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(71) Demandeur/Applicant:
YEDA RESEARCH AND DEVELOPMENT CO., LTD., IL
(72) Inventeur/Inventor:
KLINGER, ETY, IL
(74) Agent: AITKEN KLEE LLP

(54) Titre : THERAPIE A L'ACETATE DE GLATIRAMERE A BASSE FREQUENCE
(54) Title: LOW FREQUENCY GLATIRAMER ACETATE THERAPY

(57) Abrégé/Abstract:

Expression of a transgene is driven in a host cell using a pol I promoter which is not endogenous to an organism from the same taxonomic order from which the host cell is derived.



ABSTRACT

Expression of a transgene is driven in a host cell using a pol I promoter which is not endogenous to an organism from the same taxonomic order from which the host cell is derived.

LOW FREQUENCY GLATIRAMER ACETATE THERAPY

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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
20 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:

25 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,
30 however, progress into other forms of multiple sclerosis.

2) *Relapsing-Relmitting 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.

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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.

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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.

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20 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](http://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).

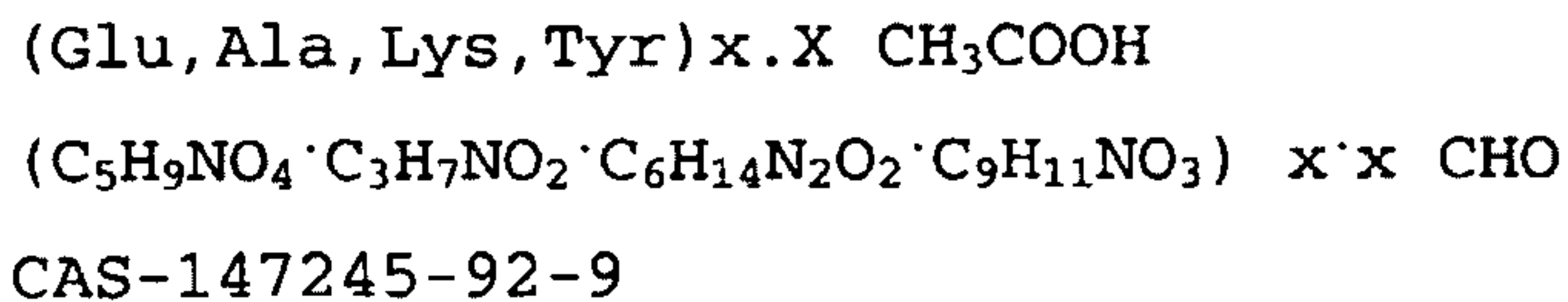
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30 Chronic progressive multiple sclerosis is a term used to collectively refer to SPMS, PPMS, and PRMS (Types of Multiple Sclerosis (MS), 2005, themcfox.com/multiple-sclerosis/types-of-ms/types-of-multi-ple-sclerosis.htm). The relapsing forms of multiple 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
 5 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",
 10 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).

15 Its structural formula is:



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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
 25 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
 30 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,
5 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
10 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
15 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.

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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
25 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.

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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

- 7 -

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
5 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
10 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.

15 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
20 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.

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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 T₂ lesions in the brain of the patient.

In a further embodiment, alleviating a symptom comprises reducing the cumulative number of enhancing lesions on T₁-weighted images in the patient.

- 5 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.

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

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

- 20 In another embodiment, alleviating a symptom comprises reducing total volume of T₂ lesions in the patient.

In another embodiment, alleviating a symptom comprises reducing the number of new hypointense lesions on enhanced T₁ scans in the patient.

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In another embodiment, alleviating a symptom comprises reducing the total volume of hypointense lesions on enhanced T₁ scans in the patient.

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

- 10 -

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

5 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.

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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.

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

20 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.

25 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.

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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.

- 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
10 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
15 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
20 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
25 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
30 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

- 12 -

site induration, injection site inflammation, injection site mass, injection site pain, injection site pruritus, injection site urticaria, injection site welt, neck pain, pain, migraine, 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.

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

10 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.

15

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

- 15 -

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)
5 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
10 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, migraine,
15 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,
20 laryngismus, rhinitis, erythema, herpes simplex, pruritus, rash, skin nodule, sweating, urticaria, ear pain, eye

- 16 -

disorder, dysmenorrhea, urinary urgency, and vaginal moniliasis.

As used herein, injection site reaction (ISR) refers to a
5 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
10 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
15 lesions that result from a breakdown of the blood-brain barrier, which appear in contrast studies using gadolinium contrast agents. Gadolinium enhancement provides information as to the age of a lesion, as Gd-enhancing lesions typically
20 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
25 visualized. Abnormal areas in a T_1 -weighted 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
30 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

- 17 -

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
5 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
10 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.

15 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,
20 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,
25 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
30 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
- 5 • 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
10 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
15 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
20 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
25 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-
30 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

- 19 -

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

Experimental Details**Example 1:**

5 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
10 placebo in a double-blind design.

Methods:

15 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
- 20 • Placebo Controlled (PC) Phase: 12 months of 40mg/ml or
matching placebo administered three times weekly by
subcutaneous injection.
- 25 • 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:

30 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
5 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
10 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
15 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
20 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
25 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.

- 23 -

- 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).

- 24 -

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

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

Re-consent criteria

10 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:

- 15 • 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.

20

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.

25

Inclusion/Exclusion:

Inclusion Criteria:

- 30 • 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.

- 25 -

- 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:
 - At least one documented relapse in the 12 months prior to screening, or
 - At least two documented relapses in the 24 months prior to screening, or
 - One documented relapse between 12 and 24 months prior to screening with at least one documented T₁-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.

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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.
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- 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.
10
- Use of cladribine within 2 years prior to screening.
- Previous treatment with immunomodulators (including IFN β 1a and 1b, and IV Immunoglobulin (IVIg) within 2 months prior to screening.
15
- 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.
20
- Previous stem-cell treatment, autologous bone marrow transplantation or allogenic bone marrow transplantation.
- Known human immunodeficiency virus (HIV) positive status.
- Pregnancy or breastfeeding.
25
- 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

- 27 -

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.

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

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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).

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Outcome Measures:Primary Outcome Measure:

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

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Secondary Outcome Measure:

- The number of new T₂ lesions at month 12 (end of PC phase) as compared to baseline scan.
- The cumulative number of enhancing lesions on T₁-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).

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

- 28 -

- The time to the first confirmed relapse during the placebo-controlled phase.
- The proportion of relapse-free subjects during the placebo-controlled phase.
- 5 • 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
10 (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.
15
- The total volume of T₂ lesions at month 12 (end of placebo-controlled phase)
- The number of new hypointense lesions on enhanced T₁ scans at month 12 (end of placebo-controlled phase) as compared
20 to the baseline scan.
- The total volume of hypointense lesions on enhanced T₁ 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
25 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
30 severity on work, using the work productivity and

- 29 -

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

Safety and Tolerability Outcome Measures:

5

Safety:

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

Tolerability:

- Proportion of subjects (%) who prematurely discontinued
15 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:

20 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 λ_i , and this individual subject
25 rates λ_i 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
30 subject population is $\theta=0.35$ relapses per year.

- 30 -

- 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 $\theta=0.245$ 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 T₂ lesions at month 12 and of the cumulative number of enhancing lesions on T₁-weighted

- 31 -

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:

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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.

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Secondary Outcome Measures:

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- Treatment with 40mg s.c. GA three times weekly significantly reduces the number of new T₂ 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 T₂ lesions at month 12.

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- Treatment with 40mg s.c. GA three times weekly significantly reduces the cumulative number of enhancing lesions on T₁-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 T₁-weighted images taken at months 6 and 12.

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- 32 -

- 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:

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- 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.

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- 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.

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- 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.

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- 33 -

- 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
5 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.
- 10 • 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
15 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 T₂ lesions at
20 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 T₂ lesions at month 12.
- 25 • Treatment with 40mg s.c. GA three times weekly significantly reduces the number of new hypointense lesions on enhanced T₁ scans at month 12 as compared to the baseline scan. Treatment with 40mg s.c. GA three
30 times weekly is at least as effective as 20mg s.c. GA daily administration at reducing the number of new hypointense lesions on enhanced T₁ scans at month 12 as compared to the baseline scan.

- 34 -

- Treatment with 40mg s.c. GA three times weekly significantly reduces the total volume of hypointense lesions on enhanced T₁ 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 T₁ scans at month 12.
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- 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.
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- 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.
20
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- 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
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- 35 -

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

- 5 • 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.
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- 15 • 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.
- 20 • 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.
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- 30 • 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

5 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
10 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,
15 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
20 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.
25 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,
30 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

- 37 -

efficacy of IFN β -1b in the treatment of MS, patient compliance, efficacy and tolerability are affected by the dosage regimen used. Merely increasing the dose of IFN β -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).

CLAIMS:

1. A pharmaceutical product for use in treating a human patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the pharmaceutical product comprises at least one group of three unit doses of glatiramer acetate, each said unit dose comprising 40 mg of glatiramer acetate.
2. The pharmaceutical product of claim 1, wherein treating comprises increasing the time to a confirmed relapse and wherein the human patient is a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.
3. The pharmaceutical product of claim 1, wherein treating comprises reducing frequency of relapses or exacerbations and wherein the human patient is a human patient suffering from relapsing-remitting multiple sclerosis.
4. The pharmaceutical product of claim 1, wherein treating comprises reducing the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reducing the mean number of new T₂ lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T₁-weighted images in a human patient, reducing the total volume of T₂ lesions in a human patient, reducing the number of new hypointense lesions on enhanced T₁ scans in a human patient or reducing the total volume of hypointense lesions on enhanced T₁ scans in a human patient.
5. The pharmaceutical product of claim 1 or claim 4, wherein the human patient is suffering from relapsing-remitting multiple sclerosis.

6. The pharmaceutical product of claim 1 or claim 4, wherein the human patient has experienced a single demyelinating event and is at high risk of developing clinically definite multiple sclerosis.

7. The pharmaceutical product according to any one of Claims 1 to 6, in which each unit dose is prepared as a pharmaceutical composition having a pH in the range of 5.5 to 7.0, wherein the pharmaceutical composition comprises 40 mg/ml glatiramer acetate and manitol.

8. The pharmaceutical product according to any one of Claims 1 to 7, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 5.

9. The pharmaceutical product according to any one of Claims 1 to 7, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 6.

10. The pharmaceutical product according to any one of Claims 1 to 7, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 4 and Day 6.

11. The pharmaceutical product according to any one of Claims 1 to 7, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 6.

12. The pharmaceutical product according to any one of Claims 1 to 7, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 7.

13. The pharmaceutical product according to any one of Claims 1 to 7, wherein the unit doses are administered over a

7 day period and a unit dose is administered on Day 2, Day 5 and Day 7.

14. The pharmaceutical product according to any one of Claims 1 to 7, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 3, Day 5 and Day 7.

15. The pharmaceutical product according to any one of Claims 1 to 14, prepared for administration as subcutaneous injections.

16. The pharmaceutical product according to any one of Claims 1 to 15, wherein the unit doses are prefilled syringes.

17. The pharmaceutical product according to any one of Claims 1 to 16, 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, bowel problems, impotence, diminished sexual arousal, loss of sensation, sensitivity to heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning.

18. The pharmaceutical product according to any one of Claims 1 to 17, wherein the human patient has MRI features consistent with multiple sclerosis.

19. The pharmaceutical product according to any one of Claims 1 to 18, wherein the human 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.

20. The pharmaceutical product according to Claim 19, 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.

21. The pharmaceutical product according to any one of Claims 1 to 20, wherein the human patient has at least 2 cerebral lesions detectable by an MRI scan and suggestive of multiple sclerosis.

22. The pharmaceutical product according to any one of Claims 1 to 21, wherein the human patient has not previously received glatiramer acetate.

23. Use of glatiramer acetate for the manufacture of a pharmaceutical product for use in treating a human patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the medicament comprises one group of three unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate.

24. The use of claim 23, wherein the treating comprises increasing the time to a confirmed relapse and wherein the human patient is a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.

25. The use of claim 23, wherein the treating comprises reducing frequency of relapses or exacerbations and wherein the human patient is a human patient suffering from relapsing-remitting multiple sclerosis.

26. The use of claim 23, wherein the treating comprises reducing the mean cumulative number of Gd-enhancing lesions in

the brain of a human patient, reducing the mean number of new T₂ lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T₁ lesions in a human patient, reducing the number of new hypointense lesions on enhanced T₁ scans in a human patient or reducing the total volume of hypointense lesions on enhanced T₁ scans in a human patient.

27. The use of claim 23 or claim 26, wherein the human patient is suffering from relapsing-remitting multiple sclerosis.

28. The use of claim 23 or claim 26, wherein the human patient has experienced a single demyelinating event and is at high risk of developing clinically definite multiple sclerosis.

29. The use according to any one of Claims 23 to 28, wherein the pharmaceutical product in which each unit dose is prepared as a pharmaceutical composition having a pH in the range of 5.5 to 7.0, wherein the pharmaceutical composition comprises 40 mg/ml glatiramer acetate and manitol.

30. The use according to any one of claims 23 to 29, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 5.

31. The use according to any one of claims 23 to 29, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 6.

32. The use according to any one of claims 23 to 29, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 4 and Day 6.

33. The use according to any one of claims 23 to 29, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 6.

34. The use according to any one of claims 23 to 29, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 7.

35. The use according to any one of claims 23 to 29, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 5 and Day 7.

36. The use according to any one of claims 23 to 29, wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 3, Day 5 and Day 7.

37. The use according to any one of Claims 23 to 36, wherein the medicament is prepared for administration as subcutaneous injections.

38. The use according to any one of Claims 23 to 37, wherein the unit doses are prefilled syringes.

39. The use according to any one of Claims 23 to 38, 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, bowel problems, impotence, diminished sexual arousal, loss of sensation, sensitivity of heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning.

40. The use according to any one of Claims 23 to 39, wherein the human patient has MRI features consistent with multiple sclerosis.

41. The use according to any one of Claims 23 to 40, wherein the human 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.

42. The use according to Claim 41, 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.

43. The use according to any one of Claims 23 to 42, wherein the human patient has at least 2 cerebral lesions detectable by an MRI scan and suggestive of multiple sclerosis.

44. The use according to any one of Claims 23 to 43, wherein the human patient has not previously received glatiramer acetate.

45. A pharmaceutical product consisting of three unit doses each comprising 40 mg of glatiramer acetate.

46. The pharmaceutical product according to Claim 45, in which each unit dose is prepared as a pharmaceutical composition having a pH in the range of 5.5 to 7.0, wherein the pharmaceutical composition comprises 40 mg/ml glatiramer acetate and manitol.

47. The pharmaceutical product according to claims 45 or 46 wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 5.

48. The pharmaceutical product according to claims 45 or 46 wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 6.

49. The pharmaceutical product according to claims 45 or 46 wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 4 and Day 6.

50. The pharmaceutical product according to claims 45 or 46 wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 6.

51. The pharmaceutical product according to claims 45 or 46 wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 7.

52. The pharmaceutical product according to claims 45 or 46 wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 5 and Day 7.

53. The pharmaceutical product according to claims 45 or 46 wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 3, Day 5 and Day 7.

54. The dosage form according to any one of Claims 45 to 53, configured for administration as subcutaneous injections.

55. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 5.

56. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 6.

57. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing

tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 4 and Day 6.

58. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 4 and Day 5.

59. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 6.

60. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 7.

61. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing

tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 5 and Day 7.

62. A pharmaceutical product comprising 3 unit doses each comprising 40 mg of glatiramer acetate for use in increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experience a first clinical episode and is at high risk of developing clinically definite multiple sclerosis wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 3, Day 5 and Day 7.

63. Use of glatiramer acetate in the preparation of a medicament for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the medicament is contained in 3 unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 5.

64. Use of glatiramer acetate in the preparation of a medicament for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the medicament is contained in 3 unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate and wherein the

unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 6.

65. Use of glatiramer acetate in the preparation of a medicament for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the medicament is contained in 3 unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 4 and Day 6.

66. Use of glatiramer acetate in the preparation of a medicament for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the medicament is contained in 3 unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 6.

67. Use of glatiramer acetate in the preparation of a medicament for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the medicament is contained in 3 unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 7.

68. Use of glatiramer acetate in the preparation of a medicament for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the medicament is contained in 3 unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 5 and Day 7.

69. Use of glatiramer acetate in the preparation of a medicament for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the medicament is contained in 3 unit doses of glatiramer acetate, each unit dose comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 3, Day 5 and Day 7.

70. Use of glatiramer acetate for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the glatiramer acetate is contained in three unit doses, each comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 3 and Day 6.

71. Use of glatiramer acetate for increasing tolerability of glatiramer acetate treatment in a human patient suffering

from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the glatiramer acetate is contained in three unit doses, each comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 4 and Day 6.

72. Use of glatiramer acetate for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the glatiramer acetate is contained in three unit doses, each comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 7.

73. Use of glatiramer acetate for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the glatiramer acetate is contained in three unit doses, each comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 1, Day 2 and Day 5.

74. Use of glatiramer acetate for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the glatiramer acetate is contained in three unit doses, each comprising 40 mg of glatiramer acetate and wherein the unit

doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 4 and Day 6.

75. Use of glatiramer acetate for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the glatiramer acetate is contained in three unit doses, each comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 2, Day 5 and Day 7.

76. Use of glatiramer acetate for increasing tolerability of glatiramer acetate treatment in a human patient suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk of development clinically definite multiple sclerosis wherein the glatiramer acetate is contained in three unit doses, each comprising 40 mg of glatiramer acetate and wherein the unit doses are administered over a 7 day period and a unit dose is administered on Day 3, Day 5 and Day 7.

77. The product of claims 55 to 62 or the use of claims 74 to 76, wherein the glatiramer acetate treatment comprises alleviating a symptom of relapsing-remitting multiple sclerosis.

78. The product of claims 55 to 62 or the use of claims 63 to 76, wherein alleviating a symptom of relapsing-remitting multiple sclerosis comprises reducing the frequency of relapses, reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient, reducing the mean number of new T₂ lesions in the brain of the patient, reducing the cumulative number of enhancing lesions on T₁-weighted images, reducing brain atrophy in the patient, increasing the time to

a confirmed relapse in the patient, reducing the total number of confirmed relapses in the patient, reducing the progression of MRI-monitored disease activity in the patient, reducing the total volume of T₂ lesions in the patient, reducing the number of new hypointense lesions on enhanced T₁ scans in the patient, reducing the total volume of hypointense lesions on enhanced T₁ scans, reducing the level of disability as measured by EDSS Score in the patient, reducing the change in EDSS Score in the patient, reducing the change in Ambulation Index in the patient, reducing the level of disability as measured by EuroQol (EQ5D) questionnaire in the patient, or reducing the level of disability as measured by the work productivity and activities impairment - General Health (WPAI-GH) questionnaire in the patient.

79. The product of claims 55 to 62, 77 to 78 or the use of claims 63 to 76, 77 to 78, wherein alleviating a symptom of relapsing-remitting multiple sclerosis comprises reducing the frequency of relapses in the patient.

80. The product of any one of claims 55 to 62, or the use of any one of claims 63 to 76, wherein the human patient is a human patient suffering from relapsing-remitting multiple sclerosis.

81. The product of any one of claims 55 to 62, 77 to 80 or the use of any one of claims 63 to 76, 77 to 80, wherein the human patient is a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.

82. The product of any one of claims 55 to 62, 77 to 81 or the use of any of claims 63 to 76, 77 to 81, 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, bowel problems, impotence, diminished sexual arousal, loss of sensation, sensitivity to heat, loss of short term memory, loss of concentration, or loss of judgment or reasoning.

83. The product of any one of claims 55 to 62, 77 to 82 or the use of any one of claims 63 to 76, 77 to 82, wherein the patient has MRI features consistent with multiple sclerosis.

84. The product of any one of claims 55 to 62, 77 to 83 or the use of any one of claims 63 to 76, 77 to 83, 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.

85. The product or use of claim 84, 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.

86. The product of any one of claims 55 to 62, 77 to 83 or the use of any one of claims 63 to 76, 77 to 85 wherein the patient has at least 2 cerebral lesions detectable by an MRI scan and suggestive of multiple sclerosis.

87. The product or the use of any one of claims 55 to 62, 63 to 76 or 77, wherein alleviating a symptom of relapsing-remitting multiple sclerosis further comprises reducing the mean cumulative number of Gd-enhancing lesions in the brain of the patient, reducing the mean number of new T₂ lesions in the

brain of the patient or reducing the cumulative number of enhancing lesions on T₁-weighted images.

88. The product of any one of claims 55 to 62, 77 to 87 or the use of any one of claims 63 to 76, 77 to 87, wherein increasing tolerability comprises reducing the frequency of immediate post injection reaction relative to the frequency experienced glatiramer acetate treatment with 20 mg glatiramer acetate prepared for daily subcutaneous injection.

89. The product or use of claim 88, wherein the immediate post injection reaction is palpitations, feeling hot, flushing, hot flushes, tachycardia, chest discomfort, chest pain, non-cardiac chest pain, 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 urticarial, injection site welt, neck pain, pain, migraine, syncope, vasodilation, 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, urticarial, ear pain, eye disorder, dysmenorrhea, urinary urgency, or vaginal moniliasis.

90. The product of any one of claims 55 to 62, 77 to 89 or the use of any one of claims 63 to 76, 77 to 89, wherein increasing tolerability comprises reducing the frequency of injection site reaction each relative to the frequency experienced glatiramer acetate treatment with 20 mg glatiramer acetate prepared for daily subcutaneous injection.

91. The product or use of claim 90, wherein the injection site reaction is erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticarial, or welt that occurs immediately around the site of the injection.

92. The product of any one of claims 55 to 62, 77 to 91 or the use of any one of claims 63 to 76, 77 to 91, wherein the human patient has not received glatiramer acetate prior to initiation of the regimen.

93. The product of any one of claims 55 to 62, 77 to 92 or the use of any one of claims 63 to 76, 77 to 92, wherein the 40 mg unit dose is present in a 1 ml pharmaceutical composition comprising manitol, and having a pH in the range of 5.5 to 7.0.

94. The product of any one of claims 55 to 62, 77 to 93 or the use of any one of claims 63 to 76, 77 to 93, wherein the 40 mg unit dose is present in a prefilled syringe for self administration by the patient.

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

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

97. A medicament comprising glatiramer acetate for use in increasing the time to a confirmed relapse in a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

98. Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection to increase the time to a confirmed relapse in a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis.

99. A medicament comprising glatiramer acetate for use in reducing the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reducing the mean number of new T2 lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T1-weighted images in a human patient, reducing the total volume of T2 lesions in a human patient, reducing the number of new hypointense lesions on enhanced T1 scans in a human patient or reducing the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient has experienced a single demyelinating event and is at high risk of developing clinically definite multiple sclerosis, and wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

100. Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection to reduce the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reduce the mean number of new T2 lesions in the brain of a human patient, reduce the cumulative number of enhancing lesions on T1-weighted images in a human patient, reduce the total volume of T2 lesions in a human patient, reduce the number of new hypointense lesions on enhanced T1 scans in a human patient or reduce the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient has experienced a single demyelinating event and is at high risk of developing clinically definite multiple sclerosis.

101. The medicament of any one of claims 95, 97 or 99, or glatiramer acetate of any one of claims 96, 98 or 100, 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.

102. The medicament of any one of claims 95, 97, 99 or 101, or glatiramer acetate of any one of claims 96, 98, 100 or 101, wherein the human patient has MRI features consistent with multiple sclerosis.

103. The medicament of any one of claims 95, 97, 99, 101 or 102, or glatiramer acetate of any one of claims 96, 98, 100, 101, or 102, wherein the human 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, preferably 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.

104. The medicament of any one of claims 95, 97, 99, 101, 102 or 103, or glatiramer acetate of any one of claims 96, 98, 100-102 or 103, wherein the human patient has at least 2 cerebral lesions detectable by an MRI scan and suggestive of multiple sclerosis.

105. The medicament of any one of claims 95, 101-103 or 104, or glatiramer acetate of any one of claims 96, 101-103 or 104, wherein the regimen is effective for reducing the frequency of relapses in the human patient, reducing the mean cumulative number of Gd-enhancing lesions in the brain of the human patient, reducing the mean number of new T2 lesions in the brain of the human patient, reducing the cumulative number of enhancing lesions on T1-weighted images in the human patient, reducing brain atrophy in the human patient, increasing the time to a confirmed relapse in the human patient, reducing the total number of confirmed relapses in the human patient, reducing the progression of MRI-monitored disease activity in the human patient, reducing the total volume of T2 lesions in the human patient, reducing the number

of new hypointense lesions on enhanced T1 scans in the human patient, reducing the total volume of hypointense lesions on enhanced T1 scans, reducing the level of disability as measured by EDSS Score in the human patient, reducing the change in EDSS Score in the human patient, reducing the change in Ambulation Index in the human patient, reducing the level of disability as measured by EuroQoL (EQ5D) questionnaire in the human patient, or reducing the level of disability as measured by the work productivity and activities impairment - General Health (WPAI-GH) questionnaire in the human patient.

106. The medicament of any one of claims 95, 101-104 or 105, or glatiramer acetate of any one of claims 96, 101-104 or 105, wherein the regimen is effective for reducing the frequency of relapses or exacerbations in the human patient.

107. A medicament comprising glatiramer acetate for use in reducing frequency of relapses or exacerbations in a human patient suffering from relapsing-remitting multiple sclerosis wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

108. Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection to reduce frequency of relapses or exacerbations in a human patient suffering from relapsing-remitting multiple sclerosis.

109. A medicament comprising glatiramer acetate for use in reducing the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reducing the mean number of new T2 lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T1-weighted images

in a human patient, reducing the total volume of T2 lesions in a human patient, reducing the number of new hypointense lesions on enhanced T1 scans in a human patient or reducing the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient is suffering from relapsing-remitting multiple sclerosis, and wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

110. Glatiramer acetate for use in a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection to reduce the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reduce the mean number of new T2 lesions in the brain of a human patient, reduce the cumulative number of enhancing lesions on T1-weighted images in a human patient, reduce the total volume of T2 lesions in a human patient, reduce the number of new hypointense lesions on enhanced T1 scans in a human patient or reduce the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient is suffering from relapsing-remitting multiple sclerosis.

111. The medicament of any one of claims 95, 97, 99, 101-107 or 109, or glatiramer acetate of any one of claims 96, 98, 100-106, 108 or 110, wherein the regimen is further effective for reducing the mean cumulative number of Gd-enhancing lesions in the brain of the human patient, reducing the mean number of new T2 lesions in the brain of the human patient or reducing the cumulative number of enhancing lesions on T1-weighted images in the human patient.

112. The medicament of any one of claims 95, 97, 99, 101-107, 109 or 111, or glatiramer acetate of any one of claims 96, 98, 100-106, 108, 110 or 111, wherein frequency of immediate post injection reaction or of injection site reaction of the medicament relative to frequency experienced with 20mg glatiramer acetate prepared for daily subcutaneous injection is reduced.

113. The medicament of any one of claims 95, 97, 99, 101-107, 109, 111 or 112, or glatiramer acetate of any one of claims 96, 98, 100-106, 108, 110, 111 or 112, wherein the tolerability of the medicament by the human patient is increased relative to 20mg glatiramer acetate prepared for daily subcutaneous injection, wherein the increased tolerability comprises reduced frequency of immediate post injection reaction or reduced frequency of injection site reaction of the medicament, each relative to the frequency experienced with 20 mg glatiramer acetate prepared for daily subcutaneous injection.

114. The medicament or glatiramer acetate, of claim 112 or claim 113, 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, migraine, 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, dysmenorrhea, urinary urgency, or vaginal moniliasis.

115. The medicament or glatiramer acetate, of claim 112 or claim 113, wherein the injection site reaction is erythema, hemorrhage, induration, inflammation, mass, pain, pruritus, urticaria, or welt that occurs immediately around the site of injection.

116. The medicament of any one of claims 95, 97, 99, 101-107, 109, 111-114 or 115, or glatiramer acetate of any one of claims 96, 98, 100-106, 108, 110-114 or 115, wherein the human patient has not received glatiramer acetate prior to initiation of the regimen.

117. The medicament of any one of claims 95, 97, 99, 101-107, 109, 111-115 or 116, or glatiramer acetate of any one of claims 96, 98, 100-106, 108, 110-115 or 116, wherein the medicament is prepared as a pharmaceutical composition having a pH in the range of 5.5 to 7.0 or the glatiramer acetate is present in a pharmaceutical composition having a pH in the range of 5.5 to 7.0, wherein the pharmaceutical composition comprises 40 mg/ml glatiramer acetate and manitol.

118. The medicament of any one of claims 95, 97, 99, 101-107, 109, 111-116 or 117, or glatiramer acetate of any one of claims 96, 98, 100-106, 108, 110-116 or 117, wherein the glatiramer acetate is prepared for administration using a prefilled syringe by self administration.

119. Use of glatiramer acetate for the manufacture of a medicament for use in treating a human patient who is suffering from relapsing-remitting multiple sclerosis or who has experienced a first clinical episode and is at high risk

of developing clinically definite multiple sclerosis, wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

120. Use of glatiramer acetate in the manufacture of a medicament for use in increasing the time to a confirmed relapse in a human patient who has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

121. Use of glatiramer acetate in the manufacture of a medicament for use in reducing the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reducing the mean number of new T2 lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T1-weighted images in a human patient, reducing the total volume of T2 lesions in a human patient, reducing the number of new hypointense lesions on enhanced T1 scans in a human patient or reducing the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient has experienced a first clinical episode and is at high risk of developing clinically definite multiple sclerosis, and wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

122. Use of glatiramer acetate in the manufacture of a medicament for use in reducing frequency of relapses or exacerbations in a human patient suffering from relapsing-

remitting multiple sclerosis wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

123. Use of glatiramer acetate in the manufacture of a medicament for use in reducing the mean cumulative number of Gd-enhancing lesions in the brain of a human patient, reducing the mean number of new T2 lesions in the brain of a human patient, reducing the cumulative number of enhancing lesions on T1-weighted images in a human patient, reducing the total volume of T2 lesions in a human patient, reducing the number of new hypointense lesions on enhanced T1 scans in a human patient or reducing the total volume of hypointense lesions on enhanced T1 scans in a human patient, wherein the human patient is suffering from relapsing-remitting multiple sclerosis, and wherein the medicament is prepared for a regimen of three subcutaneous injections of a 40mg dose of glatiramer acetate every seven days with at least one day between each subcutaneous injection.

124. The use of any one of claims 119-123, wherein the medicament is a pharmaceutical composition comprising 40 mg/ml glatiramer acetate and mannitol, and having a pH in the range of 5.5 to 7.0.

125. The use of any one of claims 119-124, wherein the medicament is administered using a prefilled syringe by self administration.

Figure 1

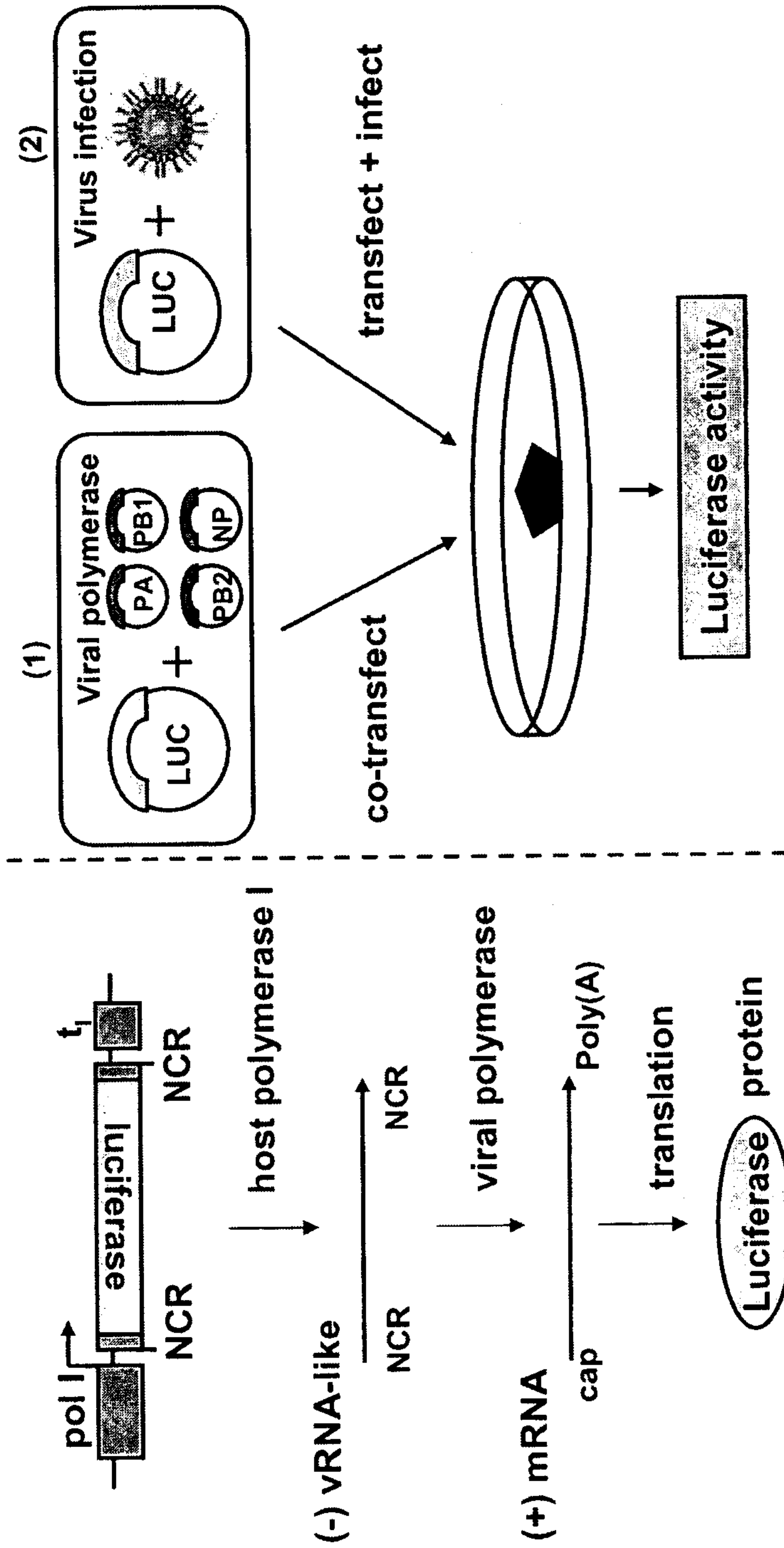


Figure 2

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Figure 4

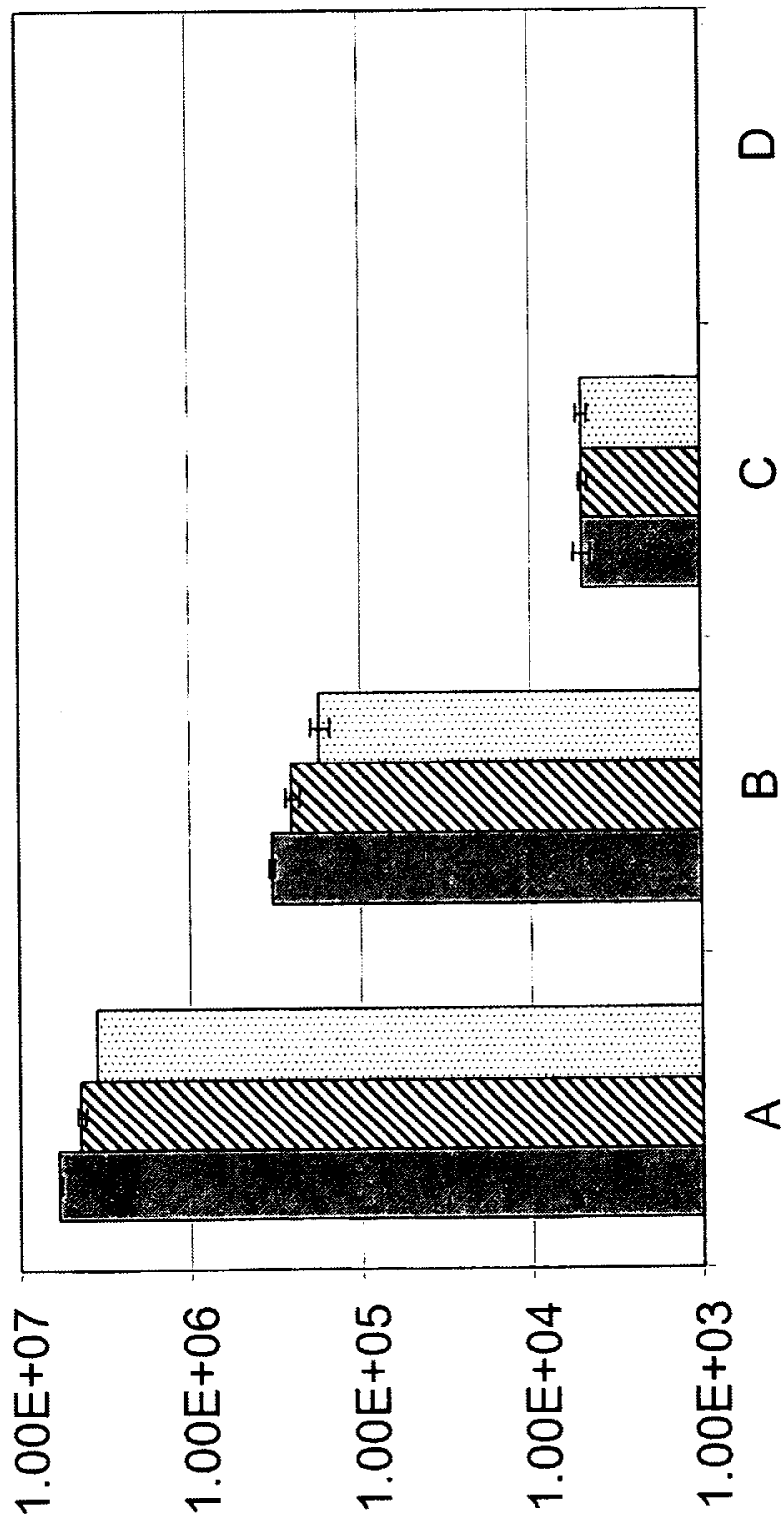


Figure 5

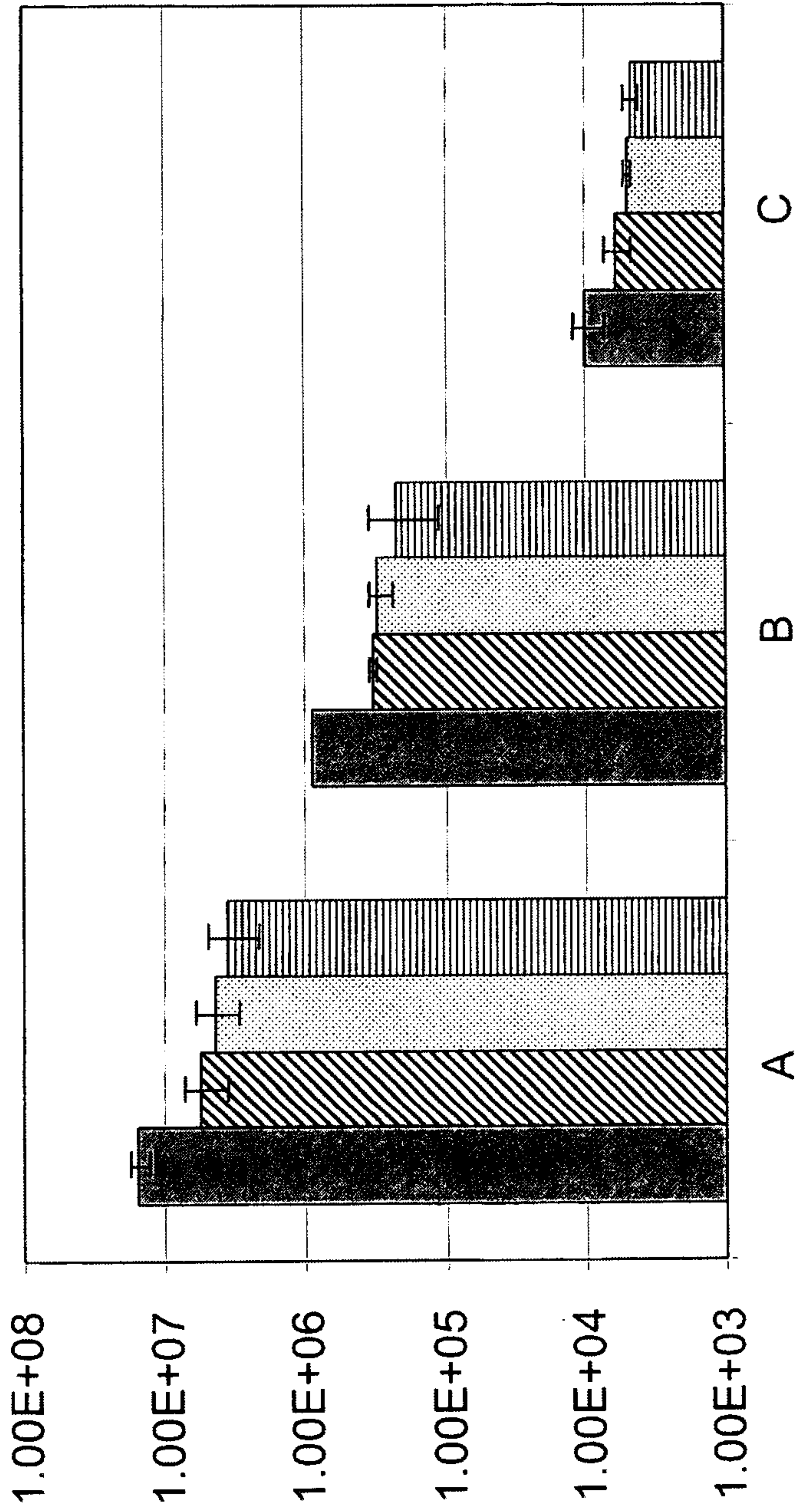


Figure 6

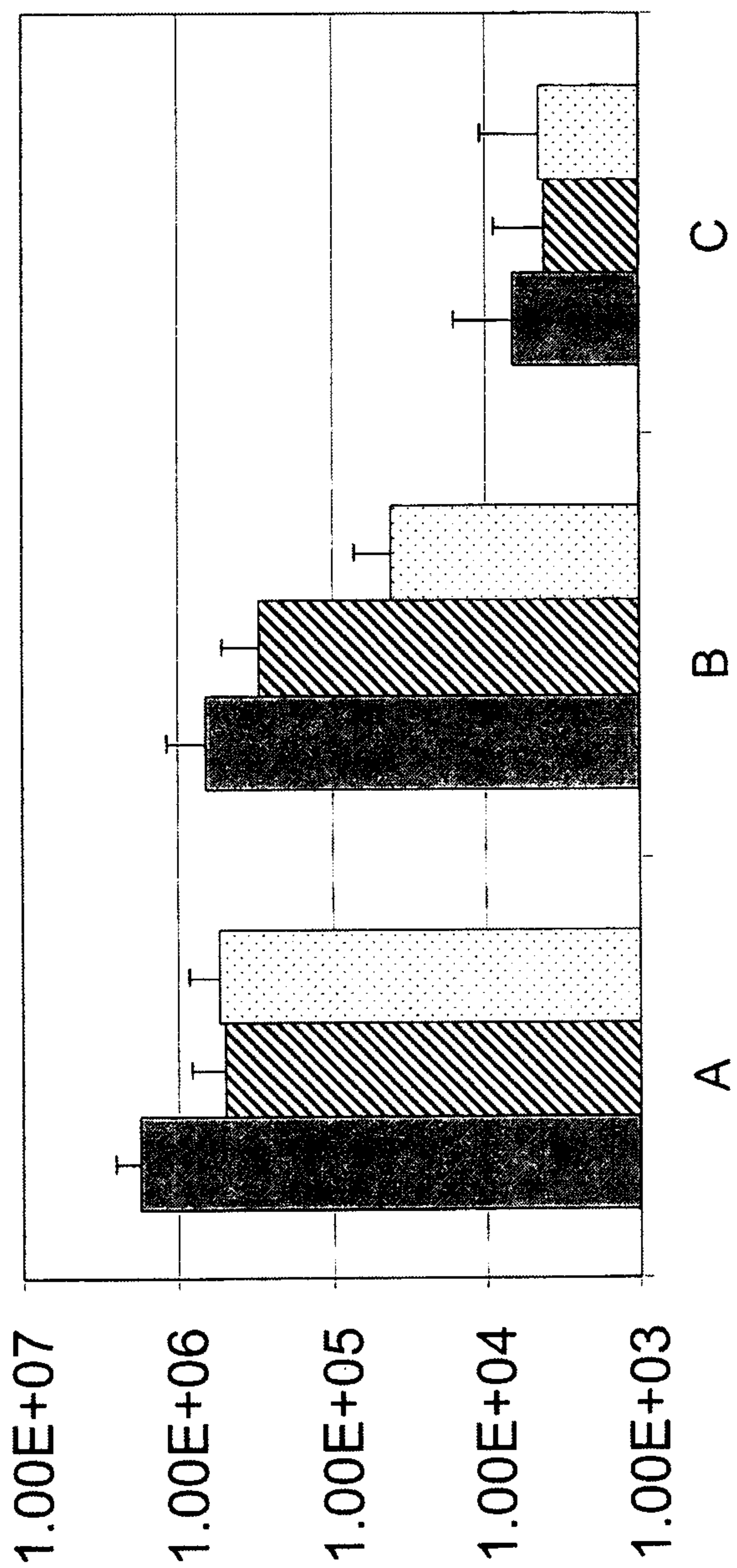


Figure 7

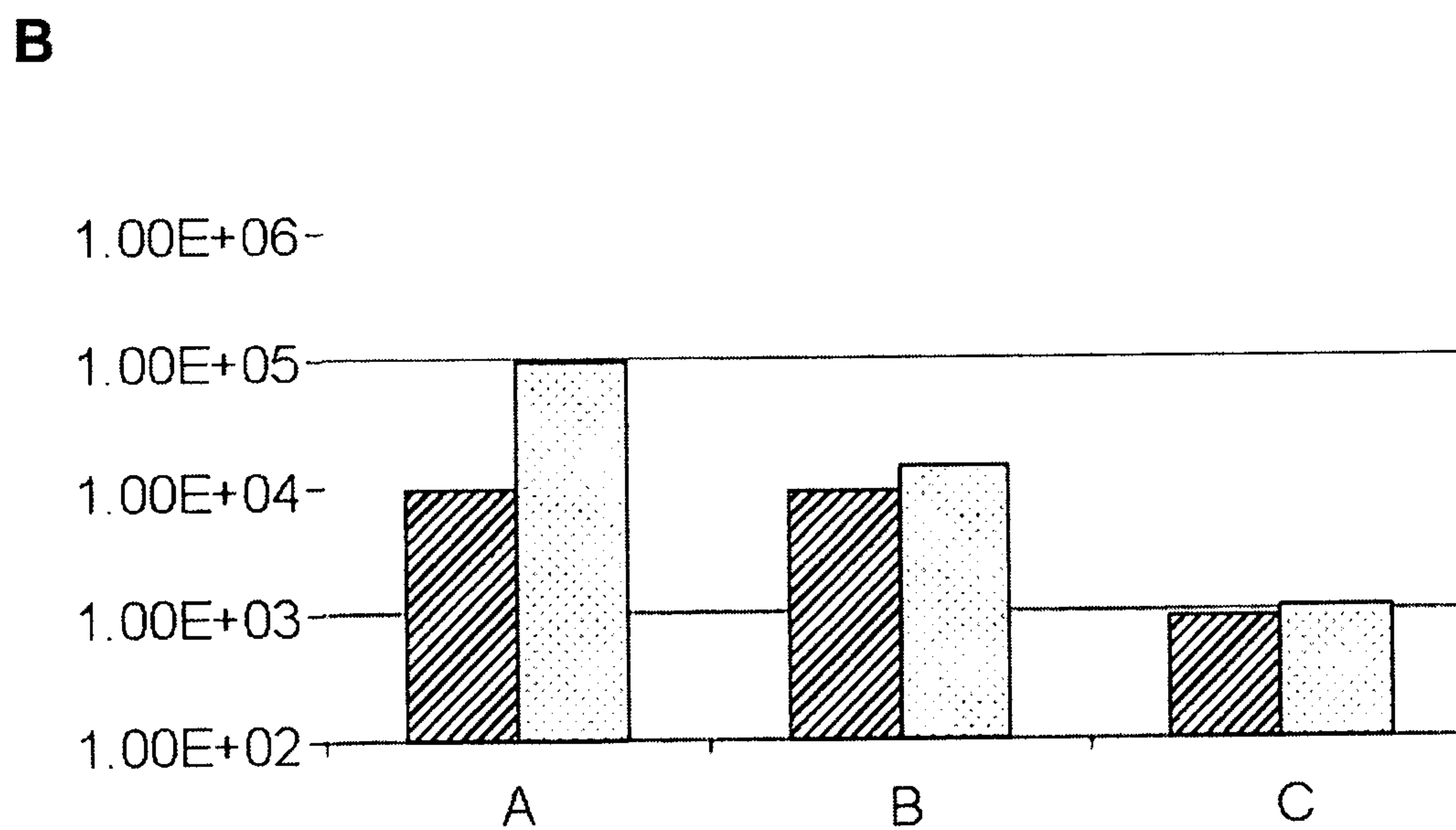
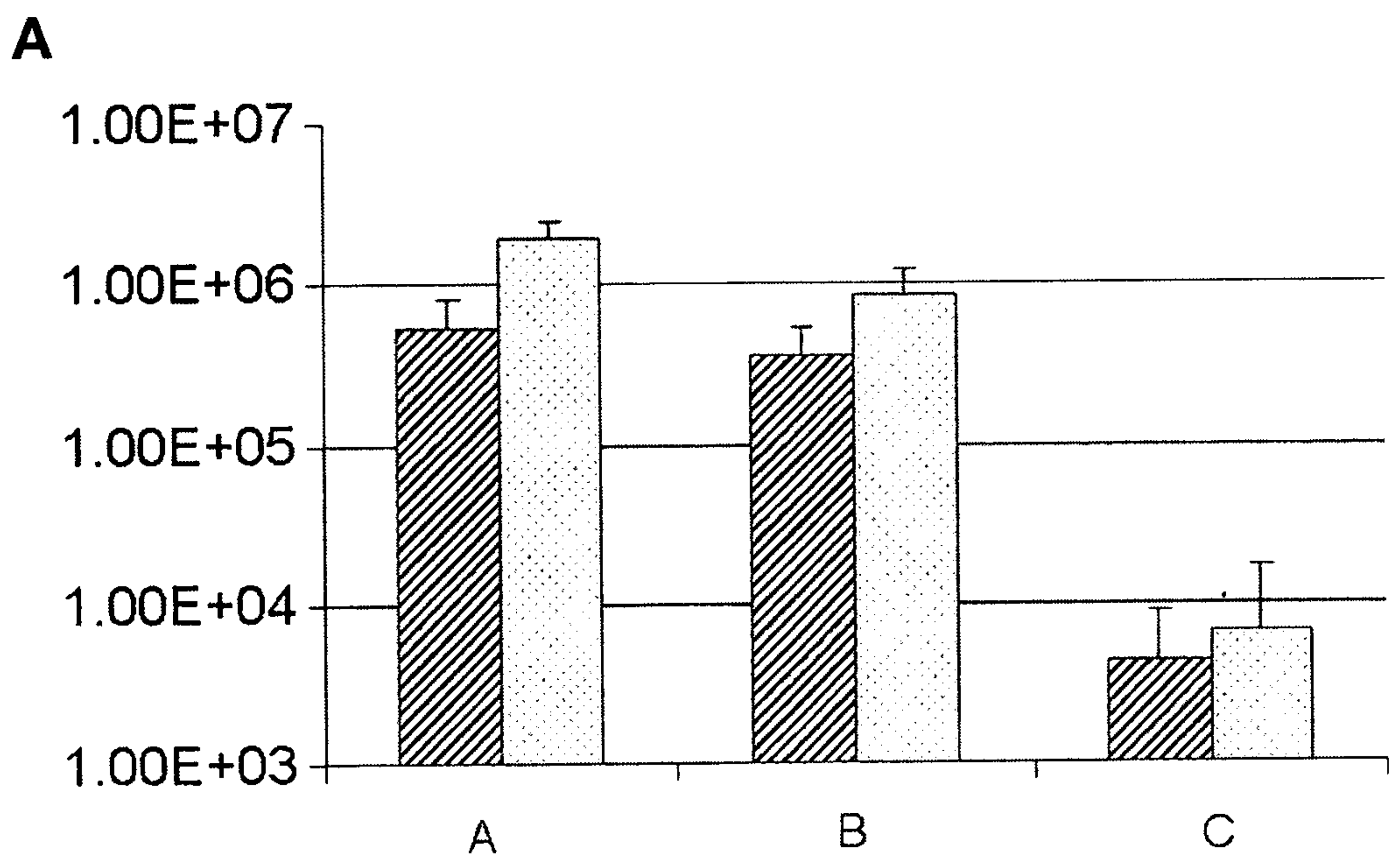


Figure 8

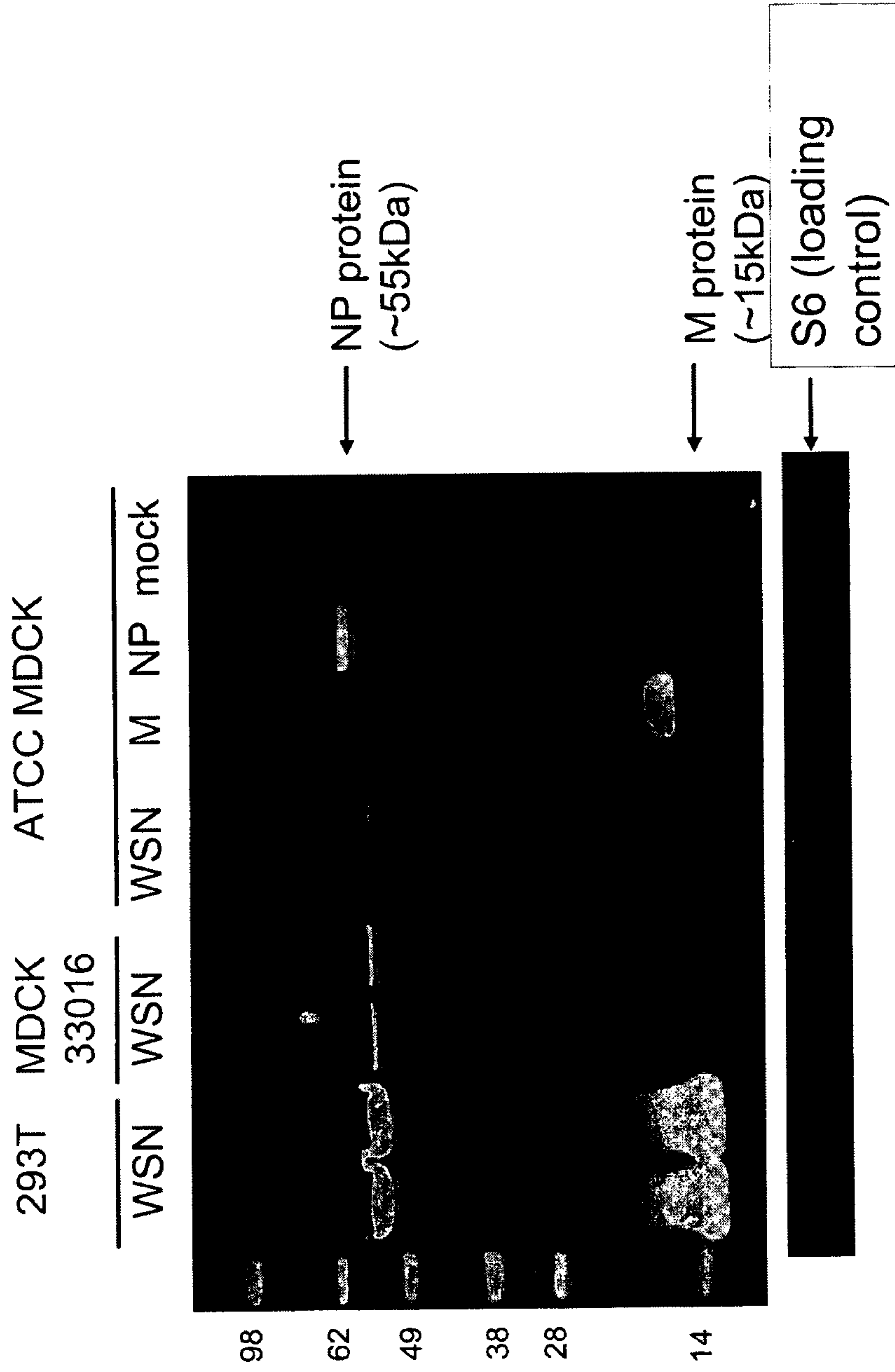


Figure 9

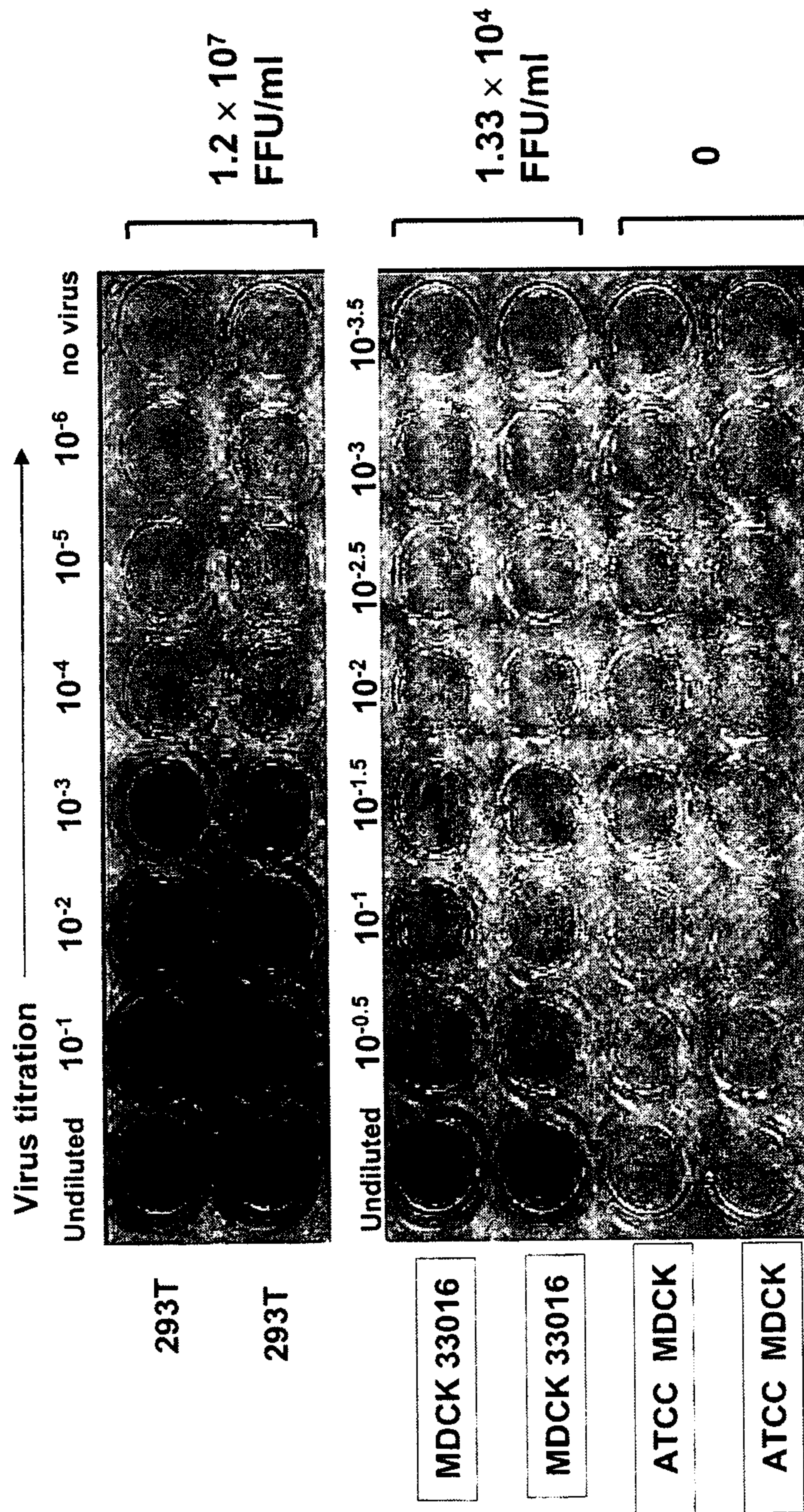
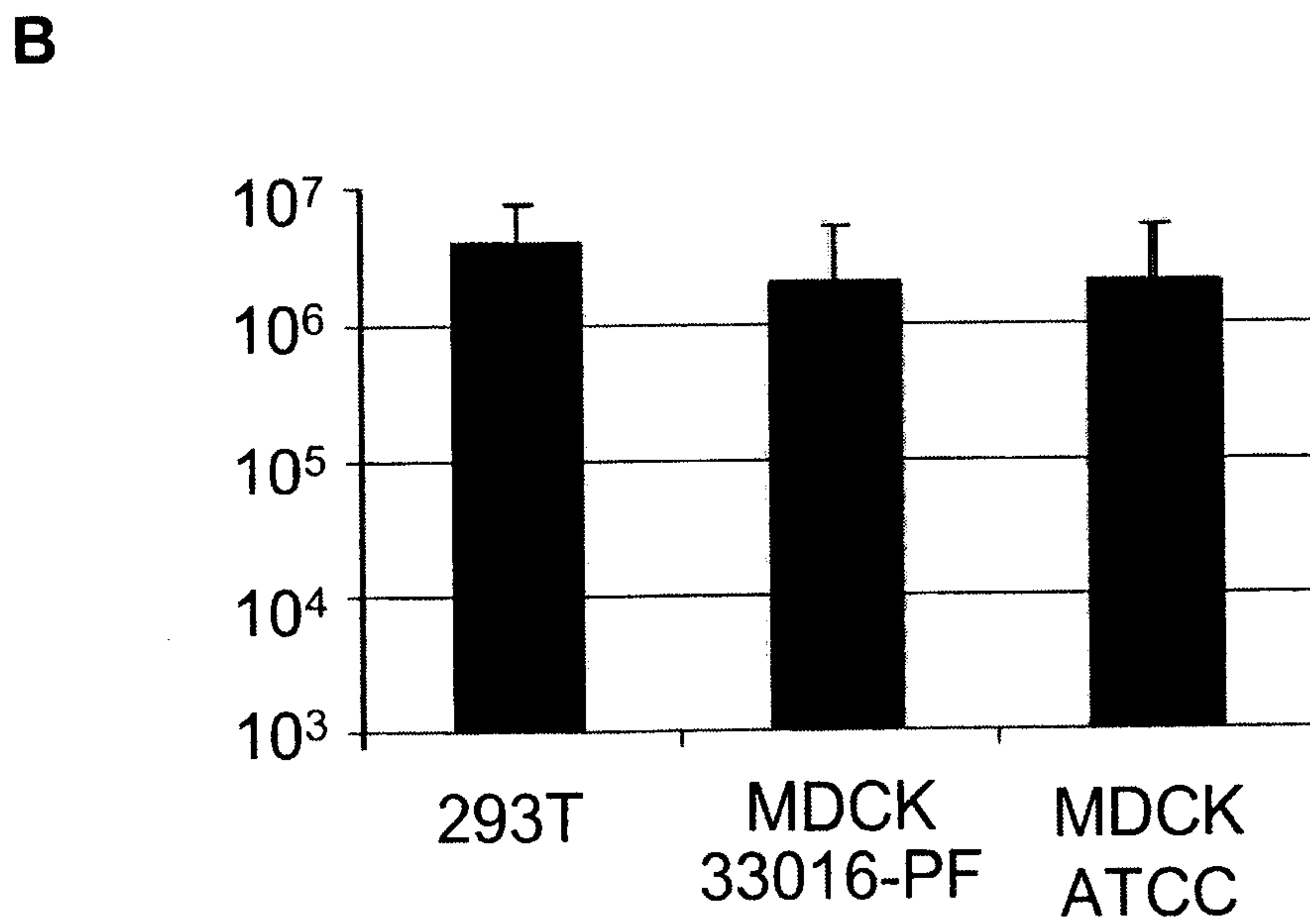
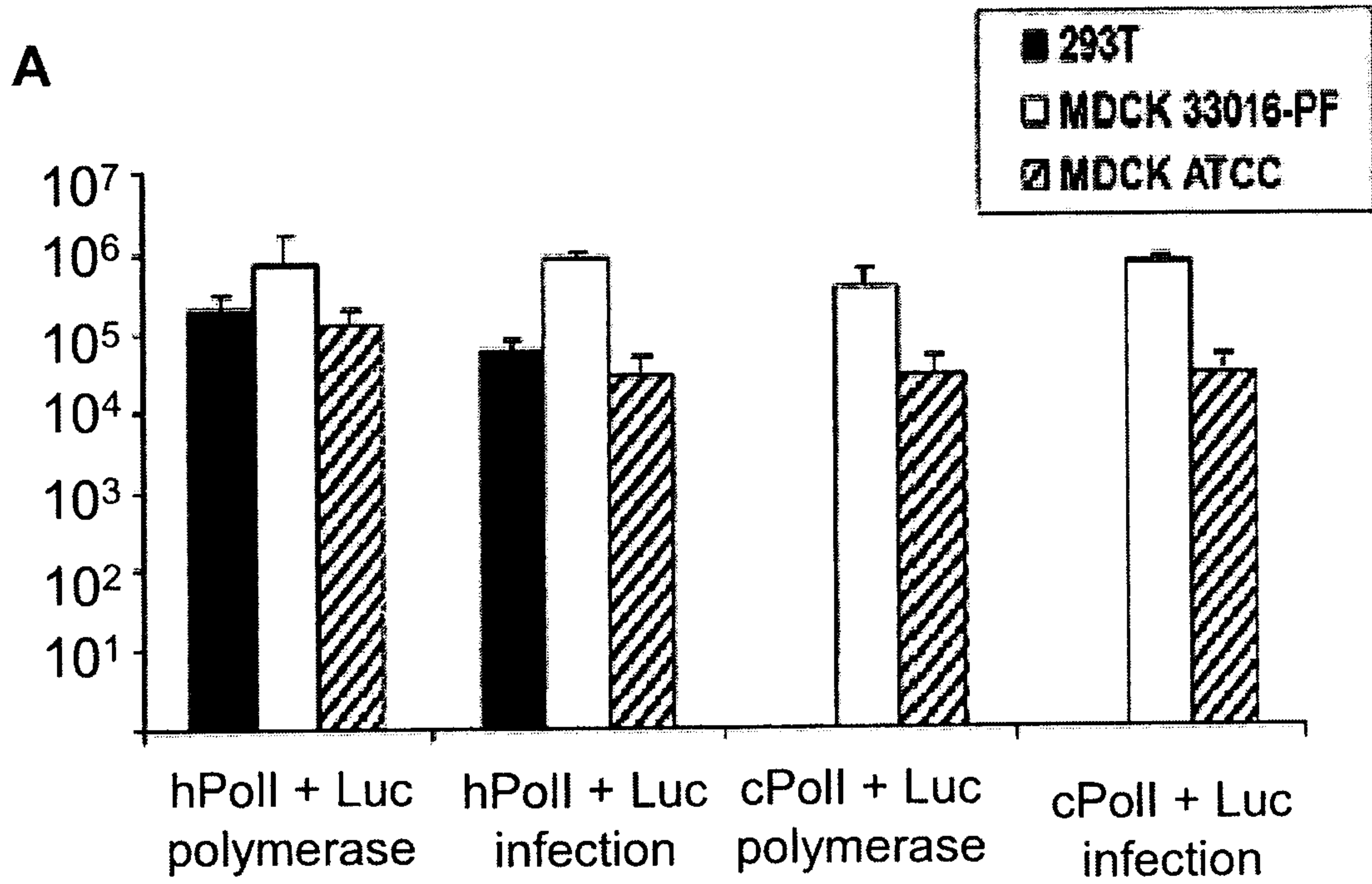


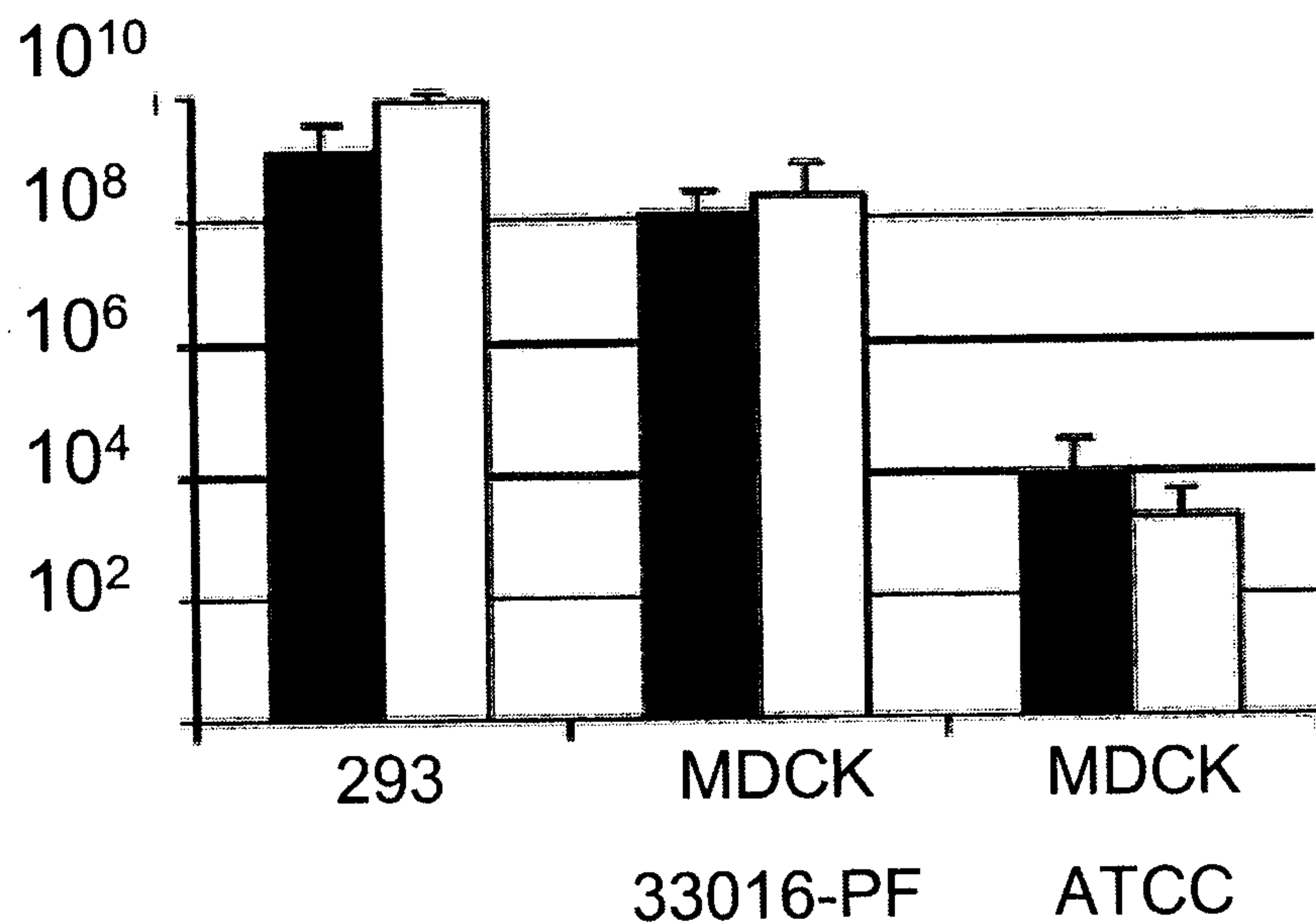
Figure 11



12/13

Figure 12

A



B

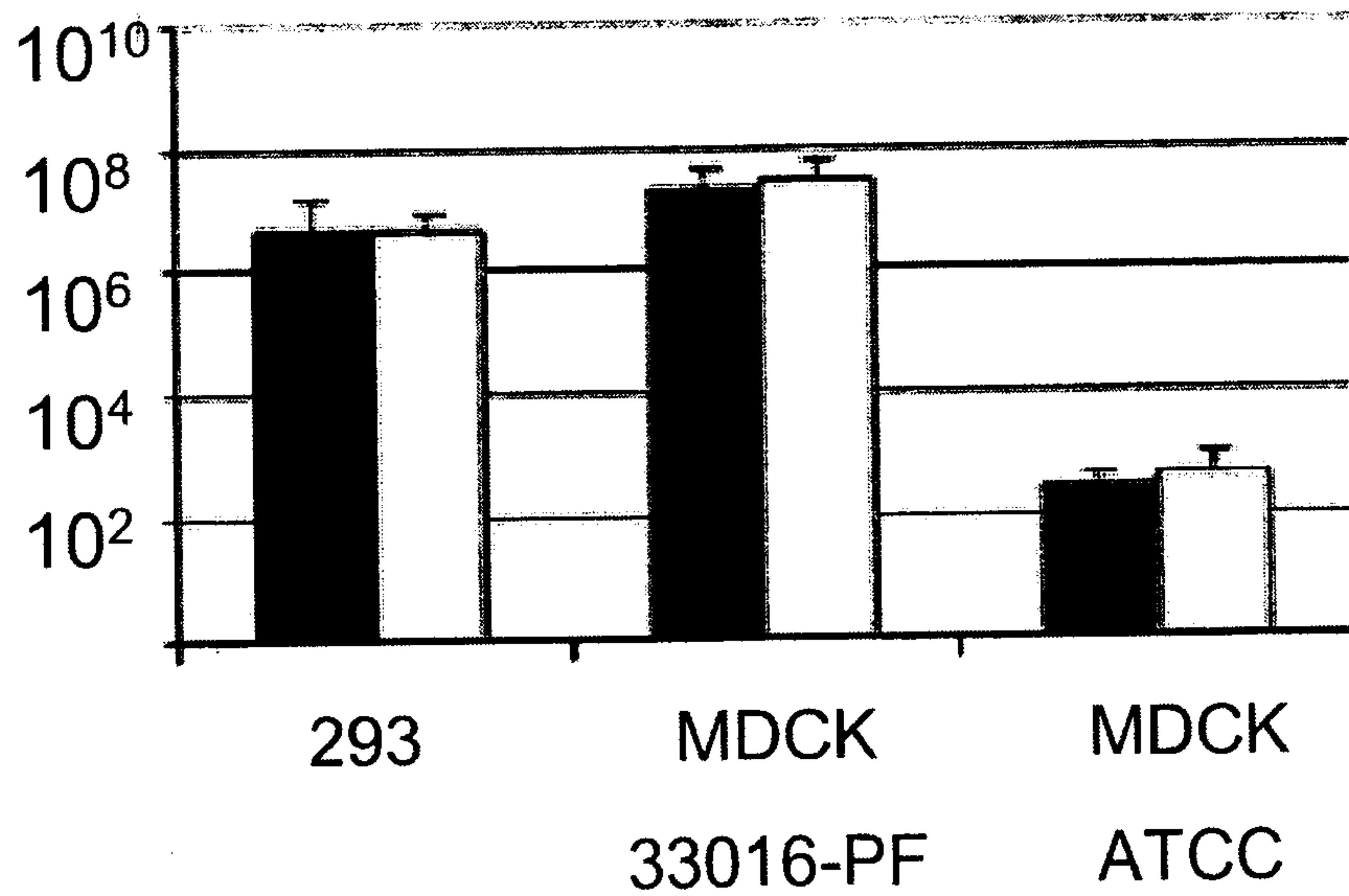


Figure 13

