reducing the mean number of new T_2 lesions in the brain of the patient.

34. (New) The method of claim 3, further comprising reducing the cumulative number of enhancing lesions on T_1-weighted images.

35. (New) The method of claim 4, further comprising reducing the cumulative number of enhancing lesions on T_1-weighted images.

36. (New) The method of claim 33, further comprising reducing the cumulative number of enhancing lesions on T_1-weighted images.

37. (New) The method of claim 1, wherein the pharmaceutical composition has a pH in the range of 5.5 to 8.5.

38. (New) The method of claim 37, wherein the pharmaceutical composition has a pH in the range of 5.5 to 7.0.

39. (New) The method of claim 1, wherein the patient has at least 1 cerebral lesion detectable by an MRI scan and wherein the lesion is associated with brain tissue inflammation, myelin sheath damage or axonal damage.

40. (New) The method of claim 40, wherein, the lesion is a demyelinating white matter lesion visible on brain MRI and wherein the white matter lesion is at least 3 mm in diameter.

41. (New) The method of claim 1, wherein the patient has experienced a first clinical episode and wherein the first clinical episode 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.

42. (New) The method of claim 41, wherein the patient has at least 1 cerebral lesion detectable by an MRI scan and wherein the lesion is associated with brain tissue inflammation, myelin sheath damage or axonal damage.

43. (New) The method of claim 42, wherein, the lesion is a demyelinating white matter lesion visible on brain MRI and wherein the white matter lesion is at least 3 mm in diameter.

44. (New) A method of reducing the frequency of relapses in a human patient suffering from relapsing-remitting multiple sclerosis comprising administering to the human patient a therapeutically effective dosage regimen of three subcutaneous injections of 1ml of a pharmaceutical composition comprising 40mg of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, wherein the pharmaceutical composition is in a prefilled syringe for self administration by the patient, wherein the pharmaceutical composition further comprises mannitol, and wherein the

pharmaceutical composition has a pH in the range of 5.5 to 7.0, the regimen being sufficient to reduce the frequency of relapses in the patient.

45. (New) A method of reducing the frequency of relapses in a human patient who has experienced a first clinical episode and has MRI features consistent with multiple sclerosis comprising administering to the human patient a therapeutically effective dosage regimen of three subcutaneous injections of 1ml of a pharmaceutical composition comprising 40mg of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection, wherein the pharmaceutical composition is in a prefilled syringe for self administration by the patient, wherein the pharmaceutical composition further comprises mannitol, and wherein the pharmaceutical composition has a pH in the range of 5.5 to 7.0, the regimen being sufficient to reduce the frequency of relapses in the patient.

REMARKS

Claims 1-26 are pending and under examination in the subject application. By this amendment applicant has cancelled claims 2, 6-17, 19 and 22-26 without disclaimer as to Applicant's right to pursue the subject matter of these claims in the future, amended claims 1 and 3-5, and added new claims 33-45. Upon entry of this amendment claims 1, 3-5, 18, 20-21 and 33-45 will be pending and under examination.

Support for the amendments can be found in the specification as originally filed, *inter alia*, as follows: claim 1: page 8, lines 22-23, page 4, lines 19-23, page 11, lines 19-22 and page 27, lines 12-14; claim 3: claim 3 as originally filed; claim 4: claim 4 as originally filed; claim 5: claim 5 as originally filed; claim 33: claim 4 as originally filed; claims 34-36: claim 5 as originally filed; claim 37: page 11, lines 2-3; claim 38: page 11, lines 5-6; claims 39 and 42: page 13, lines 6-11; claims 40 and 43: page 13, lines 13-17; claim 41: page 12, line 24 to page 13, line 4; and claims 44-45: page 8, lines 2-12, page 8, lines 22-23, page 4, lines 19-23, page 11, lines 19-22, page 27, lines 12-14, page 10, lines 16-17, page 10, lines 31-32 and page 11, lines 5-6.

Claim Rejections Under 35 U.S.C. § 112, First Paragraph

In the February 6, 2012 Office Action, the Examiner rejected claims 1-26 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with written description and enablement requirements. The Examiner alleged that the claims encompass subject matter not described in the specification in such a way as to demonstrate that the inventors were in

possession of the claimed and enable one skilled in the art to use the invention.

Specifically, the Examiner alleged that the claims encompass a method of alleviating a symptom of multiple sclerosis by administering "as few as three subcutaneous injections of 40mg of glatiramer acetate (a.k.a. copolymer-1) on alternate days [during] a one week period." February 6, 2012 Office Action, page 2, subsection 2). The Examiner further alleged that neither the specification nor the art of record provides evidence that a benefit has been shown, or can reasonably be predicted, to result from administration of as few as three doses of glatiramer acetate; and that the applicant has not demonstrated measurable benefit from the administration of only three doses of glatiramer acetate.

Applicant's Response

In response, applicant respectfully traverses. The Examiner's position is based on the view that the claims are so broad as to read on a therapy consisting of three, and only three administrations of glatiramer acetate, the three administrations occurring in a single seven day period. Applicant submits that this is an unreasonably broad claim construction which a person skilled in the art would not reach. Rather, a person skilled in the art would interpret the claims as being directed at a dosage regimen at least because the claims recite "so as thereby alleviate the symptom."

During examination claims should be "given their broadest reasonable interpretation consistent with the specification." M.P.E.P. § 2111, Claim Interpretation; Broadest Reasonable Interpretation, citing *Phillips v. AWH Corp.*, 415 F.3d 1303,

75 USPQ2d 1321 (Fed. Cir. 2005). Here, in the specification, the invention is illustrated in the Examples by a study assessing "efficacy, safety and tolerability of Glatiramer Acetate (GA) injection 40mg/ml administered three times weekly by subcutaneous injection." Specification at page 20, Example 1. The Discussion section explains that "the subject application discloses an effective low frequency dosage regimen of GA administration." Specification at page 37, lines 8-9.

In light of this, a person of ordinary skill in the art would clearly understand that recitation of administering to the human patient a therapeutically effective regimen of three subcutaneous injections over a period of seven days with at least one day between every subcutaneous injection defined a regimen for therapeutic effect. Applicant submits that when given their broadest reasonable interpretation the claims are clearly drawn to a glatiramer acetate dosage regimen which is both sufficiently described and fully enabled by the specification.

Notwithstanding the foregoing, and to remove any purported ambiguity, applicant has clarified the claims by amendment herein. Applicant has amended claim 1 to recite a "therapeutically effective regimen" and that the "regimen" is "sufficient to reduce the frequency of relapses." Other claims have been similarly amended. As amended the claims cannot be reasonably construed to read on only a single seven day period of administration, at least because the claims as amended require a "regimen."

Accordingly, applicant requests that this rejection be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

In the February 6, 2012 Office Action, the Examiner rejected claims 14-17 and 22-26 under 35 U.S.C. § 112, second paragraph, for allegedly failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Claim 14

The Examiner alleged that claim 14 is indefinite because there is no antecedent basis for "the change in EDSS Score."

In response, applicant has canceled claim 14. Accordingly, this rejection is moot and applicant requests that it be reconsidered and withdrawn.

Claims 15-17

The Examiner alleged that claims 15-17 are indefinite because there is no antecedent basis for "the level of disability."

In response, applicant has canceled claims 15-17. Accordingly, this rejection is moot and applicant requests that it be reconsidered and withdrawn.

Claims 22-26

The Examiner alleged that claims 22-26 are indefinite because there is no antecedent basis for "the frequency." In addition the Examiner alleged that the terms "increasing the tolerability" and "reducing the frequency" are relative terms for which no point of reference is given.

In response, applicant has canceled claims 22-26. Accordingly, this rejection is moot and applicant requests that it be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 102(b)

In the February 6, 2012 Office Action, the Examiner rejected claims 1-17 and 20-26 under 35 U.S.C. § 102(b) as being allegedly anticipated by Flechter et al. The Examiner alleged that Flechter et al. teaches administration of glatiramer acetate in an alternate day administration schedule, requiring administration of glatiramer acetate on three alternate days every other week. The Examiner alleged that this expressly meets the limitations of claim 1.

The Examiner further alleged that specific therapeutic outcomes required in certain of the dependent claims would have been inherent in the treatment protocol of Flechter et al., "as shown by the fact that the instant specification fails to identify any particular dosage that has been shown to be effective in achieving a specific outcome." February 6, 2012 Office Action, page 4, subsection 4, first paragraph.

Applicant's Response.

In response, applicant respectfully traverses. As noted above in applicant's response to the rejections under 35 U.S.C. § 112, first paragraph, the claims of the instant invention are drawn to a regimen. Flechter et al., which teaches alternate day administration cannot anticipate a "regimen" requiring administration 3 times during a seven day period because the treatment protocol of Flechter et al. results in four

administrations every other successive seven day period. Thus, Flechter et al. does not anticipate the instant claims.

In addition, by this amendment, applicant has amended the claims to require administration of a 40mg dose of glatiramer acetate. As the Examiner has recognized, Flechter et al. does not teach the administration of a 40mg dose of glatiramer acetate.

Accordingly, applicant requests that the rejection be reconsidered and withdrawn.

Claim Rejections Under 35 U.S.C. § 102(b) or § 103

In the February 6, 2012 Office Action, the Examiner rejected claims 1-18 under 35 U.S.C. § 102(b) as allegedly anticipated by or, in the alternative, unpatentable under 35 U.S.C. § 103 over Flechter et al. Specifically, the Examiner alleged that the requirement that the dose of glatiramer acetate be contained in a prefilled syringe for administration by the patient is anticipated by or obvious in view of Flechter et al. The Examiner asserted that Flechter et al. teaches a lyophilized material supplied in a single use vial. The Examiner further alleged that either 1) this satisfies the requirement of a prefilled syringe for administration by the patient, or 2) transfer of said material to a syringe prior to injection would provide the pre-filled syringe.

Applicant's response

In response, applicant submits that, as amended, the claims are both novel and nonobvious over Flechter et al. As amended, the claims require a 40mg dose of glatiramer acetate. The

Examiner has acknowledged that Flechter et al. do not teach a 40mg dose of glatiramer acetate. Accordingly, this rejection is moot.

Claim Rejections Under 35 U.S.C. § 103

In the February 14, 2012 Office Action, the Examiner rejected claims 1-19 under 35 U.S.C. § 103 as allegedly unpatentable over Flechter et al. in view of Cohen et al. The Examiner acknowledged that Flechter et al. do not teach the use of a 40mg dose of glatiramer acetate but asserted that Cohen et al. "suggested that a [daily] 40mg dose of copolymer-1 may be more effective than the currently approved 20mg daily dose in reducing MRI activity and clinical relapse…." The Examiner further asserted that it would have been obvious for a person of ordinary skill in the art to combine the 40mg dose of Cohen et al. with the alternate day administration of Flechter et al.

Applicant's response

In response, applicant respectfully traverses on the basis that 1) a combination of Cohen et al. with Flechter et al. is not rational in view of the prior art as a whole, *i.e.* the prior art as a whole did not motivate such a combination, 2) even if combined, the hypothetical combination of Flechter et al. and Cohen et al. does not teach every element of the claims, and 3) even if it did, the hypothetical combination of Flechter et al and Cohen et al. does not provide a reasonable expectation that a dosage regimen as claimed would result in a successful therapy.

1) The proposed combination of Flechter et al. and Cohen et al. was not rational in view of the prior art as a whole.

The prior art, taken as a whole, provides no motivation to combine Flechter et al. with Cohen et al. The Examiner asserted that such motivation can be found in the theory of Cohen et al. that 40mg glatiramer acetate daily "may be" more effective than 20mg glatiramer acetate daily. However, at the time of the invention, a person of ordinary skill in the art would not have accepted this theory because this theory had already been tested and proven wrong.

The small scale study presented in Cohen et al. was interpreted by Cohen et al. to demonstrate a "trend favoring" 40mg GA daily vs. 20mg GA daily. Cohen el al., Abstract; page 943, second column, Discussion. However, the Cohen et al. report was not conclusive, and would have been understood as such by a person of ordinary skill in the art. Notably, the study reported by Cohen et al. was funded by Teva Pharmaceuticals, who also has an exclusive license to the subject application. Id. at page 939, Disclosure.

The apparently promising report by Cohen et al. was followed by a large scale Phase III trial to compare 40mg GA daily with 20mg GA daily in 1,155 patients with RRMS; the FORTE trial. The results of the FORTE trial were announced by Teva Pharmaceuticals Industries Ltd. on July 7, 2008, prior to the effective filing date of the subject application. Teva Provides Update on FORTE Trial, attached hereto as **Exhibit A.** The update states that "[t]he 40mg dose did not demonstrate increased efficacy" and further that "the study confirms that COPAXONE® 20mg … remains the optimal treatment dose with

unmatched long term efficacy confirmed over 10 years." Emphasis added; see, Exhibit A.

In addition to providing no demonstrated clinical benefit over 20mg GA, the 40mg GA dose of Cohen et al. required twice as much drug substance and would be expected to roughly double the cost of the resulting drug product.

When considering the art as a whole, a person of ordinary skill in the art at the relevant time would have recognized that substituting a 40mg dose of GA for a 20mg dose would not increase efficacy but would increase cost. Accordingly, the proposed combination of the 40mg GA dose of Cohen et al. with the alternate day administration pattern of Flechter et al., as proposed by the Examiner, would not have been considered reasonable in view of the prior art as a whole at the relevant time.

As the Examiner is aware, MPEP 2143.01(III) guides that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc., 550 U.S. 398, 409, 82 USPQ2d 1385, 1396 (2007)*". The *KSR* Court also reiterated the need for a fact finder to be aware "of the distortion caused by hindsight bias" and to "be cautious of arguments reliant upon ex post reasoning." *Id.* at 1397.

Here, the hypothetical combination of Flechter et al. and Cohen et al. would have been expected, by a person of ordinary skill in the art at the relevant time, to provide a more expensive treatment without an efficacy increase. Accordingly,

a *prima facie* case of obviousness has not been set forth, and the rejection of record should be withdrawn.

2) The combination of Flechter et al. and Cohen et al. does not teach all the elements of the claims.

The hypothetical combination of Flechter et al. and Cohen et al., even if proper, yields alternate day 40mg GA. This combination does not provide "a therapeutically effective regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate over a period of seven days … the regimen being sufficient to alleviate the symptom of the patient" as required by claim 1.

As discussed above, the alternate day administration of Flechter et al. does not anticipate the claimed "regimen". The dosage regimen of Flechter et al. is alternate days; the regimen of Cohen et al. is daily. The claimed dosage regimen requires "three subcutaneous doses … over a period of seven days…." Nothing in either Flechter et al. or Cohen et al. suggests such a regimen.

Accordingly, the claimed regimen cannot be obvious to a person having ordinary skill in the art from the combination of Flechter et al. and Cohen et al.

3) Combination of Flechter et al. with Cohen et al. could not be reasonably expected to provide as effective a therapy as the 20mg daily therapy.

Even if, *arguendo*, one were to combine the teachings of Flechter et al. with those of Cohen et al., the expected

result would be a less effective therapy than that provided by 20mg daily. Flechter et al. showed in their results that alternate day dosing with 20mg GA is demonstrably worse therapeutically than 20mg GA daily. Flechter et al. stated that alternate day GA therapy "compar[es] favorably with the effects of daily injections." Flechter et al., page 11, Abstract. A closer look at the results section of Flechter et al. sheds meaning to their term "favorably."

Patients treated with alternate day 20mg GA experienced substantial disease progression during the course of their treatment as measured by a change in EDSS score. Flechter et al., page 13, Table 3, seventh column (showing an increase of 0.132 over the first year and 0.426 over the two year study).

Cohen et al. showed that there was no change in EDSS score and no difference in the change in EDSS score between 40mg daily and 20mg daily GA. Cohen et al, page 942, Table 2, 12th row (showing no difference between EDSS score at each visit vs. baseline). Moreover, despite the theory proposed by Cohen et al., the FORTE trial taught that "[t]he 40mg dose did not demonstrate increased efficacy" over the 20mg daily dose. Exhibit A, first paragraph.

Therefore, a person having ordinary skill in the art would a) expect that reducing the frequency of GA injections would result in a less effective therapy, as demonstrated by Flechter et al., and b) would also expect that changing the dose from 20mg to 40mg would not increase efficacy in view of the results of the FORTE study which failed to confirm hypothesis of Cohen et al. Based on Flechter at al. taken together with Cohen et al. and the FORTE study, a person of

ordinary skill in the art could reasonably expect that 40mg GA on alternate days would be less effective than 20mg GA daily. Therefore, the disclosed result that treatment with 40mg s.c. GA three times weekly is at least as effective as 20mg s.c. GA daily is unexpected.

Accordingly, the rejection of record is improper, and applicant respectfully requests that it be reconsidered and withdrawn.

Double Patenting

In the February 6, 2012 Office Action, the Examiner provisionally rejected claims 1-26 on the ground of nonstatutory double patenting over claims 3 and 18-20 of co-pending Application No. 13/308,299. The rejection was made provisional because the conflicting claims have not yet issued. The Examiner alleged that the subject matter claimed is fully disclosed in co-pending Application No. 13/308,299 and would be covered by any patent issued thereon. U.S. Patent Application No. 13/308,299 issued on July 31, 2012 as U.S. Patent No. 8,232,250.

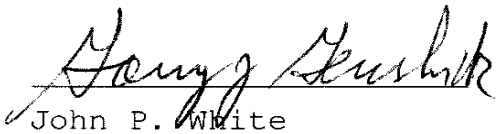
Applicant's Response

In response, applicant respectfully traverses. The claims herein have been revised to recite features which are not recited in the claims of U.S. Patent No. 8,232,250 which issued from U.S. Patent Application No. 13/308,299. Therefore applicant requests that the Examiner reconsider and withdraw this rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee, other than the fee of ONE THOUSAND TWO HUNDRED SEVENTY DOLLARS ($1,270) for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
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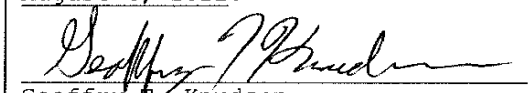
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
30 Rockefeller Plaza
20th Floor
New York, New York 10112
(212) 278-0400

Certificate of Transmission
I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on August 6, 2012.



Geoffry T. Knudsen

TEVA PHARMACEUTICAL INDUSTRIES LTD.

Website: www.tevapharm.com

Contact:	**Elana Holzman**	Teva Pharmaceutical Industries Ltd.	972 (3) 926-7554
	Kevin Mannix	Teva North America	(215) 591-8912

For Immediate Release

TEVA PROVIDES UPDATE ON FORTE TRIAL

Jerusalem, Israel July 7, 2008 – Teva Pharmaceutical Industries Ltd. (NASDAQ: TEVA) today announced top-line results from a Phase III study designed to assess the efficacy, safety and tolerability of glatiramer acetate (GA) 40mg as compared to the approved COPAXONE® 20mg in the treatment of relapsing-remitting multiple sclerosis (RRMS). The 40mg dose did not demonstrate increased efficacy in reducing the relapse rate; however, the higher dose maintained the favorable safety and tolerability profile of COPAXONE® 20mg.

Seventy-eight percent (78%) of COPAXONE® 20mg treated patients remained relapse-free throughout the study. Moreover, patients that completed one year of treatment with COPAXONE® 20mg experienced a very low annualized relapse rate of 0.27. This robust effect was also reflected in a remarkable reduction of inflammatory activity as measured by MRI.

"While the trial did not demonstrate an enhanced efficacy at the higher dose level, the study reaffirms that COPAXONE® 20mg, the leading multiple sclerosis therapy, remains the optimal treatment dose with unmatched long term efficacy confirmed over 10 years," said **Moshe Manor, Group Vice President – Global Innovative Resources**. "Teva is committed to ongoing research in the field of multiple sclerosis and will continue to move forward towards providing additional treatment options to multiple sclerosis patients".

Teva will continue to analyze the study results to better understand the effect of GA 40mg on patients. The Company is also evaluating the use of GA for additional indications.

About the Study
A randomized, double-blind study, designed to assess the efficacy, safety and tolerability of 40mg glatiramer acetate, as compared to the currently approved COPAXONE® (glatiramer acetate) 20mg dose.

The study was conducted in 136 centers in North America, Argentina, Europe and Israel, and included 1,155 patients with RRMS. The trial's primary clinical outcome measure was rate of confirmed relapses.

About COPAXONE®
Current data suggest COPAXONE® (glatiramer acetate injection) is a selective MHC (Major Histocompatability Complex) class II modulator. COPAXONE® is indicated for the reduction of the frequency of relapses in RRMS. COPAXONE® is very well tolerated and the most common side effects of COPAXONE® are redness, pain, swelling, itching, or a lump or an indentation at the site of injection, weakness, infection, pain, nausea, joint pain, anxiety and muscle stiffness.

Exhibit A

COPAXONE® is now approved in 51 countries worldwide, including the United States, all European countries, Canada, Mexico, Australia and Israel. In Europe, COPAXONE® is marketed by Teva Pharmaceutical Industries Ltd. and sanofi-aventis. In North America, COPAXONE® is marketed by Teva Neuroscience, Inc.

See additional important information at http://www.COPAXONE.com/pi/index.html or call 1-800-887-8100 for electronic releases.

About Multiple Sclerosis
Multiple Sclerosis (MS) is the leading cause of neurological disability in young adults. It is estimated that 400,000 people in the United States are affected by this disease, and that over one million people are affected worldwide. MS is a progressive, demyelinating disease of the central nervous system affecting the brain, spinal cord and optic nerves.

Patients with MS may experience physical symptoms and/or cognitive impairments, including weakness, fatigue, ataxia, physical dysfunction, bladder and bowel problems, sensory effects, and visual impairment. MS also has a significant impact on the sufferers' social functioning and overall quality of life.

About Teva
Teva Pharmaceutical Industries Ltd., headquartered in Israel, is among the top 20 pharmaceutical companies in the world and is the world's leading generic pharmaceutical company. The Company develops, manufactures and markets generic and innovative human pharmaceuticals and active pharmaceutical ingredients, as well as animal health pharmaceutical products. Over 80 percent of Teva's sales are in North America and Europe. Teva's innovative R&D focuses on developing novel drugs for diseases of the central nervous system.

Safe Harbor Statement under the U. S. Private Securities Litigation Reform Act of 1995:
This release contains forward-looking statements, which express the current beliefs and expectations of management. Such statements are based on management's current beliefs and expectations and involve a number of known and unknown risks and uncertainties that could cause Teva's future results, performance or achievements to differ significantly from the results, performance or achievements expressed or implied by such forward-looking statements. Important factors that could cause or contribute to such differences include risks relating to: Teva's ability to accurately predict future market conditions, potential liability for sales of generic products prior to a final resolution of outstanding patent litigation, including that relating to the generic versions of Allegra®, Neurontin®, Lotrel®, Famvir® and Protonix®, Teva's ability to successfully develop and commercialize additional pharmaceutical products, the introduction of competing generic equivalents, the extent to which Teva may obtain U.S. market exclusivity for certain of its new generic products and regulatory changes that may prevent Teva from utilizing exclusivity periods, competition from brand-name companies that are under increased pressure to counter generic products, or competitors that seek to delay the introduction of generic products, the impact of consolidation of our distributors and customers, the effects of competition on our innovative products, especially Copaxone® sales, the impact of pharmaceutical industry regulation and pending legislation that could affect the pharmaceutical industry, the difficulty of predicting U.S. Food and Drug Administration, European Medicines Agency and other regulatory authority approvals, the regulatory environment and changes in the health policies and structures of various countries, our ability to achieve expected results though our innovative R&D efforts, Teva's ability to successfully identify, consummate and integrate acquisitions (including the pending acquisition of Bentley Pharmaceuticals, Inc.), potential exposure to product liability claims to the extent not covered by insurance, dependence on the effectiveness of our patents and other protections for innovative products, significant operations worldwide that may be adversely affected by terrorism, political or economical instability or major hostilities, supply interruptions or delays that could result from the complex manufacturing of our products and our global supply chain, environmental risks, fluctuations in currency, exchange and interest rates, and other factors that are discussed in Teva's Annual Report on Form 20-F and its other filings with the U.S. Securities and Exchange Commission. Forward-looking statements speak only as of the date on which they are made and the Company undertakes no obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

Electronic Patent Application Fee Transmittal

Application Number:	12806684
Filing Date:	19-Aug-2010
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Filer:	John P. White/Cindy Shu
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1270	1270

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1270**

Electronic Acknowledgement Receipt

EFS ID:	13425488
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Cindy Shu
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	06-AUG-2012
Filing Date:	19-AUG-2010
Time Stamp:	14:51:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1270
RAM confirmation Number	1287
Deposit Account	033125
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		120806_2609_80798-A_Amendment_Rsp_OA_GTK.pdf	6134655 8945178013398a27c7a98f70d015763e5af84012	yes	21

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	18
Amendment/Req. Reconsideration-After Non-Final Reject	19	21

Warnings:

Information:

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Warnings:

Information:

Total Files Size (in bytes):	6164999

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office	Application Number	12/806,684
	Filing Date	August 19, 2010
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	First Named Inventor	Ety Klinger
	Art Unit	John Ulm
	Examiner Name	1649
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	1	7,625,861	12-01-2009	Konfino et al.
	2	7,615,580	07-22-2006	Gad et al.
	3	7,923,215	04-12-2011	Klinger
	4	2007-0021324	01-25-2007	Dolitzky
	5	2010-0285600	11-11-2010	Lancet et al.
	6	7,855,176	12-21-2012	Altman et al.
	7	2011-0066112	03-17-2011	Altman et al.
	8	13/384,021	07-14-2010	Altman et al.
	9	13/083,112	04-08-2011	Klinger
	10	11/651,212	01-09-2007	Pinchasi
	11	12/806,684	08-19-2010	Klinger

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Exhibit A

Electronic Patent Application Fee Transmittal

Application Number:	12806684
Filing Date:	19-Aug-2010
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Filer:	John P. White/Cindy Shu
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	13425795
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Cindy Shu
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	06-AUG-2012
Filing Date:	19-AUG-2010
Time Stamp:	15:06:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	1627
Deposit Account	033125
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

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	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	4
	Information Disclosure Statement (IDS) Form (SB08)	5	5

Warnings:

Information:

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Warnings:

Information:

Total Files Size (in bytes):	1166941

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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New International Application Filed with the USPTO as a Receiving Office

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Docket No. 2609/80798-A/JPW/GJG/GTK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ety Klinger
Serial No.	:	12/806,684
Filed	:	August 19, 2010
For	:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
August 6, 2012

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following references, which are listed on Form PTO-1449 (substitute), attached hereto as **Exhibit A.**

According to 37 C.F.R. §1.97(c) an Information Disclosure Statement filed after the period specified in 37 C.F.R. §1.97(b) shall be considered if accompanied by the fee set forth in the 37 C.F.R. §1.17(p) or a statement under 37 C.F.R. §1.97(e). The required fee set forth in 37 C.F.R. §1.97(p) is one hundred and eighty dollars ($180.00) and authorization is hereby given to charge this amount to Deposit Account No. 03-3125. Accordingly, this Information Disclosure Statement should be considered.

Reference items 1-11 are U.S. Patent Applications and U.S. Patent Application Publications. Pursuant to 37 C.F.R. §1.98(a)(2), copies of references 1-11 are not being submitted.

1. U.S. Patent No. 7,625,861, issued December 1, 2009 (Konfino, et al.);

2. U.S. Patent No. 7,615,359, issued November 11, 2009 (Gad et al.);

3. U.S Patent No. 7,923,215, issued April 12, 2011 (Klinger);

4. U.S. Patent Application Publication No. US-2007-0021324, published January 25, 2007 (Dolitzky);

5. U.S. Patent Application Publication No. US 2010-0285600 A1, published November 11, 2010 (Lancet et al.);

6. U.S. Patent No. 7,855,176, issued December 21, 2010 (Altman et al.);

7. U.S. Patent Application Publication No. 2011-0066112 A1, published March 17, 2011 (Altman et al.);

8. U.S. Serial No. 13/384,021, filed July 14, 2010 (Altman et al.);

9. U.S. Serial No. 13/083,112, filed April 8, 2011 (Klinger);

10. U.S. Serial No. 11/651,212, filed January 9, 2007 (Pinchasi);

11. U.S. Serial No. 12/806,684, filed August 19, 2010 (Klinger);

The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO 1449.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee, other than the fee of one hundred and eighty dollars ($180.00) for submission of an Information Disclosure Statement, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicant
Cooper & Dunham LLP
30 Rockefeller Plaza
New York, New York 10112
(212) 278-0400

Certificate of Transmission

I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on August 6, 2012.

Geoffry Knudsen

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office	Application Number	12/806,684
	Filing Date	August 19, 2010
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	First Named Inventor	Ety Klinger
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]
	7	WO 2007/081975	07-19-2007	Pinchasi	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Exhibit A

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office	Application Number	12/806,684
	Filing Date	August 19, 2010
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	First Named Inventor	Ety Klinger
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	February 14, 2012 Office Action Issued in Connection With U.S. Serial No. 13/308,299, filed November 30, 2011 (Klinger)	
	2	Amendment in Response to February 14, 2012 Office Action filed May 14, 2012 in connection with U.S. Serial No. 13/308,299, filed November 30, 2011 (Klinger)	
	3	November 25, 2011 Examiner's Report Issued in connection with Australian Application No. 2010284666, filed August 19, 2012 (Klinger)	
	4	February 29, 2012 Official Action Issued in connection with Canadian Application No. 2,760,802, filed August 19, 2012 (Klinger)	
	5	Response to the February 29, 2012 outstanding Examiner's Report filed May 29, 2012 in connection with Canadian Application No. 2,760,802, filed August 19, 2012 (Klinger)	
	6	Supplementary European Search Report issued July 13, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011	
	8	Flechter S. et al. (2002) "Comparison of glatiramer acetate (Copaxone(R)) and interferon beta-1b (Betaferon(R)) in multiple sclerosis patients: An open-label 2-year follow up" Journal of the Neurological Sciences vol. 197, no. 1-2 pages 51-55	
	9	Khan et al. (2008) "Randomized, prospective, rater-blinded, four-year, pilot study to compare the effect of daily versus every - other - day injections in relapsing -remitting multiple" Mult. Scler. 14 Suppl. 1 S296	
	10	Caon Christina et al. (2009) "Randomized, prospective, rater-blinded, four year pilot study to compare the effect of daily versus every other day glatiramer acetate 20 mg subcutaneous injections in RRMS" Neurology vol. 72, no. 11, page A317	
	11	Simpson Dene et al. (2002) "Glatiramer acetate: A review of its use in relapsing-remitting multiple sclerosis" CNS DRUGS vol. 16, no. 12 pages 825-850	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

Electronic Acknowledgement Receipt

EFS ID:	13425969
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Cindy Shu
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	06-AUG-2012
Filing Date:	19-AUG-2010
Time Stamp:	15:32:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		120806_2609_80798-A_SIDS_GTK.pdf	1860893 9f81cd809a0c10d9adb89821b8c0fed7037b6510	yes	6

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	4	
	Information Disclosure Statement (IDS) Form (SB08)		5	6	
Warnings:					
Information:					
2	Non Patent Literature	120806_2609_80798-A_Exhibit_1_GTK.pdf	777836 88e0a6e570bd73984a9a2a16646f08686b34fd8c	no	11
Warnings:					
Information:					
3	Non Patent Literature	120806_2609_80798-A_Exhibit_2_GTK.pdf	1674262 ecc88fe1129a5989d234bb0baccc4061606fc278	no	23
Warnings:					
Information:					
4	Non Patent Literature	120806_2609_80798-A_Exhibit_3_GTK.pdf	145236 9e1a531d205c60eed7bc2a1ce1ae11bf16ccb72d	no	2
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Information:					
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Warnings:					
Information:					
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Warnings:					
Information:					
8	Non Patent Literature	120806_2609_80798-A_Exhibit_7_GTK.pdf	1767995 657352a21a5c1238c490c3c188c2761712db7f02	no	32
Warnings:					
Information:					

9	Non Patent Literature	120806_2609_80798-A_Exhibit_8_GTK.pdf	671954 12397f3af36d9f68e4bbaf9e75cfbeab834994e7	no	5
Warnings:					
Information:					
10	Non Patent Literature	120806_2609_80798-A_Exhibit_9_GTK.pdf	185140 17c66c7c4ac325c1094f91ddb3dde0cda3022d89	no	1
Warnings:					
Information:					
11	Non Patent Literature	120806_2609_80798-A_Exhibit_10_GTK.pdf	316831 5f02262549e3caf3565c9456cd6bc708afb8b5b4	no	1
Warnings:					
Information:					
12	Non Patent Literature	120806_2609_80798-A_Exhibit_11_GTK.pdf	3262978 116df8ab53dd7bb1d28ddfb5d974e1ea9b74c712	no	26
Warnings:					
Information:					
		Total Files Size (in bytes):	14620542		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 2609/80798-A/JPW/GJG/GTK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ety Klinger
Serial No.	:	12/806,684
Filed	:	August 19, 2010
For	:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
August 6, 2012

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, Applicant directs the Examiner's attention to the following items, which are listed on the Substitute PTO-1449 form attached hereto as **Exhibit A**.

According to 37 C.F.R. §1.97(c) an Information Disclosure Statement filed after the period specified in 37 C.F.R. §1.97(b) shall be considered if accompanied by the fee set forth in the 37 C.F.R. §1.17(p) or a statement under 37 C.F.R. §1.97(e). The required fee set forth in 37 C.F.R. §1.97(p) is one hundred and eighty dollars ($180.00) and this amount has been paid in the first Information Disclosure Statement filed herewith. Accordingly, this Information Disclosure Statement should be considered.

Items 1-5 were issued in counterpart applications to the subject application. Items 6-11 were cited in items 3, 4, or 6. Other references cited in items 3, 4, or 6 are either

cited in the above-identified application or are disclosed in the first Information Disclosure Statement filed herewith.

Copies of items 1-11 are attached hereto as **Exhibits 1-11**, respectively.

1. February 14, 2012 Office Action Issued in Connection With U.S. Serial No. 13/308,299, filed November 30, 2011 (Klinger) **(Exhibit 1)**;

2. Amendment in Response to February 14, 2012 Office Action filed May 14, 2012 in connection with U.S. Serial No. 13/308,299, filed November 30, 2011 (Klinger) **(Exhibit 2)**;

3. November 25, 2011 Examiner's Report Issued in connection with Australian Application No. 2010284666, filed August 19, 2012 (Klinger) **(Exhibit 3)**;

4. February 29, 2012 Official Action Issued in connection with Canadian Application No. 2,760,802, filed August 19, 2012 (Klinger) **(Exhibit 4)**;

5. Response to the February 29, 2012 outstanding Examiner's Report filed May 29, 2012 in connection with Canadian Application No. 2,760,802, filed August 19, 2012 (Klinger) **(Exhibit 5)**

6. Supplementary European Search Report issued July 13, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011 **(Exhibit 6)**;

7. PCT International Application No. PCT/US07/00575 (WO 2007/081975), published July 19, 2007 (Pinchasi) **(Exhibit 7);**

8. Flechter S. et al. (2002) "Comparison of glatiramer acetate (Copaxone(R)) and interferon beta-1b (Betaferon(R)) in multiple sclerosis patients: An open-label 2-year follow up" Journal of the Neurological Sciences vol. 197, no. 1-2 pages 51-55 **(Exhibit 8);**

9. Khan et al. (2008) "Randomized, prospective, rater-blinded, four-year, pilot study to compare the effect of daily versus every - other - day injections in relapsing -remitting multiple" Mult. Scler. 14 Suppl. 1 S296 **(Exhibit 9);**

10. Caon Christina et al. (2009) "Randomized, prospective, rater-blinded, four year pilot study to compare the effect of daily versus every other day glatiramer acetate 20 mg subcutaneous injections in RRMS" Neurology vol. 72, no. 11, page A317 **(Exhibit 10);**

11. Simpson Dene et al. (2002) "Glatiramer acetate: A review of its use in relapsing-remitting multiple sclerosis" CNS DRUGS vol. 16, no. 12 pages 825-850 **(Exhibit 11);**

The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO 1449.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Certificate of Transmission
I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on August 6, 2012.

Geoffry Knudsen

John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicant
Cooper & Dunham LLP
30 Rockefeller Plaza
New York, New York 10112
(212) 278-0400

Form PTO-1449 (Substitute) **U.S. Department of Commerce**
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Klinger Ety
Art Unit	1649
Examiner Name	John Ulm
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
	1	2007/161566	07-12-2007	Pinchasi
	2	2006/0154862	07-13-2006	Anup Kumar Ray et al.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]
	3	WO 2004/091573 A1	10-28-2004	Pinchasi et al.	
	4	WO 2006/029036 A2	03-16-2006	Schipper and Godin	
	5	WO 2007/081975 A1	07-19-2007	Pinchasi	
	6	WO 2011/008274 A2	01-20-2011	Altman et al.	

EXAMINER SIGNATURE **DATE CONSIDERED**

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Exhibit A

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office		
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	**Application Number**	12/806,684
	Filing Date	August 19, 2010
	First Named Inventor	Klinger Ety
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	7	Office Action issued July 20, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
	8	Amendment filed July 1, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
	9	Office Action issued April 2, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
	10	Amendment filed December 22, 2008 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
	11	Office Action issued June 20, 2008 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
	12	Response filed September 23, 2010 in connection with U.S. Serial No. 12/785,125, filed May 21, 2010	
	13	Office Action issued August 24, 2010 in connection with U.S. Serial No. 12/785,125, filed May 21, 2010	
	14	Communication issued July 29, 2010 in connection with EPO Application No. 10160099.7	
	15	Response filed December 17, 2010 in connection with European Patent Application No. 10160099.7	
	16	Communication Pursuant to Article 94(3) EPC issued February 11, 2011 in connection with European Patent Application No. 10160099.7	
	17	Response filed June 13, 2011 in connection with European Patent Application No. 10160099.7	
	18	Written Opinion of the International Searching Authority issued October 5, 2007 in connection with PCT International Application No. PCT/US07/00575, filed January 9, 2007	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office		
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	**Application Number**	12/806,684
	Filing Date	August 19, 2010
	First Named Inventor	Klinger Ety
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	19	PCT International Search Report issued October 5, 2007 in connection with PCT International Application No. PCT/US07/00575, filed January 9, 2007	
	20	Written Opinion of the International Searching Authority issued June 9, 2011, in connection with PCT International Application No. PCT/US2010/001972, filed July 14, 2010	
	21	PCT International Search Report issued June 9, 2011 in connection with PCT International Application No. PCT/US2010/001972, filed July 14, 2010	
	22	Polin. The Ins and Outs of Prefilled Syringes. May 2003, Pharmaceutical & Medical Packaging News/Medical Device Link	
	23	Jorgensen J.T. et al. (1996) "Pain assessment of subcutaneous injections" Annals of Pharmacotherapy, Harvey Whitney Books Company, Vol. 30. No. 7-8, pp.729-732	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
WHITE, John P.
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	05 OCT 2007
Applicant's or agent's file reference 75667-PCT/JWP/YC	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US07/00575	09 January 2007 (09.01.2007)	11 January 2006 (11.01.2006)

International Patent Classification (IPC) or both national classification and IPC

IPC: **A61K 38/16**(2006.01);**A61K 31/59**(2006.01)
USPC: 424/78.18;514/904

Applicant

TEVA PHARMACEUTICAL INDUSTRIES, LTD

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	28 August 2007 (28.08.2007)	Shanon Foley Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/00575

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/00575

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 10, 21, 29	YES
	Claims 1-9, 11-20, 22-28	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-29	NO
Industrial applicability (IA)	Claims 1-21	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Form PCT/ISA/237 (Box No. V) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/00575

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The description is objected to as containing the following defect(s) under PCT Rule 66.2(a)(iii) in the form or contents thereof:
The specification has embebed hyperlinks (page 1 lines 25-26, 29-30; page 2 line 28).
The trademark Copaxone ® should be capitalized.

Form PCT/ISA/237 (Box No. VII) (April 2005)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US07/00575

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claim 22-29 provides for the use of glatiramer acetate, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.
In the interest of prosecution, the claims 22-29 are interpreted as being drawn
to a product.

Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

V. 2. Citations and Explanations:
Claims 1-9, 11-20 and 22-28 lack novelty under PCT Article 33(2) as being anticipated by PINCHASI *et al.* 2004.

The present claims are drawn to a method of alleviating **a symptom** of a patient suffering form a **relapsing form of multiple sclerosis** (MS), the method comprise **periodically** administering to the patient, by subcutaneous injection, a single dose of a pharmaceutical composition **comprising** 40 mg of glatiramer acetate (GA).

Pinchasi et al. discloses a method of treatment a relapsing-remitting form of multiple sclerosis, this method comprises administering to the subject an amount of **glatiramer acetate** in different **periods** of time between 20 hours to 11 days (page 8 lines 22-34 and claims 13-15) by **subcutaneous** injection; this prior art also includes an amount of alphacalcidol. In the specification (page 7 lines 16-19) and claims (claims 4-24) the reference recites that the **effective amount of glatiramer acetate** alone or in combination (page 11 lines 8-17 and claims 4 and 24) is effective to alleviate the symptom of multiple sclerosis, and the **range** of the glatiramer acetate goes **from 10 to 80 mg** (page 8 lines 30-32 and claim 11), thus, 40 mg is included in this invention.

Pinchasi et al. (page 7 lines 26-28), defines the **multiple sclerosis symptoms**, like "frequency of relapses, the frequency of clinical exacerbation or the accumulation of physical disability", the experimental details of the reference evaluate the treatment for multiple sclerosis by frequency of relapses and measure the (MS) lesions by MRI. The present application does not describe MS symptoms but the frequency of relapses is implicit. The application also measures MRI lesions. For this and the reasons given above the claim 1 of the present application lacks novelty.

The claims 2 and 3 of the present application are dependent of claim 1 and are directed to the frequency of the administration of GA, these periods have been anticipated by Pinchasi et al. (see citation).

Claims 4, 5, 23 and 24 refer to the relapsing remitting MS form and the symptom of frequency of relapse, these claims are anticipated by Pinchasi et al. (see citation).

Claim 22 is drawn to a **pharmaceutical composition** for subcutaneous administration to alleviate a symptom of a relapsing form of multiple sclerosis in a human patient; this claim lacks novelty as being anticipated by Pinchasi et al. (page 11 lines 25-28) wherein one embodiment of the reference is a pharmaceutical combination where the amount of glatiramer acetate is effective to alleviate the symptom of multiple sclerosis.

Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

Claims 6-9 are directed to the method of treating MS with a pharmaceutical composition and claims 16-20, 25-28 are directed to the pharmaceutical composition which is: in a sterile solution and further comprises mannitol; the range pH range of the composition is 5.5 to 8.5 or to 7. The present application uses COPAXONE ® as GA source to compare the treatment, is known in the art that COPAXONE ® also contains mannitol thus, the GA (at any dose) in combination with mannitol is not novel. Even when the present application does not cite any reference for COPAXONE ® in MS treatment, the reference Pinchasi et al. refers to the same compound and trademark COPAXONE ® as a common treatment to MS (page 3 lines 4-7 and 21-26), these known methods to make GA involve a final pH in a range of 5.5 to 6.0. The COPAXONE ® is diluted in sterile water.

As said above, Pinchasi et al. (page 7 lines 26-28), defines the multiple sclerosis symptoms, like "frequency of relapses, the frequency of clinical exacerbation or the accumulation of physical disability", the experimental details of the reference evaluate the treatment for multiple sclerosis by frequency of relapses and measure the (MS) lesions by MRI. The present application does not describe MS symptoms but the frequency of relapses is implicit. The application also measures MRI lesions.

Claims 11-13 refer to the reduction or MS lesions monitored by MRI, this effect of the treatment is anticipated by Pinchasi et al., the treatment of the reference also reduces MRI activity (T1 and T2 Gd-enhancing lesions) (page 17 lines 6-9).

Claims 14 and 15 are drawn to the reduction of the MS symptom which is the frequency of relapses; Pinchasi et al. also anticipates these claims, the treatment of the reference also measures the reduction of the frequency of relapses (page 17 lines 9-13).

Claims 10, 21 and 29 lack an **inventive step** under PCT Article 33(3) as being obvious over Pinchasi et al.

These claims are drawn to the method of treating (MS) and the pharmaceutical composition wherein the pharmaceutical composition is in a prefilled syringe and is self administered by the patient. The prefilled syringe is a conventional method of delivery known in the art.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: JOHN P. WHITE
COOPER & DUNHAM LLP
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	09 JUN 2011

Applicant's or agent's file reference	FOR FURTHER ACTION
80700-B-PCT/JPW/WS	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/01972	14 July 2010 (14.07.2010)	15 July 2009 (15.07.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 38/00 (2010.01)
USPC - 514/18

Applicant TEVA PHARMACEUTICAL INDUSTRIES LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	02 November 2010 (02.11.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2009)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01972

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 10/01972

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-35, 40 and 52-63

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4-35, 40 and 52-63 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-35, 40 and 52-63 are improper multiple dependent clams because they are depenent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 4-35, 40 and 52-63

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01972

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the appicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-3, 36-39 and 41-48, drawn to various methods and compositions of glatimer acetate, etc.

Group II: claims 49-51, drawn to an injection assisting device, etc.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The claims of the various groups as defined above do not share any special technical feature. There is no requirement that the methods and compositions of the claims of group I use the device of the claims of group II, and vice versa; there being no other basis for having a shared technical feature.

Thus, the inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

In this case the first named invention that will be searched without additional fees is Group I represented by claims 1-3, 36-39 and 41-48.

Claims 4-35, 40 and 52-63 are improper multiple dependent clams because they are depenent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-3, 36-39 and 41-48

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.: PCT/US 10/01972

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-3, 36-39 and 41-48	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-3, 36-39 and 41-48	NO
Industrial applicability (IA)	Claims	1-3, 36-39 and 41-48	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 3, 36-37, 39, 41, 43, 45 and 47 lack an inventive step under PCT Article 33(3) as being obvious over WO 2007/081975 A2 to Pinchasi (hereinafter 'Pinchasi').

Regarding claim 1, Pinchasi discloses a method (pg 5, ln 2-4) for reducing frequency of relapses (pg 8, ln 12-13) in a human patient (pg 5, ln 19-23) afflicted with relapsing-remitting multiple sclerosis (RRMS) (pg 8, ln 14-15) comprising administering to the patient by subcutaneous injection (pg 5, ln 4-5) an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution glatiramer acetate and mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16). Pinchasi does not expressly disclose such a method comprising 0.5ml of an aqueous pharmaceutical solution which contains in solution 20mg glatiramer acetate and 20mg mannitol. Such dosing regimen particulars would have been determined through routine experimentation by one of ordinary skill in the art.

Regarding claim 3, Pinchasi discloses the method of claim 1, as above, where the pH of the aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) is 5.5 to 7.0 (pg 11, ln 11-15).

Regarding claim 36, Pinchasi discloses the method of claim 1, as above, where the administered 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16) is utilized for reducing the frequency of relapses (pg 8, ln 12-13) in a human patient (pg 5, ln 19-23) afflicted with relapsing remitting multiple sclerosis (RRMS) (pg 8, ln 14-15). Pinchasi does not expressly disclose where the 0.5ml of such a solution is at least as effective as 1.0ml of an aqueous pharmaceutical solution of 20mg glatiramer acetate and 40mg mannitol in reducing the frequency of relapses in a human patient afflicted with relapsing remitting multiple sclerosis. This would have been determined through routine experimentation by one of ordinary skill in the art.

Regarding claim 37, see the discussion set forth above for claim 1. Pinchasi discloses a unit dose (pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2) of 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16).

Regarding claim 39, Pinchasi discloses the unit dose of claim 37, as above, where the 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) has a pH of 5.5-7.0 (pg 11, ln 11-15).

Regarding claim 41, see the discussion set forth above for claim 1. Pinchasi discloses a unit dose (pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2) of 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16) for use in reducing frequency of relapses (pg 8, ln 12-13) in a human patient (pg 5, ln 19-23) afflicted with relapsing, remitting multiple sclerosis (RRMS) (pg 8, ln 14-15).

Regarding claim 43, see the discussion set forth above for claim 1. Pinchasi discloses a unit dose (pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2) of 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16) for use in reducing the number of active MRI brain lesions (pg 9, ln 7-12; pg 12, ln 15-26) in a human patient (pg 5, ln 19-23) afflicted with relapsing remitting multiple sclerosis (RRMS) (pg 8, ln 14-15). Pinchasi does not expressly disclose such a unit dose for use in reducing the volume of the active MRI brain lesions. This would have been determined through routine experimentation by one of ordinary skill in the art.

Regarding claim 45, see the discussion set forth above for claim 43. Pinchasi discloses the use of 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16) for reducing the number and volume of active MRI brain lesions (pg 9, ln 7-12; pg 12, ln 15-26) in a human patient (pg 5, ln 19-23) afflicted with relapsing-remitting multiple sclerosis (RRMS) (pg 8, ln 14-15).

Regarding claim 47, see the discussion set forth above for claim 1. Pinchasi discloses a pharmaceutical composition (pg 5, ln 6-8, 15-18; pg 8, ln 16-26) for use in treating a human patient (pg 5, ln 19-23) afflicted with relapsing-remitting multiple sclerosis (RRMS) (pg 8, ln 14-15) comprising a unit dose (pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2) of 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01972

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V 2. Citations and explanations:

Claims 2, 42, 44, 46 and 48 lack an inventive step under PCT Article 33(3) as being obvious over Pinchasi in view of WO 2009/070298 A1 to Stark et al. (hereinafter 'Stark').

Regarding claim 2, see the discussion set forth above for claim 1. Pinchasi discloses a method (pg 5, ln 2-4) for reducing frequency of relapses (pg 8, ln 12-13) in a human patient (pg 5, ln 19-23) afflicted with relapsing-remitting multiple sclerosis (RRMS) (pg 8, ln 14-15) comprising administering to the patient by subcutaneous injection (pg 5, ln 4-5) 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5), which contains in solution 20mg glatiramer acetate and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16). Pinchasi does not expressly disclose such a human patient who experienced a first clinical episode consistent with multiple sclerosis and who has at least one lesion consistent with multiple sclerosis. Stark discloses a method for delaying the onset of clinically definite multiple sclerosis in a patient at risk of developing clinically definite multiple sclerosis, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of glatiramer acetate to the patient (pg 5, ln 3-10). Further, administration of such a pharmaceutical composition also provides a method for reducing the frequency of relapse in a patient who experienced a first clinical episode consistent with multiple sclerosis and who has at least one lesion consistent with multiple sclerosis (pg 6, ln 1-9). It would have been obvious to one of ordinary skill in the art to add the teachings of Stark concerning a method for reducing the frequency of relapse in a patient who experienced a first clinical episode consistent with multiple sclerosis and who has at least one lesion consistent with multiple sclerosis, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of glatiramer acetate to the patient, to the teachings of Pinchasi concerning a method for reducing frequency of relapses in a human patient afflicted with relapsing-remitting multiple sclerosis (RRMS) comprising administering to the patient by subcutaneous injection 0.5ml of an aqueous pharmaceutical solution which contains in solution 20mg glatiramer acetate and 20mg mannitol, as the technology is so similar (i.e., both teach a method for reducing the frequency of relapse in a patient with multiple sclerosis, the method comprising administering a pharmaceutical composition comprising a therapeutically effective amount of glatiramer acetate), in order to practice the claim as described without undue experimentation. This would have provided for variation of therapeutic indications in order to have optimized the scope of multiple sclerosis species to have been treated, given such practice in the art.

Regarding claim 42, see the discussion set forth above for claim 2. The combination of Pinchasi and Stark discloses a unit dose (Pinchasi - pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2) of 0.5ml of an aqueous pharmaceutical solution (Pinchasi - pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (Pinchasi - pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16) for use in treating a human patient (Pinchasi - pg 5, ln 19-23) who experienced a first clinical episode consistent with multiple sclerosis (Stark - pg 6, ln 1-9) and who has been determined to be at risk of developing clinically definite multiple sclerosis (CDMS) (Stark - pg 6, ln 21-28). The combination of Pinchasi and Stark does not expressly disclose where such a patient has been determined to be at high risk of developing clinically definite multiple sclerosis. This would have been determined through undue experimentation by one of ordinary skill in the art.

Regarding claim 44, see the discussion set forth above for claim 2. The combination of Pinchasi and Stark discloses a unit dose (Pinchasi - pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2) of 0.5ml of an aqueous pharmaceutical solution (Pinchasi - pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (Pinchasi - pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16) for use in delaying the onset of clinically definite multiple sclerosis (Stark - pg 5, ln 3-10) in a human patient (Pinchasi - pg 5, ln 19-23) who experienced a single demyelinating event (Stark - pg 6, ln 30 - pg 7, ln 3) and who is considered to be at risk of developing clinically definite multiple sclerosis (Stark - pg 6, ln 21-28).

Regarding claim 46, see the discussion set forth above for claim 2. The combination of Pinchasi and Stark discloses the use of 0.5ml of an aqueous pharmaceutical solution (Pinchasi - pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (Pinchasi - pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16) for delaying the onset of clinically definite multiple sclerosis (Stark - pg 5, ln 3-10) in a human patient (Pinchasi - pg 5, ln 19-23) who experienced a single demyelinating event (Stark - pg 6, ln 30 - pg 7, ln 3) and who is considered to be at risk of developing clinically definite multiple sclerosis (Stark - pg 6, ln 21-28).

Regarding claim 48, see the discussion set forth above for claim 2. The combination of Pinchasi and Stark discloses a pharmaceutical composition (Pinchasi - pg 5, ln 6-8, 15-18; pg 8, ln 16-26) for use in treating a human patient (Pinchasi - pg 5, ln 19-23) who experienced a single demyelinating event (Stark - pg 6, ln 30 - pg 7, ln 3) and who is considered to be at risk of developing clinically definite multiple sclerosis (Stark - pg 6, ln 21-28) comprising a unit dose (Pinchasi - pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2) of 0.5ml of an aqueous pharmaceutical solution (Pinchasi - pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate and 20mg mannitol (Pinchasi - pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16).

----------continued in next Supplemental Box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/01972

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Prior Supplemental Box:

Claim 38 lacks an inventive step under PCT Article 33(3) as being obvious over Pinchasi in view of Stark and further in view of US 6,448,225 B2 to O'Connor et al. (hereinafter 'O'Connor').

Regarding claim 38, Pinchasi, in view of Stark, discloses the unit dose of claim 37, as above (pg 10, ln 9-12; pg 12, ln 27 - pg 13, ln 2), of 0.5ml of an aqueous pharmaceutical solution (pg 8, ln 16-17; pg 13, ln 17 - pg 14, ln 5) which contains in solution 20mg glatiramer acetate [Glatiramer acetate consists of the acetate salts of synthetic polypeptides] and 20mg mannitol (pg 5, ln 15-18; pg 8, ln 18-19; pg 10, ln 15-16). Pinchasi does not expressly disclose where the 20mg of glatiramer acetate does not form polypeptide aggregates in the 0.5ml of aqueous pharmaceutical solution. O'Connor discloses a pharmaceutically acceptable, aqueous formulation of human growth hormone comprising human growth hormone [a protein-based peptide hormone i.e., a 191-amino acid, single-chain polypeptide], a buffer in order to adjust the pH range from about 5.5 to about 7 (col 3, ln 60-64) and mannitol (col 2, ln 30-34), where such a pharmaceutical formulation has increased stability in aqueous formulation by controlling the degradative pathway of aggregation (col 1, ln 19-22; col 2, ln 13-24). It would have been obvious to one of ordinary skill in the art to add the teachings of O'Connor concerning a pharmaceutically acceptable, aqueous formulation of a polypeptide, a buffer in order to adjust the pH range from about 5.5 to about 7 and mannitol, where such a pharmaceutical formulation has increased stability in aqueous formulation by controlling the degradative pathway of aggregation, to the teachings of Pinchasi and Stark concerning the unit dose of 0.5ml of an aqueous pharmaceutical solution, which contains in solution 20mg glatiramer acetate [Glatiramer acetate consists of the acetate salts of synthetic polypeptides] and 20mg mannitol, where the aqueous pharmaceutical solution has a pH of 5.5-7.0, as the technology is so similar (i.e., both teach an aqueous formulation of a polypeptide, a buffer in order to adjust the pH range from about 5.5 to about 7 and mannitol), in order to practice the claim as described without undue experimentation. This would have provided for controlling polypeptide aggregation in aqueous solution, given the teachings of O'Connor.

Claims 1-3, 36-39 and 41-48 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 80700-B-PCT/JPW/WS	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/01972	International filing date *(day/month/year)* 14 July 2010 (14.07.2010)	(Earliest) Priority Date *(day/month/year)* 15 July 2009 (15.07.2009)
Applicant TEVA PHARMACEUTICAL INDUSTRIES LTD.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☒ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/01972

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-35, 40 and 52-63
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
see extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 36-39 and 41-48

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/01972

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00 (2010.01)
USPC - 514/18
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/18

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/2; 514/12; 530/300; 530/335 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: treating, multiple sclerosis, relapsing form, RRMS, alleviating, symptom, frequency of relapses, glatiramer acetate, mannitol, human patient, administering, subcutaneous injection, pH, 5.5 to 7.0, pharmaceutical composition, unit dose, lesions, brain, onset, clinically definite multiple sclerosis, fir

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2007/081975 A2 (PINCHASI) 19 July 2007 (19.07.2007) pg 5, ln 2-8, 15-23; pg 8, ln 12-26; pg 9, ln 7-12; pg 10, ln 9-12, 15-16; pg 11, ln 11-15; pg 12, ln 15 - pg 13, ln 2; pg 13, ln 17 - pg 14, ln 5	1, 3, 36-37, 39, 41, 43, 45 and 47 --- 2, 38, 42, 44, 46 and 48
Y	WO 2009/070298 A1 (STARK et al.) 04 June 2009 (04.06.2009) pg 5, ln 3-10; pg 6, ln 1-9, ln 21 -28; pg 6, ln 30 - pg 7, ln 3	2, 42, 44, 46 and 48
Y	US 6,448,225 B2 (O'CONNOR et al.) 10 September 2002 (10.09.2002) col 1, ln 19-22; col 2, ln 13-24, 30-34; col 3, ln 60-64	38

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 November 2010 (01.11.2010)	09 JUN 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/01972

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-3, 36-39 and 41-48, drawn to various methods and compositions of glatimer acetate, etc.

Group II: claims 49-51, drawn to an injection assisting device, etc.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The claims of the various groups as defined above do not share any special technical feature. There is no requirement that the methods and compositions of the claims of group I use the device of the claims of group II, and vice versa; there being no other basis for having a shared technical feature.

Thus, the inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.

In this case the first named invention that will be searched without additional fees is Group I represented by claims 1-3, 36-39 and 41-48.

Claims 4-35, 40 and 52-63 are improper multiple dependent clams because they are depenent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Electronic Acknowledgement Receipt

EFS ID:	13426638
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Cindy Shu
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	06-AUG-2012
Filing Date:	19-AUG-2010
Time Stamp:	16:17:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		120806_2609_80798-A_2ndSIDS_GTK.pdf	2538746 6ec422e2e5cb9bf4fe28fa388551353743c90aca	yes	9

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	6	
	Information Disclosure Statement (IDS) Form (SB08)		7	9	
Warnings:					
Information:					
2	Non Patent Literature	120806_2609_80798-A_Exhibit_1a_GTK.pdf	1338463 542244667cbe5314da9a4324fd97d7df298de3fd	no	32
Warnings:					
Information:					
3	Non Patent Literature	120806_2609_80798-A_Exhibit_2a_GTK.pdf	1293385 3d37465edad1b0d0781292cb07419661fcf694cc	no	32
Warnings:					
Information:					
4	Non Patent Literature	120806_2609_80798-A_Exhibit_3a_GTK.pdf	927292 230bc8b41f9caa850339814b185ea94712a76f90	no	32
Warnings:					
Information:					
5	Non Patent Literature	120806_2609_80798-A_Exhibit_4a_GTK.pdf	5656426 2cee580110c318f9af1d33006fd8955ed8a5a0ff	no	137
Warnings:					
Information:					
6	Non Patent Literature	120806_2609_80798-A_Exhibit_5a_GTK.pdf	360964 b676b5ca08ebde63c3dd523a80519f40d30b1264	no	9
Warnings:					
Information:					
7	Non Patent Literature	120806_2609_80798-A_Exhibit_6a_GTK.pdf	584279 bfb1eb5e5a660a173b11edf8390b8912ca608fb6	no	15
Warnings:					
Information:					
8	Non Patent Literature	120806_2609_80798-A_Exhibit_7a_GTK.pdf	390104 7458faf07375115df9014b7aa0c79966bfad08e2	no	9
Warnings:					
Information:					

9	Non Patent Literature	120806_2609_80798-A_Exhibit_8a_GTK.pdf	730446 cdb261c247c4c1eebea770f999d6d057c56917bd	no	21
Warnings:					
Information:					
10	Non Patent Literature	120806_2609_80798-A_Exhibit_9a_GTK.pdf	320800 22230144f87f6a5d5a7fd968ffc4ae5ff09d4e68	no	8
Warnings:					
Information:					
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22	Non Patent Literature	120806_2609_80798-A_Exhibit_21a_GTK.pdf	659845 a9fc3317c1d42c0e369568827cf9211a3bec60c3	no	4
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Docket No. 2609/80798-A/JPW/GJG/GTK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ety Klinger
Serial No.	:	12/806,684
Filed	:	August 19, 2010
For	:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
August 6, 2012

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, Applicant directs the Examiner's attention to the following items, which are listed on the Substitute PTO-1449 form attached hereto as **Exhibit A.**

According to 37 C.F.R. §1.97(c) an Information Disclosure Statement filed after the period specified in 37 C.F.R. §1.97(b) shall be considered if accompanied by the fee set forth in the 37 C.F.R. §1.17(p) or a statement under 37 C.F.R. §1.97(e). The required fee set forth in 37 C.F.R. §1.97(p) is one hundred and eighty dollars ($180.00) and this amount has been paid in the first Information Disclosure Statement filed herewith. Accordingly, this Information Disclosure Statement should be considered.

Reference items 1-2 are U.S. Patent Application Publications. Pursuant to 37 C.F.R. §1.98(a)(2), copies of references 1-2 are not being submitted.

Copies of items 3-23 are attached hereto as **Exhibits 1-21**, respectively.

1. U.S. Patent Application Publication No. US 2007/161566, published July 12, 2007 (Pinchasi);

2. U.S. Patent Application Publication No. US 2006/0154862 A1, published July 13, 2006 (Anup Kumar Ray et al.);

3. PCT International Application Publication No. WO 2004/091573 A1, published October 28, 2004 (Pinchasi et al.) (**Exhibit 1**);

4. PCT International Application Publication No. WO 2006/029036 A2, published March 16, 2006 (Schipper and Godin) (**Exhibit 2**);

5. PCT International Application Publication No. WO 2007/081975 A1, published July 19, 2007 (Pinchasi) (**Exhibit 3**);

6. PCT International Application Publication No. WO 2011/008274 A2, published January 20, 2011 (Altman et al.) (**Exhibit 4**);

7. Office Action issued July 20, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007 (**Exhibit 5**);

8. Amendment filed July 1, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007 (**Exhibit 6**);

9. Office Action issued April 2, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007 (**Exhibit 7**);

10. Amendment filed December 22, 2008 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007 (**Exhibit 8**);

11. Office Action issued June 20, 2008 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007 (**Exhibit 9**);

12. Response filed September 23, 2010 in connection with U.S. Serial No. 12/785,125, filed May 21, 2010 (**Exhibit 10**);;

13. Office Action issued August 24, 2010 in connection with U.S. Serial No. 12/785,125, filed May 21, 2010 (**Exhibit 11)**;

14. Communication issued July 29, 2010 in connection with EPO Application No. 10160099.7 (**Exhibit 12**);

15. Response filed December 17, 2010 in connection with European Patent Application No. 10160099.7 (**Exhibit 13**);

16. Communication Pursuant to Article 94(3) EPC issued February 11, 2011 in connection with European Patent Application No. 10160099.7 (**Exhibit 14**;

17. Response filed June 13, 2011 in connection with European Patent Application No. 10160099.7 (**Exhibit 15**);

18. Written Opinion of the International Searching Authority issued October 5, 2007 in connection with PCT International Application No. PCT/US07/00575, filed January 9, 2007 (**Exhibit 16**);

19. PCT International Search Report issued October 5, 2007 in connection with PCT International Application No. PCT/US07/00575, filed January 9, 2007 (**Exhibit 17**);

20. Written Opinion of the International Searching Authority issued June 9, 2011, in connection with PCT International Application No. PCT/US2010/001972, filed July 14, 2010 (**Exhibit 18**);

21. PCT International Search Report issued June 9, 2011 in connection with PCT International Application No. PCT/US2010/001972, filed July 14, 2010 (**Exhibit 19**);

22. Polin. The Ins and Outs of Prefilled Syringes. May 2003, Pharmaceutical & Medical Packaging News/Medical Device Link (**Exhibit 20**);

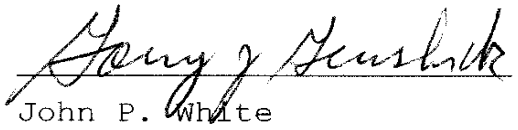
23. Jorgensen J.T. et al. (1996) "Pain assessment of subcutaneous injections" Annals of Pharmacotherapy, Harvey Whitney Books Company, Vol. 30. No. 7-8, pp.729-732 (**Exhibit 21**);

The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO 1449.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	**Application Number**	12/806,684
	Filing Date	August 19, 2010
	First Named Inventor	Ety Klinger
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	Anderson, et al. (1992) "Revised estimate of the prevalence of multiple sclerosis in the United States". Ann Neurol. 31:333-36	
	2	Anderson, et al. "Injection pain decreases..." The Consortium of Multiple Sclerosis Centers 2010 Annual Meeting, June 2-5, 2010, San Antoinio, Texas (Abstract only)	
	3	Arnon and Aharoni (2007) "Neurogenesis and neuroprotection in the CAN - Fundamental elements in the effect of...". Mol Neurobiol. 36:245-53	
	4	Bjartmar C, et al. (2002) "Pathological mechanisms and disease progression of multiple sclerosis: therapeutic implications". Drugs of Today. 38:7-29	
	5	Bornstein, et al., "Treatments of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results," Ann. Neurol., 1980, 8, 117 (Abstract)	
	6	Bornstein, et al., "Treatments of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results," Trans. Am. Neurol. Assoc., 1980, 105, 348-350	
	7	Bornstein, et al., "Multiple Sclerosis: Trial of a Synthetic Polypeptide," Ann. Neurol., 1982, 11, 317-319	
	8	Bornstein, et al., "Clinical Trials of Copolymer 1 in Multiple Sclerosis," Ann. N.Y. Acad. Sci. (USA), 1984, 366-372	
	9	Bornstein, et al., "Clinical Trials of a Synthetic Polypeptide (Copolymer 1) for the treatment of Mutliple Sclerosis" in Gonsett et al., Immunological and Clinical Aspects of Multiple Sclerosis (MTP Press, The Hague, 1984) 144-150	
	10	Bornstein, et al., "Multiple Sclerosis: Clinical Trials of a Synthetic Polypeptide, Copolymer 1," Neurol., 1985, 35, (Suppl. 1), 103 (Abstract)	
	11	Bornstein, "Cop 1 may be Beneficial for Patients with Exacerbating-remitting Form of Multiple Sclerosis," Adv. Ther. (USA), 1987, 4, 206 (Abstract) (Exhibit 45)	
	12	Bornstein, et al., "A Pilot Trial of Cop 1 in Exacerbating-remitting Multiple Sclerosis," New Eng. J. Med., 1987, 317(7), 408-414	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

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	13	Bornstein, et al., "Clinical Experience with COP-1 in Multiple Sclerosis," Neurol., 1988, 38(Suppl. 2) 66-69	
	14	Bornstein et al., "Rationale For Immunomodulating Therapies of Multiple Sclerosis: Clinical Trial Design in Multiple Sclerosis Therapy," Neurol., 1988, Vol. 38 (Suppl.2), pp. 80-81 [R]	
	15	Bornstein, et al., "Pilot Trial of COP-1 in Chronic Progressive Multiple Sclerosis: Preliminary Report," from The International Multiple Sclerosis Conference: An Update on Multiple Sclerosis, Roma (Italy), September 15-17, 1988, in Elsevier Science Publisher, 1989, 225-232	
	16	Bornstein, et. al., "Clinical Trials of Cop 1 in Multiple Sclerosis," in Handbook of Multiple Sclerosis (S.D. Cook Marcel Rekker, ed., 1990) 469-480	
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	20	Brazeau GA, et al. (1998) "Current perspectives on pain upon injection of drugs". J Pharmaceutical Sci.(87)6:667-677	
	21	Chantelau e, et al. (1991) "What make insulin injections painful?" BMJ. 303:26-27	
	22	Comi, et al. (2008) "Results from a phase III, one-year, randomized, double-blind, parallel-group...". Mult Scler. 14(suppl 1):S299	
	23	Comi G. "Treatment with glatiramer...". Program and abstracts of the American Academy of Neurology 60th Annual Meeting; April 12-19, 2008; Chicago, Illinois. LBS.003.	
	24	Comi, et al. (2001) "European/Canadian multicenter, double-blind, randomized, placebo-controlled study...". Ann Neurol. 49:290-7	

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	25	Dhib-Jalbut S. (2003) "Glatiramer acetate (Copaxone) therapy for multiple sclerosis" Pharmacology & Therapeutics. 98:245-55	
	26	Dhib-Jalbut S. (2002) "Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis". Neurology. 58(Suppl 4):S3-S9	
	27	Frenken LA, et al. (1994) "Analysis of the efficacy of measures to reduce pain after subcutaneous administration of epoetin alfa". Nephrol Dial Transplant. 9:1295-1298	
	28	Johnson, et al. (1998) "Extended use of glatiramer acetate (Copaxone) is well tolerated ...". Neurology. 50:701-8	
	29	Kansara, et al. (2009) "Subcutaneous Delivery". Drug Deliv Technol. June 2009; 9(6):38-42	
	30	Miller D, et al. (2005) "Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history...". Lancet Neurol. 4(5):281-288	
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	32	Neuhaus O, et al. (2003) "Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection". Trends Pharmacol Sci. 24:131-138	
	33	Noseworthy, et al. (2000) "Multiple sclerosis". N Engl J Med. 343:938-52	
	34	Polman, et al. (2005) "Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald" Criteria". Ann Neurol. 58:840-846	
	35	Ruggiere, et al. (2007) "Glatiramer acetate in multiple sclerosis: A review". CNS Drug Reviews. 13(2):178-91	
	36	Schrempf W, et al. (2007) "Glatiramer acetate: Mechanisms of action in multiple sclerosis". Autoimmunity Reviews 2007. 6:469-475	

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	37	Shire, et al. (2004) "Challenges in the Development of High Protein Concentration Formulations". J Pharm Sci. 93(6):1390-1402	
	38	Thrower BW. (2007) "Clinically isolated syndromes. Predicting and delaying multiple sclerosis". Neurology. 68 (Suppl 4):S12-S15	
	39	Tselis, et al. (2007) "Glatiramer acetate in the treatment of multiple sclerosis". Neuropsychiatric Dis Treat. 3(2):259-67	
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	41	Wolinsky J.S. (2006) "The use of glatiramer acetate in the treatment of multiple sclerosis" Advances in Neurology 98: 273-292	
	42	Wolinsky, JS (2006) "The use of glatiramer acetate in the treatment of multiple sclerosis". Adv Neurol. 273-92	
	43	Van Metre TE, et al. (1996) "Pain and dermal reaction caused by injected glycerin in immunotherapy solutions". J Allergy Clin Immunol. 97:1033-9	
	44	Ziemssen and Schrempf (2007) "Glatiramer acetate: Mechanisms of action in multiple sclerosis". International Rev of Neurobiol. 79:537-70	
	45	Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis EMEA, London 16 November 2006 CPMP/EWP/561/98 REV.1	
	46	Product Monograph, Copaxone, Revised April 2, 2010: 1-35	
	47	The National MS Society (USA) [cited 2010 Feb 5]. Available from: www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx	
	48	Medical News Today. July 8, 2008. Web: September 9, 2010. www.medicalnewstoday.com/articles/114183.php	

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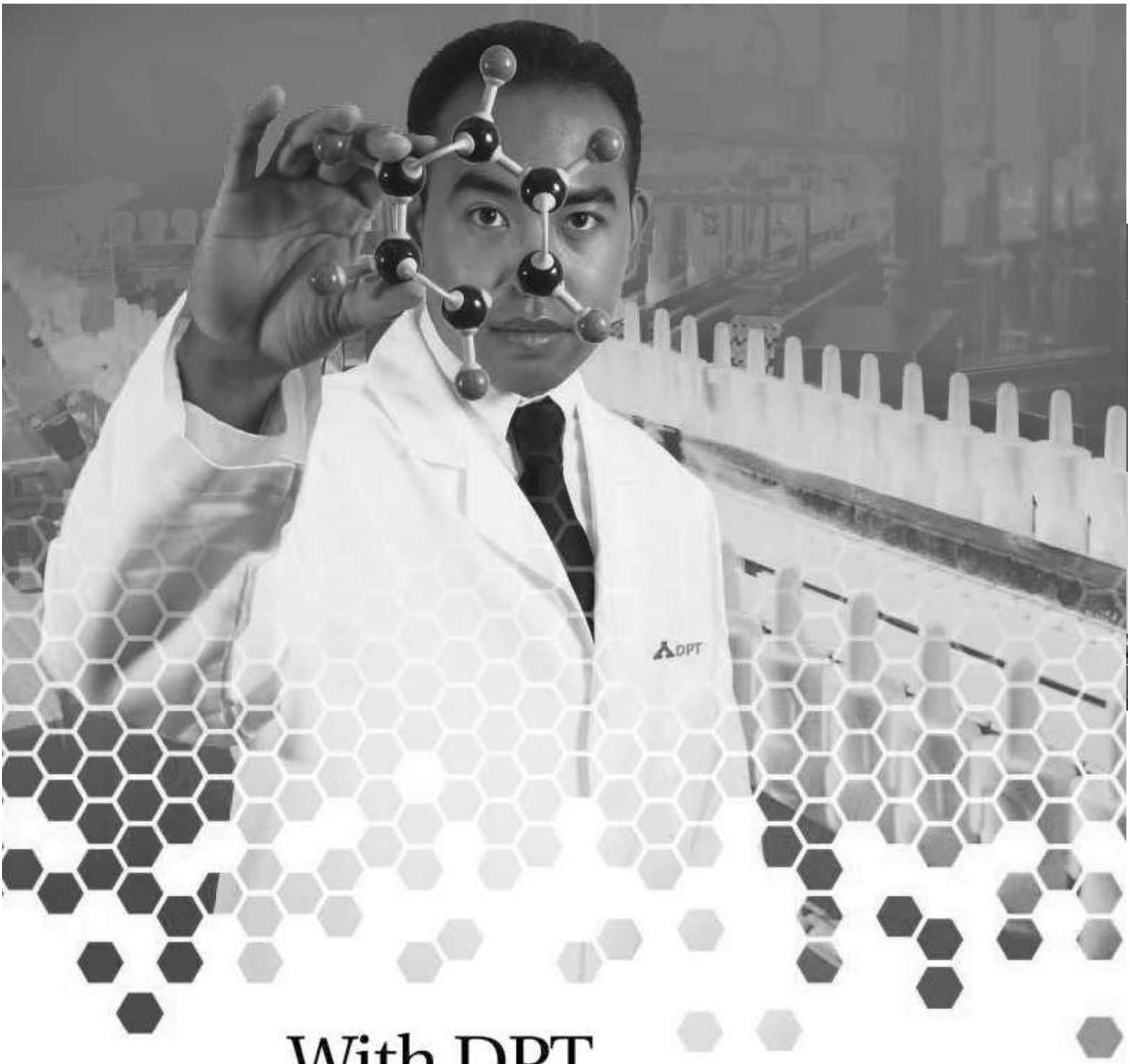

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June 2009 Vol 9 No 6

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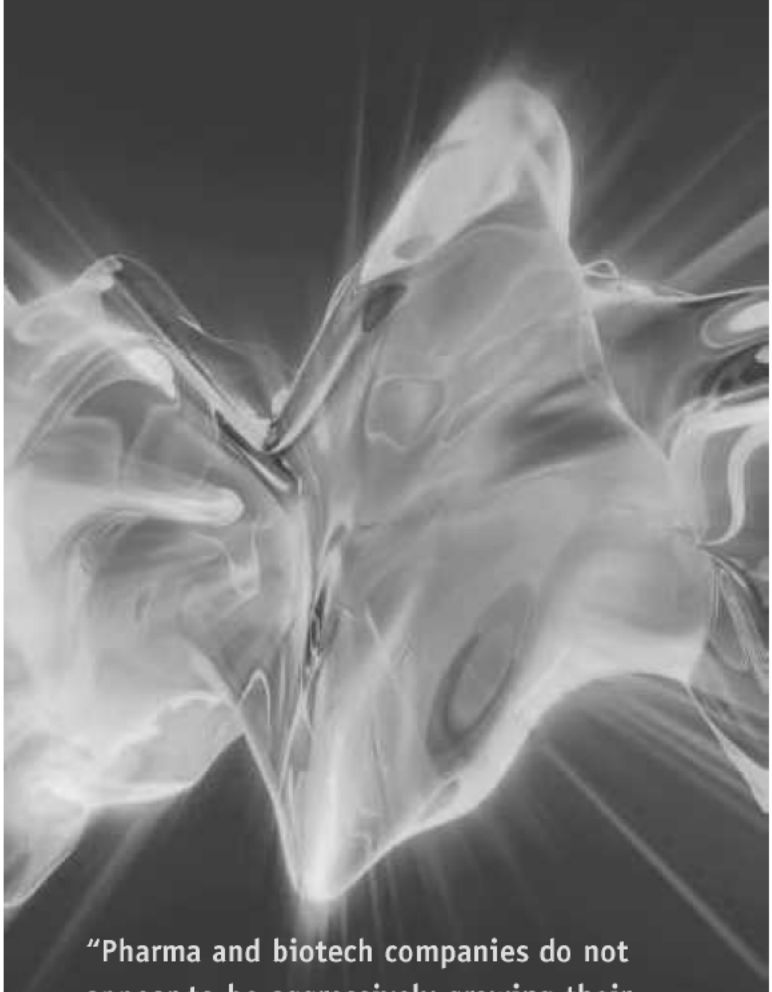
Changing Tides



"Pharma and biotech companies do not appear to be aggressively growing their pipelines or developing blockbuster drugs at the same pace they had in previous years. Thus, the business strategy of outsourcing formulation development has slowed a bit; it is more cost effective to keep this process in-house while pipelines get reconstructed to their previous strength. However, as the economy turns around, CROs are expected to see a revival."

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Departments

SUBCUTANEOUS DELIVERY

Subcutaneous Delivery of Small Molecule Formulations: An Insight Into Biopharmaceutics & Formulation Strategies

By: Viral Kansara, PhD; Amitava Mitra, PhD; and Yunhui Wu, PhD

ABSTRACT

Subcutaneous (SC) drug delivery systems are becoming increasingly important injectable techniques to administer a wide range of therapeutic formulations. This review provides an insight into biopharmaceutical and formulation aspects of systemic delivery of small molecules upon SC administrations. The review also provides an overview of the factors that govern SC absorption and describes research and technologies focused on utilizing or modifying SC absorption mechanisms. General guidance on conducting pharmacokinetics and tolerability studies has been briefly covered. Various SC formulation strategies and marketed and in-pipeline SC formulations for delivering small molecules have been thoroughly reviewed. It was summarized that even though SC administration continues to be the main route for the delivery of protein and polypeptide formulations, successful application of SC formulations for the delivery of small molecules with poor aqueous solubility is somewhat limited. Integration of various biopharmaceutical and formulation factors into the overall SC formulation strategies should be carefully considered in designing safe and effective SC drug delivery systems.

INTRODUCTION

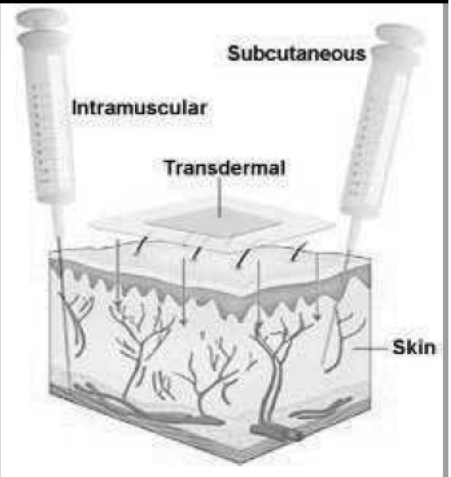
SC injections are usually administered in small volumes (0.5 to 1 mL; upto 2 mL) into the outer surface of the upper arm, anterior surface of the thigh, abdomen, or buttock, and can be self-administered. As shown in Figure 1, during SC administration, a needle is inserted through the epidermal and dermal layers of the skin and into the fatty subcutaneous tissue.[1] Following SC administration, drug molecules enter the systemic circulation by direct absorption into SC blood capillaries or indirectly via absorption into the lymphatic capillaries, which are present within the interstitial space. Therefore, characterization of the SC absorption process is crucial to the design of improved SC drug delivery systems and the interpretation and development of useful pharmacokinetic-pharmacodynamic relationships.

OPPORTUNITIES & LIMITATIONS

SC injections have several immediate advantages over intramuscular (IM) or intravenous (IV) administrations. In contrast to the skilled personnel required for the administration of IV and IM injections, SC injections can be administered by the patient.[2] Slower absorption of subcutaneously administered drug, as compare to IV administration, may avoid the risks of bolus administration. A small needle is required (length of 3⁄8 to 5⁄8 of an inch), and the injections are not generally painful and carry a reduced risk of infection and other complications. For infectious agent delivery, SC injection may prove beneficial by restricting the infection to local site of injection. For patients requiring multiple doses, SC injections offer a broader range of alternative sites.

From many perspectives, including reduced pain, improved patient quality of life, reduced cost of patient care, and reduced risk of infection, SC represents a

FIGURE 1



Comparative sites of injection for subcutaneous, intramuscular, and transdermal administration. (http://publications.nigms.nih.gov/medbydesign/chapter1.html)

TABLE 1

Species	Dosing Volumes (mL/kg)
Mouse	10 (40)
Rat	5 (10)
Rabbit	1 (2)
Dog	1 (2)
Macaque	2 (5)
Minipig	1 (2)

Recommended dosing volumes for SC administration routes. Values in parenthesis represent maximum dosing volume per day.

preferred route for administering a drug by self-injection. Many drugs, including insulin and heparin, have been delivered subcutaneously for many years with excellent outcomes. Compared with IV drugs, SC drugs are considered clinically safer and more cost-effective, resulting in higher patient satisfaction.[4]

Despite the aforementioned advantages, there are limited marketed formulations available as SC injection as compare to oral formulations. This may be explained by well-known disadvantages/limitations associated with SC drug delivery. Limited injection volume (not more than 1 to 2 mL) is a major disadvantage of this route of administration.[5] Degradation of the drug at the site of injection may result in poor plasma bioavailability and can be a challenging issue. Moreover, based on the physicochemical properties, potent active compounds may get trapped into the interstitial SC fluid, which may lead to the irritation, precipitation, and concentration-dependant adverse effects. These limitations need to be carefully considered in assessing feasibility of SC formulation development.

PHYSIOLOGY OF SC INJECTION SITE & EFFECT ON ABSOPRTION

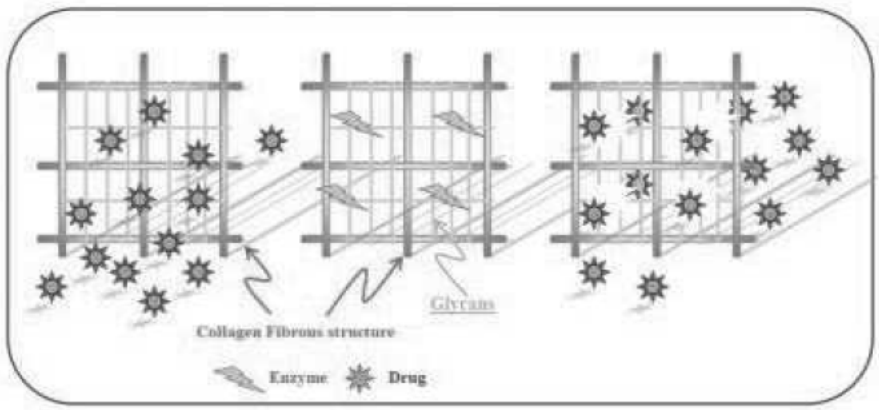
Drug administration by SC injection results in delivery to the interstitial area underlying the dermis of the skin. The interstitium consists of a fibrous collagen network supporting a gel-phase comprising negatively charged glycosaminoglycans (largely hyaluronan), salts, and plasma-derived proteins.[6] The proteins present within the interstitial space are essentially the same as those in plasma, although they are thought to be present at a much lower concentration. The physiology of the SC environment likely dictates the patterns of absorption of both typical small drug molecules as well as macromolecular and particulate systems after SC administration. In general, small drug molecules are thought to be preferentially absorbed by the blood capillaries due to their largely unrestricted permeability across the vascular endothelium together with the high rate of filtration and reabsorption of fluid across the vascular capillaries. By contrast, the absorption of small particulates (generally less than about 100 nm) and macromolecules into the blood is restricted by their limited permeability across the vascular endothelia, and in this case, the lymphatics provide an alternative absorption pathway from the interstitial space.[7,8]

The influence of different SC injection sites on the rate and extent of protein absorption has been shown for several different proteins in humans.[9] Although the extent of absorption is typically consistent for different injection sites, variability in the rate of absorption could be a result of differences between SC blood and lymph flow in different anatomical regions. Passage through the interstitium to the vascular or lymphatic capillaries can also present a barrier to efficient drug absorption after SC administration. Interstitial diffusion of drug molecules is likely to be influenced by their physiochemical characteristics, including size, charge, and hydrophilicity, and their interactions with endogenous components present within the interstitium. Transient enzymatic breakdown of glycosaminoglycans in the extracellular matrix, particularly hyaluranon, have been used to increase the injection volume and bioavailability after SC injection.[10] Simple formulation characteristics, such as drug concentration, injection volume, ionic strength, viscosity, and pH, together with the presence of formulation excipients can also influence the rate of diffusion from the SC injection site.[11] Other factors that can limit the extent of absorption of drugs from the interstitial space include susceptibility to enzymatic degradation at the injection site, cellular uptake by endocytic and phagocytic mechanisms, and simple precipitation, aggregation, or poor resolubilization.[12]

PHARMACOKINETICS FOLLOWING SC ADMINISTRATION

The rate of drug absorption from SC injection site into the blood is proportional to the amount of drug at the site. The penetration coefficient from the site of injection depends on the diffusion coefficient of the drug, the area of membrane exposed to the solution, the distance of diffusion, and the concentration gradient of drug across the absorption membranes. The primary absorption membrane in SC connective tissue is the blood capillary wall. Drug absorption might also be influenced by the buffer capacity of the surrounding tissue and fluids. For example, the rate of absorption

FIGURE 2



A cartoon illustrating a mechanism of enzyme-based SC delivery. Interstitial matrix, primarily composed of collagen fibrils and glycosaminoaglycans, may act as a barrier to drug diffusion following SC administration. Enzyme (Hyuronidase)-based degradation of aminoglycans results in faster diffusion of drug molecules (blue) through the SC space. Basic structure of collagen fibrils remains intact.

TABLE 2

Product/Drug Molecule	Indication/ Therapy	Admin. Mode/ Dose	Formulation Technology	Formulation Characteristics	PK Characteristics
Marketed Formulations					
Imitrex I® Stat Dose Pen Injection (Sumatriptan succinate)	Migraine/Acute	SC: solution (12 mg/mL)	Imigran Injection (Pen Injector) containing 2 prefilled single-dose syringe cartridges, 1 IMITREX STATdose Pen®	Clear, colorless to pale yellow, sterile, non-pyrogenic solution Each 0.5 mL of solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP in water for injection, USP pH: 4.2 to 5.3. Osmolality: 291 mOsmol	Clearance: 1.02 ± 0.13 L/h/kg Distribution $T_{1/2}$: 15 ± 2 min Terminal $T_{1/2}$: 115 ± 19 min V_d (plasma): 0.71 ± 0.11 L/kg Protein Binding: 14% to 21%
Brethine Injectable (Terbutaline sulfate)	Bronchospasm	SC: solution (1 mg/mL)	Injectable solution Dosage strength: 0.25 mg	Each mL of solution contains 1 mg of terbutaline sulfate USP (0.82 mg of the free base), sodium chloride for isotonicity, and hydrochloric acid for adjustment to a target pH of 4	First-pass metabolism in the liver and the gut wall ~60% excreted unchanged in the urine CL: 311 (112) mL/min $T_{1/2}$: 2.9 hr
Opana® Injection (Oxymorphone hydrochloride)	Pain, dyspnea, obstetrical analgesia	Solution: SC/IM/IV (1 mg/mL 1.5 mg/mL)	Injectable solution 1 mg/mL (1 mL) ampoules (paraben /sodium dithionite-free) and 1.5 mg/mL (10 mL) multiple dose vials (sodium dithionite-free)	Each 1 mg/mL ampoule contains 8.0 mg/mL sodium chloride Each 1.5 mg/mL vial contains 8 mg/mL sodium chloride, 1.8 mg/mL methylparaben, and 0.2 mg/mL propylparaben pH adjusted with hydrochloric acid	After an IV dose: Vd_{ss}: 3.08 ± 1.14 L/kg Extensive hepatic metabolism Mean terminal $T_{1/2}$: 1.3 ± 0.7 h Mean systemic clearance: 2.0 ± 0.5 L/min
APO-go PEN (Apomorphine HCl)	Parkinson's Disease/ Chronic	SC: solution (10 mg/mL)	Disposable multiple dose pen injector system incorporating a clear glass (type I) cartridge Each pen contains 3 ml of solution for injection Packs containing 1, 5, or 10 x 3ml pens in a moulded plastic tray	A solution formulation in a single use cartridge contains sodium bisulphite, hydrochloric acid to adjust pH to 3 to 4 and water for injection uses	T_{max}: 10 to 60 min Linear pharmacokinetics over a dose range of 2 to 8 mg Mean terminal $T_{1/2}$: 30 to 60 min V_d: 123 to 404 L Mean apparent CL: 125 to 401 L/hr
Apokyn Pen (Apomorphine HCl)	Parkinson's Disease/ Chronic	SC: solution (10 mg/mL)	Disposable multiple dose pen injector Manual; reusable The pen can deliver doses up to 1.0 mL in 0.02 mL increments	Clear, colorless, sterile solution for subcutaneous injection and is available in 3-mL cartridges Each mL of solution contains 10 mg of apo morphine hydrochloride, USP as apomorphine hydrochloride hemihydrate and 1 mg of sodium metabisulfite, NF in water for injection, USP, sodium hydroxide, NF and/or hydrochloric acid, NF to adjust the pH of the solution and 5 mg/mL of benzyl alcohol, NF as a preservative	T_{max}: 10 to 60 min Linear pharmacokinetics over a dose range of 2 to 8 mg Mean terminal $t_{1/2}$: 30 to 60 min Vd: 123 to 404 L Mean apparent CL: 125 to 401 L/hr
Metoject® (Methotrexate disodium)	Rheumatoid-, Juvenile-, Psoratic-Arthritis/Chronic	Solution: SC, IV, IM (10 mg/mL)	Injectable solution prefilled syringe Dosage strengths: 10, 15, 20, 25 mg	Clear, yellow solution Excipients: Sodium chloride, sodium hydroxide for pH adjustment, water for injections	$T_{1/2}$: 3 to 17 hr Plasma protein binding :50% Liver metabolism: 10%;excreted unchanged in the liver Caution: Once a week only
Remodulin Injection (Treprostinil Na)	Pulmonary artery hypertension	Solution: SC/IV infusion (1, 2.5, 5 & 10 mg/mL)	Injectable solution Infusion rate is initiated at 1.25 ng/kg/min	Each mL contains 5.3 mg sodium chloride (except for the 10 mg/mL strength that contains 4 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6 and 7.2	Rapid and complete absorption $T_{1/2}$: 2-4 h Hepatic metabolism Absolute BA: ~100% V_d: 0.2 L/kg. PPB: ~91% CL: 0.43 L/h/kg
Dilaudid-HP Injection (Hydromorphone hydrochloride)	Moderate-to-severe pain	Solution: IV/SC/IM (10 mg/mL)	Injectable solution, Lyophilized powder Dosage strength: 1-14 mg	Inactive ingredients: 0.2% sodium citrate, and 0.2% citric acid solution Available in amber ampoules or single-dose vials	$T_{1/2}$: 2.3 hr V_d: 302.9 L (4.33 L/kg) CL: 1.96 L/min (1.68 L/h/kg) PPB: 8% to 19% Extensive liver metabolism, small amount is excreted unchanged in the urine.
Prolixin Decanoate (Fluphenazine decanoate)	Psychiatric disorders	SC/IM (25 mg/mL)	Injectable solution	Each mL of injectable solution contains Fluphenazine decanoate 25 mg (5-ml vial) or 100 mg (1-ml vial) in sesame oil with	Very slowly absorbed from the site of SC or IM injection. They both gradually release Fluphenazine into the body and are therefore suitable for use as depot injections

Marketed SC formulations for small molecule drug delivery. (Source: PharmaCircle)

(after SC administration) of lidocaine HCl is affected by pH changes at the injection site. Absorption of drugs administered SC is generally slower than that of drugs administered IM because of the less efficient regional blood circulation of the former. Coadministration of vasodilators generally increases rate of drug absorption after SC administration whereas vasoconstrictors have been shown to lower the rate of absorption.[13]

Drug absorption can be increased at the SC site by rubbing the skin around the injection site and by exercise. This net effect could be due to changes in the interstitial fluid pressure of SC tissue owing to contractions of underlying musculature or movements of the injected limb. Drug action of SC-administered drugs may be prolonged by making deeper SC injection, by co-administering drugs that prolong absorption, or by cooling the injection site, which can cause local vasoconstriction. The bioavailability might also differ between administration sites, eg, thigh, abdomen; therefore, in the exploratory in vivo studies, the injection site should be consistent throughout the study to evaluate the relative bioavailability in a specific animal species.

TOLERABILITY & PK STUDIES IN PRECLINICAL SPECIES

General Guidance

The tolerance studies should be performed to elicit any potential risk of local irritation associated with the formulation (both active and excipients) upon SC administration.[14,15] Tolerance testing should be determined at sites that come into contact with the formulations as a result of the method of administration, and also at the sites that might come into contact through accidental or unavoidable exposure of the formulations. The testing strategy should be such that any mechanical effects of administration or purely physicochemical actions of the formulations can be distinguished from toxicological or pharmacodynamic ones. The tolerance testing for long-acting formulations (after SC dosing) should cover the entire period for which the formulation is expected to remain at the site of injection.[16] It is recommended to have appropriate positive and negative controls for all tolerance tests.

Animal Model Selection

The species selection is not restricted by any official guidelines as long as the species is considered to be scientifically appropriate. Ideally, a species of selection is both "most sensitive" and "most relevant" with regard to dosing routes and dose levels.[17] Rats are the preferred species for the preliminary PK and local tolerance testing of SC dosing, due to ease of dosing and accessibility of the samples for histological examination after euthanasia. To assess local tolerability, rabbits are the most sensitive species that often react to tissue irritation with purulent inflammation. With average body weight of 2 to 3 kg, clinically relevant doses could be tested in rabbits without exceeding the maximum tolerated dose (MTD). However, rabbits are considerably more expensive than rats, and handling of rabbits require special training. Monkeys and/or dogs could be dosed with clinically equivalent doses without exceeding the MTD. However, studies in non-rodent species are typically not terminal, and samples would require a biopsy for histological assessment.

Recommended SC Dosing Volume

Table 1 presents recommended SC administration volumes in the most frequently used species. These are consensus figures based on published literature and internal guidelines. If maximal values are exceeded, animal welfare or scientific implications may result and reference to the responsible veterinary surgeon should be made. The scientific validity of PK studies could be compromised by physiological reaction to high-dose volumes or repeated SC injections. Therefore, it is essential to fully consider these issues before protocols are finalized and work commences. It is also strongly recommended for ethical as well as scientific reasons that in vitro physicochemical compatibility studies and small-scale pilot studies are carried out on any new formulation before conducting larger-scale studies. Dose volumes should be the minimum compatible with SC formulation and accuracy of administration.

Sample Collection

Biological sample collection for PK studies generally includes plasma at predefined time points. In addition, tissue samples from the injection site can be collected at the end of the PK study for preliminary irritation assessment, or a separate tolerability/irritation study can be designed according to the program needs. Sampling collection should follow the general good practice for animal studies according to protocol(s) approved by the Institutional Animal Care and Usage Committee. The maximum volume of blood that can be withdrawn during a PK study is dependent on the species, body weight, animal health, frequency of blood collection, as well as method of blood collection. It is of utmost importance to remain within the blood sampling limits as removal of excessive blood will result in hypovolemia, cardiovascular collapse, anemia, excessive morbidity, and unexpected mortality, which might lead to data invalidation and compromise of the study. It is generally recommended that blood withdrawal be limited to 1% of circulating blood volume per 24 hours, not to exceed 10% of circulating blood volume per 2 to 3 weeks. The recommended sites for repeated blood sampling and circulating blood volumes of commonly used preclinical species are summarized somewhere.[18] For terminal blood sampling in mice and rats, cardiac puncture can be used after euthanasia.

TABLE 3

Product/Drug Molecule	Indication/ Therapy	Admin. Mode/ Dose	Formulation Technology	Formulation Characteristics	PK Characteristics
Products in Development					
Sumitriptan Dose Pro (Sumitriptan)	Registration/ Migraine/ Acute	SC: Solution	Intraject (Needle free SC injection)	Single use, sterile, disposable injector; clear, colorless to pale yellow, sterile, non-pyrogenic solution	Bioavailability: ~96% T_{max}: ~ 25 min Intraject PK bioequivalent to marketed SC injection product.
Ceflatonin® (CGX-635) (Omacetaxine mepesuccinate)	Phase II/ Cancer, (CML & MDS)	SC	Injectable solution Dosage strength: 2.5, 1.25 mg/m^2	-	-
Tetrodin™ (Tetrodotoxin)	Phase II/Drug addiction	SC	SC Injectable A 4-day pre-treatment regimen of 30 micrograms of SC Tetrodin should be administered 2 times a day	-	-
Bimosiamose	Phase I / Psoriasis	SC	SC Injectable	-	The Phase I study demonstrated safety and tolerability of Bimosiamose after single and multiple administrations of 3 escalating doses, PK results support once-daily dosing

SC Products inDevelopement for small molecule drug delivery. (Source: PharmaCircle)

MARKETED & IN-DEVELOPMENT SC FORMULATIONS FOR DELIVERING SMALL MOLECULES

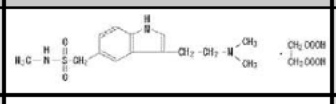
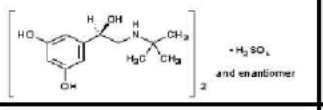
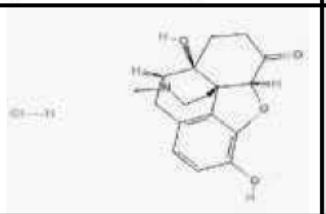
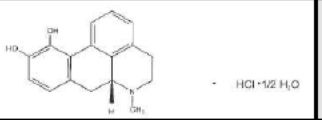
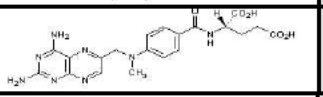
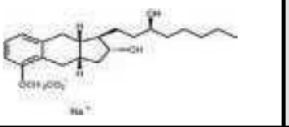
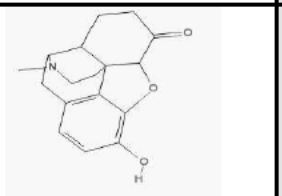
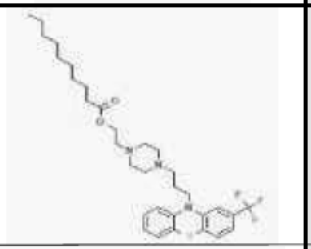
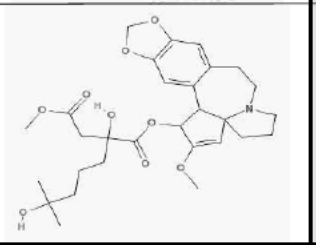
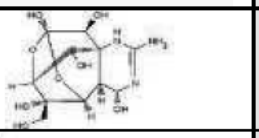
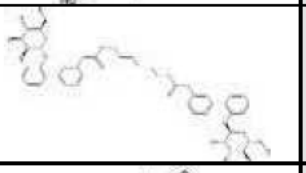
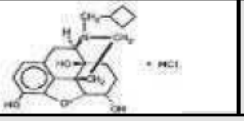
Although SC administration continues to be the main route for the delivery of protein and polypeptide drugs due to their poor stability and bioavailability by most non-parenteral routes, application of subcutaneous formulations for the delivery of small molecules with poor aqueous solubility is somewhat limited.[19-21] Various SC formulation strategies (eg, aqueous solutions, implant, microspehres, liposomes, PLGA-based depot systems) have been reported in the literature.[22-26] However, focus of this review is limited to systemic delivery of small molecules using the SC administration route. Systemic delivery of large molecules (proteins, polypeptides, and growth hormones) following SC administration and control/delayed-release formulations are topics of separate discussion. Tables 2, 3, and 4 provide a summary of currently marketed and in-development small molecule SC formulations.

Development of SC formulations of poorly soluble small molecules is a challenging task. Unlike IV formulations, a streamlined formulation strategy for SC formulation remains to be established. In general, a target product profile (TPP) essentially drives the SC formulation strategies. For example, the need for immediate-release/fast onset requirements will eliminate oil- or polymer-based particulate delivery systems, while these strategies could be of high priority for controlled-release formulation development in which maintenance of plasma therapeutic levels for a prolong period of time is a must. Additionally, development of an SC injectable device might be an integral part of the overall SC formulation strategy. Various SC injectable devices have been discussed in great detail elsewhere and beyond the scope of this current article.

Solubilization Approach

Dissolution of drug, following SC administration, depends on the availability of fluid at the site of injection and solubility of the drug in SC space. The majority of small molecules reviewed in Tables 2 and 3 have adequate aqueous solubility and therefore resulted in aqueous solution formulations. However, SC formulations of compounds with poor aqueous solubility eliminate the possibility of utilizing conventional aqueous formulation approaches. In that case, application of various solubilization techniques becomes evident to formulate unconventional formulations. Solubility of drug in oils (approved for parenteral use) and physical stability of emulsion formulations are two critical parameters for emulsion formulations and thus must be thoroughly investigated. Micronized suspensions are suitable for SC administration; however, utmost care should be taken to avoid tissue irritation and local tolerability issues by controlling particle size of the suspension. Although preferred by the IV route, emulsions and microemulsion formulations can be considered for the SC route. A number of different formulations strategies, such as depot formulations, encapsulations, and drug modifications, can be employed to modify release rate and

TABLE 4

Compound	Properties	Structure	Mol. Wt.	Aq. Solubility
Sumatriptan succinate	Weak base, salt		413.5	Freely soluble
Terbutaline sulfate	Weak base, salt		548.65	Soluble
Oxymorphone hydrochloride	Single enantiomer		337.8	Freely soluble
Apomorphine hydrochloride	Crystalline, Single enantiomer		312	Sparingly soluble
Methotrexate	Crystalline		454.45	Practically insoluble
Treprostinil sodium	Weak acid salt, Single enantiomer		412	Soluble
Hydromorphoe hydrochloride	Crystalline, single enantiomer		321.8	Freely soluble
Fluphenazine decanoate	Weak base salt		591.8	Practically insoluble
Omacetaxine mepesuccinate	Weak base salt		545.6	NA
Tetrodotoxin	Weak base, Single enantiomer		319.3	NA
Bimosiamose	Weak base, Enantiomer		862.9	NA
Nalbuphine hydrochloride	Weak base salt, Single enantiomer		393.9	Soluble

Physicochemical properties of small molecules used in marketed/in development formulations (Table 1). (Source: Wikipedia, PharmaCircle)

pharmacokinetics of a drug upon SC injection. SC administration of particulate formulations can be an interesting strategy to maintain plasma levels for a prolong period of time (days/months); however, it may fail to achieve fast onset action due to slower dissolution. Chemical modifications of an active moiety (analogues/prodrugs) may also serve as a viable approach to achieve desired physicochemical properties (enhanced aqueous solubility and adequeate in vitro/in vivo stability) and may therefore aid benefit to the SC delivery of small lipophilic molecules. Use of organic cosolvents for SC administration must be carefully assessed by safety and tolerability studies.

Enzyme (Hyaluronidase)-Mediated SC Delivery Approach

Rapid systemic absorption of drug from SC space depends on the permeability/diffusivity of drug molecules into surrounding tissues. The extracellular matrix in SC space may act as a major barrier by limiting diffusivity/permeability of drug and injection volumes. As shown in Figure 2, the transient digestion of hyaluronic acid containing extracellular matrix using hyaluronidase enzyme represents a unique strategy to overcome the volume barrier of SC injection. This strategy has been proven highly efficient in developing SC formulations of large molecules (protein and polypeptides), where volume of SC injection can be a major constraint.

Recent discovery of the molecular engineering of a purified soluble human rDNA-derived PH-20 hyaluronidase enzyme (rHuPH20) has led the clinical development of an enzyme-mediated drug delivery system.[27,28] A higher C_{max} and earlier T_{max} have been achieved using this approach. Thus, SC co-administration of rHuPH20 represents a broad platform technology for large molecules. However, application of this strategy remains to be evaluated for the delivery of small and poorly water-soluble molecules in which solubility rather than diffusivity of drug molecule can be a major constraint.

SUMMARY

Despite the fact that SC administration continues to be the main route for the delivery of protein and polypeptide drugs due to their poor stability and bioavailability by most non-parenteral routes, application of SC formulations for the delivery of small molecules with poor aqueous solubility is somewhat limited. Integration of various biopharmaceutical and formulations factors into the overall SC formulation strategies are highly recommended and should be carefully considered in designing SC drug delivery systems.

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Luca Durelli

Dose and frequency of interferon treatment matter

INCOMIN and OPTIMS

Abstract Three different interferon beta (IFNβ) products are currently approved for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS). However, the recommended method of administration, the dosage and the frequency of administration differ widely between each of the three products. Although controlled clinical trials have demonstrated the efficacy of both alternate-day IFNβ-1b (Betaferon®/Betaseron®) and once-weekly IFNβ-1a (Avonex™) compared with placebo, it is likely that patient compliance, efficacy and tolerability are affected by the dosage regimen used.

There are several issues to consider. Once-weekly administration may be associated with fewer adverse events and greater convenience, and it has been suggested that this may increase compliance. Conversely, frequent administration may be associated with increased overall efficacy. There is a convincing pharmacological rationale indicating that frequent dosing, with an interval of less than 72 h, is necessary to sustain the activity of intracellular molecular signalling pathways responsible for regulating IFNβ-induced gene expression. However, there was a need to explore the overall effectiveness of the two administration protocols in a comparative trial.

The INCOMIN (Independent Comparison of Interferon) study compared clinical and magnetic resonance imaging (MRI) efficacy of IFNβ-1b 250 µg (8 MIU) subcutaneously (s. c.) on alternate days and IFNβ-1a 30 µg (6 MIU) intramuscularly (i. m.) once weekly in patients with RRMS. INCOMIN demonstrated convincingly that clinical and MRI outcome measures were significantly better in the IFNβ-1b-treated group. Blinded MRI evaluation confirmed the clinical results. Despite some limitations of the study design, imposed by the ethical and practical challenges of conducting comparative trials of injectable therapies, the concordance of the clinical and MRI findings indicate that frequently administered IFNβ-1b reduced evidence of disease activity more effectively than once-weekly administered IFNβ-1a, with the clinical benefits for patients becoming more pronounced over time.

Given that the response to IFNβ appears to be dose dependent, the question that might be asked is whether greater efficacy can be obtained by increasing doses beyond those currently approved. OPTIMS (Optimization of Interferon dose for MS) is currently examining the safety and efficacy of a dose of IFNβ-1b that is higher than any currently marketed IFNβ. While OPTIMS is still underway, preliminary safety analyses indicate that higher doses are well tolerated.

Key words interferon beta-1b · interferon beta-1a · clinical trial · relapsing-remitting · multiple sclerosis · relapse

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Introduction

There are three interferon beta (IFNβ) products currently approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). One product containing IFNβ-1b (Betaferon®/Betaseron®) is administered subcutaneously (s. c.) every other day at a dose of 250 µg (8 MIU). The other two are IFNβ-1a products, one administered intramuscularly (i. m.) once weekly (Avonex™) at a dose of 30 µg (6 MIU), the other s. c. three times a week (Rebif®) at a dose of 22 (6 MIU) or 44 µg (12 MIU).

The efficacy of all three IFNβ products has been demonstrated in patients with RRMS in randomised clinical trials [5–7, 10, 11, 14]. Beneficial effects have been observed on relapse-related measures of disease and on magnetic resonance imaging (MRI) outcomes, compared with placebo. However, questions regarding the optimal dose and administration frequency, and the duration of treatment remain unanswered.

Many patients are currently treated with once-weekly IFNβ – the perceived increase in convenience from fewer injections each week may be thought to increase the likelihood of compliance, although there is no published evidence to date to support this hypothesis. The requirement for prolonged treatment, particularly if disease stabilisation has occurred, could also push patients towards fewer weekly doses, again for reasons of convenience. However, any perceived increased convenience may be gained at the expense of efficacy.

Clinical and pharmacological evidence to date suggests that the efficacy of IFNβ is dosage dependent [5–9, 14, 16]. There is also evidence that simply increasing the dose is insufficient – more frequent administration is required [1, 13, 14]. Until recently, no data from direct comparisons of the different IFNβ formulations to support the superiority of high dose and frequent administration have been available. However, two studies comparing different IFNβ products, INCOMIN (Independent Comparison of Interferons) [2] and EVIDENCE (Evidence for Interferon Dose Effect: European-North American Comparative Efficacy) [9] have now been published. In addition, the findings from INCOMIN have been further extended to examine the possibility of reducing the IFNβ dose from every other day to once weekly in patients with RRMS and stable disease. These studies, together with other ongoing trials, will help to answer the question of the most appropriate IFNβ dose and frequency to use. This paper will provide an overview of the studies and the other evidence relating to these questions of dose and administration frequency.

The rationale for high-dose therapy

There is a body of evidence from a number of clinical and pharmacological studies indicating that clinical and biological responses are greater at higher IFNβ doses. A study comparing the biological effects of i.m. IFNβ-1a once weekly and s.c. IFNβ-1b every other day demonstrated a significant increase in the levels of several biological markers in favour of more frequent/higher dosing [17]. Levels of MxA, neopterin, β_2-microglobulin and interleukin (IL)-10 were maintained at a high level throughout the 1-week study period with IFNβ-1b, while after a single dose of i.m. IFNβ-1a, they typically returned to baseline within 5 days of administration. Rothuizen et al. [13] studied the immunological effects of IFNβ (the interferon-induced inhibition of pro-inflammatory cytokine production) by administering a weekly IFNβ dose of 66 μg to healthy volunteers, either as a single once-weekly dose, or as three separate 22 μg doses given during the week. The biological activity of IFNβ, as assessed by the inhibition of cytokine production, increased by as much as threefold when the IFNβ dose was administered three times weekly.

Clinical studies comparing different treatment regimens of IFNβ consistently demonstrate the greater efficacy of the higher dose [5, 6, 8, 11]. The original pivotal study of IFNβ-1b, which examined the efficacy of 50 and 250 μg every other day indicated significant benefits in relapse rate and MRI parameters for the 250 μg dose compared with both placebo and the 50 μg dose. In the case of the 50 μg dose, only the effect on relapse rate was significant relative to placebo [5, 6, 10]. Data from the PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in MS) trial examining the efficacy of s.c. IFNβ-1a indicated a significant benefit for the higher dose (44 μg) and a lower dose (22 μg) given three times weekly, compared with placebo [11]. Both doses had significant effects on relapse rate, time to first relapse, the proportion of patients remaining relapse free and time to disability progression. There were also significant reductions in MRI burden of disease and new lesion development. For each outcome measure, there were dose-related increases in effect, although only with the MRI parameters did these become significant [11].

When once-weekly s.c. IFNβ-1a (44 and 22 μg) was assessed in the OWIMS (Once-Weekly Interferon for MS) study, significantly greater effects on MRI measures were seen using the higher dose compared with either the lower dose or placebo. However, no significant clinical effects were observed relative to placebo [14].

The data from both PRISMS [9] and the original pivotal trial of IFNβ-1b [5], together with data from the Multiple Sclerosis Collaborative Research Group trial of once-weekly i.m. IFNβ-1a [7] were recently compared using evidence-based medicine measures and an intent-to-treat analysis [3]. Three evidence-based medicine measures were used for comparison – number needed to treat (NNT), relative risk (RR) and absolute risk reduction (ARR). Although all three studies demonstrated significant improvements in relapse-related and MRI measures of disease relative to placebo [5–7, 10, 11], only the analyses from the pivotal study of IFNβ-1b and PRISMS were based on the ITT population [5, 6, 10, 11]. Analyses based on the ITT population include data from all patients who begin therapy, regardless of whether they remain in the study, therefore providing a more accurate assessment of drug effects. The results of this comparison showed that significant reductions in relapse rates and MRI measures of disease were obtained only with frequently administered regimes, and that

once-weekly dosing failed to produce any significant effects [3].

When taken together, the results from these studies and analyses indicate that higher doses are more effective. This observation has been echoed by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, which, in a recent report on disease modifying therapies, suggested that there was evidence to support a clinically relevant dose-response relationship for IFNβ [4]. However, there is also evidence that simply increasing dose while maintaining once-weekly administration is insufficient to significantly increase efficacy [1] – more frequent administration may also be needed.

While there is obviously an emerging pattern in the clinical trials performed to date, the comparison of different studies performed at different times and on different cohorts is problematic at best. The only way to establish the most effective dose and administration regimen is to perform direct comparative studies on the different IFNβ preparations. Until recently, no such comparative clinical studies of different IFNβ doses and administration schedules had been performed. INCOMIN was designed to provide answers to the question of the most appropriate IFNβ dose and frequency of administration [2].

INCOMIN

INCOMIN was a prospective, randomised, 2-year study comparing IFNβ-1b (250 µg s. c.) administered every other day and IFNβ-1a (30 µg i. m.) administered once weekly in 188 patients with RRMS. The study was carried out independently of the pharmaceutical industry, with support from the Italian Ministry of Health and the Italian MS Society [2]. The primary clinical outcome measure was the proportion of patients remaining relapse free and the primary MRI outcome measure was the proportion of patients remaining free from new T2 lesions. The clinical evaluations were unblinded; however, MRI evaluations were performed in a blinded fashion. The INCOMIN study demonstrated that the higher dose frequently administered IFNβ-1b was superior to once weekly IFNβ-1a [2].

Significant benefits were seen in clinical outcomes, including the primary clinical outcome measure, the proportion of patients remaining relapse free (51% versus 36%, $P < 0.036$), and many of the secondary clinical outcome measures [2] (Fig. 1). The MRI results confirmed the clinical results. The proportion of patients remaining free of new T2 lesions was significantly increased relative to IFNβ-1a (55% patients remaining free of new T2 lesions versus 26%, respectively, $P < 0.0003$). Secondary MRI outcomes were also significantly improved in the IFNβ-1b-treated group [2]. The incidence of adverse events was similar between the two treatment groups with the exception of injection-site reactions, which were significantly higher in IFNβ-1b-treated patients, most likely associated with the 3.5-fold greater number of injections administered [2].

A second study, EVIDENCE, compared the efficacy of three-times-weekly s. c. IFNβ-1a (44 µg) with once-weekly i. m. IFNβ-1a (30 µg) over 48 weeks [9]. The results of this study demonstrated significantly greater clinical and MRI benefit for the more frequently administered treatment, both confirming the results seen in INCOMIN and providing further data in support of the rationale for higher dose, frequent administration of IFNβ [9].

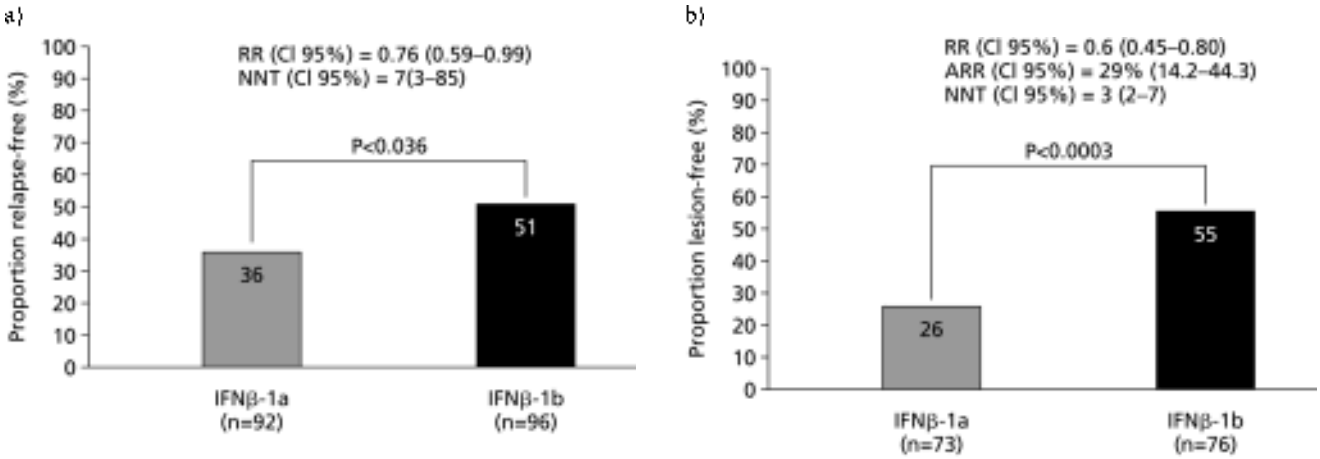


Fig. 1 INCOMIN primary outcome measures, **a** clinical, **b** MRI. Both are significantly improved with IFNβ-1b treatment compared to once-weekly IFNβ-1a

The consequences of reducing IFNβ dose – the Dose Reduction Study

Both INCOMIN and EVIDENCE support the notion that high-dose, frequently administered IFNβ is the more effective treatment for RRMS [2, 9]. However, MS is a chronic disease, requiring equally long-term treatment. Faced with the prospect of multiple injections each week for the foreseeable future, many patients might wish to reduce the dose and frequency of administration, in the hope of improved convenience, if they have achieved disease stability.

A further study was designed to test whether patients achieving disease stabilisation using IFNβ-1b (250 µg s. c. every other day) could maintain their clinical benefit if switched to once-weekly IFNβ-1a (30 µg i. m.) (Fig. 2).

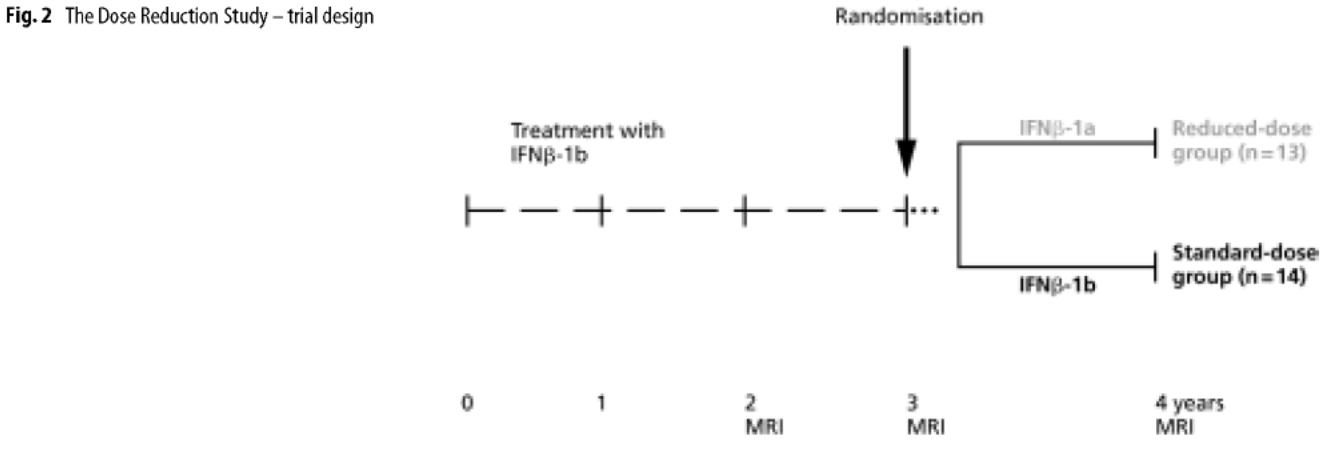
Some of the patients who participated in INCOMIN with definite RRMS and stable disease (defined as no relapses or progression of no more than 0.5 points in the previous 24 months, and no MRI activity in the last 12 months) who had been receiving IFNβ-1b for at least 36 months were included in the study. Patients were randomised either to continue receiving IFNβ-1b, or to gradually reduce the dose of IFNβ until they were receiving once-weekly i. m. IFNβ-1a (30 µg), then followed for 12 months.

Patients remaining on IFNβ-1b did significantly better than those receiving once-weekly IFNβ-1a. The number of patients remaining relapse free, the annual relapse rate and MRI outcome measures were all significantly better in those continuing to receive IFNβ-1b every other day (Fig. 3). The data from this study support the concept that not only are high dose and frequent administration important determinants of response, but also that, in order to maintain the clinical and MRI benefits, high-dose, high-frequency administration must be maintained.

The tolerability of higher doses – OPTIMS

As we have seen, the evidence obtained to date would appear to support the assertion that a regimen of high, multiple-weekly doses of IFNβ is more effective than once-weekly dosing [2, 9]. There is also evidence indicating that a dose-response relationship for IFNβ exists [5, 6, 8, 10, 11]. Not all patients respond optimally to the approved doses of IFNβ currently marketed and, given the above observations, it is reasonable to ask whether

Fig. 2 The Dose Reduction Study – trial design



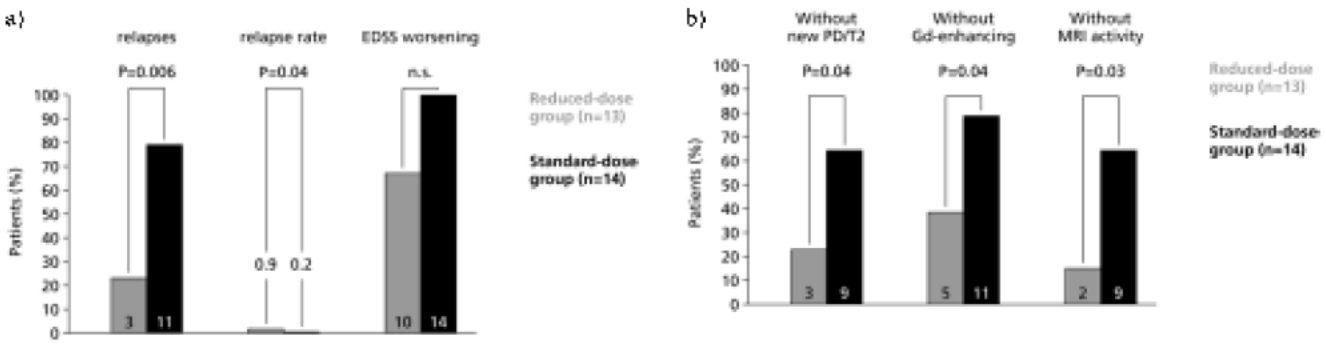


Fig. 3 High-frequency IFNβ-1b must be maintained in order to ensure continued treatment benefits for both **a** clinical and **b** MRI outcomes

using IFNβ doses higher than those currently approved could generate an improved response in these patients. There is some evidence from a pilot study that treatment responses to IFNβ-1b extend beyond the currently approved dose. In this study, IFNβ-1b was given to patients at doses of up to 500 µg. While none of the patients receiving this higher dose experienced relapses during the study period, adverse events – in the absence of any titration or forms of prophylaxis – meant that the majority had to be switched to a lower dose [8].

Since completion of this pilot study, much has been learned regarding the management of adverse events. While IFNβ is well tolerated, with a good safety profile, a number of adverse events are associated with therapy with these drugs. Typically, skin reactions (rash, erythema, pain) and flu-like symptoms (fever, chills, headache) predominate, and may be worse at the higher doses [15]. However, these adverse events can now be managed very effectively. Skin reactions can be reduced by measures that include injection-site rotation, and the use of automated injection systems [15]. Flu-like reactions become less frequent over time, and can also be managed with non-steroidal anti-inflammatory drugs (NSAIDs) or ibuprofen [12]. Gradually titrating the drug over a period of several weeks, to achieve the therapeutic dose, is also effective.

Given that adverse events can now be managed more effectively, there has been a greater focus on the use of doses above those currently approved, with the aim of increasing the number of patients benefiting from IFNβ-treatment. The first study designed to look at the question of higher dose therapy is the OPTIMS (OPTimization of Interferon for MS) study, which is investigating the use of 375 µg (12 MIU) IFNβ-1b administered s. c. every other day (Fig. 4). OPTIMS is a multicentre randomised 12-month study with a planned enrolment of 230 patients with RRMS. Patients will receive the standard IFNβ-1b dose for a 6-month run-in period, during which time they will undergo monthly MRI scans. Those patients assessed as responding optimally to the approved dose will continue with IFNβ-1b at the approved dose. Those patients with a sub-optimal response, as assessed by relapses, or the presence of new or enlarging T2 or Gd-enhancing lesions, will be randomised to receive either the standard treatment (250 µg), or 375 µg (12 MIU) IFNβ-1b s. c. every other day. All patients will then be followed for a further 6 months. It is hoped that a total of 100 sub-optimal responders and 100 normal responders will be recruited.

To date, some patients have completed the full year in the study, enabling comparison of adverse events in the two dose groups. Currently, the incidence of adverse events is no higher in the higher dose group, indicating that the higher dose is as well tolerated as the approved dose.

Conclusions

While IFNβ has been shown to be effective in the treatment of RRMS, the question of the optimal dose and frequency of administration remains a controversial one. Data from a number of different studies indicate that the response to IFNβ is dose dependent.

Data from INCOMIN and EVIDENCE suggest that frequent administration of IFNβ, several times per week, coupled with a high dose offers significantly better clinical and MRI benefits compared to once-weekly schedules. In addition, an extension of the INCOMIN study has shown that this treatment must be maintained, even after long periods of disease stability, in order to maintain these benefits. These data indicate that not only should patients receive frequent, high-dose IFNβ treatment in order to achieve the greatest clinical effect, but also that this therapy must be maintained in order to sustain this treatment benefit. Reducing dose to once-weekly IFNβ-1a may offer perceived benefits in terms of convenience, but this preference has a clinical cost.

Finally, it may also be possible to increase the IFNβ doses currently used in order to increase the number of patients benefiting from treatment. Several studies are

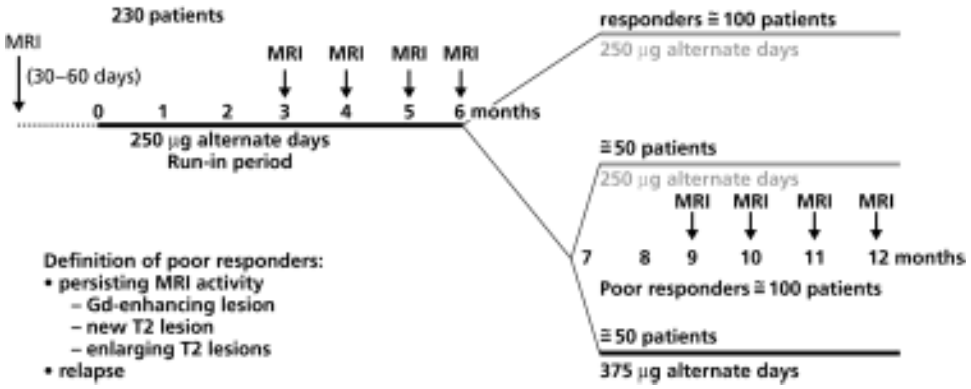


Fig. 4 The OPTIMS study – trial design

currently ongoing to investigate this possibility, but there are no efficacy data at present. However, the initial safety analysis from OPTIMS suggests that higher IFNβ doses are well tolerated. Other studies to investigate the possibility of using higher than approved IFNβ doses are planned.

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15. Walther EU, Hohlfeld R (1999) Multiple sclerosis: side effects of interferon beta therapy and their management. Neurology 53:1622–1627
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Electronic Acknowledgement Receipt

EFS ID:	13427807
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Cindy Shu
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	06-AUG-2012
Filing Date:	19-AUG-2010
Time Stamp:	17:30:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		120806_2609_80798-A_3rdSIDS_GTK.pdf	3935362 20549722c0eef67657325b16401ce258be286a50	yes	13

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6	Non Patent Literature	120806_2609_80798-A_Exhibit_5b_GTK.pdf	259464 b852d78b417db9333622eb2c081f89792172dbb4	no	3
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 2609/80798-A/JPW/GJG/GTK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ety Klinger
Serial No.	:	12/806,684
Filed	:	August 19, 2010
For	:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
August 6, 2012

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

THIRD SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with the duty of disclosure under 37 C.F.R. §1.56, Applicant directs the Examiner's attention to the following items, which are listed on the Substitute PTO-1449 form attached hereto as **Exhibit A**.

According to 37 C.F.R. §1.97(c) an Information Disclosure Statement filed after the period specified in 37 C.F.R. §1.97(b) shall be considered if accompanied by the fee set forth in the 37 C.F.R. §1.17(p) or a statement under 37 C.F.R. §1.97(e). The required fee set forth in 37 C.F.R. §1.97(p) is one hundred and eighty dollars ($180.00) and this amount has been paid in the first Information Disclosure Statement filed herewith. Accordingly, this Information Disclosure Statement should be considered.

Copies of items 1-48 are attached hereto as **Exhibits 1-48**, respectively.

1. Anderson, et al. (1992) "Revised estimate of the prevalence of multiple sclerosis in the United States". Ann Neurol. 31:333-36 **(Exhibit 1);**

2. Anderson, et al. "Injection pain decreases with new 0.5 mL formulation of glatiramer acetate" The Consortium of Multiple Sclerosis Centers 2010 Annual Meeting, June 2-5, 2010, San Antoinio, Texas (Abstract only) **(Exhibit 2);**

3. Arnon and Aharoni (2007) "Neurogenesis and neuroprotection in the CAN -Fundamental elements in the effect of glatiramer acetate on treatment of autoimmune neurological disorders". Mol Neurobiol. 36:245-53 **(Exhibit 3);**

4. Bjartmar C, et al. (2002) "Pathological mechanisms and disease progression of multiple sclerosis: therapeutic implications". Drugs of Today. 38:7-29 **(Exhibit 4);**

5. Bornstein, et al., "Treatments of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results," Ann. Neurol., 1980, 8, 117 (Abstract) (**Exhibit 5**);

6. Bornstein, et al., "Treatments of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results," Trans. Am. Neurol. Assoc., 1980, 105, 348-350(**Exhibit 6**);

7. Bornstein, et al., "Multiple Sclerosis: Trial of a Synthetic Polypeptide," Ann. Neurol., 1982, 11, 317-319(**Exhibit 7**);

8. Bornstein, et al., "Clinical Trials of Copolymer 1 in Multiple Sclerosis," Ann. N.Y. Acad. Sci. (USA), 1984, 366-372(**Exhibit 8**);

9. Bornstein, et al., "Clinical Trials of a Synthetic Polypeptide (Copolymer 1) for the treatment of Mutliple Sclerosis" in Gonsett et al., Immunological and Clinical Aspects of Multiple Sclerosis (MTP Press, The Hague, 1984) 144-150 (**Exhibit 9**);

10. Bornstein, et al., "Multiple Sclerosis: Clinical Trials of a Synthetic Polypeptide, Copolymer 1," Neurol., 1985, 35, (Suppl. 1), 103 (Abstract) (**Exhibit 10**);

11. Bornstein, "Cop 1 may be Beneficial for Patients with Exacerbating-remitting Form of Multiple Sclerosis," Adv. Ther. (USA), 1987, 4, 206 (Abstract) (**Exhibit 11**);

12. Bornstein, et al., "A Pilot Trial of Cop 1 in Exacerbating-remitting Multiple Sclerosis," New Eng. J. Med., 1987, 317(7), 408-414 (**Exhibit 12**);

13. Bornstein, et al., "Clinical Experience with COP-1 in Multiple Sclerosis," Neurol., 1988, 38(Suppl. 2) 66-69 (**Exhibit 13**);

14. Bornstein et al., "Rationale For Immunomodulating Therapies of Multiple Sclerosis: Clinical Trial Design in Multiple Sclerosis Therapy," Neurol., 1988, Vol. 38 (Suppl.2), pp. 80-81 [R] (**Exhibit 14**);

15. Bornstein, et al., "Pilot Trial of COP-1 in Chronic Progressive Multiple Sclerosis: Preliminary Report," from The International Multiple Sclerosis Conference: An Update on Multiple Sclerosis, Roma (Italy), September 15-17, 1988, in Elsevier Science Publisher, 1989, 225-232 (**Exhibit 15**);

16. Bornstein, et. al., "Clinical Trials of Cop 1 in Multiple Sclerosis," in Handbook of Multiple Sclerosis (S.D. Cook Marcel Rekker, ed., 1990) 469-480 (**Exhibit 16**);

17. Bornstein , et al., "A Placebo-controlled, Double-blind, Randomized Two-center, Pilot Trial of Cop 1 in Chronic Prgressive Multiple Sclerosis," Neurol., 1991, 41, 533-539 (**Exhibit 17**);

18. Bornstein, et al., " Treatment of Multiple Sclerosis with Copolymer 1" in Treatment of Multiple Sclerosis: Trial Design, Results and Future Perspectives (Rudick R.A. & Goodkin D.E., eds., Springer Lerlag, London, 1992) 173-198 (**Exhibit 18**);

19. Bornstein, "Clincal Experience: Hopeful Prospects In Multiple Sclerosis," Hospital Practice (Off. Ed.), 1992, Vol. 27, No. 5, pp. L135-158, 141-142, 145-158 (**Exhibit 19**);

20. Brazeau GA, et al. (1998) "Current perspectives on pain upon injection of drugs". J Pharmaceutical Sci.(87)6:667-677 **(Exhibit 20);**

21. Chantelau e, et al. (1991) "What make insulin injections painful?" BMJ. 303:26-27 (**Exhibit 21);**

22. Comi, et al. (2008) "Results from a phase III, one-year, randomized, double-blind, parallel-group, dose-comparison study with glatiramer acetate in relapsing-remitting multiple sclerosis". Mult Scler. 14(suppl 1):S299 **(Exhibit 22);**

23. Comi G. "Treatment with glatiramer acetate delays

conversion to clinically definite multiple sclerosis (CDMS) in patients with clinically isolated syndromes (CIS)". Program and abstracts of the American Academy of Neurology 60th Annual Meeting; April 12-19, 2008; Chicago, Illinois. LBS.003. **(Exhibit 23);**

24. Comi, et al. (2001) "European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imagine-measured disease activity and burden in patients with relapsing multiple sclerosis". Ann Neurol. 49:290-7 **(Exhibit 24);**

25. Dhib-Jalbut S. (2003) "Glatiramer acetate (Copaxone) therapy for multiple sclerosis". Pharmacol Ther. 98:245-55 **(Exhibit 25);**

26. Dhib-Jalbut S. (2002) "Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis". Neurology. 58(Suppl 4):S3-S9 **(Exhibit 26);**

27. Frenken LA, et al. (1994) "Analysis of the efficacy of measures to reduce pain after subcutaneous administration of epoetin alfa". Nephrol Dial Transplant. 9: 1295-1298 **(Exhibit 27);**

28. Johnson, et al. (1998) "Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability". Neurology. 50:701-8 **(Exhibit 28);**

29. Kansara, et al. (2009) "Subcutaneous Delivery". Drug Deliv Technol. June 2009; 9(6):38-42 **(Exhibit 29);**

30. Miller D, et al. (2005) "Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis,diagnosis, and prognosis". Lancet Neurol. 4(5):281-288 **(Exhibit 30)**;

31. Miller D, et al. (2005) "Clinically isolated syndromes suggestive of multiple sclerosis, part II: non-conventional MRI, recovery process, and management". Lancet Neurol. 4(6):341-348 **(Exhibit 31)**;

32. Neuhaus O, et al. (2003) "Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection". Trends Pharmacol Sci. 24:131-138 **(Exhibit 32)**;

33. Noseworthy, et al. (2000) "Multiple sclerosis". N Engl J Med. 343:938-52 **(Exhibit 33)**;

34. Polman, et al. (2005) "Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald" Criteria". Ann Neurol. 58:840-846 **(Exhibit 34)**;

35. Ruggiere, et al. (2007) "Glatiramer acetate in multiple sclerosis: A review". CNS Drug Reviews. 13(2):178-91 **(Exhibit 35)**;

36. Schrempf W, et al. (2007) "Glatiramer acetate: Mechanisms of action in multiple sclerosis". Autoimmunity Reviews 2007. 6:469-475 **(Exhibit 36)**;

37. Shire, et al. (2004) "Challenges in the Development of High Protein Concentration Formulations". J Pharm Sci. 93(6):1390-1402 **(Exhibit 37)**;

38. Thrower BW. (2007) "Clinically isolated syndromes. Predicting and delaying multiple sclerosis". Neurology. 68 (Suppl 4):S12-S15 **(Exhibit 38);**

39. Tselis, et al. (2007) "Glatiramer acetate in the treatment of multiple sclerosis". Neuropsychiatric Dis Treat. 3(2):259-67 **(Exhibit 39);**

40. Weber, et al. (2007) "Mechanism of action of glatiramer acetate in treatment of multiple sclerosis". Neurotherapeutics. 4(4):647-53 **(Exhibit 40);**

41. Wolinsky, et al. (2007) "Glatiramer acetate in primary progressive multiple sclerosis: Results of a multinational, multicenter, double-blind, placebo-controlled trial". Ann Neurol. 61:14-24 **(Exhibit 41);**

42. Wolinsky, JS (2006) "The use of glatiramer acetate in the treatment of multiple sclerosis". Adv Neurol. 273-92 **(Exhibit 42);**

43. Van Metre TE, et al. (1996) "Pain and dermal reaction caused by injected glycerin in immunotherapy solutions". J Allergy Clin Immunol. 97:1033-9 **(Exhibit 43);**

44. Ziemssen and Schrempf (2007) "Glatiramer acetate: Mechanisms of action in multiple sclerosis". International Rev of Neurobiol. 79:537-70 **(Exhibit 44);**

45. Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis EMEA, London 16 November 2006 CPMP/EWP/561/98 REV.1 **(Exhibit 45);**

46. Product Monograph, Copaxone, Revised April 2, 2010: 1-35 **(Exhibit 46);**

47. The National MS Society (USA) [cited 2010 Feb 5]. Avalable from: http://www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx **(Exhibit 47)**;

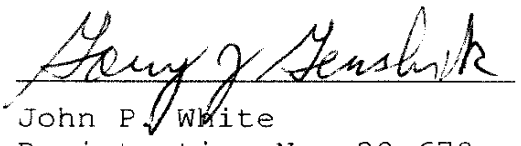
48. Medical News Today. July 8, 2008. Web. September 9, 2010. http://www.medicalnewstoday.com/articles/114183.php **(Exhibit 48)**.

The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO 1449.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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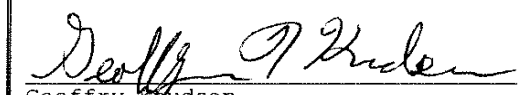

Geoffry Knudsen

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/806,684	08/19/2010	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 08/06/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 11	Minus	** 20	= 0	X $ =		OR	X $60=	0
Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $ =		OR	X $250=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANDREA FREEMAN/

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/806,684	Filing Date 08/19/2010	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
	08/06/2012	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 20	Minus	** 26	= 0	X $ =		OR	X $60=	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $ =		OR	X $250=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**0**

		(Column 1)		(Column 2)	(Column 3)					
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANDREA FREEMAN/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/806,684	08/19/2010	Ety Klinger	2609/80798-A/JPW/GJG/ML	3109

23432 7590 10/10/2012

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

EXAMINER	
ULM, JOHN D	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
10/10/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/806,684	KLINGER, ETY	
	Examiner	Art Unit	
	JOHN ULM	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,3-5,18,20,21 and 33-45* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3-5,18,20,21 and 33-45* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/06/12 x 4*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1) Claims 1, 3 to 5, 18, 20, 21 and 33 to 45 are pending in the instant application. Claims 1 and 3 to 5 have been amended, claims 2, 6 to 17, 19 and 22 to 26 canceled, and claims 33 to 35 added as requested by Applicant in the correspondence filed 06 August of 2012.

2) Any objection or rejection of record that is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4) The four information disclosure statements (IDSs) submitted on 06 August of 2012 are in compliance with the provisions of 37 CFR 1.97 and have been considered by the examiner.

Double Patenting

5) Claims 1, 3 to 5, 18, 20, 21 and 33 to 45 are rejected on the ground of nonstatutory double patenting over claims 1to 20 of US Patent Number 8,232,250. The subject matter claimed in the instant application is fully disclosed in the referenced patent and is covered thereby since the referenced patent and the instant application are claiming essentially the same subject matter. The only distinguishing limitations recited in either the instant claims or the patent claims are "three subcutaneous injections" of "40mg of glatiramer acetate over a period of seven days with at least one day between every subcutaneous injection". These are the very limitations that have

been argued by Applicant in each application as distinguishing the claimed method from those that were described in the prior art of record.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application in the application which matured into the '250 patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Applicant has essentially traversed this rejection on the premise the instant claims and the patent claims are not identical. This has not been found persuasive because the instant claims and the patented claims reflect the same distinguishing inventive concept and, consequently, each set of claims is obvious in view of the other set.

Conclusion

6) **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN ULM whose telephone number is (571)272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John D. Ulm/
Primary Examiner, Art Unit 1649

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office		
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	**Application Number**	12/806,684
	Filing Date	August 19, 2010
	First Named Inventor	Ety Klinger
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]
/J.U./	7	WO 2007/081975	07-19-2007	Pinchasi	

EXAMINER SIGNATURE	DATE CONSIDERED

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Exhibit A

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office	Application Number	12/806,684
	Filing Date	August 19, 2010
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	First Named Inventor	Ety Klinger
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.U./	1	February 14, 2012 Office Action Issued in Connection With U.S. Serial No. 13/308,299, filed November 30, 2011 (Klinger)	
/J.U./	2	Amendment in Response to February 14, 2012 Office Action filed May 14, 2012 in connection with U.S. Serial No. 13/308,299, filed November 30, 2011 (Klinger)	
/J.U./	3	November 25, 2011 Examiner's Report Issued in connection with Australian Application No. 2010284666, filed August 19, 2012 (Klinger)	
/J.U./	4	February 29, 2012 Official Action Issued in connection with Canadian Application No. 2,760,802, filed August 19, 2012 (Klinger)	
/J.U./	5	Response to the February 29, 2012 outstanding Examiner's Report filed May 29, 2012 in connection with Canadian Application No. 2,760,802, filed August 19, 2012 (Klinger)	
/J.U./	6	Supplementary European Search Report issued July 13, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011	
/J.U./	8	Flechter S. et al. (2002) "Comparison of glatiramer acetate (Copaxone(R)) and interferon beta-1b (Betaferon(R)) in multiple sclerosis patients: An open-label 2-year follow up" Journal of the Neurological Sciences vol. 197, no. 1-2 pages 51-55	
/J.U./	9	Khan et al. (2008) "Randomized, prospective, rater-blinded, four-year, pilot study to compare the effect of daily versus every - other - day injections in relapsing -remitting multiple" Mult. Scler. 14 Suppl. 1 S296	
/J.U./	10	Caon Christina et al. (2009) "Randomized, prospective, rater-blinded, four year pilot study to compare the effect of daily versus every other day glatiramer acetate 20 mg subcutaneous injections in RRMS" Neurology vol. 72, no. 11, page A317	
/J.U./	11	Simpson Dene et al. (2002) "Glatiramer acetate: A review of its use in relapsing-remitting multiple sclerosis" CNS DRUGS vol. 16, no. 12 pages 825-850	

EXAMINER SIGNATURE	/John Ulm/	DATE CONSIDERED	10/02/2012

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

Form PTO-1449 (Substitute) **U.S. Department of Commerce**
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Klinger Ety
Art Unit	1649
Examiner Name	John Ulm
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/J.U./	1	2007/161566	07-12-2007	Pinchasi
/J.U./	2	2006/0154862	07-13-2006	Anup Kumar Ray et al.

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]
/J.U./	3	WO 2004/091573 A1	10-28-2004	Pinchasi et al.	
/J.U./	4	WO 2006/029036 A2	03-16-2006	Schipper and Godin	
/J.U./	5	WO 2007/081975 A1	07-19-2007	Pinchasi	
/J.U./	6	WO 2011/008274 A2	01-20-2011	Altman et al.	

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Exhibit A

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	Filing Date	August 19, 2010
	First Named Inventor	Klinger Ety
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.U./	7	Office Action issued July 20, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
/J.U./	8	Amendment filed July 1, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
/J.U./	9	Office Action issued April 2, 2009 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
/J.U./	10	Amendment filed December 22, 2008 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
/J.U./	11	Office Action issued June 20, 2008 in connection with U.S. Serial No. 11/651,212, filed January 9, 2007	
/J.U./	12	Response filed September 23, 2010 in connection with U.S. Serial No. 12/785,125, filed May 21, 2010	
/J.U./	13	Office Action issued August 24, 2010 in connection with U.S. Serial No. 12/785,125, filed May 21, 2010	
/J.U./	14	Communication issued July 29, 2010 in connection with EPO Application No. 10160099.7	
/J.U./	15	Response filed December 17, 2010 in connection with European Patent Application No. 10160099.7	
/J.U./	16	Communication Pursuant to Article 94(3) EPC issued February 11, 2011 in connection with European Patent Application No. 10160099.7	
/J.U./	17	Response filed June 13, 2011 in connection with European Patent Application No. 10160099.7	
/J.U./	18	Written Opinion of the International Searching Authority issued October 5, 2007 in connection with PCT International Application No. PCT/US07/00575, filed January 9, 2007	

EXAMINER SIGNATURE	/John Ulm/	DATE CONSIDERED	10/02/2012

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Form PTO-1449 (Substitute) **U.S. Department of Commerce Patent and Trademark Office**

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Klinger Ety
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Examiner Name	John Ulm
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

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/J.U./	19	PCT International Search Report issued October 5, 2007 in connection with PCT International Application No. PCT/US07/00575, filed January 9, 2007	
/J.U./	20	Written Opinion of the International Searching Authority issued June 9, 2011, in connection with PCT International Application No. PCT/US2010/001972, filed July 14, 2010	
/J.U./	21	PCT International Search Report issued June 9, 2011 in connection with PCT International Application No. PCT/US2010/001972, filed July 14, 2010	
/J.U./	22	Polin. The Ins and Outs of Prefilled Syringes. May 2003, Pharmaceutical & Medical Packaging News/Medical Device Link	
/J.U./	23	Jorgensen J.T. et al. (1996) "Pain assessment of subcutaneous injections" Annals of Pharmacotherapy, Harvey Whitney Books Company, Vol. 30. No. 7-8, pp.729-732	

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	10/02/2012

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

Form PTO-1449 (Substitute) **U.S. Department of Commerce Patent and Trademark Office**

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Ety Klinger
Art Unit	1649
Examiner Name	John Ulm
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.U./	1	Anderson, et al. (1992) "Revised estimate of the prevalence of multiple sclerosis in the United States". Ann Neurol. 31:333-36	
/J.U./	2	Anderson, et al. "Injection pain decreases..." The Consortium of Multiple Sclerosis Centers 2010 Annual Meeting, June 2-5, 2010, San Antoinio, Texas (Abstract only)	
/J.U./	3	Arnon and Aharoni (2007) "Neurogenesis and neuroprotection in the CAN - Fundamental elements in the effect of...". Mol Neurobiol. 36:245-53	
/J.U./	4	Bjartmar C, et al. (2002) "Pathological mechanisms and disease progression of multiple sclerosis: therapeutic implications". Drugs of Today. 38:7-29	
/J.U./	5	Bornstein, et al., "Treatments of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results," Ann. Neurol., 1980, 8, 117 (Abstract)	
/J.U./	6	Bornstein, et al., "Treatments of Multiple Sclerosis with a Synthetic Polypeptide: Preliminary Results," Trans. Am. Neurol. Assoc., 1980, 105, 348-350	
/J.U./	7	Bornstein, et al., "Multiple Sclerosis: Trial of a Synthetic Polypeptide," Ann. Neurol., 1982, 11, 317-319	
/J.U./	8	Bornstein, et al., "Clinical Trials of Copolymer 1 in Multiple Sclerosis," Ann. N.Y. Acad. Sci. (USA), 1984, 366-372	
/J.U./	9	Bornstein, et al., "Clinical Trials of a Synthetic Polypeptide (Copolymer 1) for the treatment of Mutliple Sclerosis" in Gonsett et al., Immunological and Clinical Aspects of Multiple Sclerosis (MTP Press, The Hague, 1984) 144-150	
/J.U./	10	Bornstein, et al., "Multiple Sclerosis: Clinical Trials of a Synthetic Polypeptide, Copolymer 1," Neurol., 1985, 35, (Suppl. 1), 103 (Abstract)	
/J.U./	11	Bornstein, "Cop 1 may be Beneficial for Patients with Exacerbating-remitting Form of Multiple Sclerosis," Adv. Ther. (USA), 1987, 4, 206 (Abstract) (Exhibit 45)	
/J.U./	12	Bornstein, et al., "A Pilot Trial of Cop 1 in Exacerbating-remitting Multiple Sclerosis," New Eng. J. Med., 1987, 317(7), 408-414	

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	10/02/2012

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Exhibit A

Form PTO-1449 (Substitute) U.S. Department of Commerce Patent and Trademark Office		
INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	**Application Number**	12/806,684
	Filing Date	August 19, 2010
	First Named Inventor	Ety Klinger
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.U./	13	Bornstein, et al., "Clinical Experience with COP-1 in Multiple Sclerosis," Neurol., 1988, 38(Suppl. 2) 66-69	
/J.U./	14	Bornstein et al., "Rationale For Immunomodulating Therapies of Multiple Sclerosis: Clinical Trial Design in Multiple Sclerosis Therapy," Neurol., 1988, Vol. 38 (Suppl.2), pp. 80-81 [R]	
/J.U./	15	Bornstein, et al., "Pilot Trial of COP-1 in Chronic Progressive Multiple Sclerosis: Preliminary Report," from The International Multiple Sclerosis Conference: An Update on Multiple Sclerosis, Roma (Italy), September 15-17, 1988, in Elsevier Science Publisher, 1989, 225-232	
/J.U./	16	Bornstein, et. al., "Clinical Trials of Cop 1 in Multiple Sclerosis," in Handbook of Multiple Sclerosis (S.D. Cook Marcel Rekker, ed., 1990) 469-480	
/J.U./	17	Bornstein , et al., "A Placebo-controlled, Double-blind, Randomized Two-center, Pilot Trial of Cop 1 in Chronic Prgressive Multiple Sclerosis," Neurol., 1991, 41, 533-539	
/J.U./	18	Bornstein, et al., "Treatment of Multiple Sclerosis with Copolymer 1" in Treatment of Multiple Sclerosis: Trial Design, Results and Future Perspectives (Rudick R.A. & Goodkin D.E., eds., Springer Lerlag, London, 1992) 173-198	
/J.U./	19	Bornstein, "Clincal Experience: Hopeful Prospects In Multiple Sclerosis," Hospital Practice (Off. Ed.), 1992, Vol. 27, No. 5, pp. L135-158, 141-142, 145-158	
/J.U./	20	Brazeau GA, et al. (1998) "Current perspectives on pain upon injection of drugs". J Pharmaceutical Sci.(87)6:667-677	
/J.U./	21	Chantelau e, et al. (1991) "What make insulin injections painful?" BMJ. 303:26-27	
/J.U./	22	Comi, et al. (2008) "Results from a phase III, one-year, randomized, double-blind, parallel-group...". Mult Scler. 14(suppl 1):S299	
/J.U./	23	Comi G. "Treatment with glatiramer...". Program and abstracts of the American Academy of Neurology 60th Annual Meeting; April 12-19, 2008; Chicago, Illinois. LBS.003.	
/J.U./	24	Comi, et al. (2001) "European/Canadian multicenter, double-blind, randomized, placebo-controlled study...". Ann Neurol. 49:290-7	

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	10/02/2012

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	First Named Inventor	Ety Klinger
	Art Unit	1649
	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

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/J.U./	25	Dhib-Jalbut S. (2003) "Glatiramer acetate (Copaxone) therapy for multiple sclerosis" Pharmacology & Therapeutics. 98:245-55	
/J.U./	26	Dhib-Jalbut S. (2002) "Mechanisms of action of interferons and glatiramer acetate in multiple sclerosis". Neurology. 58(Suppl 4):S3-S9	
/J.U./	27	Frenken LA, et al. (1994) "Analysis of the efficacy of measures to reduce pain after subcutaneous administration of epoetin alfa". Nephrol Dial Transplant. 9:1295-1298	
/J.U./	28	Johnson, et al. (1998) "Extended use of glatiramer acetate (Copaxone) is well tolerated ...". Neurology. 50:701-8	
/J.U./	29	Kansara, et al. (2009) "Subcutaneous Delivery". Drug Deliv Technol. June 2009; 9(6):38-42	
/J.U./	30	Miller D, et al. (2005) "Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history...". Lancet Neurol. 4(5):281-288	
/J.U./	31	Miller D, et al. (2005) "Clinically isolated syndromes suggestive of multiple sclerosis, part II: non-conventional MRI...". Lancet Neurol. 4(6):341-348	
/J.U./	32	Neuhaus O, et al. (2003) "Immunomodulation in multiple sclerosis: from immunosuppression to neuroprotection". Trends Pharmacol Sci. 24:131-138	
/J.U./	33	Noseworthy, et al. (2000) "Multiple sclerosis". N Engl J Med. 343:938-52	
/J.U./	34	Polman, et al. (2005) "Diagnostic Criteria for Multiple Sclerosis: 2005 Revisions to the "McDonald" Criteria". Ann Neurol. 58:840-846	
/J.U./	35	Ruggiere, et al. (2007) "Glatiramer acetate in multiple sclerosis: A review". CNS Drug Reviews. 13(2):178-91	
/J.U./	36	Schrempf W, et al. (2007) "Glatiramer acetate: Mechanisms of action in multiple sclerosis". Autoimmunity Reviews 2007. 6:469-475	

EXAMINER SIGNATURE	/John Ulm/	DATE CONSIDERED	10/02/2012

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	Examiner Name	John Ulm
	Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

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/J.U./	37	Shire, et al. (2004) "Challenges in the Development of High Protein Concentration Formulations". J Pharm Sci. 93(6):1390-1402	
/J.U./	38	Thrower BW. (2007) "Clinically isolated syndromes. Predicting and delaying multiple sclerosis". Neurology. 68 (Suppl 4):S12-S15	
/J.U./	39	Tselis, et al. (2007) "Glatiramer acetate in the treatment of multiple sclerosis". Neuropsychiatric Dis Treat. 3(2):259-67	
/J.U./	40	Weber, et al. (2007) "Mechanism of action of glatiramer acetate in treatment of multiple sclerosis". Neurotherapeutics. 4(4):647-53	
/J.U./	41	Wolinsky J.S. (2006) "The use of glatiramer acetate in the treatment of multiple sclerosis" Advances in Neurology 98: 273-292	
/J.U./	42	Wolinsky, JS (2006) "The use of glatiramer acetate in the treatment of multiple sclerosis". Adv Neurol. 273-92	
/J.U./	43	Van Metre TE, et al. (1996) "Pain and dermal reaction caused by injected glycerin in immunotherapy solutions". J Allergy Clin Immunol. 97:1033-9	
/J.U./	44	Ziemssen and Schrempf (2007) "Glatiramer acetate: Mechanisms of action in multiple sclerosis". International Rev of Neurobiol. 79:537-70	
/J.U./	45	Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis EMEA, London 16 November 2006 CPMP/EWP/561/98 REV.1	
/J.U./	46	Product Monograph, Copaxone, Revised April 2, 2010: 1-35	
/J.U./	47	The National MS Society (USA) [cited 2010 Feb 5]. Available from: www.nationalmssociety.org/about-multiple-sclerosis/what-we-know-about-ms/treatments/index.aspx	
/J.U./	48	Medical News Today. July 8, 2008. Web: September 9, 2010. www.medicalnewstoday.com/articles/114183.php	

EXAMINER SIGNATURE	/John Ulm/	DATE CONSIDERED	10/02/2012

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12806684	KLINGER, ETY
	Examiner	Art Unit
	JOHN ULM	1649

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Searched inventor's name in NPL & PALM; Searched Medline, WEST & Google for: sclerosis, glatimer acetate, copolymer 1, alternate-day, dosage	02/02/2012	JDU
Updated, reviewed prosecution in 13/308,299, now US Pat. No. 8,232,250, patentably indistinct invention	10/02/2012	JDU

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Form PTO-1449 (Substitute) U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Ety Klinger
Art Unit	John Ulm
Examiner Name	1649
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/J.U./	1	7,625,861	12-01-2009	Konfino et al.
/J.U./	2	7,615,580	07-22-2006	Gad et al.
/J.U./	3	7,923,215	04-12-2011	Klinger
/J.U./	4	2007-0021324	01-25-2007	Dolitzky
/J.U./	5	2010-0285600	11-11-2010	Lancet et al.
/J.U./	6	7,855,176	12-21-2012	Altman et al.
/J.U./	7	2011-0066112	03-17-2011	Altman et al.
/J.U./	8	13/384,021	07-14-2010	Altman et al.
/J.U./	9	13/083,112	04-08-2011	Klinger
/J.U./	10	11/651,212	01-09-2007	Pinchasi
/J.U./	11	12/806,684	08-19-2010	Klinger

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	10/02/2012

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Exhibit A

Docket No. 2609/80798-A/JPW/GJG/GTK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Ety Klinger	
Serial No.	:	12/806,684	Examiner: John Ulm
Filed	:	August 19, 2010	Group Art Unit: 1649
Conf. No.	:	3109	
For	:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY	

30 Rockefeller Plaza, 20th Floor
New York, New York 10112
January 10, 2013

BY EFS
Commissioner for Patents
Alexandria, VA

Sir:

RESPONSE TO OCTOBER 10, 2012 FINAL OFFICE ACTION AND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

This is a response to an October 10, 2012 Final Office Action issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the October 10, 2012 Final Office Action is due January 10, 2013. Accordingly, this response is being timely filed.

Remarks begin on page 2 of this paper.

A **Supplemental Information Disclosure Statement** begins on page 3 of this paper.

REMARKS

Double Patenting

In the October 10, 2012 Office Action, the Examiner rejected claims 1, 3-5, 18, 20-21 and 33-45 on the ground of nonstatutory double patenting over claims 1-20 of U.S. Patent No. 8,232,250 for the reason set forth in the October 10, 2012 Final Office Action.

Applicant's Response

In response, without conceding the correctness of the rejection and for the purpose of expediting prosecution, Applicant attaches hereto as **Exhibit A** a Terminal Disclaimer signed by an authorized representative of Yeda Research and Development Co., Ltd., the sole assignee of record of both the subject application and U.S. Patent No. 8,232,250. In accordance with 37 C.F.R. §1.321(b), the Terminal Disclaimer submitted herewith as **Exhibit A** specifies the portion of the term of the patent being disclaimed and states the present extent of the assignee's ownership interest in the patent to be granted.

The filing of a Terminal Disclaimer requires a one hundred sixty dollar ($160.00) fee as set forth in 37 C.F.R. §1.20(d) and authorization is hereby given to charge the amount of this fee to Deposit Account No. 03-3125.

Supplemental Information Disclosure Statement

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following references, which are listed on Form PTO-1449 (substitute), attached hereto as **Exhibit B.**

According to 37 C.F.R. § 1.97(d), a Supplemental Information Disclosure Statement filed after the period specified in 37 C.F.R. § 1.97(c) shall be considered if accompanied by the fee set forth in 37 C.F.R. § 1.17(p) and a statement under 37 C.F.R. § 1.97(e). The required fee set forth in 37 C.F.R. §1.17(p) is one hundred and eighty dollars ($180.00) and authorization is hereby given to charge this amount to Deposit Account No. 03-3125.

In accordance with 37 C.F.R. §1.97(e)(1) applicants state that Items 1-5 submitted in this Supplemental Information Disclosure Statement were a communication from or to a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Supplemental Information Disclosure Statement. Accordingly, this Information Disclosure Statement should be considered.

Copies of the documents listed herein as items 1-8 are attached hereto as **Exhibits 1-8**, respectively.

1. Official Action issued November 28, 2012 in connection with Eurasian patent application No. 201270292 including English translation thereof (**Exhibit 1**). Item 1 is an Office Action issued in counterpart Eurasian patent application No. 201270292;

2. Preliminary Conclusion of Substantive Examination issued November 8, 2012 in connection with Ukrainian patent application No. 2012 03259 including English translation thereof (**Exhibit 2**). Item 2 is an Office Action issued in counterpart Ukrainian patent application No. 2012 03259;

3. Examination Report issued November 5, 2012 in connection with New Zealand patent application No. 598661 (**Exhibit 3**). Item 3 is an Office Action issued in counterpart New Zealand patent application No. 598661;

4. Response to the November 25, 2011 Examiner's Report filed October 15, 2012 in Connection With Australian Application No. 2010284666, filed August 19, 2012 (**Exhibit 4**). Item 4 is a Response to an Office Action issued in counterpart Australian Application No. 2010284666. The Office Action to which Item 4 responds was disclosed on August 6, 2012 and considered by the Examiner on October 2, 2012;

5. Response to the July 24, 2012 outstanding Examiner's Report filed October 24, 2012 in connection with Canadian Application No. 2,760,802, filed August 19, 2012 (**Exhibit 5**). Item 5 is a Response to an Office Action issued in counterpart Canadian Application No. 2,760,802. The Office Action to which Item 5 responds is Item 6, below;

6. July 24, 2012 Official Action Issued in Connection With Canadian Application No. 2,760,802, filed August 19, 2012 (**Exhibit 6**). Item 6 is an Office Action issued in counterpart Canadian Application No. 2,760,802, to which item 5 above is the response;

7. Communication Pursuant to Article 94(3) EPC issued August 8, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011 (**Exhibit 7**). Item 7 is an Office Action issued in counterpart European Patent Application No. 10810282.3. The references cited in Item 7 were previously cited in the European Search Report issued July 13, 2012 which, together with the references were disclosed on August 6, 2012 and considered by the Examiner on October 2, 2012; and

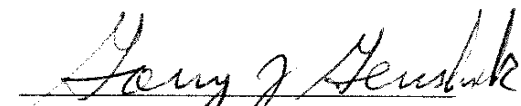
8. Response to August 8, 2012 Communication Pursuant to Article 94(3) EPC filed September 13, 2012 in connection with European Patent Application No. 10810282.3, filed October 11, 2011 (**Exhibit 8**). Item 8 is a Response to an Office Action issued in counterpart European Patent Application No. 10810282.3 which was filed in response to Item 7, above.

The Examiner is respectfully requested to make these references of record in the present application by initialing and returning a copy of the enclosed Form PTO 1449.

If a telephone interview would be of assistance in advancing prosecution of the subject application, the undersigned attorney invites the Examiner to telephone him at the telephone number provided below.

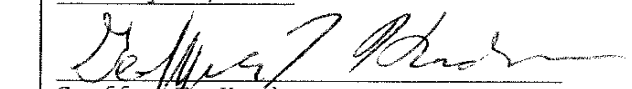
No fee, other than the fee of THREE HUNDRED FOURTY DOLLARS ($340) (ONE HUNDRED SIXTY DOLLARS ($160) for the filing of a Terminal Disclaimer and ONE HUNDRED EIGHTY DOLLARS ($180) for the filing of a Supplemental Information Disclosure Statement), is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
30 Rockefeller Plaza
20th Floor
New York, New York 10112
(212) 278-0400

Certificate of Transmission
I hereby certify that this correspondence is being transmitted via the Electronic Filing System (EFS) to the U.S. Patent and Trademark Office on January 10, 2013.



Geoffrey P. Knudsen

2009-106

Docket No. 2609/80798-A/JPW/GJG/GTK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Ety Klinger

U.S. Serial No.: 12/806,684 Examiner: John Ulm

Filed : August 19, 2010 Art Unit: 1614

For : LOW FREQUENCY GLATIRAMER ACETATE THERAPY

Conf. No. : 3109

30 Rockefeller Plaza
20th Floor
New York, New York 10112

BY EFS
Commissioner for Patents
Alexandria, VA 22313-1450

Sir:

TERMINAL DISCLAIMER UNDER 37 C.F.R. §1.321(b)

Yeda Research & Development Co., Ltd., ("Yeda"), P.O. Box 95, Rehovot, 76100, Israel, is the owner of (assignee of record of the entire right, title and interest in) the above-identified application by virtue of an assignment from Ety Klinger to Teva Pharmaceutical Industries, Ltd. of U.S. Serial No. 12/806,684, filed August 19, 2010, the above-identified application, which assignment was recorded with the U.S. Patent and Trademark Office on August 19, 2010 at Reel No. 024910, Frame 0853, a copy of the which is attached hereto as **Exhibit 1**, and by virtue of an assignment from Teva Pharmaceutical Industries, Ltd. to Yeda Research & Development Co., Ltd. of U.S. Serial No. 12/806,684, filed August 19, 2010, the above-identified application, which assignment was recorded with the U.S. Patent and Trademark Office on March 3, 2011 at Reel No. 025898, Frame 0365, a copy of the which is attached hereto as **Exhibit 2.**

Yeda is also the owner of (assignee of record of the entire right, title and interest in) U.S. Patent No. 8,232,250, by

virtue of the assignments (attached hereto as **Exhibits 1 and 2**) of U.S. Serial No. 13/308,299, filed November 29, 2011, from which U.S. Patent No. 8,232,250 issued. U.S. Serial No. 13/308,299, filed November 29, 2011 is a continuation of U.S. Serial No. 12/806,684, filed August 19, 2010, and the attached assignments expressly refer to continuation applications

Yeda hereby disclaims, except as provided below, the terminal part of any patent granted on the above-identified application which would extend beyond the expiration date of U.S. Patent No. 8,232,250 and hereby agrees that any patent issued from the subject application shall be enforceable only for and during such period that the owner of such patent is the same as the owner of U.S. Patent No. 8,232,250 and this agreement to run with any patent granted on the subject application and to be binding upon the grantee, its successors and assigns.

In making the above disclaimer, Yeda does not disclaim the terminal part of any patent granted on the subject application that would extend until the expiration date of such patent in the event that such patent expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. §1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration date which such patent would otherwise have had.

We have reviewed the assignment attached hereto and certify that, to the best of my knowledge and belief, Yeda is the assignee of all right, title and interest in and to the subject application and U.S. Patent No. 8,232,250. We further certify that we are authorized to sign this Terminal

Disclaimer on behalf of Yeda.

We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that any such willful false statement and the like so made is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Yeda Research & Development Co., Ltd.

By: _____ Date: Dec 23rd, 2012
Ruth Granoth
Chief Intellectual Property Officer

By: _____ Date: Dec 23rd, 2012
Meir Fast
Chief Financial Officer

5817 A

Attorney Docket No. 2609/80798-A/JPW/GIG/ML

Assignment

In consideration of One Dollar ($1.00), and other good and valuable considerations, the receipt of which is hereby acknowledged, I, the undersigned,

Ety Klinger residing at 16 Agadati Street, Tel Aviv, Israel 39930

Hereby sell, assign and transfer *to* Teva Pharmaceutical Industries, Ltd., *a corporation of the State of* Israel, *having a place of business at* 5 Basel Street P.O. Box 3190, Petach-Tikva, Israel 49131 *and its successors, assigns and legal representatives, the entire right, title and interest for all countries, in and to any and all inventions which are disclosed and claimed, and any and all inventions which are disclosed but not claimed, in the application for United States Patent, which has been executed by the undersigned on* December 16, 2007 and December 20, 2007 *and is entitled*

LOW FREQUENCY GLATIRAMER ACETATE THERAPY
(U.S. SERIAL NO. Not Yet Known , FILED Herewith , CLAIMING BENEFIT OF U.S. PROVISSIONAL APPLICATION NOS. 61/274,687, FILED AUGUST 20, 2009 AND 61/337,612, FILED FEBRUARY 11, 2010)

and in and to said application and all divisional, continuing, substitute, renewal, reissue, and all other applications for U.S. Letters Patent or other related property rights in any and all foreign countries which have been or shall be filed on any of said inventions disclosed in said application; and in and to all original and reissued patents or related foreign documents which have been or shall be issued on said inventions;

Authorize and request *the Commissioner for Patents of the United States to issue to said Assignee, the corporation above named, its successors, assigns and legal representatives, in accordance with this assignment, any and all United States Letters Patent on said inventions or any of them disclosed in said application;*

Agree that said Assignee may apply for and receive foreign Letters Patent or rights of any other kind for said inventions, or any of them; and may claim, in applications for said foreign Letters Patent or other rights, the priority of the aforesaid United States patent application under the provisions of the International Convention of 1883 and later modifications thereof, under the Patent Cooperation Treaty, under the European Patent Convention or under any other available international agreement; and that, when requested, without charge to, but at the expense of, said Assignee, its successors, assigns and legal representatives, to carry out in good faith the intent and purpose of this assignment, the undersigned or the undersigned's executors or administrators will, for the United States and all foreign countries, execute all divisional, continuing, substitute, renewal, reissue, and all other patent applications or other documents on any and all said inventions; execute all rightful oaths, assignments, powers of attorney and other papers; communicate to said Assignee, its successors, assigns and representatives, all facts known and documents available to the undersigned relating to said inventions and the history thereof; testify in all legal proceedings; and generally do everything possible which said Assignee, its successors, assigns or representatives shall consider desirable for aiding in securing, maintaining and enforcing proper patent protection for said inventions and for vesting title to said inventions and all applications for patents or related foreign rights and all patents on said inventions, in said Assignee, its successors, assigns and legal representatives; and

***Covenant** with said Assignee, its successors, assigns and legal representatives that no assignment, grant, mortgage, license or other agreement affecting the rights and property herein conveyed has been made to others by the undersigned, and that full right to convey the same as herein expressed is possessed by the undersigned.*

Date: Aug 15 2010
Witness: _____ [signature]
_____ [printed name]
_____ [address]
_____

_____ [L.S.]
Ety Klinger

JPW Rev. April 19, 2007

US-

5817

Dockets 2609/80798 JPW/GJG/ACK

ASSIGNMENT

WHEREAS, **Teva Pharmaceutical Industries, Ltd.**, having a principle place of business at **5 Basel Street, P.O.B 3190, Petach-Tikva, 49131, Israel,** is an assignee of an undivided right, title and interest in and to the Patent Applications identified in **Schedule A** attached hereto, and the inventions described therein, along with all rights arising under or pursuant to any and all international agreements, treaties or laws relating to the protection of intellectual property, except for the right to apply for patents in Barbados, by virtue of an assignment of rights from **Ety Klinger of the Patent Applications identified in Schedule A** (the "Patent Rights"); and

WHEREAS, **Yeda Research and Development Co., Ltd.,** having a principal place of business at **P.O. Box 95, Rehovot, 76100, Israel,** is entitled to have assigned to it all right, title and interest in and to the Patent Rights, except for the right to apply for patents in Barbados.

NOW, THEREFORE, in consideration of ONE DOLLAR ($1.00) and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, **Teva Pharmaceutical Industries, Ltd.** hereby assigns and transfers to **Yeda Research and Development Co., Ltd.,** its successors and assigns, the entire right, title and interest in and to the Patent Rights, as well as all other patent rights that may be based thereon, including all renewals, divisions, substitutes, continuations, reissues or extensions thereof, and every priority right that is or may be predicated upon or arise from the Patent Rights, to the full end of the term of such Patent Rights and any extensions thereof, except for the right to apply for patents in Barbados.

Teva Pharmaceutical Industries, Ltd. hereby authorizes and requests all proper governmental authorities to issue all documents evidencing ownership of right, title and interest, in and to the Patent Rights by **Yeda Research and Development Co., Ltd.** and their lawful successors and assigns.

Teva Pharmaceutical Industries, Ltd. (Assignor)

By: _____
Printed Name: Richard Egosi
Title: Corporate Vice President and Chief Legal Officer
Date: Feb. 22, 2011
Witness:
_____ [signature]
Vivian Saha [printed name]
5 Basel St [address]
Petah Tikva Israel

By: _____
Printed Name: Rinat Shiran-Rasky
Title: General Patent Counsel
Date: Feb. 22, 2011
Witness:
_____ [signature]
Vivian Saha [printed name]
5 Basel St. [address]
Petach Tikva Israel

Yeda Research and Development Co., Ltd. (Assignee) hereby accepts this assignment.

By: _____
Printed Name: Amir Naiberg
Title: Chief Executive Officer
Date: _____
Witness:
_____ [signature]
_____ [printed name]
_____ [address]

By: _____
Printed Name: Mudi Sheves
Title: Chairman
Date: _____
Witness:
_____ [signature]
_____ [printed name]
_____ [address]

Schedule A – Docket 2609/80798 (Teva Ref. 5817)
to Assignment from Teva Pharmaceutical Industries, Ltd.
to Yeda Research and Development Co, Ltd.

I United States

Country	**Application No.**	**Filing Date**
US	12/806,684	August 19, 2010
US	61/274,687	August 20, 2010
US	61/337,612	February 11, 2010

II Countries other than the United States

Country	**Application No.**	**Filing Date**
PCT	PCT/US10/02283	August 19, 2010
Taiwan	099128023	August 20, 2010

Yeda

for Taiwan 5 817

Same - USA.

Dockets 2609/80798 JPW/GJG/ACK

ASSIGNMENT

WHEREAS, **Teva Pharmaceutical Industries, Ltd.**, having a principle place of business at **5 Basel Street, P.O.B 3190, Petach-Tikva, 49131, Israel,** is an assignee of an undivided right, title and interest in and to the Patent Applications identified in **Schedule A** attached hereto, and the inventions described therein, along with all rights arising under or pursuant to any and all international agreements, treaties or laws relating to the protection of intellectual property, except for the right to apply for patents in Barbados, by virtue of an assignment of rights from **Ety Klinger of the Patent Applications identified in Schedule A** (the "Patent Rights"); and

WHEREAS, **Yeda Research and Development Co., Ltd.**, having a principal place of business at **P.O. Box 95, Rehovot, 76100, Israel,** is entitled to have assigned to it all right, title and interest in and to the Patent Rights, except for the right to apply for patents in Barbados.

NOW, THEREFORE, in consideration of ONE DOLLAR ($1.00) and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, **Teva Pharmaceutical Industries, Ltd.** hereby assigns and transfers to **Yeda Research and Development Co., Ltd.**, its successors and assigns, the entire right, title and interest in and to the Patent Rights, as well as all other patent rights that may be based thereon, including all renewals, divisions, substitutes, continuations, reissues or extensions thereof, and every priority right that is or may be predicated upon or arise from the Patent Rights, to the full end of the term of such Patent Rights and any extensions thereof, except for the right to apply for patents in Barbados.

Teva Pharmaceutical Industries, Ltd. hereby authorizes and requests all proper governmental authorities to issue all documents evidencing ownership of right, title and interest, in and to the Patent Rights by **Yeda Research and Development Co., Ltd.** and their lawful successors and assigns.

Teva Pharmaceutical Industries, Ltd. (Assignor)

By:_____
Printed Name: Richard Egosi
Title: Corporate Vice President and Chief Legal Officer
Date:_____
Witness:
_____ [signature]
_____ [printed name]
_____ [address]

By:_____
Printed Name: Rinat Shiran-Rasky
Title: General Patent Counsel
Date:_____
Witness:
_____ [signature]
_____ [printed name]
_____ [address]

Yeda Research and Development Co., Ltd. (Assignee) hereby accepts this assignment.

By:_____ Amir Naiberg
Printed Name: Amir Naiberg
Title: Chief Executive Officer C.E.O.
Date: 3 Feb 2011
Witness:
Vivian Saka [signature]
Vivian Saka [printed name]
5 Basel St. [address]
Petach Tikva Israel

By:_____ Prof. Mudi Sheves
Printed Name: Mudi Sheves
Title: Chairman Chairman
Date: 3 Feb 2011
Witness:
Vivian Saka [signature]
Vivian Saka [printed name]
5 Basel St. [address]
Petach Tikva Israel

for Taiwan
5817

Dockets 2609/80798 JPW/GJG/ACK

Schedule A – Docket 2609/80798 (Teva Ref. 5817)
to Assignment from Teva Pharmaceutical Industries, Ltd.
to Yeda Research and Development Co, Ltd.

I United States

Country	Application No.	Filing Date
US	12/806,684	August 19, 2010
US	61/274,687	August 20, 2010
US	61/337,612	February 11, 2010

II Countries other than the United States

Country	Application No.	Filing Date
PCT	PCT/US10/02283	August 19, 2010
Taiwan	099128023	August 20, 2010

Form PTO-1449 (Substitute) **U.S. Department of Commerce**
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Klinger Ety
Art Unit	1649
Examiner Name	John Ulm
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	1	Official Action issued November 28, 2012 in connection with Eurasian patent application No. 201270292 including English translation thereof	
	2	Preliminary Conclusion of Substantive Examination issued November 8, 2012 in connection with Ukrainian patent application No. 2012 03259 including English translation thereof	
	3	Examination Report issued November 5, 2012 in connection with New Zealand patent application No. 598661	
	4	Response to the November 25, 2011 Examiner's Report filed October 15, 2012 in Connection With Australian Application No. 2010284666, filed August 19, 2012	
	5	Response to the July 24, 2012 outstanding Examiner's Report filed October 24, 2012 in connection with Canadian Application No. 2,760,802, filed August 19, 2012	
	6	July 24, 2012 Official Action Issued in Connection With Canadian Application No. 2,760,802, filed August 19, 2012	
	7	Communication Pursuant to Article 94(3) EPC issued August 8, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011	
	8	Response to August 8, 2012 Communication Pursuant to Article 94(3) EPC filed September 13, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011	

EXAMINER SIGNATURE	**DATE CONSIDERED**

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

Exhibit B

Electronic Patent Application Fee Transmittal

Application Number:	12806684
Filing Date:	19-Aug-2010
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Filer:	John P. White/Chris Sun
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
Statutory or terminal disclaimer	1814	1	160	160
		Total in USD ($)		**340**

Electronic Acknowledgement Receipt

EFS ID:	14670041
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	Low frequency glatiramer acetate therapy
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Chris Sun
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	10-JAN-2013
Filing Date:	19-AUG-2010
Time Stamp:	17:45:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$340
RAM confirmation Number	5219
Deposit Account	033125
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if app.)

1		130110_2609_80798-A_Amendment_Rsp_FOA_GTK.pdf	4768132 0bc58f1316448203119dbe5b9314e8cc7cd7688a	yes	16

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment After Final	1	1
Applicant Arguments/Remarks Made in an Amendment	2	2
Transmittal Letter	3	5
Amendment After Final	6	6
Terminal Disclaimer Filed	7	15
Transmittal Letter	16	16

Warnings:					
Information:					
2	Non Patent Literature	130110_2609_80798-A_Exhibit_1_GTK.pdf	336094 06822ae4eefe29877cddaed7f0162e349f9a8e56	no	4
Warnings:					
Information:					
3	Non Patent Literature	130110_2609_80798-A_Exhibit_2_GTK.pdf	1051965 7a5f0cc9917cb78827aec4862753f363d1b8a9c5	no	8
Warnings:					
Information:					
4	Non Patent Literature	130110_2609_80798-A_Exhibit_3_GTK.pdf	43659 e9b60a09447209ea61dcb246eee962dc2468576a	no	1
Warnings:					
Information:					
5	Non Patent Literature	130110_2609_80798-A_Exhibit_4_GTK.pdf	2524502 9754bb158dde042effa80b1b9cf31950e45656c1	no	29
Warnings:					
Information:					
6	Non Patent Literature	130110_2609_80798-A_Exhibit_5_GTK.pdf	3724093 69adc059416f439a5562c24677486a1412800ba8	no	34
Warnings:					
Information:					

7	Non Patent Literature	130110_2609_80798-A_Exhibit_6_GTK.pdf	476493 7309767a634a8c22a9dd134aa2152799181 3f951	no	4
Warnings:					
Information:					
8	Non Patent Literature	130110_2609_80798-A_Exhibit_7_GTK.pdf	613417 e5760048728ac6abc274aacea33b7f7aba2a 3730	no	8
Warnings:					
Information:					
9	Non Patent Literature	130110_2609_80798-A_Exhibit_8_GTK.pdf	1583044 c85191f74b1cdb43f7ae4a0ea231465c4f43 ea0b	no	25
Warnings:					
Information:					
10	Fee Worksheet (SB06)	fee-info.pdf	31609 e0b84a33033b3ceb0ce9415345f8f0b6e90 275f1	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	15153008		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	12/806,684	KLINGER, ETY	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 1/10/13	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:

Felicia D. Roberts

8,232,250

U.S. Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23432 7590 01/17/2013
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

EXAMINER
ULM, JOHN D

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 01/17/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/806,684	08/19/2010	Ety Klinger	2609/80798-A/JPW/GJG/ML	3109

TITLE OF INVENTION: LOW FREQUENCY GLATIRAMER ACETATE THERAPY

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	04/17/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23432 7590 01/17/2013
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/806,684	08/19/2010	Ety Klinger	2609/80798-A/JPW/GJG/ML	3109

TITLE OF INVENTION: LOW FREQUENCY GLATIRAMER ACETATE THERAPY

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	04/17/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
ULM, JOHN D	1649	514-017900

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/806,684	08/19/2010	Ety Klinger	2609/80798-A/JPW/GJG/ML	3109

23432 7590 01/17/2013

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

EXAMINER	
ULM, JOHN D	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 01/17/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 18 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 18 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	12/806,684	KLINGER, ETY	
	Examiner	Art Unit	
	JOHN ULM	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the correspondence filed 10 January, 2013*.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *1,3-5,18,20,21 and 33-45*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.

   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 01/10/13
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/John D. Ulm/
Primary Examiner, Art Unit 1649

DETAILED ACTION

1) Claims 1, 3 to 5, 18, 20, 21 and 33 to 45 are pending in the instant application.

2) Any objection or rejection of record that is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4) The information disclosure statement (IDS) submitted on 10 January of 2014 was filed after the mailing date of the final rejection on 10 October of 2012. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

EXAMINER'S AMENDMENT

5) An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Gary J. Gershik on 15 January of 2013.

The application has been amended as follows:

IN THE CLAIMS:

40. (Currently Amended) The method of claim 39 ~~40~~, wherein, the lesion is a demyelinating white matter lesion visible on brain MRI and wherein the white matter lesion is at least 3 mm in diameter.

Allowable Subject Matter

6) Claims 1, 3 to 5, 18, 20, 21 and 33 to 45 are allowed and have ben renumbered 1 to 20, respectively.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JOHN ULM whose telephone number is (571)272-0880. The examiner can normally be reached on 9:00AM to 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/John D. Ulm/
Primary Examiner, Art Unit 1649

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 3109

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/806,684	08/19/2010	514	1649	2609/80798-A/JPW/GJG/ML

APPLICANTS
Ety Klinger, Tel Aviv, ISRAEL;

**** CONTINUING DATA ***************************
This appln claims benefit of 61/274,687 08/20/2009
and claims benefit of 61/337,612 02/11/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****
09/08/2010

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /JOHN D ULM/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		ISRAEL	0	26	2

ADDRESS

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112
UNITED STATES

TITLE

Low frequency glatiramer acetate therapy

FILING FEE RECEIVED		
1402	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

Form PTO-1449 (Substitute) **U.S. Department of Commerce**
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Klinger Ety
Art Unit	1649
Examiner Name	John Ulm
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
/J.U./	1	Official Action issued November 28, 2012 in connection with Eurasian patent application No. 201270292 including English translation thereof	
/J.U./	2	Preliminary Conclusion of Substantive Examination issued November 8, 2012 in connection with Ukrainian patent application No. 2012 03259 including English translation thereof	
/J.U./	3	Examination Report issued November 5, 2012 in connection with New Zealand patent application No. 598661	
/J.U./	4	Response to the November 25, 2011 Examiner's Report filed October 15, 2012 in Connection With Australian Application No. 2010284666, filed August 19, 2012	
/J.U./	5	Response to the July 24, 2012 outstanding Examiner's Report filed October 24, 2012 in connection with Canadian Application No. 2,760,802, filed August 19, 2012	
/J.U./	6	July 24, 2012 Official Action Issued in Connection With Canadian Application No. 2,760,802, filed August 19, 2012	
/J.U./	7	Communication Pursuant to Article 94(3) EPC issued August 8, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011	
/J.U./	8	Response to August 8, 2012 Communication Pursuant to Article 94(3) EPC filed September 13, 2012 in connection with European Patent Application No. 10810282.3 filed October 11, 2011	

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	01/15/2013

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1]Applicant's unique citation designation number (optional). [2]Applicant is to place a checkmark here if English language Translation is attached.

Exhibit B

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12806684	KLINGER, ETY
Examiner	**Art Unit**
JOHN ULM	1649

ORIGINAL		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
514	17.9	A 6 1 K 36 / 00 (2006.01.01)	

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
514	1.1				

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	17	42												
2	3	18	43												
3	4	19	44												
4	5	20	45												
5	18														
6	20														
7	21														
8	33														
9	34														
10	35														
11	36														
12	37														
13	38														
14	39														
15	40														
16	41														

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	20	
/JOHN ULM/ Primary Examiner.Art Unit 1649	01/15/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12806684	KLINGER, ETY
	Examiner	Art Unit
	JOHN ULM	1649

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Searched inventor's name in NPL & PALM; Searched Medline, WEST & Google for: sclerosis, glatimer acetate, copolymer 1, alternate-day, dosage	02/02/2012	JDU
Updated, reviewed prosecution in 13/308,299, now US Pat. No. 8,232,250, patentably indistinct invention	10/02/2012	JDU
Updated	01/15/2013	JDU

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
	Updated from 13/308,299	01/15/2013	JDU

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23432 7590 01/17/2013
COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/806,684	08/19/2010	Ety Klinger	2609/80798-A/JPW/GJG/ML	3109

TITLE OF INVENTION: LOW FREQUENCY GLATIRAMER ACETATE THERAPY

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1770	$300	$0	$2070	04/17/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
ULM, JOHN D	1649	514-017900

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 John P. White
2 Gary J. Gershik
3 Cooper & Dunham LLP

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: YEDA RESEARCH & DEVELOPMENT CO., LTD.
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Rehovot, Israel

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☒ Advance Order - # of Copies Three(3)

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 03-3125 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27. ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature John P. White Date February 14, 2013

Typed or printed name John P. White Registration No. 28,678

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	12806684
Filing Date:	19-Aug-2010
Title of Invention:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY
First Named Inventor/Applicant Name:	Ety Klinger
Filer:	John P. White/Chris Sun
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1770	1770
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Printed copy of patent - no color	8001	3	3	9
		Total in USD ($)		**2079**

Electronic Acknowledgement Receipt

EFS ID:	14964004
Application Number:	12806684
International Application Number:	
Confirmation Number:	3109
Title of Invention:	LOW FREQUENCY GLATIRAMER ACETATE THERAPY
First Named Inventor/Applicant Name:	Ety Klinger
Customer Number:	23432
Filer:	John P. White/Chris Sun
Filer Authorized By:	John P. White
Attorney Docket Number:	2609/80798-A/JPW/GJG/ML
Receipt Date:	14-FEB-2013
Filing Date:	19-AUG-2010
Time Stamp:	16:56:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2079
RAM confirmation Number	4252
Deposit Account	033125
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	130214_2609_80798-A_Base_Issue_Fee_Transmittal_SZ.pdf	186860 2b54316d575080c3c4dd80763c8c4ec9b347f0f4	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	33894 6b362dd6ebea2171d89d60a2f102ab95b2461176	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	220754		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Form PTO-1449 (Substitute) U.S. Department of Commerce
Patent and Trademark Office

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Ety Klinger
Art Unit	John Ulm
Examiner Name	1649
Attorney Docket No.	2609/80798-A/JPW/GJG/GTK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/J.U./	1	7,625,861	12-01-2009	Konfino et al.
/J.U./	2	~~7,615,500~~	07-22-2006	7,074,580 Gad et al.
/J.U./	3	7,923,215	04-12-2011	Klinger
/J.U./	4	2007-0021324	01-25-2007	Dolitzky
/J.U./	5	2010-0285600	11-11-2010	Lancet et al.
/J.U./	6	7,855,176	12-21-~~2012~~	2010 Altman et al.
/J.U./	7	2011-0066112	03-17-2011	Altman et al.
/J.U./	8	13/384,021	07-14-2010	Altman et al.
/J.U./	9	13/083,112	04-08-2011	Klinger
/J.U./	10	11/651,212	01-09-2007	Pinchasi
/J.U./	11	12/806,684	08-19-2010	Klinger

Change(s) applied to document, /M.A./ 2/20/2013

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	10/02/2012

***EXAMINER:** Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Exhibit A

Form PTO-1449 (Substitute) **U.S. Department of Commerce Patent and Trademark Office**

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Ety Klinger
Art Unit	1614
Examiner Name	
Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/J.U./	45	6,844,314	01-18-2005	Eisenbach-Schwartz et al.
/J.U./	46	2002-0037848-A1	03-28-2002	Eisenbach-Schwartz et al.
/J.U./	47	2006-0240463 A1	~~04-24-2006~~ October 26, 2006	Lancet
/J.U./	48	12/861,655	08-23-2010	Stark et al.
/J.U./	49	12/231,292	08-29-2008	Aharoni et al.
/J.U./	50	12/761,367	04-15-2010	Altman et al.
/J.U./	51	12/785,125	05-21-2010	Altman et al.

Change(s) applied to document, /M.A./ 2/20/2013

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]
/J.U./	52	WO 00/027417	05-18-2000	Aharoni et al.	
/J.U./	53	WO 05/041933	~~06-12-2003~~	Rosenberger 2005-05-12	
/J.U./	54	WO 2004/043995	05-27-2004	Bejan et al.	
/J.U./	55	WO 2006/050122	05-11-2006	Ray et al.	
/J.U./	56	WO 2008/006026	01-10-2008	Iyer et al.	
/J.U./	57	WO 2009/070298	06-04-2009	Stark et al.	
/J.U./	58	WO 00/20010	04-13-2000	Flechter, et al.	

Change(s) applied to document, /M.A./ 2/19/2013

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	01/24/2012

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

Form PTO-1449 (Substitute) **U.S. Department of Commerce Patent and Trademark Office**

INFORMATION DISCLOSURE STATEMENT
(Use several sheets if necessary)

Application Number	12/806,684
Filing Date	August 19, 2010
First Named Inventor	Ety Klinger
Art Unit	1614
Examiner Name	
Attorney Docket No.	2609/80798-A/JPW/GJG/ACK

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
/J.U./	24	2005/0019322 A1	01-27-2005	Rodriguez, et al.
/J.U./	25	7,279,172	10-09-2007	Aharoni et al.
/J.U./	26	7,425,332	09-16-2008	Aharoni et al.
/J.U./	27	6,514,938	02-04-2003	Gad et al.
/J.U./	28	6,800,287	10-05-2004	Gad et al.
/J.U./	29	7,074,580	07-22-2006	Gad et al.
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/J.U./	31	2007-0048794 A1	03-01-2007	Gad et al.
/J.U./	32	2010-0210817 A1	08-19-2010	Gad et al.
/J.U./	33	7,429,374	09-30-2008	Ety Klinger
/J.U./	34	2009-0053253 A1	02-26-2009	Klinger
/J.U./	35	2007-0173442	07-26-2007	Vollmer
/J.U./	36	2005-0170004	08-04-2005	Rosenberger
/J.U./	37	7,560,100 July	~~08~~-14-2009	Pinchasi et al.
/J.U./	38	2007-0054857	03-08-2007	Pinchasi et al.
/J.U./	39	2007-0037740 A1	02-15-2007	Pinchasi et al.
/J.U./	40	2010-0167983 A1	07-01-2010	Kreitman et al.
/J.U./	41	7,495,072	02-24-2009	Dolitzky
/J.U./	42	2006-0172942 A1	08-03-2006	Dolitzky
/J.U./	43	2006-0264354 A1	11-23-2006	Aharoni et al.
/J.U./	44	2007-0059798	03-15-2007	Gad

Change(s) applied to document, /M.A./ 2/20/2013

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	T[6]

EXAMINER SIGNATURE	/John Ulm/	**DATE CONSIDERED**	01/24/2012

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609: Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds of Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English Language Translation is attached.

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/806,684	03/19/2013	8399413	2609/80798-A/JPW/GJG/ML	3109

23432 7590 02/27/2013

COOPER & DUNHAM, LLP
30 Rockefeller Plaza
20th Floor
NEW YORK, NY 10112

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 18 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Ety Klinger, Tel Aviv, ISRAEL;

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/10/2014	for the District of Delaware

PLAINTIFF	DEFENDANT
Teva Pharmaceuticals USA, Inc., et al.	Sandoz, Inc., et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,232,250	7/31/2012	Yeda Research and Development Co. Ltd.
2	8,399,413	3/19/2013	Yeda Research and Development Co. Ltd.
3			
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5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	9/10/2014	District of Delaware

PLAINTIFF	DEFENDANT
TEVA PHARMACEUTICALS USA, INC., et al.	DOCTOR REDDY'S LABORATORIES, LTD. AND DOCTOR REDDY'S LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,232,250 B2	7/31/2012	Teva Pharmaceutical Industries, Ltd.
2	US 8,399,413 B2	3/19/2013	Teva Pharmaceutical Industries, Ltd.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

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AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

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____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–05672–MAS–TJB	9/11/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
TEVA PHARMACEUTICALS USA, INC.	DOCTOR REDDY'S LABORATORIES, LTD.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 8,232,250	7/31/2012	YEDA RESEARCH AND DEVELOPMENT CO., LTD.
2 US 8,399,413	3/19/2013	YEDA RESEARCH AND DEVELOPMENT CO., LTD.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Marlene Kalbach	9/11/2014

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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the Northern District of West Virginia on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/7/2014	for the Northern District of West Virginia

PLAINTIFF	DEFENDANT
TEVA PHARMACEUTICALS USA, INC., et al.	MYLAN PHARMACEUTICALS INC., MYLAN INC., and NATCO PHARMA LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,232,250 B2	7/31/2012	Yeda Research & Development Co., Ltd.
2	US 8,399,413 B2	3/19/2013	Yeda Research & Development Co., Ltd.
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

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DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	10/6/2014	District of Delaware

PLAINTIFF	DEFENDANT
TEVA PHARMACEUTICALS USA, INC., et al.	MYLAN PHARMACEUTICALS INC., MYLAN INC. and NATCO PHARMA LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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